HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Long-Term Effectiveness and Safety of Enzyme Replacement Therapy in Mucopolysaccharidoses Type I, II, IVA and Pompe Disease

Systematic Review

AIHTA Decision Support Document: 169 | ISSN-online: 1998-0469

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Long-Term Effectiveness and Safety of Enzyme Replacement Therapy in Mucopolysaccharidoses Type I, II, IVA and Pompe Disease

Systematic Review

Vienna, December 2025

Project Team

Project Leader: Dr. MMag. Sabine Geiger-Gritsch

Authors: MSc Ana Pantović
PharmDr. Eva Malíková, PhD

Project Support

Systematic Literature Search: Tarquin Mittermayr, BA(Hons), MA

Internal Review: Judit Erdös, MA

External Review: ao. Univ.-Prof. Dr. Daniela Karall, Medizinische Universität Innsbruck,
Department für Kinder- und Jugendheilkunde, Universitätsklinik für Pädiatrie I, Innsbruck

Correspondence: sabine.geiger-gritsch@aihta.at

This report should be referenced as follows:

Pantović A, Malíková E, Erdos J, Geiger-Gritsch S. Long-Term Effectiveness and Safety of Enzyme Replacement Therapy in Mucopolysaccharidoses Type I, II, IVA and Pompe Disease: Systematic Review. AIHTA Decision Support Documents No. 169; 2025. Vienna: HTA Austria – Austrian Institute for Health Technology Assessment GmbH.

Conflict of interest

All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org).

Disclaimer

The external reviewers did not co-author the scientific report and do not necessarily all agree with its content.
Only the AIHTA is responsible for errors or omissions that could persist. The final version and the policy recommendations are under the full responsibility of the AIHTA.

IMPRINT

Publisher:
HTA Austria – Austrian Institute for Health Technology Assessment GmbH
Josefstädter Straße 39 | 1080 Vienna – Austria
https://www.aihta.at/

Responsible for content:
Dr. rer. soc. oec. Ingrid Zechmeister-Koss, MA, managing director

AIHTA Decision Support Documents do not appear on a regular basis and serve to publicize the research results of the Austrian Institute for Health Technology Assessment.

AIHTA Decision Support Documents are only available to the public via the Internet at http://eprints.aihta.at/view/types/hta_report.html.

AIHTA Decision Support Documents No.: 169

ISSN online 1998-0469

Content

List of figures

List of tables

List of abbreviations

6MWD .....Six-minute walking distance
AE/SAE.....(Serious) adverse event
ADR .....Adverse Drug Reaction
ADR(s) .....Adverse drug reaction(s)
AHI.....Apnea–Hypopnea Index
ALG.....Alglucosidase alfa
ANCOVA.....Analysis of covariance
AVAL .....Avalglucosidase alfa
BSID-II .....Bayley Scales of Infant and Toddler Development, Second Edition
CDIIT .....Comprehensive Developmental Inventory for Infants and Toddlers
CFT .....Culture Fair Intelligence Test
CFT (1R, 20R) ... Culture Fair Intelligence Test (1-R for <9y, 20-R for ≥9y)
CHAQ/HAQ ... Child Health Assessment Questionnaire/Health Assessment Questionnaire
CHO .....Chinese hamster ovary
CI.....Confidence interval
CoI.....Conflict of interest
CNS .....Central nervous system
CRIM .....Cross-reactive immunological material
CTCAE .....Common Terminology Criteria for Adverse Events
CTR.....Culture Fair Intelligence Test (typo variant, see CFT)
DAS .....Differential Abilities Scales
DAS-II.....Differential Ability Scales, Second Edition
EC.....European Commission
EF .....Ejection fraction
EMA .....European Medicines Agency
ERT .....Enzyme replacement therapy
EU .....European Union
FAERS .....FDA Adverse Event Reporting System
FDA.....Food and Drug Administration
FEV1 .....Forced expiratory volume in 1 second
FU .....Follow-up
FVC .....Forced vital capacity
GAA.....Acid alpha-glucosidase
GAG .....Glycosaminoglycan
GALNS N-acetylgalactosamine-6-sulfatase
GCA .....General Conceptual Ability (DAS-II composite)
GKV/PKV.....Gesetzliche Krankenversicherung/ Private Krankenversicherung
GRADE.....Grading of Recommendations, Assessment, Development, and Evaluation
GSD.....Glycogen storage disorder
HCM .....Hypertrophic cardiomyopathy
HCT .....Hematopoietic cell transplantation
HEX4 .....Urinary hexose tetrasaccharide
HMV .....Home mechanical ventilation
HOS.....Hunter Outcome Survey
HR.....Hazard ratio
HSCT .....Hematopoietic stem cell transplantation
I2S .....Iduronate-2-sulfatase (enzyme)
IAR.....Infusion-associated reaction
IAR(s).....Infusion-related reaction(s)
ICTRP.....International Clinical Trials Registry Platform
IDS .....Iduronate-2-sulfatase (gene/enzyme)
IgG.....Immunoglobulin G
INAHTA.....International Network of Agencies for Health Technology Assessment
IQ .....Intelligence quotient
IQR.....Interquartile range
IT.....Intrathecal
ITT .....Intention-to-Treat
IV.....Intravenous
IVSd .....Interventricular septal thickness, diastole
IVSd (alt.) .....Interventricular Septal thickness in diastole *(if used, prefer "IVSd")*
KM .....Kaplan–Meier
LLN.....Lower Limit of Normal
LOPD.....Late-onset Pompe disease
LSD.....Lysosomal storage disorder
LSDs .....Lysosomal Storage Disorders
LSM .....Least squares mean
LVIDd.....Left ventricular internal diameter, diastole

LVMI.....Left ventricular mass index
LVPWd .....Left ventricular posterior wall thickness, diastole
LWPVd .....Left ventricular posterior wall thickness, diastole
M6P Mannose-6-phosphate
MAH .....Marketing authorization holder
MCID.....Minimal Clinically Important Difference
MCS .....Mental component summary
MedDRA.....Medical Dictionary for Regulatory Activities
MOR-002 .....Elosulfase alfa dose-escalation study
MOR-00 .....Pivotal 24-week phase 3 elosulfase alfa trial
MOR-005 .....Open-label phase 3 extension of MOR-004
MOR-100 .....Long-term extension of MOR-002
MorCAP.....Morquio A Clinical Assessment Program (MOR-001)
MRI .....Magnetic Resonance Imaging
MPP .....Modified-Per-Protocol
MPS.....Mucopolysaccharidosis
MPS HAQ.....Mucopolysaccharidosis Health Assessment Questionnaire
MPS I .....Mucopolysaccharidosis type I (Hurler-Scheie syndrome)
MPS II.....Mucopolysaccharidosis type II (Hunter syndrome)
MPS IVA.....Mucopolysaccharidosis type IVA (Morquio A)
N/A.....Not applicable
NB .....Newborn
NBS .....Newborn screening
NCT .....National Clinical Trial
NEO1 .....Neo1 phase trial
NR .....Not reported
NRCs.....Non-randomized comparative studies
ns. .....Not significant
PCS .....Physical component summary
PBO.....Placebo
PFT .....Pulmonary Function Test
PICO .....Population, Intervention, Comparator, Outcomes
pp .....Percentage point
pp/y .....Percentage point per year
Pt(s).....Patient(s)
QW .....Once weekly
QW-QW .....Weekly-to-weekly dosing regimen (elosulfase alfa, 2 mg/kg)
QoL .....Quality of Life
RCT.....Randomized controlled trial
RHS.....Rotterdam Handicap Scale
rhGAA.....Recombinant human acid α-glucosidase
ROBINS-I.....Risk Of Bias In Non-randomized Studies – of Interventions
ROBIS.....Risk of Bias Assessment Tool for Systematic Reviews
ROM.....Range of motion
R-PAct.....Rasch-built Pompe-specific Activity scale
RQ .....Research question
RWT.....Relative wall thickness
SE .....Standard error
SEM .....Standard error of mean
SF .....Shortening fraction
SF-12.....Short Form-12 Health Survey
SF-36.....Short-Form 36-Health Survey
SNC.....Special Nonverbal Composite (DAS-II composite)
SOPs.....Standard Operating Procedures
sp/sp/y .....Score points/Score points per year
SRM .....Standardized response mean
TEAE .....Treatment-emergent adverse event
VC .....Vital capacity
WHO.....World Health Organization

Executive Summary

Introduction

ERT for Pompe disease and MPS I, II, and IVA

This systematic review aims to evaluate and synthesize available evidence on the long-term effectiveness and safety of enzyme replacement therapies (ERTs) for mucopolysaccharidoses (MPS) Type I, II, and IVA, and Pompe disease.

Health Problem

rare inherited metabolic disorders

Lysosomal storage diseases (LSDs) are rare inherited metabolic disorders resulting from lysosomal enzyme deficiencies, leading to multi-organ involvement. They are commonly classified by the type of accumulated substrate, for example, mucopolysaccharidoses (MPS) involve lysosomal accumulation of glycosaminoglycans (GAG), while Pompe disease (glycogen storage disease type II) involves lysosomal glycogen accumulation. This systematic review focuses on MPS Type I, II, IVA, and Pompe disease.

MPS types I, II, IVA: severity and symptoms vary by subtype

Mucopolysaccharidoses (MPS) comprise subtypes defined by the specific enzyme affected and the resulting GAG storage pattern; severity and central nervous system involvement vary by subtype.

- MPS I results from α-L-iduronidase deficiency, leading to dermatan and heparan sulfate accumulation. Historically, it was classified into Hurler, Hurler-Scheie, and Scheie syndromes, ranging from severe early-onset disease with cognitive decline and early mortality to milder, later-onset forms with preserved cognitive function.
- MPS II (Hunter syndrome) is the only X-linked MPS, caused by iduronate-2-sulfatase deficiency, leading to dermatan and heparan sulfate accumulation. It presents as a progressive multisystem disorder with severe (neuronopathic) and attenuated (non-neuronopathic) forms; the severe phenotype, affecting about two-thirds of patients, typically manifests between ages two and four.
- MPS IVA (Morquio A syndrome) is an autosomal recessive disorder due to N-acetylglucosamine-6-sulfatase deficiency, causing keratan and chondroitin-6-sulfate accumulation that primarily affects bone, cartilage, heart valves, and cornea, leading to skeletal dysplasia and growth abnormalities.

MPS birth prevalence data: from 1.56 to 3.51 per 100,000

Robust Austrian prevalence data for MPS are lacking. Estimates from neighbouring countries suggest a combined MPS birth prevalence of 1.56 per 100,000 in Switzerland and 3.51 per 100,000 in Germany, with MPS I, II, and IVA accounting for 0.69, 0.64, and 0.38 per 100,000 live births, respectively.

Pompe disease: deficiency of enzyme acid α-glucosidase

Pompe disease (PD; Glycogen Storage Disease type II): is a lysosomal storage disorder caused by a deficiency of the enzyme acid α-glucosidase (GAA) due to mutations in the GAA gene on chromosome 17. This enzyme defect prevents the proper breakdown of glycogen inside lysosomes, leading to its accumulation in various tissues – especially skeletal, cardiac, smooth muscle, and nervous tissue. Symptoms can occur at any age. Pompe disease is therefore classified by age of onset into:

- Infantile-onset Pompe disease (IOPD; classic and non-classic): Presents early in life, with more severe symptoms, significant organ involvement, and very low or absent GAA activity.

- Late-onset Pompe disease (LOPD, childhood/juvenile or adult): Presents later with slowly progressive muscle weakness and varying degrees of residual GAA activity.

This classification reflects differences in disease severity, progression, and clinical features. The estimated birth prevalence of Pompe disease in Europe is 1:283,000, with reported estimates ranging from about 1 in 40,000 births in the Netherlands to approximately 1:350,914 in Austria, highlighting substantial variation between regions.

PD estimated birth prevalence: 1:283,000

Description of Technology

Approved ERTs for Pompe disease, which are part of this systematic review, include alglucosidase alfa (Myozyme®), a recombinant human acid α-glucosidase produced in Chinese hamster ovary cells, and avalglucosidase alfa (Nexviadyme®), a next-generation GAA enzyme designed with enhanced mannose-6-phosphate receptor targeting to improve cellular uptake.

approved ERTs: for IOPD, LOPD: alglucosidase alfa and avalglucosidase alfa

Laronidase (Aldurazyme®) is the only approved ERT for MPS I. It is a recombinant form of human α-L-iduronidase. Aldurazyme® is indicated for long-term treatment of patients with confirmed MPS I to treat the non-neurological manifestations of the disease.

approved ERT for MPS I: laronidase

Idursulfase (Elaprase®) was approved for the long-term treatment of MPS II. Elaprase® provides exogenous iduronate-2-sulfatase produced in a continuous human cell line. Mannose-6-phosphate residues enable receptor-mediated uptake and lysosomal targeting, promoting degradation of accumulated GAGs and helping to slow disease progression.

approved ERT for MPS II: idursulfase

Elosulfase alfa (Vimizim®) is approved for the treatment of MPS IVA in patients of all ages. It is a recombinant human N-acetylgalactosamine-6-sulfatase produced in Chinese hamster ovary cells. The enzyme's mannose-6-phosphate residues facilitate receptor-mediated uptake and lysosomal targeting, where elosulfase alfa cleaves sulfate groups from keratan and chondroitin-6-sulfate, thereby reducing substrate accumulation and mitigating disease manifestations.

approved ERT for MPS IV: elosulfase alfa

Methods

The review adopted a two-step literature-search approach. First, systematic reviews addressing the same Population, Intervention, Comparator, Outcomes (PICO) questions were identified, and their quality was assessed using the Risk of Bias Assessment Tool for Systematic Reviews (ROBIS). Reviews of alglucosidase alfa (IOPD, LOPD), laronidase (MPS I), and idursulfase (MPS II) were judged to be of sufficient quality; therefore, as a second step, updated searches were performed for these agents. For avalglucosidase alfa (IOPD, LOPD) and elosulfase alfa (MPS IVA), no suitable prior reviews were identified, and systematic searches for primary studies were conducted from inception. A comprehensive literature search was performed in four databases in May 2025 for English and German language publications, supplemented by manual search. Two reviewers independently conducted study selection, data extraction, and quality assessment. Evidence certainty was evaluated using the GRADE approach. Only prospective studies (randomized or observational) were included for assessing ERT long-term effectiveness and safety. Risk of bias of prospective controlled observational studies was assessed using the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool.

2-step approach in the literature search:
1. **systematic reviews**
2. **primary studies**

in 4 bibliographic databases

evidence certainty assessed with GRADE

RoB assessments

critical effectiveness outcomes

For all PICO questions, survival and quality of life were predefined as key effectiveness outcomes, with cognitive function additionally specified for IOPD. To identify outcomes critical for assessing long-term ERT effectiveness across the four LSDs, a questionnaire was distributed to clinical experts. Experts rated each outcome using the GRADE scale (1 = least important, 9 = most important). Outcomes with a mean score ≥ 7 were classified as critical.

a priori defined safety outcomes

For all PICO questions, the safety outcomes were defined a priori: mortality, the occurrence of adverse events and infusion-associated reactions.

Results and Discussion

Available evidence

included studies:
alglucosidase alfa: 28
avalglucosidase alfa: 3
laronidase: 4
idursulfase: 11
elosulfase alfa: 4

Ten publications reporting long-term effectiveness and safety were identified for alglucosidase alfa in IOPD, three for avalglucosidase alfa in Pompe disease (one for IOPD and two for LOPD), 18 for alglucosidase alfa in LOPD, four for laronidase in MPS I, eleven for idursulfase in MPS II, and four for elosulfase alfa in MPS IVA. All were prospective studies, either non-randomized controlled or single arm, no RCTs were identified.

Clinical effectiveness

IOPD: suggested survival benefit with alglucosidase alfa vs. no treatment with 2-year follow-up

other outcomes: inconclusive results

long-term outcomes lacking

very low certainty evidence

Across controlled studies, survival suggests a consistent benefit of alglucosidase alfa over no treatment in IOPD (2 studies; 30 vs 95; 2.3-year median follow-up), with overall certainty very low. However, due to the observational nature of studies, small sample sizes, and moderate to serious risk of bias, the certainty of this evidence is very low. Prospective long-term data also suggest improvements in left ventricular mass index (LVMI), though these findings come exclusively from single-arm studies with variable follow-up and dosing, making the certainty likewise very low. Evidence for other outcomes – motor function, ventilatory support, cardiac measures beyond LVMI, cognition, and quality of life – remains limited and inconsistent. Most data are drawn from small, uncontrolled cohorts with incomplete baseline assessments and heterogeneous regimens. Long-term evidence for avalglucosidase alfa is even more limited, based on a single non-comparative study. Overall, confidence in the estimates is very low, and conclusions about the magnitude or durability of benefit should be interpreted with caution.

LOPD:
early motor gains with alglucosidase alfa diminish over time,

avalglucosidase:
long-term outcomes lacking

very low evidence certainty

Furthermore, the available long-term evidence indicates that alglucosidase alfa is associated with early improvements in motor function in patients with late-onset Pompe disease (LOPD), which are most pronounced during the initial years of therapy but tend to attenuate over time. Evidence for a survival benefit is inconclusive, as it is derived from a single uncontrolled study. Similarly, the evidence regarding respiratory outcomes, ventilator dependence, and health-related quality of life is insufficient to allow definitive conclusions. In LOPD, avalglucosidase alfa shows short-term gains in motor outcomes such as the Quick Motor Function test (QMFT) and 6-minute walking distance percent predicted (6MWD%) and possible greater benefit in treatment-naïve patients, though long-term evidence is lacking. The overall certainty of evidence for long-term ERT effectiveness in LOPD is very low across outcomes.

MPS I:
inconsistent results, very low evidence certainty

The certainty of evidence for all outcomes in MPS I is very low. Most data come from a single small, controlled trial lacking complete between-group comparisons, while the remaining studies were single-arm with variable outcome measures and inconsistent assessment tools, limiting both interpretability and reliability of the findings.

The available evidence suggests that idursulfase is associated with improvements in survival and motor function, as measured by the 6-minute walk distance (6MWD), in patients with MPS II. However, these findings are primarily based on uncontrolled studies and include heterogeneous patient populations comprising both attenuated and severe disease phenotypes, which limits the robustness of the conclusions. Due to methodological limitations, the certainty of this evidence is very low. Data on joint range of motion (JROM), quality of life, cognition, and respiratory outcomes are limited and inconsistent, with heterogeneous reporting and outcome measures further constraining interpretation.

MPS II: suggested survival and motor benefit with idursulfase; very low evidence certainty

Finally, the available evidence on elosulfase alfa in MPS IVA indicates short-term improvements in 6MWD and functional abilities, mainly based on a single two-year controlled trial showing the greatest benefits in patients maintained on standard-dose ERT. However, the certainty of evidence is very low, indicating that long-term controlled studies are needed to confirm the durability of these effects and to clarify potential impacts on cardiac function and survival, where evidence remains insufficient.

MPS IVA: short-term motor function improvements with elosulfase alfa

It should also be noted that all these disorders are rare, making RCTs particularly difficult to conduct. Moreover, their progressive nature adds further challenges, as the natural disease course can vary greatly between individuals.

rarity and variability hinder RCT feasibility

Safety

Across LSDs, ERTs are generally well tolerated. Most adverse events (AEs) are mild to moderate infusion reactions – rash, fever, transient respiratory symptoms, headache, or urticaria/angioedema. Serious treatment-related events are rare. Mortality reported in long-term studies was not attributed to treatment, and discontinuation rates were low (<10%). Serious AEs occur more often in MPS II and IVA but are rarely related to treatment. Severe reactions, including anaphylaxis, are isolated and typically manageable with premedication or infusion adjustments. Safety data remain limited by small, heterogeneous cohorts, variable follow-up (usually ≤5 years), and inconsistent use of standardized assessment tools. Many studies report overall AE rates without indicating treatment-relatedness.

ERTs generally safe, mild to moderate infusion reactions

serious AEs are rare

discontinuation rate due to AE were low

Upcoming evidence

For Pompe disease, two novel investigational therapies were identified – zocaglusagene nuzaparvovec and S-606001 – along with three planned indication extensions for two already authorised enzymes, avalglucosidase alfa and cipaglucosidase alfa. In MPS I, three investigational agents are currently under development: OTL-203, iduronicrin genleukocel-T, and lepunafusp alfa. For MPS II, three drug candidates were identified: tividenofusp alfa, pabinafusp alfa, and clemidsogene lanparvovec. No investigational products were identified for MPS IV.

novel investigational therapies in the pipeline for Pompe disease, MPS I and II

Limitations

The evidence base for enzyme replacement therapies (ERTs) in lysosomal storage disorders is limited. Long-term RCTs are largely absent, and few prospective controlled studies exist, many with moderate to serious risk of bias. Common limitations include heterogeneous follow-up durations, dosing regimens, and study populations, lack of baseline assessments, non-standardized outcomes (especially quality of life), and absence of validated minimal clini-

limitations of evidence and review methods

cally important differences (MCIDs) for most outcomes. Definitions of clinically meaningful change are inconsistent, further complicating interpretation and evidence assessment.

This systematic review itself has methodological limitations. Despite a comprehensive search, some grey literature and non-English studies may have been missed. Risk-of-bias assessments were mostly adopted from included reviews without full independent re-assessment. High heterogeneity across studies precluded quantitative synthesis, so findings were summarized narratively, limiting precision. Safety reporting was often incomplete, requiring recalculations in some cases, which may have introduced minor uncertainties.

Conclusion

some suggested benefits; long-term data are lacking

safety: generally favourable

Evidence suggests that ERTs might improve survival (particularly alglucosidase alfa in IOPD and idursulfase in MPS II) and short-term functional outcomes in some LSDs; however most outcomes are inconclusive, and long-term evidence is lacking. Overall, the certainty of evidence is very low due to small, uncontrolled studies. ERTs are generally well tolerated, with mostly mild to moderate infusion reactions and few serious adverse events.

Due to the lack of robust and standardized long-term data, the use of ERT requires careful patient selection and structured monitoring to ensure clinical benefit and safety. Clear guidelines, standardized outcome measures, and defined criteria for treatment continuation or discontinuation are essential to support safe and effective therapy in routine and home-based settings.

Zusammenfassung

Einleitung

Diese systematische Übersichtsarbeit untersucht die Langzeit-Wirksamkeit und -Sicherheit von ausgewählten Enzymersatztherapien (ERTs) für Mucopolysaccharidose (MPS) Typ I, II und IVA sowie für Morbus Pompe.

ERT: Langzeit-Wirksamkeit und Sicherheit in MPS I, II, IVA und Morbus Pompe

Indikation

Lysosomale Speicherkrankheiten (LSDs) sind seltene, genetisch bedingte Stoffwechselstörungen, die durch Defekte oder eine verminderte Aktivität lysosomaler Enzyme verursacht werden. Dadurch kommt es zur intralysosomalen Akkumulation spezifischer Substrate, was eine Vielzahl von Organsystemen betreffen kann. Die Einteilung der LSDs erfolgt in der Regel nach der Art des gespeicherten Substrats. So kommt es bei den Mucopolysaccharidosen (MPS) zu einer lysosomalen Akkumulation von Glykosaminoglykanen (GAG), während bei Morbus Pompe (Glykogenspeicherkrankheit Typ II) eine Speicherung von Glykogen in den Lysosomen vorliegt. Diese systematische Übersichtsarbeit umfasst MPS-Typ I, II und IVA sowie Morbus Pompe.

LSD: seltene, genetisch bedingte Stoffwechselstörungen

Mucopolysaccharidosen (MPS) umfassen Subtypen, die durch das jeweils betroffene Enzym und das daraus resultierende GAG-Speichermuster definiert werden; Schweregrad und Beteiligung des zentralen Nervensystems variieren je nach Subtyp.

MPS: Schweregrad und Symptome unterschiedlich je nach Subtyp

- MPS I entsteht durch einen Mangel an α-L-Iduronidase, was zur Anreicherung von Dermatan- und Heparansulfat führt. Historisch wurden die Unterformen Hurler, Hurler-Scheie und Scheie unterschieden, mit einem Spektrum von schwerer, früh beginnender Erkrankung mit kognitivem Abbau und früher Mortalität bis hin zu milderen, später beginnenden Formen mit erhaltener kognitiver Funktion.
- MPS II (Hunter-Syndrom) ist die einzige X-chromosomal vererbte Form der Mucopolysaccharidosen und wird durch einen Mangel an Iduronat-2-Sulfatase verursacht. Dies führt zur Akkumulation von Dermatan- und Heparansulfat. Klinisch manifestiert sich die Erkrankung als progrediente Multisystemerkrankung mit schweren (neuronopathischen) und attenuierten (nicht-neuronopathischen) Verlaufsformen. Der schwere Phänotyp betrifft etwa zwei Drittel der Patient:innen und beginnt typischerweise im Alter zwischen zwei und vier Jahre.
- MPS IVA (Morquio-A-Syndrom) ist eine autosomal-rezessiv vererbte Erkrankung, die durch einen Mangel an N-Acetylglucosamin-6-Sulfatase verursacht wird. Dadurch kommt es zur Speicherung von Keratan- und Chondroitin-6-Sulfat, was vor allem Knochen, Knorpel, Herzklappen und die Hornhaut betrifft und zu einer ausgeprägten Skelettdysplasie sowie Wachstumsstörungen führt.

Für Österreich fehlen robuste Prävalenzdaten zu MPS. Schätzungen aus Nachbarländern ergeben eine kombinierte MPS-Geburtsprävalenz von 1,56 pro 100.000 in der Schweiz und 3,51 pro 100.000 in Deutschland, wobei MPS I, II und IVA mit 0,69, 0,64 bzw. 0,38 pro 100.000 Lebendgeburten angegeben werden.

Geburtsprävalenz: 1,56 bis 3,51 pro 100.000

Morbus Pompe (Pompe Disease, PD; Glykogenspeicherkrankheit Typ II) ist eine lysosomale Speicherkrankheit, die durch einen Mangel des Enzyms saure α-Glucosidase (GAA) infolge von Mutationen im GAA-Gen auf Chro-

PD: Mangel des Enzyms saure α-Glucosidase

mosom 17 entsteht. Durch diesen Enzymdefekt kommt es zu einer unzureichenden Glykolyse in den Lysosomen und folglich zu einer Glykogenakkumulation in verschiedenen Geweben – insbesondere Skelett-, Herz-, glatter Muskulatur sowie Nervengewebe. Symptome können in jedem Lebensalter auftreten. Daher wird Morbus Pompe entsprechend dem Manifestationsalter eingeteilt in:

- Infantile-onset Pompe disease (IOPD; klassische und nicht-klassische Form) manifestiert sich bereits im frühen Säuglingsalter und ist gekennzeichnet durch eine ausgeprägte klinische Symptomatik, eine erhebliche Organbeteiligung und eine sehr niedrige bzw. fehlende Aktivität der sauren α-Glucosidase (GAA).
- Late-onset Pompe disease (LOPD; Manifestation im Kindes-, Jugend- oder Erwachsenenalter) tritt später auf und zeigt sich typischerweise durch eine langsam progrediente Muskelschwäche bei gleichzeitig variabler residualer GAA-Aktivität.

Geburtsprävalenz 1:283.000

Diese Einteilung spiegelt Unterschiede in Schweregrad, Progression und klinischer Präsentation wider. Die geschätzte Geburtsprävalenz in Europa beträgt 1:283.000, wobei regionale Werte stark variieren (z. B. ca. 1:40.000 in den Niederlanden versus 1:350.914 in Österreich).

Beschreibung der Technologie

zugelassene ERT für PD: Alglucosidase alfa und Avalglucosidase alfa

Die beiden zugelassenen ERTs für Morbus Pompe, die in diese systematische Übersichtsarbeit eingeschlossen wurden, umfassen **Alglucosidase alfa (Myozyme®)**, ein rekombinantes humanes GAA-Enzym, das in Ovarialzellen des chinesischen Hamsters produziert wird, sowie **Avalglucosidase alfa (Nexviadyme®)**, ein weiterentwickeltes GAA-Enzym mit verbesserter Mannose-6-Phosphat-Rezeptorbindung zur effizienteren zellulären Aufnahme.

zugelassene ERT bei MPS I: Laronidase

Laronidase (Aldurazyme®) ist die einzige zugelassene ERT für MPS I. Sie ist eine rekombinante Form der humanen α-L-Iduronidase und zugelassen für die langfristige Behandlung bestätigt erkrankter Patient:innen zur Therapie nicht-neurologischer Manifestationen.

zugelassene ERT bei MPS II: Idursulfase

Idursulfase (Elaprase®) ist zugelassen für die Langzeitbehandlung von MPS II. Es handelt sich dabei um exogen zugeführte Iduronat-2-Sulfatase, produziert in einer kontinuierlichen humanen Zelllinie. Mannose-6-Phosphat-Reste ermöglichen eine rezeptorvermittelte Aufnahme und lysosomale Zielsteuerung, wodurch der GAG-Abbau verbessert und die Krankheitsprogression verlangsamt wird.

zugelassene ERT bei MPS IVA: Elosulfase alfa

Elosulfase alfa (Vimizim®) ist für die Behandlung von MPS IVA in allen Altersgruppen zugelassen. Es ist ein rekombinantes humanes N-Acetylgalactosamin-6-Sulfatase-Enzym, ebenfalls hergestellt in CHO-Zellen. Mannose-6-Phosphat-Reste ermöglichen die Aufnahme in Lysosomen, wo das Enzym Sulfatgruppen von Keratan- und Chondroitin-6-Sulfat entfernt, die Substratakkumulation reduziert und Krankheitsmanifestationen mildert.

Methoden

zweistufiger Ansatz der Literatursuche

Die Übersichtsarbeit folgte einem zweistufigen Ansatz der Literatursuche. Zunächst wurden systematische Übersichtsarbeiten identifiziert, die dieselben Fragestellungen adressieren, und deren Qualität (Risk of Bias, RoB) wurde mithilfe des ROBIS-Tools bewertet. Systematische Übersichtsarbeiten zu Alglucosidase alfa (IOPD, LOPD), Laronidase (MPS I) und Idursulfase (MPS

II) wurden als qualitativ ausreichend eingestuft; anschließend wurden für diese Wirkstoffe die Literatursuche in den eingeschlossenen systematischen Übersichtsarbeiten aktualisiert. Für Avalglucosidase alfa (IOPD, LOPD) und Elosulfase alfa (MPS IVA) wurde keine geeigneten systematischen Übersichtarbeiten identifiziert, sodass für diese Wirkstoffe eine vollständige systematische Literatursuche durchgeführt wurde.

Literatursuche in 4 Datenbanken

Die systematische Literatursuche erfolgte im Mai 2025 in vier elektronischen Datenbanken und wurde um eine manuelle Recherche ergänzt. Eingeschlossen wurden englisch- und deutschsprachige Publikationen. Zwei unabhängige Reviewer führten die Studienauswahl, Datenextraktion und Qualitätsbewertung durch. Die Evidenzsicherheit wurde nach der GRADE-Methodik beurteilt. Eingeschlossen wurden ausschließlich prospektive Studien. Das Risiko für Verzerrungen (RoB) in prospektiven kontrollierten Beobachtungsstudien wurde mithilfe von ROBINS-I bewertet.

GRADE Methodik zur Beurteilung der Evidenzsicherheit und Risk of Bias Assessment

Definition kritischer Endpunkte

Für die Beurteilung der Langzeit-Wirksamkeit wurden Überleben und Lebensqualität als relevante Outcomes vorab definiert; für IOPD wurde zusätzlich kognitive Funktion berücksichtigt. Zur Priorisierung weiterer relevanter Outcomes wurde ein Expert:innenbefragung durchgeführt, in dem klinische Expert:innen die Bedeutung einzelner Outcomes nach der GRADE-Skala (1-9) bewerteten. Outcomes mit einem mittleren Score von ≥7 wurden als entscheidungsrelevant eingestuft.

Die Sicherheitsendpunkte wurden ebenfalls a priori definiert und umfassten Mortalität, das Auftreten unerwünschter Ereignisse sowie infusionsassoziierter Reaktionen.

Ergebnisse

Verfügbare Evidenz

eingeschlossene Studien:
Alglucosidase alfa: 28
Avalglucosidase alfa: 3
Laronidase: 4
Idursulfase: 11
Elosulfase alfa: 4

Es wurden zehn Publikationen, welche Ergebnisse zur Langzeit-Wirksamkeit und -Sicherheit berichten, zu Alglucosidase alfa bei IOPD, drei zu Avalglucosidase alfa (eine für IOPD, zwei für LOPD), 18 zu Alglucosidase alfa bei LOPD, vier zu Laronidase (MPS I), 11 zu Idursulfase (MPS II) sowie vier zu Elosulfase alfa (MPS IVA) anhand der definierten Fragestellungen identifiziert. Alle Publikationen berichten prospektive Studien (entweder nichtrandomisiertes kontrolliertes oder einarmiges Design); es wurden keine RCTs zu Langzeitdaten gefunden.

Klinische Wirksamkeit

IOPD: Alglucosidase Überlebensvorteil gegenüber keiner Behandlung (medianes FU 2,3 Jahre)

sehr niedrige Evidenzsicherheit

Inkonsistente Evidenz für andere Endpunkt

Die Evidenz aus kontrollierten Studien weist auf einen Überlebensvorteil von Alglucosidase alfa gegenüber keiner Behandlung bei IOPD hin (medianes Follow-up 2,3 Jahre). Die Evidenzsicherheit ist jedoch sehr niedrig, bedingt durch kleine Patientenkohorten, beobachtende Studiendesigns und substanzielle Biasrisiken. Prospektive Langzeitdaten zeigen zudem Hinweise auf eine Verbesserung des linksventrikulären Massenindex (LVMI), allerdings ausschließlich aus einarmigen Studien mit heterogenen Nachbeobachtungszeiten und variierenden Dosierungsregimen. Für weitere patient:innenrelevante Endpunkte – Motorik, Beatmung, kardiale Parameter, Kognition und gesundheitsbezogene Lebensqualität – ist die Evidenz begrenzt und inkonsistent.

Für Avalglucosidase alfa bei IOPD liegen aktuell nur sehr begrenzte Langzeitdaten vor, basierend auf einer einzigen nicht-vergleichenden Studie.

In LOPD zeigen Langzeitbeobachtungen zu Alglucosidase alfa initiale Verbesserungen motorischer Funktionen, die im Verlauf jedoch abnehmen. Die Evidenz zum Überleben ist unzureichend (einarmige Studien). Aussagen zu respiratorischen Endpunkten, Beatmungsabhängigkeit und Lebensqualität sind ebenfalls von sehr geringer Evidenzsicherheit. Für Avalglucosidase alfa finden sich Hinweise auf kurzfristige Verbesserungen (QMFT, 6MWD%), möglicherweise ausgeprägter bei therapienaiven Patient:innen; belastbare Langzeitdaten fehlen jedoch. Insgesamt ist die Evidenzsicherheit für LOPD sehr gering.

LOPD: Alglucosidase initiale Verbesserungen motorischer Funktionen

sehr niedrige Evidenzsicherheit

fehlende Langzeitdaten zu Avalglucosidase

Für MPS I liegt durchgängig Evidenz sehr niedriger Sicherheit gemäß GRADE vor. Die Daten stammen überwiegend aus einer einzelnen kleinen kontrollierten Studie ohne vollständige Gruppenvergleiche; weitere Studien weisen einarmige Designs und heterogene Endpunktdefinitionen auf.

MPS I: sehr niedrige Evidenzsicherheit

Für MPS II deuten die verfügbaren Daten auf mögliche Verbesserungen des Überlebens sowie der 6-Minuten-Gehstrecke (6MWD) unter Idursulfase hin. Diese Ergebnisse basieren überwiegend auf unkontrollierten Studien mit gemischten Phänotypen, sodass die Evidenzsicherheit insgesamt sehr niedrig ist. Für weitere Endpunkte – Gelenkbeweglichkeit (JROM), Lebensqualität, Kognition und pulmonale Funktion – ist die Evidenz limitiert und inkonsistent.

MPS II: Überlebensvorteil und Verbesserung 6MWD

sehr niedrige Evidenzsicherheit

Für MPS IVA liegen Hinweise auf kurzfristige Verbesserungen (6MWD, funktionelle Fähigkeiten) unter Elosulfase alfa vor, basierend auf einer zweijährigen kontrollierten Studie, wobei die größten Effekte unter Standarddosierung beobachtet wurden. Die Evidenzsicherheit ist jedoch sehr niedrig, und es besteht Bedarf an langfristigen kontrollierten Studien.

MPS IVA: kurzfristige Verbesserungen

sehr niedrige Evidenzsicherheit

Insgesamt handelt es sich um seltene Erkrankungen, was die Durchführung randomisierter kontrollierter Studien erheblich einschränkt. Zusätzlich erschwert die variabel ausgeprägte natürliche Progression die Interpretation der Ergebnisse und die Ableitung belastbarer Langzeiteffekte.

Sicherheit

Über alle lysosomalen Speicherkrankheiten hinweg werden ERTs im Allgemeinen gut vertragen. Die meisten unerwünschten Ereignisse (AEs) sind milde bis moderate, infusionsassoziierte Reaktionen, wie Hautausschlag, Fieber, vorübergehende respiratorische Symptome, Kopfschmerzen oder Urtikaria/Angioödem. Schwerwiegende, therapiebezogene Ereignisse sind selten. In Langzeitstudien berichtete Mortalität konnte nicht der Behandlung zugeschrieben werden; Abbruchraten lagen unter 10 %.

ERTs: gute Verträglichkeit

Milde bis moderate AEs berichtet

Schwere unerwünschte Ereignisse treten häufiger bei MPS II und MPS IVA auf, sind jedoch nur selten direkt behandlungsbedingt. Isolierte schwere Reaktionen, einschließlich Anaphylaxie, wurden beobachtet, ließen sich jedoch meist durch Prämedikation oder Anpassung der Infusionsrate kontrollieren.

schwere AEs selten behandlungsbedingt

Die Sicherheitsdaten sind durch kleine, heterogene Patient:innenkohorten, variable Nachbeobachtungszeiten (meist ≤5 Jahre) und uneinheitliche Erfassungsmethoden limitiert. Viele Studien berichten lediglich Gesamtraten unerwünschter Ereignisse, ohne die kausale Beziehung zur Therapie differenziert anzugeben.

Limitationen: unterschiedliche Nachbeobachtungszeiten in Studien und uneinheitliche Erfassungsmethoden

Laufende Studien

neue Wirkstoffe in der Pipeline und Studien zu Indikationserweiterungen

Für Morbus Pompe wurden zwei neue Wirkstoffe in klinischer Prüfung identifiziert – Zocaglusagene nuzaparvovec und S-606001 – sowie drei geplante Indikationserweiterungen für bereits zugelassene ERTs (Avalglucosidase alfa und Cipaglucosidase alfa). Für MPS I befinden sich drei Wirkstoffe in Entwicklung: OTL-203, Iduronicrin genleukocel-T und Lepunafusp alfa. Für MPS II wurden drei Arzneimittelkandidaten identifiziert: Tividenofusp alfa, Pabinafusp alfa und Clemidsogene lanparvovec. Für MPS IV wurden keine neuen Wirkstoffe in klinischer Prüfung gefunden.

Limitationen

Limitationen der Evidenz: nur wenige prospektive kontrollierte Studien verfügbar

Die Evidenzlage zu ERTs bei lysosomalen Speicherkrankheiten ist begrenzt. Langzeitdaten aus RCTs fehlen weitgehend, und nur wenige prospektive kontrollierte Studien liegen vor, von denen viele ein moderates bis hohes Verzerrungsrisiko aufweisen. Häufige Limitationen betreffen heterogene Nachbeobachtungszeiten, unterschiedliche Dosierungsschemata und heterogene Studienpopulationen, fehlende Baseline Assessments, nicht standardisierte Endpunkte (insbesondere zur Lebensqualität) sowie das Fehlen validierter minimal klinisch relevanter Unterschiede (MCIDs) für die meisten Outcomes. Die Definition klinisch relevanter Veränderungen ist inkonsistent, was die Interpretation und Bewertung der Evidenz zusätzlich erschwert.

methodische Limitationen des Berichtes

Die vorliegende systematische Übersichtsarbeit weist methodische Limitationen auf. Trotz einer umfassenden Literatursuche könnte graue Literatur und nicht englischsprachige Publikationen übersehen worden sein. Die Risikobewertungen (Risk-of-Bias) wurden größtenteils aus den eingeschlossenen Übersichtsarbeiten übernommen, ohne eine vollständige, unabhängige Neubewertung durchzuführen, was zu Variabilität in der Beurteilung führen kann. Aufgrund der hohen Heterogenität der Studien – u. a. hinsichtlich Patientengruppen, Dosierung, Follow-up-Dauer und Endpunkten – war eine quantitative Synthese nicht möglich, sodass die Ergebnisse narrativ zusammengefasst wurden, was die Präzision der Effektabschätzungen einschränkt. Die Berichterstattung von Nebenwirkung in den Publikationen war häufig unvollständig; in einigen Fällen mussten Nachberechnungen durchgeführt werden, wodurch geringe Unsicherheiten entstehen können.

Schlussfolgerung

valide Beurteilung der Langzeit-Wirksamkeit und -Sicherheit nicht abschließend möglich

Die derzeit verfügbare Evidenz deutet darauf hin, dass Enzymersatztherapien (ERTs) das Überleben – insbesondere Alglucosidase alfa bei IOPD und Idursulfase bei MPS II – sowie kurzfristige funktionelle Endpunkte bei einigen lysosomalen Speicherkrankheiten verbessern könnten. Aufgrund der überwiegend kleinen, unkontrollierten Studien, heterogenen Designs und methodischen Einschränkungen ist die Evidenzsicherheit jedoch sehr niedrig. Eine verlässliche Beurteilung der langfristigen Wirksamkeit, einschließlich Effekte auf Überleben, respiratorische Funktion und gesundheitsbezogene Lebensqualität, ist derzeit nicht möglich.

niedrige bis sehr niedrige Evidenzsicherheit

ERTs werden im Allgemeinen gut vertragen. Die meisten unerwünschten Ereignisse sind mild bis moderat und infusionsassoziiert, während schwerwiegende therapiebezogene Ereignisse selten auftreten. Kurz- bis mittelfristige Verbesserungen oder Stabilisierung motorischer Funktionen wurden in mehreren Erkrankungen beobachtet, die Nachhaltigkeit dieser Effekte über längere Behandlungszeiträume bleibt jedoch unklar. Insgesamt bestehen wei-

terhin erhebliche Evidenzlücken, die die Ableitung robuster Empfehlungen zur Langzeittherapie mit ERTs erschweren.

sorgfältige Indikationsstellung und strukturiertes Monitoring in der klinischen Praxis notwendig

Aufgrund fehlender robuster und standardisierter Langzeitdaten erfordert der Einsatz von ERT eine sorgfältige Indikationsstellung und strukturiertes Monitoring, um klinischen Nutzen und Sicherheit für Patient:innen zu gewährleisten. Klare Leitlinien, standardisierte Endpunkte sowie definierte Kriterien für Fortführung oder Abbruch der Therapie sind entscheidend, um eine sichere und effektive Anwendung sowohl in der Routineversorgung als auch in Heimtherapie zu gewährleisten.

1 Health Problem and Current Use

Lysosomal storage diseases (LSDs) are a group of rare inherited metabolic disorders caused by defects in lysosomal function. Lysosomes are sacs of enzymes within cells which are crucial for breaking down macromolecules. When these enzymes malfunction, undigested substances accumulate within lysosomes, leading to cellular dysfunction and tissue damage. Clinical symptoms vary based on the enzyme deficiency and the affected tissues and can affect multiple organs [1]. Multiple classification systems have been proposed for lysosomal storage disorders. The most widely used approach categorizes them according to the nature of the accumulated substrate, encompassing the mucopolysaccharidoses and Pompe disease (glycogen storage disease type II), among others. The present systematic review specifically addresses MPS I, II, IVA and Pompe disease.

LSDs: seltene erbliche Stoffwechselstörungen

Enzymdefekte führen zu Ansammlung unverdauter Stoffe und Zellschäden

mehrere Klassifikationen

Bericht bezieht sich auf MPS I, II, Iva & Pompe

1.1 Glycogen storage disease type II

Most glycogen storage diseases (GSDs) are not lysosomal disorders; however, GSD type II (Pompe disease) is classified as an LSD caused by acid α-glucosidase deficiency (GAA). This condition is characterized by mutations in the GAA gene located on chromosome 17 which impair the breakdown of glycogen in the lysosomes, leading to its accumulation in several tissue types, including skeletal, cardiac, smooth muscle, and nervous tissue [2].

Pompe-Krankheit: lysosomale Speicherkrankheit durch GAA-Mangel

Symptoms of Pompe disease can appear at any age. The most widely accepted classification of Pompe disease is based on age of onset, distinguishing between infantile-onset (classic and non-classic) and late-onset (childhood/juvenile and adult) forms. Classic and non-classic forms differ in their clinical presentation, severity of organ involvement, and residual GAA enzyme activity [3].

Symptome können in jedem Alter auftreten, Klassifikation nach Krankheitsbeginn (infantil vs. spätbeginnend)

Infantile-onset Pompe disease

Classic infantile-onset Pompe disease (IOPD) is marked by rapidly progressive muscle weakness, pronounced hypertrophic cardiomyopathy, feeding difficulties, and early respiratory insufficiency. Symptoms typically emerge around 3 months of age, with death occurring between 6 and 9 months, although about 10% of patients survive beyond 18 months. Symptom onset and cardiomegaly before 6 months are considered indicators of poor prognosis. Non-classic IOPD is less common, and it manifests in the first year of life, and is characterized with muscle weakness without cardiomegaly [4]. The residual enzyme activity in this form of IOPD is below 20% [5]. Compared with the classic form, disease progression is slower. In this milder phenotype, onset of symptoms is delayed, with about half of cases manifesting between 4 and 11 months, and patients generally show a more gradual clinical decline [6].

klassische infantile Pompe-Krankheit zeigt rasche Muskelschwäche, Kardiomyopathie, Atemprobleme, meist Todesfall im 1. Lebensjahr

nicht-klassische Form: ohne Kardiomegalie, langsamere Verschlechterung, spätere Symptomentwicklung

Beyond phenotype, cross-reactive immunological material (CRIM) status – presence or absence of endogenous GAA protein – serves as a prognostic and stratification marker.

CRIM-Status als wichtiger Faktor

Overall, CRIM-negative patients receiving enzyme replacement therapy (ERT) tend to have poorer prognosis due to the development of anti-rhGAA IgG antibodies [7] and they experience less favourable clinical outcomes with therapy [8].

CRIM-negative Pts. sprechen schlechter auf Enzymersatztherapie an

Late-onset Pompe disease

Late-onset Pompe disease (LOPD) is less severe, however it is progressive, and causes muscle weakness and respiratory complications in later stages in life. LOPD manifests after the age of one year, most commonly during childhood, adolescence, or adulthood, with a variable course characterized primarily by progressive skeletal and respiratory muscle involvement. According to a study from the Netherlands, disease presented in the mean age of 28 years, with 18% of people experiencing first clinical symptoms under 12 years of age [9].

LOPD: milder, aber fortschreitend; Muskelschwäche und Atemprobleme ab Kindheit oder Erwachsenenalter

The initial clinical manifestations of LOPD in paediatric patients are often gradual and subtle. Children aged 12 months to 12 years show symptoms such as upper limb and trunk muscle weakness, scoliosis, developmental delays, delayed motor milestones, and shortness of breath post-exercise. Children over 12 years with LOPD often experience muscle weakness in the hips and lower limbs, difficulty running and walking upstairs, shortness of breath after exercise, and hypotonia [10, 11].

LOPD bei Kindern: schleichender, unauffälliger Beginn

Before the onset of muscle disease, the first abnormal biochemical finding may be elevated creatine kinase [12]. However, this is neither a reliable nor a Pompe-specific biomarker. Although LOPD patients may be able to walk into adulthood, they still face an increased risk of respiratory failure, because muscle weakness is often presented in the diaphragm [13]. Common symptoms of patients who develop the disease in adulthood are impairment of hip flexors, after which progressive proximal weakness in a limb-girdle distribution occurs [14]. Heart function is not directly implicated in LOPD disease course, however, respiratory function impairment [15] can cause compensatory cardiac involvement and can further cause sleep disordered breathing, that are followed by other symptoms such as morning headache, daytime somnolence, and fatigue [16]. If untreated, muscle function and respiratory insufficiency decline is inevitable. The rate and predominance of motor weakness or respiratory failure vary among individuals, with some patients requiring non-invasive nocturnal ventilation and some requiring invasive ventilation. Survival rates are estimated to be 95% at five years after diagnosis and 40% at thirty years after diagnosis [17].

Herz: nicht typisch betroffen, aber Folgeerscheinungen durch Atemprobleme möglich

Prognose: Überleben nach 5 Jahren 95 %, nach 30 Jahren 40 %

Diagnosis of infantile-onset and late-onset Pompe disease

IOPD is typically diagnosed by confirming the complete absence of GAA activity in tissues (for example, cultured fibroblasts from skin biopsy, muscle biopsy, purified lymphocytes, mononuclear cells and lymphoid cell lines) and it is usually combined with clinical and laboratory data. In case of IOPD, the GAA activity is less than 1% of healthy counterparts [3], while LOPD shows a significantly reduced GAA activity in tissues.

IOPD: keine GAA-Aktivität

LOPD: stark vermindert

Among the used biochemical markers, there is none that is 100% reliable to monitor Pompe disease. For instance, there is no strong association between creatine kinase value and the clinical stage of Pompe disease [18]. Urinary hexose tetrasaccharide (HEX4) is another biomarker used for diagnosis and monitoring; however, its utility still warrants further investigation [19, 20].

Biomarker begrenzt aussagekräftig

Epidemiology of infantile- and late-onset Pompe disease

höhere Prävalenz bei afrikanischen und chinesischen Populationen

The worldwide birth prevalence of Pompe disease is approximately 1 in 40,000 newborns (NBs), with the prevalence of IOPD being about 1 in 138,000 NBs and the late-onset form about 1 in 57,000 NBs. There are notable ethnic variations, with higher rates observed among African American (1 in 12,000 NBs) and Chinese (1 in 40,000–1 in 50,000 NBs) populations [21].

in Europa und Österreich deutlich niedriger

The estimated birth prevalence of Pompe disease in Europe is 1:283,000. It is estimated that the prevalence ranges from one in 40,000 in the Netherlands [22], to 1:350,914 in Austria [23].

Metaanalyse & SR mit Prävalenzdaten

Finally, a recent systematic review and meta-analysis that included 22 studies and 15 areas/countries estimated a global birth prevalence of Pompe disease to be 2.0 cases (95% CI: 1.5-2.4) per 100,000 live births. The global birth prevalence of IOPD was 1.0 cases (95% CI: 0.5-1.5), while for LOPD it was 2.4 cases (95% CI: 1.8-3.0) per 100,000 live births [24].

1.2 Mucopolysacharidoses

MPS: seltene Stoffwechselerkrankungen durch fehlende Enzyme für GAG-Abbau

Mucopolysaccharidoses (MPS) represent a group of rare inherited metabolic disorders that arise from deficiencies in one of the 11 enzymes that degrade glycosaminoglycans (GAGs.) These GAGs, also known as mucopolysaccharides, are crucial for providing structural support in various tissues and play essential roles in neurodevelopment and inflammation [25].

Akkumulation von GAGs schädigt Organe und Gewebe

GAGs are degraded within lysosomes – cellular organelles responsible for degrading large proteoglycans, a process that requires the activity of several acid hydrolases. A deficiency in any of these hydrolases leads to the accumulation of these GAGs in lysosomes which disrupts cell function, causing progressive damage to various organs and tissues [25]. MPSs comprise seven main subtypes, of which MPS I, II, and IVA are the focus of this review.

Fokus hier: MPS I, II, IVA.

Mucopolysacharidosis I

MPS I

Mucopolysaccharidosis type I (MPS I) occurs due to a deficiency in the enzyme alpha-L-iduronidase, which impairs the lysosomes' ability to degrade two particular GAGs, dermatan sulfate and heparan sulfate.

Ursache: Alpha-L-Iduronidase-Mangel, Akkumulation von Dermatan- & Heparansulfat

Earlier MPS I classification included three phenotypic disease categories: Hurler, Hurler-Scheie and Scheie syndrome. The traditional nosology of MPS I was based on age of symptom onset and the presence of progressive intellectual disability. Hurler syndrome represents the most severe phenotype, with symptoms appearing in early infancy, progressive cognitive decline, and – if untreated – death typically within the first decade of life. Hurler-Scheie and Scheie syndromes describe later-onset disease with slower progression and preserved intelligence. While Hurler syndrome is relatively well defined, Hurler-Scheie and Scheie phenotypes encompass a broad and overlapping clinical spectrum with less clear boundaries.

schwere & milde Form

From a clinical management perspective, it is most practical to classify patients into two categories: severe disease (Hurler syndrome) and attenuated disease (Hurler-Scheie and Scheie syndromes). This binary classification aligns with current therapeutic strategies, notably hematopoietic stem cell transplantation (HSCT) and ERT with laronidase [26].

schwere Form (Hurler): frühe Symptome, geistige Behinderung, Tod meist < 10 Jahre

milde Form: spätere Symptome, kaum neurologisch, Lebenserwartung meist normal

hohe Morbidität in allen Formen

Infants with severe MPS-I (Hurler syndrome) show early signs like hernias, frequent respiratory infections, coarsening facial features by age one, corneal clouding by age two, stunted growth by age three, hearing loss, skeletal dysplasia, cognitive impairment, and upper airway disease leading to sleep apnea. Death usually occurs from cardiorespiratory failure within the first ten years of life [27]. Attenuated MPS-I typically begins between ages 3 and 10, with variable severity and progression. Common symptoms include hepatomegaly, dysostosis multiplex, corneal clouding, sleep disturbance, cardiac valve abnormalities, hernia, joint contractures, carpal tunnel syndrome, and hearing loss. Cognitive impairment is rare, but learning disabilities may occur. Depending on disease progression, patients may live a normal lifespan. The two forms differ in the presence (Hurler syndrome) or absence (attenuated MPS I) of neurological involvement, resulting in different treatment regimens – patients with Hurler syndrome will benefit from early HSCT, coupled with prior ERT administration, when the graft fails, while patients with the attenuated form of disease will benefit from early start of ERT [27]. In case of Hurler syndrome, children can live up to 10 years, if untreated, while in case of Hurler-Scheie syndrome, patients can reach the second or third decade. The life expectancy of patients with mild MPS I is near normal, however, all phenotypes suffer from extensive morbidity [28-30].

Mucopolysacharidosis II

MPS II

Mucopolysaccharidosis II (MPS II or Hunter syndrome) is the only X-linked recessive MPS, all other MPS types are autosomal recessive. This syndrome is caused by the deficiency of iduronate-2-sulfatase, leading to lysosomal accumulation of the urinary GAG concentration (namely dermatan sulphate and heparan sulphate). The iduronate 2-sulfatase gene has over 350 known mutations, including various deletions, splice-site alterations, and point mutations, which probably contributes to the high clinical variability of MPS II [31, 32].

schwere & milde Form

MPS II is a progressive, multisystem disorder spanning severe (neuronopathic) and attenuated (non-neuronopathic) forms. The more severe form with CNS involvement occurs in approximately two-thirds of individuals, and clinical symptoms appear between two and four years of age. These cases feature severe progressive neurological damage, resulting in significant mental impairment. Death typically occurs by the second decade due to airway obstruction or cardiac failure associated with neurological decline. The attenuated form is characterized by the onset of clinical signs and symptoms slightly later, with a minimal neurologic dysfunction, but with obvious somatic symptoms, and longer survival [32].

früher Verlauf oft unauffällig

Early development in MPS II may appear normal, delaying diagnosis. The attenuated form is marked by preserved intellect but abnormal cranial MRI findings, while the severe form shows developmental delay from 18.24 months, progressing to a plateau by age 3.5 years. Severe cases are distinguished by hyperactive behaviour, progressive neurological decline, skeletal, respiratory, and cardiac involvement, and eventual full dependence by the second decade of life [32].

Prognose bei kognitiver Beeinträchtigung schlechter

Across the spectrum, cognitive involvement is a key prognostic marker: patients with cognitive impairment have a significantly reduced median survival compared with those without [33].

Mucopolysacharidosis IVA

MPS IVA

Mucopolysaccharidosis type IVA (MPS IVA, also known as Morquio syndrome type A) is an autosomal recessive inherited disorder caused by the deficiency of lysosomal hydrolytic enzyme, N-acetylglucosamine-6-sulfatase [34] leading to GAG accumulation, specifically keratan sulfate and chondroitin-6-sulfate. This accumulation affects multiple tissues, mainly bone, cartilage, heart valves, and cornea, which can manifest in severe symptoms such as skeletal dysplasia with incomplete ossification and successive imbalance of growth [35].

Geburt meist unauffällig, Skelettveränderungen bis ins Kleinkindalter

schwere & milde Form

unterschiedliche Lebenserwartungen

Infants often appear look healthy at birth; however, skeletal deformities can develop within a few years of age. Severe form of MPS IVA are characterized by skeletal dysplasia features, such as short neck and trunk, cervical spinal cord compression, tracheal obstruction, pectus carinatum, laxity of joints, kyphoscoliosis, coxa valga, and genu valgum [36, 37]. Progressive musculoskeletal and cardiorespiratory involvement leads to increasing disability. Many patients require wheelchair use by adolescence. Severe forms of this disease present with significant respiratory problems, cervical spinal cord complications, or heart valve disease, and death occurs in the second or third decade of life in untreated [38, 39]. However, the attenuated form of the disease can present with fewer and milder bone manifestations, and patients experience a longer life span (up to 70 years) compared with the patients with severe form [38].

Diagnosis of Mucopolysaccharidoses I, II and IVA

Leitsymptome für die Diagnose

The initial step in MPS diagnosis involves identifying individuals with clinical suspicion or those at high risk. Clinical features suggestive of an MPS disorder include the following:

1. Head and neck manifestations (in case of MPS I, II and IV) – coarse facial features, hearing loss, abnormal dentition.
2. Osteoarticular manifestations (in case of MPS I, II and IV) – hip dysplasia, thoracolumbar kyphosis, coxa valga, genu valgum, odontoid dysplasia.
3. Cardiovascular manifestations (in case of MPS I, II and IV) – valve thickening/dysfunction, left ventricular hypertrophy.
4. Neurological manifestations (only in case of MPS I and II) – developmental delay/intellectual disability, ventriculomegaly, dilated perivascular spaces.
5. Airways manifestations (in case of MPS I, II and IV) – recurrent respiratory infections, obstructive airway disease.
6. Abdomen manifestations (in case of MPS I and II) – hepatomegaly/splenomegaly, umbilical/inguinal hernia.
7. Other manifestations (in case of MPS I, II and IV) – abnormal granulation in leukocytes.

Urin-GAGs als erster Schritt, dann Enzym- & Gentest je nach Subtyp

Frühdiagnose verbessert Therapiechancen …

After identifying a clinically suspected case of MPS, further assessment includes measuring urinary GAGs and determining GAG pattern in the urine. If results are increased or abnormal, enzyme activity is measured according to the suspected subtype: α-L-iduronidase for MPS I, iduronate-2-sulfatase for MPS II, and N-acetylgalactosamine-6-sulfatase for MPS IVA. Subsequently, genetic variant identification is performed by extracting DNA from blood and sequencing the corresponding gene [40]. Since therapy outcomes are more

likely to provide greater benefit in case of timely initiation, when the diagnosis is made early in life, several jurisdictions have implemented targeted high-risk screening and newborn screening programs. For instance, screening for MPS I started in 2016 in the US, and the state of Illinois has also implemented statewide screening for MPS II. MPS I, II and VI screening is also routinely performed in Taiwan [41, 42], and in some parts of Italy [43, 44]. Austria conducted a pilot study in 2011 [45, 46], Belgium followed its example a few years afterwards [47].

… Screening in vielen Ländern etabliert

Epidemiology of Mucopolysaccharidoses I, II and IVA

keine offiziellen Zahlen für Österreich

No official data on the incidence or prevalence of MPS is available for Austria; however, epidemiological estimates have been reported from neighbouring countries and mainly refer to incidence (birth prevalence) data. For instance, in Switzerland the combined MPS incidence (assessed between 1975 and 2008) was 1.56 per 100,000 live births, with MPS II having the highest of 0.46 per 100,000 live births. Birth prevalence for MPS I was 0.19 and for MPS IV it was 0.38 per 100,000 live births [48].

Schätzungen aus der Schweiz, Tschechien & Deutschland

In Czech Republic, the Prague Institute of Inherited Metabolic Disorders reported 119 MPS cases among 4,261,897 live births that occurred between 1975 and 2008. The overall birth prevalence of all MPS types was 3.72 per 100,000 live births. The specific birth prevalences were 0.72 for MPS I, 0.43 for MPS II, and 0.73 per 100,000 live births for MPS IV [49].

Finally, a German retrospective epidemiological survey study that included data over a 16 years' time span (between 1980 and 1995) identified 474 cases diagnosed with MPS among 13,410,924 live births. The combined birth prevalence of MPS was 3.51 per 100,000 live births, out of which the birth prevalence of MPS I, II, and IVA were 0.69, 0.64, and 0.38 per 100,000 live births, respectively [50].

2 Enzyme Replacement Therapy

2.1 Therapeutic Approaches in Lysosomal Storage Diseases

ERT ist Standard bei LSDs

lebenslange Infusion, Symptomkontrolle, Heiminfusion möglich

Currently, enzyme replacement therapy (ERT) represents the standard of care in treating lysosomal storage diseases (LSDs), like Pompe disease and the mucopolysaccharidosis (MPS) MPS I, MPS II and MPS IVA. ERT involves intravenous administration of recombinant enzymes that are taken up into cells via mannose-6-phosphate receptor-mediated endocytosis and delivered to lysosomes, where they restore the deficient enzymatic activity and reduce pathological substrate accumulation. This systemic approach can alleviate symptoms, slow disease progression, and improve quality of life in patients with LSDs, but requires lifelong regular infusions, which place a substantial burden on patients and caregivers [51]. In Austria, LSDs are typically diagnosed and ERT is initiated in specialized hospital centers. To reduce treatment burden, home infusion programs have been established for eligible patients.

2.1.1 Enzyme replacement therapy for Pompe disease

zugelassene Produkte:

Alglucosidase alfa (Myozyme®)

Avalglucosidase alfa (Nexviadyme®)

Current approved ERTs include alglucosidase alfa (Myozyme®), a recombinant human acid α-glucosidase produced in Chinese hamster ovary cells, and avalglucosidase alfa (Nexviadyme®), a next-generation GAA enzyme with enhanced mannose-6-phosphate receptor targeting for improved cellular uptake. Intravenously administered enzymes are internalized by muscle and other affected cells via receptor-mediated endocytosis and delivered to lysosomes, where they degrade accumulated glycogen, thereby mitigating cellular dysfunction, slowing disease progression, and improving clinical outcomes.

Cipaglucosidase alfa + Miglustat (Pombiliti®/Opfolda®)

A more recent therapy, cipaglucosidase alfa (Pombiliti®) in combination with the stabilizer miglustat (Opfolda®), has also been approved for adult patients with LOPD, enhancing enzyme stability and uptake [52]; however, this treatment was not included in the present systematic review.

Standarddosis meist 20 mg/kg alle 2 Wochen (IV), individuelle Anpassungen v. a. bei IOPD möglich

The EMA issued marketing authorization for alglucosidase alfa (Myozyme®) in March 2006 for both IOPD and LOPD treatment [53]. The recommended dosage of alglucosidase alfa is 20 mg/kg body weight administered biweekly intravenously [52]. Studies report variable dosages, specifically in IOPD patients, and the reported dosages ranged from 10 mg/kg/week to 40 mg/kg/week. Nonetheless, the impact of dosage on treatment outcomes remains a subject of debate.

Avalglucosidase alfa received approval by the EMA in the EU in June 2022, as long-term ERT for treating Pompe disease (both IOPD and LOPD) [54], and is marketed under the name Nexviadyme®. The recommended avalglucosidase alfa dosage is 20 mg/kg every other week, however, dosage modifications may apply to IOPD patients in case of clinical deterioration, ranging from 20 to 40 mg/kg every two weeks [55].

Hersteller/Zulassungsinhaber: Sanofi Enzyme

Both alglucosidase alfa and avalglucosidase alfa are developed by Sanofi Genzyme (formerly Genzyme Corporation), which also serves as the marketing authorization holder (MAH) for both products.

2.1.2 Enzyme replacement therapy for Mucopolysacharidosis I

Laronidase (Aldurazyme®, Sanofi Genzyme) als einzige zugelassene ERT

Laronidase (Aldurazyme®) is the only approved ERT for MPS I. It is a recombinant human α-L-iduronidase, developed by Genzyme Corporation (now part of Sanofi Genzyme). The drug obtained marketing authorization in the EU in June 2003 [56]. Aldurazyme® is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of MPS I to treat the non-neurological manifestations of the disease.

wöchentlich & intravenös

wirkt nicht auf das ZNS

The recommended dose is 0.58 mg/kg administered intravenously once per week [56]. The pharmacodynamic effects have been assessed by monitoring urinary GAG levels, which are found to significantly decrease after laronidase administration. At this recommended dosage, laronidase does not cross the blood-brain barrier and thus has no impact on the central nervous system (CNS) [57].

schwere Fälle: Kombination von ERT & HSCT wird zur Erhaltung der kognitiven Funktion empfohlen

In recent years, for children younger than two years with severe MPS I, a combination of laronidase (ERT) and hematopoietic stem cell transplantation (HSCT) is recommended. HSCT is preferred in this population because it provides an endogenous source of α-L-iduronidase, reduces or may eliminate the need for long-term ERT, and has superior potential to preserve cognitive function. Typically, laronidase is administered between diagnosis and transplantation to improve the patient's clinical condition, which may help reduce HSCT-related morbidity and mortality. ERT is generally continued during the conditioning regimen and until successful donor engraftment is achieved [27].

2.1.3 Enzyme replacement therapy for Mucopolysacharidosis II

Idursulfase (Elaprase®, Takeda) seit 2007

Idursulfase (Elaprase®) was approved in January 2007 in the EU [58] for long-term treatment of MPS II. The Marketing authorisation holder is Takeda Pharmaceuticals International AG Ireland Branch. Elaprase® provides exogenous iduronate-2-sulfatase produced in a continuous human cell line. Mannose-6-phosphate residues facilitate receptor-mediated uptake and lysosomal targeting, enabling degradation of accumulated glycosaminoglycans (GAGs) and aiming to attenuate disease progression. Elaprase® is administered at a dose of 0.5 mg/kg body weight every week by intravenous infusion [59].

Ziel: GAG-Abbau, Verlaufsmilderung

2.1.4 Enzyme replacement therapy for Mucopolysacharidosis IVA

Elosulfase alfa (VIMIZIM®, BioMarin) seit 2014

Elosulfase alfa (VIMIZIM®) is indicated for the treatment of mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA) in patients of all ages and received approval by EMA in April 2014 [60].

Wirkung auf Keratan- & Chondroitinsulfat

The marketing authorization holder is BioMarin Pharmaceutical Inc. It is a recombinant form of human N-acetylgalactosamine-6-sulfatase, produced in Chinese hamster ovary (CHO) cells. The enzyme contains mannose-6-phosphate (M6P) residues at two glycosylation sites, enabling receptor-mediated cellular uptake and lysosomal targeting. Within lysosomes, elosulfase alfa hydrolyzes sulfate groups from keratan sulfate and chondroitin-6-sulfate, thereby reducing their pathological accumulation. This mechanism aims to preserve organ function and alleviate clinical manifestations of MPS IVA. The recommended regimen is 2 mg/kg body weight administered once weekly as an intravenous infusion.

Ziel: Organschutz und Symptomlinderung

2.2 Challenges associated with enzyme replacement therapy

kein Rückgang bestehender Schäden, lebenslange Therapie, Antikörperrisiko, kaum Wirkung im ZNS, wenig Langzeitdaten

langfristige Wirksamkeit und Sicherheit im Fokus

While ERT is central to current care, several important considerations remain. ERT does not reverse tissue damage present before treatment initiation and generally requires lifelong administration, which poses a substantial burden for patients and caregivers. Furthermore, ERT is associated with the potential development of anti-drug antibodies and has limited impact on central nervous system manifestations due to poor penetration across the blood-brain barrier [61]. Moreover, long-term real-world evidence is still sparse for many subgroups, creating uncertainty about durability of benefit and safety. The aim of this systematic review is to assess the long-term effectiveness and safety of ERTs for LSDs, specifically Pompe disease and MPS I, II, and IVA.

3 Scope

3.1 Research questions

Forschungsfragen

This systematic review aims to evaluate and synthesize available evidence on the long-term effectiveness and safety of ERTs in Pompe disease, MPS I, MPS II, and MPS IVA. The following research questions (RQs) will be addressed in this systematic review:

- **RQ1**: What is the long-term effectiveness and safety of alglucosidase alfa and avalglucosidase alfa in the treatment of patients with Pompe disease (infantile- and late-onset Pompe disease)?
- **RQ2**: What is the long-term effectiveness and safety of laronidase in the treatment of patients with mucopolysacharidosis I (MPS I)?
- **RQ3**: What is the long-term effectiveness and safety of idursulfase in the treatment of patients with Hunter syndrome – mucopolysacharidosis II (MPS II)?
- **RQ4**: What is the long-term effectiveness and safety of elosulfase alfa in the treatment of patients with Morquio A syndrome – mucopolysacharidosis IVA (MPS IVA)?

3.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies to address the above RQs are summarised in Table 3-1 – Table 3-5.

Table 3-1: Alglucosidase alfa and avalglucosidase alfa for IOPD

Population	Patients of all ages with infantile-onset Pompe disease. *Alternative terms*: type II glycogenosis, glycogen storage disease type II, acid maltase deficiency, acid α-glucosidase deficiency, infantile-onset Pompe disease (IOPD).
Intervention	Alglucosidase alfa Avalglucosidase alfa *Alternative terms*: enzyme replacement therapy OR ERT
Control	Any kind of control intervention will be included
Outcomes	
Efficacy	■ Cardiac function (LVMI; ejection fraction; relative wall thickness; shortening fraction) ■ Motor function (QMFT; achievement of motor milestones – sitting, walking, 6MWD) ■ Cognitive function ■ Respiratory function (use of invasive/non-invasive ventilation; time spent on ventilation) ■ Survival and ventilation-free survival ■ Quality of life
Safety	■ Mortality ■ Adverse events ■ Infusion-associated reactions

Study design	■ Systematic reviews ■ RCTs with a minimum follow-up of 2 years ■ NRCs with a minimum follow-up of 2 years A hierarchical approach will be applied when selecting studies by giving preference to RCTs, NRCs and observational studies with a prospective design. The minimum sample size should be 5 patients. If at least ten studies are identified, only those with a larger sample size (n>10), will be included. Excluded: in vitro, animal, case studies, conference abstracts, letters to the editors and authors responses.

Abbreviations: 6MWD … 6-minute walking distance, ERT … enzyme replacement therapy, IOPD … infantile-onset Pompe disease, LVMI … left ventricular mass index, n … number of patients, NRCs … non-randomized comparative studies, QMFT … Quick Motor Function Test, RCTs … randomized controlled trials.

Table 3-2: Alglucosidase alfa and avalglucosidase alfa for LOPD

Population	Patients of all ages with late-onset Pompe disease. *Alternative terms*: type II glycogenosis, glycogen storage disease type II, acid maltase deficiency, acid α-glucosidase deficiency, late-onset Pompe disease (LOPD).
Intervention	Alglucosidase alfa Avalglucosidase alfa *Alternative terms*: enzyme replacement therapy OR ERT
Control	Any kind of control intervention will be included
Outcomes	
Efficacy	■ Motor function (6MWD; QMFT) ■ Respiratory function (FVC, FEV1, the use of non-invasive or tracheostomy-assisted ventilation; time spent on ventilation) ■ Quality of life ■ Survival
Safety	■ Adverse events ■ Infusion associated reactions ■ Mortality
Study design	■ Systematic reviews ■ RCTs with a minimum follow-up of 2 years. ■ NRCs with a minimum follow-up of 2 years. A hierarchical approach will be applied when selecting studies by giving preference to RCTs, NRCs and observational studies with a prospective design. The minimum sample size should be 5 patients. If at least ten studies are identified, only those with a larger sample size (n>10), will be included. Excluded: in vitro, animal, case studies, conference abstracts, letters to the editors and authors responses.

Abbreviations: 6MWD … Six-minute walking distance, ERT … Enzyme replacement therapy, FEV1 … Forced expiratory volume at one second, FVC … Forced vital capacity, LOPD … Late-onset Pompe disease, n … Number of patients, NRCs … non-randomized comparative studies, RCTs … randomized controlled trials.

Table 3-3: Laronidase for MPS I

Population	Patients of all ages with Mucopolysaccharidosis Type I, including all three disease forms (Hurler, Hurler-Scheie and Scheie syndrome). *Alternative terms*: Mucopolysaccharidosis I OR MPS I OR Alpha-L-iduronidase deficiency
Intervention	Laronidase *Alternative terms*: Enzyme replacement therapy OR ERT
Control	Any kind of control intervention will be included

Outcomes	
Efficacy	■ Motor function (6MWD) ■ Spinal cord compression ■ Range of motion (joint range of motion, single joint or combination, shoulder range of motion) ■ Sleep apnea (apnea/hypopnea index, polysomnography) ■ Quality of life
Safety	■ Mortality ■ Adverse events ■ Infusion associated reactions
Study design	■ Systematic reviews ■ RCTs with a minimum follow-up of 2 years. ■ NRCs with a minimum follow-up of 2 years. A hierarchical approach will be applied when selecting studies by giving preference to RCTs, NRCs and observational studies with a prospective design. The minimum sample size should be 5 patients. If at least ten studies are identified, only those with a larger sample size (n>10), will be included. Excluded: in vitro, animal, case studies, conference abstracts, letters to the editors and authors responses.

Abbreviations: 6MWD … Six-minute walking distance, ERT … Enzyme replacement therapy, MPS I … Mucopolysaccharidosis Type I, n … Number of patients, NRCs … non-randomized comparative studies, RCTs … randomized controlled trials.

Table 3-4: Idursulfase for MPS II

Population	Patients of all ages with Hunter syndrome (Mucopolysaccharidosis Type II). *Alternative terms*: Mucopolysaccharidosis II OR MPS II
Intervention	Idursulfase *Alternative terms*: enzyme replacement therapy OR ERT
Control	Any kind of control intervention will be included
Outcomes	
Efficacy	■ Motor function (6MWD) ■ Cognitive function (DAS) ■ Joint range of motion ■ Sleep apnea ■ Airway obstruction ■ Survival ■ Quality of life
Safety	■ Mortality ■ Adverse events ■ Infusion associated reactions
Study design	■ Systematic reviews ■ RCTs with a minimum follow-up of 2 years. ■ NRCs with a minimum follow-up of 2 years. A hierarchical approach will be applied when selecting studies by giving preference to RCTs, NRCs and observational studies with a prospective design. The minimum sample size should be 5 patients. If at least ten studies are identified, only those with a larger sample size (n>10), will be included. Excluded: in vitro, animal, case studies, conference abstracts, letters to the editors and authors responses.

Abbreviations: 6MWD … Six-minute walking distance, ERT … Enzyme replacement therapy, DAS … Differential Abilities Scales; MPS II … Mucopolysaccharidosis Type II, n … Number of patients, NRCs … non-randomized comparative studies, RCTs … randomized controlled trials.

Table 3-5: Elosulfase alfa for MPS IVA

Population	Patients of all ages with Mucopolysaccharidosis Type IVA *Alternative terms*: Mucopolysaccharidosis Type IVA OR MPS IVA OR Morquio A syndrome OR Morquio–Brailsford syndrome
Intervention	Elosulfase alfa *Alternative terms*: enzyme replacement therapy OR ERT
Control	Any kind of control intervention will be included
Outcomes	
Efficacy	■ Cardiac function (LVMI, ejection fraction, IVSd, LWPVd, LVIDd) ■ Motor function (6MWD) ■ Quality of Life
Safety	■ Adverse events ■ Infusion associated reactions ■ Mortality
Study design	■ Systematic reviews ■ RCTs with a minimum follow-up of 2 years. ■ NRCs with a minimum follow-up of 2 years. A hierarchical approach will be applied when selecting studies by giving preference to RCTs, NRCs and observational studies with a prospective design. The minimum sample size should be 5 patients. If at least ten studies are identified, only those with a larger sample size (n>10), will be included. Excluded: in vitro, animal, case studies, conference abstracts, letters to the editors and authors responses.

Abbreviations: 6MWD … Six-minute walking distance, ERT … Enzyme replacement therapy, IVSd … Interventricular septal thickness, diastole, LWPVd … Left ventricular posterior wall thickness, diastole; LVIDd … Left ventricular internal diameter, diastole, MPS IVA … Mucopolysaccharidosis Type IVA, n … Number of patients, NRCs … non-randomized comparative studies, RCTs … randomized controlled trials.

4 Methods

4.1 Sources

5 relevante Übersichtsarbeiten

Before initiating the systematic search for primary studies, we first examined whether recently published systematic reviews addressing our research questions were already available. Therefore, in April 2025, a targeted hand search for relevant systematic reviews was conducted in the PubMed database. Five systematic reviews fulfilling our inclusion criteria were identified. These assessed alglucosidase alfa for the treatment of IOPD [62], alglucosidase alfa for the treatment of LOPD [63], laronidase for the treatment of MPS I [64], idursulfase for the treatment of MPS II [65], and elosulfase alfa for the treatment of MPS IVA [66]. No published systematic review was found evaluating the long-term effectiveness and safety of avalglucosidase alfa in Pompe disease.

3 methodisch robust

tlw. unklarer & hoher RoB

ROBIS für Qualitätsbewertung

The quality of the identified systematic reviews was critically appraised using the Risk of Bias Assessment Tool for Systematic Reviews (ROBIS) [67]. Of the identified reviews, three were rated as having a low risk of bias in study eligibility criteria and identification and selection of studies (alglucosidase alfa for LOPD, laronidase for MPS I, and idursulfase for MPS II). These reviews were therefore considered methodologically robust and suitable to serve as a basis for conducting an update of the existing systematic evidence.

The review on alglucosidase alfa in IOPD was rated as having an unclear risk of bias in study identification and selection due to the restriction to two databases. This limitation was addressed by performing an updated search in at least three databases, supplemented with manual searching, and the review was therefore considered suitable for updating.

The reviews judged at high risk of bias in the domains of data collection/appraisal and synthesis/findings were not excluded, as they were used solely to identify studies relevant to the predefined PICO questions. Their original search strategies were replicated and extended to cover the period from the end of the original search to the date of the update.

für Elosulfase und Avalglucosidase alfa keine Reviews: vollständige Literatursuche durchgeführt

The review on elosulfase alfa for MPS IVA was assessed as high risk of bias in study identification and selection, primarily due to the absence of a table of study characteristics, which precluded the identification of eligible studies. Accordingly, a de novo search from inception was conducted.

Likewise, as no systematic review was available for avalglucosidase alfa in Pompe disease, a de novo search from inception was performed.

4.2 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search for all research questions was conducted in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- INAHTA

The systematic search was conducted between 8 and 16 May 2025. Updated searches covered the period from the cut-off date of the respective reviews, while de novo searches were performed from inception. In addition to database searches, the reference lists of all included studies and relevant systematic reviews were manually screened. The detailed search strategies for all five ERTs across the four patient populations are presented in the Appendix.

Suche nach laufenden Studien

To identify ongoing studies without available publications, clinical trial registries (ClinicalTrials.gov, WHO ICTRP, and EU Clinical Trials Register) were searched. Searches were conducted on May 30, 2025, for all interventions except alglucosidase alfa, which was searched on May 27, 2025. Additionally, the International Horizon Scanning Initiative database [68] was used to search for new drugs not yet approved for the treatment of Pompe disease, MPS I, MPS II and MPS IV. Retrieved records were screened for eligibility according to predefined criteria.

4.3 Flow chart of study selection

Literaturauswahl

After deduplication, titles and abstracts were independently screened in parallel by two reviewers (A.P. and E.M.). Any discrepancies were resolved through discussion or, if necessary, by consulting a third reviewer (E.J.). The same procedure was applied during full-text screening, with all articles assessed against the predefined inclusion criteria. Flow charts of the study selection process are presented below for each of the five PICOs.

prospektive Studien mit ≥2 Jahren Nachbeobachtung eingeschlossen

Prospective trials with a minimum follow-up of two years were eligible for inclusion. For most conditions, studies with at least five enrolled patients were considered, while for late-onset Pompe disease (LOPD) a minimum of ten patients was required, reflecting the greater availability of long-term data. When multiple publications reported identical outcomes from the same study, data were extracted from the publication with the longest follow-up and largest sample size. If different outcomes of interest were reported across publications from the same study, all relevant reports were included in the synthesis.

Study selection process for alglucosidase alfa in IOPD

8 Studien aus 10 Publikationen inkludiert

After deduplicating, a total of 489 records were screened at the title and abstract level. Of these, 451 records were excluded as irrelevant to the research question, leaving 38 articles for full-text assessment. Following full-text screening, 28 articles were excluded for not meeting the predefined inclusion criteria. Ultimately, 8 studies, reported across 10 publications, were included in the qualitative synthesis. The complete screening process is presented in Figure 4-1.

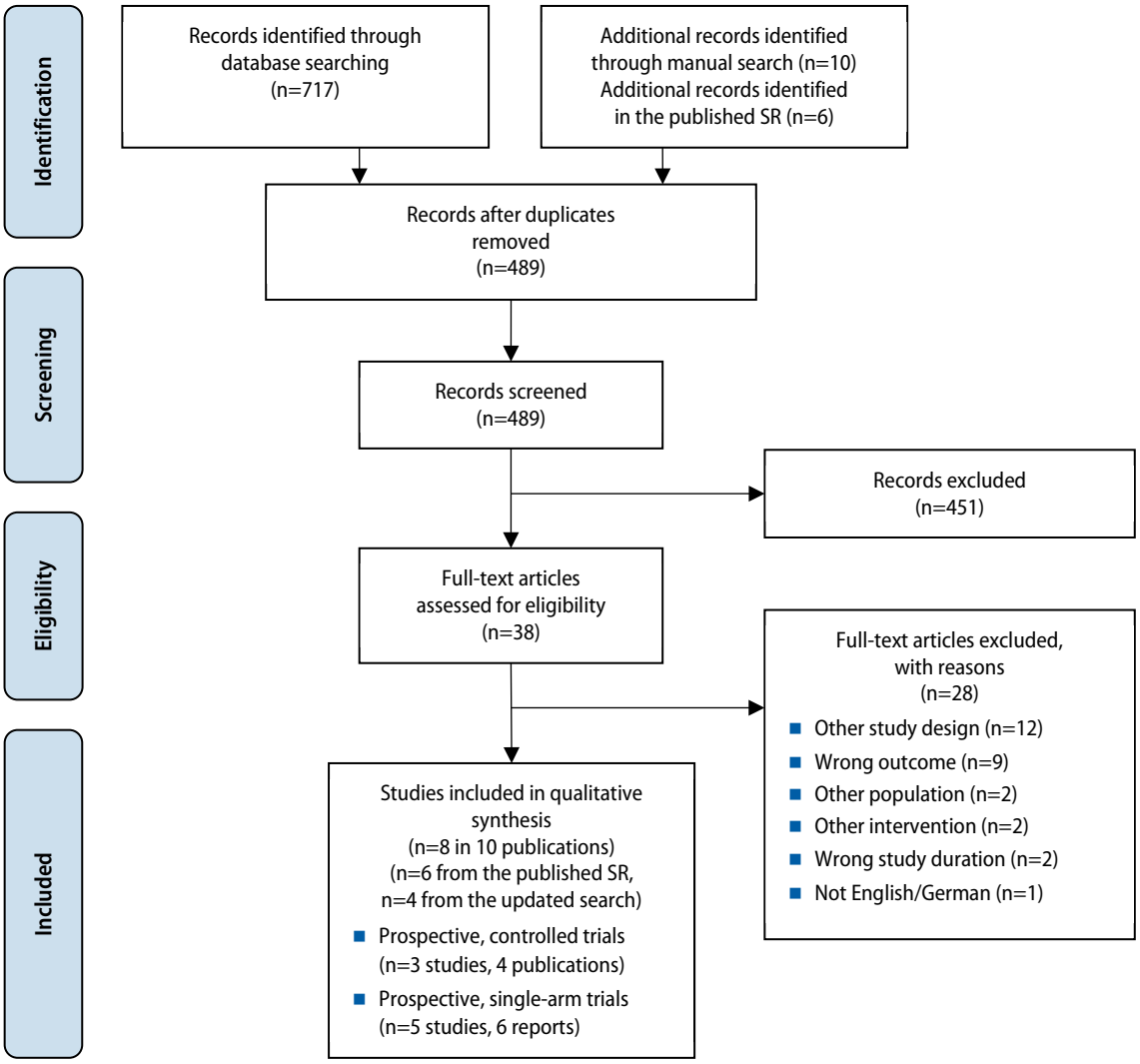

Figure 4-1: Flow chart of study selection for alglucosidase alfa in IOPD patients.

Study selection process for avalglucosidase alfa in IOPD and LOPD

Literaturauswahl: 3 Studien

A total of 100 studies were screened at the title and abstract level after deduplication. Title and abstract screening identified 19 articles eligible for full-text assessment. Of these, 16 articles were excluded for not meeting the predefined inclusion criteria, resulting in 3 studies being included in the qualitative synthesis: one investigating avalglucosidase alfa in IOPD patients and two in LOPD patients. The complete screening process is presented in Figure 4-2.

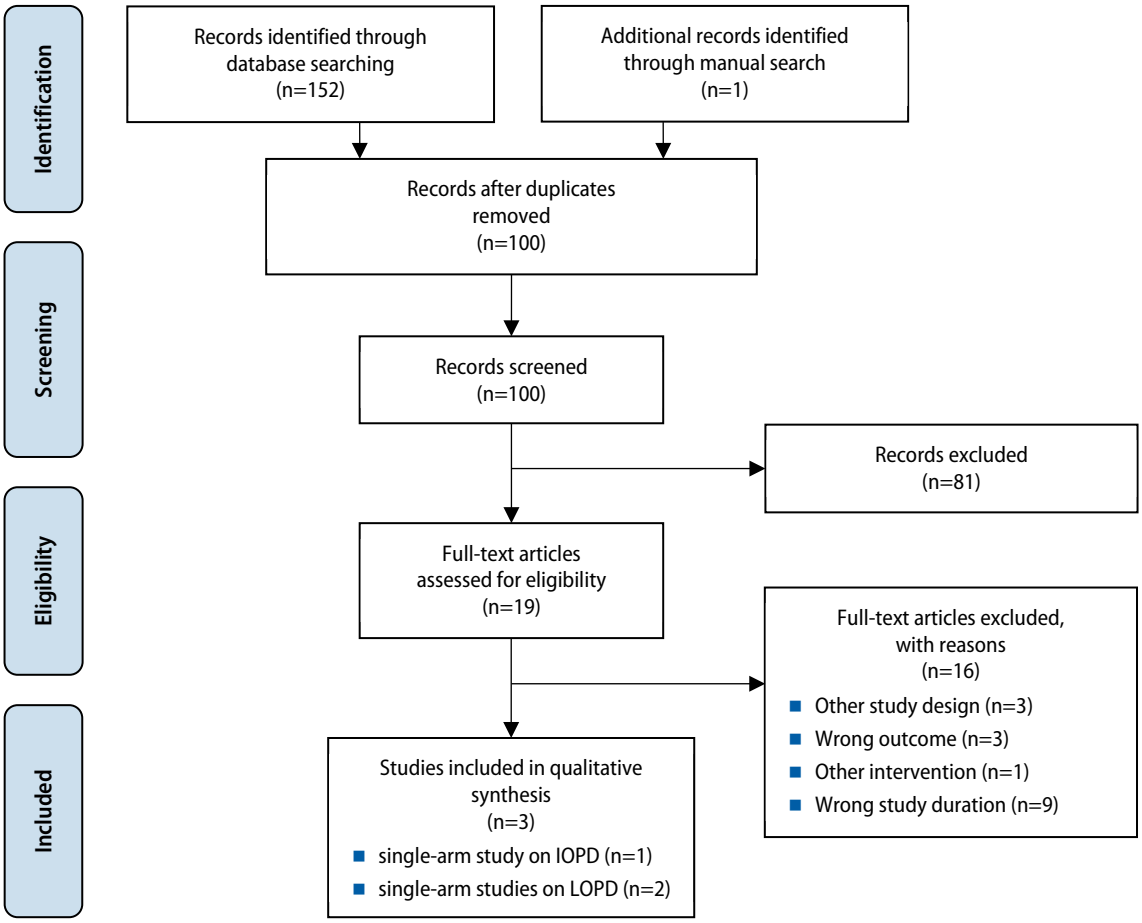

Figure 4-2: Flow chart of study selection for avalglucosidase alfa in IOPD and LOPD patients.

Study selection process for alglucosidase alfa in LOPD

Literaturauswahl: 17 Studien in 18 Publikationen

After deduplication, a total of 650 records were screened at the title and abstract level. Of these, 590 records were excluded as irrelevant to the research question, leaving 60 articles for full-text assessment. Following full-text screening, 42 articles were excluded for not meeting the predefined inclusion criteria, resulting in 17 studies, reported across 18 publications, being included in the qualitative synthesis. The complete screening process is presented in Figure 4-3.

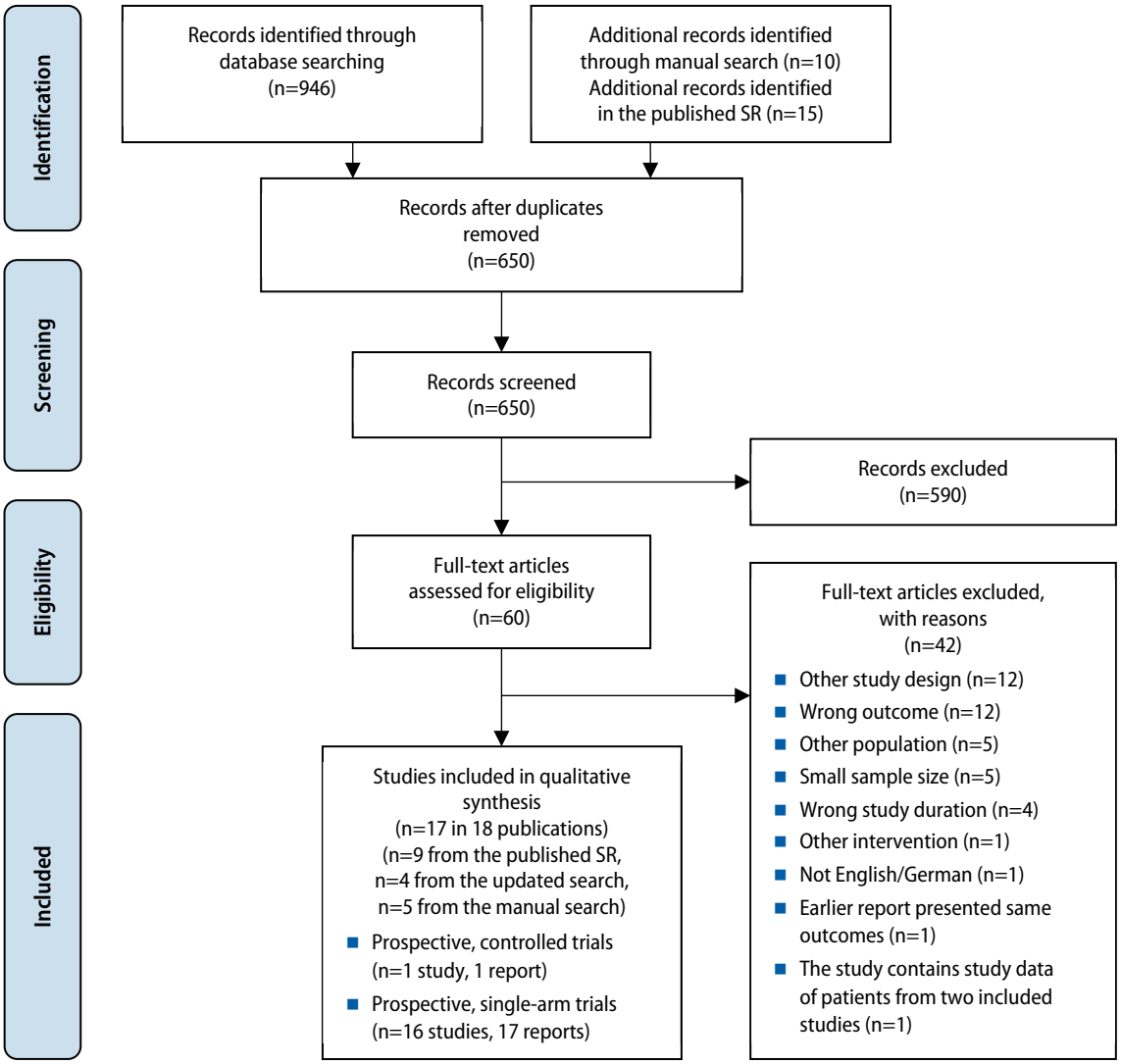

Figure 4-3: Flow chart of study selection for alglucosidase alfa in LOPD patients

Study selection process for laronidase in MPS I

Literaturauswahl: 4 Studien

After deduplication, a total of 671 records were screened at the title and abstract level. Of these, 627 records were excluded as irrelevant to the research question, leaving 44 articles for full-text assessment. Following full-text screening, 40 articles were excluded for not meeting the predefined inclusion criteria, resulting in 4 studies being included in the qualitative synthesis. The complete screening process is shown in Figure 4-4.

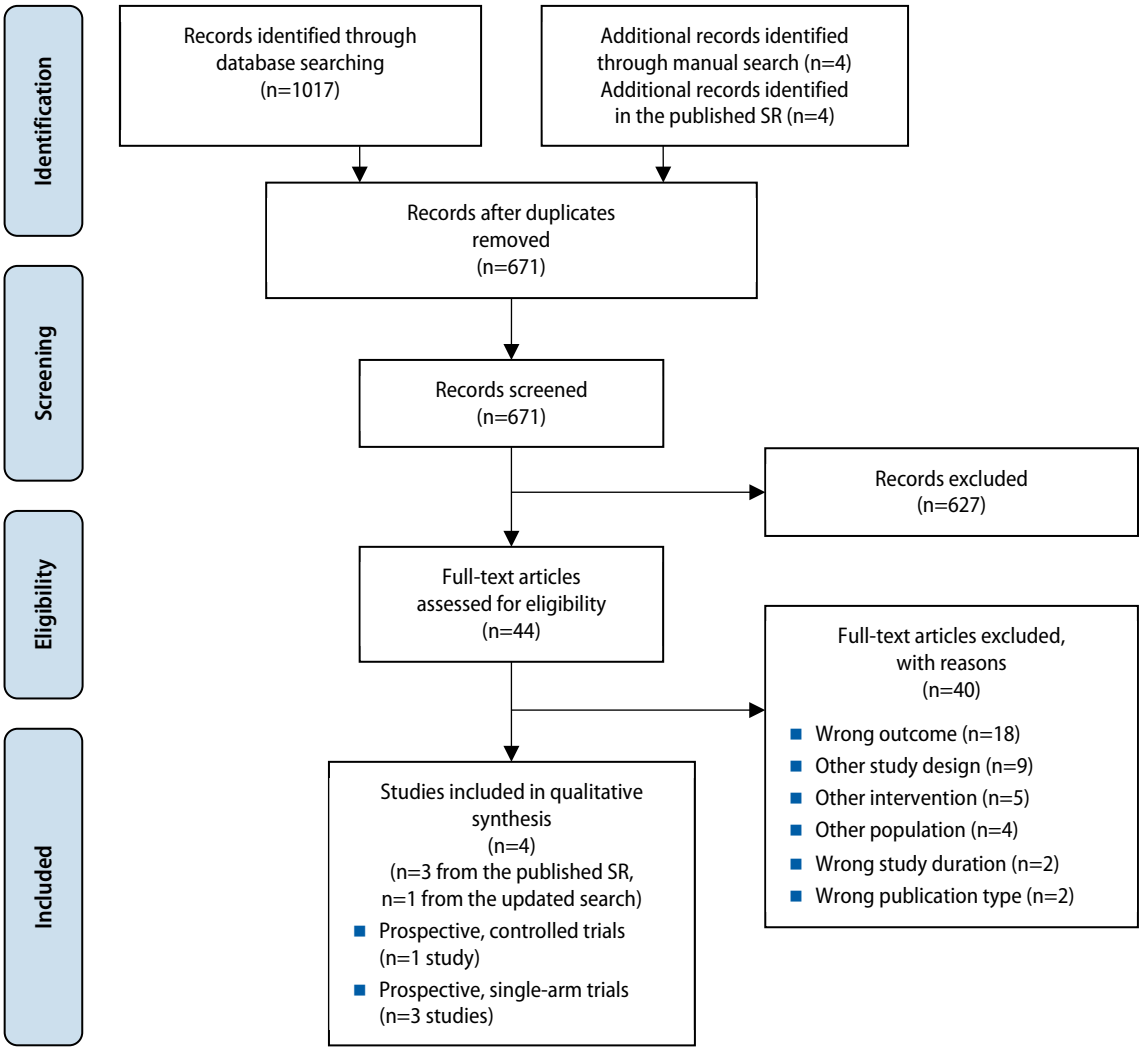

Figure 4-4: Flow chart of study selection for laronidase in MPS I patients

Study selection process for idursulfase in MPS II

Literaturauswahl: 11 Studien

After deduplication, a total of 485 records were screened at the title and abstract level. Of these, 453 records were excluded as irrelevant to the research question, leaving 32 articles for full-text assessment. Following full-text screening, 21 articles were excluded for not meeting the predefined inclusion criteria, resulting in 11 studies being included in the qualitative synthesis. The complete screening process is shown in Figure 4-5.

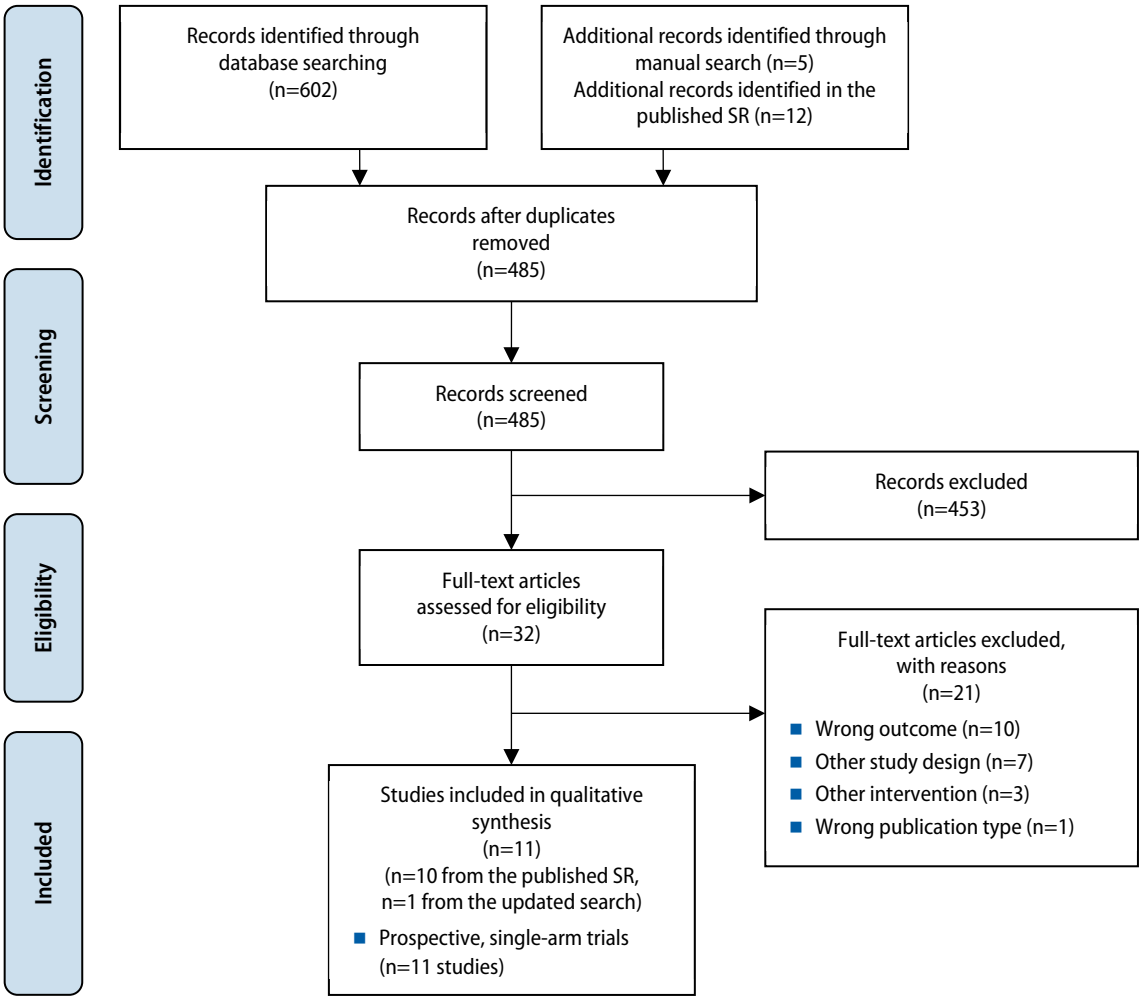

Figure 4-5: Flow chart of study selection for idursulfase in MPS II patients

Study selection process for elosulfase alfa in MPS IVA

Literaturauswahl: 3 Studien

After removing duplicates, a total of 231 records were screened at the title and abstract level. Of these, 202 were excluded as irrelevant to the research question, leaving 29 articles for full text assessment. Following full-text screening, 25 articles were excluded for not meeting the predefined inclusion criteria, resulting in 3 studies, reported across 4 publications, being included in the qualitative synthesis, The complete screening process is shown in Figure 4-6.

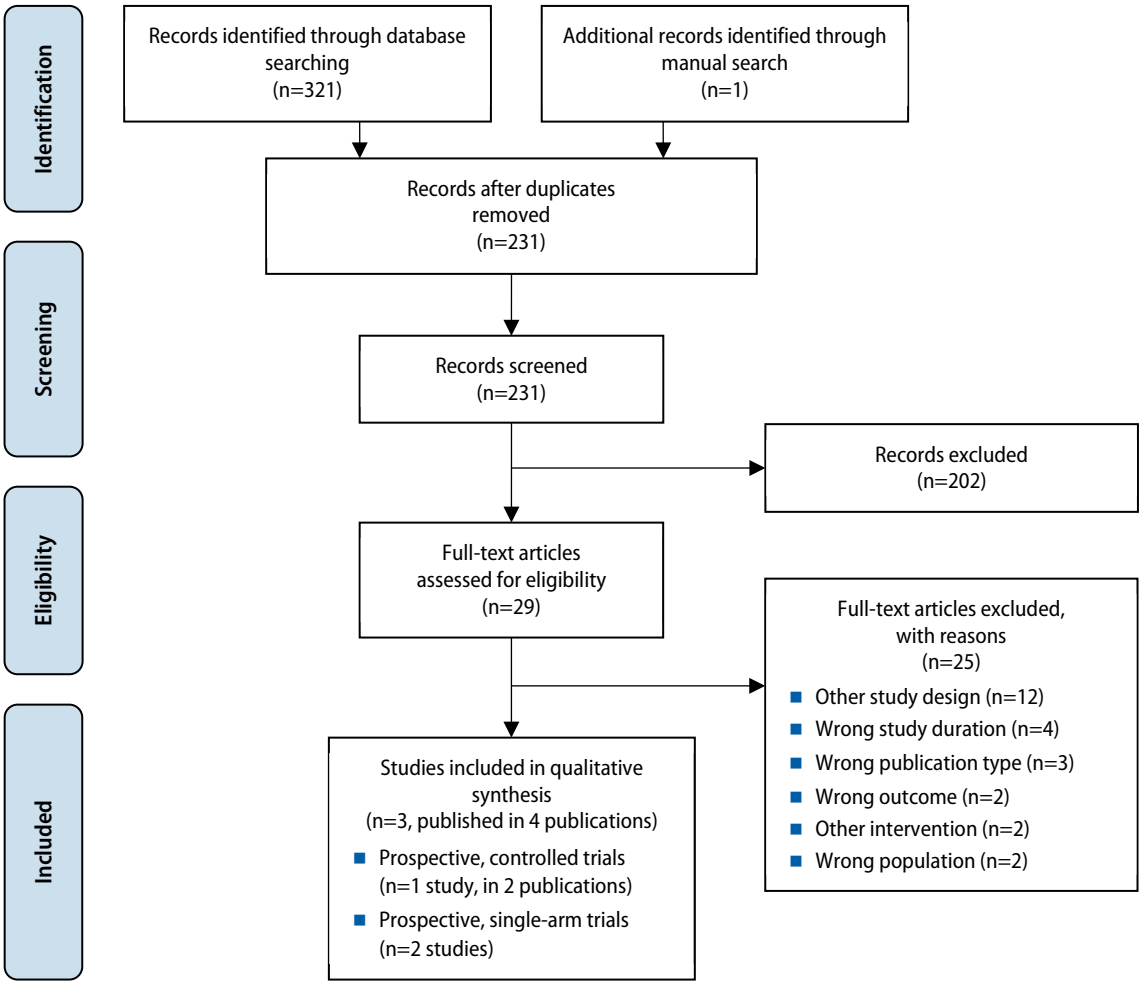

Figure 4-6: Flow chart of study selection for elosulfase alfa in MPS IVA patients

4.4 Data extraction and analysis

Daten von 2 Reviewern geprüft

Data of interest were independently extracted by the first reviewer (A.P.) and subsequently checked for accuracy by the second reviewer (E.M.). Study characteristics and main findings are summarized in tables. Results are presented according to study design, with prospective controlled studies reported first, followed by prospective single-arm studies. In addition to the tabular presentation, key findings are described in the text and accompanied by GRADE evidence tables.

Ergebnisse tabellarisch und als Text nach Studiendesign präsentiert

4.5 Risk of bias assessment of included studies and quality of evidence rating

RoB & Studienqualität

As only prospective observational studies were identified, the risk of bias was assessed using the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool [69]. This assessment was applied exclusively to prospective controlled studies, defined as studies including both an ERT intervention arm and a non-ERT (or placebo) control arm. All other studies, including those comparing different ERT dosages, were classified as prospective single-arm studies and were not assessed for risk of bias. Uncontrolled trials are generally of very limited value for assessing relative effectiveness; therefore, risk of bias assessment is typically not required [70].

ROBINS-I-Tool für kontrollierte Beobachtungsstudien,

einarmige Studien nicht bewertet

For studies identified through the previously published systematic reviews included in our update, we relied on the risk of bias assessments reported in those reviews, provided that the respective review was judged to be at low risk of bias in the domain “data collection and appraisal”. In such cases, the corresponding assessments are presented in Table A-1 of the Appendix. For the remaining PICO questions, risk of bias assessments for included controlled studies were performed by the authors, as these studies were identified through the updated searches. The risk of bias assessments of included studies is presented in Appendix Table A-18 to Table A-21.

Bestehende Bias-Assessments aus robusten Reviews übernommen, neue Studien selbst bewertet

GRADE-Ansatz zur Evidenzbewertung kritischer Endpunkte:

The certainty of evidence for critical outcomes was evaluated by one author (A.P.) and reviewed by a second author (E.M.) following the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach [71]. Findings are summarized by study design and follow-up duration, and the certainty of the evidence was rated per outcome.

vier Kategorien (hoch, moderat, niedrig, sehr niedrig)

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

4.6 Defining critical outcomes

kritische Endpunkte durch Expertenpanel per GRADE-Fragebogen definiert (Mittelwert ≥7 auf 1-9-Skala)

To define outcomes critical for evaluating the long-term efficacy of different ERTs across the four lysosomal storage disorders (LSDs), a questionnaire was distributed to a panel of clinical experts with experience in at least one of the conditions of interest. The questionnaire listed outcomes identified during full-text screening, and experts were asked to rate each outcome according to the GRADE methodology on a scale from 1 (least important) to 9 (most important). Following collection of all responses, mean scores were calculated, and outcomes with a mean score of ≥7 were classified as critical.

Sicherheit, Lebensqualität, Überleben und Kognition als zentrale Endpunkte

Safety, quality of life and survival were defined as critical outcomes a priori. Additionally, for IOPD, cognitive function outcomes were included as critical regardless of the ranking, due to their relevance in this condition. The results of the ranking process are presented inTable A-7 to Table A-11 in the Appendix. All final critical outcomes are incorporated into the PICO questions.

5 Clinical effectiveness

5.1 Alglucosidase alfa in infantile-onset Pompe disease

5.1.1 Description of Outcomes

Cardiac Function

Herzfunktion: LVMI, EF, SF, RWT zur Beurteilung von Hypertrophie und systolischer Funktion

Cardiac function was assessed using echocardiographic parameters, including left ventricular mass index (LVMI), ejection fraction (EF), shortening fraction (SF), and relative wall thickness (RWT):

- LVMI is calculated using the Devereux formula and indexed to body surface area to define left ventricular hypertrophy [72].
- Ejection fraction (EF): Parameter of left ventricular systolic function, determined by echocardiography.
- Shortening fraction (SF): Echocardiographic index of systolic function; values between 28–44% were considered normal [73].
- Relative wall thickness (RWT): Geometric measure of the left ventricle. An RWT < 0.42 was classified as within the reference range, whereas an RWT > 0.42 indicated concentric remodelling [73].

Motor Function

Motorik: Entwicklung von grobmotorischen Meilensteinen, QMFT und 6-Minuten-Gehtest

Motor function outcomes were assessed using the following standardized measures:

- Motor development milestones: Achievement of key gross motor milestones (e.g., sitting, crawling, walking) was evaluated according to the standardized definitions and age norms established by the World Health Organization (WHO).
- Quick Motor Function Test (QMFT): A disease-specific, 16-item assessment tool designed and validated for Pompe disease. Scores are expressed as a percentage of the maximum achievable score, with 100% indicating normal motor function [74].
- 6-minute walk distance (6MWD): Functional exercise capacity was measured using the six-minute walk test (6MWT), expressed as the total distance walked within a six-minute period.

Cognitive Function

Kognition: entwicklungsdiagnostische Tests (BSID-II, CDIIT) und Intelligenztests (CFT)

Cognitive function was assessed using the following standardized instruments:

- Bayley Scales of Infant and Toddler Development, Second Edition (BSID-II): A standardized developmental test designed to identify developmental delays in early childhood. It comprises motor and mental domains, as well as a behaviour rating scale, and can be applied to children aged 1–42 months [75].
- Comprehensive Developmental Inventory for Infants and Toddlers (CDIIT): A standardized, norm-referenced developmental assessment tool for children aged 3-72 months. It evaluates five developmental domains (cognitive, language, motor, social, and self-help) and provides

both norm-referenced scores and criterion-referenced information to support diagnosis, intervention planning, and monitoring of developmental progress [76].

- Culture Fair Intelligence Test (CFT): the CFT 1-R is designed for children younger than 9 years and CFT 20-R for children 9 years or older. The average score reflecting standard development is 100 with a standard deviation of 15. Mild developmental delay is indicated with an IQ between 84 and 70, while intellectual disability is reflected with a score below 70 [77, 78].

Respiratory status

Kognition: entwicklungsdiagnostische Tests (BSID-II, CDIIT) und Intelligenztests (CFT)

Respiratory function in IOPD patients was evaluated using the following parameters:

- Ventilatory support: Dependence on non-invasive ventilation or tracheostomy-assisted ventilation, expressed as the number of patients requiring support.
- Duration of ventilation: Cumulative time spent on ventilatory support.

Survival

Überleben: Gesamtüberleben und beatmungsfreies Überleben (Kaplan–Meier, Hazard Ratios, Zeitpunkte)

Survival outcomes were reported as:

- Overall survival: Defined as the time from diagnosis (or treatment initiation) until death from any cause. Data were reported as survival probability based on Kaplan–Meier analysis, hazard ratios from time-to-event models, or survival rates at predefined time points.
- Ventilator-free survival: Defined as the time until the initiation of invasive ventilation or death, reported in the same manner as overall survival.

Quality of life

Lebensqualität: SF-36 (Elternversion)

Quality of life is assessed with:

- Short-Form 36-Health (SF-36) – the parental version. The maximum score that can be achieved on this test is 100. Scores indicate the percentage of the maximum achievable health-related quality of life [79].

5.1.2 Included studies

8 Studien inkludiert

A total of eight unique studies, reported across ten publications, were included in this systematic review. All studies assessed at least one long-term efficacy outcome of alglucosidase alfa treatment in patients with IOPD. Six publications were identified through the previously published systematic review, two additional records were identified through the updated electronic database search, and two further publications were retrieved via manual reference searching.

Of the included studies, three (reported in four publications) were prospective, observational controlled studies (Table 5-1). The remaining five studies (reported in six publications) were prospective, observational single-arm studies (Table 5-2).

Characteristics of prospective, observational controlled studies

teils kontrolliert, teils einarmig, multinational; durch Genzyme-Sanofi finanziert

Two publications reported on the same study population [80, 81]. The 2009 publication included a smaller sample size and a shorter follow-up period. Both reports were retained in this review because the earlier publication provided data on one outcome not reported in the later publication, namely the achievement of motor function milestones. For all other outcomes of interest, data were extracted from the 2015 report.

Two multicenter studies were conducted across multiple countries [82, 83], and one was conducted in Taiwan [80, 81]. All studies reported Genzyme-Sanofi as the funding source. Conflicts of interest were disclosed in each publication, with the highest level reported in one study [82], where more than half of the authors declared at least one conflict. Reported conflicts included honoraria, research funding, and consultancy with Genzyme–Sanofi.

Dosierungen meist 20 mg/kg alle 2 Wochen, bei klinischer Verschlechterung teils Steigerung auf 40 mg/kg

Vergleich mit unbehandelten historischen Kohorten

ERT dosages varied among patients across the studies. In one study, the standard dose of alglucosidase alfa (20 mg/kg every other week) was administered, with two intervention groups: patients diagnosed via newborn screening and those diagnosed clinically [80, 81]. In two other studies, patients initially received the standard dose, but those showing clinical decline were escalated to 40 mg/kg every other week [82, 83]. All three studies used untreated historical cohorts as comparators. Reported follow-up durations ranged from a median of 2.3 years [82, 83] to 5.25 years [80]. One study [80] presented only individual patient-level data, from which only ranges could be extracted. None of the studies explicitly reported loss to follow-up. However, one study [83] noted that endpoint cardiac data were available for only 10 of 21 patients (≈50%), primarily due to death or clinical deterioration that precluded further assessments.

Patient characteristics in prospective, observational controlled studies

Interventionsgruppen 6-21, Kontrollen 11-86 Pts. Diagnosealter meist um 3 Monate, bei Screening <1 Monat

The number of patients in the intervention groups ranged from six [81] to 21 [83], whereas comparator groups included from 11 [80, 81] to 86 [83]. All studies included patients with classic IOPD, with symptom onset reported at a median age of approximately 3 months. Patients identified through newborn screening had the earliest diagnosis (median age of 0.2 months [81] and 0.3 months [80]), whereas the latest median age at diagnosis was 6.8 months [83].

ERT-Beginn sehr früh bei gescreenten Kindern

Consistent with earlier detection, ERT was initiated at the earliest ages in screened patients, whereas the latest reported median age at ERT initiation was 13 months. Two studies [82, 83] included both cross-reactive immunologic material (CRIM)-positive and CRIM-negative patients, with CRIM-positive predominating, while the third study [80, 81] included only CRIM-positive patients. All studies enrolled both ventilator-dependent and non-ventilator-dependent patients.

Table 5-1: Study and patients' characteristics of controlled studies investigating alglucosidase alfa in IOPD.

Author, year	Chien et al., 2015[a] [80]	Chien et al., 2009 [81]	Kishnani et al,. 2009 [82]	Nicolino et al., 2009 [83]
Study design	Prospective, observational, single-center study		Prospective, observational, open-label, multi-center study	Prospective, observational, open-label, multi-center study
Country	Taiwan		Multiple countries, 13 primary sites (six centers in the United States, five in Europe, one in Taiwan, and one in Israel)	United States, Europe, Japan, and Israel

Author, year	Chien et al., 2015[a] [80]	Chien et al., 2009 [81]	Kishnani et al,. 2009 [82]	Nicolino et al., 2009 [83]
Funding/ Conflict of interest (CoI)	Funding: The National Science Council, Genzyme-Sanofi Chien et al., 2009: 4/12 authors with CoI: Genzyme Chien et al., 2015: 2/10 authors with CoI: Genzyme-Sanofi		Funding: Genzyme 10/18 authors with CoI: Genzyme research/grant support; Pompe Advisory Board; consultancy, honoraria	Funding: Genzyme 4/24 authors with CoI: Genzyme advisory board members; consultancy
Description of the intervention (alglucosidase alfa dosage)	Group 1 (NBS patients) and Group 2 (clinically diagnosed patients) – 20 mg/kg every other week.		20 or 40 mg/kg every other week	All patients initially received a dose of 20 mg/kg every other week; dose augmentation to 40 mg/kg every other week was allowed after 26 weeks.
Comparator	Untreated historical controls		Untreated historical control group	Untreated historical control group
Number of patients, n (female)	Intervention (NBS) group: 10 Intervention (clinically diagnosed) group: 10 Comparator (untreated historical control) group: 11[a]	Intervention (NBS) group: 6 (3) Intervention (clinically diagnosed) group: 10 Comparator (untreated historical control) group: 11	18 (7) Intervention (standard-dosage) group: 9 Intervention (high dosage) group: 9 Comparator (untreated historical control) group: 61[b]	Intervention group: 21 (11) Comparator (untreated historical control) group: 86 (50)
Inclusion criteria	Classic IOPD patients identified through NBS presented left ventricular hypertrophy at the newborn period; they received ERT immediately.		Classic IOPD, <7 months old at enrollment, skin fibroblast GAA activity 1% of the normal mean, and hypertrophic cardiomyopathy.	Classic IOPD patients – symptoms by 12 months; skin fibroblast GAA activity ≤ 2% of the normal mean; age 6-36 months at enrolment, and abnormal LVMI indices.
Age of symptom onset (median (range) unless otherwise specified), months	Group 1 (NBS patients) – some were asymptomatic, some presented with feeding-related cyanosis and an enlarged tongue.	NBS – none had obvious clinical symptoms at birth	Intervention group: 1.0 (0.0, 5.5)	Intervention group: 3.0 (0.0, 12.6) Comparator group: 3.0 (0.0, 12.0)
Age at diagnosis (median (range), unless otherwise specified), months	Group 1 (NBS patients): 0.3 (0-1.1)	NBS patients: 0.2-1.3	Intervention group: 4.3 (0.2, 6.8)	Intervention group: 6.8 (1.5, 22.6) Comparator group: 5.7 (5.1, 22.7)
Age of ERT onset (median (range), unless otherwise specified), months	Group 1 (NBS patients): 0.5 (0.2-1.1) Clinically diagnosed patients: range (2-6) Untreated patients: N/A	Group 1 (NBS patients): 2.9 (0.4-14)	Intervention group: 5.3 (1.2–6.1)	Intervention group: 13.0 (3.7, 43.1) Comparator group: N/A
CRIM status (n of positive patients/n of total patients)	Group 1 (NBS patients): 10/10 Clinically diagnosed patients: 10/10	Group 1 (NBS patients): 6/6	Intervention group: 14/18	Intervention group: 19/21
Patients on ventilation (n)	Group 1 (NBS patients): 5/10. The other two groups: NR	NR	9/18 (all invasive)	Intervention group: 7/21 (5 invasive, 2 non-invasive)
Follow-up (median (range), unless otherwise specified), years	5.25 (2.33–7.50)[c]	Range (1.2–2.7)[d]	2.30 (1.10–3.00)	2.30 (0.01–3.23), but results are presented for FU of 104 weeks (~2 years).
Loss to follow-up, n	None reported		None reported	None reported

Abbreviations: CoI … conflict of interest, CRIM … cross-reactive immunological material, ERT … enzyme replacement therapy, FU … follow-up, GAA … acid alpha-glucosidase, IOPD … infantile-onset Pompe disease, LVMI … left ventricular mass index, NA … not applicable, n … number, NBS … newborn screening, NR … not reported, SD … standard deviation.

Notes:

[a] *The extension study of Chien et al., 2009. The study population of Chien 2015 includes the 6 patients enrolled in Chien 2009.*

[b] *Two patients did not enroll in the intervention group in this extension study (one died, and the other continued therapy in an international Expanded Access Program); however, their data were included in the analysis.*

[c] *The follow-up duration is based on the age at the last assessment of the included patients.*

[d] *The follow-up duration is based on the duration of ERT.*

Characteristics of prospective, observational single-arm studies

The study and patient characteristics are presented in Table 5-2. The results of one study were reported in two publications [73, 84] – with the latter publication including a larger sample size and longer duration of follow-up.

die meisten Studien legten Finanzierung offen

Two studies were conducted in the Netherlands [73, 84, 85], one in the USA and Europe [86], one across multiple European countries [87], and one in Germany and Austria [88]. Most studies reported their funding sources, except for two [73, 74, 88]; and one study explicitly stated that it was unfunded [84]. In two studies, funding was provided by pharmaceutical companies involved in ERT development, including Genzyme-Sanofi [85, 86]. Conflicts of interest were disclosed in all studies. In each study at least two authors reported potential conflicts; in two studies approximately half of the authors declared conflicts [87, 88].

Interessenskonflikte

Reported conflicts included honoraria, research grants, and consultancy agreements with pharmaceutical companies, including Genzyme-Sanofi and BioMarin.

früher ERT-Beginn, variable Dosierungen

Intervention regimens varied, ranging from 20 mg/kg every other week to 40 mg/kg weekly. Two studies [85, 87] stratified patient groups by dosage and reported outcomes accordingly. One study [84] also included data from 103 healthy children for myocardial deformation analysis, while its earlier report [73] used echocardiographic data from age- and sex-matched healthy controls. As these control groups were not designed to estimate intervention effects, this study is classified as prospective, observational, single arm by design.

Reported follow-up durations ranged from a median of 2.9 years [86] to 9.9 years [84]. One study [88] did not provide a mean follow-up, but reported individual patient follow-up durations, with a minimum of 5 years. Only one withdrawal was reported due to relocation outside the treatment center [84]. No other explicit losses to follow-up were reported.

Patient characteristics in prospective, observational single-arm studies

Pts.-Zahl klein, überwiegend CRIM-positiv

The number of patients varied across studies, ranging from eight [86] to 116 [87]. In the latter study, only 64 patients received a consistent ERT regimen; this subgroup was further stratified by treatment dosage, and outcomes were reported accordingly. All studies included patients diagnosed with the classic form of IOPD. The age of symptom onset and diagnosis were similar between the studies. All patient population groups started ERT until a median of 5 months of age. In all studies, CRIM positive patients represented the majority of the study population. Information on baseline respiratory support requirements was mostly not reported; where reported, no patients required support in one study [86], and only one patient required support in another [73].

Table 5-2: Study and patients' characteristics in single-arm studies investigating alglucosidase alfa in IOPD.

Author, year	Pfrimmer et al., 2024 [88]	Scheffers et al., 2023[a] [84]	van Capelle et al., 2018 [73]	Ditters et al., 2022 [87]	Poelman et al., 2020 [85]	Kishnani et al., 2006 [86]
Study design	Prospective, observational, multi-center study	Prospective, observational, single-center study		Prospective, observational, multi-center cohort study	Prospective, observational, single-center study	Prospective, phase II open-label clinical trial and extension study
Country	Austria and Germany	The Netherlands		France, Germany, Italy, the Netherlands	The Netherlands	USA and Europe
Funding/Conflict of interest (CoI)	Funding: NR 4/8 authors with CoI – consultancy, research grants (Sanofi-Aventis, Amicus, Avrobio, Nutricia, SOBI, Aeglea, and Recordati)	Funding: None 2/9 authors with CoI: consultancy, research grants (Sanofi/Genzyme, Amicus, Denali, and others, through agreements with Erasmus University Medical Center)	Funding: NR 2/9 authors with CoI: consultancy; a speaker's grant and travel fees (Shire and Genzyme)	Funding: Prinses Beatrix Spierfonds, Wishdom Foundation 7/15 authors with CoI: Sanofi-Genzyme, Biomarin, Amicus, Ultragenyx, Sarepta, Audentes, Spark, and Chiesi	Funding: Prinses Beatrix Spierfonds, ZonMW, Erasmus Universitair Medisch Centrum, Sarepta Therapeutics, Amicus Therapeutics, Ministry of Economic Affairs, Sanofi-Genzyme, CNPq (Brazil), Metakids Tex Net Sophia Foundation for Medical Research 3/8 authors with CoI: Sanofi-Genzyme, Amicus Therapeutics, Biomarin, Spark Therapeutics, Sarepta Therapeutics, GSK, Shire, and Audentes Therapeutics	Funding: General Clinical Research Centers Program, Division of Research Resources, National Institutes of Health, and Genzyme Corporation 3/13 authors with CoI: Genzyme support, consultancy
Description of the intervention (alglucosidase alfa dosage)	20 mg/kg every other week (n=12). 20 mg/kg every week (n=2). 40 mg/kg every week (n=1). Note: Three CRIM-positive patients (20%) received immunomodulation.	15 or 20 mg/kg every week; 20 mg/kg every other week or 40 mg/kg every week. After 2008, all but one patient received a dose of 40 mg/kg every week.	20 mg/kg every other week or 40 mg/kg every week	Standard-dosage group: 20 mg/kg every other week. Intermediate-dosage group: 20 mg/kg every week or 40 mg/kg every other week. High-dosage group: 40 mg/kg every week.	Standard-dosage group: 20 mg/kg every other week High-dosage group: 40 mg/kg/week for newly diagnosed patients. Some patients switched from standard to high dosage, and some received immunomodulation.	Initial phase of 12.7 months: 10 mg/kg every week. Extension phase up to 38.2 months: 10-20 mg/kg every week or 20 mg/kg every other week.
Comparator	/	Healthy children (N=103[b]	Healthy age- and sex-matched controls[b]	/	/	/
Number of patients n (female)	15 (6)	27 (16)	14 (7)	116 (58) 64 patients remained in the same ERT regimen: Standard-dosage group: 31 Intermediate-dosage group: 15 High-dosage group: n=18	18 (9) Standard-dosage group: 6 High-dosage group: 12	8 (4)

Author, year	Pfrimmer et al., 2024 [88]	Scheffers et al., 2023[a] [84]	van Capelle et al., 2018 [73]	Ditters et al., 2022 [87]	Poelman et al., 2020 [85]	Kishnani et al., 2006 [86]
Inclusion criteria	Classic IOPD patients – reduced GAA activity, pathogenic variants on both alleles of the GAA gene, HCM, and onset of clinical symptoms before the age of 6 months.	Classic IOPD patients – deficiency of α-glucosidase and/or two pathogenic GAA variants, hypertrophic cardiomyopathy. At least one echocardiogram available for analysis with ERT treatment.		Classic IOPD patients with disease onset and diagnosis ≤ 12 months, with hypertrophic cardiomyopathy, deficiency of α-glucosidase, or two pathogenic GAA variants, started ERT ≤ 1 year of age.	Classic IOPD patients– with symptoms of muscle weakness within 6 months after birth, hypertrophic cardiomyopathy, deficiency of GAA (<1% of the normal values), and GAA pathogenic variants – receiving ERT from the start.	IOPD patients with skin fibroblast GAA activity <1% of the normal mean, cardiomegaly and left ventricular hypertrophy.
Age of symptom onset (median (range), unless otherwise specified), months	1.0 (0.0-5.0)	NR		Mean 1.2 (IQR 0.1-2.7)	NR	1.6 (0.4–4.8)
Age at diagnosis (median (range), unless otherwise specified), months	4.5 (1.0-31.0)	3.22 (0.1-7.6)	NR	Mean 3.0 (IQR 1.5-4.6)	NR	4.6 (1.8–6.5)
Age of ERT onset (median (range), unless otherwise specified), months	5.0 (1.5-31.0)	3.53 (0.1-8.3)	2.7 (0.1-8.3)	Mean 3.3 (IQR 0.03-11.8)	Standard-dosage group: 1.5 (0.1-3.6) High-dosage group: 3.6 (0.3-5.9)	4.7 (2.7–14.6)
CRIM status (n of positive patients/n of total patients)	13/15	21/27	12/14	72/96 (controls N/A) 20 patients – CRIM status unknown.	13/18 (4 in the standard-dosage group and 9 in the high-dosage group)	6/8
Patients on ventilation (n)	NR	NR	1 (invasive)	NR	NR	None
Follow-up (median (range), unless otherwise specified), years	At least 5.0 years	9.9 (IQR: 7.5-16.3)	4.8 (1.1-13.9)	Mean 5.0 ± 4.78	Standard dosage group: 9.6 (0.6-12.6) High dosage group: 4.4 (3.0-8.3)	Mean 2.9
Loss to follow-up, n	None reported	1/27 (moved outside the treatment center)	None reported	None reported	None reported	None reported

Abbreviations: CRIM … cross-reactive immunologic material, ERT … enzyme replacement therapy, GAA … acid alpha-glucosidase, HCM … hypertrophic cardiomyopathy, IOPD … infantile-onset Pompe disease, IQR … interquartile range, n … number, NR … not reported.

Notes:

[a] *An extension study of van Capelle et al., 2018, with a larger sample size and a longer follow-up.*

[b] *Since this study does not involve a standard comparator group that would allow estimating the treatment effect, it is classified as an observational study without a comparator arm.*

Standard-dosage group– received 20 mg/kg of alglucosidase alfa every other week. Intermediate-dosage group – received 20 mg/kg per week– 40 mg/kg alglucosidase alfa every other week. High-dosage group – received 40 mg/kg alglucosidase alfa per week.

5.1.3 Results

nur Interventionsdaten zu LVMI/Motorik

It should be noted that for outcomes related to LVMI and motor function, the three controlled trials did not provide data for both intervention and control groups, but reported results for the intervention group only [80-83]. Consequently, these findings were considered together with those from the single-arm trials [85, 86, 89]. The results of long-term effectiveness of alglucosidase alfa in IOPD is presented in Table 5-3 for controlled studies and in Table 5-4 for single-arm studies.

Cardiac function

LVMI

LVMI nach ERT meist deutlich verbessert, teils normalisiert; EF nicht berichtet, RWT nur in einer kleinen Studie erhoben

LVMI generally improved after ERT, according to six studies [80, 82-86].

Among the three studies (n=46) [82, 83, 86], with up to three years of follow-up, two reported marked reductions in LVMI of more than 60% [83, 86]. It should be noted, however, that in one study, the timing of the endpoint assessment varied across patients, ranging from 52 weeks to an undefined duration [86]. The third study reported stabilization of LVMI, with mean z-scores remaining slightly above the normal range at follow-up [82]. In two studies ERT was administered with dosages ranging from 20 to 40 mg/kg every other week [82, 83], the third study [86] reported the use of 10 to 20 mg/kg weekly.

Two studies [80, 85] with approximately five years of follow-up (28 participants) reported sustained improvements in LVMI. One study [80], initially designed as a controlled trial but reporting only on newborn-screened IOPD patients, showed stable LVMI after treatment with the standard ERT regimen (20 mg/kg every other week), although endpoint values were presented only graphically. One dose-stratified study [85] compared patients receiving the standard (20 mg/kg every other week) with those receiving higher regimen (40 mg/kg every other week). While exact endpoint values were not provided, normalization of LVMI was observed in 83% of patients on the standard dose and 92% of those on the higher dose.

Finally, one prospective, single-arm trial (27 participants) reported that after a mean follow-up of 9.9 years with ERT (20 mg/kg every other week up to 40 mg/kg every week), LVMI decreased from 292.3 g/m^2 to 65.8 g/m^2 [84].

Ejection fraction

This outcome was not reported in any of the included studies.

Relative wall thickness

This outcome was assessed in one single-arm trial (n=14) [73]. After a mean follow-up of approximately 4 years and 10 months, with ERT administered either as 20 mg/kg every other week or 40 mg/kg every week, patients showed a decline, although the statistical significance of this finding was not reported [73].

Shortening fraction (SF)

SF über 10 Jahre stabil, vergleichbar zu gesunden Kindern

This outcome was evaluated in a single-arm trial of 23 patients [84]. Baseline values were reported, but endpoint values were not provided. After a mean follow-up of 9.9 years of ERT, shortening fraction was observed to remain stable and did not differ from that of a cohort of healthy children. Participants in this study received both standard and higher doses of alglucosidase alfa.

Motor function

QMFT

QMFT stark eingeschränkt, keine Verlaufsdaten

This outcome was reported in a single-arm study of 15 participants [88] with a minimum follow-up of five years. No baseline assessments were conducted; only endpoint results were available. At follow-up, the median raw QMFT score was 14, corresponding to 21.9% of the maximum possible score (range 0-73.4%). As baseline values were not collected, changes over time could not be determined.

Motor milestone achievement

motorische Meilensteine: heterogene Verläufe, teils Vorteil bei höherer Dosis, frühe Diagnose fördert Gehen

This outcome was assessed in one controlled trial involving 31 patients [81], with a follow-up between 1.2 and 2.7 years. The Kaplan-Meier curves showed that patients diagnosed through newborn screening and treated with the standard ERT dose achieved independent walking earlier than those diagnosed clinically ($p=0.009$) or untreated patients($p=0.006$). However, when all treated patients – those diagnosed either clinically or through newborn screening – were pooled, no statistically significant difference was observed between the treated and untreated groups ($p=0.22$).

Two studies with follow-up durations of up to three years (26 patients in total) – a single-arm trial [86] and a controlled trial that reported data only for the ERT group [82] – reported the proportions of participants achieving motor function milestones by study end. Although both studies evaluated the same outcomes, their effect sizes were not pooled due to differences in follow-up duration (27.6 vs. 35.2 months). Both studies demonstrated heterogeneous responses to treatment: some patients achieved independent walking or sitting without support, while others showed only minimal motor gains.

Three single-arm studies (69 patients) [85, 87, 88] evaluated motor milestone achievement over follow-up periods of up to five years. One dose-stratified study [87] reported no significant difference in walking ability between high- and standard-dose groups, or between standard- and intermediate-dose groups (HR 1.71 (95% CI: 0.74-3.98), and 0.97 (95% CI: 0.35-2.07)). In contrast, another dose-stratified study [85] observed a substantially higher proportion of walkers in the high-dose group compared with the standard-dose group (83% vs. 17%, p not reported). The third dose-stratified study [88] found that loss of motor functions occurred only in patients on standard or intermediate regimens, not in those receiving high-dose therapy.

6MWD

6MWD nur einmalig erhoben, keine Veränderung beurteilbar

This outcome was reported in one prospective, single-arm study including 15 participants. As no baseline assessment was available for this outcome, changes in 6MWD following treatment with alglucosidase alfa could not be determined [88].

Cognitive function

BSID II score

BSID-II: tendenziell bessere Entwicklung unter Hochdosis

This outcome was reported in one single-arm dose-stratified study including 18 participants. The study found higher median BSID-II age-equivalent scores at 36 months of age in patients receiving a high dose of alglucosidase alfa (40 mg/kg every week) compared with those receiving the standard dose (20 mg/kg every other week). Children in the high-dose group had a median developmental score equivalent to 30 months of age, whereas those in the standard-dose group had a median score equivalent to 20 months [85].

BSID II/CDIIT assessments

Kognition insgesamt häufig unter Norm, teils Verzögerung

One controlled trial reported this outcome, but only for the ERT group identified through newborn screening (n=10). At five-year follow-up, scores were slightly lower than those observed at year one (approximately 90), although values were presented only graphically [80].

IQ assessment with CFT

In one prospective single-arm study (15 participants) [88], no baseline assessments were performed. After at least five years of follow-up, 36.4% of the tested children (n=11) had an IQ value within the normal range, while the remainder showed either mild cognitive delay or intellectual disability.

Respiratory function

Dependence on ventilation (invasive or non-invasive)

Beatmung: ERT senkt Risiko für (invasive) Ventilation deutlich

One prospective controlled study (including 18 participants) showed that IOPD patients treated with either the standard ERT regimen (20 mg/kg every other week) or a higher regimen (40 mg/kg every other week) had, after a median of 2.3 years, a significantly lower risk of requiring invasive ventilation, any type of ventilation, or death compared with untreated patients (HR 0.09 (95% CI: 0.04-0.22), and 0.13 (95% CI: 0.06-0.29), respectively) [82].

Two single-arm studies including 29 patients [73, 88] reported respiratory outcomes up to 4.8 years of follow-up. One study [88] did not provide baseline respiratory status, only the follow-up data, which does not allow drawing conclusions about the potential impact of ERT on this outcome. The second study [73] reported an increase in the number of patients requiring ventilatory support, from one patient at baseline to four at the last assessment, out of 14 participants.

Time spent on ventilation

This outcome was not assessed in any of the studies.

Survival

Overall survival

Gesamtüberleben klar besser mit ERT, besonders bei früher Diagnose und Hochdosis

Three prospective controlled trials [80, 82, 86] consistently demonstrated improved overall survival in IOPD patients treated with ERT compared with untreated controls. In studies with up to 2.3 years of follow-up [82, 83], ERT was associated with a lower risk of death. A longer-term follow-up study of median five years confirmed these findings, showing superior survival among patients diagnosed through newborn screening compared with both untreated patients and those diagnosed clinically [80].

Two single-arm dose-stratified trials evaluated survival in classic IOPD patients treated with ERT for 3 to 5 years. One study [87] reported significantly improved survival in the high-dose group compared with the standard-dose group (HR 0.17, p=0.02), while an intermediate-dose group showed a non-significant reduction in risk (HR 0.44, p=0.19). In the second study [85], survival rates were 26% higher in the high-dose group compared with the standard-dose group.

Ventilator-free survival

beatmungsfreie Zeit unter ERT deutlich verlängert, Hochdosis meist im Vorteil

Controlled trials consistently demonstrated that ERT markedly improved ventilator-free survival in classic IOPD. In two studies with up to 2.3 years of follow-up [82, 83], 20-40 mg/kg every other week of ERT substantially reduced the risk of invasive ventilation or death, with one trial also suggesting a non-significant reduction for overall ventilation, compared to untreated patients. Another study [80] further showed that patients identified by newborn screening and treated early had significantly higher ventilator-free survival than clinically diagnosed or untreated patients, although exact values were not reported.

One dose-stratified single-arm study reported significantly higher ventilator-free survival in the high-dose group compared with the standard-dose group after 5-years of follow-up, although the analysis did not account for the time-varying nature of ERT [85].

Quality of life

SF-36

Lebensqualität: körperlich stark eingeschränkt, mentale Bereiche besser

One single-arm trial including 14 participants [88] reported only endpoint results, which does not allow conclusions about the effect of ERT on this outcome. Findings showed that physical health summary scores were below normal values in 92.9% of participants. The largest negative deviation (–90.2 points) was observed in the "Physical functioning" domain, while the largest positive deviation was observed in the "Mental well-being" domain.

Table 5-3: Effectiveness results for alglucosidase alfa in IOPD patients in controlled studies.

Author, year	Chien et al., 2015 [80]	Chien et al., 2009 [81]	Kishnani et al., 2009 [82]	Nicolino et al., 2009 [83]
Effectiveness Outcomes				
Cardiac function				
LVMI/LVMI z-score	Intervention (NBS) group: Baseline: median 122 (range 70-186 g/m^2) 5.25-year endpoint: graphically presented. In most patients, LVMI resolved and remained stable. [a]	NR	Intervention group: Baseline mean z-score: 7.1. 2.3-year endpoint: graphically presented. At the end of the extension study, mean LVMI z-scores remained stable at slightly above the upper limit of the normal range (2.0). [a]	Intervention group Baseline: mean 193.8 ± 98.5 g/m^2 Baseline: mean z-score 6.5 ± 2.6 2-year endpoint mean: 53.1 ± 13.9 g/m^2 2-year endpoint mean z-score: 0.9 ± 0.8 Mean change from baseline: -62.7% for LVMI and -5.3% for LVMI z-score.[a]
Ejection fraction	NR	NR	NR	NR
Relative wall thickness	NR	NR	NR	NR
Shortening fraction	NR	NR	NR	NR
Motor function				
QMFT	NR	NR	NR	NR
Achievement of motor function milestones	NR	FU between 1.2–2.7 years Independent walking – earlier in the NBS group vs. both untreated (p=0.009) and treated clinical cohorts (p=0.006). The treated and untreated clinical groups – no difference (p=0.22).	2.3-year endpoint Minimal gains: 7/18 (38.89%) Walking: 7/18 (38.89%) Sitting: 4/18 (22.22%)[a]	NR
6MWD	NR	NR	NR	NR
Cognitive function				
BSID-II/CDIIT	1-year endpoint: normal scores (nearly 90) 2-year endpoint: slight impairment 5-year endpoint: improvement similar to year 1 (graphically presented).	NR	NR	NR
BSID-II	NR	NR	NR	NR
CFR (1R and 20R)	NR	NR	NR	NR
Respiratory status				
Dependence on non-invasive or tracheostomy-assisted ventilation	NR	NR	2.3-year endpoint HR for invasive ventilation or death: 0.09 (95% CI: 0.04-0.22) HR for any type of ventilation or death: 0.13 (95% CI: 0.06-0.29). [b]	NR
Time spent on ventilation	NR	NR	NR	NR

Author, year	Chien et al., 2015 [80]	Chien et al., 2009 [81]	Kishnani et al., 2009 [82]	Nicolino et al., 2009 [83]
Survival				
Overall survival	5.25-year endpoint NBS patients compared with untreated controls: higher, p=0.01 NBS patients compared with clinically diagnosed patients: higher, p=0.028 [c] Results presented with a KM curve.	Data extracted from the report of Chien et al., 2015, because of the larger sample size and longer follow-up.	Intervention group Survival rate at 24 months: 94.4% (95% CI: 83.9%-100%) Survival rate at age 36 months: 72% (95% CI: 47.9-96.0%). Untreated historical control group Survival rate at 24 and 36 months: 1.9% (95% CI: 0-5.5%).	2-year endpoint Intervention group Survival rate: 71.1% (95% CI: 51.6%, 90.6%). Control group Survival rate: 3% (95% CI: 6.5%, 46.1%) Survival HR 0.209 (95% CI: 0.083-0.524), p=0.0009 [b]
Ventilator-free survival	5.25-year endpoint NBS patients compared with both untreated controls and clinically diagnosed patients – higher rates, p<0.01 [c]	Data extracted from the report of Chien et al., 2015, because of the larger sample size and longer follow-up.	Survival rate at 24 months: 66.7% (95% CI: 44.9- 88.4%) Survival rate at 36 months: 49.4% (95% CI: 26.0%-72.8%) 2.3-year endpoint HR for the risk of invasive ventilation or death: 0.09 (95% CI: 0.04-0.22) 2.3-year endpoint HR for any type of ventilation or death: 0.13 (95% CI: 0.06-0.29) [b] There was no difference between the dose groups.	2-year endpoint HR for invasive ventilator-free survival: 0.421 (0.202-0.876), p=0.0207. HR for any ventilator-free survival: 0.533 (95% CI: 0.247-1.150), p=0.1088 [b]
Quality of life				
NA	NR	NR	NR	NR

Abbreviations: 6MWD … 6-minute walking distance, BSID-II … Bayley Scales of Infant Development II, CDIIS … Comprehensive Developmental Inventory for Infants and Toddlers, CFT (1R and 20R) … Culture Fair Intelligence Test 1-R and 20-R, CI … confidence interval, HR … hazard ratio, KM … Kaplan-Maier, LVMI … left ventricular mass index, NA … not applicable, NBS … newborn screening, NR … not reported, QMFT … the Quick Motor Function Test.

Notes:

[a] *Only pre- and post-intervention values are available for this outcome; no between-group comparisons were conducted.*

[b] *The HRs were calculated by comparing outcomes between the treatment and no treatment groups.*

[c] *Exact results presented in a KM curve.*

Table 5-4: Effectiveness results for alglucosidase alfa in IOPD patients in single-arm studies.

Author, year	Pfrimmer et al., 2024 [88]	Scheffers et al., 2023 [84]	Ditters et al., 2022 [87]	Poelman et al., 2020 [85]	van Capelle et al., 2018 [73]	Kishnani et al., 2006 [86]
Effectiveness Outcomes						
Cardiac function						
LVMI	NR	Baseline: mean 292.3 g/m^2 (95% CI: 202.8-381.8). 9.9-year endpoint: within the normal range (65.8 g/m^2).	NR	Baseline median z-score Standard dosage group: 6.15 (2.4-8.6) High dosage group: 7.1 (3.0-13.7) 5-year end-point z-score: Normalization in 83% (standard dosage group) vs 92% (high-dosage group)	Data were extracted from the report of Scheffer et al., 2023, because of the larger sample size and longer follow-up.	Baseline: mean 266.9 ± 64.4 g/m^2 2.9-year endpoint: Long-term endpoint data not available Mean change from baseline to week 52 or the last assessment of -68.7%: all 6 patients showed decreases in LVMI (significantly lower than at baseline)
Ejection fraction	NR	NR	NR	NR	NR	NR
Relative wall thickness	NR	NR	NR	NR	Baseline: median 0.9 (0.4-3.1) Endpoint: median 0.4 (0.3-0.7)	NR
Shortening fraction	NR	Baseline: mean 36.4% (95% CI: 29.9-43). 9.9-year endpoint: N/A. Shortening fraction remained stable and unchanged compared to healthy controls (+0.16%/yr, p=0.464, 35.5 vs 39.3%).	NR	NR	Data were extracted from the report of Scheffer et al., 2023, because of the larger sample size and longer follow-up.	NR
Motor function						
QMFT	Minimum 5-year endpoint: median 14 (21.9%, range 0–73.4%)	NR	NR	NR	NR	NR
Achievement of motor function milestones	Minimum 5-year endpoint Independent walking by age 2: 47% Follow-up Long-term walking: 5/15 (33.3%) Sitting without support: 6/15 (40%) Tetraplegic: 5/15 (27%) Motor milestone loss occurred only in standard/intermediate dosage groups, not in the high-dosage group.	NR	4.8-year endpoint HR for walking for high vs. standard dosage group: 1.71 (95% CI: 0.74-3.98), p=0.21. HR for walking for standard vs intermediate dosage group 0.97 (95% CI: 0.35-2.07), p=0.96[a]	5-year endpoint Walking achieved by 67% in the standard- and 92% in the high-dosage group. By age 3, 33% vs. 92% maintained walking (p=0.02), and by study end, 17% vs. 83% remained walkers in the standard- vs. high-dosage groups.	NR	2.9-year endpoint: Walking: 3/6 (50%) Sitting without support: 2/6 (33.3%) Minimal gains: 1/6 (16.67%)

Author, year	Pfrimmer et al., 2024 [88]	Scheffers et al., 2023 [84]	Ditters et al., 2022 [87]	Poelman et al., 2020 [85]	van Capelle et al., 2018 [73]	Kishnani et al., 2006 [86]
6MWD (median, range), m	Minimum 5-year endpoint: 262.5 (200-373)[b]	NR	NR	NR	NR	NR
Cognitive function						
BSID-II/CDIIT	NR	NR	NR	NR	NR	NR
BSID-II	NR	NR	NR	Assessment at 36 months High-dosage group vs. standard-dosage group: higher median BSID-II age-equivalent score (30 vs. 20 months) Only 50% in the standard-dosage group were testable vs. 92% in the high-dosage group [c]	NR	NR
CFT (1R and 20R)	Minimum 5-year endpoint assessment Normal IQ: 4/11 (36.4%) Mild delay: 1/11 (9.1%) Intellectual disability: 6/11 (54.5%) Three (20%) couldn't complete testing, and one (6.7%) ended early due to exhaustion.	NR	NR	NR	NR	NR
Respiratory status						
Dependence on non-invasive or tracheostomy-assisted ventilation	Minimum 5-year endpoint Non-invasive ventilation during sleep: 2/15 (13.3%) Invasive (via tracheostomy): 5/15 (33.3%)[b]	NR	NR	NR	Baseline: n=1 Endpoint: n=4	NR
Time spent on ventilation	NR	NR	NR	NR	NR	NR
Survival						
Overall survival	NR	NR	4.8-year endpoint HR for high vs standard dosage group: 0.17 (95% CI: 0.04-0.76), p=0.02 HR for intermediate vs standard dosage group: 0.44 (95% CI: 0.13-1.51), p=0.19	5-year endpoint Standard dosage group: 66% High dosage group: 92% p=0.25 [c]	Data extracted from the report of Scheffer et al., 2023, because of the larger sample size and longer follow-up.	NR
Ventilator-free survival	NR	NR	NR	5-year endpoint Standard dosage group: 50% High dosage group: 92% Mean difference: p=0.08 [c]	NR	NR

Author, year	Pfrimmer et al., 2024 [88]	Scheffers et al., 2023 [84]	Ditters et al., 2022 [87]	Poelman et al., 2020 [85]	van Capelle et al., 2018 [73]	Kishnani et al., 2006 [86]
Quality of life						
SF-36	Minimum 5-year endpoint Physical health sum scores below normal: 13/14 patients (92.9%) Largest negative deviation: –90.2 points in "Physical functioning" subscale Largest positive deviation: in "Mental well-being" subscale	NR	NR	NR	NR	NR

Abbreviations: 6MWD … 6-minute walking distance, BSID-II … Bayley Scales of Infant Development II, CDIIT … Comprehensive Developmental Inventory for Infants and Toddlers, CFT (1R and 20R) … Culture Fair Intelligence Test 1-R and 20-R, CI … confidence interval, ERT … enzyme replacement therapy, HR … hazard ratio, IOPD … infantile-onset Pompe disease, LVMI … left ventricular mass index, NR … not reported, QMFT … the Quick Motor Function Test, SF-36 … Short-Form 36-Health Survey.

Notes:

[a] *Results for follow-up longer than 2y available for n=86.*

[b] *No baseline data available.*

[c] *Outcome was reported by initial dose group, without accounting for 4 patients who switched from standard to higher dose.*

5.2 Avalglucosidase-alfa in infantile-onset Pompe disease

5.2.1 Description of Outcomes

The list of critical outcomes for evaluating long-term effectiveness in IOPD is presented in chapter 5.1.1.

5.2.2 Included studies

prospektive, multizentrische, einarmige Studie zu Avalglucosidase alfa bei IOPD mit 1,86 Jahren Follow-up

One prospective study reporting at least one long-term efficacy outcome of avalglucosidase alfa treatment in patients with IOPD was included in this systematic review. Although the study had a shorter follow-up than specified in the PICO (1.86 years versus 2 years), it was included because it was the only prospective study identified reporting the outcomes of interest [90].

Characteristics of the prospective, observational single-arm study

The characteristics of the identified prospective single-arm trial [90] are summarized in Table 5-5. This multicenter study was conducted in the USA, United Kingdom, France, Japan, and Taiwan. It was funded by Sanofi, and 15 of the 18 authors declared at least one conflict of interest, including employment or stock ownership in Sanofi, as well as associations with other pharmaceutical companies. The intervention was avalglucosidase alfa administered either at the standard dose (20 mg/kg every other week) or the high dose (40 mg/kg every other week). The study represents the extension phase of a previously published RCT [91]. Three cohorts were included: cohort 1 received the standard dose, cohort 2 received the high dose, and cohort 3 was divided into two groups – one initiated on variable doses of alglucosidase alfa for the first 25 weeks before switching to high-dose avalglucosidase alfa, and the other started directly on the high-dose regimen. As all three cohorts received either the standard or high dose of avalglucosidase alfa without a comparator arm during the extension phase, the study is classified as a prospective single-arm trial. No patients were lost to follow-up.

Patient characteristics in the prospective, observational single-arm study

IOPD-Kinder mit früher Kardiomyopathie, meist CRIM-positiv

trotz stabiler Alglucosidase-Vor-behandlung mit klinischer Verschlechterung

The study enrolled patients with a confirmed diagnosis of IOPD (based on GAA deficiency), who were younger than 18 years and had cardiomyopathy onset before 1 year of age and had been on stable alglucosidase alfa therapy for at least 6 months prior to enrollment. Eligibility criteria differed by cohort: for cohorts 1 and 2, patients were required to show clinical decline in at least one IOPD-related domain (respiratory, motor, or cardiac), whereas for cohort 3, inclusion required either a suboptimal response in at least one domain or the development of new ptosis, confirmed on at least two IOPD-related assessments.

The age of symptom onset ranged from 0.0 months (0.0-0.9) in the avalglucosidase alfa arm of cohort 3 to 4.40 months (0.1-6.5) in cohort 2. Age at diagnosis varied from 1.10 months (0.3-5.5) in cohort 1 to 4.47 months (0.3-8.7) in cohort 2, while age at ERT initiation ranged from 1.94 months (0.2-5.7) in the avalglucosidase alfa arm of cohort 3 to 4.63 months (0.5-10.4) in cohort 2. Most patients were CRIM-positive, with exceptions in two of six patients in

cohort 2 and one of six patients in the alglucosidase alfa arm of cohort 3. Overall, five of 23 patients (21.7%) required invasive ventilation.

Table 5-5: Study and patients' characteristics in the single-arm study investigating avalglucosidase alfa in IOPD.

Author, year	Kronn et al., 2025 [90]
Study design	Extension study of a phase 2, open-label, ascending-dose, multicenter, 3-cohort study
Country	United States (3 sites); United Kingdom, France, Japan (2 sites each) and Taiwan (1 site)
Funding/Conflict of interest (CoI)	Funding: Sanofi 15/18 authors with CoI: consultancy, grants, employment at Sanofi, owning stock options at Sanofi. Other companies mentioned: BioMarin, Takeda, Regenxbio, Amicus Therapeutics, Asklepios BioPharmaceutical, Bayer, Pfizer, Immedica
Description of the intervention (avalglucosidase alfa dosage)	Cohort 1: 20 mg/kg every other week Cohort 2: 40 mg/kg every other week Cohort 3 (avalglucosidase arm): 40 mg/kg every other week Cohort 3 (alglucosidase arm): during the first 25 weeks received alglucosidase alfa 20 mg/kg every other week – 40 mg/kg weekly; 25-97 weeks: avalglucosidase alfa 40 mg/kg every other week
Comparator	/
Number of patients (n female)	22 (10) Cohort 1: 5 (1) Cohort 2: 5 (2) Cohort 3: 11 (7); avalglucosidase arm 5 (3), aglucosidase arm 6 (4)
Inclusion criteria	IOPD diagnosis (GAA deficiency), age <18, cardiomyopathy onset <1 year old, stable alglucosidase alfa ≥6 months before enrolment. Cohorts 1 & 2: Clinical decline in ≥1 domain (respiratory, motor, cardiac), IOPD-related. Cohort 3: Suboptimal response in ≥1 domain or new ptosis (confirmed by ≥2 assessments), IOPD-related.
Age of symptom onset (median (range)), months	Cohort 1: 0.34 (0.0-4.4) Cohort 2: 4.40 (0.1-6.5) Cohort 3: 0.0 (0.0-0.9) (avalglucosidase arm) and 1.79 (0.0-3.7) (alglucosidase arm) [a]
Age at diagnosis (median (range)), months	Cohort 1: 1.10 (0.3-5.5) Cohort 2: 4.47 (0.3-8.7) Cohort 3: 1.84 (0.0-3.5) (avalglucosidase arm) and 3.45 (0.3-15.9) (alglucosidase arm) [a]
Age of ERT onset (median (range)), months	Cohort 1: 2.41 (0.4-5.7) Cohort 2: 4.63 (0.5-10.4) Cohort 3: 1.94 (0.2-5.7) (avalglucosidase arm) and 4.44 (0.3-19.4) (alglucosidase arm) [a]
CRIM status (n of positive patients/ n of total patients)	Cohort 1: 6/6 Cohort 2: 4/6 Cohort 3: 10/11 (avalglucosidase arm 5/5; alglucosidase arm: 5/6) [a]
Patients on ventilation (n, %)	5/23 (21.74%) (invasive)
Follow-up (median, range, unless otherwise specified), months	1.86 years[b]
Loss to follow-up, n	None reported

Abbreviations: CoI … Conflict of Interest, CRIM … cross-reactive immunological material, ERT … enzyme replacement therapy, GAA … acid alpha-glucosidase enzyme, IOPD … infantile-onset Pompe disease.

Notes:

[a] *The characteristics correspond to the baseline characteristics of the study population at the beginning of the study.*

[b] *The follow-up was 7 weeks less than the proposed follow-up of two years.*

5.2.3 Results

All results regarding long-term effectiveness of avalglucosidase alfa in patients with IOPD are presented in Table 5-6.

Cardiac function

LVMI

At baseline, all patients had values within the normal range, except for one patient in cohort 2; however, this patient's LVMI had normalized by week 25. At the end of the study, all patients had LVMI within the normal range [90].

LVMI normal, geringe QMFT-Zunahme, 6MWD unter Hochdosis stabil, übrige Endpunkte nicht erhoben

Ejection fraction

This outcome was not assessed in the study.

Relative wall thickness

This outcome was not assessed in the study.

Shortening fraction

This outcome was not assessed in the study.

Motor function

QMFT

The smallest change from baseline was observed in cohort 1 which received the standard dose of avalglucosidase alfa (20 mg/kg every other week +0.50 ± 6.89), followed by cohort 2 which received the high dose (40 mg/kg every other week; +2.33 ± 8.74). The largest changes from baseline were observed in cohort 3, with +4.00 ± 6.48 in the avalglucosidase alfa arm and +7.17 ± 7.36 in the alglucosidase alfa arm [90].

Achievement of motor milestones

This outcome was not assessed in in the study.

6MWD

Individual patient data were graphically presented for nine of the 23 enrolled patients who were eligible for this test. By the end of the study, two patients in cohort 1 showed a decline despite dose escalation, while a third patient did not meet the functional criteria for 6MWD assessment at week 13, although baseline data were available. In contrast, all six patients in cohorts 2 and 3 who received the higher ERT dose demonstrated stabilization [90].

Cognitive function

This outcome was not assessed in the study.

Respiratory function

Dependence on non-invasive or tracheostomy-assisted ventilation

This outcome was not assessed in the study.

Time spent on ventilation

This outcome was not assessed in the study.

Survival

Overall survival

This outcome was not reported in the included study.

Ventilator-free survival

This outcome was not assessed in the study.

Quality of life outcomes

This outcome was not assessed in the study.

Table 5-6: Effectiveness results for avalglucosidase alfa in IOPD in the single-arm study.

Author, year	Kronn et al., 2025 [90]
Effectiveness Outcomes	
Cardiac function	
LVMI	1.86-year endpoint Baseline: all patients with normal values, except 1 in cohort 2, which normalized at week 25. Endpoint: all patients within normal values.
Ejection fraction	NR
Relative wall thickness	NR
Shortening fraction	NR
Motor function	
QMFT (mean change from baseline, SD)	1.86-year endpoint Cohort 1: +0.50 (6.89) Cohort 2: +2.33 (8.74) Cohort 3 (avalglucosidase alfa arm): +4.00 (6.48) Cohort 3 (alglucosidase alfa arm): +7.17 (7.36)
Achievement of motor function milestones	NR
6MWD % predicted	1.86-year endpoint Note: only graphical, individual patient data available for 8 ambulatory children ≥6 years of age in all three cohorts Endpoint (Cohort 1): decline (2/2), even when the avalglucosidase alfa dose was increased Endpoint (Cohorts 2 and 3): stabilisation (6/6)
Cognitive function	
NA	NR
Respiratory status	
Dependence on non-invasive or tracheostomy-assisted ventilation	NR
Time spent on ventilation	NR
Survival	
Overall survival	NR
Ventilator-free survival	NR
Quality of life	
NA	NR

Abbreviations: 6MWD% … 6-minute walking distance percentage predicted, IOPD … infantile-onset Pompe disease, LVMI … left ventricular mass index, NA … not applicable, NR … not reported, QMFT … the Quick Motor Function Test, SD … standard deviation.

5.3 Alglucosidase-alfa in late-onset Pompe disease

5.3.1 Description of Outcomes

Motor Function

Motor function was assessed using the Quick Motor Function Test (QMFT) and the 6-minute walk distance (6MWD), as described in chapter 5.1.1.

LVMI normal, leichte Motorikverbesserung, kaum weitere Langzeitendpunkte

Respiratory function

Respiratory status in patients with LOPD was assessed with the following parameters:

- **Forced vital capacity (FVC):** measured by spirometry, in sitting and/or supine position. Results were expressed either as a percentage of the predicted normal value or in liters (L) [92].
- **Forced expiratory volume in 1 second (FEV1):** assessed by standard spirometry in the standing position [93].
- **Dependence on non-invasive or tracheostomy-assisted ventilation:** this outcome is described in chapter 5.1.1.
- **Duration of time spent on ventilation:** this outcome is described in chapter 5.1.1.

Survival outcomes

Survival is reported as:

- **Overall survival:** this outcome is described in chapter 5.1.1.
- **Ventilator-free survival:** this outcome is described in chapter 5.1.1.

Quality of life

Quality of life is assessed with:

- **The Short-Form 36-Health Survey (SF-36):** this outcome is described in chapter 5.1.1.
- **Rotterdam Handicap Scale (RHS):** a scale used to assess patients' level of participation, defined as involvement in life situations. The scale covers nine domains, including mobility, domestic tasks and leisure activities (assessed indoors and outdoors), kitchen tasks, transportation (driving a car, using public transport, cycling), and work/study. Scores range from 1 (unable to fulfil the task or activity) to 4 (complete fulfilment), with a score of 0 assigned if an item is not applicable. The total score is calculated by summing the item scores, dividing by the number of applicable items, and multiplying the result by nine [94].
- **The Rasch-built Pompe-specific activity scale (R-PAct):** a patient-based interval scale using Rasch analysis, specifically designed to quantify the impact of Pompe disease on patients' ability to participate in daily life and social activities. The scale can detect limitations in activities and social participation across the full spectrum of Pompe disease severity [95].

5.3.2 Included studies

17 prospektive Studien, eine kontrolliert, übrige einarmig

A total of 17 prospective studies (reported in 18 publications) reported at least one of the long-term efficacy outcomes of alglucosidase alfa treatment in patients with LOPD. One study [96] employed a controlled design (Table 5-7), while the remaining studies were classified as single-arm studies (Table 5-8 and Table 5-9). Nine publications [93, 96-103] were identified from a previously published systematic review, four [104-107] were retrieved through the updated systematic search, and five [108-112]were identified via manual search.

Characteristics of the prospective, observational controlled study

Italienische multizentrische kontrollierte Studie

This Italian multi-center study did not report the funding source, and none of the authors declared any conflict of interest. The intervention group received the standard alglucosidase alfa dose (20 mg/kg every other week, n=8), in combination with home mechanical ventilation, as all patients were ventilatory dependent. The comparator group received home mechanical ventilation alone without ERT (n=6). The duration of follow-up differed between groups, with approximately 3 years for the intervention group and 4.4 years for the control group. No losses to follow-up were reported.

Patient characteristics in the prospective, observational controlled study

ähnliches Ausgangsprofil beider Gruppen

Baseline characteristics were generally comparable between groups. Symptom onset occurred in the late 20s to early 30s, with diagnosis typically in the late 30s to early 40s. Patients in the intervention group initiated ERT at a mean age of approximately 51 years, corresponding to study enrolment. All patients required ventilatory support, with invasive ventilation being more common in the control group (67%) than in the intervention group (25%). The use of walking aids was infrequent, though slightly higher in controls (33%) compared with the intervention group (13%).

Table 5-7: Study and patients' characteristics of a controlled study investigating the effects of alglucosidase alfa in LOPD

Author, year	Vianello et al., 2013 [96]
Study design	Prospective, observational, multicenter study
Country	Italy
Funding/Conflict of interest (CoI)	Funding: NR CoI: None
Description of the intervention (alglucosidase alfa dosage)	20 mg/kg every other week + HMV
Comparator	Historical untreated group on HMV alone
Number of patients, n (female)	Intervention group: 8 (3) Comparison group: 6 (5)
Inclusion criteria	Diagnosis based on GAA deficiency (blood, fibroblasts, or muscle) and confirmed by molecular analysis, especially in highly ventilator-dependent patients.
Age of symptom onset (mean ± SD), years	Intervention group: 33.5 ± 12 Control group: 28.2 ± 15.9
Age at diagnosis (mean ± SD), years	Intervention group: 42.9 ± 14 Control group: 39.6 ± 18
Age of ERT onset (mean ± SD), years	Intervention group: 51.5 ± 2.2[a]

Author, year	Vianello et al., 2013 [96]
Patients on ventilation (n)	Intervention group: 8/8 – 2 invasive (25%), 6 non-invasive (75%) Control group: 6/6 – 4 invasive (66.7%), 2 non-invasive (33.3%)
Wheelchair/walking device use (n, %)	Intervention group: 1/8 (12.5%) Control group: 2/6 (33.3%)
Follow-up (mean), years	Intervention group: ~3 Control group: ~ 4.4
Loss to follow-up, n	None reported

Abbreviations: CoI … conflict of interest, ERT … enzyme replacement therapy, GAA … acid alpha-glucosidase, HMV … home mechanical ventilation, LOPD … late-onset Pompe disease, NR … not reported, SD … standard deviation.

Note:

[a] *The age of study entry; however, the patients started ERT upon enrollment.*

Characteristics of the prospective, observational single-arm studies

prospektive LOPD-Einarmstudien, teils Extensions- und QoL-Surveys, vereinzelt mit unbehandelten Verlaufskohorten

The remaining 16 studies were single-arm studies [93, 97, 99-112] (Table 5-8 and Table 5-9). One study [102] was an extension of a prior RCT [113], while another was a longitudinal survey assessing quality of life in LOPD patients receiving ERT through annual online questionnaires [99]. Two studies [99, 103] included both treated and untreated patients, using natural history data primarily for survival analyses; as these were not conventional controlled trials, they were also categorized as single-arm studies. In addition, two publications [98, 100] reported interim results from the same ongoing study, with the earlier report contributing efficacy data and the later focusing on safety outcomes.

Three studies were conducted in Italy [93, 97, 106], two in the Netherlands [98, 100, 103], one of each in Germany [101], Japan [109], Spain [105], France [107], Belgium [104], and the remaining were conducted across multiple European and US countries.

Funding sources were variably reported: one study did not report its funding source [97], one reported no funding [104], three reported Genzyme-Sanofi as the sole funder [102, 107, 109], and the remaining studies received funding from multiple sources. Two studies did not report information on conflicts of interest [93, 107], two declared none [104, 106], one study reported it for all authors [110], and the remaining studies reported conflicts of interest for several authors.

meist Standarddosis 20 mg/kg alle 2 Wochen, sehr unterschiedliche Fallzahlen und Follow-up bis zu 12 Jahren, selten klar berichtete Verluste

In most studies patients received the standard alglucosidase alfa dose (20 mg/g every other week) [93, 97, 100-104, 106-109, 111]. The number of patients varied from 12 [104] to 396 [110], while the follow-up duration ranged from two years [104] to a median of 12 years [106]. Most studies did not report any loss to follow-up, while one study [102] reported that 49.1% of data were not available for the last endpoint assessment [102]. The reason for this high number was not due to dropouts or losses to follow-up, but because the study design restricted extended follow-up to US sites only.

Patient characteristics in the prospective, observational single-arm studies

Überwiegend juvenile/adulte LOPD, breites Spektrum bei Symptombeginn, Diagnose- und ERT-Startalter, teils beatmungs- oder gehilfenpflichtige Pts.

All studies included patients diagnosed with LOPD, with the exception of one post-marketing surveillance study [109], that enrolled all Pompe disease patients receiving the ERT of interest, including those with IOPD. For this review, only data from juvenile- and adult-onset LOPD patients were included. One study [93] reported outcomes separately for juvenile- and adult-onset LOPD patients.

Three studies included LOPD patients at least eight years of age [93, 99, 102], three studies included only adult patients (minimum 18 years of age) [98, 100, 103, 112], while the rest of the studies did not specify age eligibility.

The age of symptom onset varied from a median of 2.5 (0.5-13) years [111], to a mean 36.49 (SD 14.48) [107]. Among the studies that report the age when the diagnosis was made it ranged from a mean of 2.8 (SD 1.4) years in juvenile-onset LOPD patients [93], to a median of 41.3 (1.4-72.2) years [98]. ERT onset time varied from 11.9 (1.1-16.4) years [111] to 53 (28-82) years [106]. All studies included some patients who were dependent on ventilatory support and/or walking aids, although several studies did not report this information.

Table 5-8: Study description and patients' characteristics of single-arm studies investigating the effects of alglucosidase alfa in LOPD (part 1).

Author, year	Bembi et al., 2010 [93]	Angelini et al., 2012 [97]	de Vries et al., 2012 [100]	de Vries et al., 2017 [98]	Regnery et al., 2012 [101]	van der Ploeg et al., 2012 [102]	Güngör et al., 2013 [112]	Gungor et al., 2016 [99]	Kuperus et al., 2017 [103]
Study design	Prospective, observational, multi-center, open-label study	Prospective, observational, multi-center, open-label study	Prospective, observational, single-center, open-label study		Prospective, observational, multi-center, open-label study	Prospective, observational, multi-center, open-label study	Prospective, observational, multi-center, open-label study	Ongoing prospective observational survey-type study	Prospective, observational, single-center, open-label study
Country	Italy	Italy	The Netherlands		Germany	US, Australia, Canada, France, The Netherlands	Multiple countries (UK, US, Netherlands, Germany, others)	Multiple countries (UK, US, Netherlands, Germany, others)	The Netherlands
Funding/Conflict of interest (CoI)	Funding: Agenzia Italiana del Farmaco; I.R.C.C.S. Burlo Garofolo-Trieste; the Istituto Superiore di Sanità, Rome; the Italian Association of Glycogenosis CoI: NR	Funding: NR. 6/21 authors with CoI: advisory board membership or financial support for scientific meetings, Genzyme	Funding: Erasmus MC Revolving Fund; European Union, 7th Framework Programme EUCLYD, ZonMW, and the Princess Beatrix Fund 2/15 authors with CoI: consultancy, Genzyme	Funding. Prinses Beatrix Spierfonds/ Stichting Spieren voor Spieren; SSWO, ZonMW 1/12 authors with CoI: consulting services for multiple companies in the Pompe disease field	Funding: European Union, 7th Framework Programme, EUCLYD 7/12 authors with CoI: honoraria from Genzyme	Funding: Genzyme 4/13 authors with CoI: Genzyme employees	Funding: ZonMW, the Dutch TI Pharma initiative "Sustainable Orphan Drug Development through Registries and Monitoring" (T6-208), EUCLYD, the Princess Beatrix Fonds, and Genzyme Corporation, USA 2/8 authors with CoI: consultancy, Genzyme.	Funding: ZonMw; the Dutch TI Pharma initiative Sustainable Orphan Drug Development through Registries and Monitoring (T6-208), EUCLYD, the Princess Beatrix Fonds; Colciencias and Genzyme2/9 authors with CoI: Genzyme	Funding: ZonMW, the Prinses Beatrix Spierfonds, SSWO, TKI, Colciencias, and Sanofi-Genzyme3/11 authors with CoI: speaking engagements, research funding, advisory/speaker roles; Sanofi-Genzyme
Description of the intervention (alglucosidase alfa dosage)	20 mg/kg every 14 ± 4 days	20 mg/kg every other week	20 mg/kg every other week		20 mg/kg every other week	20 mg/kg every other week	NR	NR	20 mg/kg every other week
Comparator	/	/	/		/	/	Data from patients not receiving ERT were included in the analysis.	/	Data from patients not receiving ERT were included in the analysis.
Number of patients, n (female)	Juvenile: 7 (2) Adult: 17 (8)	74 (41)	69 (33) [a]	73 (36) [b]	38 (20)	ERT group: 60 (26) [c]	283 (149) ERT group: 204 (104) Non-ERT group: 79 (45)	174 (93)	Total: 102 (49) [d]
Inclusion criteria	Patients aged 7-65 years with GAA deficiency and muscle or respiratory impairment (Walton ≥1 or VC <80%); diagnosis confirmed genetically. Juvenile phenotype: <16 years; adult: >16 years.	Patients with confirmed GSDII (low GAA activity or pathogenic GAA mutations), symptom onset ≥2 years, and signs/symptoms (e.g. Walton ≥1).	Patients >18 years with confirmed diagnosis (enzyme + mutation analysis), ERT-naive before treatment, received ERT ≥5 mo, and were symptomatic.		Patients with a confirmed diagnosis with low GAA levels and genetic analysis.	Patients ≥ 8 years with confirmed diagnosis (low GAA + genetic testing), able to walk ≥40 m on 6MWD, upright FVC 30-80% predicted, ≥10% postural FVC drop, and lower limb weakness.	The current study included only patients aged 18 years or older at study entry.	Patients ≥ 8 on ERT ≥ 6 months with ≥ 6 months pre-ERT follow-up.	Patients >18 years of age at the first study assessment, with symptomatic Pompe disease and had not yet received ERT before enrollment.

Author, year	Bembi et al., 2010 [93]	Angelini et al., 2012 [97]	de Vries et al., 2012 [100]	de Vries et al., 2017 [98]	Regnery et al., 2012 [101]	van der Ploeg et al., 2012 [102]	Güngör et al., 2013 [112]	Gungor et al., 2016 [99]	Kuperus et al., 2017 [103]
Age of symptom onset (mean ± SD, unless otherwise specified) years	Juvenile: 2.5 ± 1.3 Adult: 26.6 ± 12.8	28.3 ± 15	Median (range): 32.0 (1.4-62.0)	Median (range): 32.1 (1.4-62.2)	36.2 ± 10.5	30.3 ± 12.3	NR	NR	Median (range): 33 (1-62)
Age at diagnosis (median (range), unless otherwise) years	Juvenile (mean ± SD): 2.8 ± 1.4 Adult (mean ± SD): 34.5 ± 14.9	NR	40.9 (1.4-63.0)	41.3 (1.4-72.2)	Mean ± SD: 41.6 ± 10.8	NR	NR	37 (1-66)	NR
Age of ERT onset (median (range), unless otherwise specified) years	Juvenile: 12.0 ± 3.3 Adults: 47.6 ± 10.7	NR	50.1 (26.2-74.0)	52 (26-74)	Mean ± SD: 50.7 ± 10.7	45.3 (12.4)	51 (24-76)	50 (24-76)	52 (24-76)
Patients on ventilation (n, %)	Juvenile: 1 invasive (14.28%), 1 non-invasive (14.28%) Adult: 3 invasive (17.65%), 8 non-invasive (47.1%)	27 (36.5%)	3 invasive (6.12%), 10 non-invasive (20.41%)	4 invasive (5.5%), 18 non-invasive (24.66%)	7 invasive (18.42%), 6 non-invasive (15.8%)	20 (33%)	42 (15%)	84 (48%)	27 (26.47%)
Wheelchair/ walking device use (n, %)	NR	22/74 (30%)	16/71 (32.65%)	24/73 (32.9%)	NR	23/60 (38%)	37/283 (13%)	90/174 (52%)	32/102 (31.37%)
Follow-up (median (range), unless otherwise specified), years	3.0	Range: (1-4.5)	Before ERT: 1.2 (0.3-2.8) During ERT: 1.8 (0.5-3.4) Total: 3.0 years	3.0	3.0	2.0 and 2.5	6.0 (0.04-9)	7.0 (1-10)	6.1 (0.4-7.9) 5.0 (0.2-7.3) during ERT
Loss to follow-up (n, %)	None reported.	3/74: 1 drop-off (unspecified reason), 2 stopped ERT due to worsening of condition	1/71 (withdrawal)	1/73 (withdrawal)	None reported [e]	At 2 years: 5/60 (8.33%) Between 2 and 2.5 years: 27/60 (49.1%)[f]	None reported.	None reported.	None reported [g]

Abbreviations: 6MWT … 6-minute walking test, CHO … Chinese hamster ovary, CoI … conflict of interest, ERT … enzyme replacement therapy, EUCLYD … a European Consortium for Lysosomal Storage Diseases, FVC … forced vital capacity, GAA … acid alpha-glucosidase, GSDII … Glycogen Storage Disease Type II, mo= months, NR … not reported, SD … standard deviation, SSWO … Sophia Children's Hospital Foundation, TKI … Health Holland Tex Net, VC … vital capacity, ZonMW … The Netherlands Organisation for Health Research and Development.

Notes:

[a] *n=49 (28) with pre/post ERT data, and all patient characteristics are presented for them.*

[b] *n=58 with pre/post ERT data, but characteristics are presented for the whole sample.*

[c] *An open-label extension study of an RCT (Late-Onset Treatment Study). In the RCT, the placebo group (n=30) switched to ERT in the extension phase presented here; however, the data are not used due to short follow-up*

[d] *96 with natural-course data, 88 with ERT data; 82 had both pre-ERT and ERT data, 14 natural-course only, and 6 ERT only.*

[e] *The data for the outcomes is variable and lower due to the inability of the patients to perform the assessments.*

[f] *The missing data at 2.5 years were not due to dropouts or losses to follow-up but rather because the study design restricted extended follow-up to US sites only.*

[g] *45 patients had received ERT for the duration of 5 years. For the patients who had not yet been treated for 5 years, their last follow-up measurement was taken for comparison in the analysis.*

Table 5-9: Study description and patients' characteristics of single-arm studies investigating the effects of alglucosidase alfa in LOPD (part 2).

Author, year	van der Meijden et al., 2018 [111]	Nagura et al., 2019 [109]	Harlaar et al., 2019 [108]	Nuñez-Peralta et al., 2020 [105]	Semplicini et al., 2020[a] [107]	Stockton et al., 2020 [110]	Claeys et al., 2022 [104]	Ravaglia et al., 2022 [106]
Study design	Prospective, observational, multi-center, open-label study	Prospective, observational, multi-center, open-label study (post-marketing surveillance study)	Prospective, observational, multi-center, open-label study	Prospective, observational, single-center, open-label study	Prospective, observational, multi-center, open-label study	Prospective, observational, multi-center, open-label study	Prospective, observational, single-center study	Prospective, observational, single-center, open-label study
Country	The Netherlands, Belgium, Germany, the UK, and the USA	Japan	The Netherlands and France	Spain	France	Multiple countries	Belgium	Italy
Funding/Conflict of interest (CoI)	Funding: by ZonMW, the Princess Beatrix Spierfonds, TKI, SSWO, Metakids, the National Council of Technological and Scientific Development (Brazil), Colciencias, and Sanofi Genzyme 1/6 author with CoI: consultancy, Sanofi Genzyme, Biomarin, and Amicus	Funding: Sanofi 3/3 authors with CoI: employment at Sanofi	Funding: by ZonMW, the Princess Beatrix Spierfonds, the Sophia Children's Hospital Foundation, and the Ministry of Economic Affairs under TKI Allowance under the TKI program Life Sciences & Health and Sanofi-Genzyme 3/12 authors with CoI: consultancy, Sanofi-Genzyme, and Spark Therapeutics.	Funding: Spanish Ministry of Health, by the Spanish Ministry of Economy and Competitiveness, and by CIBERER 3/12 authors with CoI: speaker honoraria, consulting fees; Sanofi-Genzyme, Amicus, Audentes	Funding: Genzyme-Sanofi, the Myology Institute, and INSERM CoI: NR	Funding: Genzyme-Sanofi All authors with CoI: research support, consulting fees, advisory boards, speaker honoraria, company employment/stockholding; Sanofi Genzyme (main sponsor/employer), Amicus, BioMarin, Alexion, Pfizer, Ultragenyx, etc	Funding: None CoI: None	Funding: Italian Ministry of Health, Ricerca Corrente CoI: None
Description of the intervention (alglucosidase alfa dosage)	All but 2 patients received 20 mg/kg ERT every other week[a]	20 mg/kg every other week	20 mg/kg every other week	NR[b]	20 mg/kg every other week	NR	20 mg/kg every other week	20 mg/kg every 14 ± 4 days
Comparator	/	/	/	/	Historical untreated group[a]	/	/	/
Number of patients, n (female)	17 (6)	73 (32) IOPD: 10 Juvenile-onset: 42 Adult-onset: 21[c]	30 (16)	36 (20) 23 received ERT	158 (82) [d]	396 (198)	12 (7) LOPD patients 12 (7) [e]	18 (11) [f]
Inclusion criteria	Children with Pompe disease in whom ERT had been initiated before the age of 18 years.	Post-marketing surveillance of all Japanese Pompe patients treated with alglucosidase alfa from 2007 to 2016 (9 years).	LOPD patients able to walk ≥40 m on the 6MWD, with lower limb weakness, upright FVC 30-80% predicted, ≥10% drop in FVC supine vs upright, and no invasive or daytime non-invasive ventilation.	LOPD patients (enzyme deficiency and/or GAA mutations per EPC), no MRI contraindications; both symptomatic and asymptomatic.	Pompe disease patients (GAA deficiency and/or two GAA mutations) who provided informed consent.	LOPD patients enrolled in the Registry (GAA deficiency and/or two mutations), symptom onset >12 months or ≤12 months without cardiomyopathy, ≥5 y old, and ≥2 follow-up FVCs over a minimal duration of 6 months.	Ambulatory adults with symptomatic, genetically confirmed LOPD on ERT (20 mg/kg) and 12 age- and sex-matched healthy controls were included.	Patients with LOPD, with low GAA levels and genetic analysis.

Author, year	van der Meijden et al., 2018 [111]	Nagura et al., 2019 [109]	Harlaar et al., 2019 [108]	Nuñez-Peralta et al., 2020 [105]	Semplicini et al., 2020[a] [107]	Stockton et al., 2020 [110]	Claeys et al., 2022 [104]	Ravaglia et al., 2022 [106]
Age of symptom onset (median (range) years	2.5 (0.5-13)	Juvenile (mean (range): 4.7 (0.1-15.0) Adult-onset (mean (range): 32.6 (16.7-72.7)	NR	Range (14-62)	Mean (SD): 36.49 (14.48)	Median (IQ): 33.7 (17.0, 45.0)	32.8 (1-52)	36 (7-68)
Age at diagnosis (median (range) years	3 (0.0-14.0)	Juvenile-onset (mean (range): 9.5 (1.0-47.4) Adult-onset (mean (range): 36.1 (16.6-72.9)	NR	NR	NR	41.1 (29.2-53.1)	NR	NR
Age of ERT onset (median (range), unless otherwise specified) years	11.9 (1.1-16.4)	Juvenile-onset (mean (range): 15.1 (1.4-48.2) Adult-onset (mean (range): 42.0 (18.2-76.2)	Median (IQR): 49 (41-60)	Range (22-67)	NR	45.1 (34.7-56.4)	NR	53 (28-82)
Patients on ventilation (n, %)	3/17 (17.65%): 1 invasive, 2 non-invasive	NR	7/30 (23%)	11/36 (30.56%, all non-invasive)	82/158 (51.89%): 17 invasive, 65 non-invasive	30/396 (16%)	4/12 (33.33%) (non-invasive)	6/18 (33.33%): 1 invasive, 5 non-invasive
Wheelchair/ walking device use (n, %)	3 (17.65%)	NR	7 (23%)	10 (27.78%)	NR	50 (26.7%)	NR	7
Follow-up (median (range) unless otherwise specified), years	6.8 (1.8-15.1)	Up to 9.0 years	Median (IQR): 9.8 (8.3-10.2)	3.0	Median (IQR): 5.34 (2.6, 8.5)	4.0 (0.5-5)	2.0	12.0 (2-15)
Loss to follow-up, n	None reported.	1 (missing data)	None reported.[g]	None reported.[h]	None reported.	None – patients were selected based on the availability of FVC measurements.	None reported.	None reported.

Abbreviations: 6MWD … 6-minute walking distance, CIBERER … Centro de Investigación Biomédica en Red de Enfermedades Raras, CoI … conflict of interest, ERT … enzyme replacement therapy, FVC … Forced Vital Capacity, GAA … acid alpha-glucosidase, IOPD … infantile-onset Pompe disease, IQR … interquartile range, LOPD … late-onset Pompe disease, MRI … magnetic resonance imaging, NR … not reported, SD … standard deviation, SSWO … Sophia Children's Hospital Foundation, TKI … Health Holland Tex Net, ZonMW … The Netherlands Organization for Health Research and Development.

Notes:

[a] *Two patients started on transgenic rabbit milk–derived ERT (10-20 mg/kg weekly), then switched after ~3 years to 20, later 30-40 mg/kg every other week of CHO-derived ERT.*

[b] *23 patients were already being treated with ERT with Myozyme for a mean period of 4.1 years; the rest started upon enrollment.*

[c] *Only data for LOPD will be presented – juvenile and adult-onset.*

[d] *The study initially included a non-ERT group, but due to major differences from the intervention group, it was excluded from analysis. Since 2004, 197 patients have been registered in the French Pompe Registry (158 treated, 39 untreated), with data presented only for the treated group.*

[e] *Healthy controls data not reported.*

[f] *Six with severe disease were described separately; 12 were used for analysis.*

[g] *The availability of data for certain outcomes at year 10 was only 8/9 out of the initial 30, because the patients were not able to perform these assessments.*

[h] *Four patients initiated treatment during follow-up due to hip flexion/extension weakness. Excluded from statistical analyses; results reported separately.*

5.3.3 Results

The long-term effectiveness of alglucosidase alfa is presented in Table 5-10 for the controlled study and in Table 5-10, Table 5-11 and Table 5-12 for the single-arm studies.

Motor Function

QMFT

QMFT: uneinheitliche Ergebnisse, teils erst nach fast 7 Jahren signifikante Verbesserung.

This outcome was reported in three single-arm studies, with inconsistent results. After three years (n=49 patients) [100] and five years of follow-up (n=82 patients) [103], changes were not statistically significant. In contrast, after 6.8 years of treatment, one study involving 17 patients reported a significant improvement [111].

6MWD

6MWD: kurzfristig häufig Zuwächse, langfristig gemischte Verläufe mit teils späterem Rückgang.

Across five single-arm studies with a follow-up duration up to five years, effects of alglucosidase alfa on 6MWD were variable. One study observed a significant increase of 63 m in this outcome in patients after 1-4.5 years of alglucosidase alfa treatment [97], while two reported significant improvements after three years of follow-up [93, 102]. Some studies showed gains at earlier follow-up that were not sustained at later follow-up [101], whereas others reported only non-significant changes [105]. In contrast, one study found a significant decline after two years of treatment [104].

Three single-arm studies [103, 106, 107] assessed long-term changes in 6MWD over 5-12 years of follow-up. One reported an initial improvement during the first two years, followed by a progressive decline after up to 5.3 years of follow-up [107]. Another found a significant increase after five years of treatment [103]. The longest follow-up study showed early gains but a significant decline by 12 years (from 367 m to 314 m, p=0.007) [106].

Two studies reported this outcome as 6MWD% predicted. One showed a significant improvement after nearly seven years of ERT [111], while the other reported initial gains followed by a significant decline after 10 years of treatment [108].

Respiratory Function

Upright FVC

Upright FVC: kurz- bis mittelfristig uneinheitlich, langfristig meist Rückgang mit einzelnen Ausnahmen

The results for upright FVC are inconsistent across studies. In the controlled study, no significant difference in FVC change from baseline was observed between the intervention and control groups after 4.4 years of follow-up; the change in the intervention group alone was also not significant [96].

Four prospective single-arm studies (involving 181 patients) with up to three years of follow-up report variable findings regarding the change in upright FVC after ERT. Two studies observed a non-significant increase [97, 102], one study a non-significant decrease (−0.2 pp/year) [100], while one study observed a significant decrease in symptomatic patients [105].

Five studies assessed changes in upright FVC during longer follow-up. One large study with four years of follow-up found a non-significant decline [110]. Among studies with 5-7 years of follow-up, two reported a decline at five years, significant in one [107] and non-significant in the other [103], though the latter

also showed a better trajectory compared to the extrapolated natural course. Another study reported a significant decrease after 6.8 years of treatment [111].

Finally, the studies with the longest follow-up concluded that after ten years of ERT patients experienced a significant decline in upright FVC [108], while the other study observed no significant variation in this parameter over twelve years of follow-up, except a mild decline that occurred between year six and nine [106].

Supine FVC

Supine FVC: zunächst stabil, ab etwa 5 Jahren ERT überwiegend signifikante Abnahmen

Results for this outcome were variable across single-arm trials. In three studies with up to 3 years of follow-up (97 patients in total), ERT was associated with no significant change [100, 104, 105].

Four studies with 5-10 years of follow-up (215 patients) consistently reported declines in supine FVC during ERT. Significant decreases were observed at five years [103, 107] and again at ten years [108], though one study also noted higher values compared with extrapolated natural history. In contrast, one study found a non-significant decline after 6.8 years [111].

FEV1

FEV1: über 2-3 Jahre unverändert

FEV1 was evaluated in one prospective single-arm trial [93], which found no significant change over 2-3 years of follow-up in either juvenile- or adult-onset patients.

Dependence on non-invasive or tracheostomy-assisted ventilation

Ventilationsabhängigkeit: kurzfristig teils weniger, teils mehr beatmungspflichtige Pts., insgesamt gemischte Verläufe

This outcome was reported both in the controlled study and the single-arm studies. In a controlled trial of ventilator-dependent patients [96], a small proportion achieved ventilator independence after 4.4 years, with similar rates in the intervention and control groups.

Four single-arm studies [93, 97, 104, 105] (146 patients) assessed ventilation outcomes over up to three years of follow-up. One found no change over two years [104]. Two reported fewer ventilator-dependent patients compared to baseline [93, 97]. Another observed an increase in ventilator dependence from baseline to study end [105]. Additionally, one study reported that additional 16.5% of patients required ventilatory support by four years [110]. None of the studies provided statistical analyses for the reported changes.

langfristig (bis ~10 Jahre) eher Zunahme

Ventilation outcomes during 5-10 years of ERT were mixed. After five years, one study reported an increase in approximately 10% of patients requiring support [103], while another observed a slight increase in non-invasive ventilation among 52 patients (presented graphically) [107]. No change was seen after 6.8 years in 17 patients [111]. In contrast, a 9.8-year study reported an increase in ventilation use from 23% to 80% [108]. Again, no statistical analysis for the reported changes were provided.

Time spent on ventilation

This outcome was evaluated in the controlled trial and in three single-arm studies. The controlled trial [96] found a significant difference in mean change from baseline between groups after 4.4 years of follow-up. Among three single-arm trials with up to three years of follow-up, two reported a reduction in ventilation time – significant in one [93] and without statistical testing in the other [97] – while the third found no change [101].

Survival

Overall survival

Überleben unter ERT verbessert, besonders bei juveniler LOPD

One trial with a median follow-up of 6 years reported a significantly reduced risk of death (HR 0.41, 95% CI: 0.19-0.87) [112]. Another single-arm study with nine years of follow-up found survival rates of 95.2% in juvenile-onset and 70.2% in adult-onset patients [109].

Ventilator-free survival

This outcome was not assessed in any of the studies.

Quality of life

SF-36

Lebensqualität unter US-Norm; geringe Veränderungen

Two single-arm trials assessed quality of life with the SF-36. Over three years, patients scored below U.S. norms at baseline and showed no significant change in one study [101]. In a seven-year study, physical health (PCS) improved during the first two years, followed by a non-significant decline, while mental health (MCS) remained stable throughout [99].

Rotterdam Handicap Scale (RHS)

RHS: unter ERT Stabilisierung

A single-arm study [99] reported that prior to ERT, patients showed a significant decline in RHS scores. During ERT, scores stabilized, with no further significant change.

Rasch-built Pompe-specific Activity Scale (R-PAct)

R-PAct: signifikante Funktionsverbesserung

At five years, one single-arm study reported a significant improvement from baseline and compared with extrapolated natural history cohort [98].

Table 5-10: Effectiveness results for alglucosidase alfa in LOPD patients in the controlled study.

Author, year	Vianello et al., 2013 [96]
Motor function	
QMFT	NR
6MWD/6MWD% predicted	NR
Respiratory function	
FVC upright (absolute absolute in L or percent predicted in %)	4.4-year endpoint Change in absolute FVC from baseline: Intervention group: LSM of 0.1 (95% CI: -0.65-0.5), p=0.15 Control group: LSM of 0.12 (95% CI: -0.31-0.67), p=0.16 Difference between groups: LSM of 0.02 (95% CI: –0.23-0.23), p=0.993 Change in FVC % from baseline: Intervention group: LSM of 9.65 (95% CI: –3.4-12,3), p=0.48 Control group: LSM of 12.5 (95% CI: –4.1-13.6), p=0.05 Difference between groups: LSM of 2.85 (95% CI: –2.1-6.2), p=0.3
FEV1	NR
Dependence on non-invasive or tracheostomy-assisted ventilation	Baseline Intervention group: 2 invasive, 6 non-invasive (100%); Control group: 4 invasive, 2 non-invasive (100%) Follow-up 1 patient per group had tracheostomy removed and remained decannulated (16.67% and 12.5% were without ventilation, in the control and intervention group, respectively).
Time spent on ventilation(h)	Mean change from baseline (Intervention vs Control group): -4.8 (95% CI: -8.2-1.5) vs. -0.16 (95% CI: -4.5-3.7) p=0.004
Survival	
Overall survival	NR
Ventilator-free survival	Free from tracheostomy Intervention group: 1/8 (12.5%) Control group: 1/6 (16.7%)
Quality of life	
SF-36	NR
R-Pact	NR

Abbreviations: 6MWD … 6-minute walking distance, 6MWD% … 6-minute walking distance percentage predicted, CI … confidence interval, FEV1 … forced expiratory volume in 1 second, FVC … forced vital capacity, LOPD … late-onset Pompe disease, LSM … least square means, NR … not reported, QMFT … the Quick Motor Function Test, R-PAct … the Rasch-built Pompe-specific activity scale, SF 36 … Short Form 36.

Table 5-11: Effectiveness results for alglucosidase alfa in LOPD patients in single-arm studies (part 1).

Author, year	Bembi et al., 2010[93]	Angelini et al., 2012[97]	de Vries et al., 2012 [103]	Regnery et al., 2012 [101]	van der Ploeg et al., 2012 [111]	Güngör et al., 2013 [112]	Gungor et al., 2016 [99]	Kuperus et al., 2017 [103]
Motor function								
QMFT	NR	NR	3-year endpoint: 0.7 pp/y (95% CI: −0.2-1.7), p=0.14	NR	NR	NR	NR	Difference 5-year vs baseline: -0.2, p=0.87.
6MWD/6MWD% predicted	Juvenile-onset (n=7), median (range) Baseline: 572.9 (104.0-616.9) m 2-year endpoint: 630.0 (565.0-770.6) m 3-year endpoint: 664.0 (590.0-748.0) Adult-onset (n=17), median (range) Baseline: 116.6 (40.0-411.5) m 2-year endpoint: 206.0 (69.0-467.5) m 3-year endpoint: 265.0 (56.0-426.0) m	Baseline, mean ± SD: 320 ± 161 1-4.5 years of FU, mean ± SD: 383 ± 178 (p<0.0001)	NR	Baseline, mean ± SD: 312 ± 165.5 1-year endpoint, mean ± SD: 344 ± 165.8 (p=0.006), 2-year endpoint, mean ± SD: 356.4 ± 155.9 (p=0.033) 3-year endpoint, mean ± SD: 325.6 ± 174.8 (p=0.49)	n=53 Baseline, mean ± SD: 332.2 ± 126.7 2-year endpoint, mean ± SD: + 21.3 ± 78.0 (95% CI:−0.2-42.8) n=27 Baseline, mean ± SD: 365.0 ± 94.1 2.5-year endpoint, mean ± SD: +22.9±50.0 (95% CI: 2.3-43.5)	NR	NR	Difference 5-year vs baseline: +40.9m, p=0.03 Improved/stable vs baseline: 69%
Respiratory function								
FVC upright (absolute in L or percent predicted in %)	NR	Baseline: 65.2 ± 26.5% 1-4.5 years of FU: 66.5 ± 26.6 (p=0.22), n=69	3-year endpoint vs baseline (mean −0.2 pp/y (95% CI: −1.6-1.2), p=0.76 ERT vs natural course (mean 1.8 pp/y (95% CI: −0.2-3.7), p=0.08	Baseline: 80.27±14.08% 1-year endpoint: 79.19±13.09% 2-year endpoint: 78.62±16.55% 3-year endpoint: 77.19±18.05% Mean change at 3 years vs baseline: -3.08% of FVC% Note: all p=n.s.	n=53 Baseline: 55.4%±14.4% 2-year endpoint: +0.8%±6.7% (95% CI: −1.1-2.6) n=27 Baseline: 54.0%±15.7% 2.5-year endpoint: +0.2%±6.9% (95% CI:−2.6-2.9)	NR	NR	5-year endpoint: -0.1, p=0.84; 5-year endpoint improved/stable: 48% ERT vs extrapolated natural course: +7.3 pp higher (p=0.0006)
FVC supine (absolute in L or percent predicted in %)	NR	NR	3-year endpoint vs baseline: mean −1.0 pp/y (95% CI: −2.3-0.3), p=0.12 ERT vs natural course (mean 0.8 pp/y (95% CI: −0.9-2.4), p=0.38	NR	NR	NR	NR	5-year endpoint: −2.9, p=0.005; Endpoint improved/stable: 37% ERT vs extrapolated natural course: + 7.6 pp higher (p=0.0003)

Author, year	Bembi et al., 2010[93]	Angelini et al., 2012[97]	de Vries et al., 2012 [103]	Regnery et al., 2012 [101]	van der Ploeg et al., 2012 [111]	Güngör et al., 2013 [112]	Gungor et al., 2016 [99]	Kuperus et al., 2017 [103]
FEV1 (%)	Juvenile-onset + adult-onset (n=24) Baseline: 44.0 (27.0-83.0) 2-year endpoint: 43.5 (29.5-83.5) 3-year endpoint: 45.0 (29.8-82.0) p=0.2537 Note: the values present the median (range)	NR	NR	NR	NR	NR	NR	NR
Dependence on non-invasive or tracheostomy-assisted ventilation	Baseline: 13 (54.2%) 3-year endpoint: 10 (41.7%)	Baseline: n=27 1-4.5 years of FU: n=23 (6 stopped, 2 started)	NR	NR	NR	NR	NR	Baseline: 27/82 (32.92%) patients – mechanical ventilation. 5-year endpoint: 35/82 (42.68%) patients – mechanical ventilation
Time spent on ventilation	Baseline: 14 (8-24) h 3-year endpoint: 8 (8-12) h p<0.0001	Baseline: 15 h 3-year endpoint: 12.1 h	NR	3-year endpoint: No reduction of hours of ventilation. Non-invasive ventilation: 10.29±1.28 hours/day (7 patients) Invasive ventilation: 24 hours/day (6 patients)	NR	NR	NR	NR
Survival								
Overall survival	NR	NR	NR	NR	NR	6-year endpoint HR: 0.41 (95% CI: 0.19-0.87)	NR	NR
Ventilator-free survival	NR	NR	NR	NR	NR	NR	NR	NR
Quality of life								
SF-36	NR	NR	NR	Baseline: 1.5 points below the 1998 U.S. general population (mean 50 (±10) 3-year endpoint: no change from baseline (all p=n.s.).	NR	NR	PCS (mean sp/y (95 % CI) Baseline: –0.73 (–1.07, –0.39) 0-2 years endpoint: 1.49 (0.76, 2.21) >2 years endpoint: –0.15 (-0.43, 0.13)	NR

Author, year	Bembi et al., 2010[93]	Angelini et al., 2012[97]	de Vries et al., 2012 [103]	Regnery et al., 2012 [101]	van der Ploeg et al., 2012 [111]	Güngör et al., 2013 [112]	Gungor et al., 2016 [99]	Kuperus et al., 2017 [103]
SF-36 *(continuation)*							MCS (mean sp/y (95 % CI) Baseline: 0.16 (-0.25, 0.57) 0-2 years endpoint: 1.03 (–0.07, 2.13) >2 years endpoint: 0.02 (–0.41, 0.46)	
R-Pact	NR	NR	NR	NR	NR	NR	NR	5 years vs baseline: +3.6 (p=0.004) 5-year endpoint improved/stable: 59% R-PAct higher than natural course by 110.8 pp (p=0.002)

Abbreviations: 6MWD … 6-minute walking distance, 6MWD% … 6-minute walking distance percentage predicted, CI … confidence interval, ERT … enzyme replacement therapy, FEV1 … forced expiratory volume in 1 second, FVC … forced vital capacity, FU … follow-up, HR … hazard ratio, LOPD … late-onset Pompe disease, MCS … mental component summary, NR … not reported, n.s. … non-significant, PCS … physical component summary, pp … percentage point, pp/y … percentage point per year, QMFT … the Quick Motor Function Test, R-PAct … the Rasch-built Pompe-specific activity (R-PAct) scale, SD … standard deviation, SF 36 … Short Form 36, sp … score points.

Table 5-12: Effectiveness results for alglucosidase alfa in LOPD patients in single-arm studies (part 2).

Author, year	van der Meijden et al., 2018 [111]	Nagura et al., 2019 [109]	Harlaar et al., 2019 [108]	Nuñez-Peralta et al., 2020 [105]	Semplicini et al., 2020 [107]	Stockton et al., 2020 [110]	Claeys et al., 2022 [104]	Ravaglia et al., 2022 [106]
Effectiveness Outcomes								
Motor function								
QMFT	Baseline: median 92% (44-100%) 7-year endpoint: stabilization and a significant increase by 9.2 pp (95% CI: 1.8-16.6; p=0.006)	NR	NR	NR	NR	NR	NR	NR
6MWD/6MWD % predicted	Baseline, median (range): 79% (32-91%) 7-year endpoint: significant increase by 7.4 pp (95% CI: 2.4-12.3) p < 0.001	NR	Baseline: median (IQR) 49% (41-62) 3-year endpoint: improvement 10-year endpoint: decline vs baseline (−22.2 pp, p < 0.001)	Symptomatic treated patients Baseline, mean ± SD: 394.4 ± 150.4 3-year endpoint, mean ± SD: 422.3 ± 140.1 SRM=0.1, p=0.16	Baseline vs. 2.2-year endpoint: increase by 1.4% ± 0.5/year, p<0.01). After 2.2 years: decline by −2.3%/year; change of slope: −3.7 ± 0.6, p < 0.001)	NR	Baseline: 451.9 m 2-year endpoint: 368.1 m (mean decline of 83.8 m, p < 0.003)	Year 1 Improved: n=7; Stable: n=4; Worsened: n=1 Year 6 Improved: n=5; Stable: n=3; Worsened: n=4 Years 8-14 Improved: n=1; Stable: n=5 Worsened: n=6 Mean distance: 367 m → 424 m at 1y (p=0.010), returned to baseline at 3y, declined to 350 m at 9y and 314 m at 12y (p=0.007)[a]
Respiratory function								
FVC upright (absolute in L or percent predicted in %)	7-year endpoint: −5.2 pp (95% CI: 0.05-10.4) p=0.047	NR	Baseline, median (IQR): 54% (47-68%) 5-year endpoint: stabilization 10-year endpoint: −11 pp (p<0.001)	Symptomatic treated patients Baseline, mean ± SD: 75.9 ± 22.9 3-year endpoint, mean ± SD: 69 ± 25.4 SRM=0.8, p=0.0001	5.3-year endpoint: −0.9±0.1%/year (p<0.001) The sitting – supine FVC difference stable (+0.15±0.2%/year, ns.)	4-year endpoint: −0.17%/year (95% CI: −0.42/0.09, p=0.21)	NR	Year 1 Improved: n=2; Stable: n=7; Worsened: n=3 Year 6 Improved: n=4; Stable: n=3; Worsened: n=5 Years 8-14 Improved: n=1; Stable: n=4; Worsened: n=7 No sig. change during most follow-up; mild decline between year 6 and 9 (p=0.011). [a]

Author, year	van der Meijden et al., 2018 [111]	Nagura et al., 2019 [109]	Harlaar et al., 2019 [108]	Nuñez-Peralta et al., 2020 [105]	Semplicini et al., 2020 [107]	Stockton et al., 2020 [110]	Claeys et al., 2022 [104]	Ravaglia et al., 2022 [106]
FVC supine (absolute in L or percent predicted in %)	7-year endpoint: −4.7 pp (CI −4.5 to 13.9; p=0.34)	NR	Baseline: 33% (IQR 24-53%) 10-year endpoint: −9.2 pp (p<0.001)	Baseline, mean ± SD: 67.6 ± 25.3 L 3-year endpoint, mean ± SD: 65.7 ± 24.1 L SRM=0.4, p=0.74	5.3-year endpoint: −0.82 ± 0.1%/year (p<0.001)	NR	No sig. changes over 2 years	NR
FEV1 (%)	NR	NR	NR	NR	NR	NR	NR	NR
Dependence on non-invasive or tracheostomy-assisted ventilation	No patients started respiratory support during follow-up	NR	Baseline: 7 patients (23%) – non-invasive ventilation 3-year endpoint: 24 patients (80%) non-invasive ventilation	Baseline: 11 (47.82%) non-invasive ventilation 3-year endpoint: 13 (56.52%) non-invasive ventilation	After 3, 4 and 6 years of ERT – a slight increase of patients requiring non-invasive ventilation (data presented graphically)	4-year endpoint: additional 26/158 patients (16.5%) required respiratory support.	No change in ventilation status during the 2-year study period (4/12 – 33.3% required non-invasive during the night)	NR
Time spent on ventilation	NR	NR	NR	NR	NR	NR	NR	NR
Survival								
Overall survival	NR	9-years endpoint Juvenile-onset survival rates: 95.2% (95% CI: 82.1-98.8) Adult-onset survival rates: 70.2% (95% CI: 37.2-88.1)	NR	NR	NR	NR	NR	NR
Ventilator-free survival	NR	NR	NR	NR	NR	NR	NR	NR
Quality of life								
SF-36	NR	NR	NR	NR	NR	NR	NR	NR
R-Pact	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: 6MWD … 6-minute walking distance, 6MWD% … 6-minute walking distance percentage predicted, CI … confidence interval, ERT … enzyme replacement therapy, FEV1 … forced expiratory volume in 1 second, FVC … forced vital capacity, FU … follow-up, IQR … interquartile range, LOPD … late-onset Pompe disease, NIV … non-invasive ventilation, NR … not reported, n.s. … not significant, pp … percentage point, pp/y … percentage point per year, QMFT … the Quick Motor Function Test, R-PAct … the Rasch-built Pompe-specific activity (R-PAct) scale, SD … standard deviation, SF 36 … short form 36, sig. … significant, sp … score points, SRM … standardized response mean.

Notes:

[a] *6MWD improvement = +10% or +30m; FVC improvement = +10% or +0.2L.*

5.4 Avalglucosidase-alfa in late-onset Pompe disease

5.4.1 Description of Outcomes

The list of critical outcomes is presented in chapter 5.3.1. The only difference is that, for quality-of-life assessment, the shorter SF-12 version was used instead of the SF-36.

5.4.2 Included studies

Two prospective, single-arm studies were identified in the systematic search [114, 115]. Their characteristics are presented in Table 5-13.

Characteristics of the prospective, observational single-arm studies

2 prospektive einarmige Studien (Sanofi-finanziert, COI)

AVAL/AVAL vs. ALG/AVAL

Follow-up: 1,86-6 Jahre; Dropout: 13-21 %

Both studies were conducted in multiple countries, were funded by Sanofi and all their authors declared a conflict of interest. In one study the participants first received escalating doses of avalglucosidase alfa in 5, 10, or 20 mg/kg every other week for 6 months during the first phase of the study (NEO1 phase) [116], and then continued their NEO1 dose until all proceeded with 20 mg/kg every other week in the extension trial [114]. In the other study patients were first divided into two groups – one received 20 mg/kg of avalglucosidase alfa and the other the same dose of alglucosidase alfa every other week for 49 weeks; in the extension study all patients received 20 mg/kg of avalglucosidase alfa every other week [115]. One study included a total of 24 patients – 10 in the ERT-naive group who started with avalglucosidase alfa treatment from the beginning (for the purposes of this review it will also be named as AVAL/AVAL), and 14 in the other group (ALG/AVAL), who first received alglucosidase alfa and then switched to avalglucosidase alfa; 19 patients entered the extension trial [114], The second study initially included a total of 100 participants, divided into the first group that received avalglucosidase alfa from the start (AVAL/AVAL n=51), and into the second group that first received alglucosidase alfa and then switched to avalglucosidase alfa (ALG/AVAL n=49); 95 patients entered the extension trial (51 in the AVAL/AVAL and 44 in the ALG/AVAL group) [115]. The length of follow-up was six years in one study [114] and 1.86 in the second study [115]. In one study the loss to follow-up was around 21% (due to personal reasons, IARs) [114], and in the other study the rate was 13 % (due to adverse events, personal reasons, visit difficulties, COVID-19 concerns/travel restrictions) [115].

Patient characteristics in the prospective, observational single-arm studies

ähnlicher Symptombeginn

AVAL-Gruppe älter bei Diagnose

21 % Gehhilfen (1 Studie)

The age of symptoms onset was similar between the study groups (a mean of 32.9 in the AVAL/AVAL and 37.7 in the ALG/AVAL group) [115]; the second study did not report this information [114]. In both groups the patients in the AVAL/AVAL groups were older when the diagnosis was made, One study did not include patients on ventilation and 21% were reliant on some walking device [114], while the second study did not report these information [115].

Table 5-13: Study description and patients' characteristics of single-arm studies investigating avalglucosidase-alfa in LOPD.

Author, year	Dimachkie et al., 2022 [114]	Kishnani et al., 2023 [115]
Study design	Prospective, observational, multi-center, single-arm, dose-escalating trial[a]	Prospective, observational, multi-center, single-arm trial[b]
Country	USA, Belgium, Germany, France, Denmark (17 centers)	20 countries (55 referral centers)
Funding/Conflict of interest (CoI)	Funding: Sanofi. All authors with CoI.	Funding: Sanofi. All authors with CoI.
Description of the intervention	5, 10, or 20 mg/kg every other week for 6 months (NEO1 study) and continued their NEO1 dose until all proceeded with 20 mg/kg every other week.	20 mg/kg of avalglucosidase alfa or alglucosidase alfa every other week for 49 weeks; then, all patients received 20 mg/kg of avalglucosidase alfa every other week.
Comparator	/	/
Number of patients, n (female)	AVAL/AVAL: 10 (7) ALG/AVAL: 14 (5)	Baseline: 100 Extension: 95 (44) AVAL/AVAL: 51 (24) ALG/AVAL: 44 (20)
Inclusion criteria	Adults (≥18 years) with confirmed Pompe disease; treatment-naive (Naive Group) or ≥9 months on alglucosidase alfa (Switch Group); able to walk ≥50 m unaided; upright FVC ≥50% predicted.	Patients ≥3 years old, confirmed Pompe disease (GAA deficiency and/or 2 pathogenic GAA variants), treatment-naive.
Age of symptom onset (mean ± SD) years	NR	AVAL/AVAL: 32·9 ± 16·6[c] ALG/AVAL: 37.7 ± 15.7[c]
Age at diagnosis (mean ± SD) years	AVAL/AVAL: 43.3 ± 23.8 ALG/AVAL: 36.3 ±16.4	AVAL/AVAL: 44.7 ± 14.7[c] ALG/AVAL; 48.2 ± 14.6[c]
Age of ERT onset (mean ± SD) years	NR	AVAL/AVAL: 46.0 ± 14.5[c] ALG/AVAL: 50·3 ± 137[c]
Patients on ventilation (n)	None	NR
Wheelchair/walking device use (n, %)	5/24 (21%)	NR
Follow-up, years	6.0	At least 1.86
Loss to follow-up, n	5/24 (personal reasons – 2, discontinuation due to IARs – 2, withdrawal of consent)	13/100 (discontinuations due to adverse events – 9, patient decision, visit difficulties, COVID-19 concerns/travel restrictions – 4)

Abbreviations: ALG … alglucosidase alfa, AVAL … avalglucosidase alfa, CoI … conflict of interest, ERT … enzyme replacement therapy, FVC … forced vital capacity, GAA … acid alpha-glucosidase, IAR … infusion-associated reactions, LOPD … late-onset Pompe disease, NR … not reported, SD … standard deviation.

Notes:

[a] *NEO-EXT, an extension study of NEO1, a phase 1, open-label, multicenter, multinational, ascending dose.*

[b] *An extension of the COMET trial, a phase 3, randomized, multicenter trial.*

[c] *These baseline data cover all enrolled patients (n=100), as such data were unavailable for those entering the extension phase (n=95).*

AVAL/AVAL refers to the group of patients who received avalglucosidase alfa throughout the whole study.

ALG/AVAL refers to the group of patients who first received alglucosidase alfa and then switched to avalglucosidase alfa.

5.4.3 Results

The long-term effectiveness of avalglucosidase alfa in LOPD is presented in Table 5-14.

Motor function

QMFT

This outcome was reported in one study with data available from 82 patients [115]. After 1.86 years of follow-up, an increase in QMFT scores from baseline was observed; however, the data were presented graphically, and exact values were not provided.

QMFT: Verbesserung nach 1,86 Jahren; nur grafische Daten, keine genauen Werte

6MWD

This outcome was reported in both studies [114, 115]. One study (n=83) observed a considerably higher increase from baseline after 1.86 years in the AVAL/AVAL group compared with those that switched from alglucosidase alfa (ALG/AVAL) [115]. On the other hand, the second study (n=24 patients) observed a decline in both the AVAL/AVAL and the ALG/AVAL groups [114].

6MWD: Unterschiedliche Studienergebnisse

Respiratory function

Upright FVC

This outcome was reported in both studies. One study (n=78 patients), observed after 1.86 years of ERT that patients receiving avalglucosidase alfa from the start experienced a greater increase compared with those that switched [115]. The second study (n=24 patients) after six years observed the opposite. In both groups, the patients experienced a decline in this parameter, with a greater decrease in those that switched from alglucosidase alfa and a smaller decrease in those receiving avalglucosidase alfa from the start [114].

Atemfunktion Upright FVC: Studie 1 (1,86 Jahre): bessere Zunahme in AVAL/AVAL

Studie 2 (6 Jahre): Abnahme in beiden Gruppen, stärker bei Wechsel

FEV1

This outcome was not reported in the included studies.

Dependence on non-invasive or tracheostomy-assisted ventilation

This outcome was not reported in the included studies.

Time spent on ventilation

This outcome was not reported in the included studies.

Survival outcomes

Overall survival

This outcome was not assessed in any of the studies included.

Ventilator-free survival

This outcome was not assessed in any of the studies included.

Quality of life

SF-12

This outcome was reported in one study (n=86 patients) [115]. After 1.86 years of follow-up, patients receiving avalglucosidase alfa from the start showed greater increases in both the physical and mental component scores compared with those who switched from alglucosidase alfa. P values were not reported.

Lebensqualität SF-12: größere Zunahmen in physischen & mentalen Scores bei AVAL/AVAL

Rasch-built Pompe-specific Activity Scale (R-PAct)

This outcome was reported in one study (n=38 patients) [115]. After a 1.86-year of ERT, patients receiving avalglucosidase alfa from the start experienced an increase while those that switched from alglucosidase alfa experienced a decrease in this parameter.

R-PAct: Zunahme bei AVAL/AVAL, Abnahme bei ALG/AVAL nach 1,86 Jahren

Rotterdam Handicap Scale (RHS)

This outcome was not reported in the included studies.

Table 5-14: Effectiveness results for avalglucosidase alfa in LOPD patients in single-arm studies.

Author, year	Dimachkie et al., 2022 [114]	Kishnani et al., 2023 [115]
Motor function		
QMFT	NR	Increase (data presented graphically).
6MWD	6-year endpoint Slope estimates % predicted per year (95% CI): AVAL/AVAL: −0.70 (−1.57 to 0.17) ALG/AVAL: −0.85 (−1.57 to −0.13)	1.86-year endpoint vs. Baseline – least-squares mean (SE): AVAL/AVAL: +18.60 (12.01) m ALG/AVAL: + 4.56 (12.44) m
Respiratory function		
FVC upright (absolute in L or % predicted)	6-year endpoint Slope estimates % predicted per year (95% CI): AVAL/AVAL: −0.473 per year (−1.188 to 0.242) ALG/AVAL: −0.648 per year (−1.061 to −0.236)	1.86-year endpoint vs. Baseline – least-squares mean (SE): AVAL/AVAL: +2.65 (1.05) points ALG/AVAL: + 0.36 (1.12) points
FEV1	NR	NR
Dependence on non-invasive or tracheostomy-assisted ventilation	NR	NR
Time spent on ventilation	NR	NR
Survival		
Overall survival	NR	NR
Ventilator-free survival	NR	NR
Quality of life		
SF-12	NR	1.86-year endpoint vs. Baseline SF-12 PCS: AVAL/AVAL: +3.24 (0.28) ALG/AVAL: +2.13 (1.03) SF-12 MCS: AVAL/AVAL: +2.47 (1.32) ALG/AVAL: +1.62 (1.27)
R-Pact	NR	Baseline vs. Week 97 AVAL/AVAL: +3.56 (7.96) ALG/AVAL: -0.09 (4.69)

Abbreviations: 6MWD … 6-minute walking distance, ALG … alglucosidase alfa, AVAL … avalglucosidase alfa, CI … confidence interval, FEV1 … forced expiratory volume in 1 second, FVC … forced vital capacity, MCS … mental component score, NR … not reported, PCS … physical component score, R-PAct … the Rasch-built Pompe-specific activity (R-PAct) scale, SE … standard error, SF 12 … short form 12., QMFT … the Quick Motor Function Test.

Notes:
AVAL/AVAL refers to the group of patients who received avalglucosidase alfa throughout the whole study.
ALG/AVAL refers to the group of patients who first received alglucosidase alfa and then switched to avalglucosidase alfa.

5.5 Laronidase for Mucopolysaccharidosis I

5.5.1 Description of Outcomes

Neurological Function

Spinal cord compression

This outcome is a neurological outcome and a common complication in patients with MPS I. It results from thickening of the ligaments surrounding the spinal canal due to glycosaminoglycan (GAG) accumulation, which progressively narrows the canal and may lead to neurological deficits [117].

Spinalkanalkompression durch GAG-Akkumulation; führt zu Defiziten

Motor Function

6MWD

This outcome is described in chapter 5.1.1.

Joint Function

Joint range of motion (JROM)

This outcome refers to the measurable degree of movement that a joint can perform in a specific direction or plane. It is typically expressed in degrees and measured using a goniometer or similar device. Assessment can be performed for a single joint (e.g., knee flexion, elbow extension) or as a combined movement across multiple joints (e.g., shoulder abduction with scapular rotation). JROM is commonly categorized as active or passive: active ROM represents movement performed by the patient's own muscular effort, while passive ROM represents movement achieved when an external force (therapist or device) moves the joint without patient effort [118].

JROM: aktive/passive Beweglichkeit in Grad (Goniometer)

einzeln oder kombiniert

Joint mobility, range of motion (single joint or combination)

This outcome is a broader concept that describes the capacity of a joint to move freely and efficiently within its normal anatomical limits. Unlike ROM, which is a quantitative measure, mobility also considers the quality of movement, including the influence of soft tissues (muscles, ligaments, joint capsule) and neuromuscular control. It reflects how well the joint functions during movement and daily activities, rather than just the maximal angle achieved [119].

Respiratory Function

Sleep apnoea

This outcome is defined as multiple episodes of either complete (apnoea) or partial (hypopnea) collapse of the upper airway during sleep, causing oxygen desaturation and arousal from sleep. The apnoea-hypopnea index (AHI) is defined as the number of apnoeic or hypopnoeic episodes occurring per hour of sleep. It is commonly used to quantify the severity of sleep-disordered breathing [120].

Atemfunktion Schlafapnoe: AHI: Apnoen/Hypopnoen pro Stunde; O2-Desaturation

Survival

Overall survival

This outcome is described in chapter 5.1.1.

Quality of life outcomes

Child Health Assessment Questionnaire/ Health Assessment Questionnaire (CHAQ/HAQ) disability index

This outcome is a validated tool that evaluates eight domains of physical function through 30 questions, providing an overall summary score expressed as a disability index. The domains include dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. Greater score indicates greater difficulty [121].

Lebensqualität CHAQ/HAQ: 8 Domänen (z. B. Greifen, Gehen); höherer Score = mehr Handicap

MPS Health Assessment Questionnaire (HAQ)

This outcome is a comprehensive tool designed to measure functional abilities in children and adults with MPS. The instrument was developed by clinicians and healthcare professionals for use in the MPS I Registry. The HAQ Disability Index provides a summary score across eight domains: eating/ drinking, dressing, bathing, grooming, toothbrushing, toileting, mobility, and walking/stair climbing [122].

MPS HAQ: MPS-spezifisch; 8 Domänen (z. B. Mobilität, Treppensteigen)

5.5.2 Included studies

Four prospective studies [123-126] investigating laronidase in MPS I patients were included in the qualitative synthesis. One of them had a controlled design [124] (Table 5-15), and the rest were single-arm studies [123, 125, 126] (Table 5-16). Three publications were included from the published systematic review [123, 125, 126], and one was identified by the updated search [124]; no additional study was identified by the manual search.

4 prospektive Studien (1 kontrolliert, 3 einarmig)

3 aus SR, 1 aus Update-Suche

Characteristics of the prospective, controlled study

The controlled study [124] was conducted in the USA, received funding from several sources (including Sanofi-Genzyme), and nine out of twelve authors declared at least one conflict of interest. Patients received a standard laronidase dosage (0.58 mg/kg every week) and a hematopoietic cell transplantation (HCT) at least two years before enrolment to the study. The results for ROM were compared against the data from a control historic group from a 9-year observational study that received only HCT without an ERT (n=23). The intervention group included initially 11 patients, of whom 10 completed the study after one withdrawal at month six. The follow-up duration was 2 years.

kontrollierte Studie: USA, Sanofi-finanziert (COI) Laronidase + HCT vs. HCT allein; n=11 (10 beendet)

2 Jahre Follow-up

Patient characteristics in the prospective, controlled study

All patients in the controlled study had the Hurler phenotype and had undergone HCT at least two years before study entry, with a minimum donor engraftment of 10%. Participants were aged between 5 and 13 years at baseline [124].

Hurler-Phänotyp; HCT ≥2 Jahre vor Studie; Alter 5-13 Jahre

Table 5-15: Study and patients' characteristics of the controlled study investigating laronidase in MPS I.

Author, year	Polgreen et al., 2020 [124]
Study design	Observational, controlled, open-label study
Country	USA
Funding/Conflict of interest (CoI)	Funding: Sanofi/Genzyme, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute of Neurological Disorders and Stroke, and the National Center for Advancing Translational Sciences of the National Institutes of Health 9 out of 12 authors with CoI: Sanofi/Genzyme, Shire, Sangamo Therapeutics, BioMarin, and others
Description of the intervention (laronidase dosage)	0.58 mg/kg weekly + HCT
Comparator	Historical controls with HCT but without ERT (n=23)
Number of patients, n (female)	Intervention group: 11 (4) Comparator (historic) group: 23 (12)
Inclusion criteria	MPS IH patients aged <14 years, who received HCT >2 y ago with >10% donor engraftment.
Age at baseline, mean ± SD, years	Intervention group: 9 ± 2.8 Comparator (historic) group: 9.3 ± 3.5
Severity of phenotype (n)	Intervention group: MPS IH 10/11 Comparator (historic) group: MPS IH 23/23
Follow-up, years	2.0
Loss to follow-up, n	1/11 (9.1%) (withdrawal)

Abbreviations: HCT … hematopoietic cell transplantation, ERT … enzyme replacement therapy, MPS IH … Hurler phenotype, CoI … conflict of interest.

Characteristics of the prospective, single-arm studies

je 1 Studie in USA, mehreren Ländern, Polen; unterschiedlich Angaben zur Finanzierung, COI teils angegeben

One study was conducted in the USA [125], one in multiple countries [123] and one in Poland [126]. Two studies did not report the funding sources [123, 126], and the third reported receiving funding from several sources (including Sanofi-Genzyme) [125]. This study also reported that two out of eleven authors declared at least one conflict of interest [125], while in the second study all authors declared a conflict [123].

Standard-Laronidase-Dosis (0,58 mg/kg/Woche)

2 Extension-Studien mit Follow-up 4-6 Jahre

bis zu 10 % Dropout in 2 Studien

In all studies the patients received the standard laronidase dose (0.58 mg/kg weekly). Two of the studies represent extension trials. One study [125] reported a long-term follow-up of a 1/2 phase clinical trial in which 10 patients initially received laronidase for 52 weeks, after which 5 of them entered the extension trial (4 patients died, one opted out). The other study was an extension trial of a 26-weeks RCT in which one group of the participants received laronidase and the other received placebo; all 45 patients entered the 3.5-years extension trial period [123]. The duration of follow-up ranged from 4 years [123] to 6 years [125]. Loss to follow-up was up to 10% in two studies [123, 125], while one study reported no loss to follow-up [126].

Patient characteristics in the prospective, single-arm studies

2 Studien mit schwerem und attenuiertem Verlauf, eine Studie nur attenuiert

All three studies included MPS I patients with classical clinical presentations. Two studies included patients with both the severe and attenuated phenotypes [125, 126], with more patients presented with the attenuated type. One study included only patients with the attenuated phenotype [123].

Table 5-16: Study description and patients' characteristics of single-arm studies investigating laronidase in MPS I.

Author, year/Reference	Sifuentes et al., 2007 [125]	Clarke et al., 2009 [123]	Tylki- Szymanska et al., 2010 [126]
Study design	Observational, single-center, open-label study[a]	Observational, multi-center, open-label study[b]	Observational, single-center, open-label study
Country	USA	Multiple countries	Poland
Funding/Conflict of interest (CoI)	Funding: grants from BioMarin Pharmaceutical Inc. and Genzyme Corp, Ryan Foundation for MPS Children, and General Clinical Research Centers at Harbour-UCLA. 2/11 authors with CoI – employment; BioMarin Pharmaceutical Inc.	Funding: NR 10/11 authors with CoI: honoraria, consultancy, advisory boards, unrestricted grants, employment; Genzyme, BioMarin	Funding: NR CoI: NR
Description of the intervention (laronidase dosage)	0.58 mg/kg weekly	0.58 mg/kg weekly	0.58 mg/kg weekly
Comparator	/	/	/
Number of patients, n (female)	10 (4) [c]	45 (23)	17 (4)
Inclusion criteria	Patients with MPS I with clinical manifestations and a diagnosis confirmed by leukocyte α-L-iduronidase deficiency.	Age ≥5 y; leukocyte α-L-iduronidase ≤10% normal; FVC ≥80% of normal; able to walk ≥5 m in 6 min. Note: baseline characteristics.	MPS I patients; laronidase-naïve; diagnosis confirmed by leukocyte α-L-iduronidase deficiency and molecular analysis.
Age at baseline (mean (range), unless otherwise specified), years	12.0 (8-17)	Mean ± SD: 15.7 ± 8.03	8.1 (1–39)
Severity of phenotype (n)	MPS IH/S (8), MPS IH (1), MPS IS (1)	MPS IH/S (38), MPS IS (7)	MPS IH (10), MPS IH/S (2), MPS IS (5)
Follow-up, years	6	4 years[d]	1-4
Loss to follow-up, n	1/10 (10%) (opted out)	4/45 (8.89%) (3 withdrawals due to personal reasons, 1 due to anaphylaxis)	None reported

Abbreviations: CoI … conflict of interest, FVC … forced vital capacity, MPS I … Mucopolysaccharidosis Type I, MPS IH … Hurler phenotype, MPS IH/S … Hurler-Scheie phenotype, MPS IS … Scheie phenotype, NR … not reported, SD … standard deviation, y … years.

Notes:

[a] *An extension study of the phase 1/2 study.*

[b] *An extension of a 26-week placebo-controlled RCT.*

[c] *Data refers to the study baseline. Five patients entered the extension study.*

[d] *0.5 years – RCT + 3.5 years – extension trial = 4 years in total.*

5.5.3 Results

The long-term effectiveness of laronidase in MPS I is presented in Table 5-17 for the controlled study [124] and in Table 5-18 for the single-arm studies [123, 125, 126].

Neurological Function

Spinal cord compression

This outcome was not assessed in any of the included studies.

Motor Function

6MWD

This outcome was assessed in two studies. In the controlled study, after two years of ERT, an increase in 6MWD was observed in the intervention group (n=10). However, no p-values were reported, and results for the historical control group (n=23) were not provided [124]. In a single-arm study, a decrease in 6MWD was reported after 4 years of ERT in 45 patients, with no p-values reported [123].

kontrollierte Studie: Anstieg nach 2 Jahren ERT (n=10); keine p-Werte

Joint Function

Joint range of motion

This outcome was assessed in all studies. In the controlled study [124] ERT resulted in variable changes in joint ROM depending on the joint (shoulder, elbow, hip), with improvements reported in 40-50% of patients and worsening in 10-30%. Similar rates were observed for shoulder flexion and hip extension. No differences in ROM changes were observed between the ERT group (n=10) and historical controls (n=23).

variable Änderungen; 40-50 % Verbesserung, 10-30 % Verschlechterung; keine Unterschiede ggü. historischen Kontrollen

Three single-arm studies reported variable findings with heterogeneous effect sizes. After 1-4 years of follow-up, one study with 17 patients reported changes in passive ROM: improvement was most frequent in shoulder flexion (11/17), stability in elbow flexion (15/17), and deterioration in wrist flexion (7/17) [126]. Active range of motion was assessed only in patients with attenuated MPS I phenotypes (n=7). The greatest proportion of patients with improvement was observed in shoulder flexion (5/7), stability was most frequently noted in elbow flexion (7/7), and the highest proportion of worsening was seen in elbow and wrist extension (4/7) [126]. Further, after four years of ERT, one study reported an increase in shoulder ROM [123]. Another study, with six years of follow-up, observed improvements in shoulder flexion/extension and resolution of knee restriction, whereas elbow extension and knee flexion declined [125].

Range of motion (single joint or combination)

This outcome was not assessed in any of the included studies.

Respiratory Function

Sleep apnoea

One single-arm study reported a decrease in apnoea–hypopnoea index (AHI) of up to 7.6 events per hour. Among 16 patients with abnormal baseline AHI, ten improved, two declined, and four remained stable [123].

AHI-Verbesserung bei Mehrheit; hypoxische Ereignisse blieben aus

Another single-arm study reported smaller decreases in AHI, apnoea, and hypopnoea counts after six years of ERT. Hypoxic events were absent at baseline and remained absent throughout follow-up [125].

Survival

Overall survival

This outcome was not reported in any of the included studies.

Quality of life

CHAQ/HAQ disability index

CHAQ/HAQ: 57 % Verbesserung nach 4 J

After four years of ERT 57% of the patient's experienced improvement in a single-arm trial [123].

MPS Health Assessment Questionnaire (MPS HAQ)

MPS HAQ: Verbesserungen in mehreren Domänen; einige Änderungen nicht signifikant

After up to 5 years of ERT, a single-arm trial reported a significant decrease in MPS HAQ scores (indicating improvement) in the domains of eating, dressing, toileting, toothbrushing, walking. Scores also decreased in bathing, grooming, and mobility, but these changes did not reach statistical significance [126].

Table 5-17: Effectiveness results for laronidase in MPS I patients in the controlled study.

Author, year	Polgreen et al., 2020 [124]
Neurological function	
Spinal cord compression	NR
Motor function	
6MWD	Change 2-year vs baseline (mean ± SD (range)): 50 ± 92 (104-264) m
Joint function	
Joint range of motion	Passive joint ROM – change 2-year vs baseline (mean ± SD (range), >5° improvement vs >5° worsening – N/Total (%) Shoulder flexion left (n=8): 8 ± 33 (−44 to 72); improvement – 4/8 (40), worsening – 3/8 (30) Shoulder flexion right (n=8): 5 ± 24 (−32 to 36); improvement – 4/8 (40), worsening – 3/8 (30) Elbow extension left (n=5) 3 ± 9 (−12 to 16); improvement – 3/5 (30), worsening – 1/5 (10) Elbow extension right (n=5): −1 ± 5 (−9 to 10); improvement – 1/5 (10); worsening: 1/5 (10) Hip extension left (n=8): 1 ± 14 (−15 to 22); improvement – 4/8 (40); worsening – 3/8 (30) Hip extension right (n=8): 0 ± 14 (−25 to 17); improvement – 5/8 (50); worsening – 3/8 (30) Change in ROM was not different from historical controls (shoulder flexion: −0.6°/yr; 95% CI −5.3 to 4.2°/yr; p=0.82; hip extension: 1.1°/yr; 95% CI: −1.9-4.0°/yr; p=0.48; elbow extension: 2.4°/yr; 95% CI: −0.3-5.1°/yr; p=0.08).
Joint mobility: Range of motion (single joint or combination)	NR
Respiratory function	
Sleep apnoea	NR
Survival	
Overall-survival	NR
Quality of life	
NA	NR

Abbreviations: 6MWD … 6-minute walking distance, CI … confidence interval, NA … not applicable, NR … not reported, ROM … range of motion, SD … standard deviation, yr … year.

Table 5-18: Effectiveness results for laronidase in MPS I patients in single-arm studies.

Author, year	Sifuentes et al., 2007 [125]	Clarke et al., 2009 [123]	Tylki-Szymanska et al., 2010 [126]
Neurological function			
Spinal cord compression	NR	NR	NR
Motor function			
6MWD	NR	Baseline (mean ± SD): 334.0 ± 129.5m 4-year endpoint (mean ± SD): 373.3 ± 133.0 m Mean change from baseline (mean ± SEM): 17.1 ± 16.8 m	NR
Joint mobility			
Joint range of motion	Baseline vs 6-year endpoint Shoulder flexion: 100.5°→133.7° (right), 106.2° → 131.2° (left) Shoulder extension: 25.2°→ 63.9° (right), 26.7°→ 58.8° (left). Elbow extension: 17.2° (right)/8.8° (left) at baseline → ~3° decline at 6 y on both sides (variable; stable in 3 patients). Knee: baseline restriction 1–3° → 0.4° at 6 y; flexion ↓ ~9° (on both sides)	Shoulder range of motion Baseline (mean ± SD): 90.1 ± 31.7° 4-year endpoint (mean ± SD): 108.1 ± 20.8° Mean change vs baseline (mean ± SEM): 17.4 ± 3.6°	1-4 years of follow-up: Passive joint ROM (n=17) Shoulder flexion: 11 improved, 3 worsened, 3 no change Shoulder abduction: 7 improved, 5 worsened, 5 no change Elbow extension: 5 improved, 6 worsened, 6 no change Elbow flexion: 1 improvement, 1 worsened, 15 no change Wrist extension: 3 improved, 5 worsened, 9 no change Wrist flexion: 4 improved, 6 worsened, 7 no change Active joint ROM (n=7) Shoulder flexion: 5 improved, 1 worsened, 1 no change Shoulder abduction: 3 improved, 1 worsened, 3 no change Elbow extension: 4 improved, 1 worsened, 2 no change Elbow flexion: 0 improvement, 0 worsened, 7 no change Wrist extension: 4 improved, 1 worsened, 2 no change Wrist flexion: 3 improved, 1 worsened, 3 no change
Joint mobility: Range of motion (single joint or combination)	NR	NR	NR
Respiratory function			
Sleep apnoea (AHI)	Baseline vs. 6-year endpoint: Mean number of apneas: 2.2 → 1.0 (−1.2). Mean number of hypopneas: 4.8→ 2.0 (−2.8). Hypoxic events: none, with no new events. AHI: 1.1→0.6 (−0.5)	AHI baseline vs. 4-year endpoint (mean ± SD): −7.6 ± 4.5 events/h Out of 16 patients with baseline abnormal AHI values, 10 improved, 2 declined, and 4 were stable.	NR

Author, year	Sifuentes et al., 2007 [125]	Clarke et al., 2009 [123]	Tylki-Szymanska et al., 2010 [126]
Survival			
Overall-survival	NR	NR	NR
Quality of life			
CHAQ/HAQ disability index	NR	Baseline: 1.91 ± 0.61 4-year endpoint: 1.53 ± 0.77 Change vs baseline: -0.31 ± 0.11 All results: (mean ± SD)	NR
MPS HAQ	NR	NR	1-4 years of follow-up: Eating/drinking (total no. of points: 560) Baseline: 203; Endpoint: 95 (p=0.028) Dressing (total no. of points: 720) Baseline: 432; Endpoint: 269 (p=0.046) Bathing (total no. of points: 240) Baseline: 145; Endpoint: 97 (p=0.208) Grooming (total no. of points: 160) Baseline: 112; Endpoint: 71 (p=0.080) Toothbrushing (total no. of points: 160) Baseline: 50; Endpoint: 33 (0.043) Toileting (total no. of points: 320) Baseline: 137; Endpoint: 88 (p=0.028) Mobility (total no. of points: 400) Baseline: 148; Endpoint: 102 (p=0.094) Walking (total no. of points: 400) Baseline: 106; Endpoint: 9 (p=0.028)[a]

Abbreviations: 6MWD … 6-minute walking distance, AHI … Apnea–Hypopnea Index, CHAQ/HAQ disability index … Childhood Health Assessment Questionnaire/Health Assessment Questionnaire Disability Index, h … hours, MPS I … Mucopolysaccharidosis Type I, MPS HAQ … MPS Health Assessment Questionnaire, no. … number, NR … not reported, ROM … range of motion, SD … standard deviation, SEM … standard error of mean.

Note:

[a] *Lower scores indicate improvement.*

5.6 Idursulfase for Mucopolysaccharidosis II

5.6.1 Description of Outcomes

Motor Function

6MWD

This outcome is described in chapter 5.1.1.

Joint Function

Joint range of motion

This outcome is described in chapter 5.1.1.

Cognitive Function

Differential Ability Scales, Second Edition (DAS II)

A standardized assessment tool designed to evaluate cognitive functioning in children and adolescents across a broad spectrum of abilities relative to a normative sample [127]. The assessment consists of a series of tasks administered by a qualified psychologist, with item selection tailored to the child's age and developmental level. The DAS-II provides multiple scores: two composite scores – General Conceptual Ability (GCA) and Special Nonverbal Composite (SNC) – three cluster scores (verbal, nonverbal, and spatial), and ten core subtest scores. The GCA provides a global measure of cognitive ability, with a normative mean of 100 and a standard deviation of 15; higher scores indicate stronger cognitive functioning.

DAS-II: Standardisiertes Tool für Kinder/Jugendliche

GCA (M=100, SD=15), SNC, Cluster (verbal, nonverbal, spatial)

Respiratory Function

Sleep apnoea

This outcome is described in chapter 5.1.1.

Airway obstruction

This outcome refers to a blockage or narrowing of the airways that can occur at any point along the respiratory tract, from the lips to the lungs [128]. In the included studies, along with standard evaluations, this outcome was additionally assessed with multi-detector computed tomography of the upper airways.

Verengung/Blockade der Atemwege; MDCT-Untersuchung der oberen Atemwege

Survival

Overall survival

This outcome is described in chapter 5.1.1.

Quality of life

CHAQ disability index

This outcome is described in chapter 5.1.1.

MPS Health Assessment Questionnaire (MPS HAQ)

This outcome is described in chapter 5.1.1.

5.6.2 Included studies

Eleven single-arm studies were included in this systematic review, ten [129-137] were identified in the published systematic review, and one was identified after performing the updated search [133]. No additional study was found through the manual search.

11 Single-Arm-Studien, 10 aus SR, 1 nach Aktualisierung

Characteristics of the prospective, single-arm studies

The study and patients' characteristics of the included studies are presented in Table 5-19 and Table 5-20. Most studies (7/11) were conducted in multiple centers [130, 132-134, 136, 138, 139]. Three studies reported outcome from the Hunter Outcome Survey (HOS) [130, 134, 136]. Five studies were conducted in multiple countries [130, 132-134, 136], two in Italy [137, 139], two in Poland [129, 135], one in South Korea [131] and Japan [138]. Most studies (8/11) reported receiving funding, four of which included funds from Shire, a Takeda company, that developed idursulfase treatment [130, 133, 134, 136].

meist multizentrisch (7/11), mehrere Länder, v. a. Hunter Outcome Survey (HOS) Daten; Länder: Italien, Polen, Südkorea, Japan, u. a.

In six studies either all or a great portion of authors declared a conflict of interest that included pharmaceutical companies involved in LSD ERTs development (such as Shire, Sanofi-Genzyme, among others) [130, 132-134, 136, 138], in two studies these rates were 15% and 30% [137, 139], and in three studies no conflict of interest was declared [129, 131, 135].

8/11 Studien mit Finanzierung

kein COI in nur 3 Studien

The patients mainly received the standard ERT dose (0.5 mg/kg weekly). The number of patients ranged from 895 [136] to 16 [129], and most studies included only male patients, which reflects the X-chromosomal trait of inheritance of this MPS. The follow-up ranged from a total of 2 years [133] to a median of 13 for treated and 15.1 years for untreated patients [136].

Pts.-zahl zwischen 16-895, meist männlich

Standard ERT: 0,5 mg/kg/Woche

Losses to follow-up ranged from none [129, 131] to a considerable number of drop-outs in three studies. One study reported approximately 35% loss to follow-up due to discontinuations due to investigator termination, withdrawal of consent, other reasons [130]. Another study reported 58% discontinuation, primarily because patients enrolled in a phase 2/3 idursulfase-intrathecal trial; the authors noted that patients experiencing cognitive decline may have been underrepresented in the final study population [133]. The authors noted that given that any patients who were enrolled into the phase 2/3 trial were subsequently discontinued from the current study, patients actively undergoing cognitive decline from the baseline values stated above may be underrepresented in the final study population. In one study 67% of the patients discontinued the study mainly due to clinical decline. However, the authors presented the analysis on ERT-induced changes separately for the patients who discontinued and those who did not [135].

bis zu 67 % Abbruch in Einzelfällen

Gründe: klinischer Rückgang, Studienwechsel, Verlauf der Kognition

Patient characteristics in the prospective, single-arm studies

Diagnose-& Zusatzkriterien

Included studies enrolled patients with a confirmed diagnosis of MPS II, established by clinical features (e.g., hepatosplenomegaly, dysostosis multiplex, valvular heart disease, airway obstruction), biochemical evidence of deficient iduronate-2-sulfatase (I2S/IDS) activity with normal activity of other sulfatases, elevated urinary glycosaminoglycans, and/or pathogenic IDS gene variants. Some trials additionally required abnormal pulmonary function (FVC <80% predicted) [132], minimum DAS-II scores, adequate hearing [133], age restrictions (≥2 to 31 years), absence of prior tracheostomy or hematopoietic transplant [132, 134], and enrolment in the Hunter Outcome Survey (HOS) [130, 134].

Alter Baseline: 5,6-14,5 Jahre (Mittel); Diagnosealter 3,1-4,0 Jahre (Median)

The baseline age of enrolled patients varied from a mean 5.6 years [133] to a mean of 14.5 years [132]. Age at diagnosis ranged from a median of 3.1 years [134] to a median of 4.0 years [137]. Age of symptom onset ranged from a median of 0.9 [137] to a median of 1.5 years [134], while age of ERT initiation ranged from a median of 5.3 years [139] to a median of 14.5 years [132]. However, this information was not reported in all studies.

Phänotypen: schwere (neuronopathisch) und attenuiert

All studies included individuals with both the severe (neuronopathic) and the attenuated (non-neuronopathic) phenotype. One study reported outcomes separately for these phenotypes; however, follow-up for patients with the attenuated phenotype was less than two years, and therefore, these results were not extracted or presented in this review [129].

Table 5-19: Study and patients' characteristics of single-arm studies investigating idursulfase in MPS II (part 1).

Author, year	Muenzer et al., 2011 [132]	Kim et al., 2013 [131]	Tomanin et al., 2014 [139]	Parini et al., 2015 [137]	Bik-Multanowski et al., 2017 [135]
Study design	Observational, multi-center, open-label study	Observational, single-center, open-label study	Observational, multi-center, open-label study	Observational, single-center, open-label study	Observational, open-label study
Country	Multiple countries	South Korea	Italy	Italy	Poland
Funding/Conflict of interest (CoI)	Funding: National Center of Research Resources, National Institutes of Health. 16/20 authors with CoI: honoraria, consultancy, travel grants, or research funding; Shire HGT, Genzyme, Biomarin.	Funding: None declared. Authors with CoI: None declared.	Funding: AIFA (Italian Medicine Agency). 2/13 with CoI: research grants, honoraria, and travel support; Actelion, Shire HGT, Genzyme Corporation, and BioMarin.	Funding: Fondazione Pierfranco and Luisa Mariani, Milano. 7/23 with CoI: honoraria; Genzyme, Shire, and BioMarin.	Funding: None declared. Authors with CoI: None declared.
Description of the intervention (idursulfase dosage)	0.5 mg/kg weekly and every other week[a]	0.5 mg/kg weekly	0.5 mg/kg weekly	0.5 mg/kg weekly	0.5 mg/kg weekly
Comparator	/	/	/	/	/
Number of patients, n (female)	Baseline: 32 (0.5 mg/kg weekly) 32 (0.5 mg/kg every other week) 32 (placebo) Extension: 94 (total)	34 (0)	27 (NR)	17 (0)	45 (NR)
Inclusion criteria	MPS II patients aged 5-31 years. Required abnormal FVC (<80% predicted) and the ability to perform PFT, with no prior tracheostomy or bone marrow/cord blood transplant.	MPS II patients; diagnosis based on clinical findings and increased urinary GAGs, confirmed by genetic testing and leukocyte enzyme assays.	MPS II patients confirmed by low/absent IDS activity, normal activity of other sulfatases (excluding multiple sulfatase deficiency), and elevated urinary heparan- and dermatan-sulfate.	MPS II patients confirmed by low I2S activity and pathogenic I2S gene mutations.	MPS II patients aged >5 years
Age at baseline (mean ± SD), years	14.5 ± 0.68	NR	NR	NR	NR
Age at diagnosis (median (range), years	NR	NR	3.5 (0.9-15.5)	4.0 (2.0-4.6)	NR
Age at symptom onset (median (range)), years	NR	NR	NR	0.9 (0-3)	NR
Age at start of ERT (median (range), unless otherwise specified), years	14.5 (5.4-30.9)	12 (3-38)	5.3 (1.6-27)	8 (2.3-25.5)	Range: (0.3-32.5)
Patients with neuronopathic MPS II, Y/N (n/N)	NR	Y (15/34)	Y (17/27)	Y (11/17)	NR
Follow-up (median (range), unless otherwise specified, years)	3.0[b]	~ 3.0 (0.3-3.5)	Median: ~3.3	7.8 (3.0-10.3)	Range: (<0.5-6.0)
Loss to follow-up, n	8/94 (8.51%)—transferred to their home countries, continued treatment, but no follow-up data available	None reported.	1 (death)	1/17 (5.88%)—discontinuation due to tracheotomy, followed by death	30/45 (66.67%) discontinuation – 25 due to clinical decline, 3 died, and 2 had anaphylaxis. [c]

Abbreviations: CoI … conflict of interest, ERT … enzyme replacement therapy, FU … follow-up, FVC … forced vital capacity, I2S … iduronate-2-sulfatase, GAGs … glycosaminoglycans, IDS … iduronate-2-sulfatase (gene/enzyme), MPS II … mucopolysaccharidosis II, n … number, NR … not reported, PFT … pulmonary function test, SD … standard deviation, Y/N … Yes/No.

Notes:

[a] *Patients in the active treatment groups received idursulfase for 36 months, while those in the placebo group received it for 24 months.*

[b] *An extension study of an RCT: 1 year (RCT) + 2 years (extension study), resulting in a total of 3 years.*

[c] *The analysis was done separately for the patients who discontinued and those who did not.*

Table 5-20: Study and patients' characteristics of single-arm studies investigating idursulfase in MPS II (part 2).

Author, year	Giugliani et al., 2017 [130]	Burton et al., 2017 [136]	Muenzer et al., 2017 [134]	Ueda et al., 2020 [138]	Marucha et al., 2022 [129]	Muenzer et al., 2023 [133]
Study design	Observational, multi-center, open-label HOS study	Observational, multi-center, open-label HOS study	Observational, multi-center, open-label HOS study	Observational, multi-center, post-marketing study	Observational, single-center, open-label study	Observational, multi-center, open-label study
Country	Multiple countries	Multiple countries	Multiple countries	Japan	Poland	Argentina, Mexico, Spain, the UK, and the USA
Funding/ Conflict of interest (CoI)	Funding: Shire, US. 9/9 authors with CoI: advisory board/ consultancy, honoraria, or research funding, employment; Actelion, BioMarin, GSK, Sanofi-Genzyme, Shire, Amicus, Synageva.	Funding: Shire US Inc All authors with CoI: employment at Shire, Cytel Inc, consultancy/ honoraria; Shire, BioMarin, Sanofi, etc.	Funding: Shire, Switzerland All authors with CoI: consultancy, research support, advisory boards, employment; Actelion Pharmaceuticals, Alexion, Amicus, BioMarin, Cytel Inc., Eloxx, Green Cross, Janssen Pharmaceuticals, PTC Therapeutics, Sanofi Genzyme, Shire, Synageva BioPharma.	Funding: Sanofi Both authors with CoI: employment, salary support, and Sanofi.	Funding: NR. Authors with CoI: None declared.	Funding: Shire (now Takeda) All authors with CoI: consultancy, speaker fees, or research support; 44 companies, including Sanofi Genzyme and Takeda, among others.
Description of the intervention (idursulfase dosage)	0.5 mg/kg weekly	0.5 mg/kg weekly	NR	0.5 mg/kg weekly	0.5 mg/kg weekly	0.5 mg/kg weekly
Comparator	/	Untreated patients [a]	/	/	/	/
Number of patients, n (female)	26 (0)	895 (0) Treated: 800 Untreated: 95	639 (0)	145 (1)	16 (1)	55 (0)
Inclusion criteria	Male Hunter syndrome patients ≥5 y, enrolled in HOS, on idursulfase or starting within 30 days.	Male patients with biochemically or genetically confirmed MPS II, prospectively enrolled in the HOS. Treated = ≥1 dose IV idursulfase; untreated = never received.	Male patients on idursulfase ≥6 months, followed prospectively, without a bone marrow transplant, and enrolled at HOS.	All Japanese patients diagnosed with MPS II, treated with idursulfase 0.5 mg/kg weekly, centrally registered.	MPS II patients – reduced IDS activity and IDS gene sequencing.	Male patients ≥2 – <18 y with confirmed MPS II (I2S ≤10% LLN + IDS variant or normal other sulfatase), DAS-II GCA ≥55, and adequate hearing.
Age at baseline (mean ± SD (unless otherwise specified)), years	12.8 ± 8.0	Treated: Median (P10, P90): 7.9 (2.6-21.1) Untreated: Median (P10, P90): 10.1 (2.8-21.0)	NR	13.01 ± 10.89	NR	5.60 ± 3.32

Author, year	Giugliani et al., 2017 [130]	Burton et al., 2017 [136]	Muenzer et al., 2017 [134]	Ueda et al., 2020 [138]	Marucha et al., 2022 [129]	Muenzer et al., 2023 [133]
Age at diagnosis (median (range) unless otherwise specified), years	3.8 (0.1-20.0)	Treated: Median (P10, P90): 3.3 (1.0-7.1) Untreated: Median (P10, P90): 3.2 (0.9-10.8)	Median (P10, P90): 3.1 (1.0, 6.7)	4.0 (0-53)	Mean (range): 3.3 (<1-8.5)	NR
Age at symptom onset (median (range)), years	NR	Treated: Median 1.6 (P10: 0.3, P90: 4.3) Untreated: Median (P10, P90): 1.5 (0.2-4.2)	1.5 (0.3, 4.0)	1.0 (0-12)	NR	NR
Age at start of ERT (median (range), unless otherwise specified), years	NR	6.9 (P10, P90: (2.1-19.8)	(P10, P90): 6.2 (2.1, 18.2)	10.0 (0-54)	8.7 (<1-28)	NR
Patients with neuronopathic MPS II, Y/N (n/N)	Y (13/24)	Treated: 464/800 Untreated: 55/95 Overall: 519/895	Y (385/626)	72/141	Y (12/16)	NR
Follow-up (median (range), unless otherwise specified), years	~2.1 [b]	13 (treated) 15.1 (untreated)	4.7 (1.5-8.1) [c]	8 years post-treatment initiation Mean treatment duration: ~5.4 years	1.3-1.6 years (non-neuronopathic patients) [d] 4.4 (2.1-6.4) years (neuronopathic patients)	2[c]
Loss to follow-up, n	9/26 (34.61%) (discontinuations due to investigator termination – 3, lost to follow-up – 2, withdrawal of consent – 1, other reasons – 3).	NR	NA – patients with insufficient follow-up initially excluded.	26/145 (12 transfers, 5 ADRs, 9 other – e.g., HSCT, personal)	None reported. [e]	32 (58.2%) discontinued – noncompliance (1), withdrawal (4), loss to FU (2), enrolled in phase 2/3 idursulfase-IT trial (25). [f]

Abbreviations: ADR … adverse drug reaction, CoI … conflict of interest, DAS-II … Differential Ability Scales, Second Edition, ERT … enzyme replacement therapy, FU … follow-up, GCA … General Conceptual Ability (from DAS-II), HOS … Hunter Outcome Survey, HSCT … hematopoietic stem cell transplantation, I2S … iduronate-2-sulfatase, IDS … iduronate-2-sulfatase (gene/enzyme), IV … intravenous, LLN … lower limit of normal, MPS II … mucopolysaccharidosis type II, n … number, NA … not applicable, NR … not reported, P10 … 10th percentile, P90 … 90th percentile, SD … standard deviation, Y/N … Yes/No.

Notes:

[a] *Single-arm in design but divided patients into treated and untreated for survival analysis.*

[b] *The value represents the total duration, rather than a mean or median.*

[c] *The total duration of idursulfase therapy received by the patients; however, the results are reported for a three-year time frame.*

[d] *Due to a follow-up period of less than 2 years, data for the non-neuronopathic patient group were not extracted.*

[e] *Long-term follow-up data are available only for the severe MPS II phenotype patients (n=12).*

[f] *Since patients enrolled in the phase 2/3 trial were later discontinued, those experiencing cognitive decline from baseline may be underrepresented in the final population.*

5.6.3 Results

Long-term effectiveness of idursulfase in MPS II is presented in Table 5-21 and Table 5-22.

Motor Function

6MWD

Three studies reported 6MWD with follow-up up to three years (total n=88) and observed an overall increase in 6MWD after idursulfase therapy. One study presented these findings graphically without providing exact values [132]. Another study observed that five out of six patients experienced improvement [139], while the third study reported an increase from baseline, without reporting the p-values [134].

6MWD: Anstieg bis 3 J. (n=88)

Further, two studies with seven years of follow-up reported similar findings among patients with non-neuronopathic MPS II phenotype. One showed an average increase of ~30 m in 6MWD [138], while the other reported stable or improved motor function [137]. There was no improvement among patients with the severe phenotype, most of whom were untestable due to hyperactive behaviour or wheelchair dependence [137]. In one study with follow-up from 0.5 to 6 years, among the patients who continued ERT at the time of assessment (n=13), the majority experienced an improvement, while among those who had discontinued ERT (n=30), half of them experienced a decline, and almost half remained stable [135].

non-neuronopathische MPS II: +30m nach 7 J;

keine oder Verschlechterung bei schwer Erkrankten

nach Abbruch der ERT meist Verschlechterung

Joint Function

Joint range of motion (JROM)

Two studies with up to three years of follow-up generally did not observe statistically significant changes in JROM after ERT. One study (n=56) reported significant improvement only in shoulder ROM, with no consistent changes in other joints [132]. Another study (n=27) found no significant improvement in upper or lower limb ROM [139].

kaum signifikante Änderungen in 3-jährigen Studien; einzelne Verbesserungen (Schulter)

A study with 4.4 years of follow-up in neuronopathic MPS II patients (n=12) observed significant declines in shoulder flexion, shoulder abduction, elbow flexion, elbow extension, and knee extension ($p < 0.05$), whereas declines in wrist flexion and extension, and hip extension were not statistically significant ($p > 0.05$) [129]. In the longest follow-up study (7.8 years, n=17), the greatest gains in JROM occurred during the first two years for both phenotypes (shoulder, elbow, hip, knee). At year five, significant improvement was observed only in right shoulder flexion (n=13, p=0.03), and no patient experienced decline in JROM over 7.8 years [137].

längere Studien zeigten nach 2 Jahren Stabilisierung; bei neuronopathischem Verlauf teils Verschlechterungen in mehreren Gelenken

Cognitive Function

Differential Ability Scales, Second Edition (DAS II)

After 2 years of ERT, decreases were observed across all DAS-II clusters (verbal, nonverbal and spatial) and in composite scores (GCA and SNC), with declines ranging from –6.4 to –3.8 [133].

Abnahmen alle Cluster (–6,4 bis –3,8) nach 2 J ERT

Respiratory Function

Sleep apnoea

In the study with the longest follow-up [137], two patients with severe obstructive apnoea were present before and following 7 and 5 years of ERT, respectively.

schwere Apnoen persistent nach 5-7 J

Airway obstruction

The same study reported that four patients had severe obstructive airway disease at study end; two of these patients had worsened from baseline [137].

bei 4 Pts. schwere Obstruktion am Studienende, davon 2 mit Verschlechterung

Survival

Overall survival

This outcome was not reported in any of the included studies.

Quality of life

Childhood Health Assessment Questionnaire (CHAQ) disability index

Parent-reported CHAQ disability index scores (n=81) showed a significant decrease at 2 years, which remained significant at 30 months but not at 3 years. Similarly, child-reported CHAQ scores (n=44) demonstrated significant improvement at 2 years, with this effect persisting at both 30 and 36 months [132].

signifikante Verbesserung nach 2 J; keine nach 3 J (n=81) bei Eltern

The MPS Health Assessment Questionnaire (MPS-HAQ)

One study with 5-9 years of follow-up (n=15) reported outcomes as proportions of domains showing improvement, decline, or stability. Non-neuronopathic patients (n=5) had more favourable outcomes than neuronopathic patients (n=10): improvement in 44% vs. 17% of domains, decline in 6% vs. 62%, and stability in 52% vs. 21%, respectively [137].

non-neuronopathisch: bei 44 % besser, 52 % stabil;

neuronopathisch: bei 17 % besser, bei 62 % schlechter

Table 5-21: Effectiveness results for idursulfase in MPS II patients in single-arm studies (part 1).

Author, year	Muenzer et al., 2011 [132]	Kim et al., 2013 [131]	Tomanin et al., 2014 [139]	Parini et al., 2015 [137]	Bik-Multanowski et al., 2017 [135]
Motor function					
6MWD	Baseline (mean ± SE): 400 ± 10 m 3-year endpoint: sig. increase (graphically presented)	NR	3.3-year endpoint: 4 patients: ~20% improvement vs age-matched norms; one patient improved by 37%, one patient declined by 13%. [a]	7-year endpoint (neuronopathic phenotype): no improvement; mostly untestable 7-y endpoint (non-neuronopathic phenotype): stable/improved; mean +70.8 (0-174).	During 0.5-6 years of FU (patients still receiving ERT, n=13, ≤6 y): 10 improved, 2 stable, 1 declined. During 0.5-6 years of FU (patients who discontinued ERT): 15 declined, 14 were stable, and 1 improved.
Joint mobility					
Joint range of motion	3-year endpoint: sig. improvement only in the shoulder; no consistent change in other joints.	NR	3.3-year endpoint: no sig. improvement in lower or upper limbs.	Greatest gains in the first 2 years (shoulder, elbow, hip, knee). At 5 years (n=13), only the right shoulder improved sig. (p=0.03). None of the patients declined after 7.8 years.	NR
Cognitive function					
DAS II	NR	NR	NR	NR	NR
Respiratory function					
Sleep apnoea	NR	NR	NR	Two patients with severe obstructive apneas before and following 5 and 7 years of ERT.	NR
Airway obstruction	NR	NR	NR	7.8-year endpoint: 4 patients with severe obstructive airway disease; 2 patients worsened from baseline.	NR
Survival					
Overall survival	NR	NR	NR	NR	NR
Quality of life					
CHAQ/HAQ disability index	Parent-assessed CHAQ 2-year vs. baseline: −0.13 ± 0.064 (p=0.047) Stat. sig. improvements present at month 30, not at 36. Childhood-assessed CHAQ 2-year vs. baseline: −0.15 ± 0.65 (n=44, p=0.031). Stat. sig. improvements also at months 30 and 36.	NR	NR	NR	NR

Author, year	Muenzer et al., 2011 [132]	Kim et al., 2013 [131]	Tomanin et al., 2014 [139]	Parini et al., 2015 [137]	Bik-Multanowski et al., 2017 [135]
MPS HAQ	NR	NR	NR	After 5-9 years of FU, Non-neuronopathic phenotype: 23/52 HAQ domains improved, 3/52 declined, and 27/52 remained stable. Neuronopathic phenotype: 9/52 HAQ domains improved, 32/52 declined, and 11/52 remained stable.	NR

Abbreviations: 6MWD … 6-minute walking distance, CHAQ/HAQ disability index … Childhood Health Assessment Questionnaire/Health Assessment Questionnaire Disability Index, ERT … enzyme replacement therapy, FU … follow-up, MPS HAQ … MPS Health Assessment Questionnaire, NR … not reported, SE … standard error, stat. sig. … statistically significant.

Note:

[a] *Only 6 patients were able to perform these assessments.*

Table 5-22: Effectiveness results for idursulfase in MPS II patients in single-arm studies (part 2).

Author, year	Giugliani et al., 2017 [130]	Burton et al., 2017 [136]	Muenzer et al., 2017 [134]	Ueda et al., 2020 [138]	Marucha et al., 2022 [129]	Muenzer et al., 2023 [133]
Motor function						
6MWD	NR	NR	3-year endpoint: Median change vs. baseline (P10, P90): +41 (−138-158) m Median % change (P10, P90): +10.6% (−33.6-50.8)	7-year endpoint: Mean change vs. baseline: +31.8 m (95% CI: −4.1-67.7)	NR	NR
Joint function						
Joint range of motion (mean ± SD), °	NR	NR	NR	NR	Passive JROM – 4.4 years endpoint Improvements were noted in 3/17 patients in several joints Shoulder flexion: 147.5 ± 19.1 → 129.2 ± 13.8 (p=0.027) Shoulder abduction: 140.0 ± 22.2 → 105.0 ± 18.3 (p=0.003) Elbow flexion: 148.8 ± 9.3 → 130.8 ± 14.0 (p=0.008) Elbow extension: -15.8 ± 16.2 → −31.7 ± 13.2 (p=0.008) Wrist flexion: 70.8 ± 21.9 → 60.0 ± 25.9 (p=0.114)	NR

Author, year	Giugliani et al., 2017 [130]	Burton et al., 2017 [136]	Muenzer et al., 2017 [134]	Ueda et al., 2020 [138]	Marucha et al., 2022 [129]	Muenzer et al., 2023 [133]
Joint range of motion (mean ± SD), ° *(continuation)*					Wrist extension: 57.5 ± 24.5 → 26.7 ± 17.2 (p=0.070) Hip extension: 11.7 ± 10.3 → −7.5 ± 18.6 (p=0.077) Knee extension: -7.5 ± 7.2 → −17.9 ± 11.2 (p=0.023)[a]	
Cognitive function						
DAS II (mean ± SD)	NR	NR	NR	NR	NR	DAS II Verbal cluster score 2-year FU vs. baseline: −6.4 ± 17.66 DAS II Nonverbal cluster score 2-year FU vs. baseline: −5.3 ± 16.81 DAS II Spatial cluster score 2-year FU vs. baseline: −3.9 ± 18.19 DAS II GCA Composite score 2-year FU vs. baseline: −3.8 ± 12.71 DAS II SNC Composite score 2-year FU vs. baseline: −5.4 ± 16.43
Respiratory function						
Sleep apnoea	NR	NR	NR	NR	NR	NR
Airway obstruction	NR	NR	NR	NR	NR	NR
Survival						
Overall-survival	NR	13-15 years endpoint Median survival (95% CI) Treated: 33.0 (30.4-38.4) years Untreated: 21.2 (16.1-31.5) years	NR	7-year endpoint survival rate All patients: 82.7% Mild phenotype: 91.2% Severe phenotype: 76.7%.	NR	NR
Quality of Life						
CHAQ/HAQ disability index	NR	NR	NR	NR	NR	NR
MPS HAQ	NR	NR	NR	NR	NR	NR

Abbreviations: 6MWD … 6-minute walking distance, CHAQ/HAQ disability index … Childhood Health Assessment Questionnaire/Health Assessment Questionnaire Disability Index, CI … confidence interval, DAS II … Differential Ability Scales, Second Edition, FU … follow-up, GCA … General Conceptual Ability, JROM … joint range of motion, MPS HAQ … MPS Health Assessment Questionnaire, n … number, NR … not reported, p … p-value, P10 … 10th percentile, P90 … 90th percentile, SD … standard deviation, SNC … special nonverbal composite, vs. … versus.

Note:

[a] *Passive JROM for non-neuronopathic (attenuated) phenotype patients was not extracted due to the short FU.*

5.7 Elosulfase alfa for Mucopolysaccharidosis IVA

5.7.1 Description of Outcomes

Outcomes im jeweiligen Kapitel erklärt

Motor Function

6MWD

See chapter 5.1.1 for description.

Cardiac Function

Left ventricular mass index

See chapter 5.1.1 for description.

Interventricular septal thickness, diastole

This outcome is the thickness of the interventricular septum measured at end-diastole [140].

Left ventricular internal diameter, diastole

This outcome is the internal dimension of the left ventricular cavity, measured at end-diastole, typically in the parasternal long-axis view [140].

Left ventricular posterior wall thickness, diastole

This outcome is the thickness of the left ventricular posterior wall, measured at end-diastole [140].

Ejection fraction

See chapter 5.1.1 for description.

Survival

Overall survival

See chapter 5.1.1 for description.

Quality of life

MPS Health Assessment Questionnaire (MPS HAQ)

See chapter 5.6.1 for description.

5.7.2 Included studies

Three studies were identified through the systematic search – one controlled study reported in two publications [141, 142] is presented in Table 5-23, and two single-arm trials [143, 144] are presented in Table 5-24.

1 kontrollierte (MOR-005, Phase 3 Extension MOR-004), 2 einarmige Studien

Characteristics of the prospective, controlled study

kontrollierte Studie: open-label, multizentrisch/ international; BioMarin-finanziert

One controlled study [141, 142] (MOR-005) was identified. MOR-005 was an open-label, multi-center, multi-national, phase 3 extension study of the pivotal 24-week, placebo-controlled trial MOR-004 [145]. The study was funded by BioMarin Pharmaceutical Inc. In both publications, most authors reported conflicts of interest, including grants, personal fees, or support from BioMarin and other pharmaceutical companies (Genzyme, Shire, Alexion, Ultragenyx, etc.) [141, 142].

3 Dosierungs-Arme in MOR-004

alle 2,0 mg/kg wöchentlich (nach 36–96 Wochen) in MOR-005

In MOR-004, three groups of treatment-naïve patients were included: one received 2.0 mg/kg of elosulfase alfa weekly, one received 2.0 mg/kg every other week, and one received placebo. In the extension study (MOR-005), all patients received 2.0 mg/kg weekly after 36-96 weeks. The comparator population comprised untreated patients from the MorCAP natural history study (MOR-001) [146], matched by age and baseline 6MWD.

Due to the long-term design of MOR-005, surgeries were not restricted, and a modified-per-protocol (MPP) population was defined. The MPP population excluded 49 patients: 38 who underwent orthopaedic surgery and 14 with ≥20% missed infusions. Final sample sizes for MOR-004 and MOR-005 ITT, and MPP populations are presented in Table 5-23. Over 2-3 years of follow-up, one publication reported that 17 patients did not complete the study (1 withdrawal, 16 discontinued, mainly due to early switch to commercial drug) [141], and in the other publication not all endpoint data were available, without specifying the reasons [142].

Patient characteristics in the prospective, controlled study

therapienaive MPS IVA, mittleres Alter: 14,4 Jahre

The RCT part of the study (MOR-004) included treatment-naive MPS IVA patients, with a mean 14.4 years. Age at diagnosis, symptom onset, and phenotype severity (classical vs attenuated) were not reported [141, 142].

Table 5-23: Study and patients' characteristics of controlled study investigating elosulfase alfa in MPS IVA.

Author, year	Hendriksz et al., 2016 [147]	Hendriksz et al., 2018a [142]
Study design	MOR-005, open-label, multi-center, phase 3 extension study	
Country	Multiple countries	
Funding/Conflict of interest (CoI)	Funding: BioMarin Pharmaceutical Inc 18/21 authors with CoI: grants, personal fees, or support from BioMarin and other companies (Genzyme, Shire, Alexion, Ultragenyx, etc.).	Funding: BioMarin Pharmaceutical Inc 11/14 authors with CoI: grants, personal fees, or support from BioMarin and other companies (Genzyme, Shire, Alexion, Ultragenyx, etc.).
Description of the intervention (elosulfase alfa dosage)	Initially: 2.0 mg/kg weekly or every other week. After 36–96 weeks, all patients transitioned to 2.0 mg/kg weekly.	
Comparator, n (female)	Untreated population from the MorCAP natural history study (MOR-001) MORCap ITT 97 (56) MORCap MPP 78 (47)[c]	
Number of patients, n (female)	MOR-004 176 (89) MOR-005 ITT 173 (87) MOR-005 MPP 124 (58)[a]	MOR-004 176 (89) MOR-005 ITT 169 (84) MOR-005 MPP 124 (58)[a]
Inclusion criteria	MPS IVA patients ≥ 5 years of age, with a baseline 6MWD distance between 30 and 325 m, with no major surgery within 3 months before entry, who completed the pivotal 24-week placebo-controlled MOR-004 trial.	
Age at baseline (mean ± SD), years	14.4 ± 10.2	
Age at diagnosis (median (range), years	NR	

Author, year	Hendriksz et al., 2016 [147]	Hendriksz et al., 2018a [142]
Age at symptom onset (median [range]), years	NR	
Age at start of ERT (mean ± SD, years)	14.4 ± 10.2	
Classical vs attenuated phenotype, n	NR	
Follow-up, years	~2.3[b]	
Loss to follow-up, n	1 patient withdrew 16 discontinued (mainly early switch to commercial drug)	11/169 (6.5%) – not available for the 2-year FU for the ITT group 2/124 (1.6%) – not available for the 2-year FU for the MPP group

Abbreviations: 6MWD … 6-minute walking test, ERT … Enzyme replacement therapy, FU … follow-up, ITT … Intention-to-treat, MPP … modified per-protocol, MorCAP … Morquio A Clinical Assessment Program, MPS IVA … Mucopolysaccharidosis type IVA (Morquio A syndrome), n … number, NR … not reported, SD … standard deviation.

Notes:

[a] *An intention-to-treat population for the ERT group and for the untreated group, and a modified-per-protocol (MPP) population. The MPP population excluded 49 patients: 38 with orthopedic surgery and 14 with ≥20% missed infusions (non-compliance).*

[b] *Initial phase (MOR-004 study), the pivotal, placebo-controlled trial, 24 weeks long + the open-label extension phase (MOR-005 study), 96 weeks long.*

Characteristics of the prospective, single-arm studies

Two single-arm trials were included – one conducted in Australia [143] and one in the United Kingdom [144]. Both were funded by BioMarin Pharmaceutical Inc. and in both publications most authors reported a conflict of interest, such as grants, honoraria, consultancy, and trial funding from BioMarin, and other pharmaceutical companies (Amicus, Shire, Actelion, Sanofi Genzyme, etc).

je 1 einarmige Studie in Australien & UK; beide BioMarin-finanziert

hoher COI

Both studies were extension studies of open-label, non-controlled trials, evaluating long-term effectiveness and safety of elosulfase alfa in MPS IVA patients. One study used a standard dose of 2.0 mg/kg weekly throughout [143]. The other study included a dose-escalation phase (0.1, 1.0, and 2.0 mg/kg weekly for 12 weeks each), followed by 1.0 mg/kg weekly for 36–48 weeks in MOR-002, and 2.0 mg/kg weekly for up to 192 weeks in the long-term extension (MOR-100). Total follow-up durations were approximately 2.5 years [143] and 5 years [144]. Loss to follow-up was up to 10% in both studies.

Erweiterungsstudien, offen und unkontrolliert, Langzeitwirksamkeit, Sicherheit

unterschiedliche Dosierungen

Patient characteristics in the prospective, single-arm studies

Both studies included MPS IVA patients. One study restricted enrolment to ages 5-18 years [144]. Mean age at baseline for both populations were similar 9.3 [143] and 8.4 years [144]. As all patients were ERT-naïve at baseline, age at study entry corresponded to age at ERT initiation. One study reported most patients had classical (severe) MPS IVA phenotype [143] and the other did not disclose this information.

Pts. auf 5-18 J in einer Studie beschränkt, durchschnittlich ca. 8-9 J; therapienaive MPS IVA

Table 5-24: Study description and patients' characteristics of single-arm studies investigating elosulfase alfa in MPS IVA.

Author, year	Bhattacharya et al., 2020 [143]	Hendriksz et al., 2018b [144]
Study design	Prospective, observational, open-label, phase 3b, extension, multicenter study	MOR-002/MOR-100, open-label, multi-center, long-term extension study
Country	Australia	United Kingdom
Funding/Conflict of interest (CoI)	Funding: BioMarin Pharmaceutical Inc. 11/12 authors with CoI: grants, honoraria, consultancy, and trial funding from BioMarin + activities with Genzyme, Amicus, Shire, Actelion, and Sanofi Genzyme.	Funding: BioMarin Pharmaceutical Inc. 9/14 authors with CoI: employment and stock-holding of BioMarin; research funding, consultancy, honoraria, or advisory board fees from BioMarin, Shire, Genzyme, Ultragenyx, Alexion, Orchard.
Description of the intervention (elosulfase alfa dosage)	2.0 mg/kg weekly.	MOR-002: dose-escalation phase with 0.1, 1.0, and 2.0 mg/kg weekly (each for 12 weeks), then continuation on 1.0 mg/kg weekly for 36–48 weeks. MOR-100: long-term extension with 2.0 mg/kg weekly for up to 192 weeks.
Comparator	/	/
Number of patients, n (female)	13 (5)	MOR-002 20 (8) MOR-100 17 (8)
Inclusion criteria	MPS IVA patients via documented GALNS enzyme deficiency	MPS IVA patients, aged 5-18 years
Age at baseline (mean ± SD), years	9.3 ± 7.7	8.4 ± 2.9
Age at diagnosis (mean ± SD), years	2.2 ± 1.4	NR
Age at symptom onset (median [range]), years	NR	NR
Age at start of ERT (mean ± SD), years	9.3 ± 7.7	8.4 ± 2.9
Classical vs attenuated phenotype, n	Classical phenotype (majority of patients)	NR
Follow-up, years	~2.5[a]	~5[b]
Loss to follow-up, n	1/13 (7.7%) discontinued at week 104 (spinal cord infarction, not drug-related).	2/20 (10%) withdrew during 0.1 mg/kg (1 hypersensitivity, 1 sibling); 1 discontinued at week 45 due to infusion reactions (remained in follow-up up to week 72).

Abbreviations: CoI … conflict of interest, ERT … enzyme replacement therapy, GALNS … N-acetylgalactosamine-6-sulfatase, MPS IVA … Mucopolysaccharidosis type IVA (Morquio A syndrome), n … number, NR … not reported, SD … standard deviation.

Notes:

[a] *Initial phase: 49 weeks. Extension: up to ~138 weeks (~2.5 years mean total exposure).*

[b] *MOR-002 study: up to 72 weeks + MOR-100 study: additional 192 weeks.*

5.7.3 Results

Long-term effectiveness of elosulfase alfa in MPS IVA is presented in Table 5-25 for the controlled study, and Table 5-26 for the single-arm studies.

Motor Function

6MWD

6MWD (kontrolliert): Anstieg ITT/MPP nach 2,3 J; größer bei optimaler Dosis

unbehandelte Abnahme (signifikant)

In the controlled study 6MWD was assessed after 2.3 years of follow-up [141]. Increases from baseline were reported in both the ITT and MPP populations. Improvements were observed in patients receiving the optimal elosulfase alfa dose (2 mg/kg weekly) as well as in the overall pooled cohort, which included patients who initially received 1 mg/kg weekly or placebo before transitioning to the standard dose. Gains were greater in the MPP population, particularly among patients on the optimal regimen. Analysis of covariance (ANCOVA)

analyses indicated that untreated patients experienced a decline in 6MWD over the follow-up period. Differences between untreated and treated patients were statistically significant in both the ITT and MPP populations, irrespective of the ERT regimen.

In the single-arm trial (n=17), 6MWD was reported to remain stable over the 5-year treatment period [144].

6MWD (Single-Arm): Stabil über 5 J (n=17)

Cardiac Function

Left ventricular mass index

This outcome was not assessed in the included studies.

Herzfunktion: keine Parameter berichtet

Interventricular septal thickness, diastole

This outcome was not assessed in the included studies.

Left ventricular internal diameter, diastole

This outcome was not assessed in the included studies.

Left ventricular posterior wall thickness, diastole

This outcome was not assessed in the included studies.

Ejection fraction

This outcome was not assessed in the included studies.

Survival

Overall survival

This outcome was not assessed in the included studies.

Überleben: nicht berichtet

Quality of life outcomes

MPS Health Assessment Questionnaire (MPS HAQ)

In the controlled study (MOR-005), after 2 years of follow-up, patients receiving elosulfase alfa showed improvements from baseline in the mobility and self-care domains of the MPS-HAQ, with greater gains observed in the weekly-to-weekly (QW-QW) dosing cohort. In contrast, untreated patients from the MorCAP natural history cohort showed no improvement, and in some cases experienced worsening of functional abilities. Between-group comparisons indicated statistically significant advantages for treated patients in the ITT population for both mobility (−0.7, p=0.049) and self-care (−0.7, p=0.0146). Improvements in the caregiver-assistance domain were observed and reached statistical significance in the MPP population; however, between-group differences were not significant [142].

MPS-HAQ (kontrolliert): Mobilität/ Selbstversorgung verbessert; signifikant behandelt vs. unbehandelt

In the single-arm study, no notable changes were observed in the mobility, self-care, or caregiver-assistance domains at 1.4 years. By the 5-year endpoint, there was a slight decline in least squares mean scores across all three domains, suggesting maintenance of, or possible improvement in, quality of life. The data were presented graphically, and exact numerical values were not provided [144].

MPS-HAQ (single-arm): 1,4 J unverändert; 5 J leichter Rückgang (QoL stabil)

Table 5-25: Effectiveness results for elosulfase alfa in MPS IVA patients in single-arm studies.

Author, year	Hendriksz et al., 2016 [147]	Hendriksz et al., 2018a [142]
Motor function		
6MWD	ITT Population – QW–QW Cohort (Optimal Dosing)[a] 2.3-year endpoint: +32.0 m (SE 11.3) MPP Population – QW–QW Cohort 2.3-year endpoint: +39.9 m (SE 10.1) Pooled Cohorts (All Regimens Combined) ITT 2.3-year endpoint: +15.1 m (SE 7.1) Pooled Cohorts (All Regimens Combined) MPP 2.3-year endpoint: +31.7 m (SE 6.8) ITT Population/MorCAP 1 (untreated comparator): MorCAP: −16.4 m (SE 12.50) QW–QW cohort: +32.1 m (SE 11.75), p=0.005 Pooled cohorts: +16.8 m (SE 6.72), p=0.0198 MPP Population/MorCAP 2 (untreated comparator): MorCAP: −21.9 m (SE 12.30) QW–QW cohort: +39.0 m (SE 11.32), p=0.0003 Pooled cohorts: +32.9 m (SE 6.66), p=0.0001	NR
Cardiac function		
Left ventricular mass index	NR	NR
Interventricular septal thickness, diastole	NR	NR
Left ventricular internal diameter, diastole	NR	NR
Left ventricular posterior wall thickness, diastole	NR	NR
Ejection fraction	NR	NR
Survival		
Overall survival	NR	NR
Quality of life		
MPS-HAQ	NR	Mobility Domain ITT Population MOR-005 (all regimens): −0.5 (SE 0.1), p=0.0016 MOR-005 QW–QW cohort: −0.6 (SE 0.2), p=0.0116 MorCAP (untreated): +0.3 (SE 0.3), n.s. Difference MOR-005 vs. MorCAP: −0.7 (SE 0.4), p=0.0490 MPP Population MOR-005 (all regimens): −0.6 (SE 0.2), p < 0.0001 MOR-005 QW–QW cohort: −0.7 (SE 0.3), p=0.0111 MorCAP (untreated): +0.1 (SE 0.3), n.s. Difference MOR-005 vs. MorCAP: not significant Self-Care Domain ITT Population MOR-005 (all regimens): −0.4 (SE 0.1), p=0.0011 MOR-005 QW–QW cohort: −0.7 (SE 0.2), p=0.0018 MorCAP (untreated): +0.4 (SE 0.2), n.s. Difference MOR-005 vs. MorCAP: −0.7 (SE 0.3), p=0.0146 MPP Population MOR-005 (all regimens): −0.4 (SE 0.1), p=0.0036 MOR-005 QW–QW cohort: −0.8 (SE 0.2), p < 0.0001 MorCAP (untreated): +0.2 (SE 0.2), n.s. Difference MOR-005 vs. MorCAP: not significant Caregiver-Assistance Domain ITT Population MOR-005 (all regimens): −1.0 (SE 0.5), p=0.0625

Author, year	Hendriksz et al., 2016 [147]	Hendriksz et al., 2018a [142]
MPS-HAQ *(continuation)*		MOR-005 QW–QW cohort: −1.9 (SE 1.0), p=0.0625 MorCAP (untreated): −0.5 (SE 0.8), n.s. Difference MOR-005 vs. MorCAP: not significant MPP Population MOR-005 (all regimens): −1.3 (SE 0.6), p=0.0288 MOR-005 QW–QW cohort: −2.3 (SE 1.1), p=0.0387 MorCAP (untreated): −0.3 (SE 0.9), n.s. Difference MOR-005 vs. MorCAP: not significant

Abbreviations: 6MWD … 6-minute walking distance, ANCOVA … analysis of covariance, ITT … intention-to-treat, MPP … modified-per-protocol, MorCAP … Morquio A Clinical Assessment Program, MPS-HAQ … Mucopolysaccharidosis Health Assessment Questionnaire, NR … not reported, ns … not significant, SE … standard error. QW … once weekly.

Notes:

[a] *QW-QW – patients receiving the standard ERT regimen (elosulfase alfa 2.0 mg/kg/week) during the whole study.*

[b] *Higher scores mean worsening in the reported MPS-HAQ domain.*

[c] *P-value determined by t-test and the repeated measures ANCOVA model for the comparison between the treated and untreated population.*

Table 5-26: Effectiveness results for elosulfase alfa in MPS IVA patients in single-arm studies.

Author, year	Bhattacharya et al., 2020 [143]	Hendriksz et al., 2018b [144]
Motor function		
6MWD	NR[a]	Baseline: 266.9 ± 137.39 m 5-year endpoint: ~270 m (stable)
Cardiac function		
Left ventricular mass index	NR	NR
Interventricular septal thickness, diastole	NR	NR
Left ventricular internal diameter, diastole	NR	NR
Left ventricular posterior wall thickness, diastole	NR	NR
Ejection fraction	NR	NR
Survival		
Overall survival	NR	NR
Quality of life		
MPS-HAQ	NR	Self-care domain Baseline: 5.0 ± 2.96 Week 72: 5.5 ± 3.03 Mobility domain Baseline: 4.9 ± 2.69 Week 72: 4.9 ± 2.72 Caregiver assistance Baseline: 31.1 ± 7.59 Week 72: 31.4 ± 10.52 5-year endpoint: slight decline in least squares mean scores in all three domains, suggestive of maintenance or possible improvement (graphically presented).[b]

Abbreviations: 6MWD … 6-minute walking distance, MPS-HAQ … Mucopolysaccharidosis Health Assessment Questionnaire, NR … not reported.

Notes:

[a] *The study reported 6MWD data, but for a shorter follow-up (49 weeks). Only safety data are extracted and presented in Chapter 6.*

[b] *Self-care and mobility scores 0–10 (0 = not difficult; 10 = extremely difficult; 11 = unable to do). Caregiver assistance scores 0–48 (48 = complete assistance required).*

6 Safety

6.1 Alglucosidase-alfa in infantile-onset Pompe disease

6.1.1 Description of Outcomes

To evaluate the long-term safety of alglucosidase alfa in patients with IOPD, the following safety outcomes were defined as *critical* to derive a conclusion:

Kritische Outcomes: Mortalität, IARs, AEs/TEAEs (meist mild/moderat)

- **Mortality**: the number of deaths due to any cause.
- **Infusion-related reactions (IARs):** defined by the study authors as any treatment-related events that occurred during the infusion, within two hours afterward, or at any time on the day of infusion, as assessed by the investigator and deemed to be related to the treatment.
- **Adverse events (AEs):** defined by the study authors as clinical events occurring after initiation of ERT; in some reports, these are presented as treatment-emergent adverse events (TEAEs). A subset of studies coded AEs using the Medical Dictionary for Regulatory Activities (MedDRA), though most did not specify a coding dictionary. For this review AE/TEAE are summarized under the collective heading "Safety and tolerability outcomes," with treatment discontinuation rates reported where available.

6.1.2 Included studies

Three controlled trials and five single-arm trials reported safety outcomes of alglucosidase alfa treatment in IOPD. The characteristics of these studies are presented in chapter 5.1.2, Table 5-1 (for controlled studies) and Table 5-2 (for single-arm studies).

Studien: 3 kontrollierte, 5 single-arm

6.1.3 Results

Long-term safety outcomes of alglucosidase alfa in IOPD are presented in Table 6-1 and Table 6-2.

Mortality

All-cause mortality

Two controlled studies with up to 2.5 years of follow-up observed either a 95% lower mortality risk in 18 patients receiving variable ERT doses [82], or a 44.7% higher mortality rate in the control (non-ERT) group compared to the intervention group [83]. Another controlled-trial with a 5-year follow-up did not directly present mortality data as part of the survival Kaplan-Mayer curve, however, it is previously noted that ERT treatment and newborn screening led to significantly higher survival rates compared with no treatment or when patients received ERT but were diagnosed in clinical settings [80].

Mortalität (kontrolliert): 95 % geringeres Risiko; 44,7 % höher bei KG; höhere Überlebensrate mit ERT/Neugeborenen-Screening

The mortality rates among the five prospective, single-arm trials varied from 6.7% in a 5-year study involving 16 patients [88] to 75% after 3 years of variable dosages of ERT in eight patients [86]. Two studies reported lower mortality rates with higher ERT doses [85, 87]. However, the latter study did not account for the time-varying nature of the ERT, and the follow-up for the high-dosage group was half that of the follow-up in the standard-dosage group [85]. None of the deaths were treatment related.

Mortalität (single-arm): 6,7-75 %; höhere Dosen tendenziell besser; keine behandlungsbedingten Todesfälle

Safety and tolerability outcomes

The majority of IARs and AEs that were reported in the included studies were characterized as mild to moderate and manageable by slowing/pausing the infusion rate and administrating appropriate symptomatic treatment (non-serious and other AEs see Appendix Table A-7 and Table A-8). No patients discontinued treatment, and no serious or severe events were reported (Table 6-1 and Table 6-2).

Sicherheit: meist milde/moderate IARs/AEs; Infusionsanpassung/ Symptomtherapie; keine Abbrüche, keine schweren Ereignisse

Table 6-1: Safety of alglucosidase alfa in IOPD in controlled studies.

Author, year	Chien et al., 2015 [80]	Kishnani et al., 2009 [82]	Nicolino et al., 2009[83]
Mortality			
Any-cause mortality (n, %)	NR	2.3-year endpoint HR: 0.05 (95% CI: 0.02-0.14)	2-year endpoint Intervention group: 6/21 (29%) Comparator (non-treated group): 63/86 (73.7%)
Safety and tolerability outcomes			
Serious AEs	NR	NR	NR
Serious TEAEs	NR	NR	NR
Serious IARs	NR	NR	NR
Severe AEs	NR	NR	NR
Severe TEAEs	NR	NR	NR
Severe IARs	NR	NR	NR
Discontinuations due to IARs, AEs/TEAEs (n, %)	NR	2.3-year endpoint None reported.	2-year endpoint –0

Abbreviations: AE … adverse event, HR= hazard ratio, IAR … infusion-associated reactions, NR … not reported, TEAE … treatment-emergent adverse event.

Note: None of the reported deaths were considered to be treatment-related.

Table 6-2: Safety of alglucosidase alfa in IOPD in single-arm studies.

Author, year	Pfrimmer et al., 2024 [88]	Scheffers et al., 2023 [84]	Ditters et al., 2022 [87]	Poelman et al., 2020 [85]	Kishnani et al., 2006 [86]
Mortality					
Any-cause mortality (n, %)	Minimum 5-year endpoint 1/15 (6.7%)	9.9-year endpoint 6/27 (22%)	4.8-year endpoint 36/116 (31%). Results for the 64 patients that remained on the same ERT regime: Standard-dosage group: 15/31 (48%) Intermediate-dosage group: 3/15 (20%) High-dosage group: 2/18 (11%).	5-year endpoint Standard dosage group: 2/6 (34%) High dosage group: 1/12 (8%)[a]	2.9-year endpoint 6/8 (75%)
Safety and tolerability outcomes					
Serious AEs	NR	NR	NR	NR	NR
Serious TEAEs	NR	NR	NR	NR	NR
Serious IARs	NR	NR	NR	NR	NR

Author, year	Pfrimmer et al., 2024 [88]	Scheffers et al., 2023 [84]	Ditters et al., 2022 [87]	Poelman et al., 2020 [85]	Kishnani et al., 2006 [86]
Severe AEs	NR	NR	NR	NR	NR
Severe TEAEs	NR	NR	NR	NR	NR
Severe IARs	NR	NR	NR	NR	NR
Discontinuations due to IARs, AEs/ TEAEs (n, %)	NR	NR	NR	5-year endpoint None reported.	0

Abbreviations: AE … adverse event, ERT … enzyme replacement therapy, IAR … infusion-associated reactions, n … number, NR … not reported, TEAE … treatment-emergent adverse event.

Note: None of the reported deaths were considered to be treatment-related.

6.2 Avalglucosidase-alfa in infantile-onset Pompe disease

6.2.1 Description of Outcomes

The list of safety outcomes of interest is presented in chapter 6.1.1.

6.2.2 Included studies

One single-arm study reported safety outcomes of avalglucosidase alfa in IOPD; its characteristics are presented in Chapter 5.2.2, Table 5-5.

1 single-arm Studie zu Sicherheit

6.2.3 Results

Long-term safety of avalglucosidase alfa in IOPD is presented in Table 6-3.

Mortality

The rates of all-cause mortality in both cohorts were 0% [90].

0 % Mortalität

Safety and tolerability outcomes

All patients reported at least one treatment-emergent adverse event (TEAE) (non-serious and other AEs see Appendix Table A-9). Higher proportion of patients in the standard-dose than in the high-dose group reported experiencing serious or severe TEAEs (Table 6-3). None of the serious and severe TEAEs were deemed to be related to the treatment, and none of the TEAEs led to permanent treatment discontinuation.

≥1 TEAE; mehr schwere TEAEs bei Standarddosis; keine behandlungs-bedingten schweren Ereignisse & Abbrüche

Table 6-3: Safety of avalglucosidase alfa in IOPD in the single-arm study.

Kronn et al., 2025 [90]	Avalglucosidase alfa initial: 20 mg/kg every other week (n=6)	Avalglucosidase alfa initial planned dose: 40 mg/kg every other week (n=16)
Mortality		
Any-cause mortality (n, %)	1.86-year endpoint – 0	1.86-year endpoint – 0
Safety and tolerability outcomes		
Serious TEAEs (n, %)	1.86-year endpoint 5 (83%); related to treatment – 0	1.86-year endpoint 6 (38%); related to treatment – 0
Serious AEs	NR	NR
Serious IARs	NR	NR
Severe AEs	NR	NR
Severe TEAEs (n, %)	1.86-year endpoint 3 (50%); related to treatment – 0	1.86-year endpoint 4 (25%); related to treatment – 0
Severe IARs	NR	NR
Discontinuations due to IARs, AEs/TEAEs (n, %)	1.86-year endpoint – 0	1.86-year endpoint – 0
Death due to IARs, AEs/TEAEs (n, %)	1.86-year endpoint – 0	1.86-year endpoint – 0

Abbreviations: AE … adverse event, IAR … infusion-associated reaction, n … number, NR … not reported, TEAE … treatment-emergent adverse event.

6.3 Alglucosidase-alfa in late-onset Pompe disease

6.3.1 Description of Outcomes

The outcomes of interest are defined in chapter 6.1.1.

6.3.2 Included studies

One controlled and 16 single-arm studies reported safety outcomes of alglucosidase alfa in LOPD, and their characteristics are presented in chapter 5.3.2, Table 5-7 to Table 5-9.

Studien: 1 kontrolliert, 16 single-arm

6.3.3 Results

Long-term safety of alglucosidase alfa is presented in Table 6-4 and Table 6-5.

Mortality

The controlled trial reported higher mortality rates in the control group compared with the ERT group after 4.4 years of follow-up (33.33% vs 0) [96].

Mortalität: kontrolliert vs. single-arm

Three single-arm trials, which lasted up to 3 years reported mortality rates lower than 5% [97, 98, 102].

Among the four studies [103, 107, 111, 112] with a follow-up between 5 and 7 years (431 patients), the mortality rates ranged from 0% [111] to 16% [99].

Mortalität nach 5-7 J: 0-16 % (n=431)

Two studies [108, 109] lasted between 7 and 10 years (93 patients). One study observed a 15% lower mortality rate in juvenile-onset patients than in adult-onset patients after up to 9 years of follow-up [109]. The second study reported a 6% mortality rate among LOPD patients [108]. The study with the longest follow-up (12 years) reported a 28% mortality rate [106]. None of the deaths were treatment-related.

nach 7-10 J: 6-15 % (n=93)
nach 12 J: 28 %;

nie behandlungsbedingt

Safety and tolerability outcomes

The majority of IARs and AEs were mild to moderate (non-serious and other AEs see Appendix Table A-10 and Table A-11). In one study, 25% of patients experienced at least one serious AE (3 were anaphylaxis) during 3 years of follow-up [102]. The second study reported that after 5 years of ERT, two patients developed anaphylaxis (which was classified as an AE), corresponding to 1% of the studied population [107].

Sicherheit: meist milde/moderate IARs/AEs; Anaphylaxie selten (1-3 %); Abbruchraten 2-17 %

Two studies reported no discontinuations due to IARs and AEs [97, 101], while two studies reported rates of 2% [98, 103]. Higher discontinuation rates were observed in longer studies: 17% over 5 years [107], and 7% over ten years [108] (Table 6-5 to Table 6-6).

Table 6-4: Safety of alglucosidase alfa in LOPD in the controlled study.

Author, year	Vianello et al., 2013 [96]
Mortality	
Any-cause mortality (n, %)	4.4-year endpoint Intervention group: 0 Control group: 2/6 (33.33%)
Safety and tolerability outcomes	
Serious AEs	NR
Serious TEAEs	NR
Serious IARs	NR
Severe AEs	NR
Severe TEAEs	NR
Severe IARs	NR
Discontinuations due to IARs, AEs/TEAEs	NR
Deaths due to IARs, AEs/TEAEs	NR

Abbreviations: AE … adverse event, IAR … infusion-associated reactions, NR … not reported, n … number, TEAE … treatment-emergent adverse event.
Note: None of the reported deaths were considered to be treatment-related.

Table 6-5: Safety of alglucosidase alfa in LOPD in single-arm studies (part 1).

Author, year	Bembi et al., 2010 [93]	Angelini et al., 2012 [97]	de Vries et al., 2017 [98]	Regnery et al., 2012 [101]	van der Ploeg et al., 2012 [102]	Güngör et al., 2013 [112]	Gungor et al., 2016 [99]	Kuperus et al., 2017 [103]
Mortality								
Any-cause mortality	NR	1-4.5 years of FU: 1 (1.35%)	3-year endpoint: 2 (2.74%)	3-year endpoint: 0/38 (0%)	2-year endpoint: 1/60 (1.67%)	6-year endpoint: 46/283 (16%)	NR	5-year endpoint: 7/102 (6.86%).

Author, year	Bembi et al., 2010 [93]	Angelini et al., 2012 [97]	de Vries et al., 2017 [98]	Regnery et al., 2012 [101]	van der Ploeg et al., 2012 [102]	Güngör et al., 2013 [112]	Gungor et al., 2016 [99]	Kuperus et al., 2017 [103]
Safety and tolerability outcomes								
Serious AEs	NR	NR	NR	NR	2-year endpoint: 15 (25%) 3 were anaphylaxis; the majority was unrelated to study drug	NR	NR	NR
Serious TEAEs	NR	NR	NR	NR	NR	NR	NR	NR
Serious IARs	NR	NR	NR	NR	NR	NR	NR	NR
Severe AEs	NR	NR	NR	NR	NR	NR	NR	NR
Severe TEAEs	NR	NR	NR	NR	NR	NR	NR	NR
Severe IARs	NR	NR	NR	NR	NR	NR	NR	NR
Discontinuations due to IARs, AEs/ TEAEs (n, %)	NR	1-4.5 years of FU: None.	3-year endpoint: 1 (1.36)	3-year endpoint: None	NR	NR	NR	5-year endpoint: 2 (1.96)

Abbreviations: AE … adverse event, FU … follow-up, IAR … infusion-associated reactions, n … number, NR … not reported, TEAE … treatment-emergent adverse event.

Note: None of the reported deaths were considered to be treatment-related.

Table 6-6: Safety of alglucosidase alfa in late-onset Pompe disease in single-arm studies (part 2).

Author, year	van der Meijden et al., 2018 [111]	Nagura et al., 2019 [109]	Harlaar et al., 2019 [108]	Nuñez-Peralta et al., 2020 [105]	Semplicini et al., 2020 [107]	Stockton et al., 2020 [110]	Claeys et al., 2022 [104]	Ravaglia et al., 2022 [106]
Mortality								
Any-cause mortality (n, %)	7-year endpoint: 0	9-years endpoint: 2 (4.76%) – juvenile-onset; 4 (19.05) – adult-onset	3-year endpoint: 2 (6%)	NR	5.3-year endpoint: 15 (9.49%)	NR	NR	12-year endpoint: 5 (27.78%)
Safety and tolerability outcomes								
Serious AEs (n, %)	NR	NR	NR	NR	5.3-year endpoint: 2 (1.26%) – anaphylaxis	NR	NR	NR
Serious TEAEs	NR	NR	NR	NR	NR	NR	NR	NR
Serious IARs	NR	NR	NR	NR	NR	NR	NR	NR
Severe AEs	NR	NR	NR	NR	NR	NR	NR	NR
Severe TEAEs	NR	NR	NR	NR	NR	NR	NR	NR
Severe IARs	NR	NR	NR	NR	NR	NR	NR	NR
Discontinuations due to AEs/IARs (n, %)	NR	NR	3-year endpoint: 2 (6.67%)	NR	5.3-year endpoint: 6 (17.3%)	NR	NR	NR

Abbreviations: AE … adverse event, IAR … infusion-associated reactions, n … number, NR … not reported, TEAE … treatment-emergent adverse event.

Note: None of the reported deaths were considered to be treatment-related.

6.4 Avalglucosidase-alfa in late-onset Pompe disease

6.4.1 Description of Outcomes

The list of all critical safety outcomes is presented in chapter 6.1.1.

6.4.2 Included studies

Two single-arm studies reported safety outcomes of avalglucosidase alfa in LOPD and their characteristics are presented in chapter 5.4.2, Table 5-13.

6.4.3 Results

Long-term safety of avalglucosidase alfa in LOPD is presented in Table 6-7.

Mortality

The mortality rate in one study after 1.86 years of follow-up (n=100 patients) was 2% [115], and in the second study, after 6 years of follow-up (n=24 patients) it was 0% [114]. None of the deaths were treatment-related.

keine behandlungsbedingten Todesfälle

Safety and tolerability outcomes

The rates of IARs and TEAEs were comparable between the groups that received avalglucosidase alfa from the beginning and the groups that switched from alglucosidase alfa in both studies [114, 115] (non-serious and other AEs see Appendix Table A-12).

Sicherheit: IARs/TEAEs vergleichbar

In the study with a minimum of 1.86-year follow-up, the rate of serious TEAEs was almost 10% higher in the AVAL/AVAL group, and less than 10% were deemed by the study investigators to be related to the treatment. The rates of severe TEAEs were similar between groups (approximately 20%). None of the TEAEs led to death among the patients who received avalglucosidase alfa all the time, while there was one TEAE-related death (2.3%) in the group that switched. A total of 5 patients discontinued ERT due to TEAEs – 2 in the AVAL/AVAL and 3 in the ALG/AVAL group [115].

5 Abbrüche wegen TAEs nach 1,86 J.

During the 6-year follow-up, nine patients reported experiencing a severe AE in total; two of them were considered to be related to treatment (in patients who received avalglucosidase alfa from the start) [114]. The study investigators deemed 75% of any TEAEs to be related to the treatment. None resulted in death, while one led to treatment discontinuation (Table 6-7).

9 Pts. mit schweren AEs nach 6 J., 75 % TEAEs behandlungsbezogen; 1 Abbruch

Table 6-7: Safety of avalglucosidase alfa in LOPD in single-arm trials.

Author, year	Dimachkie et al., 2022 [114]	Kishnani et al., 2023 [115]
Mortality		
Any-cause mortality (n, %)	6-year endpoint: 0	1.86-year endpoint: 2 (2%)
Safety and tolerability outcomes		
Serious AEs (n, %)	6-year endpoint AVAL/AVAL: 5 (50%); related to treatment – 2 (20%) ALG/AVAL: 4 (29%); related to treatment – 0	NR
Serious TEAEs (n, %)	NR	1.86-year endpoint AVAL/AVAL: 17 (33.3%); related to treatment – 4 (7.8%) ALG/AVAL: 10 (22.7%); related to treatment – 2 (4.5%)
Serious IARs	NR	NR
Severe AEs	NR	NR
Severe TEAEs (n, %)	NR	1.86-year endpoint AVAL/AVAL:11 (21.6%) ALG/AVAL: 9 (20.5%)
Severe IARs	NR	NR
Discontinuations due to IARs/ TEAEs (n, %)	6-year endpoint AVAL/AVAL: 1 (10%) ALG/AVAL: 0	1.86-year endpoint AVAL/AVAL: 2 (3.9%) ALG/AVAL: 3 (6.8%)

Abbreviations: AE … adverse event, ALG … alglucosidase alfa, AVAL … avalglucosidase alfa, IAR … infusion-associated reactions, n … number, NR … not reported, TEAE … treatment-emergent adverse event.
Note: None of the reported deaths were considered to be treatment-related.

6.5 Laronidase in MPS I

6.5.1 Outcomes

The list of all critical safety outcomes is presented in chapter 6.1.1.

6.5.2 Included studies

The characteristics of the three studies that report safety outcomes of laronidase in MPS I are presented in chapter 5.5.2, Table 5-16.

6.5.3 Results

Long-term safety of laronidase in MPS I is presented in Table 6-8.

Mortality

Mortalität: nicht behandlungsbedingt; nach 4 J. bei 2,2 %, nach 6 J. bei 50 %

In the single-arm trials, one study reported a death rate of 2.22% after 4 years of follow-up [123]. Another study reported that four patients died during the study, and one subsequently, resulting in a 50% mortality rate after 6 years of ERT [125]. The other two studies did not disclose this information. None of the deaths were treatment-related.

Safety and tolerability outcomes

alle Pts. nach 4 J. mit TAEs 70 % behandlungsbedingt

schwere AEs/IARs bei <10 % der Pts.;

nach 6 J nur 1 milder AE bei 10 % der Kohorte

Two single-arm studies reported safety outcomes. In one study, over 4 years, all patients experienced at least one TEAE (e.g., mild-moderate abdominal pain, fever, hypotension, vomiting, anaphylaxis), with approximately 70% judged treatment-related (non-serious and other AEs see Appendix Table A-13) [123]. Serious AEs and IARs each occurred in <10% of patients; reported events included anaphylaxis and venous disorder, while non-serious events comprised mild-moderate abdominal pain, fever, hypotension, and vomiting (Table 6-8). In the second study, during 6 years of follow-up, only one AE meeting protocol reporting criteria was recorded (10% of the cohort), which was mild abdominal pain (non-serious and other AEs see Appendix Table A-13) [125]. Although some laboratory values and vital signs fell outside reference ranges, none were considered clinically significant.

Table 6-8: Safety of laronidase in mucopolysaccharidosis I in single-arm trials.

Author, year	Sifuentes et al., 2007 [125]	Clark et al., 2009 [123]	Tylki-Szymanska et al., 2010 [126]
Mortality			
Any-cause mortality (n, %)	6-year endpoint 5/10 (50%)	4-year endpoint 1/45 (2.22%)	NR
Safety and tolerability outcomes			
Serious AEs (n, %)	NR	4-year endpoint 3 (7%) – IARs, back pain and vein disorder	NR
Serious TEAEs	NR	NR	NR
Serious IARs (n, %)	NR	4-year endpoint 2 (8.33%) – mild to moderate abdominal pain, fever, hypotension, and vomiting; anaphylaxis	NR
Severe AEs	NR	NR	NR
Severe TEAEs	NR	NR	NR
Severe IARs	NR	NR	NR
Discontinuations due to IARs, AEs/TEAEs (n, %)	NR	4-year endpoint 1 (4.2%) – anaphylaxis	NR

Abbreviations: AE … adverse event, IAR … infusion-associated reactions, n … number, NR … not reported, TEAE … treatment-emergent adverse event.

Notes:

None of the reported deaths were considered to be treatment-related.

Only single-arm trials reported safety outcomes, the controlled trial did not, thus only the findings from the single-arm trials were presented.

6.6 Idursulfase in MPS II

6.6.1 Description of Outcomes

The list of all critical safety outcomes is presented in chapter 6.1.1.

6.6.2 Included studies

Eleven single-arm studies reported safety outcomes of idursulfase in MPS II, and their characteristics are presented in chapter 5.6.2, Table 5-19 and Table 5-20.

Sicherheit:
11 single-arm Studien

6.6.3 Results

Long-term safety of idursulfase in MPS II is presented in Table 6-9 and Table 6-10.

Mortality

In studies with follow-up of up to three years, five reported mortality rates below 10% [130, 131, 133]. One study documented a higher rate of 15.2% after 3-year follow-up [134]. Two studies with longer follow-up also reported mortality rates below 10%, one after 7.8 years [137] and the other after 0.5-6 years [135]. None of the deaths were treatment-related.

Mortalität:
unter 10 % bei nach 7,8 J.;
keine behandlungsbedingten Todesfälle

Safety and tolerability outcomes

The rates of IARs and TEAEs varied across studies, which primarily reported common events such as headache, urticaria, and pyrexia [132]; urticaria/angioedema and anaphylaxis [131]; infections and infestations, followed by respiratory, thoracic, and mediastinal disorders [134]; and pyrexia, upper respiratory tract infection, diarrhoea, and carpal tunnel syndrome [133] (non-serious and other AEs see Appendix Table A-14 and Table A-15).

SAEs zwischen 8,8-61,5 %;
selten behandlungsbedingt

weniger als 10 % Abbrüche

Single-arm trials of up to three years reported serious AE rates ranging from 8.8% (anaphylaxis [131]) to 61.5%, although only 3.9% were treatment-related (central line infection [130]). Rates of severe AEs ranged from 61.5% [130] to 16.4%, with 10.9% related to treatment [133]. Severe TEAEs were reported in 28.7% of patients [132] and 14.6% [134] during 3-5 years of follow-up (708 patients). Common events included bacteremia, chronic otitis media, carpal tunnel syndrome, obstructive airway disorder, sleep apnea, and abdominal strangulated hernia [132]. The rate of discontinuations due to safety events was below 10% in the studies that reported this outcome [130, 135, 137] (Table 6-9 and Table 6-10).

Table 6-9: Safety of idursulfase in mucopolysaccharidosis II in single-arm trials (part 1).

Author, year	Muenzer et al., 2011 [132]	Kim et al., 2013 [131]	Tomanin et al., 2014 [139]	Parini et al., 2015 [137]	Bik-Multanowski et al., 2017 [135]
Mortality					
Any-cause mortality (n, %)	3-year endpoint: 1 (1.06%)	~3-year endpoint: 0	3.3-year endpoint: 1 (3.7%)	7-year endpoint: 1 (5.88%)	0.5-6 years of FU: 3 (6.67%)
Safety and tolerability outcomes					
Serious AEs (n, %)	NR	~3-year endpoint 3 (8.82%) – anaphylaxis[a]	NR	NR	NR
Serious TEAEs	NR	NR	NR	NR	NR
Serious IARs	NR	NR	NR	NR	NR
Severe AEs	NR	NR	NR	NR	NR
Severe TEAEs (n, %)	3-year endpoint 27 (28.7%) – bacteremia, otitis media chronic, carpal tunnel syndrome, obstructive airway disorder, sleep apnea, and abdominal strangulated hernia.	NR	NR	NR	NR
Severe IARs	NR	NR	NR	NR	NR
Discontinuations due to IARs; AEs/TEAEs (n, %)	3-year endpoint None reported	NR	NR	7-year endpoint 1 (5.88%) – due to IARs and progressive CNS involvement	0.5-6 years of FU 2 (4.45%) – anaphylaxis

Abbreviations: AE … adverse event, FU … follow-up, IAR … infusion-associated reactions, n … number, NR … not reported, TEAE … treatment-emergent adverse event.

Notes:

None of the reported deaths were considered to be treatment-related.

[a] *Not explicitly reported as a serious AE in the study.*

Table 6-10: Safety of idursulfase in MPS II in single-arm studies (part 2).

Author, year	**Giugliani et al., 2017 [130]**	**Burton et al., 2017 [136]**	**Muenzer et al., 2017 [134]**	**Ueda et al., 2020 [138]**	**Marucha et al., 2022 [129]**	**Muenzer et al., 2023 [133]**
Mortality						
Any-cause mortality (n, %)	~2.1-year endpoint 2 (7.7%)	13-15-year endpoint Treated: 15.5% Untreated: 29.5% Adjusted HR 0.46 (95% CI: 0.29-0.72) Cognitive impairment patients: HR 4.84 (95%CI: 3.13-7.47)	3-year endpoint 97 (15.18%)	7-year endpoint 18/145 (12.41%) Severe type n=12 Attenuated type n=4 Unknown type n=2	NR	0
Safety and tolerability outcomes						
Serious AE (n, %)	~2.1-year endpoint 16 (61.54%) – convulsion, lower respiratory tract infection, central line infection, upper respiratory tract infection, carpal tunnel syndrome, psychiatric disorder, agitation, death. Related to treatment – 1 (3.85%), central line infection.	NR	NR	7-year endpoint 62 (42.8%); respiratory, thoracic and mediastinal disorders, acute respiratory failure.	NR	2-year endpoint 9 (16.4%); related to treatment – 6 (10.9%)
Serious TEAE	NR	NR	NR	NR	NR	NR

Author, year	Giugliani et al., 2017 [130]	Burton et al., 2017 [136]	Muenzer et al., 2017 [134]	Ueda et al., 2020 [138]	Marucha et al., 2022 [129]	Muenzer et al., 2023 [133]
Serious IARs	NR	NR	NR	NR	NR	NR
Severe AEs (n, %)	~2.1-year endpoint 12 (46.2%)	NR	3-year endpoint 34 (14.6%)	NR	NR	NR
Severe TEAEs	NR	NR	NR	NR	NR	NR
Severe IARs	NR	NR	NR	NR	NR	NR
Discontinuations due to IARs, AEs/ TEAEs (n, %)	~2.1-year endpoint 2 (7.7%)	NR	3-year endpoint None reported	7-year endpoint 5 (3.45%)	NR	2-year endpoint None reported

Abbreviations: AE … adverse event, CI … confidence interval, HR … hazard ratio, IAR … infusion-associated reactions, n … number, NR … not reported, TEAE … treatment-emergent adverse event.

Note: None of the reported deaths were considered to be treatment-related, except for one death in Ueda et al., 2020, for which the cause of death was unknown.

6.7 Elosulfase alfa in MPS IVA

6.7.1 Description of Outcomes

The list of all critical safety outcomes is presented in chapter 6.1.1.

6.7.2 Included studies

One controlled and two single-arm studies reported safety outcomes of elosulfase alfa in MPIVA, and their characteristics are presented in chapter 5.7.2, Table 5-23 and Table 5-24.

Studien: ,
1 kontrolliert,
2 single-arm

6.7.3 Results

Long-term safety of elosulfase alfa in MPS IVA is presented in Table 6-11 and Table 6-12.

Mortality

Two studies reported no deaths [143, 144], and one study reported a 0.6% mortality rate [141]. None of the deaths were deemed to be related to the study treatment.

Mortalität: 0-0,6 %;
keine behandlungsbedingt

Safety and tolerability outcomes

One controlled study and two single-arm studies reported these outcomes. Since the controlled trial presented safety only for the ERT-treated arms, we summarized its' results with those reported by the single-arm studies by follow-up duration. Over 2.5 years (n=186) in one study, serious AEs occurred in 40.7-55.2% across groups; only 6.9% were judged treatment-related (in the cohort that switched from placebo to ERT every other week) [141]. The sec-

schwere AEs: 40-70 %;
wenige behandlungs-bedingt (6,9-8 %);

1 Hypersensitivität-Abbruch; Abbrüche <10 %

ond study also reported high serious AE rates (≈70%), with ≈8% considered treatment-related [143]. After ~5 years of ERT nearly all patients experienced at least one serious AE, with about 50% related to treatment; one grade-4 hypersensitivity event led to discontinuation at week 11 [144]. The rates of discontinuation due to IARs or AEs/TEAEs were lower than 10% in all studies [141, 143, 144] (non-serious and other AEs see Appendix Table A-16 and Table A-17)

Table 6-11: Safety of elosulfase alfa in MPS IVA in controlled studies.

Author, year	Hendriksz et al., 2016 [147]	Hendriksz et al., 2018a [142]
Mortality		
Any-cause mortality (n, %)	2.3-year endpoint 1 (0.6%) in QOW-QOW group	NR
Safety and tolerability outcomes		
Serious AEs (n, %)	2.3-year endpoint PBO-QOW: 16 (55.2%), related to drug – 2 (6.9%) – anaphylaxis (grade 4) and hematuria (grade 2) PBO-QW: 14 (48.3%); related to drug – 0 QOW-QOW: 24 (40.7%); related to drug – 0 QW-QW: 23 (41.1%); related to drug – 0	NR
Serious TEAEs	NR	NR
Serious IARs	NR	NR
Severe AEs	NR	NR
Severe TEAEs	NR	NR
Severe IARs	NR	NR
Discontinuation due to IARs, AE/TEAEs (n, %)	2.3-year endpoint PBO-QOW: 0 (0%) PBO-QW: 0 (0%) QOW-QOW: 3 (5.1%) QW-QW: 1 (1.8%)	NR

Abbreviations: AE … adverse event, IAR … infusion-associated reactions, n … number, NR … not reported, PBO … placebo, QOW … every other week, QW … every week, TEAE … treatment-emergent adverse event.

Notes:

None of the reported deaths were considered to be treatment-related.

PBO-QOW – the group that switched from placebo to elosulfase alfa 2.0 mg/kg/every other week.

PBO-QW – the group that switched from placebo to elosulfase alfa 2.0 mg/kg/every week.

QOW-QOW – the group that received elosulfase alfa 2.0 mg/kg/every other week throughout the whole study.

QW-QW – the group that received elosulfase alfa 2.0 mg/kg/every week throughout the whole study.

Table 6-12: Safety of elosulfase alfa in MPS IVA in single-arm studies.

Author, year	Bhattacharya et al., 2020 [143]	Hendriksz et al., 2018b [144]
Mortality		
Any-cause mortality (n, %)	2.5-year endpoint 0	5-year endpoint 0
Safety and tolerability outcomes		
Serious AEs (n, %)	2.5-year endpoint 9 (69.23%) – knee deformity, sleep apnea; related to drug – 1 (7.69%) (grade 4 respiratory failure, resolved with dexamethasone; no change to elosulfase alfa treatment)	5-year endpoint 19 (95.0%) – injection site reactions and pyrexia; most remaining SAEs were primarily a result of hypersensitivity reactions; related to treatment – 9 (45%)
Serious TEAEs	NR	NR
Serious IARs	NR	NR

Author, year	Bhattacharya et al., 2020 [143]	Hendriksz et al., 2018b [144]
Severe AEs (n, %)	2.5-year endpoint 3 (23.1%) – grades 3 and 4, 2 dyspnea episodes, 1 umbilical hernia (likely unrelated)	5-year endpoint 1 (5%) – severe hypersensitivity AE (grade 4, discontinued at week 11)
Severe TEAEs	NR	NR
Severe IARs	NR	NR
Discontinuation due to IARs, AEs/TEAEs (n, %)	2.5-year endpoint 1 (7.7%) – spinal cord infarction, deemed unrelated to drug	5-year endpoint 2 (10%) – hypersensitivity reaction and recurrent IARs

Abbreviations: AE … adverse event, IAR … infusion-associated reactions, n … number, NR … not reported, TEAE … treatment-emergent adverse event.

Note: None of the reported deaths were considered to be treatment-related.

7 Quality of evidence

7.1 Alglucosidase-alfa for infantile-onset Pompe disease

7.1.1 Risk of bias assessment

RoB (2 Studien): moderat; fehlendes Blinding, Konfundierung, Selektion

The risk of bias assessment for two studies [80-82] was extracted from the published systematic review, on which this update is based [62]. Both were judged to have moderate risk of bias, mainly due to the lack of blinding which might have influenced the assessment of outcomes. For one study [82] additional concerns were noted regarding confounding, participant selection, and classification of interventions (seeAppendix Table A-18). The authors of the review specifically noted that patients with cardiac insufficiency were excluded from the study, which may have limited the generalizability of the findings and introduced potential selection bias.

RoB (Update): hoch; historische Kontrolle nicht gematcht, fehlende Vergleiche, Verblindung fehlt

In our update search, we identified one additional prospective, observational, controlled study, which was judged to have a serious risk of bias [83]. The primary concern was confounding since the historical non-treated cohort was not matched to the intervention group based on several disease-relevant parameters, and data for these parameters were not reported. Additionally, some outcomes were analysed only in the intervention group, precluding between-group comparisons. Finally, the lack of blinding was judged as posing a serious risk of bias in the measurement of outcomes, particularly those involving subjective assessments, such as cognitive function and safety (see Table Appendix Table A-18).

7.1.2 Certainty of evidence according to GRADE

The evidence profile for all critical efficacy and safety outcomes is presented according to the length of follow-up in the Table 7-1 below.

GRADE: sehr niedrig für alle Outcomes; single-arm/Beobachtungsstudien RoB, kleine Stichproben, Unschärfe

Overall, the certainty of evidence for all efficacy and safety outcomes is rated to be very low. However, it should be noted that all of these disorders are rare, which makes the conduct of RCTs particularly challenging. In addition, the progressive nature of these diseases poses further difficulties, as the natural course may vary considerably between individuals. The main reasons are the observational and single-arm nature of the studies, precluding estimation of relative treatment effects. Additionally, for some outcomes (LVMI and motor function gains), controlled trials reported results only for the ERT-arm, necessitating combined evaluation with single-arm trials and further downgrading. Additional downgrades were applied for serious risk of bias, small sample sizes, and imprecision (wide confidence intervals) in the prospective controlled studies (Table 7-1).

Table 7-1: Evidence profile of alglucosidase alfa in IOPD.

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
EFFECTIVENESS										
Cardiac function										
Cardiac function – LVMI after up to 3 years of FU										
3 [b]	Prospective single-arm trials	Serious	Not serious	Serious	Serious	Two studies are controlled in design but reported only the ERT-group values[82, 83].	46	NA	Normalization and stabilization (values not reported) [82]. 2 studies – decrease from baseline by 62.7% [83] and by 68.7% [86].	Very low
Cardiac function – LVMI after 3–5 years of FU										
2 [c]	Prospective single-arm trials	Serious	Not serious	Serious	Serious	Chien 2015 was initially controlled in design but reported only the ERT-group values.	28	NA	Normalization in LVMI after ERT (values not reported) [80]. Normalization in 83% (standard dosage group) and 92% (high dosage group) [85].	Very low
Cardiac function – LVMI after 5–10 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	27	NA	Mean LVMI decreased from 292.3 g/m^2 to within the normal range (≤65.8 g/m^2) [84].	Very low
Cardiac function – Ejection fraction										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cardiac function —Relative wall thickness after 4 years and 10 months of FU										
1	Prospective single-arm trials	Serious	Not serious	Serious	Serious	No p-values.	14	NA	Median values decreased from 0.9 to 0.4 (improvement) [73].	Very low
Cardiac function – Shortening fraction after 9.9 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	No endpoint result presented.	23	NA	Stabilization and comparable to healthy controls [84].	Very low
MOTOR FUNCTION										
Motor function – QMFT after at least 5 years of FU										
1	Prospective single-arm trials	Serious	Not serious	Serious	Serious	Mixed ERT doses, no baseline data.	15	NA	No baseline values. Endpoint median QMFT score=14 [88].	Very low

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
Motor function – Achievement of motor milestones after 1.2 to 2.7 years										
1	Prospective controlled trial	Moderate	Serious	Not serious	Serious	No information on the CIs and effect sizes.	Group 1 n=10 Group 2 n=10	n=11	Independent walking – earlier in the NBS group vs. untreated (p=0.009) and treated (p=0.006); no difference between treated and untreated (p=0.22) [81].	Very low
Motor function – Achievement of motor milestones after up to 3 years of FU										
2	Prospective single-arm trials	Serious	Serious	Serious	Serious	Small sample size, no information on the CIs.	26	NA	Minimal gains: 38.89%, walking: 38.89%, sitting: 22.22% [82]. Minimal gains: 16.67%, walking: 50%, sitting: 33.3% [86].	Very low
Motor function – Achievement of motor milestones in single-arm trials with 3-5 years of FU										
3	Prospective single-arm trials	Serious	Serious	Serious	Serious	Poelman et al., 2020 did not account for the time-varying nature of ERT.	69	NA	N.s. HRs for walking (high vs. standard, intermediate vs. standard dose) [87]. Walking ability was 83% and 17% in the high vs standard-dose group [85]. Long-term walking: 33.3%; sitting without support: 40%; tetraplegic: 27% [88].	Very low
Motor function– 6MWD										
1	Prospective single-arm trial	Serious	Serious	Serious	Serious	Mixed ERT doses, no baseline data.	15	NA	No baseline values; endpoint median (range): 262.5 (200-373) m[88].	Very low
Cognitive function – BSID II at 2 and 3 years										
1	Prospective single-arm trial	Serious	Serious	Serious	Serious	No information about CIs. The study did not account for the time-varying nature of ERT.	Standard-dosage group n=6 High-dosage group n=12	NA	Patients in the high-dose group had better performance than those in the standard-dose group (age-equivalent score 30 vs. 20 months) [85]	Very low
1 [b]	Prospective single-arm trial	Moderate	Not serious	Not serious	Serious	Initially controlled design, only data for the NBS ERT group presented.	10	NA	Year 1: normal (~90); Year 2: slight impairment; Year 5: improved, similar to Year 1 (graph only [80].	Very low
Cognitive function – CTR (1R and 20R) after 9.9 years of FU										
1	Prospective single-arm trial	Serious	Serious	Serious	Serious	No baseline values for this outcome.	11	NA	No baseline values. Endpoint assessments: normal IQ – 36.4%; mild delay – 9.1%; intellectual disability – 54.5% [88].	Very low

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
RESPIRATORY FUNCTION										
Respiratory function – Dependence on non-invasive or tracheostomy-assisted ventilation after 2.3 years of FU										
1	Prospective controlled trial	Moderate	Serious	Not serious	Not serious	Not serious.	n=18	n=61	ERT vs no-ERT HR for invasive ventilation or death: 0.09 (95% CI: 0.04-0.22). HR for any type of ventilation or death: 0.13 (95% CI: 0.06-0.29) [82].	Very low
Respiratory function – Dependence on non-invasive or tracheostomy-assisted ventilation after 5 years of FU										
2	Prospective single-arm trials	Serious	Serious	Serious	Serious	No p-values in the other.	29	NA	1 study – no baseline values, only endpoint: non-invasive 13.3%, invasive 33.3% [88]. 2nd study – Increase in ventilation requirements in 3 patients [73].	Very low
Respiratory function – Time spent on ventilation										
0	NA	NA	NA	NA	NA	NA	NA	NA	This outcome was not assessed in any study.	NA
SURVIVAL										
Survival – Overall survival after 2.3 years of FU										
2	Prospective controlled trials	Serious	Not serious	Not serious	Serious	None	30	95	In both studies, comparable survival rates: 72% and 71.1% in the intervention group; 1.9% and 3% in the control group [82, 83].	Very low
Survival – Overall survival after 5 years of FU										
1	Prospective controlled trial	Moderate	Not serious	Not serious	Serious	None	Group 1: 10 Group 2: 10	11	NBS patients had significantly higher survival rates vs non-treated and clinically diagnosed (both p<0.05) [80].	Very low
Survival – Overall survival after 3-5 years of FU										
2	Prospective single-arm trials	Serious	Not serious	Serious	Serious	Poelman et al., 2020 – the FU for the standard-dosage group was 115.2, and in the high-dosage group it was 52.8 months. This could introduce bias.	114	NA	1st study: HR (high vs standard dosage): 0.17, p=0.02 and HR (intermediate vs standard dosage): 0.44, p=0.19 [87]. 2nd study: higher survival rates in the high- vs standard-dosage group (92% vs 66%) [85].	Very low

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
Survival – Ventilator-free survival after 2.3 years of FU										
2	Prospective controlled trials	Serious	Not serious	Not serious	Serious	None	30	95	1st study: HR (risk of invasive ventilation or death): 0.09 (95% CI: 0.04–0.22); HR (any type of ventilation or death): 0.13 (95% CI: 0.06-0.29) [82]. 2nd study: HR (invasive ventilator): 0.421 (0.202-0.876), p=0.0207; HR (any ventilator-free survival): 0.533 (95% CI: 0.247–1.150), p=0.1088 [83].	Very low
Survival – Ventilator-free survival after 5 years of FU										
1	Prospective controlled trial	Moderate	Not serious.	Not serious	Serious	None	Group 1: 10 Group 2: 10	11	NBS patients compared with both untreated controls and clinically diagnosed patients – higher rates, p<0.01[c] [80].	Very low
Survival – Ventilator-free survival after 5 years of FU										
1	Prospective single-arm trials	Serious	Not serious	Serious	Serious	The study did not account for the time-varying nature of ERT. No baseline values reported.	18	NA	High vs. standard dose group: 92% vs. 50%, p=0.08 [85].	Very low
QUALITY OF LIFE										
Quality of life – SF-36 after 9.9 years of FU										
1	Prospective single-arm trial	Serious	Serious	Not serious	Serious	No baseline values for this outcome.	14	NA	No baseline values. Most patients (93%) had impaired physical health, with relatively preserved mental well-being at endpoint assessments [88].	Very low
SAFETY										
MORTALITY										
Mortality – All-cause mortality after up to 2.5 years of FU										
2	Prospective controlled trials	Serious	Not serious	Not serious	Serious	None	125	NA	1st study: HR 0.05 (95% CI: 0.02-0.14) [82]. 2nd study: intervention vs. control group: 29% vs. 73.7% [83].	Very low
Mortality – All-cause mortality after 3 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	8	/	Mortality rate: 75% [86].	Very low

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
Mortality – All-cause mortality after 3-5 years of FU										
3	Prospective single-arm trials	Serious	Not serious	Serious	Serious	Poelman et al., 2020 – the FU for the standard-dosage group was 115.2 and in the high-dosage group it was 52.8 months.	114	NA	1st study: standard vs high-dosage group: 34% vs 8% [85]. 2nd study: standard vs intermediate vs high-dosage group: 48% vs 20% vs 11% [87]. 3rd study: mortality rate was 6.7% [88].	Very low
Mortality – All-cause mortality after 5-10 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	27	NA	Mortality rate: 22% [84]	Very low
Safety and tolerability outcomes										
Serious/Severe TEAEs/AEs/IARs										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: AE … adverse event, BSID-II … Bayley Scales of Infant Development II, CFT (1R and 20R) … Culture Fair Intelligence Test 1-R and 20-R, CI … confidence interval, ERT … enzyme replacement therapy, FU … follow-up, HR … hazard ratio, IAR … infusion-associated adverse event, IQ … intelligence quotient, LVMI … left ventricular mass index, n … number, NA … not applicable, NBS … newborn screening, NR … not reported, QMFT … Quick Motor Function Test, TEAE … treatment-emergent adverse event, sig. … significant, vs. … versus.

Notes:

[a] *The number of patients corresponds to the number of patients included in the analysis of that specific outcome.*

[b] *Nicolino et al., 2009 and Kishnani et al., 2009 are prospective, controlled trials, but they reported this outcome only for the intervention group, which is why they are summarized with the results reported from the prospective, single-arm trials.*

[c] *Chien et al., 2015 is a prospective, controlled trial, but it reported this outcome only for the intervention group, which is why they are summarized with the results reported from the prospective, single-arm trials.*

[d] *The follow-up was not specified in the report; this information was derived based on the age of ERT onset and the median age at the last assessment.*

[e] *The controlled trials are evaluated together with the single-arm trials because the data on treatment-related events are applicable only to the intervention (ERT) arms.*

7.2 Avalglucosidase-alfa for infantile-onset Pompe disease

7.2.1 Risk of bias assessment

Since the only included prospective study did not have a controlled design, a formal risk of bias assessment was not performed.

RoB: keine Bewertung

7.2.2 Certainty of evidence according to GRADE

The evidence profile for all critical efficacy and safety outcomes is presented according to the length of follow-up in Table 7-2 below.

Overall, the certainty of evidence for all efficacy and safety outcomes is rated to be very low. This is due to the non-controlled observational design of the study. However, it should be noted that all of these disorders are rare, which makes the conduct of RCTS particularly challenging. In addition, the progressive nature of these diseases poses further difficulties, as the natural course may vary considerably between individuals.

sehr niedrige Evidenzqualität für Wirksamkeit und Sicherheit wegen Beobachtungsdesign

7.3 Alglucosidase-alfa for treating late-onset Pompe disease

7.3.1 Risk of bias assessment

The results of the assessment for one controlled study [96] were extracted from the published systematic review [63]. The study was assessed as at moderate risk of bias due to confounding and outcome-measurement issues (see Appendix Table A-19).

moderates RoB

7.3.2 Certainty of evidence according to GRADE

The evidence profile for critical outcomes is presented according to the length of follow-up in the Table 7-3 below.

The certainty of evidence for all effectiveness and safety outcomes is rated to be very low. However, it should be noted that all of these disorders are rare, which makes the conduct of RCTs particularly challenging. In addition, the progressive nature of these diseases poses further difficulties, as the natural course may vary considerably between individuals.

sehr niedrige Evidenzqualität für Wirksamkeit und Sicherheit wegen Beobachtungsdesign

This is because all studies were of observational design, and because all (but one) were single-arm studies, which prevents from evaluating the treatment effect. The single controlled trial was judged to be of moderate risk of bias and involved a small sample size (n=14 patients in both groups), which does not warrant upgrading the certainty of evidence from Low, but rather justifies downgrading it to Very Low (Table 7-3).

Table 7-2: Evidence profile of avalglucosidase-alfa in IOPD.

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
CARDIAC FUNCTION										
Cardiac function – LVMI after 1.9 years of FU										
1	Prospective single-arm trials	Serious	Serious	Serious	Serious	None.	Cohort 1: n=6 Cohort 2: n=6 Cohort 3: n=11	/	Endpoint: stabilization in all patients. Note: almost all patients had a normal LVMI at baseline [90].	Very low
Cardiac function – Ejection fraction										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cardiac function – Relative wall thickness										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cardiac function – Shortening fraction										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
MOTOR FUNCTION										
Motor function – QMFT after 1.9 years of FU										
1	Prospective single-arm trials	Serious	Serious	Serious	Serious	None.	Cohort 1: n=6 Cohort 2: n=6 Cohort 3: n=11	/	Higher increases after high ERT dosage: +0.50 (standard ERT) vs +2.33, +4.00 and +7.17 (all high ERT) [90].	Very low
Motor function – Achievement of motor milestones										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Motor function – 6MWD% predicted after 1.9 years of FU										
1	Prospective single-arm trial	Serious	Serious	Serious	Serious	None	Cohort 1: n=6 Cohort 2: n=6 Cohort 3: n=11	/	2 patients on standard ERT showed a decline; all patients on higher ERT showed an improvement [90].	Very low
COGNITIVE FUNCTION										
Cognitive function										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
RESPIRATORY FUNCTION										
Respiratory function – Dependence on non-invasive or tracheostomy-assisted ventilation										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Respiratory function – Time spent on ventilation										
0	N/A	NA	NA	NA	NA	NA	NA	NA	NA	NA

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
SURVIVAL										
Survival – Overall survival after 1.9 years of FU										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Survival —Ventilator-free survival										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
QUALITY OF LIFE										
Quality of life										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SAFETY OUTCOMES										
MORTALITY										
Mortality – All-cause mortality after 1.9 years of FU										
1	Prospective single-arm trial	Serious	Serious	Serious	Serious	Small sample size, non-controlled design.	Cohort 1: n=6 Cohort 2: n=6 Cohort 3: n=11	/	0% [90].	Very low
Safety and tolerability outcomes										
Serious TEAEs after 1.9 years of FU										
1	Prospective single-arm trial	Serious	Serious	Serious	Serious	None.	Cohort 1: n=6 Cohort 2: n=6 Cohort 3: n=11	/	20 mg/kg dose: 83% 40 mg/kg dose: 38% Treatment-related: 0 [90].	Very low
Severe TEAES after 1.9 years of FU										
1	Prospective single-arm trial	Serious	Serious	Serious	Serious	None.	Cohort 1: n=6 Cohort 2: n=6 Cohort 3: n=11	/	20 mg/kg dose: 50% 40 mg/kg dose: 25% Treatment-related: 0 [90].	Very low

Abbreviations: 6MWD% predicted … 6-minute walking distance percent predicted, AE … adverse event, FU … follow-up, IAR … infusion-associated reaction, LVMI … left ventricular mass index, NA … not applicable, QMFT … Quick Motor Function Test, TEAE … treatment-emergent adverse event.

Note:

[a] *The number of patients corresponds to the number of patients included in the analysis of that specific outcome.*

Table 7-3: Evidence profile of alglucosidase-alfa in LOPD.

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	49	NA	+0.7 pp/year (95% CI: –0.2-1.7), ns [100].	Very low
2	Prospective single-arm trials	Serious	Not serious	Serious	Serious	None	97	NA	Change after 5 years ranged from a ns. decline –0.2 pp [103]to a sig.+9.2 pp [111].	Very low
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	58	NA	Sig. increase from 320 ± 161 to 383 ± 178 m [97].	Very low
5	Prospective single-arm trials	Serious	Serious	Serious	Serious	None	146	NA	Effects ranged from a sig. decline (–83.8 m) [104] to sig. improvements [93]. Other findings: ns. increase after 2-y (+ 21.3m), sig. increase after 3-y FU (+ 22.9m) [102]; sig. increase after 2-y FU (+44.4m), ns after 3-y FU (+13.6m) [101]; ns increase (SRM=0.1) [105].	Very low
2	Prospective single-arm trials	Serious	Not serious	Serious	Not serious	None	124	NA	Sig. increase of +40.9 m after 7 years [103]. Up to 2.2 years of FU: significant increase (1.4% ± 0.5/year, $p < 0.01$); afterwards progressive decline (–2.3%/year; change of slope: –3.7 ± 0.6, $p < 0.001$) [107].	Very low
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	12	NA	An initial incline was followed by a sig. decline after 12 y of FU (-53m) [106].	Very low
2	Prospective single-arm trial	Serious	Not serious	Serious	Not serious	None	21	NA	An initial incline was followed by a sig. decline after 10 years of FU (–22.2 pp vs baseline) [108]. Sig. increase by 7.4 pp (95% CI: 2.4-12.3) [111].	Very low
1	Prospective controlled trial	Moderate	Serious	Not serious	Serious	None	8	6	FVC (change from baseline): no between-group difference; within-ERT change not significant [96].	Very low
4	Prospective single-arm trials	Serious	Serious	Serious	Serious	None	207	NA	Changes ranged from n.sdecline of 0.2 pp/year [100] to a n.s. increase of 1.3% and 0.2% [97, 102]. 1 study– sig. decrease (SRM = 0.8) [105].	Very low
1	Prospective single-arm trial	Serious	Not serious	Serious	Not serious	None	396	NA	N.s. decline: –0.17%/year (95% CIs: –0.42-0.09) [110].	Very low
3	Prospective single-arm trials	Serious	Serious	Serious	Serious	None	206	NA	Sig. declines after 5 y (–0.9 ± 0.1%/year [107] and 7 y (–5.2 pp, 95% CI: 0.05-10.4 [111]. A n.s. decline after 5 y (–0.1 pp), but improvement versus the extrapolated natural course (+7.3 pp, p=0.0006) [103].	Very low
1	Prospective single-arm trial	Serious	Serious	Serious	Not serious	None	Baseline: 30 Endpoint: 11	NA	After 10 years sig. decline (–11 pp) [108].	Very low
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	12	NA	No sig. variation in FVC over 12 y of FU [106].	Very low

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
3	Prospective single-arm trial	N/A	Not serious	Serious	Serious	None	97	NA	All studies show an n.s. change: −1.0 pp/y) [100], SRM = 0.4 [105], and textually presented [104].	Very low
3	Prospective single-arm trial	Serious	Serious	Serious	Serious	None	194	NA	Effects ranged from a sig. decline in 2 studies (−0.82%/year [107] and (-2.9 pp) [103] to a n.s. decline (−4.7 pp) [111]. ERT vs extrapolated natural course: 7.6 pp higher (p= 0.0003) [103].	Very low
1	Prospective single-arm trial	Serious	Not serious	Serious	Not serious	None	Baseline: 30 Endpoint: 8	NA	After 10-y of FU: sig. decline of −9.2 pp [108].	Very low
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	24 (7 juvenile-onset, 17 adult-onset)	NA	N.s. variation over time (from a median of 44.0 at baseline to 43.5 after 2 y to 45.0 at 3 y) [93].	Very low
1	Prospective controlled trial	Moderate	Not serious	Not serious	Serious	None	8	6	Study endpoint: without ventilation– 16.67% in the control group and 12.5% in the intervention group (out of 100% at baseline) [96].	Very low
4	Prospective single-arm trials	Serious	Serious	Serious	Serious	None	146	NA	Effects ranged from a decrease in the number of patients dependent on ventilation (no comparisons conducted) [93, 97] to an increase in the number of patients [105]. One study reports no change in ventilation status during the 2-year study period [104].	Very low
1	Prospective single-arm trial	Serious	Not serious	Serious	Not serious	None	396	NA	4-year endpoint: an additional 26/158 patients (16.5%) required respiratory support [110].	Very low
3	Prospective single-arm trials	Serious	Serious	Serious	Serious	None	99	NA	Effects varied from a slight increase (data presented graphically) [107] and an increase of 8 additional patients after 5 years [103] to no change in ventilation requirements after 7 years [111].	Very low
1	Prospective single-arm trials	Serious	Not serious	Serious	Not serious	None	30	NA	Change from baseline: increase in ventilation dependence from 23% to 80% [108].	Very low
1	Prospective controlled trial	Moderate	Not serious	Not serious	Serious	None	8	6	Sig. difference in mean change from baseline (Intervention vs. Control Group): –4.8 vs. –0.16 [96].	Very low
3	Prospective single-arm trials	Serious	Serious	Serious	Serious	None	136	NA	Effects ranged from a sig. decrease from 14 to 8 h [93] and a decrease from 15.6 to 12.1 (p not reported) [97] to no reduction (exact values and p-value not reported) [101].	Very low
1	Prospective single-arm trial	Serious	Not serious	Serious	Not serious	None	N total=283 ERT group n=204 Non-ERT group n=79	NA	HR: 0.41 (95% CI: 0.19-0.87) [112].	Very low
1	Prospective single-arm trial	Serious	Not serious	Serious	Not serious	None	63	NA	Survival rates ranged from 70.2% (adult-onset) to 95.2% (juvenile-onset) [109].	Very low
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	38	NA	SF-36 – baseline: 1.5 points below U.S. norm (mean 50); no change at 36 months (p = n.s.)[101].	Very low
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	174	NA	PCS: Improved in first 2 years [+1.49 (95% CI: 0.76-2.21)]; ns. decline thereafter [>2y: −0.15 (−0.43 to 0.13)]. MCS: No significant change over time [0-2 y: +1.03 (−0.07 to 2.13); >2y: +0.02 (−0.41 to 0.46)] [99].	Very low
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	82	NA	R-Pact – significant improvement 5y vs baseline (+3.6 points) +110.8 pp vs natural course (p=0.002) (Kuperus et al., 2017).	Very low
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	174	NA	Before starting ERT: mean 0.49 sp/y (95% Cis: –0.63 to –0.34). During ERT: stabilization (–0.02 sp/y, 95 % CIs, –0.17-0.13) [99].	Very low
1	Prospective controlled trial	Moderate	Not serious	Serious	Not serious	None	8	6	Mortality rates in the ERT group were 0% vs 33.33% in the control group [96].	Very low
3	Prospective single-arm trials	Serious	Not serious	Serious	Not serious	None	207	NA	Rates ranged from 0% [102]; to 1.35%[97]; and 2.74% [98].	Very low
4	Prospective single-arm trials	Serious	Not serious	Serious	Not serious	None	431	NA	Rates ranged from 9.49% [107] and 6.86% [103] after 5 years of FU to 16% [112] after 6 years and 0% [99, 111] after 7 years of FU.	Very low
2	Prospective single-arm trials	Serious	Serious	Serious	Serious	None	93	NA	Rates ranged from 4.76% (juvenile-onset) to 19.05% (adult-onset) [109] and 6% for overall LOPD patients [108].	Very low
1	Prospective single-arm trial	Serious	N/A	Serious	Serious	None	12	NA	Mortality rate – 27.78% [106].	Very low
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	60	NA	15 (25%) 3 were anaphylaxis; the majority was unrelated to the study drug [102].	Very low
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	158	NA	2 (1.26%) – anaphylaxis [107].	Very low

Abbreviations: 6MWD … 6-minute walking distance, CI … confidence interval, CHAQ/HAQ … Childhood Health Assessment Questionnaire/Health Assessment Questionnaire, ERT … enzyme replacement therapy, FEV1 … forced expiratory volume in 1 second, FU … follow-up, FVC … forced vital capacity, HR … hazard ratio, IAR … infusion-associated reactions, LOPD … late-onset Pompe disease, LVMI … left ventricular mass index, MCS … Mental Component Summary, NA … not applicable, n … number, n.s. … non-significant, PCS … Physical Component Summary, pp … percentage point, pp/y … percentage point per year, QMFT … Quick Motor Function Test, R-PAct … The Rasch-built Pompe-specific activity (R-PAct) scale, RHS … Rotterdam Handicap Scale, SF36 … Short Form 36, sig. … significant, sp … score points, SRM … standardized response mean, y … years.

Note:

[a] *The number of patients corresponds to the number of patients included in the analysis of that specific outcome.*

7.4 Avalglucosidase-alfa for late-onset Pompe disease

7.4.1 Risk of bias assessment

einarmige Studien haben hohes RoB

Single-arm trials were classified as having a high risk of bias and as a result, they were not subject to formal risk of bias assessment.

7.4.2 Certainty of evidence according to GRADE

The evidence profile for critical outcomes is presented according to the length of follow-up in Table 7-4 below.

sehr niedrige Evidenzqualität für Wirksamkeit und Sicherheit wegen Beobachtungsdesign

Overall, the certainty of evidence for all efficacy and safety outcomes are rated to be very low. The main reasons include the observational design of the studies, and the single-arm design of both studies, which does not enable estimating the effect of the treatment. (presented in Table 7-4).

However, it should be noted that all of these disorders are rare, which makes the conduct of RCTs particularly challenging. In addition, the progressive nature of these diseases poses further difficulties, as the natural course may vary considerably between individuals.

Table 7-4: Evidence profile of avalglusocidase-alfa in LOPD.

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
EFFICACY OUTCOMES										
MOTOR FUNCTION										
Motor function – QMFT after at least 1.86 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	AVAL/AVAL: n=44 ALG/AVAL: n=38	NA	Increase (data presented graphically) [115].	Very low
Motor function – 6MWD after at least 1.86 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	AVAL/AVAL: n=42 ALG/AVAL: n=41	NA	Increase in both groups. AVAL/AVAL: +18.60 m and ALG/AVAL: + 4.56 m (n p-values) [115].	Very low
Motor function – 6MWD after 6 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	AVAL/AVAL: n=10 ALG/AVAL: n=14	NA	AVAL/AVAL: n.s. decrease of −0.701 per year (−1.571 to 0.169); ALG/AVAL: sig. decrease of −0.846 per year (−1.567 to −0.125) [114].	Very low
RESPIRATORY FUNCTION										
Respiratory function – Upright FVC in the controlled trial after at least 1.86 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	AVAL/AVAL: n=43 ALG/AVAL: n=35	NA	AVAL/AVAL: +2.65 (1.05) points ALG/AVAL: +0.36 (1.12) points (n p-values) [115].	Very low
Respiratory function – Upright FVC after 6 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	AVAL/AVAL: n=10 ALG/AVAL: n=14	NA	Naive group: n.s. decrease of −0.473 per year (−1.188 to 0.242) Switch group: sig. decrease of −0.648 per year (−1.061 to −0.236) [114].	Very low
Respiratory function – Supine FVC										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Respiratory function – FEV1										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Respiratory function – The use of non-invasive or tracheostomy-assisted ventilation										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Respiratory function – Time spent on ventilation										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
SURVIVAL										
Overall survival after at least 1.86 years of FU										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ventilator-free survival										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
QUALITY OF LIFE										
Quality of life after at least 1.86 years of FU (SF-12)										
1	Prospective single-arm trial	Serious	Not serious	Serious	Not serious	None	AVAL/AVAL: n=44 ALG/AVAL: n=42	NA	Increase in SF-12 PCS and MCS. PCS: AVAL/AVAL: +3.24 (0.28) ALG/AVAL: +2.13 (1.03) SF-12 MCS: AVAL/AVAL: +2.47 (1.32) ALG/AVAL: +1.62 (1.27) No p-values provided [115].	Very low
Quality of life after at least 1.86 years of FU (R-PAct)										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	AVAL/AVAL: n=16 ALG/AVAL: n=22	NA	AVAL/AVAL: +3.56 (7.96) ALG/AVAL: -0.09 (4.69) No p-values provided [115].	Very low
SAFETY										
MORTALITY										
Mortality – All-cause mortality after at least 1.86 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Not serious	None	AVAL/AVAL: n=51 ALG/AVAL: n=49	NA	Mortality rate – 2% [115].	Very low
Mortality – All-cause mortality after 6 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	AVAL/AVAL: n=10 ALG/AVAL: n=14	NA	Mortality rate – 0% [114].	Very low
Safety and tolerability outcomes										
Serious TEAEs after at least 1.86 FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Not serious	None	AVAL/AVAL: n=51 ALG/AVAL: n=49	NA	Any serious TEAE: AVAL/AVAL: 33.3% ALG/AVAL: 22.7% Related to treatment: AVAL/AVAL: 7.8% ALG/AVAL: 4.5% [115].	Very low

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
Severe TEAEs after at least 1.86 FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Not serious	None	AVAL/AVAL: n=51 ALG/AVAL: n=49	NA	Any serious TEAE: AVAL/AVAL: 21.6 % ALG/AVAL: 20.5 % [115].	Very low
Serious AEs after 6 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	AVAL/AVAL: n=10 ALG/AVAL: n=14	NA	AVAL/AVAL: 50% ALG/AVAL: 29% AVAL/AVAL: 20% ALG/AVAL: 0 [114].	Very low

Abbreviations: 6MWD … 6-minute walking distance, AE … adverse event, FEV1 … forced expiratory volume in 1 second, FU … follow-up, FVC … forced vital capacity, IAR … infusion-associated reaction, NA … not applicable, NR … not reported, pp … percentage point, pp/y … percentage point per year, R-PAct … The Rasch-built Pompe-specific activity (R-PAct) scale, SD … standard deviation, SF36 … Short Form 36, sig. … significant, sp … score points, TEAE … treatment-emergent adverse event.

Notes:

[a] *The number of patients corresponds to the number of patients included in the analysis of that specific outcome.*

AVAL/AVAL – patients who received avalglucosidase alfa throughout the whole study.

ALG/AVAL – patients who switched from alglucosidase alfa to avalglucosidase alfa.

7.5 Laronidase for treating Mucopolysaccharidosis I

7.5.1 Risk of bias assessment

hoher RoB bei 1 kontrollierten Studie (Störfaktoren, Selektion, Messung, fehlende Daten)

One prospective controlled study [124] was rated serious risk of bias overall (outcomes: ROM, 6MWD, survival; see Appendix Table A-20). The primary concerns were confounding, because intervention and historical control groups were matched only on age and prior HSCT, not on key clinical variables such as cardiac or pulmonary status; selection bias. Additionally, due to the use of a separate historical cohort with non-aligned follow-up; missing data, with no comparative data for 6MWD or survival and sparse ROM data (5-8 patients) without explanation. Lastly, measurement bias is a concern, as goniometry is assessor-dependent with different personnel across groups and the effort-dependent 6MWD was assessed without blinding.

7.5.2 Certainty of evidence according to GRADE

The evidence profile for critical outcomes is presented according to the length of follow-up in the Table 7-5 below.

Evidenzqualität als sehr niedrig eingestuft, v. a. wegen Studiendesign

The certainty of evidence for all outcomes was rated to be very low. The main reasons for this are again the observational design of the studies, and most of the, were single-arm studies which does not enable evaluating the treatment effect. The single controlled trial was judged to have a serious risk of bias due to the reasons enlisted in the chapter 7.5.1. (Table 7-5).

7.6 Idursulfase for treating Mucopolysaccharidosis II

7.6.1 Risk of bias assessment

single-arm Studien: hoher RoB

Single-arm trials were classified as having a high risk of bias and as a result, they were not subject to formal risk of bias assessment.

7.6.2 Quality of evidence according to GRADE

The evidence profile for critical outcomes is presented according to the length of follow-up in Table 7-6 below.

sehr niedrige Evidenzqualität, v. a. wegen Beobachtungs- & single-arm-Design

The evidence for all outcomes was rated to be very low. The main reasons for this are the observational single-arm design of the studies.

However, it should be noted that all of these disorders are rare, which makes the conduct of RCTs particularly challenging. In addition, the progressive nature of these diseases poses further difficulties, as the natural course may vary considerably between individuals.

Table 7-5: Evidence profile of laronidase in MPS I.

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
EFFICACY										
NEUROLOGICAL FUNCTION										
Neurological function – spinal cord compression										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
MOTOR FUNCTION										
Motor function – 6MWD after 2 years of FU										
1	Prospective controlled trial	Serious	Serious	Not serious	Serious	Data available only for the ERT group. Not possible to determine an ERT effect.	10	23	Increase vs baseline: 50 ± 92 m (104-264 m) [124].	Very low
Motor function – 6MWD after 4 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	No p-values provided.	45	NA	Increase from 334.0 ± 129.5 m to 373.3 ± 133.0 m [123].	Very low
JOINT FUNCTION										
Joint mobility – joint range of motion after 2 years of FU										
1	Prospective controlled trial	Serious	Not serious	Not serious	Serious	None	10	23	Joint ROM (shoulder, elbow, hip): Improvement in 40-50% of patients; worsening in 10-30% of patients. ERT vs. controls: no difference [124].	Very low
Joint mobility – joint range of motion after 1-4 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	17	NA	Passive joint ROM – improvement in 6-65%, worsening in 6-35% patients; active joint ROM – improvement in 0-71%, worsening in 0-14% patients [126].	Very low
Joint mobility – joint range of motion after 4-6 years of FU										
2	Prospective single-arm trials	Serious	Serious	Serious	Serious	Variable effect sizes are presented in the studies.	55	NA	At 4-year FU: mean change vs baseline in shoulder ROM was 17.4 ± 3.6 [123]. At 6-y of FU: improvement in shoulder flexion/ extension (+25-37°) and knee extension (restriction ↓ to ~0°); elbow extension declined slightly (~3°); knee flexion decreased (~9°) [125].	Very low
Joint function – range of motion (single joint or combination)										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
RESPIRATORY FUNCTION										
Respiratory function – Sleep apnoea after 4 years of FU										
1	Prospective single-arm trial	Serious	Serious	Serious	Serious	None	16	NA	Sleep apnoea (AHI): Mean decrease of −7.6 ± 4.5 events/h; among 16 patients with abnormal baseline AHI, 10 improved, 2 declined, 4 remained stable [123].	Very low
Respiratory function – Sleep apnoea after 6 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	10	NA	Decrease in mean number of apneas (−1.2), hypopneas (−2.8); and AHI (−0.5). No hypoxic events at baseline or endpoint [123].	Very low
SURVIVAL										
Overall survival										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
QUALITY OF LIFE										
Quality of life – the CHAQ/HAQ disability index after 4 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Not serious	None	35	NA	Change vs baseline: 0.31 ± 0.11 [123].	Very low
Quality of life – change in MPS HAQ after 1-4 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	17	NA	Sig. improvement in eating, dressing, toileting, toothbrushing, and walking; bathing, grooming, and mobility showed n.s. Improvement [126].	Very low
SAFETY OUTCOMES										
MORTALITY										
Mortality – all-cause mortality after 4-6 years of FU										
2	Prospective single-arm trials	Serious	Serious	Serious	Serious	None	55	NA	At 4 years of FU: 2.22 % survival [123]. At 6-years of FU: 50% [125].	Very low
SAFETY AND TOLERABILITY OUTCOMES										
Serious AEs after 4 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	45	NA	3 (7%) – IARs, back pain and vein disorder [123].	Very low

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
Serious IARs after 4 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	45	NA	2 (8.33) – mild to moderate abdominal pain, fever, hypotension, and vomiting; anaphylaxis [123].	Very low

Abbreviations: 6MWD … 6-minute walking distance, AHI … Apnea–Hypopnea Index, CHAQ/HAQ … Childhood Health Assessment Questionnaire/Health Assessment Questionnaire, ERT … enzyme replacement therapy, FU … follow-up, IAR … infusion-associated reaction, MPS HAQ … MPS Health Assessment Questionnaire, n … number, NA … not applicable, ROM … range of motion, SEM … standard error of mean, sig. … significant, TEAE … treatment-emergent adverse even, vs. … versus, y … years.

Note:

[a] *The number of patients corresponds to the number of patients included in the analysis of that specific outcome.*

Table 7-6: Evidence profile of idursulfase in MPS II.

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
EFFICACY										
MOTOR FUNCTION										
Motor function – 6MWD after 3 years of FU										
3	Prospective single-arm trials	Serious	Not serious	Serious	Serious	None.	88	NA	Sig. increase [132]. 1 study – 5/6 patients improved [139]. Median increase from baseline: +41 m, corresponding to +10.6% [134].	Very low
Motor function – 6MWD after 7 years of FU										
2	Prospective single-arm trials	Serious	Not serious	Serious	Serious	None.	162	NA	Neuronopathic phenotype: no improvement; most untestable. Non-neuronopathic phenotype: stable/↑; mean +70.8 m (0-174) [137]. Mean change vs. baseline: +31.8 m (95% CI: –4.1-67.7) [138].	Very low

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
Motor function – 6MWD after 0.5-6 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None.	43	NA	Patients still receiving ERT (n=13): 10 improved, 2 stable, 1 declined Patients who discontinued ERT (n=30): 15 declined, 14 stable, 1 improved [135].	Very low
JOINT FUNCTION										
Joint function – joint range of motion after 3 years of FU										
2	Prospective single-arm trials	Serious	Serious	Serious	Serious	None.	83	NA	Sig. improvement only in the shoulder; no consistent change in other joints [132]. No sig. improvement in lower or upper limbs [139].	Very low
Joint function – joint range of motion after 4.4 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None.	12	NA	Neuronopathic MPS II patients: sig. decline in shoulder flexion, shoulder abduction, elbow flexion, elbow extension, and knee extension. N.s. declines in wrist flexion and extension, and hip extension [129].	Very low
Joint function – joint range of motion after 7.8 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None.	17	NA	Greatest gains in the first 2 years (shoulder, elbow, hip, knee). At 5 y (n=13), only the right shoulder improved sig. (p=0.03). None of the patients declined after 7.8 years [137].	Very low
COGNITIVE FUNCTION										
Cognitive function – DAS II after 2 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None.	20	NA	Decreases were observed in all DAS-II clusters and in GCA and SNC composite scores, ranging from –6.4 to –3.8 [133].	Very low
RESPIRATORY FUNCTION										
Respiratory function – Sleep apnoea after 7.8 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None.	10	NA	Two patients with severe obstructive apneas before and following 7 and 5 years of ERT, respectively [137].	Very low

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
Respiratory function – Airway obstruction after 7.8 years of FU										
1	Prospective single-arm trial	Serious	Serious	Serious	Serious	None.	10	NA	Endpoint: 4 patients with severe obstructive airway disease; 2 patients worsened from baseline [137].	Very low
SURVIVAL										
Overall survival after 7 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Not serious	None.	145	NA	All patients: 82.7% Mild phenotype: 91.2% Severe phenotype: 76.7% [138].	Very low
Overall survival after 7 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Not serious	Not serious	Non-controlled study including treated and untreated patients; survival follow-up was 2 years longer in untreated.	800	95	Median survival of treated patients vs. untreated: 33.0 vs. 21.2 year [136].	Low
QUALITY OF LIFE										
Quality of life – the CHAQ disability index after 2 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None.	81 – for parent CHAQ 44 – for child CHAQ	NA	CHAQ (Parent): −0.13±0.064 at 2 years (p=0.047); sig at 30 months, ns at 3 years. CHAQ (Child): −0.15±0.65 at 2 years (n=44, p=0.031); sig at 30 & 36 months [132].	Very low
Quality of life – change in MPS-HAQ domains after 5-9 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None.	15	NA	Non-neuronopathic phenotype vs. neuronopathic phenotype (n=5 vs. 10): improvement in 44% vs. 17% HAQ domains; decline in 6% vs. 62% HAQ domains; stable in 52% vs. 21% HAQ domains [137].	Very low
SAFETY										
MORTALITY										
All-cause mortality after up to 3 years of FU										
6	Prospective single-arm trials	Serious	Not serious	Serious	Not serious	None	875	NA	Mortality rates ranged from 0% [131, 133] to 7.6% [130]. 1 study – 15.18% [134].	Very low

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
All-cause mortality after up to 7.8 years of FU										
2	Prospective single-arm trials	Serious	Not serious	Serious	Not serious	None	160	NA	Mortality rate: 5.8% [137] and 12.41% with severe phenotype presented the most [138].	Very low
All-cause mortality after 13-15 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Not serious	Not serious	Non-controlled study but included both ERT and non-ERT treated patients for survival analysis.	800	95	Adjusted HR 0.46 (95% CI: 0.29-0.72) Cognitive impairment patients: HR 4.84 (95% CI: 3.13-7.47)[136].	Low
All-cause mortality after 0.5-6 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Not serious	/	45	NA	Mortality rate: 6.67% [135].	Very low
SAFETY AND TOLERABILITY OUTCOMES										
Serious AEs after up to 3 years of FU										
3	Prospective single-arm trials	Serious	Serious	Serious	Serious	None	115	NA	8.82% (anaphylaxis) [131]. 61.54%, but 3.85% (central line infection) was related to treatment [130]. 16.4%, 10.9% was related to treatment [133].	Very low
Serious AEs after 7 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Not serious	None	143	NA	42.8% [138]	Very low
Severe AEs after up to 3 years of FU										
2	Prospective single-arm trials	Serious	Serious	Serious	Serious	None	81	NA	61.54% [130]; 16.4%, in 10.9% of patients it was related to the treatment [133].	Very low
Severe TEAEs after 3-5 years of FU										
2	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	708	NA	28.7% [132], and 14.6% [134].	Very low

Abbreviations: 6MWD … 6-minute walking distance, AE … adverse event, CI … confidence interval, CHAQ … Childhood Health Assessment Questionnaire, ERT … enzyme replacement therapy, FU … follow-up, HR … hazard ratio, IAR … infusion-associated reaction, MPS HAQ … Mucopolysaccharidosis Health Assessment Questionnaire, n … number, NA … not applicable, ns … not significant, ROM … range of motion, sig. … significant, TEAE … treatment-emergent adverse event, vs. … versus.

Note:

[a] *The number of patients corresponds to the number of patients included in the analysis of that specific outcome.*

7.7 Elosulfase alfa for treating Mucopolysaccharidosis IVA

7.7.1 Risk of bias assessment

kontrollierte Studie: hoher RoB

The results of the risk of bias assessment for the controlled study [141, 142] is presented in Appendix Table A-21. Overall, the study was rated as having serious risk of bias, due to several reasons: confounding from a non-randomized historical-control design without balancing key covariates, selection bias from per-protocol exclusions based on post-intervention factors without adjustment, departures from intended interventions (unbalanced co-interventions and dose transitions), and measurement bias for the effort-dependent 6MWD. Missing data posed a moderate risk overall (low in ITT, serious in MPP).

7.7.2 Certainty of evidence according to GRADE

The evidence profile for critical outcomes is presented according to the length of follow-up in Table 7-7 below.

sehr niedrige Evidenzqualität wegen Studiendesign

The certainty of evidence across all outcomes was rated as very low, primarily because the studies were observational in nature. The controlled study was judged to have a serious risk of bias, The rest were single-arm trials, which do not allow a direct evaluation of treatment effects.

Table 7-7: Evidence profile of elosulfase alfa in MPS IVA.

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
EFFICACY OUTCOMES										
MOTOR FUNCTION										
Motor function – 6MWD after 2.3 years of FU										
1	Prospective controlled trial	Serious	Not serious	Not serious	Not serious	None	QW-QW MPP=41 QW-QW ITT=51 Pooled MPP=117 Pooled ITT=174	MorCAP MPP=79 MorCAP ITT=97	Treated patients improved in 6MWD (≈+15 to +39 m) while untreated patients declined (≈−16 to −22 m); differences were statistically significant. The improvement varied between the ITT and MPP populations and depending on the dose (pooled vs QW-QW) [147].	Very low
Motor function – 6MWD after 5 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	17	NA	The outcome was stable over the 5-year FU (change from 266 m to 270 m) [144].	Very low
CARDIAC FUNCTION										
Cardiac function – Left ventricular mass index										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cardiac function – Interventricular septal thickness, diastole										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cardiac function – Left ventricular internal diameter, diastole										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cardiac function – Left ventricular posterior wall thickness, diastole										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SURVIVAL										
Overall survival										
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
QUALITY OF LIFE										
Quality of life – MPS HAQ after 2.3 years of FU										
1	Prospective controlled trial	Serious	Not serious	Not serious	Not serious	None	Pooled ITT=158 Pooled MPP=122 QW-QW ITT=53 QW-QW MPP=43	MorCAP ITT=36 MorCAP MPP=26	Treated patients improved in mobility (−0.5 to −0.7) and self-care (−0.4 to −0.8). Untreated patients worsened (+0.3 mobility, +0.4 self-care); between-group differences favored treatment (−0.7 for both domains). Caregiver-assistance showed smaller improvements (−1.0 to −2.3 vs. −0.5 untreated), significant only in MPP, not significant between-group difference [142].	Very low

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients[a]		Effect estimates	Quality
							Intervention	Comparison		
Quality of life – MPS-HAQ after 5 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	17	NA	5-year endpoint: slight decline in least squares mean scores in all three domains, suggestive of maintenance or possible improvement (graphically presented) [144].	Very low
SAFETY OUTCOMES										
MORTALITY										
All-cause mortality after up to 2.5 years of FU										
2	Prospective single-arm trials	Serious	Not serious	Serious	Not serious	None	186	NA	0% [143] and 0.6% [147].	Very low
All-cause mortality after 5 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Not serious	None	20	NA	0 [144].	Very low
SAFETY AND TOLERABILITY OUTCOMES										
Serious AEs after up to 2.5 years of FU										
2	Prospective single-arm trials	Serious	Not serious	Serious	Not serious	None	186	NA	Serious AE rates: from 55.2% to 40.7%. Related to treatment: in 6.9% in the PBO-QOW group [147]. Serious AE rates: 69.23%. Related to treatment: 7.69% [143].	Very low
Serious AEs after 5 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	20	NA	Serious AE rates: 95.0%. Related to treatment – 45% [144].	Very low
Severe AEs after 6 years of FU										
1	Prospective single-arm trial	Serious	Not serious	Serious	Serious	None	20	NA	Severe AE rate: 5% – severe hypersensitivity AE (grade 4, discontinued) [144].	Very low

Abbreviations: 6MWD … 6-minute walking distance, AE … adverse event, ERT … enzyme replacement therapy, FU … follow-up, ITT … intention-to-treat, MPP … modified per-protocol, MPS HAQ … Mucopolysaccharidosis Health Assessment Questionnaire, MorCAP … Morquio A Clinical Assessment Program, NR … not reported, PBO … placebo, QW … once weekly

Notes:

QW-QW stands for the group of patients that received the optimal (standard) elosulfase alfa dosage of 2 mg/kg every week.

[a] *Although initially controlled in design, the study by Hendriksz et al., 2016 reported this outcome only for the ERT group; therefore, these results were presented along with the results from the single-arm trials.*

8 Landscape Overview

8.1 Ongoing Studies on Enzyme Replacement Therapy

17 laufende Studien, fast alle Industrie-finanziert

A total of five ongoing clinical studies were identified for alglucosidase alfa, including registry-based evaluations. For avalglucosidase alfa, seven studies were reported, of which two are patient registries. In the case of elosulfase alfa, only a single observational study was identified. For idursulfase, four studies are ongoing, including one expanded-access program. No additional ongoing trials were found for laronidase (see Table 8-1 for ongoing studies).

In addition, the PEARL study (PrEnAtal Enzyme Replacement Therapy for Lysosomal Storage Disorders) is investigating the prenatal administration of alglucosidase alfa, idursulfase, laronidase, and elosulfase alfa.

Almost all of these trials are industry sponsored.

Table 8-1: Ongoing studies on enzyme replacement therapy

Title	Trial ID	Phase	Status	Estimated study completion date	Sponsor
alglucosidase alfa					
A Prospective Study to Observe & Describe Clinical Outcomes of Alglucosidase Alfa Treatment in Patients ≤6 Months of Age With Infantile-onset Pompe Disease	NCT04848779	Observational	Active not recruiting	28.10.2026	Sanofi
A Global Prospective Observational Registry of Patients With Pompe Disease	NCT06121011	Patient Registry	Recruiting	20.12.2034	Amicus Therapeutics
Higher Dose of Alglucosidase Alpha for Pompe Disease	NCT05017402	Observational	Not yet recruiting	31.12.2026	Taipei Veterans General Hospital
Treatment Frequency Reduction in Pompe Disease	NCT06575829	Phase 4	Not yet recruiting	31.12.2027	Erasmus Medical Center
Pompe Disease Registry Protocol	NCT00231400	Patient Registry	Recruiting	31.01.2034	Sanofi
avalglucosidase alfa					
China Post-approval Commitment Study of Avalglucosidase Alfa in Participants With IOPD	NCT06666413	Phase 4	Recruiting	02.05.2028	Sanofi
Clinical Study for Treatment-naïve IOPD Babies to Evaluate Efficacy and Safety of ERT With Avalglucosidase Alfa	NCT04910776	Phase 3	Active not recruiting	10.08.2027	Sanofi
Avalglucosidase Alfa French Post-trial Access for Participants With Pompe Disease (PTA Avalglucosidase)	NCT05164055	Phase 4	Active not recruiting	31.12.2025	Sanofi
A Study to Assess Safety and Efficacy of Avalglucosidase Alfa Administered Every Other Week in Pediatric Patients With Infantile-onset Pompe Disease Previously Treated With Alglucosidase Alfa	NCT03019406	Phase 2	Active not recruiting	30.12.2026	Sanofi
A Global Prospective Observational Registry of Patients With Pompe Disease	NCT06121011	Patient Registry	Recruiting	20.12.2034	Amicus Therapeutics
Pompe Pregnancy Sub-Registry	NCT00567073	Patient Registry	Recruiting	31.01.2034	Sanofi
An open-label, single-center study on the safety and efficacy of avalglucosidase alpha in late-onset Pompe patients	EUCTR2019-002251-42-NL	Phase 3	Active not recruiting	N/A	N/A
Elosulfase alfa					
Natural History of Atypical Morquio A Disease	NCT03204370	Observational	Recruiting	01.07.2027	GOIZET
Idursulfase					
Extension Study of Idursulfase-IT Along With Elaprase in Children and Adults With Hunter Syndrome and Cognitive Impairment	NCT06031259	Phase 2 Phase 3	Active not recruiting	01.01.2029	Takeda
Post-trial Access Program of Idursulfase-IT Along With Elaprase in Children With Hunter Syndrome	NCT05795361	Expanded Access	Available	N/A	Takeda
A Study of ELAPRASE in Treatment-naïve Participants With Hunter Syndrome (Mucopolysaccharidosis [MPS] II)	NCT04532047	Phase 1	Recruiting	31.07.2032	University of California, San Francisco
Safety and Efficacy of Idursulfase in Idursulfase naive Indian patients for treatment of Mucopolysaccharidosis Type II (MPS II or Hunter Syndrome)	CTRI/2022/03/041431	Phase 4	Active not recruiting	N/A	Shire

Abbreviations: ERT … enzyme replacement therapy, IOPD … infantile-onset Pompe disease, IT … intrathecal, MPS … mucopolysaccharidosis, NCT … National Clinical Trial.

8.2 Emerging Therapeutics for Pompe Disease and Mucopolysaccharidoses I, II and IVA

für Pompe und MPS I & II mehrere Substanzen in Entwicklung

For the treatment of Pompe disease, two novel investigational substances have been identified (zocaglusagene nuzaparvovec and S-606001), along with three planned extensions of indication for already authorised drugs, namely avalglucosidase alfa and cipaglucosidase alfa (Table 8-2).

für MPS IV keine neuen Wirkstoffe identifiziert

In MPS I, three investigational agents are currently in development: OTL-203, iduronicrin genleukocel-T, and lepunafusp alfa (Table 8-3).

For MPS II, three drug candidates were identified: tividenofusp alfa, pabinafusp alfa, and clemidsogene lanparvovec (Table 8-4).

For MPS IV, no investigational drugs were identified using the search terms "mucopolysaccharidosis IV" and "Morquio".

Zulassungserwartung zwischen 2027-2031

Based on current clinical development timelines, regulatory approval may be anticipated between 2027 and 2031, provided that ongoing clinical trials demonstrate safety and efficacy.

Table 8-2: Landscape overview for Pompe disease

Indication	Active ingredient	Registrational Trial	Study Phase	Developer	Estimated EC decision
Zocaglusagene nuzaparvovec					
Zocaglusagene nuzaparvovec monotherapy for treatment of late onset Pompe's disease in adults and elderly.	zocaglusagene nuzaparvovec	2019-003595-38	Phase 1/2	Astellas Pharma	June 2031
S-606001					
S-606001 in combination with enzyme replacement therapy for add-on treatment of Pompe's disease late onset in adults and elderly	S-606001	N/A	Phase 2	Shionogi	N/A
Avalglucosidase Alfa					
Avalglucosidase alfa monotherapy for first line treatment of infantile-onset Pompe's disease in newborns and infants and toddlers	avalglucosidase Alfa	2020-004686-39	Phase 3	Sanofi	January 2027
Cipaglucosidase Alfa					
Cipaglucosidase alfa in combination with miglustat for treatment of late-onset Pompe's disease in newborns, infants, toddlers, children and adolescents who are ERT-experienced or naïve	cipaglucosidase alfa	NCT03911505	Phase 3	Amicus Therapeutics	April 2027
Cipaglucosidase Alfa					
Cipaglucosidase alfa in combination with miglustat for treatment of infantile-onset Pompe's disease in infants and toddlers, children and adolescents who are ERT-experienced or naïve, with IOPD genotype and hypertrophic cardiomyopathy at the time of diagnosis	cipaglucosidase alfa	NCT04808505	Phase 3	Amicus Therapeutics	November 2027

Abbreviations: EC … European commission, ERT … enzyme replacement therapy, IOPD … Infantile-Onset Pompe Disease, N/A … not available, NCT … National Clinical Trial.

Note: Search terms: „Pompe", „Glycogen Storage Disease Type II"

Table 8-3: Landscape overview for MPS I

Indication	Active ingredient	Registrational Trial	Developer	Study Phase	Estimated EC decision
Otl-203					
Otl-203 monotherapy for treatment of Hurler's syndrome in infants, toddlers and children who have biallelic mutation in the IDUA enzyme gene	Otl-203	NCT06149403	Kyowa Kirin	Phase 3	July 2029
Iduronicrin Genleukocel-t					
Iduronicrin genleukocel-t monotherapy for treatment of Mucopolysaccharidosis IH/S, Mucopolysaccharidosis IS in adults and elderly	iduronicrin Genleukocel-t	NCT05682144	Immusoft	Phase 1	N/A
Lepunafusp Alfa					
Lepunafusp alfa monotherapy for treatment of Mucopolysaccharidosis I in newborns, infants, toddlers, children, adolescents, adults and elderly	lepunafusp alfa	NCT04227600 NCT04453085	JCR Pharmaceuticals	Phase 1/2	N/A

Abbreviations: EC … European commission, N/A … not available, NCT … National Clinical Trial.

Note: Search terms: "mucopolysaccharidosis I", "Hurler", "Scheie"

Table 8-4: Landscape overview for MPS II

Indication	Active ingredient	Registrational Trial	Study Phase	Developer	Estimated EC decision
Tividenofusp Alfa					
Tividenofusp alfa monotherapy for treatment of neuronopathic or non-neuronopathic Mucopolysaccharidosis II in children, adolescents and adults up to 26 years of age	tividenofusp alfa	2021-005200-35	Phase 2/3	Denali Therapeutics	April 2027
Pabinafusp Alfa					
Pabinafusp alfa monotherapy for treatment of Mucopolysaccharidosis II in children, adolescents and adults	pabinafusp alfa	2020-003200-14	Phase 3	JCR Pharmaceuticals	May 2027
Clemidsogene Lanparvovec					
Clemidsogene lanparvovec monotherapy for treatment of severe neuronopathic Mucopolysaccharidosis II in male infants, toddlers, children between 4 months up to 5 years of age	clemidsogene lanparvovec	NCT03566043	Phase 2/3	REGENXBIO	October 2026

Abbreviations: EC=European commission, NCT=National Clinical Trial.

Note: Search terms: "mucopolysaccharidosis II", "Hunter"

9 Discussion

9.1 Summary and interpretation of findings – Effectiveness

9.1.1 Alglucosidase alfa and avalglucosidase alfa in Infantile-onset Pompe Disease

Überlebensvorteil bei IOPD;

besser bei früher Behandlung mit Neugeborenenscreening

The most consistent evidence for the benefits of alglucosidase alfa in IOPD patients relates to overall and ventilator-free survival. Two controlled studies (30 ERT-treated patients vs. 95 historic controls) confirmed this benefit after 2.3 years of follow-up [82, 83]. Additionally, evidence from a 5-year study demonstrated the superiority of early treatment combined with newborn screening as these patients showed the greatest survival advantage compared with those diagnosed clinically and treated with ERT, as well as with historic controls (10, 10, and 11 patients, respectively) [80]. These findings are aligned with previous systematic reviews that point to the benefits of alglucosidase alfa in terms of survival in IOPD patients [62, 148] and remain the most robust evidence of clinical benefit in this population.

LVMI-Verbesserung vielfach nachgewiesen

Similarly, alglucosidase alfa has been consistently associated with reductions in left ventricular mass index (LVMI) in both short- and long-term follow-up. This effect has been demonstrated across multiple single-arm studies, despite variability in sample size and dosing regimens. Specifically, improvements were reported in three studies with 3 years of follow-up (n=46) [82, 83, 86], two studies with up to 5 years of follow-up (n=28) [80, 85], and one study with the longest follow-up of 10 years (n=27) [84]. Other cardiac outcomes are less certain, and their findings are derived either from single studies (for relative wall thickness and shortening fraction) or had no available evidence at all (for ejection fraction).

Motorik & Lebensqualität: inkonsistente Ergebnisse,

The evidence for motor function is less conclusive. Although some patients achieve key milestones such as independent sitting or walking, results are inconsistent across small single-arm studies with variable follow-up and incomplete baseline data. Overall, the findings suggest that walking ability is achieved in approximately 30-50% of patients after 3-5 years of follow-up (62 patients) [82, 83, 85, 88]. There is evidence that very early initiation of ERT, particularly following newborn screening, may accelerate motor development [81]. However, pooled analyses indicate that these benefits diminish when all treated patients are compared with untreated groups after 2.7 years of follow-up (27 patients) [81], pointing to the superiority of newborn screening and early treatment. Some reports also suggest that higher doses (40 mg/kg every other week) may better preserve motor function [85, 88], but these findings are highly uncertain due to treatment escalation during follow-up and small patient numbers.

andere Outcomes wie Atemunterstützung unzureichend dokumentiert

Evidence regarding ventilation outcomes is similarly limited. A single controlled study with historical controls [82] showed improved ventilator dependence in treated patients (18 treated vs 61 untreated) after 2.3 years of follow-up, while other single-arm cohorts were inconclusive due to missing baselines or absence of statistical comparisons [73, 88]. Notably, no long-term data are available on changes in the actual time spent on ventilation.

Kognition bei IOPD schwer einzuschätzen, da kleine Studien, unterschiedliche Tests, fehlende Ausgangswerte

höhere ERT-Dosen führten teils zu besseren Ergebnissen, aber Analyse methodisch schwach

Data on cognitive function are more uncertain. Three small, single-arm studies assessed cognition, but interpretation is limited by missing baseline values, heterogeneous assessment tools, and uncontrolled dose changes. Patients receiving higher ERT doses (n=12) appeared to perform better than those on standard dosing (n=6) on the 3-year assessments, but the analyses did not adequately adjust for dose switching or other confounders [85]. After approximately 10 years of treatment with alglucosidase alfa, around two-thirds of patients demonstrated performance below the expected range or could not be assessed, reflecting considerable functional impairment. Interpretation remains limited, however, by the absence of baseline data [88]. Other retrospective studies suggest that many long-term survivors may develop progressive brain MRI abnormalities in parallel with cognitive decline, which points to the need for therapeutic strategies capable of crossing the blood-brain barrier to more effectively address central nervous system involvement [149].

QoL-Daten unsicher, überwiegend körperliche Beeinträchtigung

Regarding quality of life, long-term evidence remains inconclusive due to missing baseline data and heterogeneous reporting [88]. Nevertheless, available data suggest that the majority of patients (93%) experienced impaired physical health, while mental well-being appeared relatively preserved at endpoint assessments.

avalglucosidase alfa: kleine Studie, motorische Verbesserungen möglich, Evidenz schwach

Evidence on avalglucosidase alfa in IOPD is limited to a single small single-arm study (21 patients) with approximately two years of follow-up [90]. Results suggest potential improvements in motor outcomes such as QMFT and 6MWD%, but the certainty of these findings is low due to the lack of a control group and the very small sample size.

OS ist einzig sicher belegter Vorteil von alglucosidase alfa (kontrollierte Daten)

Evidenz zu LVMI gut, andere Effekte inkonsistent, wenig robuste Daten

Overall, survival is the only outcome for which evidence from controlled studies consistently suggests a benefit of alglucosidase alfa compared with no treatment. However, due to the observational study designs, small sample sizes, and moderate to serious risk of bias, the certainty of this evidence is rated as very low. Further, all available prospective long-term evidence indicates that this enzyme replacement therapy improves left ventricular mass index (LVMI); however, these findings are derived exclusively from single-arm studies with variable follow-up durations and dosing regimens, and the certainty of evidence is likewise very low. Evidence for other outcomes – motor function, ventilatory support, cardiac measures beyond LVMI, cognition, and quality of life – remains limited and inconsistent. Most data originate from small single-arm cohorts with incomplete baseline assessments, heterogeneous dosing, and no comparator groups. Long-term evidence for avalglucosidase alfa is even more restricted, being based on a single study without a comparator arm. Given these limitations, confidence in the estimates is very limited, and conclusions regarding the magnitude or durability of benefit must be interpreted with caution.

Additional considerations

Frühbehandlung und höhere Dosierung weisen auf Vorteile hin, Evidenz aber sehr niedrig

Although some data suggest potential benefits with very early initiation or higher dosing of enzyme replacement therapy (ERT), the certainty of evidence remains very low. Observations from other studies indicate that early diagnosis of IOPD and prompt initiation of ERT are associated with improved outcomes [150, 151], and recent expert consensus similarly highlights the advantages of early therapy initiation [152]. However, the only available long-term prospective evidence derives from a single newborn screening study including 31 patients with a maximum follow-up of five years [80].

Timely administration of high-dose ERT has shown the potential to substantially alter the natural course even in the most severe IOPD phenotypes [153], and dose escalation has been recommended in current expert consensus statements [152, 153]. Nevertheless, no long-term prospective controlled studies exist to confirm these observations, and the currently available data are subject to important methodological limitations.

keine langfristigen kontrollierten Studien; methodische Einschränkungen

Furthermore, CRIM status is an important determinant of ERT efficacy, as CRIM-negative patients tend to have a poorer prognosis due to the development of anti-rhGAA IgG antibodies [7]. It should be noted that the majority of patients included in this qualitative synthesis were CRIM-positive, which limits the generalizability of these findings to the CRIM-negative population. Although immunomodulation is recommended, particularly for CRIM-negative patients [152, 153], only one prospective long-term study has assessed this intervention in patients receiving high-dose alglucosidase alfa (40 mg/kg/week, n=5). This study reported 100% ventilator-free survival and preserved ambulation compared with seven patients treated with high-dose ERT alone. However, follow-up in the immunomodulated group was shorter, and non-immunomodulated patients either initiated high-dose ERT or escalated from standard dosing, limiting the interpretability of these findings [85].

CRIM-Status entscheidend: CRIM-negativ schlechterer Verlauf durch Antikörper

Mehrheit CRIM-positiv: Ergebnisse nicht auf CRIM-negativ übertragbar

Immunmodulation empfohlen

9.1.2 Alglucosidase alfa and avalglusocidase alfa in Late-onset Pompe Disease

The certainty of evidence for the benefits of alglucosidase alfa in late-onset Pompe disease (LOPD) primarily pertains to motor function, although findings vary according to study design and follow-up duration. While most studies report no significant change in QMFT, short- to mid-term cohorts (≈3-7 years, 202 patients) frequently demonstrate significant improvements in 6MWD, although some cohorts show only non-significant changes or early gains that are not maintained over time. Longer follow-up periods (3, 5, and ≥10 years; 150 patients) often reveal attenuation of early improvements, with several cohorts reporting significant declines. Notably, the minimal clinically important difference (MCID) for 6MWD in LOPD has been estimated at approximately 25-50 meters [154]. However, observed changes cannot be confidently interpreted against this threshold, as the available data derive from uncontrolled single-arm studies with heterogeneous dosing and incomplete baseline assessments. These patterns are not fully consistent with prior systematic reviews and meta-analyses [63, 155-157], which generally reported significant 6MWD improvements but were limited to shorter follow-up durations (≤∼3 years) – a likely explanation for the discrepancy. One review, however, reported no clear association between longer treatment duration and additional motor gains; patients who experienced decline within the first 12-23 months did not show improvement with prolonged therapy [155].

Motorik bei LOPD: QMFT meist stabil; 6MWD häufig Verbesserung 3-7 Jahre (n=202); länger >3 Jahre oft Abschwächung, teils Rückgang

frühere Reviews berichten mehrheitlich 6MWD-Verbesserung bei kürzerem Follow-up (≤3 Jahre)

Evidence on survival in late-onset Pompe disease (LOPD) remains limited and should be interpreted with caution. A single-arm study including 283 patients [112], which incorporated untreated patients in a non-randomized comparison, suggested a potential 59% survival advantage with alglucosidase alfa over six years of follow-up. Additional long-term evidence derives from a 9-year single-arm study of 63 patients [109] which reported higher survival rates in juvenile- versus adult-onset LOPD.

Überleben bei LOPD mit Alglucosidase alfa begrenzt belegt

5-fach geringere Mortalität (Metaanalyse)

These observations are broadly consistent with a meta-analysis indicating an approximately five-fold lower mortality rate in treated versus untreated patients [156].

Atemfunktion: FVC stabil kurzfristig, langfristig Rückgang

In contrast, the evidence for respiratory outcomes in patients receiving alglucosidase alfa is less conclusive. Short- to mid-term studies (3-7 years; 636 patients) generally report no significant change in upright FVC, while longer-term follow-up (7-10 years; 132 patients) shows significant declines, suggesting that ERT may slow but not prevent disease progression. In the study with the longest follow-up of 12 years (15 patients) [106], a mild but significant decline was observed between years six and nine; however, by year 12, the change was no longer significantly different from baseline. Similar trends have been reported for supine FVC following ERT.

FEV1: sehr begrenzte Evidenz

Evidence for FEV1 is extremely limited, with only one single-arm study (24 patients) reporting no significant change after three years of therapy [93]. Controlled data are also inconclusive: one study (8 treated vs. 6 untreated patients) did not demonstrate a benefit of alglucosidase alfa on ventilation dependence. Single-arm cohorts report variable outcomes without statistical comparisons; the longest follow-up study (~10 years; 11 patients) reported a 57% increase in ventilator use among 30 patients [108]. A controlled trial [96] suggested a reduction in time spent on ventilation, but these results have not been replicated in other study designs. Systematic reviews [63, 155-157] generally conclude that FVC tends to remain stable in the short term but does not improve over time, and there is no clear evidence for a long-term reduction in ventilator dependence. Overall, these findings highlight substantial uncertainty regarding the long-term impact of alglucosidase alfa on respiratory function.

QoL: SF-36 unverändert; RHS/R-PAct stabil/verbessert

Overall, the effects of ERT on quality of life (QoL) appear mixed and vary depending on the assessment instrument used. No significant short- to mid-term changes were observed with the SF-36 (n=212), whereas improvements were reported at seven years using the RHS (n=174), and stabilization was observed with the R-PAct (n=82). These findings underscore the need to standardize QoL outcome assessment in future trials, as QoL is a recognized and clinically relevant endpoint for evaluating ERT effectiveness in LOPD [152].

rezente Evidenz: kurzfristig 6MWD/QMFT besser; langfristig Stabilisierung; AVAL/AVAL > ALG/AVAL

More recently, evidence on avalglucosidase alfa presents a similar pattern. Short-term follow-up (~2 years) shows improvements in 6MWD and QMFT [115], whereas longer-term data (~6 years) suggest stabilization or decline in these outcomes [114], probably reflecting the progressive underlying nature of the disease. Respiratory function and QoL measures (FVC, SF-12, RHS) exhibit a comparable trend, with short-term stabilization but no sustained long-term gains. Patients initiating therapy with avalglucosidase alfa appeared to derive greater benefit than those who switched from alglucosidase alfa, particularly with respect to larger 6MWD improvements and smaller FVC declines. However, these observations are based on only two studies and are limited by methodological shortcomings, including the absence of a control arm [114, 115].

gesamt: frühe Motorikgewinne, langfristig abnehmend; Evidenz begrenzt

Overall, ERT with alglucosidase alfa is associated with early improvements in motor function, particularly during the initial years of treatment; however, these benefits tend to diminish over longer-term follow-up. Evidence for survival benefits exists but is limited to a single uncontrolled trial. Findings for respiratory function, ventilator dependence, and quality of life (QoL) remain inconclusive or limited.

Avalglucosidase alfa shows similar short-term improvements, with some suggestion of greater efficacy in treatment-naïve patients, yet long-term data are insufficient. Overall, the certainty of evidence regarding the long-term effectiveness of ERT in LOPD is very low for most outcomes. Evidence supporting early motor improvements is somewhat stronger but remains limited to single-arm studies, and thus the overall certainty is still rated as very low.

Langzeitdaten unzureichend

Further research is needed to clarify the long-term effects of both ERTs on respiratory function, ventilator dependence, QoL, survival, and, in the case of avalglucosidase alfa, motor function. Well-designed, long-term controlled studies with a minimum follow-up of five years, standardized baseline assessments, and uniform outcome measures would substantially improve the certainty of evidence and inform clinical decision-making.

weitere kontrollierte Studien mit Follow-Up von mind. 5 J notwendig

Additional considerations

Current consensus supports ERT initiation in symptomatic patients [152] but the optimal timing in asymptomatic individuals remains unclear. Limited data suggest potential benefits of early treatment, yet evidence is insufficient to draw firm conclusions [158]. Long-term prospective studies rarely include presymptomatic patients, and those who were enrolled did not receive ERT [105], leaving this question unresolved.

Timing bei asymptomatischen Pts. unklar, begrenzte Daten, wenige prospektive Studien

While no consensus exists regarding initiation of ERT in asymptomatic patients, timely treatment remains an important determinant of therapeutic response [158]. One study analyzing Pompe Registry data from 396 patients found that respiratory function remained generally stable over five years in both early- and late-treatment groups. Patients who initiated ERT sooner after diagnosis had higher baseline FVC, and this advantage persisted throughout follow-up [110]. These findings suggest that earlier initiation of alglucosidase alfa may be associated with better long-term respiratory outcomes in LOPD [110]. Nonetheless, the long-term effectiveness and optimal timing of therapy require confirmation in well-controlled studies.

früher Behandlungsbeginn: höhere Baseline FVC & stabiler Verlauf mit früher ERT-Initiierung; Bestätigung aus kontrollierten Studien fehlt

9.1.3 Laronidase in Mucopolysaccharidosis I

The certainty of evidence for the effect of laronidase on motor function, as assessed by 6MWD, is very low. One small study reported an increase after two years of ERT (10 patients) [124], whereas another observed a decrease after four years in 45 patients [123], although no statistical comparisons were provided. A published review reported no significant changes in 6MWD following laronidase [64], and retrospective studies similarly indicate no clear benefit [159].

6MWD: sehr niedrige Evidenzqualität uneinheitliche Ergebnisse, keine signifikanten Änderungen bestätigt

Evidence on the effects of ERT on joint range of motion (JROM) in MPS I remains limited and variable across different joints. A two-year controlled trial found no difference between ERT-treated patients (n=10) and historic controls (n=23) [124], whereas single-arm studies using heterogeneous outcome measures reported inconsistent results. Two studies with 4-6 years of follow-up (55 patients) observed improvements in shoulder mobility (ROM and flexion/extension) [123, 125], and a systematic review similarly noted significant improvement in shoulder flexion [64]. Although there are indications of benefits in shoulder mobility, these findings are constrained by small sample sizes, inconsistent reporting, and lack of control groups.

JROM: begrenzte Daten; kleine Stichproben; kontrollierte vs. Einzelstudien inkonsistent; Hinweise auf Schulterverbesserung

Evidence regarding the impact of laronidase on sleep apnea is also limited. Across two small studies (55 patients, 4-6 years of follow-up), ERT was associated with reductions in sleep-disordered breathing, but the reporting was variable [123, 125]. A meta-analysis found no significant association between AHI and ERT [64], while short-term studies reported mixed findings [160, 161].

Schlafapnoe: begrenzte Daten; Reduktion Schlafstörungen, aber inkonsistent

Single-arm studies suggest that four [123] and five years [126] of ERT may improve QoL, although different instruments were used (CHAQ/HAQ and MPS HAQ, respectively). Improvements were not consistent across all functional domains [126]. Certainty of evidence is very low due to small sample sizes, lack of controlled data, and heterogeneity in outcome assessment.

QoL: Verbesserungen nach 4-5 J (CHAQ/HAQ, MPS HAQ), nicht alle Domänen; sehr niedrige Evidenzqualität

No long-term prospective evidence is available on the impact of ERT on survival in MPS I. Retrospective data suggest higher survival in treated Hurler patients compared with untreated individuals [162], though outcomes were not superior to hematopoietic stem cell transplantation (HSCT). An Australian expert panel emphasized the limitations of the evidence regarding survival benefit, but highlighted that maintaining or slowing deterioration of clinical outcomes remains an important therapeutic effect [163].

Überleben: keine prospektiven Langzeitdaten; retrospektiv besser als unbehandelt, nicht besser als HSCT

Overall, the certainty of evidence for all outcomes in MPS I is very low, with data derived primarily from a single small controlled trial that did not provide complete between-group comparisons. The remaining studies were single-arm, used variable outcome measures, and applied heterogeneous assessment tools, all of which limit the interpretation and reliability of the evidence.

gesamt MPS I: sehr niedrige Evidenzqualität; kleine kontrollierte Studie + single-arm

However, it has to be pointed out, that since the disorder is rare, conducting RCTs is very challenging. In addition, the progressive nature of the diseases is another challenge, as natural course might have relevant variation.

schwierige Durchführung von RCTs

Additional considerations

As in other LSDs, the timing of ERT initiation is critical [164]. Expert consensus indicates that progressive glycosaminoglycan (GAG) accumulation in untreated MPS I can lead to end-organ damage that worsens over time and may become irreversible. Consequently, early treatment initiation is considered essential to prevent or at least limit permanent damage, particularly in symptomatic patients [27]. Response to ERT also appears to vary with disease severity: in the included studies, younger age at treatment initiation [124] and attenuated phenotypes [126] were associated with better outcomes. However, the evidence is skewed: the only study limited to the Hurler phenotype was a small, controlled trial, while most single-cohort studies predominantly enrolled patients with attenuated phenotypes, limiting the generalizability of these findings to the Hurler population.

Frühbehandlung essenziell; jüngeres Alter/attenuiert besser

aber: schwierige Verallgemeinbarkeit

9.1.4 Idursulfase in Mucopolysaccharidosis II

The most robust long-term evidence on the effects of idursulfase pertains to survival, derived from two large single-arm studies. In one study of 145 patients, survival remained high at seven years (~80%), with higher rates observed in patients with the attenuated phenotype [138]. In another study of 895 patients followed for 13-15 years, treated individuals demonstrated a median survival advantage of nearly 12 years compared with untreated patients.

hohe Überlebensraten (80 % nach 7 J); median +12 Jahre vs. unbehandelt

These findings are consistent with retrospective analyses reporting significantly longer survival in treated patients [165]. Although these data are derived from single-arm and registry studies, the evidence is strengthened by the large sample sizes and extended follow-up, supporting a survival benefit of idursulfase.

retrospektive Analysen berichten signifikante Überlebensverlängerung

Idursulfase has been associated with short- to mid-term improvements in 6MWD in studies up to three years (n=88), with gains further supported by a long-term study including 145 patients with seven-year follow-up [138]. Benefits appeared greater in non-neuronopathic patients, although evidence was limited (17 patients) [137]. Observational data suggest that continued treatment supports stability, whereas discontinuation is often followed by functional decline (45 patients) [135]. Overall, idursulfase appears to improve endurance in the short- to mid-term, but its long-term effectiveness remains uncertain, particularly in severe disease, consistent with findings from other systematic reviews [65, 166].

6MWD: Kurz-/mittelfristig Verbesserungen; Kontinuität wichtig, Abbruch führt zu Rückgang

Evidence on JROM with idursulfase is mixed. Short-term studies up to three years (n=83) reported no overall gains, except for shoulder improvement in one trial [132]. Longer follow-up demonstrated declines in neuronopathic patients after 4.5 years (n=12) [129], whereas mixed-phenotype cohorts showed partial gains sustained over nearly eight years (n=15) [137]. Overall, idursulfase appears to have low, phenotype-dependent effects on JROM, with uncertain long-term clinical significance. These observations align with systematic reviews [65, 166, 167], which conclude that ERT has limited and inconclusive impact on JROM across ages and disease severities.

JROM: gemischt, phänotypabhängig; neuronopathisch Rückgang, attenuiert teilweise Gewinne

Evidence on QoL outcomes with idursulfase is limited. CHAQ disability index scores showed significant short-term improvements in both parent- (n=81) and child-reported (n=44) assessments at two years, although these gains were only partly sustained at 30-36 months. Longer-term results from the MPS-HAQ (5-9 years) suggested more favourable outcomes in non-neuronopathic patients (n=5) compared with neuronopathic patients (n=10) [137]. Overall, idursulfase appears to confer modest, phenotype-dependent benefits on functional disability, but the long-term impact remains uncertain, consistent with other reviews [65].

QoL: kurzfristige Verbesserungen CHAQ; langfristig attenuiert besser als neuronopathisch

Evidence on cognitive outcomes is also scarce and inconclusive. One study reported declines in DAS-II scores after two years, varying by age and baseline status [133]. Interpretation is further limited by heterogeneity in disease severity and neurological involvement. Systematic reviews suggest that attenuated patients generally remain cognitively stable regardless of treatment, whereas in severe cases, small functional gains may support daily interaction without altering underlying cognition [167].

Kognition: Rückgänge DAS-II; attenuiert stabil, schwer variabel

Evidence on respiratory outcomes (sleep apnea, airway obstruction) with idursulfase is particularly limited. A small study (n=10) reported no overall change in sleep apnea, although half of the patients with severe obstruction worsened [137].

A qualitative review similarly concluded that the current data do not allow firm conclusions [167].

Schlafapnoe unverändert bzw. verschlechtert. limitierte Evidenz

Overall, the published evidence supports improvements in overall survival and motor function (measured by 6MWD) with idursulfase in patients with MPS II. These conclusions are primarily based on non-controlled studies that included both attenuated and severe phenotypes. Due to methodological limMMitations, the certainty of evidence is very low.

GRADE: sehr niedrig; single-arm-Studien, methodische Einschränkungen

Evidence regarding JROM, QoL, cognitive function, and respiratory outcomes remains scarce and inconclusive, with heterogeneity in reporting and outcome measures further limiting interpretability. These gaps highlight the need for long-term, controlled, and standardized studies to clarify the long-term effectiveness of idursulfase in MPS II.

JROM/QoL/Kognition/ Atemwege unsicher, heterogen berichtet

In summary, it should be noted that MPS II is also a rare disorder, which makes the conduct of randomized controlled trials particularly challenging. Furthermore, the progressive nature of the disease poses additional difficulties, as its natural course may vary substantially between individuals.

schwierige Durchführung von RCTs

Additional considerations

Consistent with guidance across lysosomal storage disorders, expert consensus recommends initiating ERT as early as possible after diagnosis. For MPS II, idursulfase is recommended for patients with an attenuated (non-neuronopathic) phenotype who exhibit somatic involvement. In patients with the severe (neuronopathic) phenotype, a time-limited trial of ERT may be considered to address somatic manifestations only, as idursulfase does not cross the blood-brain barrier and is not expected to confer cognitive benefit [168, 169]. Indeed, included studies reported greater improvements in attenuated patients, including survival [138], 6MWD [137], JROM – with declines observed in neuronopathic patients [129], but partial gains in mixed-phenotype cohorts [137], and QoL (assessed with MPS-HAQ) [137]. However, these observations are derived primarily from small, uncontrolled studies, which limits the interpretability and generalizability of the findings.

Empfehlung: Frühbehandlung bei attenuiert; zeitlich begrenzt bei schwer (keine BBB-Durchdringung)

9.1.5 Elosulfase alfa in Mucopolysaccharidosis IVA

The strongest evidence for the long-term effectiveness of elosulfase alfa pertains to its impact on motor function. Overall, available data indicate short-term improvements in 6MWD, as demonstrated by a two-year controlled trial (MOR-005; n=174 treated vs. 97 untreated) [141], with stabilization or maintenance observed in longer-term follow-up in a smaller five-year study (n=17) [144]. Although the two-year trial benefits from a robust sample size, the largest improvements were observed in a subgroup of patients who received the standard elosulfase alfa dose throughout the study (51 patients in the treatment arm and 79 in the control arm). In the pooled cohort, which included patients on variable dosing regimens, improvements were modest. These findings are consistent with a meta-analysis [66] and indicate potential benefit, but confirmation in longer-term controlled trials is required.

6MWD kurzfristig verbessert (MOR-005 kontrolliert)

langfristig stabil (5 J)

Evidence on quality of life (QoL) outcomes with elosulfase alfa follows a similar pattern. In the controlled MOR-005 trial, treatment significantly improved functional abilities over two years, particularly in mobility and self-care, with trends toward reduced caregiver assistance, whereas untreated patients declined [144]. As with motor outcomes, it should be noted that sample size variability affects interpretability: 174 patients were included in the pooled analysis, while only 51 patients received the standard ERT dose throughout the study. By contrast, a small single-arm study (n=17) reported stable QoL outcomes over 1.4 years, with only slight declines by year five, suggesting maintenance of function. A meta-analysis similarly reported QoL improvements with ERT in MPS IVA, although results were heterogeneous and primarily derived from short-term studies [66].

QoL: Mobilität & Selbstversorgung signifikant besser (2 J); langfristig stabile Funktion

There is currently no robust evidence on the long-term effects of elosulfase alfa on cardiac function. Some long-term retrospective studies suggest a potential benefit, as indicated by reductions in z-scores for LVMI, IVSd, and LVPWd following ERT, with greater improvements observed when treatment was initiated earlier [170]. A prospective study with variable ERT exposure periods supports this observation, although it included a mixed MPS population, encompassing but not limited to MPS IVA [171].

Herz: keine robusten Langzeitdaten; retrospektiv LVMI/IVSd Verbesserung bei früher Behandlung

Similarly, there is no evidence on the long-term impact of elosulfase alfa on overall survival. While a UK study suggested a possible trend toward improved survival in MPS IVA patients, no study has directly evaluated survival benefits of ERT in this population [172].

Überleben: Keine direkten Daten; UK-Studie Trend

Overall, the most certain conclusions relate to short-term improvements in 6MWD and functional abilities, primarily derived from a single two-year controlled trial, where the largest effects were observed in patients maintained on standard-dose ERT throughout. Robust, long-term controlled studies are needed to confirm the durability of these benefits and to clarify effects on cardiac function and survival, for which evidence is currently lacking.

gesamt: 6MWD/QoL kurzfristig besser; Langzeitdaten fehlen

In summary, it should be noted that MPS IVA is also a rare disorder, which makes the conduct of randomized controlled trials particularly challenging. Furthermore, the progressive nature of the disease poses additional difficulties, as its natural course may vary substantially between individuals.

schwierige Durchführung von RCTs

Additional considerations

Consistent with guidance for other MPS disorders, consensus statements and clinical guidelines recommend initiating ERT immediately after diagnosis to maximize the likelihood of altering disease progression [173]. In MPS IVA, a key limitation of elosulfase alfa is its limited effect on skeletal deformities and established valvular disease, highlighting the need for multidisciplinary management [174]. In the controlled trial [141], patients with skeletal deformities who underwent surgery were excluded from the modified per-protocol population to avoid confounding of motor-function assessments. However, excluding these more severely affected patients may have biased overall estimates, as evidenced by differences between intention-to-treat and modified per-protocol analyses, with the latter showing greater apparent benefits. This further underscores the recognized limitation of ERT on skeletal pathology in MPS IVA.

Empfehlung: Frühbehandlung nach Diagnose; Wirkung bei Skelett-/etablierten Herzklappenerkrankungen begrenzt

9.1.6 The relationship between immunogenicity and clinical effectiveness of enzyme replacement therapies

Although the development of high antibody titers against a specific ERT can potentially attenuate the clinical response to therapy [175], long-term evidence supporting this association remains scarce. Among all studies with a minimum of two years follow-up, five evaluated the relationship between high anti-drug antibody levels and the effectiveness of ERT in patients with LOPD [98], MPS I [124], MPS II [132], and MPS IVA [144, 147].

Immunogenität: hohe Antikörper können Effekt mindern; kaum Langzeitdaten; 5 Studien

In a cohort of 73 LOPD patients treated with alglucosidase alfa for three years, clinically relevant antibody interference was rare, affecting only a small proportion of adults with Pompe disease [98].

Antikörper LOPD: selten klinisch relevant

In MPS I, anti-laronidase neutralizing antibodies were associated with a modest reduction in ambulatory performance (measured by the 6MWD); however, their overall impact on therapeutic effiMcacy appeared limited, as observed in a two-year study involving 11 patients [124].

MPS I: Anti-laronidase-Antikörper geringe Auswirkung auf 6MWD

In MPS II, the presence of neutralizing anti-idursulfase antibodies was associated with a smaller increase in absolute FVC among antibody-positive patients (mean gain 2.3-12.7%) compared with antibody-negative patients (6.7-31.8%) after two years of ERT. Nonetheless, antibody status did not affect other outcomes, including 6MWD, liver and spleen volumes, or urinary GAG levels [132].

MPS II: neutralisierende Antikörper mindern FVC-Gewinn, andere Outcomes unverändert

Conversely, in MPS IVA, long-term studies found no association between immunogenicity and clinical efficacy of elosulfase alfa, either after 2.3 years [147] or after 5 years of treatment [144]. These findings underscore the need for additional long-term, systematically designed studies to clarify the clinical relevance of immunogenicity and its potential impact on the sustained effectiveness of ERT across lysosomal storage disorders, especially for alglucosidase alfa in IOPD, or avalglucosidase alfa in both types of Pompe disease.

MPS IVA: kein Zusammenhang zwischen Immunogenität & Wirksamkeit

9.1.7 The long-term effectiveness of early-initiated enzyme replacement therapy

As mentioned earlier, current guidelines for all lysosomal storage disorders recommend initiating ERT as early as possible. However, long-term evidence supporting the effectiveness of early initiation remains limited. Available data are restricted to one study on alglucosidase alfa in IOPD [80] and another in LOPD [110], while a single study in MPS I [124] included patients who began treatment at a younger age but did not perform any comparative analyses with another group as a reference. This emphasizes the need for additional well-designed long-term studies on the impact of early treatment initiation in LSDs – particularly in MPS II, MPS IVA, and for avalglucosidase alfa.

Frühbehandlung: empfohlen, aber Langzeitdaten fehlen

9.2 Summary and Interpretation of Findings – Safety

Across all LSDs, ERTs are generally well tolerated. The most consistent pattern observed across IOPD/LOPD (alglucosidase alfa, avalglucosidase alfa), MPS I (laronidase), MPS II (idursulfase), and MPS IVA (elosulfase alfa) is that the majority of adverse events (AEs) are mild to moderate infusion-associated reactions, including rash, fever, transient respiratory symptoms, headache, and urticaria/angioedema. Serious treatment-related AEs are rare.

Sicherheit ERT: gut verträglich; meist milde/moderate Infusionsreaktionen

Mortality has been reported in long-term studies, but none were considered treatment-related, and discontinuation rates remain low (<10% across studies). Serious AEs are reported more frequently among MPS II and MPS IVA patients, yet treatment-related events remain uncommon. Severe reactions, including anaphylaxis, have been reported in isolated cases. Systematic reviews confirm that such events are rare and generally manageable with premedication or infusion adjustments [62-65].

schwere Ereignisse: selten behandlungsbedingt; Anaphylaxie isoliert; Abbrüche <10 %

Langzeitstudien ohne behandlungsbedingte Todesfälle

Evidence on the safety of ERTs is limited by small and heterogeneous cohorts, inconsistent follow-up durations (typically ≤5 years), lack of standardized safety assessment protocols (e.g., CTCAE, MedDRA), and variability in reporting. Importantly, while studies report rates of adverse events (AEs), they often do not specify whether events were treatment-related.

Sicherheit von ERTs begrenzt durch kleine, heterogene Kohorten, Follow-up meist ≤5 Jahre

Most controlled evidence comes from IOPD (two studies, 39 patients, 2.3 years of follow-up). For avalglucosidase alfa and MPS subtypes (I, II, IVA), the certainty of evidence is very low, being derived primarily from single-arm studies. Safety evidence is particularly limited for MPS I, as most data derive from a single four-year single-arm study [123]. Only studies in MPS IVA applied standardized protocols for safety assessments, such as grading AEs according to CTCAE or MedDRA. Notably, a recent FDA pharmacovigilance analysis identified rare but novel signals, such as chronic recurrent multifocal osteomyelitis in adolescent Pompe disease, highlighting the importance of continued long-term surveillance [176]. Overall, current evidence supports an acceptable and manageable safety profile of ERTs; however standardized, controlled, and longer-term studies remain essential, especially in rarer subtypes and with newer products.

kontrollierte Daten v. a. bei IOPD (2 Studien, N=39, Follow-Up 2,3 Jahre)

avalglucosidase alfa & MPS I/II/IVA: sehr niedrige Evidenzqualität, v. a. single-arm-Studien

ERTs gut verträglich; standardisierte, kontrollierte Langzeitstudien fehlen

9.3 Enzyme Replacement Therapy in the Home Setting

Attending ERT infusions in the clinic can pose a significant burden for patients and caregivers, as infusions typically last several hours and require a post-infusion observation period of at least two hours. This impacts school or work schedules, social life, and incurs direct travel-related costs.

Klinik-Infusion: hohe Belastung (Stunden + 2 h Beobachtung), Reisekosten, Ausfallzeiten

Home infusion programs, already approved for several genetic diseases, have generally proven to be safe, clinically effective, and reduce treatment burden, with positive effects on quality of life for patients and caregivers [177-179]. Regulatory and reimbursement challenges exist in some countries. For example, in Germany, reimbursement for home-based ERT is not uniformly regulated and handled case by case, creating a substantial administrative burden [180]. However, from a cost perspective, German data suggest that additional expenses for personnel and travel are modest and may be offset by the benefits of providing ERT at home. For patients with LSDs, the advantages of home infusion – including reduced travel, fewer work absences, and decreased need for inpatient care – are likely to outweigh these incremental costs to statutory health insurance systems [181].

Heiminfusion: sicher, wirksam, QoL-verbessernd, kostensparend

Deutschland: Fall-zu-Fall-Genehmigung, administrativer Aufwand

Although concerns have been raised regarding the management of infusion-associated reactions (IARs) at home, a systematic review confirms that home infusion is generally safe, effective, preferred by patients, and cost-saving compared with outpatient or hospital-based administration [179]. In the Netherlands, over 80% of Pompe patients now receive ERT at home, with studies demonstrating that alglucosidase alfa and avalglucosidase alfa can be safely administered in LOPD [181, 182]. Real-world data also indicate that home-based laronidase infusions have safety profiles comparable to clinic-based administration [183]. However, study result recommend that home infusion should be considered after a minimum of six months of supervised clinical treatment to ensure that patients do not experience severe infusion-Massociated reactions (IARs) [184].

Kosten: Zusatzkosten personalmäßig gering

Niederlande: >80 % Pompe-Patienten mit Heim-ERT

This initial period allows for the establishment of a stable treatment regimen and the identification of any adverse reactions under controlled conditions. Patients who experience reactions require extended observation and careful monitoring prior to transitioning to home-based therapy [184].

Nebenwirkungen überwachen vor Heimtherapie

Evidence from various studies supports the safety and efficacy of home-based ERT. A systematic review indicated that home infusion is generally safe, clinically effective, preferred by patients, and cost-saving compared with outpatient or hospital-based administration [182].

Sicherheit, Wirksamkeit, Patientenvorliebe, Kostenersparnis bei Heiminfusion

Specifically, in the Netherlands, data from 18,380 infusions showed that the incidence of IARs was lower in home settings (0.8%) compared to hospital settings (2.9%), with the majority of reactions being mild and manageable [181].

Niederlande: IARs zu Hause geringer als in Klinik

Among all long-term studies included in this systematic review, only one prospective study has evaluated home infusion ERT, specifically elosulfase alfa in 13 MPS IVA patients who received therapy for approximately 3.7 years at home [144]. Treatment compliance during home infusions was comparable to that observed in the overall study population. The safety profile was consistent with the broader MOR-100 trial. Although one grade 4 adverse event (not treatment-related) and three hypersensitivity reactions were reported, no treatment discontinuations or medical interventions were required. Comparable long-term prospective data are not available for other ERTs, highlighting the need for further controlled studies to establish the long-term safety and feasibility of home infusion across different therapies.

nur 1 prospektive Langzeitstudie zu Heiminfusion elosulfase alfa (13 MPS IVA, 3,7 Jahre)

für andere ERTs fehlen Langzeit-Heiminfusionsdaten; Bedarf an kontrollierten Studien

In Austria, reimbursement for home-infusion ERT is not uniformly regulated and must be arranged case by case with each health insurer. While drug costs for hospital-based ERT are borne by hospitals, for home infusions, medication is prescribed by the delegating physician and billed to the statutory or private insurer. Administration costs (nursing and home visits) also require individual approval, as national procedures are not standardized. Certified home-infusion providers with trained nurses and SOPs are available, with satisfactory experience in adults with Pompe disease and children with LSDs [178].

Österreich: Erstattung von Heiminfusion individuell, nicht standardisiert

Kosten für Pflege/Besuche genehmigungspflichtig

Additional considerations

The administration of enzyme replacement therapy (ERT) via home infusion has emerged as a viable alternative to hospital-based treatments in lysosomal storage disorders (LSDs), offering potential benefits in terms of patient convenience, quality of life, and healthcare resource utilization. Despite these benefits, long-term efficacy data – particularly in home settings – remain limited and its implementation necessitates careful consideration of patient selection, monitoring protocols, and clear criteria for therapy initiation, continuation, and discontinuation as ERT is administered outside specialized centers.

ERT-Heiminfusion: Alternative zu Klinik; Vorteile für Pts., Familien, Kosten

begrenzte Langzeitdaten

Monitoring Protocols & Discontinuation Criteria

Regular monitoring is essential to assess the efficacy and safety of ERT. This includes evaluations of muscle strength, respiratory function, and the occurrence of IARs. The European Pompe Consortium (EPOC) has established "triple-S" criteria – Start, Switch, and Stop – to guide clinicians in making informed decisions about initiating, modifying, or discontinuing ERT in patients with Pompe disease [185].

wichtige Kriterien: Pts, Überwachung, klare Start-/Wechsel-/Abbruchregeln

Similar structured criteria are also necessary for ERT in mucopolysaccharidoses (MPS) to ensure consistent, long-term assessment and patient-centered decision-making and would be crucial to ensure that therapy is only continued when it provides clinical benefit.

9.4 Limitations

9.4.1 Limitations of the evidence

fehlende Langzeit-RCTs, wenige kontrollierte prospektive Studien; oft moderates bis hohes RoB

The evidence base for ERTs in lysosomal storage disorders is limited by the absence of long-term randomized controlled trials (RCTs) and the small number of long-term prospective, controlled studies, many of which carry a moderate to serious risk of bias. In rare diseases, RCTs are often constrained by ethical concerns, limited funding, and challenges in recruiting adequate patient numbers. Consequently, clinical evidence typically relies on small or short-term RCTs, or single-arm observational studies. Rather than assigning patients with progressive disease to placebo, studies often use historical or external controls from prior trials, or modelled natural history comparators [186]. Regulators may accept such designs if groups are comparable; however, in the studies included in this review, matching was generally limited to age and/or sex, omitting key clinical covariates. Furthermore, natural history registries often lack critical variables, so comparisons are frequently restricted to survival outcomes [187].

Studien meist kleine, kurze RCTs oder single-arm; Kontrolle durch historische/modellierte Vergleiche, Follow-up & Dosierungen heterogen, fehlende Baselines

matching meist nur nach Alter/Geschlecht, klinische Variablen oft fehlend; Überleben häufig einzig vergleichbar

Common limitations across studies, to varying degrees by disease and ERT, include the absence of control arms, heterogeneity in follow-up duration, variation in dosing regimens (particularly in IOPD and MPS IVA), lack of baseline assessments, inconsistent outcome reporting, non-standardized outcome measures (especially for QoL), and heterogeneous study populations combining attenuated and severe phenotypes.

MCIDs fehlen meist, nur 6MWD bei LOPD bekannt, aber keine für FVC

Definition klinisch relevanter Änderungen oft substituiert oder selbst festgelegt, erschwert Interpretation und Evidenzbewertung

Additionally, minimal clinically important differences (MCIDs) have not been published or validated for key outcomes in IOPD, MPS I, II, and IVA. While an MCID exists for 6MWD in LOPD [154], no established thresholds exist for respiratory outcomes such as FVC. One study reviewed MCIDs for 6MWD from other conditions and highlighted the challenges of defining MCIDs in ultra-rare diseases, using elosulfase alfa in Morquio A as an example. The authors emphasized the need for disease-specific MCIDs and noted that current evidence suggests potential clinical benefits [188]. Some investigators proposed their own definitions of clinically meaningful change [106], while others applied cut-offs extrapolated from different diseases. This variability further complicates the interpretation of long-term data and contributes to the uncertainty surrounding the clinical significance of reported changes.

9.4.2 Limitations of the review

methodische Limitationen

The present systematic review has several methodological limitations.

First, despite applying a comprehensive search strategy, some grey literature sources and non-English publications may have been missed, which may limit the completeness of the evidence reviewed.

RoB-Bewertung meist übernommen, kein vollständiges Re-Assessment

Second, in accordance with the scope of this review, we relied on risk-of-bias assessments reported in the included reviews when available, rather than performing an independent full re-assessment for each study, which may have introduced variability in judgment across sources.

Heterogenität (Population, Dosierung, Follow-up, Outcomes) erschwert quantitative Auswertung

Third, due to the high heterogeneity across studies – including differences in patient populations, dosing regimens, follow-up duration, and outcome measures (particularly quality of life) – quantitative synthesis was rarely feasible, and findings were summarized narratively, limiting the precision of effect estimates.

Sicherheit oft unvollständig berichtet, teils nachberechnet

Fourth, reporting of safety outcomes was inconsistent and often incomplete, precluding reliable estimation of adverse event rates and robust between-study comparisons. In some cases, the review team had to perform additional calculations to harmonize or reconstruct results, which may have introduced minor uncertainties.

10 Conclusion

Across lysosomal storage disorders (LSDs), enzyme replacement therapies (ERTs) demonstrate the most consistent benefit in survival, particularly with alglucosidase alfa in infantile-onset Pompe disease (IOPD) and idursulfase in mucopolysaccharidosis type II (MPS II). Evidence indicates that early treatment initiation, including through newborn screening in IOPD, maximizes survival and ventilator-free outcomes. In late-onset Pompe disease (LOPD), short-term motor improvements and potential survival benefits are observed with alglucosidase alfa, though these effects tend to diminish over time. Functional gains in MPS I and IVA are modest, while MPS II patients – particularly those with attenuated phenotypes – show improved endurance and survival. Cardiac benefits, such as reductions in left ventricular mass index, are most robust in IOPD, but evidence for other cardiac outcomes is limited.

ERT bei LSDs verbessert Überleben, besonders bei IOPD und MPS II

Frühbehandlung, besonders Neugeborenenscreening, maximiert Nutzen

kardiale Vorteile robust bei IOPD; sonst limitiert

Across LSDs, motor, respiratory, cognitive, and quality-of-life outcomes remain highly variable and uncertain, reflecting small sample sizes, single-arm designs, heterogeneous dosing, incomplete baseline assessments, and inconsistent reporting. Avalglucosidase alfa demonstrates a similar profile to alglucosidase alfa, with early signals of motor or respiratory benefit in treatment-naïve patients, but long-term data are extremely limited.

Motorik/Atmung/ Kognition/QoL:

variabel, unsicher (kleine Pts.-Anzahl, single-arm, heterogen)

Safety profiles are generally favourable, with most adverse events being mild to moderate infusion-associated reactions; serious treatment-related events are rare.

Sicherheit: gut, meist nur milde Infusionsreaktionen

Home infusion of ERT represents a promising approach to managing LSDs, offering benefits in terms of patient convenience and healthcare efficiency and appear feasible, safe, and acceptable in real-world practice. However, its successful implementation requires adherence to established guidelines, careful patient selection, regular monitoring, and clear discontinuation criteria. Continued research and standardization of practices are necessary to optimize the safety and efficacy of home-based ERT across different LSDs. Home infusion programs, though regulatory and reimbursement barriers exist in some European settings.

Heim-ERT: sicher, wirksam, kosteneffizient; klare Kriterien & Forschung notwendig; regulatorische Barrieren europaweit

Overall, the certainty of evidence is very low for most outcomes, and conclusions regarding the magnitude and durability of ERT effects should be interpreted with caution. High-quality, long-term, controlled studies with standardized baseline assessments and outcome measures are urgently needed to clarify the effectiveness of ERT on motor, respiratory, cardiac, cognitive, and quality-of-life outcomes. Future research should also define MCIDs specifically for these diseases, and evaluate early initiation strategies, dose optimization, and immunomodulation in CRIM-negative patients. In parallel, clear clinical guidelines and standardized discontinuation criteria are necessary to ensure consistent and safe application of ERT. As long-term efficacy data – particularly in home settings – remain limited, structured monitoring is essential, since therapy is administered outside specialized centers and early detection of cases where continuation may not provide clinical benefit or may pose safety risks is critical. Home-based ERT offers clear advantages in convenience, patient preference, and healthcare efficiency, but it's safe and effective implementation requires adherence to these principles.

Evidenzqualität: sehr niedrig für die meisten Outcomes

Forschungslücken: Langzeit-RCTs, standardisierte Outcomes, MCIDs, Frühbehandlung, Dosisoptimierung, CRIM-negative Pts.

Klinikbedarf: Leitlinien, Abbruchkriterien, strukturiertes Monitoring; Heim-ERT: Bedarf an Sicherheitsstandards

11 References

[1] FM, P., et al., *Lysosomal storage diseases – PubMed.* Nature reviews. Disease primers, 10/01/2018. **4**(1).

[2] Lim, J.-A., L. Li, and N. Raben, *Frontiers | Pompe disease: from pathophysiology to therapy and back again.* Frontiers in Aging Neuroscience, 2014/07/23. **6**.

[3] Kishnani, P.S., et al., *Pompe disease diagnosis and management guideline.* Genet Med, 2006. **8**(5): p. 267–88.

[4] HG, H., *alpha-Glucosidase deficiency in generalized glycogenstorage disease (Pompe's disease) – PubMed.* The Biochemical journal, 1963 Jan. **86**(1).

[5] SC, W., et al., *Elevated Plasma Cardiac Troponin T Levels Caused by Skeletal Muscle Damage in Pompe Disease – PubMed.* Circulation. Cardiovascular genetics, 2016 Feb. **9**(1).

[6] CI, v.C., et al., *Hearing loss in Pompe disease revisited: results from a study of 24 children – PubMed.* Journal of inherited metabolic disease, 2010 Oct. **33**(5).

[7] AK, D., et al., *Characterization of immune response in Cross-Reactive Immunological Material (CRIM)-positive infantile Pompe disease patients treated with enzyme replacement therapy – PubMed.* Molecular genetics and metabolism reports, 05/10/2019. **20**.

[8] PS, K., et al., *Cross-reactive immunologic material status affects treatment outcomes in Pompe disease infants – PubMed.* Molecular genetics and metabolism, 2010 Jan. **99**(1).

[9] Hagemans, M.L., et al., *Clinical manifestation and natural course of late-onset Pompe's disease in 54 Dutch patients.* Brain, 2005. **128**(Pt 3): p. 671–7.

[10] van den Hout, H.M., et al., *The natural course of infantile Pompe's disease: 20 original cases compared with 133 cases from the literature.* Pediatrics, 2003. **112**(2): p. 332–40.

[11] Kishnani, P.S., et al., *A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease.* J Pediatr, 2006. **148**(5): p. 671–676.

[12] Pellegrini, N., et al., *Respiratory insufficiency and limb muscle weakness in adults with Pompe's disease.* Eur Respir J, 2005. **26**(6): p. 1024–31.

[13] Kishnani, P.S., et al., *Timing of diagnosis of patients with Pompe disease: data from the Pompe registry.* Am J Med Genet A, 2013. **161A**(10): p. 2431–43.

[14] Beltran Papsdorf, T.B., J.F. Howard, Jr., and N. Chahin, *Pearls & Oy-sters: clues to the diagnosis of adult-onset acid maltase deficiency.* Neurology, 2014. **82**(9): p. e73–5.

[15] Amato, A.A., et al., *A 49-year-old woman with progressive shortness of breath.* Neurology, 2011. **76**(9): p. 830–6.

[16] Johnson, E.M., et al., *Pulmonary function tests (maximum inspiratory pressure, maximum expiratory pressure, vital capacity, forced vital capacity) predict ventilator use in late-onset Pompe disease.* Neuromuscul Disord, 2016. **26**(2): p. 136–45.

[17] I, T., *Metabolic myopathies – PubMed.* Seminars in pediatric neurology, 1996 Jun. **3**(2).

[18] KM, S., et al., *Observational clinical study of 22 adult-onset Pompe disease patients undergoing enzyme replacement therapy over 5years – PubMed.* Molecular genetics and metabolism, 2016 Apr. **117**(4).

[19] Saville, J.T. and M. Fuller, *Experience with the Urinary Tetrasaccharide Metabolite for Pompe Disease in the Diagnostic Laboratory.* Metabolites, 2021. **11**(7).

[20] Piraud, M., et al., *Urine glucose tetrasaccharide: A good biomarker for glycogenoses type II and III? A study of the French cohort.* Mol Genet Metab Rep, 2020. **23**: p. 100583.

[21] Labella, B., et al., *A Comprehensive Update on Late-Onset Pompe Disease.* Biomolecules, 2023 Aug 22. **13**(9).

[22] Ausems, M.G., et al., *Frequency of glycogen storage disease type II in The Netherlands: implications for diagnosis and genetic counselling.* Eur J Hum Genet, 1999. **7**(6): p. 713–6.

[23] Loscher, W.N., et al., *Pompe disease in Austria: clinical, genetic and epidemiological aspects.* J Neurol, 2018. **265**(1): p. 159–164.

[24] Kong, W., C. Lu, and L. Wang, *Global birth prevalence of Pompe disease: A systematic review and meta-analysis.* Neuroscience, 2024. **563**: p. 167–174.

[25] M, P.-P., B. DR, and H. P, *Current and new therapies for mucopolysaccharidoses – PubMed.* Pediatrics and neonatology, 2023 Feb. **64 Suppl 1**.

[26] LA, C., et al., *Genotype-phenotype relationships in mucopolysaccharidosis type I (MPS I): Insights from the International MPS I Registry – PubMed.* Clinical genetics, 2019 Oct. **96**(4).

[27] de Ru, M.H., et al., *Enzyme replacement therapy and/or hematopoietic stem cell transplantation at diagnosis in patients with mucopolysaccharidosis type I: results of a European consensus procedure.* Orphanet J Rare Dis, 2011. **6**: p. 55.

[28] Vijay, S. and J.E. Wraith, *Clinical presentation and follow-up of patients with the attenuated phenotype of mucopolysaccharidosis type I.* Acta Paediatr, 2005. **94**(7): p. 872–7.

[29] Moore, D., et al., *The prevalence of and survival in Mucopolysaccharidosis I: Hurler, Hurler-Scheie and Scheie syndromes in the UK.* Orphanet J Rare Dis, 2008. **3**: p. 24.

[30] D'Aco, K., et al., *Diagnosis and treatment trends in mucopolysaccharidosis I: findings from the MPS I Registry.* Eur J Pediatr, 2012. **171**(6): p. 911–9.

[31] Martin, R., et al., *Recognition and diagnosis of mucopolysaccharidosis II (Hunter syndrome).* Pediatrics, 2008. **121**(2): p. e377–86.

[32] Wraith, J.E., et al., *Mucopolysaccharidosis type II (Hunter syndrome): a clinical review and recommendations for treatment in the era of enzyme replacement therapy.* Eur J Pediatr, 2008. **167**(3): p. 267–77.

[33] Jones, S.A., et al., *Mortality and cause of death in mucopolysaccharidosis type II-a historical review based on data from the Hunter Outcome Survey (HOS).* J Inherit Metab Dis, 2009. **32**(4): p. 534–43.

[34] S, K., et al., *Mucopolysaccharidosis IVA and glycosaminoglycans – PubMed.* Molecular genetics and metabolism, 2017 Jan–Feb. **120**(1-2).

[35] Sawamoto, K., et al., *Mucopolysaccharidosis IVA: Diagnosis, Treatment, and Management.* International Journal of Molecular Sciences, 2020 Feb 23. **21**(4).

[36] S, T., et al., *Obstructive airway in Morquio A syndrome, the past, the present and the future – PubMed.* Molecular genetics and metabolism, 2016 Feb. **117**(2).

[37] AM, M., et al., *International Morquio A Registry: clinical manifestation and natural course of Morquio A disease – PubMed.* Journal of inherited metabolic disease, 2007 Apr. **30**(2).

[38] S, T., et al., *Mucopolysaccharidosis type IVA (Morquio A disease): clinical review and current treatment – PubMed.* Current pharmaceutical biotechnology, 2011 Jun. **12**(6).

[39] Tomatsu, S., et al., *Current and emerging treatments and surgical interventions for Morquio A syndrome: a review.* Research and reports in endocrine disorders, 2012 Dec. **2012**(2).

[40] Kubaski, F., et al., *Diagnosis of Mucopolysaccharidoses.* Diagnostics, 2020 Mar 22. **10**(3).

[41] Chan, M.J., et al., *Taiwan National Newborn Screening Program by Tandem Mass Spectrometry for Mucopolysaccharidoses Types I, II, and VI.* J Pediatr, 2019. **205**: p. 176–182.

[42] Lin, S.P., et al., *A pilot newborn screening program for Mucopolysaccharidosis type I in Taiwan.* Orphanet J Rare Dis, 2013. **8**: p. 147.

[43] Donati, M.A., et al., *Newborn screening in mucopolysaccharidoses.* Italian Journal of Pediatrics, 2018 Nov 16. **44**(Suppl 2).

[44] Burlina, A.B., et al., *Newborn screening for lysosomal storage disorders by tandem mass spectrometry in North East Italy.* J Inherit Metab Dis, 2018. **41**(2): p. 209–219.

[45] TF, M., et al., *Simplified newborn screening protocol for lysosomal storage disorders – PubMed.* Clinical chemistry, 2011 Sep. **57**(9).

[46] Mechtler, T.P., et al., *Neonatal screening for lysosomal storage disorders: feasibility and incidence from a nationwide study in Austria.* Lancet, 2012. **379**(9813): p. 335–41.

[47] Eyskens, F., S. Devos, and S.D. Francois Eyskens, *Newborn Screening for Lysosomal Storage Disorders in Belgium.* Journal of Inborn Errors of Metabolism and Screening, 2017–11–24. **5**.

[48] SA, K., et al., *Epidemiology of mucopolysaccharidoses – PubMed.* Molecular genetics and metabolism, 2017 Jul. **121**(3).

[49] Poupetova, H., et al., *The birth prevalence of lysosomal storage disorders in the Czech Republic: comparison with data in different populations.* J Inherit Metab Dis, 2010. **33**(4): p. 387–96.

[50] F, B., et al., *Cumulative incidence rates of the mucopolysaccharidoses in Germany – PubMed.* Journal of inherited metabolic disease, 2005. **28**(6).

[51] Huang, L., et al., *Efficacy of different treatment strategies in patients with mucopolysaccharidosis: a systematic review and network meta-analysis of randomized controlled trials.* Orphanet J Rare Dis, 2025. **20**(1): p. 211.

[52] NAME, v.d.B., P. LH, and S. B, *Enzyme replacement therapies in adults with Pompe disease: from trials to real-world data – PubMed.* Current opinion in neurology, 10/01/2025. **38**(5).

[53] Agency, E.M. *Myozyme: EPAR*. Cited 22/09/2025]; Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/myozyme#overview.

[54] Agency, E.M. *Nexviadyme: EPAR*. Cited 22/09/2025]; Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/nexviadyme.

[55] Administration, U.S.F.a.D., *Nexviazyme (avalglucosidase alfa-ngpt) BLA Clinical Review*. 2021: Silver Spring, MD.

[56] Agency, E.M. *Aldurazyme: EPAR*. Cited 22/09/2025]. Available from https://www.ema.europa.eu/en/medicines/human/EPAR/aldurazyme.

[57] DJ, C., et al., *Enzyme replacement therapy and extended newborn screening for mucopolysaccharidoses: opinions of treating physicians – PubMed.* JIMD reports, 2011. **1**.

[58] Agency, E.M. *Elaprase: EPAR*. Cited 22/09/2025]. Available from https://www.ema.europa.eu/en/medicines/human/EPAR/elaprase.

[59] da Silva, E.M., et al., *Enzyme replacement therapy with idursulfase for mucopolysaccharidosis type II (Hunter syndrome).* Cochrane Database Syst Rev, 2016. **2**(2): p. CD008185.

[60] Agency, E.M. *Vimizim: EPAR*. Cited 22/09/2025]. Available from https://www.ema.europa.eu/en/medicines/human/EPAR/vimizim.

[61] Oh, D.-B., *Glyco-engineering strategies for the development of therapeutic enzymes with improved efficacy for the treatment of lysosomal storage diseases.* BMB Reports, 2015 Aug 31. **48**(8).

[62] Dornelles, A.D., et al., *Efficacy and safety of enzyme replacement therapy with alglucosidase alfa for the treatment of patients with infantile-onset Pompe disease: a systematic review and metanalysis.* Front Pediatr, 2024. **12**: p. 1310317.

[63] Dornelles, A.D., et al., *A Systematic Review and Meta-Analysis of Enzyme Replacement Therapy in Late-Onset Pompe Disease.* J Clin Med, 2021. **10**(21).

[64] Dornelles, A.D., et al., *Efficacy and safety of intravenous laronidase for mucopolysaccharidosis type I: A systematic review and meta-analysis.* PLoS One, 2017. **12**(8): p. e0184065.

[65] Al-Hertani, W., et al., *Intravenous Idursulfase for the Treatment of Mucopolysaccharidosis Type II: A Systematic Literature Review.* Int J Mol Sci, 2024. **25**(16).

[66] Lee, C.L., et al., *Efficacy of Intravenous Elosulfase Alfa for Mucopolysaccharidosis Type IVA: A Systematic Review and Meta-Analysis.* J Pers Med, 2022. **12**(8).

[67] Whiting, P., et al., *ROBIS: A new tool to assess risk of bias in systematic reviews was developed.* Journal of Clinical Epidemiology, 2016 Jan. **69**.

[68] ECRI. *IHSI HorizonScan Database*. Cited 22/09/2025]; Available from: https://ihsi-horizonscandb.ecri.org/.

[69] R; Deeks JJ; Hróbjartsson A; Kirkham J; Jüni P; Loke YK; Pigott TD; Ramsay CR; Regidor D; Rothstein HR; Sandhu L; Santaguida PL; Schünemann HJ; Shea B; Shrier I; Tugwell P; Turner L; Valentine JC; Waddington H; Waters E; Wells GA; Whiting PF; Higgins JPT., S.J.H.M.R.B.S.J.B.N.V.M.H.D.A.D.A. M.B.I.C.J.C.A.C. *ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions*. 2016 cited 22/09/2025]; Available from: https://www.riskofbias.info/welcome/home/original-2016-version-of-robins-i.

[70] Directorate-General for Health and Food Safety, E.C., *Guidance on the validity of clinical studies for joint clinical assessments*. 2024, European Commission, Directorate-General for Health and Food Safety: Brussels, Belgium.

[71] G, G., et al., *GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables – PubMed.* Journal of clinical epidemiology, 2011 Apr. **64**(4).

[72] RB, D., *Left ventricular mass in children and adolescents – PubMed.* Journal of the American College of Cardiology, 1988 Sep. **12**(3).

[73] van Capelle, C.I., et al., *Cardiac outcome in classic infantile Pompe disease after 13 years of treatment with recombinant human acid alpha-glucosidase.* Int J Cardiol, 2018. **269**: p. 104–110.

[74] Capelle, C.I.v., et al., *The quick motor function test: a new tool to rate clinical severity and motor function in Pompe patients.* Journal of Inherited Metabolic Disease, 2011 Sep 13. **35**(2).

[75] Balasundaram, P.A., Indirapriya Darshini, *Bayley Scales Of Infant and Toddler Development*, S. [Internet], Editor. 2022, StatPearls Publishing: Treasure Island, FL.

[76] AW, H., W. LJ, and L. HF, *Construct validity of the Comprehensive Developmental Inventory for Infants and Toddlers – PubMed.* Pediatrics international: official journal of the Japan Pediatric Society, 2010 Aug. **52**(4).

[77] Weiß, R.H., *Grundintelligenztest Skala 2 – Revision (CFT 20-R): Manual*. 2nd ed. 2019, Göttingen: Hogrefe.

[78] Weiß, R.H.O., J., *Grundintelligenztest Skala 1 – Revision (CFT 1-R): Manual*. 2013, Göttingen: Hogrefe.

[79] Morfeld, M., I. Kirchberger, and M. Bullinger, *SF-36 Fragebogen zum Gesundheitszustand: Deutsche Version des Short Form-36 Health Survey*. 2nd ed. 2011, Göttingen: Hogrefe.

[80] Chien, Y.H., et al., *Long-term prognosis of patients with infantile-onset Pompe disease diagnosed by newborn screening and treated since birth.* J Pediatr, 2015. **166**(4): p. 985–91 e1–2.

[81] Chien, Y.H., et al., *Pompe disease in infants: improving the prognosis by newborn screening and early treatment.* Pediatrics, 2009. **124**(6): p. e1116–25.

[82] Kishnani, P.S., et al., *Early treatment with alglucosidase alpha prolongs long-term survival of infants with Pompe disease.* Pediatr Res, 2009. **66**(3): p. 329–35.

[83] Nicolino, M., et al., *Clinical outcomes after long-term treatment with alglucosidase alfa in infants and children with advanced Pompe disease.* Genet Med, 2009. **11**(3): p. 210–9.

[84] Scheffers, L.E., et al., *Effects of enzyme replacement therapy on cardiac function in classic infantile Pompe disease.* Int J Cardiol, 2023. **380**: p. 65–71.

[85] Poelman, E., et al., *Effects of higher and more frequent dosing of alglucosidase alfa and immunomodulation on long-term clinical outcome of classic infantile Pompe patients.* J Inherit Metab Dis, 2020. **43**(6): p. 1243–1253.

[86] Kishnani, P.S., et al., *Chinese hamster ovary cell-derived recombinant human acid alpha-glucosidase in infantile-onset Pompe disease.* J Pediatr, 2006. **149**(1): p. 89–97.

[87] IAM, D., et al., *Effect of alglucosidase alfa dosage on survival and walking ability in patients with classic infantile Pompe disease: a multicentre observational cohort study from the European Pompe Consortium – PubMed.* The Lancet. Child & adolescent health, 2022 Jan. **6**(1).

[88] Pfrimmer, C., et al., *Long-Term Outcome of Infantile Onset Pompe Disease Patients Treated with Enzyme Replacement Therapy – Data from a German-Austrian Cohort.* J Neuromuscul Dis, 2024. **11**(1): p. 167–177.

[89] Yang, C-F., et al. *Long-term outcomes of very early treated infantile-onset Pompe disease with short-term steroid premedication: experiences from a nationwide newborn screening programme*. Journal of Medical Genetics 60 (5) 2023. DOI 10.1136/jmg-2022-108675.

[90] Kronn, D., et al., *The Mini-COMET Clinical Trial: Safety and Efficacy of Avalglucosidase Alfa after 97 Weeks of Treatment in Children with Infantile-Onset Pompe Disease Previously Treated with Alglucosidase Alfa.* J Pediatr, 2025. **285**: p. 114664.

[91] Kishnani, P.S., et al., *Safety and efficacy of avalglucosidase alfa in individuals with infantile-onset Pompe disease enrolled in the phase 2, open-label Mini-COMET study: The 6-month primary analysis report.* Genetics in Medicine, 2023/02/01. **25**(2).

[92] *ATS/ERS Statement on respiratory muscle testing – PubMed.* American journal of respiratory and critical care medicine, 08/15/2002. **166**(4).

[93] Bembi, B., et al., *Long-term observational, non-randomized study of enzyme replacement therapy in late-onset glycogenosis type II.* J Inherit Metab Dis, 2010. **33**(6): p. 727–35.

[94] ML, H., et al., *Impact of late-onset Pompe disease on participation in daily life activities: evaluation of the Rotterdam Handicap Scale – PubMed.* Neuromuscular disorders : NMD, 2007 Jul. **17**(7).

[95] NA, v.d.B., et al., *The Rasch-built Pompe-specific activity (R-PAct) scale – PubMed.* Neuromuscular disorders: NMD, 2013 Mar. **23**(3).

[96] Vianello, A., et al., *Enzyme replacement therapy improves respiratory outcomes in patients with late-onset type II glycogenosis and high ventilator dependency*. Lung, 2013. **191**(5): p. 537–44.

[97] Angelini, C., et al., *Observational clinical study in juvenile-adult glycogenosis type 2 patients undergoing enzyme replacement therapy for up to 4 years.* J Neurol, 2012. **259**(5): p. 952–8.

[98] de Vries, J.M., et al., *Pompe disease in adulthood: effects of antibody formation on enzyme replacement therapy*. Genet Med, 2017. **19**(1): p. 90–97.

[99] Gungor, D., et al., *Quality of life and participation in daily life of adults with Pompe disease receiving enzyme replacement therapy: 10 years of international follow-up.* J Inherit Metab Dis, 2016. **39**(2): p. 253–60.

[100] JM, d.V., et al., *Effect of enzyme therapy and prognostic factors in 69 adults with Pompe disease: an open-label single-center study – PubMed.* Orphanet journal of rare diseases, 09/26/2012. **7**(1).

[101] Regnery, C., et al., *36 months observational clinical study of 38 adult Pompe disease patients under alglucosidase alfa enzyme replacement therapy.* J Inherit Metab Dis, 2012. **35**(5): p. 837–45.

[102] van der Ploeg, A.T., et al., *Open-label extension study following the Late-Onset Treatment Study (LOTS) of alglucosidase alfa.* Mol Genet Metab, 2012. **107**(3): p. 456–61.

[103] E, K., et al., *Long-term benefit of enzyme replacement therapy in Pompe disease: A 5-year prospective study – PubMed.* Neurology, 12/05/2017. **89**(23).

[104] Claeys, K.G., et al., *Six-Minute Walk Distance Is a Useful Outcome Measure to Detect Motor Decline in Treated Late-Onset Pompe Disease Patients.* Cells, 2022. **11**(3).

[105] Nunez-Peralta, C., et al., *Follow-up of late-onset Pompe disease patients with muscle magnetic resonance imaging reveals increase in fat replacement in skeletal muscles.* J Cachexia Sarcopenia Muscle, 2020. **11**(4): p. 1032–1046.

[106] Ravaglia, S., et al., *Bioimpedance Phase Angle as a Prognostic Tool in Late-Onset Pompe Disease: A Single-Centre Prospective Study With a 15-year Follow-Up*. Front Cell Dev Biol, 2022. **10**: p. 793566.

[107] Semplicini, C., et al., *Long-term benefit of enzyme replacement therapy with alglucosidase alfa in adults with Pompe disease: Prospective analysis from the French Pompe Registry*. J Inherit Metab Dis, 2020. **43**(6): p. 1219–1231.

[108] Harlaar, L., et al., *Large variation in effects during 10 years of enzyme therapy in adults with Pompe disease*. Neurology, 2019. **93**(19): p. e1756–e1767.

[109] Nagura, H., J. Hokugo, and K. Ueda, *Long-Term Observation of the Safety and Effectiveness of Enzyme Replacement Therapy in Japanese Patients with Pompe Disease: Results From the Post-marketing Surveillance.* Neurol Ther, 2019. **8**(2): p. 397–409.

[110] Stockton, D.W., et al., *Respiratory function during enzyme replacement therapy in late-onset Pompe disease: longitudinal course, prognostic factors, and the impact of time from diagnosis to treatment start.* J Neurol, 2020. **267**(10): p. 3038–3053.

[111] van der Meijden, J.C., et al., *Long-term follow-up of 17 patients with childhood Pompe disease treated with enzyme replacement therapy.* J Inherit Metab Dis, 2018. **41**(6): p. 1205–1214.

[112] D, G., et al., *Impact of enzyme replacement therapy on survival in adults with Pompe disease: results from a prospective international observational study – PubMed.* Orphanet journal of rare diseases, 03/27/2013. **8**(1).

[113] AT, v.d.P., et al., *A randomized study of alglucosidase alfa in late-onset Pompe's disease – PubMed.* The New England journal of medicine, 04/15/2010. **362**(15).

[114] Dimachkie, M.M., et al., *Long-term Safety and Efficacy of Avalglucosidase Alfa in Patients With Late-Onset Pompe Disease.* Neurology, 2022. **99**(5): p. e536–e548.

[115] Kishnani, P.S., et al., *Efficacy and Safety of Avalglucosidase Alfa in Patients With Late-Onset Pompe Disease After 97 Weeks: A Phase 3 Randomized Clinical Trial.* JAMA Neurol, 2023. **80**(6): p. 558–567.

[116] LDM, P., et al., *Safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of the novel enzyme replacement therapy avalglucosidase alfa (neoGAA) in treatment-naïve and alglucosidase alfa-treated patients with late-onset Pompe disease: A phase 1, open-label, multicenter, multinational, ascending dose study – PubMed.* Neuromuscular disorders : NMD, 2019 Mar. **29**(3).

[117] Kim, I., et al., *Risk and clinical characteristics of spinal cord compression across different mucopolysaccharidosis types: A retrospective cohort study.* Medicine, 2024 Oct 18. **103**(42).

[118] DJ, N.C.W., *Measurement of joint motion: a guide to goniometry*. 2016, Philadelphia, PA: FA Davis.

[119] Christiansen, C., *Impaired joint mobility.* Geriatric Physical Therapy, 2012.

[120] Slowik JM, S.A., Collen JF, *Obstructive Sleep Apnea*, in *StatPearls [Internet]*. 2025, StatPearls Publishing: Treasure Island, FL.

[121] G, S., et al., *Measurement of health status in children with juvenile rheumatoid arthritis – PubMed.* Arthritis and rheumatism, 1994 Dec. **37**(12).

[122] DF, N.D.G. *MPS I Registry health assessment questionnaire*. in *9th International Symposium on Mucopolysaccharidosis and Related Diseases*. 2016. Venice, Italy.

[123] Clarke, L.A., et al., *Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I.* Pediatrics, 2009. **123**(1): p. 229–40.

[124] Polgreen, L.E., et al., *Clinical trial of laronidase in Hurler syndrome after hematopoietic cell transplantation.* Pediatr Res, 2020. **87**(1): p. 104–111.

[125] Sifuentes, M., et al., *A follow-up study of MPS I patients treated with laronidase enzyme replacement therapy for 6 years.* Mol Genet Metab, 2007. **90**(2): p. 171–80.

[126] Tylki-Szymanska, A., et al., *Efficacy of recombinant human alpha-L-iduronidase (laronidase) on restricted range of motion of upper extremities in mucopolysaccharidosis type I patients.* J Inherit Metab Dis, 2010. **33**(2): p. 151–7.

[127] C, E., *Differential ability scales: introductory and technical handbook*. 2007, San Antonio, TX: Harcourt Assessment.

[128] Dempsey, J., et al., *Prioritisation of head, neck, and respiratory outcomes in mucopolysaccharidosis type II: lessons from a rare disease consensus exercise and comparison of parental and clinical priorities.* Orphanet Journal of Rare Diseases, 2025 Feb 26. **20**(1).

[129] Marucha, J., P. Lipinski, and A. Tylki-Szymanska, *Efficacy of Enzyme Replacement Therapy on the range of motion of the upper and lower extremities in 16 Polish patients with mucopolysaccharidosis type II: A long-term follow-up study.* Acta Biochim Pol, 2022. **69**(1): p. 251–255.

[130] Giugliani, R., et al., *Evaluation of impact of anti-idursulfase antibodies during long-term idursulfase enzyme replacement therapy in mucopolysaccharidosis II patients.* Mol Genet Metab Rep, 2017. **12**: p. 2–7.

[131] Kim, J., et al., *IgE-mediated anaphylaxis and allergic reactions to idursulfase in patients with Hunter syndrome.* Allergy, 2013. **68**(6): p. 796–802.

[132] Muenzer, J., et al., *Long-term, open-labeled extension study of idursulfase in the treatment of Hunter syndrome.* Genet Med, 2011. **13**(2): p. 95–101.

[133] Muenzer, J., et al., *Neurodevelopmental status and adaptive behavior of pediatric patients with mucopolysaccharidosis II: a longitudinal observational study.* Orphanet J Rare Dis, 2023. **18**(1): p. 357.

[134] Muenzer, J., et al., *Clinical outcomes in idursulfase-treated patients with mucopolysaccharidosis type II: 3-year data from the hunter outcome survey (HOS).* Orphanet J Rare Dis, 2017. **12**(1): p. 161.

[135] Bik-Multanowski, M., et al., *Long-term clinical effects of enzyme replacement therapy in MPS II.* Pediatria Polska, 2017. **92**(4): p. 373–377.

[136] Burton, B.K., et al., *Survival in idursulfase-treated and untreated patients with mucopolysaccharidosis type II: data from the Hunter Outcome Survey (HOS).* J Inherit Metab Dis, 2017. **40**(6): p. 867–874.

[137] Parini, R., et al., *Enzymatic replacement therapy for Hunter disease: Up to 9 years experience with 17 patients.* Mol Genet Metab Rep, 2015. **3**: p. 65–74.

[138] Ueda, K. and J. Hokugo, *Safety and efficacy of idursulfase in the treatment of mucopolysaccharidosis II (Hunter syndrome): a post-marketing study in Japan.* Expert Opin Drug Saf, 2020. **19**(7): p. 891–901.

[139] Tomanin, R., et al., *Clinical efficacy of Enzyme Replacement Therapy in paediatric Hunter patients, an independent study of 3.5 years.* Orphanet Journal of Rare Diseases 2014 9:1, 2014–09–18. **9**(1).

[140] RM, L., et al., *Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging – PubMed.* Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography, 2015 Jan. **28**(1).

[141] Hendriksz, C.J., et al., *Impact of long-term elosulfase alfa treatment on respiratory function in patients with Morquio A syndrome.* J Inherit Metab Dis, 2016. **39**(6): p. 839–847.

[142] Hendriksz, C.J., et al., *Impact of long-term elosulfase alfa on activities of daily living in patients with Morquio A syndrome in an open-label, multi-center, phase 3 extension study.* Mol Genet Metab, 2018. **123**(2): p. 127–134.

[143] Bhattacharya, K., et al., *Safety and Efficacy of Elosulfase Alfa in Australian Patients with Morquio a Syndrome: A Phase 3b Study.* Journal of Inborn Errors of Metabolism and Screening, 2020. **8**.

[144] Hendriksz, C., et al., *Safety, immunogenicity, and clinical outcomes in patients with Morquio A syndrome participating in 2 sequential open-label studies of elosulfase alfa enzyme replacement therapy (MOR-002/ MOR-100), representing 5 years of treatment.* Mol Genet Metab, 2018. **123**(4): p. 479–487.

[145] CJ, H., et al., *Efficacy and safety of enzyme replacement therapy with BMN 110 (elosulfase alfa) for Morquio A syndrome (mucopolysaccharidosis IVA): a phase 3 randomised placebo-controlled study – PubMed.* Journal of inherited metabolic disease, 2014 Nov. **37**(6).

[146] Harmatz, P.R., et al., *Longitudinal analysis of endurance and respiratory function from a natural history study of Morquio A syndrome.* Molecular Genetics and Metabolism, 2015/02/01. **114**(2).

[147] Hendriksz, C.J., et al., *Long-term endurance and safety of elosulfase alfa enzyme replacement therapy in patients with Morquio A syndrome.* Mol Genet Metab, 2016. **119**(1-2): p. 131–43.

[148] Chen, M., L. Zhang, and S. Quan, *Enzyme replacement therapy for infantile-onset Pompe disease.* Cochrane Database Syst Rev, 2017. **11**(11): p. CD011539.

[149] van den Dorpel, J.J.A., et al., *Long term survival in patients with classic infantile Pompe disease reveals a spectrum with progressive brain abnormalities and changes in cognitive functioning.* J Inherit Metab Dis, 2024. **47**(4): p. 716–730.

[150] Li, C., et al., *Transforming the clinical outcome in CRIM-negative infantile Pompe disease identified via Newborn Screening: The benefits of early treatment with enzyme replacement therapy and immune tolerance induction.* Genetics in medicine : official journal of the American College of Medical Genetics, 2021 Jan 25. **23**(5).

[151] Yang, C.-F., et al., *Long-term outcomes of very early treated infantile-onset Pompe disease with short-term steroid premedication: experiences from a nationwide newborn screening programme.* Journal of Medical Genetics, 2023–05–01. **60**(5).

[152] Parenti, G., et al., *The European reference network for metabolic diseases (MetabERN) clinical pathway recommendations for Pompe disease (acid maltase deficiency, glycogen storage disease type II).* Orphanet Journal of Rare Diseases, 2024 Nov 1. **19**(1).

[153] Fatehi, F., et al., *Recommendations for Infantile-Onset and Late-Onset Pompe Disease: An Iranian Consensus.* Frontiers in Neurology, 2021 Sep 21. **12**.

[154] Claeys, K.G., et al., *Minimal clinically important differences in six-minute walking distance in late-onset Pompe disease.* Orphanet J Rare Dis, 2024. **19**(1): p. 154.

[155] Toscano, A. and B. Schoser, *Enzyme replacement therapy in late-onset Pompe disease: a systematic literature review.* J Neurol, 2013. **260**(4): p. 951–9.

[156] Schoser, B., et al., *Survival and long-term outcomes in late-onset Pompe disease following alglucosidase alfa treatment: a systematic review and meta-analysis.* J Neurol, 2017. **264**(4): p. 621–630.

[157] Sarah, B., et al., *Clinical efficacy of the enzyme replacement therapy in patients with late-onset Pompe disease: a systematic review and a meta-analysis.* J Neurol, 2022. **269**(2): p. 733–741.

[158] Marques, J.S. and J.S. Marques, *The Clinical Management of Pompe Disease: A Pediatric Perspective.* Children 2022, Vol. 9, Page 1404, 2022–09–16. **9**(9).

[159] Laraway, S., et al., *Outcomes of Long-Term Treatment with Laronidase in Patients with Mucopolysaccharidosis Type I.* J Pediatr, 2016. **178**: p. 219–226 e1.

[160] Dualibi, A.P.F.F., et al., *The impact of laronidase treatment in otolaryngological manifestations of patients with mucopolysaccharidosis.* Brazilian Journal of Otorhinolaryngology, 2016/09/01. **82**(5).

[161] Kakkis, E.D., et al., *Enzyme-Replacement Therapy in Mucopolysaccharidosis I.* New England Journal of Medicine, 2001–01–18. **344**(3).

[162] Eisengart, J.B., et al., *Long-term outcomes of systemic therapies for Hurler syndrome: an international multicenter comparison.* Genet Med, 2018. **20**(11): p. 1423–1429.

[163] Health, A.G.D.o. *Life Saving Drugs Program – MPS I – Review summary and expert panel recommendations*. 2023 23/09/2025].

[164] Muenzer, J., *Early initiation of enzyme replacement therapy for the mucopolysaccharidoses.* Molecular Genetics and Metabolism, 2014/02/01. **111**(2).

[165] Broomfield, A., et al., *Ten years of enzyme replacement therapy in paediatric onset mucopolysaccharidosis II in England.* Molecular Genetics and Metabolism, 2020/02/01. **129**(2).

[166] Perez-Lopez, J., et al., *Efficacy of Idursulfase therapy in patients with Mucopolysaccharidosis type II who initiated enzyme replacement therapy in adult age. A systematic review of the literature.* Mol Genet Metab, 2018. **124**(3): p. 216–227.

[167] Wikman-Jorgensen, P.E., et al., *Enzyme replacement therapy for the treatment of Hunter disease: A systematic review with narrative synthesis and meta-analysis.* Mol Genet Metab, 2020. **131**(1-2): p. 206–210.

[168] Giugliani, R., et al., *Guidelines for diagnosis and treatment of Hunter Syndrome for clinicians in Latin America.* Genetics and Molecular Biology, 2014 Jun. **37**(2).

[169] Scarpa, M., et al., *Mucopolysaccharidosis type II: European recommendations for the diagnosis and multidisciplinary management of a rare disease.* Orphanet Journal of Rare Diseases 2011 6:1, 2011–11–07. **6**(1).

[170] Lin, H.Y., et al., *Cardiac features and effects of enzyme replacement therapy in Taiwanese patients with Mucopolysaccharidosis IVA.* Orphanet J Rare Dis, 2018. **13**(1): p. 148.

[171] Lin, H.Y., et al., *Cardiac structure and function and effects of enzyme replacement therapy in patients with mucopolysaccharidoses I, II, IVA and VI.* Mol Genet Metab, 2016. **117**(4): p. 431–7.

[172] Lavery, C. and C. Hendriksz, *Mortality in Patients with Morquio Syndrome A*. JIMD Reports, 2014 Apr 10. **15**.

[173] Magner, M., et al., *Consensus statement on enzyme replacement therapy for mucopolysaccharidosis IVA in Central and South-Eastern European countries.* Orphanet Journal of Rare Diseases 2022 17:1, 2022–05–10. **17**(1).

[174] Tomatsu, S., et al., *Enzyme replacement therapy for treating mucopolysaccharidosis type IVA (Morquio A syndrome): effect and limitations.* Expert opinion on orphan drugs, 2015 Oct 29. **3**(11).

[175] D, C., D. F, and P. R, *Enzyme replacement therapy: efficacy and limitations – PubMed.* Italian journal of pediatrics, 11/16/2018. **44**(Suppl 2).

[176] Yin, Y., J. Jiang, and Y. Jin, *A Real-World Data Analysis of Alglucosidase Alfa in the FDA Adverse Event Reporting System (FAERS) Database.* Drugs in R&D, 2025 Jan 21. **25**(1).

[177] DA, H., M. A, and M. A, *Home therapy for lysosomal storage disorders – PubMed.* British journal of nursing (Mark Allen Publishing), 2007. **16**(22).

[178] A, H., et al., *[Home infusion therapy for Pompe disease: Recommendations for German-speaking countries] – PubMed.* Fortschritte der Neurologie-Psychiatrie, 04/27/2021.

[179] JM, P., et al., *Home infusion: Safe, clinically effective, patient preferred, and cost saving – PubMed.* Healthcare (Amsterdam, Netherlands), 2017 Mar. **5**(1-2).

[180] Heinrich, R., F. Claus, and T. Schoenfelder, *The patients ` perspective on home-based infusion: A longitudinal observational study in the German healthcare setting for patients with lysosomal storage disorders treated with enzyme replacement therapy.* Molecular Genetics and Metabolism Reports, 2023/06/01. **35**.

[181] Ditters, I.A.M., et al., *Home-Based Infusion of Alglucosidase Alfa Can Safely be Implemented in Adults with Late-Onset Pompe Disease: Lessons Learned from 18,380 Infusions.* BioDrugs, 2023. **37**(5): p. 685–698.

[182] Díaz-Manera, J., et al., *Home infusion experience in patients with Pompe disease receiving avalglucosidase alfa during three clinical trials.* Molecular Genetics and Metabolism, 2024/12/01. **143**(4).

[183] Wilson, A., R.M. Colzani, and A.L. Flores, *Real-world data assessment of safety of home-based and hospital/outpatient-based laronidase enzyme replacement therapy for mucopolysaccharidosis I.* Molecular Genetics and Metabolism Reports, 2021 Mar 4. **27**.

[184] BK, B., et al., *Home infusion therapy is safe and enhances compliance in patients with mucopolysaccharidoses – PubMed.* Molecular genetics and metabolism, 2009 Jul. **97**(3).

[185] B, S., et al., *Start, switch and stop (triple-S) criteria for enzyme replacement therapy of late-onset Pompe disease: European Pompe Consortium recommendation update 2024 – PubMed.* European journal of neurology, 2024 Sep. **31**(9).

[186] Dayer, V.W., et al., *Real-world evidence for coverage determination of treatments for rare diseases.* Orphanet Journal of Rare Diseases 2024 19:1, 2024–02–07. **19**(1).

[187] Hollak, C.E., et al., *Limitations of drug registries to evaluate orphan medicinal products for the treatment of lysosomal storage disorders.* Orphanet Journal of Rare Diseases, 2011 Apr 16. **6**(1).

[188] Schrover, R., et al., *Minimal clinically important difference for the 6-min walk test: literature review and application to Morquio A syndrome.* Orphanet Journal of Rare Diseases, 2017 Apr 26. **12**(1).

Appendix

Risk of bias assessment of relevant systematic reviews

Table A-1: The results of the risk of bias assessments conducted on the four systematic reviews of interest.

Domain	IOPD Review [62]	LOPD Review [62]	MPS I Review [64]	MPS II Review [65]	MPS IVA [66]
Eligibility criteria	Low	Low	Low	Low	Low
Identification/selection	Unclear	Low	Low	Low	High
Data collection/appraisal	Low	Low	High	Unclear	High
Synthesis /findings	High	High	High	Low	High

Abbreviations: IOPD … infantile-onset Pompe disease, LOPD … late-onset Pompe disease, MPS I … mucopolysaccharidosis I, MPS II … mucopolysaccharidosis II, MPS IVA … mucopolysaccharidosis IVA.

Critical outcomes

Table A-2: Critical outcomes for long-term effectiveness and safety of ERT in IOPD.

Outcome	Average grade
Cardiac function	
Left ventricular mass index	7.75
Ejection fraction	7.75
Relative wall thickness	7.75
Shortening fraction	7.75
Motor function	
QMFT	7.75
Achievement of motor milestones	8
6MWD	7
Cognitive function	
Any outcome	Included *a priori*
Respiratory status /ventilation support	
The use of non-invasive or tracheostomy-assisted ventilation	8.33
Time spent on ventilation	8.33
Survival	
Overall survival	Included *a priori*
Ventilator-free survival	Included *a priori*
Quality of life	Included *a priori*
Mortality	Included *a priori*
Safety	Included *a priori*

Abbreviations: 6MWD … 6-minute walking distance, QMFT … Quick Motor Function Test.

Table A-3: Critical outcomes for long-term effectiveness and safety of ERT in LOPD.

Outcome	Average grade
Motor function	
QMFT	7.75
6MWD	8.5
Respiratory status/ventilation support	
FVC	8
FEV1	7
Dependence on non-invasive or tracheostomy-assisted ventilation	7.75
Time spent on ventilation	7.75
Survival	
Overall survival	Included *a priori*
Ventilator-free survival	Included *a priori*
Other	
Quality of life	Included *a priori*
Mortality	Included *a priori*
Safety	Included *a priori*

Abbreviations: 6MWD … 6-minute walking distance, FEV1 … forced expiratory volume in 1 second, FVC … forced vital capacity, QMFT … Quick Motor Function Test.

Table A-4: Critical outcomes for long-term effectiveness and safety of ERT in MPS I.

Outcome	Average grade
Neurological function	
Spinal cord compression	8
Motor function	
6MWD	8
Joint function	
Joint range of motion	7.5
Joint mobility: Range of motion (single joint or combination)	7.5
Respiratory function	
Sleep apnoea	7
Survival	
Overall survival	Included *a priori*
Other	
Quality of life	Included *a priori*
Mortality	Included *a priori*
Safety	Included *a priori*

Abbreviation: 6MWD … 6-minute walking distance.

Table A-5: Critical outcomes for long-term effectiveness and safety of ERT in MPS II.

Outcome	Average grade
Motor function	
6MWD	7.25
Joint function	
Joint range of motion	7.25
Cognitive function	
DAS II	7
Respiratory function	
Sleep apnoea	7
Airway obstruction	7
Survival	
Overall survival	Included *a priori*
Other	
Quality of life	Included *a priori*
Mortality	Included *a priori*
Safety	Included *a priori*

Abbreviations: 6MWD … 6-minute walking distance, DAS II … Differential Ability Scales, Second Edition.

Table A-6: Critical outcomes for long-term effectiveness and safety of ERT in MPS IVA.

Outcome	Average grade
Motor function	
6MWD	8.25
Cardiac function	
Left ventricular mass index	7
Interventricular septal thickness, diastole	7
Left ventricular internal diameter, diastole	7
Left ventricular posterior wall thickness, diastole	7
Ejection fraction	7
Survival	
Overall survival	Included *a priori*
Other	
Quality of life	Included *a priori*
Mortality	Included *a priori*
Safety	Included *a priori*

Abbreviation: 6MWD … 6-minute walking distance.

Safety of enzyme replacement therapies – Non-serious and Other Events

Table A-7: Safety of alglucosidase alfa in IOPD in controlled studies.

Author, year	Chien et al., 2015 [80]	Kishnani et al. 2009 [82]	Nicolino et al., 2009 [83]
Safety and tolerability outcomes			
AEs	NR	NR	NR
TEAEs	NR	NR	NR
IARs	NR	2.3-year endpoint 11 (61.11%) – mild or moderate – decrease in oxygen saturation, or increase in blood pressure, heart rate or respiratory rate, urticaria, fever.	2-year endpoint 11/21 (52%) – skin and subcutaneous skin disorders, vascular disorders.
Discontinuations due to other reasons	NR	2.3-year endpoint 1 (5.55%) – due to disease progression	2-year endpoint None reported.

Abbreviations: AE … adverse event, IAR … infusion-associated reactions, NR … not reported, TEAE … treatment-emergent adverse event.

Table A-8: Safety profile of alglucosidase alfa in IOPD in single-arm studies.

Author, year	Pfrimmer et al., 2024 [88]	Scheffers et al., 2023 [84]	Ditters et al., 2022 [181]	Poelman et al., 2020 [85]	Kishnani et al., 2006 [86]
Safety and tolerability outcomes					
AEs	NR	NR	NR	NR	2.9-year endpoint 8 (100) – mild to moderate, disease-related not therapy-related
TEAEs	NR	NR	NR	NR	NR
IARs	NR	NR	NR	5-year endpoint Standard dosage group: 5 (83) High dosage group: 8 (67)	2.9-year endpoint 7 (87.5) – mild to moderate; skin rash (urticaria-like, maculopapular, or erythematous), fever, rigors, blood pressure or heart rate changes, or bronchospasm
Discontinuations due to other reasons	NR	NR	NR	NR	2.9-year endpoint 1 (12.5) – family wishes

Abbreviations: AE … adverse event, IAR … infusion-associated reactions, NR … not reported, TEAE … treatment-emergent adverse event.

Table A-9: Safety of avalglucosidase alfa in IOPD in the single-arm study.

Kronn et al., 2025 [90]	Avalglucosidase alfa initial: 20 mg/kg every other week (n=6)	Avalglucosidase alfa initial planned dose: 40 mg/kg every other week (n=16)
Safety and tolerability outcomes		
AEs	NR	NR
TEAEs	1.86-year endpoint 6 (100%); related to treatment – 1 (17%)	1.86-year endpoint 16 (100%); related to treatment – 9 (56%)
IARs	1.86-year endpoint 0	1.86-year endpoint 0
Discontinuations due to other reasons	1.86-year endpoint 0	1.86-year endpoint 0

Abbreviations: AE … adverse event, IAR … infusion-associated reaction, NR … not reported, TEAE … treatment-emergent adverse event.

Table A-10: Safety of alglucosidase alfa in LOPD in single-arm studies (part 1).

Author, year	Bembi et al., 2010 [93]	Angelini et al. 2012 [97]	de Vries et al. 2017 [98]	Regnery et al., 2012 [101]	van der Ploeg et al., 2012 [102]	Güngör et al., 2013 [112]	Gungor et al., 2016 [99]	Kuperus et al., 2017 [103]
Safety and tolerability outcomes								
AEs	NR	NR	NR	NR	2-year endpoint 60 (100%) – most frequent: falls, headaches, and nasopharyngitis	NR	NR	NR
TEAEs	NR	NR	NR	NR	NR	NR	NR	NR
IARs	3-year endpoint 2 (8.3%) – bronchospasm and facial rash	1-4.5 years of FU 4 (6%) – facial or infusion site erythema, flu-like syndrome, generalized itch, or bronchospasm	3-year endpoint 13 (18%) – general malaise, chills, and hyperthermia were the most frequently observed symptoms	3-year endpoint 7 (18.4%) – mild to moderate; erythema, tachycardia, drop of oxygen saturation, exanthema, globus pharynges and pruritus	2-year endpoint 21 (35%) – nausea, headache, and urticaria	NR	NR	19 (22)
Discontinuations for other reasons	NR	1-4.5 years of FU 3 (4.5%) – drop-off, worsening of clinical condition	None	3-year endpoint 2 (5.25%) – clinical deterioration	NR	NR	NR	5-year endpoint 2 (2.31%) – personal reasons

Abbreviations: AE … adverse event, FU … follow up, IAR … infusion-associated reactions, NR … not reported, TEAE … treatment-emergent adverse event.

Note: None of the reported deaths were considered to be treatment-related.

Table A-11: Safety of alglucosidase alfa in LOPD in single-arm studies (part 2).

Author, year	van der Meijden et al., 2018 [111]	Nagura et al., 2019 [109]	Harlaar et al., 2019 [108]	Nuñez-Peralta et al., 2020 [105]	Semplicini et al., 2020 [107]	Stockton et al., 2020 [110]	Claeys et al., 2022 [104]	Ravaglia et al., 2022 [106]
Safety and tolerability outcomes								
AEs	NR	NR	NR	NR	NR	NR	NR	NR
TEAEs	NR	NR	NR	NR	NR	NR	NR	NR
IARs	NR	NR	NR	NR	5.3-year endpoint 14 (8.86%) – skin reactions, dyspnea, swollen tongue and hypertension	NR	NR	NR
Discontinuations for other reasons	NR	NR	3-year endpoint 1 (3.33%) – personal reasons	NR	5.3-year endpoint 5 (14.42%) – personal reasons	NR	NR	NR

Abbreviations: AE … adverse event, IAR … infusion-associated reactions, NR … not reported, TEAE … treatment-emergent adverse event.

Note: None of the reported deaths were considered to be treatment-related.

Table A-12: Safety of avalglucosidase alfa in LOPD in single-arm studies.

Author, year	Dimachkie et al., 2022 [114]	Kishnani et al., 2023 [115]
Safety and tolerability outcomes		
AEs	NR	NR
TEAEs	6-year endpoint AVAL/AVAL: 10 (100%); related to treatment – 8 (80%) ALG/AVAL: 14 (100%); related to treatment – 10 (71%) Fatigue, headache, nausea, rash, dizziness, dyspnea, erythema, hypertension, myalgia, muscle spasms, and pruritus.	1.86-year endpoint AVAL/AVAL: 50 (98%); related to treatment – 29 (56.9%) ALG/AVAL: 49 (96.1%); related to treatment – 25 (56.8%) Headache, nasopharyngitis, arthralgia, back pain, diarrhea, and nausea.
IARs	6-year endpoint AVAL/AVAL: 3 (30%) ALG/AVAL: 3 (21%) Shivering, fever, respiratory distress, chest discomfort	1.86-year endpoint AVAL/AVAL: 20 (39.2%) ALG/AVAL: 21 (47.7%)
Discontinuations for other reasons	6-year endpoint 2 (8.33%) – personal reasons	1.86-year endpoint 4 (4%) – difficulty travelling, COVID-19, non-specified

Abbreviations: AE … adverse event, AVAL=avalglucosidase alfa, ALG … alglucosidase alfa, IAR … infusion-associated reactions, NR … not reported, TEAE … treatment-emergent adverse event.

Note: None of the reported deaths were considered to be treatment-related.

Table A-13: Safety profile of laronidase in mucopolysaccharidosis I in single-arm trials.

Author, year	Sifuentes et al., 2007 [125]	Clark et al., 2009 [123]	Tylki-Szymanska et al. 2010 [126]
Safety and tolerability outcomes			
AEs	6-year endpoint 1 (10%) – mild abdominal pain	4-year endpoint 45 (100%) – mild; caused by the disease rather than treatment. Rash, arthralgia, headache, flushing, injection site reaction, arthropathy, abdominal pain, back pain, fever, skeletal pain, and nausea; related to treatment – 30 (67%), mostly were IARs.	NR
TEAEs	NR	NR	NR
IARs	NR	4-year endpoint 24 (53%) – mild; fever, mild flushing, and/or rash.	NR
Discontinuation for other reasons	NR	4-year endpoint 3 (6.62%) – personal reasons + pregnancy (this patient continued ERT afterwards)	NR

Abbreviations: AE … adverse event, IAR … infusion-associated reactions, NR … not reported, TEAE … treatment-emergent adverse event.

Notes:

None of the reported deaths were considered to be treatment-related.

Only single-arm trials reported safety outcomes, the controlled trial did not, thus only the findings from the single-arm trials were presented.

Table A-14: Safety of idursulfase in MPS II in single-arm studies (part 1).

Author, year	Muenzer et al., 2011 [132]	Kim et al., 2013 [131]	Tomanin et al., 2014 [139]	Parini et al., 2015 [137]	Bik-Multanowski 2017 [135]
Safety and tolerability outcomes					
TEAEs	3-year endpoint 56 (59.6%)	~3-year endpoint 4 (11.76%) – urticaria/angioedema	NR	NR	NR
AEs	NR	NR	NR	NR	NR
IARs	3-year endpoint 50 (53%) – headache, urticaria, and pyrexia	NR	NR	7-year endpoint 4 (23.53%) – itching and urticaria	NR
Discontinuations for other reasons	3-year endpoint None reported.	NR	NR	7-year endpoint None reported.	0.5-6 years of FU None reported.

Abbreviations: AE … adverse event, FU … follow-up, IAR … infusion-associated reactions, NR … not reported, TEAE … treatment-emergent adverse event.

Table A-15: Safety of idursulfase in MPS II in single-arm studies (part 2).

Author, year	Giugliani et al., 2017 [130]	Burton et al., 2017 [136]	Muenzer et al., 2017 [134]	Ueda et al., 2020 [138]	Marucha et al., 2022 [129]	Muenzer et al., 2023 [133]
Safety and tolerability outcomes						
AEs	NR	NR	3-year endpoint 174 (74.7%); infections and infestations, followed by respiratory, thoracic and mediastinal disorders; related to treatment – 80 (34.3%)	NR	NR	NR
TEAEs	~2.1-year endpoint 25 (96.2%) – pyrexia, upper respiratory tract infection, cough, ear infection, lower respiratory tract infection, and fall; related to treatment – 9 (34.6%)	NR	NR	NR	NR	2-year endpoint 49 (89.1%) – pyrexia, upper respiratory tract infection, diarrhoea, and carpal tunnel syndrome; related to treatment – 80 (34.3%)
IARs	~2.1-year endpoint 9 (34.6%) – pyrexia and headache	NR	3-year endpoint 81 (34.8%)	7-year endpoint 70 (48.3%); skin and subcutaneous tissue disorders (urticaria and rash), general disorders and administration site conditions (pyrexia, respiratory, thoracic and mediastinal disorders) and nervous system disorders (tremor).	NR	NR
Discontinuations for other reasons	~2.1-year endpoint None reported.	NR	3-year endpoint None reported.	7-year endpoint 21 (14.48%) – transfer to another hospital; due to other reason(s).	NR	2-year endpoint 32 (58.2%) – noncompliance, withdrawal, loss to follow-up, enrolment into another trial

Abbreviations: AE … adverse event, IAR … infusion-associated reactions, NR … not reported, TEAE … treatment-emergent adverse event.

Table A-16: Safety of elosulfase alfa in MPS IVA in controlled studies.

Author, year	Hendriksz et al., 2016 [147]	Hendriksz et al., 2018a [142]
Safety and tolerability outcomes		
AEs	2.3-year endpoint PBO-QOW (N=29): 29 (100%); related to treatment – 23 (79.3%) PBO-QW (N=29): 29 (100%); related to treatment – 20 (69%) QOW-QOW (N=59): 59 (100%); related to treatment – 40 (67.8%) QW-QW (N=56): 56 (100%); related to treatment – 43 (76.8%) Mild to moderate IARs such as vomiting, pyrexia, and headache, which were generally manageable with symptomatic treatment and/or infusion rate modification	NR
TEAEs	NR	NR
IARs	NR	NR
Discontinuations for other reasons	2.3-year endpoint 16 (9.25%) – early transition to commercial drug	NR

Abbreviations: AE … adverse event, IAR … infusion-associated reactions, NR … not reported, TEAE … treatment-emergent adverse event.

Table A-17: Safety of elosulfase alfa in MPS IVA in single-arm studies.

Author, year	Bhattacharya et al., 2020 [143]	Hendriksz et al., 2018b [144]
Safety and tolerability outcomes		
AEs	2.5-year endpoint 13 (100%); majority mild/moderate: pyrexia, nasopharyngitis, pain, diarrhea, vomiting; drug-related – 92.31%	5-year endpoint 20 (100%); total hypersensitivity AEs flagged: 12 (6%); most were mild or moderate; pyrexia, headache, and increased total IgE levels; drug-related Aes – 19 (95.0%); drug-related hypersensitivity AEs: 5 (25%)
TEAEs	NR	NR
IARs	NR	NR
Discontinuations for other reasons	NR	NR

Abbreviations: AE … adverse event, IAR … infusion-associated reactions, IgE … immunoglobulin E, NR … not reported, TEAE … treatment-emergent adverse event.

Risk of Bias Assessment of Included Studies

Table A-18: Risk of bias assessments of studies investigating alglucosidase-alfa in IOPD.

Study reference	Bias due to confounding	Bias selection of participants into the study	Bias in measurement of intervention	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
Chien et al., 2015 [80]	Low	Low	Low	Low	Low	Moderate	Low	Moderate	RoB assessment extracted from the published SR.
Chien et al., 2009 [81]	Low	Low	Low	Low	Low	Moderate	Low	Moderate	RoB assessment extracted from the published SR.
Kishnani et al., 2009[82]	Moderate	Moderate	Moderate	Low	Low	Moderate	Low	Moderate	RoB assessment extracted from the published SR.
Nicolino et al., 2009 [83]	Serious	Serious	Low	Low	Moderate	Serious	Low	Serious	RoB assessment done by the authors.

Abbreviations: RoB … risk of bias, SR … systematic review.

Notes: Nicolino et al., 2009: Bias due to confounding — Controls defined only by GAA deficiency/mutation and symptom onset ≤12 months; no matching on key confounders (CRIM, IOPD form, cardiac/ventilatory status). Historical controls (1995) may differ in care context. Bias selection of participants into the study – Retrospective controls chosen to resemble treated group but not matched on critical parameters (many unavailable). Bias in measurement outcomes – Cognitive and safety outcomes subjective; lack of blinding may have influenced assessment.

Table A-19: Risk of bias assessments for the study investigating alglucosidase alfa in LOPD.

Study reference	Bias due to confounding	Bias selection of participants into the study	Bias in measurement of intervention	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
Vianello et al., 2013 [96]	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate	RoB assessment extracted from the published SR.

Abbreviations: RoB … risk of bias, SR … systematic review.

Table A-20: Risk of bias assessments for the study investigating laronidase in MPS I.

Study reference	Bias due to confounding	Bias selection of participants into the study	Bias in measurement of intervention	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
Polgreen et al., 2020[124]	Serious	Serious	Moderate	Moderate	Serious	Serious	Low	Serious	RoB assessment done by the authors.

Abbreviation: RoB … risk of bias.

Notes: Bias due to confounding: Groups matched only on age/HCT history; not on key clinical features (cardiac, pulmonary, time since HCT). Bias in selection of participants into the study: Follow-up not aligned with participants' schedules; controls drawn from another longitudinal study. Bias due to missing data: 6MWD and survival – serious – no comparative data; ROM – serious – small samples (5-8 patients), reasons not reported. Bias in measurement of outcomes: ROM – serious – goniometry depends on assessor/training; different staff used. 6MWT – serious – participant-dependent and subjective; unblinded assessments may have influenced results.

Table A-21: Risk of bias assessments for the study investigating elosulfase alfa in MPS IVA.

Study reference	Bias due to confounding	Bias selection of participants into the study	Bias in measurement of intervention	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
Hendriksz et al., 2016[147]	Serious	Serious	Low	Serious	Moderate	Serious	Low	Serious	RoB assessment done by the authors.

Abbreviation: RoB … risk of bias.

Notes: Bias due to confounding – no randomisation; historic controls not balanced on key clinical variables. Bias selection of participants into the study: Serious – per-protocol analysis excluded patients with ≥20% missed infusions or surgeries (both linked to treatment and outcomes), likely overestimating benefit; no adjustment methods applied. Bias due to departures from intended interventions: co-interventions (surgeries, compliance, supportive care) uneven; exclusions used instead of adjustment; transitions from placebo/low to standard dose not handled with causal methods. Bias in measurement of outcomes: 6MWT effort-based and unblinded; risk of systematic bias, esp. when compared with external MorCAP cohort.

Literature search strategies

Alglucosidase alfa in infantile-onset Pompe disease

Search strategy for Cochrane

Search Name: alglucosidase alfa for IOPD	
Search date: 08/05/2025	
ID	Search
#1	(infant* NEAR pompe) (Word variations have been searched)
#2	(IOPD):ti,ab,kw
#3	MeSH descriptor: [Glycogen Storage Disease Type II] explode all trees
#4	((type NEXT II OR type NEXT 2) NEAR glycogen*) (Word variations have been searched)
#5	((acid NEXT maltas* OR alpha-glucosidas* OR a-glucosidas*) NEAR deficien*) (Word variations have been searched)
#6	#1 OR #2 OR #3 OR #4 OR #5
#7	MeSH descriptor: [alpha-Glucosidases] explode all trees
#8	(alglucosidas*) (Word variations have been searched)
#9	(alpha-glucosidas*) (Word variations have been searched)
#10	(a-glucosidas*) (Word variations have been searched)
#11	(GAA):ti,ab,kw
#12	MeSH descriptor: [Enzyme Replacement Therapy] explode all trees
#13	(enzyme* NEXT replac*) (Word variations have been searched)
#14	(ERT):ti,ab,kw
#15	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
#16	#6 AND #15
#17	#6 AND #15 with Cochrane Library publication date Between Apr 2022 and May 2025
#18	#6 AND #15 with Publication Year from 2022 to 2025, in Trials
#19	#17 OR #18
#20	(conference proceeding):pt
#21	(abstract):so
#22	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#23	#20 OR #21 OR #22
#24	#19 NOT #23
Total hits: 19	

Search strategy for Embase

Search Name: alglucosidase alfa for IOPD		
Search date: 09.05.2025.		
No.	Query Results	Results
#25.	#21 NOT #24	446
#24.	#22 OR #23	100,098
#23.	'clinical trial':dtype	99,831
#22.	#21 AND 'conference abstract'/it	267
#21.	#20 AND [25-04-2022]/sd NOT [10-05-2025]/sd	742
#20.	#7 AND #19	4,206
#19.	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	48,587
#18.	ert:ti,ab	8,146

#17.	'enzyme* replac*'	17,066
#16.	'enzyme replacement'/exp	13,964
#15.	gaa:ti,ab	4,985
#14.	'recombinant glucan 1,4 alpha glucosidas*'	951
#13.	'recombinant glucan 1,4 alpha glucosidase'/exp	1,723
#12.	'a-glucosidas*'	635
#11.	alglucosidas*	1,117
#10.	'alpha-glucosidas*'	25,861
#9.	'alglucosidase alfa'/exp	740
#8.	'alpha glucosidase'/exp	13,306
#7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6	6,140
#6.	('acid maltas*' OR 'alpha glucosidas*' OR 'a-glucosidas*') NEAR/3 deficien*	858
#5.	('type ii' OR 'type 2') NEAR/3 glycogen*	5,917
#4.	'glycogen storage disease type 2'/exp	5,640
#3.	lopd	273
#2.	infant* NEAR/2 pompe	801
#1.	'infantile onset pompe disease'/exp	46
Total hits: 446		

Search strategy for HTA-INATHTA

Search Name: alglucosidase alfa for IOPD	
Search date: 08.05.2025.	
ID	Search
18	(((ERT) OR ((enzyme*) AND (replac*)) OR ("Enzyme Replacement Therapy"[mhe]) OR (GAA) OR (a-glucosidase) OR (alpha-glucosidase) OR (alglucosidas*) OR ("alpha-Glucosidases"[mhe])) AND ((("acid maltase" OR "alpha-glucosidase" OR "a-glucosidase") AND (deficien*)) OR ((type II OR type 2) AND (glycogen*)) OR ("Glycogen Storage Disease Type II"[mhe]) OR (IOPD) OR ((infant*) AND (pompe)))) FROM 2022 TO 2025,"4","2025-05-08T20:44:56.000000Z"
17	((ERT) OR ((enzyme*) AND (replac*)) OR ("Enzyme Replacement Therapy"[mhe]) OR (GAA) OR (a-glucosidase) OR (alpha-glucosidase) OR (alglucosidas*) OR ("alpha-Glucosidases"[mhe])) AND ((("acid maltase" OR "alpha-glucosidase" OR "a-glucosidase") AND (deficien*)) OR ((type II OR type 2) AND (glycogen*)) OR ("Glycogen Storage Disease Type II"[mhe]) OR (IOPD) OR ((infant*) AND (pompe))),"8","2025-05-08T20:44:44.000000Z"
16	((ERT) OR ((enzyme*) AND (replac*)) OR ("Enzyme Replacement Therapy"[mhe]) OR (GAA) OR (a-glucosidase) OR (alpha-glucosidase) OR (alglucosidas*) OR ("alpha-Glucosidases"[mhe])) AND ((("acid maltase" OR "alpha-glucosidase" OR "a-glucosidase") AND (deficien*)) OR ((type II OR type 2) AND (glycogen*)) OR ("Glycogen Storage Disease Type II"[mhe]) OR (IOPD) OR ((infant*) AND (pompe))),"8","2025-05-08T20:44:34.000000Z"
15	(ERT) OR ((enzyme*) AND (replac*)) OR ("Enzyme Replacement Therapy"[mhe]) OR (GAA) OR (a-glucosidase) OR (alpha-glucosidase) OR (alglucosidas*) OR ("alpha-Glucosidases"[mhe]),"80","2025-05-08T20:44:18.000000Z"
14	ERT,"10","2025-05-08T20:43:16.000000Z"
13	(enzyme*) AND (replac*),"39","2025-05-08T20:43:11.000000Z"
12	"Enzyme Replacement Therapy"[mhe],"40","2025-05-08T20:42:42.000000Z"
11	GAA,"2","2025-05-08T20:36:40.000000Z"
10	a-glucosidase,"6","2025-05-08T19:34:52.000000Z"
9	alpha-glucosidase,"6","2025-05-08T19:34:46.000000Z"
8	alglucosidas*,"3","2025-05-08T19:34:37.000000Z"
7	"alpha-Glucosidases"[mhe],"8","2025-05-08T19:34:29.000000Z"
6	(("acid maltase" OR "alpha-glucosidase" OR "a-glucosidase") AND (deficien*)) OR ((type II OR type 2) AND (glycogen*)) OR ("Glycogen Storage Disease Type II"[mhe]) OR (IOPD) OR ((infant*) AND (pompe)),"9","2025-05-08T19:33:45.000000Z"
5	("acid maltase" OR "alpha-glucosidase" OR "a-glucosidase") AND (deficien*),"0","2025-05-08T19:33:18.000000Z"
4	(type II OR type 2) AND (glycogen*),"2","2025-05-08T19:33:09.000000Z"
3	"Glycogen Storage Disease Type II"[mhe],"9","2025-05-08T19:32:58.000000Z"
2	IOPD,"0","2025-05-08T19:32:52.000000Z"
1	(infant*) AND (pompe),"1","2025-05-08T19:32:44.000000Z"
Total hits: 4	

Search strategy for Medline via Ovid

Ovid MEDLINE(R) ALL <1946 to May 07, 2025>	
Search date: 08.05.2025.	
ID	Search
#1.	(infant* adj3 pompe).mp. (433)
#2.	IOPD.mp. (150)
#3.	exp Glycogen Storage Disease Type II/ (2093)
#4.	((type II or type 2) adj5 glycogen*).mp. (2660)
#5.	((acid maltas* or alpha-glucosidas* or a-glucosidas*) adj3 deficien*).mp. (710)
#6.	1 or 2 or 3 or 4 or 5 (2981)
#7.	exp alpha-Glucosidases/ (6884)
#8.	alglucosidas*.mp. (234)
#9.	alpha-glucosidas*.mp. (16330)
#10.	a-glucosidas*.mp. (217)
#11.	GAA.ti,ab. (3267)
#12.	exp Enzyme Replacement Therapy/ (2889)
#13.	enzyme* replac*.mp. (7773)
#14.	ERT.ti,ab. (4327)
#15.	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (28090)
#16.	6 and 15 (1837)
#17.	limit 16 to dt=20220425-20250508 (242)
#18.	limit 16 to ed=20220425-20250508 (208)
#19.	17 or 18 (255)
#20.	remove duplicates from 19 (248)
Total hits: 248	

Alglucosidase alfa in late-onset Pompe disease

Search strategy for Cochrane

Search Name: alglucosidase alfa for LOPD	
Search date: 09/05/2025	
ID	Search
#1	(late* NEAR pompe) (Word variations have been searched)
#2	(LOPD):ti,ab,kw
#3	MeSH descriptor: [Glycogen Storage Disease Type II] explode all trees
#4	((type NEXT II OR type NEXT 2) NEAR glycogen*) (Word variations have been searched)
#5	((acid NEXT maltas* OR alpha-glucosidas* OR a-glucosidas*) NEAR deficien*) (Word variations have been searched)
#6	#1 OR #2 OR #3 OR #4 OR #5
#7	MeSH descriptor: [alpha-Glucosidases] explode all trees
#8	(alglucosidas*) (Word variations have been searched)
#9	(alpha-glucosidas*) (Word variations have been searched)
#10	(a-glucosidas*) (Word variations have been searched)
#11	(GAA):ti,ab,kw
#12	MeSH descriptor: [Enzyme Replacement Therapy] explode all trees
#13	(enzyme* NEXT replac*) (Word variations have been searched)
#14	(ERT):ti,ab,kw

#15	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
#16	#6 AND #15
#17	#6 AND #15 with Cochrane Library publication date Between May 2021 and May 2025
#18	#6 AND #15 with Publication Year from 2021 to 2025, in Trials
#19	#17 OR #18
#20	(conference proceeding):pt
#21	(abstract):so
#22	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#23	#20 OR #21 OR #22
#24	#19 NOT #23
Total hits: 24	

Search strategy for Embase

Search Name: alglucosidase alfa for LOPD		
Search date: 09.05.2025.		
No.	Query Results	Results
#25.	#21 NOT #24	564
#24.	#22 OR #23	100,201
#23.	'clinical trial':dtype	99,831
#22.	#21 AND 'conference abstract'/it	370
#21.	#20 AND [30-05-2021]/sd NOT [10-05-2025]/sd	963
#20.	#7 AND #19	4,207
#19.	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	48,587
#18.	ert:ti,ab	8,146
#17.	'enzyme* replac*'	17,066
#16.	'enzyme replacement'/exp	13,964
#15.	gaa:ti,ab	4,985
#14.	'recombinant glucan 1,4 alpha glucosidas*'	951
#13.	'recombinant glucan 1,4 alpha glucosidase'/exp	1,723
#12.	'a-glucosidas*'	635
#11.	alglucosidas*	1,117
#10.	'alpha-glucosidas*'	25,861
#9.	'alglucosidase alfa'/exp	740
#8.	'alpha glucosidase'/exp	13,306
#7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6	6,348
#6.	('acid maltas*' OR 'alpha glucosidas*' OR 'a-glucosidas*') NEAR/3 deficien*	858
#5.	('type ii' OR 'type 2') NEAR/3 glycogen*	5,917
#4.	'glycogen storage disease type 2'/exp	5,640
#3.	Lopd	889
#2.	late* NEAR/2 pompe	1,189
#1.	'late onset pompe disease'/exp	83
Total hits: 564		

Search strategy for HTA-INATHTA

Search Name: alglucosidase alfa for LOPD	
Search date: 09.05.2025.	
ID	Search
18	(((ERT) OR ((enzyme*) AND (replac*)) OR ("Enzyme Replacement Therapy"[mhe]) OR (GAA) OR (a-glucosidase) OR (alpha-glucosidase) OR (alglucosidas*) OR ("alpha-Glucosidases"[mhe])) AND ((("acid maltase" OR "alpha-glucosidase" OR "a-glucosidase") AND (deficien*)) OR ((type II OR type 2) AND (glycogen*)) OR ("Glycogen Storage Disease Type II"[mhe]) OR (IOPD) OR ((infant*) AND (pompe)))) FROM 2022 TO 2025,"4","2025-05-08T20:44:56.000000Z"
17	((ERT) OR ((enzyme*) AND (replac*)) OR ("Enzyme Replacement Therapy"[mhe]) OR (GAA) OR (a-glucosidase) OR (alpha-glucosidase) OR (alglucosidas*) OR ("alpha-Glucosidases"[mhe])) AND ((("acid maltase" OR "alpha-glucosidase" OR "a-glucosidase") AND (deficien*)) OR ((type II OR type 2) AND (glycogen*)) OR ("Glycogen Storage Disease Type II"[mhe]) OR (IOPD) OR ((infant*) AND (pompe))),"8","2025-05-08T20:44:44.000000Z"
16	((ERT) OR ((enzyme*) AND (replac*)) OR ("Enzyme Replacement Therapy"[mhe]) OR (GAA) OR (a-glucosidase) OR (alpha-glucosidase) OR (alglucosidas*) OR ("alpha-Glucosidases"[mhe])) AND ((("acid maltase" OR "alpha-glucosidase" OR "a-glucosidase") AND (deficien*)) OR ((type II OR type 2) AND (glycogen*)) OR ("Glycogen Storage Disease Type II"[mhe]) OR (IOPD) OR ((infant*) AND (pompe))),"8","2025-05-08T20:44:34.000000Z"
15	(ERT) OR ((enzyme*) AND (replac*)) OR ("Enzyme Replacement Therapy"[mhe]) OR (GAA) OR (a-glucosidase) OR (alpha-glucosidase) OR (alglucosidas*) OR ("alpha-Glucosidases"[mhe]),"80","2025-05-08T20:44:18.000000Z"
14	ERT,"10","2025-05-08T20:43:16.000000Z"
13	(enzyme*) AND (replac*),"39","2025-05-08T20:43:11.000000Z"
12	"Enzyme Replacement Therapy"[mhe],"40","2025-05-08T20:42:42.000000Z"
11	GAA,"2","2025-05-08T20:36:40.000000Z"
10	a-glucosidase,"6","2025-05-08T19:34:52.000000Z"
9	alpha-glucosidase,"6","2025-05-08T19:34:46.000000Z"
8	alglucosidas*,"3","2025-05-08T19:34:37.000000Z"
7	"alpha-Glucosidases"[mhe],"8","2025-05-08T19:34:29.000000Z"
6	(("acid maltase" OR "alpha-glucosidase" OR "a-glucosidase") AND (deficien*)) OR ((type II OR type 2) AND (glycogen*)) OR ("Glycogen Storage Disease Type II"[mhe]) OR (IOPD) OR ((infant*) AND (pompe)),"9","2025-05-08T19:33:45.000000Z"
5	("acid maltase" OR "alpha-glucosidase" OR "a-glucosidase") AND (deficien*),"0","2025-05-08T19:33:18.000000Z"
4	(type II OR type 2) AND (glycogen*),"2","2025-05-08T19:33:09.000000Z"
3	"Glycogen Storage Disease Type II"[mhe],"9","2025-05-08T19:32:58.000000Z"
2	IOPD,"0","2025-05-08T19:32:52.000000Z"
1	(infant*) AND (pompe),"1","2025-05-08T19:32:44.000000Z"
Total hits: 4	

Search strategy for Medline via Ovid

Ovid MEDLINE(R) ALL <1946 to May 08, 2025>	
Search date: 09.05.2025.	
ID	Search
#1.	(late* adj3 pompe).mp. (554)
#2.	LOPD.mp. (419)
#3.	exp Glycogen Storage Disease Type II/ (2095)
#4.	((type II or type 2) adj5 glycogen*).mp. (2662)
#5.	((acid maltas* or alpha-glucosidas* or a-glucosidas*) adj3 deficien*).mp. (710)
#6.	1 or 2 or 3 or 4 or 5 (3122)
#7.	exp alpha-Glucosidases/ (6894)
#8.	alglucosidas*.mp. (234)
#9.	alpha-glucosidas*.mp. (16349)
#10.	a-glucosidas*.mp. (217)
#11.	GAA.ti,ab. (3268)
#12.	exp Enzyme Replacement Therapy/ (2891)

#13.	enzyme* replac*.mp. (7777)
#14.	ERT.ti,ab. (4329)
#15.	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (28115)
#16.	6 and 15 (1821)
#17.	limit 16 to dt=20210530-20250509 (303)
#18.	limit 16 to ed=20210530-20250509 (294)
#19.	17 or 18 (361)
#20.	remove duplicates from 19 (354)
Total hits: 354	

Avalglucosidase alfa in IOPD and LOPD

Search strategy for Cochrane

Search Name: avalglucosidase alfa for IOPD and LOPD	
Search date: 13/05/2025	
ID	Search
#1	avalglucosidas*
#2	(nexvia?yme*) (Word variations have been searched)
#3	(gz NEXT 402666*) (Word variations have been searched)
#4	(gz402666*) (Word variations have been searched)
#5	(neoGAA*) (Word variations have been searched)
#6	#1 OR #2 OR #3 OR #4
#7	(conference proceeding):pt
#8	(abstract):so
#9	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#10	#7 OR #8 OR #9
#11	#6 NOT #10
Total hits: 11	

Search strategy for Embase

Search Name: avalglucosidase alfa for IOPD and LOPD		
Search date: 09.05.2025.		
No.	Query Results	Results
#11.	#7 NOT #10	94
#10.	#8 OR #9	119,906
#9.	'clinical trial':dtype	119,809
#8.	#7 AND 'Conference Abstract'/it	97
#7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6	194
#6.	neogaa*	15
#5.	gz402666*	2
#4.	'gz 402666*'	–
#3.	nexvia?yme*	31
#2.	avalglucosidas*	184
#1.	'avalglucosidase alfa'/exp	173
Total hits: 564		

Search strategy for HTA-INATHTA

Search Name: avalglucosidase alfa for IOPD and LOPD	
Search date: 13.05.2025.	
ID	Search
7	(neoGAA*) OR (gz402666*) OR ("gz 402666") OR (nexviadyme*) OR (nexviazyme*) OR (avalglucosidas*),"1","2025-05-12T17:13:10.000000Z"
6	neoGAA*,"0","2025-05-12T17:13:03.000000Z"
5	gz402666*,"0","2025-05-12T17:12:44.000000Z"
4	"gz 402666","0","2025-05-12T17:12:29.000000Z"
3	nexviadyme*,"0","2025-05-12T17:12:01.000000Z"
2	nexviazyme*,"0","2025-05-12T17:11:53.000000Z"
1	avalglucosidas*,"1","2025-05-12T17:11:32.000000Z"
Total hits: 1	

Search strategy for Medline via Ovid

Ovid MEDLINE(R) ALL <1946 to May 12, 2025>	
Search date: 13.05.2025.	
ID	Search
#1.	avalglucosidas*.mp. (47)
#2.	nexvia#yme*.mp. (9)
#3.	gz 402666.mp. (0)
#4.	gz402666*.mp. (1)
#5.	neoGAA*.mp. (4)
#6.	1 or 2 or 3 or 4 or 5 (47)
#7.	remove duplicates from 6 (46)
Total hits: 46	

Laronidase for Mucopolysaccharidosis I

Search strategy for Cochrane

Search Name: laronidase for MPS I	
Search date: 14/05/2025	
ID	Search
#1	MeSH descriptor: [Mucopolysaccharidosis I] explode all trees
#2	(muco?poly?saccharidos* NEAR (I OR 1)) (Word variations have been searched)
#3	(MPS NEXT I)
#4	(MPS NEXT 1)
#5	(MPSI)
#6	MeSH descriptor: [Iduronidase] explode all trees and with qualifier(s): [deficiency - DF]
#7	(iduronidas* NEAR deficien*) (Word variations have been searched)
#8	(IDUA):ti,ab,kw
#9	(McKusick) (Word variations have been searched)
#10	(Hurler*):ti,ab,kw (Word variations have been searched)
#11	(Scheie*) (Word variations have been searched)
#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
#13	(laronidas*) (Word variations have been searched)

#14	(aldurazyme*) (Word variations have been searched)
#15	(alronidas*) (Word variations have been searched)
#16	(bm NEXT 101) (Word variations have been searched)
#17	(bm101*) (Word variations have been searched)
#18	MeSH descriptor: [Iduronidase] explode all trees
#19	(Iduronidas*) (Word variations have been searched)
#20	MeSH descriptor: [Enzyme Replacement Therapy] explode all trees
#21	(enzym* NEXT replac*) (Word variations have been searched)
#22	(ERT):ti,ab,kw
#23	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
#24	#12 AND #23
#25	(conference proceeding):pt
#26	(abstract):so
#27	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#28	#25 OR #26 OR #27
#29	#24 NOT #28
#30	#24 NOT #28 with Cochrane Library publication date Between Dec 2016 and May 2025
#31	#24 NOT #28 with Publication Year from 2016 to 2025, in Trials
#32	#30 OR #31
Total hits: 9	

Search strategy for Embase

Search Name: laronidase for MPS I		
Search date: 14.05.2025.		
No.	Query Results	Results
#31.	#27 NOT #30	602
#30.	#28 OR #29	139,961
#29.	'clinical trial':dtype	139,628
#28.	#27 AND 'Conference Abstract'/it	333
#27.	#26 AND [31-12-2016]/sd NOT [15-05-2025]/sd	954
#26.	#13 AND #25	2,486
#25.	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	21,788
#24.	ert:ti,ab	8,163
#23.	'enzyme* replac*'	17,098
#22.	'enzyme replacement'/exp	13,996
#21.	iduronidas*	1,806
#20.	'levo iduronidase'/exp	1,406
#19.	bm101	6
#18.	'bm 101'	4
#17.	alronidas*	–
#16.	aldurazyme*	314
#15.	laronidas*	720
#14.	'laronidase'/exp	694
#13.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	10,620
#12.	scheie*	4,926
#11.	hurler*	4,637

#10.	'scheie syndrome'/exp	379
#9.	'hurler syndrome'/exp	4,068
#8.	'mckusick 25280'	8
#7.	idua:ti,ab	908
#6.	iduronidas* NEAR/3 deficien*	237
#5.	Mpsi	420
#4.	'mps 1'	460
#3.	'mps i'	1,911
#2.	mucopolysaccharidos* NEAR/2 (i OR '1')	1,920
#1.	'mucopolysaccharidosis type 1'/exp	4,306
Total hits: 602		

Search strategy for HTA-INATHTA

Search Name: laronidase for MPS I	
Search date: 14.05.2025.	
ID	Search
27	(((ERT) OR ((enzyme*) AND (replac*)) OR ("Enzyme Replacement Therapy"[mhe]) OR (Iduronidas*) OR ("Iduronidase"[mhe]) OR (bm101*) OR ("bm 101") OR (alronidas*) OR (aldurazyme*) OR (laronidas*)) AND ((Scheie*) OR (hurler*) OR (McKusick*) OR (IDUA) OR ("iduronidase deficiency") OR ((iduronidas*) AND (deficien*)) OR ("MPS 1") OR ("MPS I") OR ("mucopolysaccharidosis type 1") OR ("mucopolysaccharidosis type I") OR ("mucopolysaccharidosis 1") OR ("mucopolysaccharidosis I") OR ("Mucopolysaccharidosis I"[mhe]))) FROM 2016 TO 2025,"1","2025-05-14T16:44:24.000000Z"
26	((ERT) OR ((enzyme*) AND (replac*)) OR ("Enzyme Replacement Therapy"[mhe]) OR (Iduronidas*) OR ("Iduronidase"[mhe]) OR (bm101*) OR ("bm 101") OR (alronidas*) OR (aldurazyme*) OR (laronidas*)) AND ((Scheie*) OR (hurler*) OR (McKusick*) OR (IDUA) OR ("iduronidase deficiency") OR ((iduronidas*) AND (deficien*)) OR ("MPS 1") OR ("MPS I") OR ("mucopolysaccharidosis type 1") OR ("mucopolysaccharidosis type I") OR ("mucopolysaccharidosis 1") OR ("mucopolysaccharidosis I") OR ("Mucopolysaccharidosis I"[mhe])),"9","2025-05-14T16:44:07.000000Z"
25	(ERT) OR ((enzyme*) AND (replac*)) OR ("Enzyme Replacement Therapy"[mhe]) OR (Iduronidas*) OR ("Iduronidase"[mhe]) OR (bm101*) OR ("bm 101") OR (alronidas*) OR (aldurazyme*) OR (laronidas*),"93","2025-05-14T16:43:53.000000Z"
24	ERT,"10","2025-05-14T16:43:15.000000Z"
23	(enzyme*) AND (replac*),"39","2025-05-14T16:43:07.000000Z"
22	"Enzyme Replacement Therapy"[mhe],"40","2025-05-14T16:42:06.000000Z"
21	Iduronidas*,"0","2025-05-14T16:41:22.000000Z"
20	"Iduronidase"[mhe],"3","2025-05-14T16:41:07.000000Z"
19	bm101*,"0","2025-05-14T16:40:49.000000Z"
18	"bm 101","18","2025-05-14T16:40:31.000000Z"
17	alronidas*,"0","2025-05-14T16:40:07.000000Z"
16	aldurazyme*,"3","2025-05-14T16:39:46.000000Z"
15	laronidas*,"5","2025-05-14T16:39:19.000000Z"
14	(Scheie*) OR (hurler*) OR (McKusick*) OR (IDUA) OR ("iduronidase deficiency") OR ((iduronidas*) AND (deficien*)) OR ("MPS 1") OR ("MPS I") OR ("mucopolysaccharidosis type 1") OR ("mucopolysaccharidosis type I") OR ("mucopolysaccharidosis 1") OR ("mucopolysaccharidosis I") OR ("Mucopolysaccharidosis I"[mhe]),"12","2025-05-14T16:25:40.000000Z"
13	Scheie*,"2","2025-05-14T16:25:28.000000Z"
12	hurler*,"2","2025-05-14T16:24:56.000000Z"
11	McKusick*,"0","2025-05-14T16:24:34.000000Z"
10	IDUA,"1","2025-05-14T16:24:13.000000Z"
9	"iduronidase deficiency","0","2025-05-14T16:23:56.000000Z"
8	(iduronidas*) AND (deficien*),"0","2025-05-14T16:23:10.000000Z"
7	"MPS 1","0","2025-05-14T16:21:25.000000Z"
6	"MPS I","6","2025-05-14T16:21:15.000000Z"
5	"mucopolysaccharidosis type 1","1","2025-05-14T16:20:50.000000Z"
4	"mucopolysaccharidosis type I","1","2025-05-14T16:20:39.000000Z"

3	"mucopolysaccharidosis 1","0","2025-05-14T16:20:17.000000Z"
2	"mucopolysaccharidosis I","3","2025-05-14T16:19:59.000000Z"
1	"Mucopolysaccharidosis I"[mhe],"9","2025-05-14T16:18:58.000000Z"
Total hits: 1	

Search strategy for Medline via Ovid

Ovid MEDLINE(R) ALL <1946 to May 14, 2025>	
Search date: 14.05.2025.	
ID	Search
#1.	exp Mucopolysaccharidosis I/ (1938)
#2.	(muco?poly?saccharidos* adj2 (I or "1")).mp. (2324)
#3.	MPS I.mp. (922)
#4.	MPS 1.mp. (269)
#5.	MPSI.mp. (144)
#6.	exp Iduronidase/df [Deficiency] (130)
#7.	(iduronidas* adj3 deficien*).mp. (164)
#8.	((alpha* or a or L*) adj3 iduronidas* adj3 deficien*).mp. (258)
#9.	IDUA.mp. (482)
#10.	McKusick 25280.mp. (8)
#11.	hurler*.mp. (1473)
#12.	Scheie*.mp. (652)
#13.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (3675)
#14.	laronidas*.mp. (124)
#15.	aldurazyme*.mp. (34)
#16.	alronidas*.mp. (0)
#17.	bm 101.mp. (1)
#18.	bm101*.mp. (3)
#19.	exp Iduronidase/ (695)
#20.	Iduronidas*.mp. (1024)
#21.	exp Enzyme Replacement Therapy/ (2900)
#22.	enzyme* replac*.mp. (7798)
#23.	ERT.ti,ab. (4343)
#24.	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (10643)
#25.	13 and 24 (1158)
#26.	limit 25 to dt=20161231-20250514 (372)
#27.	limit 25 to ed=20161231-20250514 (279)
#28.	26 or 27 (398)
#29.	remove duplicates from 28 (397)
Total hits: 397	

Idursulfase for Mucopolysaccharidosis II

Search strategy for Cochrane

Search Name: idursulfase for MPS II	
Search date: 15/05/2025	
ID	Search
#1	MeSH descriptor: [Mucopolysaccharidosis II] explode all trees
#2	((muco?poly?saccharidos* OR MPS) NEAR (II OR 2 OR two)) (Word variations have been searched)
#3	(MPS NEXT II)
#4	(MPS NEXT 2)
#5	(MPSII)
#6	(Hunter*):ti,ab,kw (Word variations have been searched)
#7	MeSH descriptor: [Iduronic Acid] explode all trees
#8	((iduronic OR iduronate*) NEAR deficien*) (Word variations have been searched)
#9	(McKusick NEXT 30990) (Word variations have been searched)
#10	(hurler* NEAR hunter*) (Word variations have been searched)
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12	MeSH descriptor: [Iduronate Sulfatase] explode all trees
#13	(iduronate*) (Word variations have been searched)
#14	(can NEXT 101) (Word variations have been searched)
#15	(can101*) (Word variations have been searched)
#16	(e.c. 3.1.6.13) (Word variations have been searched)
#17	(gc NEXT 1111) (Word variations have been searched)
#18	(gc1111*) (Word variations have been searched)
#19	(gc NEXT 1123) (Word variations have been searched)
#20	(gc1123*) (Word variations have been searched)
#21	(gsk NEXT 2788723) (Word variations have been searched)
#22	(gsk2788723*) (Word variations have been searched)
#23	(hgt NEXT 2310*) (Word variations have been searched)
#24	(hgt2310*) (Word variations have been searched)
#25	(hunteras*) (Word variations have been searched)
#26	(idurono*) (Word variations have been searched)
#27	(idursulfas*) (Word variations have been searched)
#28	(jr NEXT 032) (Word variations have been searched)
#29	(jr032*) (Word variations have been searched)
#30	(shp NEXT 609) (Word variations have been searched)
#31	(shp609*) (Word variations have been searched)
#32	(tak NEXT 609) (Word variations have been searched)
#33	(tak609*) (Word variations have been searched)
#34	MeSH descriptor: [Enzyme Replacement Therapy] explode all trees
#35	(enzyme* NEXT replac*) (Word variations have been searched)
#36	(ERT):ti,ab,kw
#37	(treatment* OR therap* OR surg* OR (gen* NEXT therap*)) (Word variations have been searched)
#38	MeSH descriptor: [Cell-Penetrating Peptides] explode all trees
#39	(cargo NEXT technology) (Word variations have been searched)
#40	MeSH descriptor: [Drug Delivery Systems] explode all trees
#41	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40

#42	#11 AND #41
#43	#11 AND #41 with Cochrane Library publication date Between Jan 2023 and May 2025
#44	#11 AND #41 with Publication Year from 2023 to 2025, in Trials
#45	#43 OR #44
#46	(conference proceeding):pt
#47	(abstract):so
#48	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so (Word variations have been searched)
#49	#45 NOT #48
Total hits: 54	

Search strategy for Embase

Search Name: idursulfase for MPS II		
Search date: 15.05.2025.		
No.	Query Results	Results
#48.	#44 NOT #47	364
#47.	#45 OR #46	159,770
#46.	'clinical trial':dtype	159,582
#45.	#44 AND 'Conference Abstract'/it	188
#44.	#43 AND [01-01-2023]/sd NOT [16-05-2025]/sd	594
#43.	#10 AND #42	3,350
#42.	#11 OR #12 OR … OR #41	20,396,881
#41.	'drug delivery system'/exp	497,753
#40.	'cargo technology'	–
#39.	'cell penetrating peptide'/exp	7,611
#38.	treatment* OR therap* OR surg* OR (gen* NEAR/1 therap*)	20,212,639
#37.	ert:ti,ab	8,200
#36.	'enzyme* replac*'	17,151
#35.	'enzyme replacement'/exp	14,048
#34.	tak609	1
#33.	'tak 609'	1
#32.	shp609	2
#31.	'shp 609'	–
#30.	jr032	–
#29.	'jr 032'	2
#28.	idursulfas*	373
#27.	idurono*	64
#26.	iduronat*	1,941
#25.	hunteras*	24
#24.	hgt2310	1
#23.	'hgt 2310'	1
#22.	gsk2788723	–
#21.	'gsk 2788723'	–
#20.	gc1123	–
#19.	'gc 1123'	–
#18.	gc1111	1
#17.	'gc 1111'	1

#16.	elapras*	301
#15.	'e.c. 3.1.6.13'	3
#14.	can101	–
#13.	'can 101'	2
#12.	iduronate*	1,940
#11.	'iduronate 2 sulfatase'/exp	1,514
#10.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	4,575
#9.	hurler* NEAR/1 hunter*	45
#8.	'mckusick 30990'	–
#7.	(iduronic OR iduronate*) NEAR/2 deficien*	218
#6.	hunter* NEAR/2 (syndrome* OR disease*)	3,618
#5.	Mpsii	233
#4.	'mps 2'	227
#3.	'mps ii'	1,429
#2.	mucopolysaccharidos* NEAR/2 (ii OR 1 OR two)	1,584
#1.	'hunter syndrome'/exp	2,885
Total hits: 364		

Search strategy for HTA-INATHTA

Search Name: idursulfase for MPS II	
Search date: 15.05.2025.	
ID	Search
42	(((ERT) OR ((enzyme*) AND (replac*)) OR ("Enzyme Replacement Therapy"[mhe]) OR (tak609*) OR ("tak 609") OR (shp609*) OR ("shp 609") OR (jr032*) OR ("jr 032") OR (idursulfas*) OR (idurono*) OR (hunteras*) OR (hgt2310*) OR ("hgt 2310") OR (gsk2788723*) OR ("gsk 2788723") OR (gc1123*) OR ("gc 1123") OR (gc1111*) OR ("gc 1111") OR (elapras*) OR (can101*) OR ("can 101") OR (iduronate*) OR ("Iduronate Sulfatase"[mhe])) AND (((hurler*) AND (hunter*)) OR ("McKusick 30990") OR ((iduronic OR iduronate*) AND (deficien*)) OR ("Iduronic Acid"[mhe]) OR (Hunter*) OR (MPSII) OR ("MPS 2") OR ("MPS II") OR ("Mucopolysaccharidosis type 2") OR ("Mucopolysaccharidosis 2") OR ("Mucopolysaccharidosis type II") OR ("mucopolysaccharidosis II") OR ("Mucopolysaccharidosis II"[mhe]))) FROM 2023 TO 2025,"0","2025-05-15T20:57:52.000000Z"
41	((ERT) OR ((enzyme*) AND (replac*)) OR ("Enzyme Replacement Therapy"[mhe]) OR (tak609*) OR ("tak 609") OR (shp609*) OR ("shp 609") OR (jr032*) OR ("jr 032") OR (idursulfas*) OR (idurono*) OR (hunteras*) OR (hgt2310*) OR ("hgt 2310") OR (gsk2788723*) OR ("gsk 2788723") OR (gc1123*) OR ("gc 1123") OR (gc1111*) OR ("gc 1111") OR (elapras*) OR (can101*) OR ("can 101") OR (iduronate*) OR ("Iduronate Sulfatase"[mhe])) AND (((hurler*) AND (hunter*)) OR ("McKusick 30990") OR ((iduronic OR iduronate*) AND (deficien*)) OR ("Iduronic Acid"[mhe]) OR (Hunter*) OR (MPSII) OR ("MPS 2") OR ("MPS II") OR ("Mucopolysaccharidosis type 2") OR ("Mucopolysaccharidosis 2") OR ("Mucopolysaccharidosis type II") OR ("mucopolysaccharidosis II") OR ("Mucopolysaccharidosis II"[mhe])),"10","2025-05-15T20:57:40.000000Z"
40	(ERT) OR ((enzyme*) AND (replac*)) OR ("Enzyme Replacement Therapy"[mhe]) OR (tak609*) OR ("tak 609") OR (shp609*) OR ("shp 609") OR (jr032*) OR ("jr 032") OR (idursulfas*) OR (idurono*) OR (hunteras*) OR (hgt2310*) OR ("hgt 2310") OR (gsk2788723*) OR ("gsk 2788723") OR (gc1123*) OR ("gc 1123") OR (gc1111*) OR ("gc 1111") OR (elapras*) OR (can101*) OR ("can 101") OR (iduronate*) OR ("Iduronate Sulfatase"[mhe]),"95","2025-05-15T20:57:14.000000Z"
39	ERT,"10","2025-05-15T20:56:30.000000Z"
38	(enzyme*) AND (replac*),"39","2025-05-15T20:56:21.000000Z"
37	"Enzyme Replacement Therapy"[mhe],"52","2025-05-15T20:55:32.000000Z"
36	tak609*,"0","2025-05-15T20:54:55.000000Z"
35	"tak 609","0","2025-05-15T20:54:45.000000Z"
34	shp609*,"0","2025-05-15T20:54:27.000000Z"
33	"shp 609","0","2025-05-15T20:54:18.000000Z"
32	jr032*,"0","2025-05-15T20:53:57.000000Z"
31	"jr 032","3","2025-05-15T20:53:44.000000Z"
30	idursulfas*,"9","2025-05-15T20:53:26.000000Z"
29	idurono*,"0","2025-05-15T20:53:12.000000Z"
28	hunteras*,"0","2025-05-15T20:52:56.000000Z"
27	hgt2310*,"0","2025-05-15T20:52:34.000000Z"

26	"hgt 2310","0","2025-05-15T20:52:24.000000Z"
25	gsk2788723*,"0","2025-05-15T20:51:52.000000Z"
24	"gsk 2788723","0","2025-05-15T20:51:40.000000Z"
23	gc1123*,"0","2025-05-15T20:51:18.000000Z"
22	"gc 1123","0","2025-05-15T20:51:05.000000Z"
21	gc1111*,"0","2025-05-15T20:50:47.000000Z"
20	"gc 1111","3","2025-05-15T20:50:33.000000Z"
19	elapras*,"5","2025-05-15T20:50:07.000000Z"
18	can101*,"0","2025-05-15T20:50:03.000000Z"
17	"can 101","0","2025-05-15T20:49:53.000000Z"
16	iduronate*,"3","2025-05-15T20:47:49.000000Z"
15	"Iduronate Sulfatase"[mhe],"5","2025-05-15T20:47:26.000000Z"
14	((hurler*) AND (hunter*)) OR ("McKusick 30990") OR ((iduronic OR iduronate*) AND (deficien*)) OR ("Iduronic Acid"[mhe]) OR (Hunter*) OR (MPSII) OR ("MPS 2") OR ("MPS II") OR ("Mucopolysaccharidosis type 2") OR ("Mucopolysaccharidosis 2") OR ("Mucopolysaccharidosis type II") OR ("mucopolysaccharidosis II") OR ("Mucopolysaccharidosis II"[mhe]),"32","2025-05-15T20:46:56.000000Z"
13	(hurler*) AND (hunter*),"0","2025-05-15T20:46:06.000000Z"
12	"McKusick 30990","0","2025-05-15T20:45:38.000000Z"
11	(iduronic OR iduronate*) AND (deficien*),"2","2025-05-15T20:44:58.000000Z"
10	"Iduronic Acid"[mhe],"0","2025-05-15T20:44:20.000000Z"
9	Hunter*,"27","2025-05-15T20:43:23.000000Z"
8	MPSII,"0","2025-05-15T20:42:14.000000Z"
7	"MPS 2","0","2025-05-15T20:41:54.000000Z"
6	"MPS II","5","2025-05-15T20:41:25.000000Z"
5	"Mucopolysaccharidosis type 2","0","2025-05-15T20:40:26.000000Z"
4	"Mucopolysaccharidosis 2","0","2025-05-15T20:40:10.000000Z"
3	"Mucopolysaccharidosis type II","2","2025-05-15T20:39:47.000000Z"
2	"mucopolysaccharidosis II","2","2025-05-15T20:39:11.000000Z"
1	"Mucopolysaccharidosis II"[mhe],"9","2025-05-15T20:37:08.000000Z"
Total hits: 0	

Search strategy for Medline via Ovid

Ovid MEDLINE(R) ALL <1946 to May 14, 2025>	
Search date: 15.05.2025.	
ID	Search
#48.	#44 NOT #47 (364)
#47.	#45 OR #46 (159,770)
#46.	'clinical trial':dtype (159,582)
#45.	#44 AND 'Conference Abstract'/it (188)
#44.	#43 AND [01-01-2023]/sd NOT [16-05-2025]/sd (594)
#43.	#10 AND #42 (3,350)
#42.	#11 OR #12 OR … OR #41 (20,396,881)
#41.	'drug delivery system'/exp (497,753)
#40.	'cargo technology' (–)
#39.	'cell penetrating peptide'/exp (7,611)
#38.	treatment* OR therap* OR surg* OR (gen* NEAR/1 therap*) (20,212,639)
#37.	ert:ti,ab (8,200)
#36.	'enzyme* replac*' (17,151)
#35.	'enzyme replacement'/exp (14,048)

#34.	tak609 (1)
#33.	'tak 609' (1)
#32.	shp609 (2)
#31.	'shp 609' (–)
#30.	jr032 (–)
#29.	'jr 032' (2)
#28.	idursulfas* (373)
#27.	idurono* (64)
#26.	iduronat* (1,941)
#25.	hunteras* (24)
#24.	hgt2310 (1)
#23.	'hgt 2310' (1)
#22.	gsk2788723 (–)
#21.	'gsk 2788723' (–)
#20.	gc1123 (–)
#19.	'gc 1123' (–)
#18.	gc1111 (1)
#17.	'gc 1111' (1)
#16.	elapras* (301)
#15.	'e.c. 3.1.6.13' (3)
#14.	can101 (–)
#13.	'can 101' (2)
#12.	iduronate* (1,940)
#11.	'iduronate 2 sulfatase'/exp (1,514)
#10.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 (4,575)
#9.	hurler* NEAR/1 hunter* (45)
#8.	'mckusick 30990' (–)
#7.	(iduronic OR iduronate*) NEAR/2 deficien* (218)
#6.	hunter* NEAR/2 (syndrome* OR disease*) (3,618)
#5.	mpsii (233)
#4.	'mps 2' (227)
#3.	'mps ii' (1,429)
#2.	mucopolysaccharidos* NEAR/2 (ii OR 1 OR two) (1,584)
#1.	'hunter syndrome'/exp (2,885)
Total hits: 184	

Elosulfase alfa for Mucopolysaccharidosis IVA

Search strategy for Cochrane

Search Name: elosulfase alfa for MPS IVA	
Search date: 16/05/2025	
ID	Search
#1	(elosulfas*) (Word variations have been searched)
#2	(elosufas*) (Word variations have been searched)
#3	(bmn NEXT 110*) (Word variations have been searched)
#4	(bmn110*) (Word variations have been searched)

#5	(recombinant NEXT n NEXT acetyl?galactosamine* NEXT 6 NEXT sulfatas*) (Word variations have been searched)
#6	(rhGALNS) (Word variations have been searched)
#7	(vimiz?im*) (Word variations have been searched)
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	(conference proceeding):pt
#10	(abstract):so
#11	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#12	#9 OR #10 OR #11
#13	#8 NOT #12
Total hits: 22	

Search strategy for Embase

Search Name: elosulfase alfa for MPS IVA		
Search date: 16.05.2025.		
No.	Query Results	Results
#14.	#10 NOT #13	216
#13.	#11 OR #12	179,659
#12.	'clinical trial':dtype	179,548
#11.	#10 AND 'Conference Abstract'/it	111
#10.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	333
#9.	vimizaim*	–
#8.	vimizim*	104
#7.	Rhgalns	12
#6.	'recombinant n acetylgalactosamine 6 sulfatase'	–
#5.	bmn110*	6
#4.	'bmn 110'	20
#3.	elosufas*	1
#2.	elosulfas*	319
#1.	'elosulfase alfa'/exp	304
Total hits: 216		

Search strategy for HTA-INATHTA

Search Name: elosulfase alfa for MPS IVA	
Search date: 16.05.2025.	
ID	Search
8	(vimizaim*) OR (vimizim*) OR (rhGALNS) OR ("recombinant n acetylgalactosamine 6 sulfatase") OR (bmn110*) OR ("bmn 110") OR (elosulfas*),"6","2025-05-16T15:56:55.000000Z"
7	vimizaim*,"0","2025-05-16T15:56:38.000000Z"
6	vimizim*,"1","2025-05-16T15:56:28.000000Z"
5	rhGALNS,"1","2025-05-16T15:55:45.000000Z"
4	"recombinant n acetylgalactosamine 6 sulfatase","0","2025-05-16T15:55:16.000000Z"
3	bmn110*,"0","2025-05-16T15:54:39.000000Z"
2	"bmn 110","0","2025-05-16T15:54:28.000000Z"
1	elosulfas*,"5","2025-05-16T15:53:48.000000Z"
Total hits: 6	

Search strategy for Medline via Ovid

Ovid MEDLINE(R) ALL <1946 to May 15, 2025>	
Search date: 16.05.2025.	
ID	Search
#1.	elosulfas*.mp. (69)
#2.	elosufas*.mp. (1)
#3.	bmn 110.mp. (5)
#4.	bmn110*.mp. (0)
#5.	recombinant n acetyl?galactosamine* 6 sulfatas*.mp. (0)
#6.	rhGALNS.mp. (6)
#7.	vimiz?im*.mp. (14)
#8.	1 or 2 or 3 or 4 or 5 or 6 or 7 (77)
Total hits: 77	

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH