tirol kliniken

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

ATMPs and Gene Therapies in Development

Horizon Scanning – Update 2022

Report

AIHTA Policy Brief Nr.: 006b | ISSN 2710-3234 | ISSN online 2710-3242

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

ATMPs and Gene Therapies in Development

Horizon Scanning – Update 2022

Vienna, June 2022

Projektteam

Projektleitung: Priv. Doz. Dr. Claudia Wild

Projektbearbeitung: Ozren Sehic, MA

Projektbeteiligung

Systematische Suche in Studienregistern: Ozren Sehic, MA

Unterstützung bei Formatierung: Smiljana Blagojevic, DI

Handsuche: Ozren Sehic, MA

Externe Begutachtung: Dr. MMag. Sabine Geiger-Gritsch, Evidenzbasierte Entscheidungsunterstützung (EBEU) - Medizinisches Projektmanagement, Tirol Kliniken GmbH

Korrespondenz:

Dieser Bericht soll folgendermaßen zitiert werden/This report should be referenced as follows:

Sehic O, Wild C. ATMP and Gene Therapies in Development, Horizon Scanning. Update 2022. AIHTA Policy Brief Nr.: 006b; Jahr. Wien: HTA Austria – Austrian Institute for Health Technology Assessment GmbH.

Interessenskonflikt

Alle beteiligten AutorInnen erklären, dass keine Interessenskonflikte im Sinne der Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org) bestehen.

IMPRESSUM

Medieninhaber und Herausgeber:
HTA Austria – Austrian Institute for Health Technology Assessment GmbH
Garnisongasse 7/Top20 | 1090 Wien – Österreich
https://www.aihta.at/

Für den Inhalt verantwortlich:
Priv.-Doz. Dr. phil. Claudia Wild, Geschäftsführung

Die **AIHTA Policy Briefs** erscheinen unregelmäßig und dienen der Veröffentlichung der Forschungsergebnisse des Austrian Institute for Health Technology Assessment.

Die **AIHTA Policy Briefs** erscheinen in geringer Auflage im Druck und werden über den Dokumentenserver „https://eprints.aihta.at/view/types/policy=5Fbrief.html " der Öffentlichkeit zur Verfügung gestellt.

AIHTA Policy Brief Nr.: 006b

ISSN 2710-3234

ISSN online 2710-3242

Content

List of figures

List of tables

Zusammenfassung

Hintergrund: Dieser Bericht ist eine Aktualisierung eines früheren Horizon Scanning-Berichts aus dem Jahr 2020, in dem 32 ATMPs identifiziert wurden. Seit August 2020 wurden sechs dieser neuen ATMPs von der EMA zugelassen, und über fünf weitere wird bis 2023 entschieden werden. Nach Angaben der Europäischen Arzneimittelagentur (EMA) lassen sich ATMPs in drei Haupttypen einteilen: Gentherapie- und somatische Zelltherapie-Arzneimittel sowie Tissue-Engineered-Produkte. Laut Marktanalysen werden im Jahr 2022 535 ATMPs in Phase 1 bis 3 untersucht, weitere 1.451 befinden sich in präklinischen Stadien. Der Gerinnungsfaktor VIII (Hämophilie A) bleibt das häufigste Ziel für nicht-onkologische Indikationen und der Gerinnungsfaktor IX (Hämophilie B) ist zur zweithäufigsten Indikation aufgestiegen.

Update von 2022 HS- Bericht 2020

2020: 32 ATMPs in später klinischer Entwicklung identifiziert, 2022: 6 davon zugelassen, 5 weitere bis 2023

Dieser Bericht soll die Fragen beantworten, für welche Indikationen Gentherapien und ATMPs in der Entwicklung sind und bis wann mit einer Zulassung gerechnet werden kann.

Ziel des Berichts: ATMPs in Entwicklung?

Methode: Zur Beantwortung der Fragen wurde eine systematische Suche in Studienregistern durchgeführt, um in Entwicklung befindliche Gentherapien und ATMPs zu identifizieren, gefolgt von der Extraktion von Daten über die identifizierten laufenden klinischen Studien (beschränkt auf Phase 2/3 und 3), ergänzt durch eine Suche in der EMA-Datenbank über in Bewertung befindliche Arzneimittel, um diejenigen Therapien zu identifizieren, die kurz vor der Zulassung stehen. Schließlich wurden veröffentlichte Informationen über die Produkte und den aktuellen Entwicklungs-/Regulierungsstand gesammelt und anschließend in kurze "Vignetten" umgewandelt.

Methode: Suche in Studienregistern nach Phase 2 + 3 Studien Datenextraktion Erstellung von Vignetten

Ergebnisse: Die Suche in ClinicalTrials.gov ergab 58 Treffer (Phase 2/3, 3), von denen 34 neue Studien waren. Nach Deduplizierung und Gruppierung gleicher Therapien wurden 34 verschiedene ATMPs (ohne CAR-T) identifiziert. Die Indikationsgebiete sind eine Vielfalt von genetischen Erkrankungen und umfassen acht breite Indikationsgruppen (Hämophilie, Stoffwechsel-, Augen-, Muskel-Skelett-, Gefäß-, Nieren-, Haut- und neurologische Erkrankungen). Seit August 2020 wurden sechs neue ATMPs von der EMA zugelassen (2020: 3, 2021: 1, 2022: 2) und über weitere fünf wird bis 2023 entschieden.

58 neue Studien (Phase 2, 3) identifiziert zu 34 ATMPs in 8 Indikationsfeldern

Schlussfolgerung: Bei der Bewertung dieser Therapien gibt es zahlreiche Herausforderungen. Sie haben Vorschusslorbeeren erhalten und werden oft als "kurative" oder "disruptive" Technologien bezeichnet, obwohl für die wenigen bereits zugelassenen Therapien kaum Langzeitdaten vorliegen. Die Herausforderung besteht nun darin, dass das potenzielle Versprechen der Gentherapien den Erwartungen gerecht werden muss, und es ist die Aufgabe des HTA, die tatsächliche Wirksamkeit der jeweiligen Therapien genau zu beobachten.

Gentherapien und ATMPs werden oft als kurative Therapien bezeichnet: Versprechen müssen aber noch erfüllt werden

Dieser HS-Bericht stellt nur eine "Momentaufnahme" dar und ist nicht so verlässlich wie internationale Initiativen und deren systematische und permanente Aktivitäten, da Horizon Scanning zeitaufwändig ist: 2022 wird Österreich der Internationalen Horizon Scanning Initiative (IHSI) beitreten, was einen großen Fortschritt in den Bemühungen um die frühzeitige Identifizierung neuer Therapien darstellt, die in Zukunft Auswirkungen auf Gesundheit und Budget haben könnten.

Horizon Scanning ist zeitaufwändig und daher international

Österreich tritt 2022 IHSI bei: großer Gewinn!

Executive Summary

Update of 2020 report since 08/2020: 6 new ATMPs approved by EMA, decision on another 5 ATMPs until 2023

Background: This report is an update of an earlier Horizon Scanning report from 2020, in which 32 ATMPs were identified. Since August 2020 six of these new ATMPs have been approved by EMA and another five will be decided upon until 2023. According to the European Medicines Agency (EMA) ATMPs can be classified into three main types: Gene therapy and somatic-cell therapy medicinal products as well as tissue-engineered products. According to market analyses in 2022 535 ATMPs are investigated in Phase 1 to 3 trials, another 1451 are in preclinical stages. Coagulation factor VIII (haemophilia A) remains the most common target for non-oncology indications and coagulation factor IX (haemophilia B) has risen to second most common indication.

aim of report: which ATMPs are under development?

This report aims to address the questions, for which indications gene-therapies and ATMPs are under development and by when an approval can be expected.

systematic search in trial registries data-extraction: indications and approval status vignettes

Methods: To answer the questions a systematic search in trial registries was conducted to identify gene-therapies and ATMPs under development, followed by the extraction of data on the identified ongoing clinical trials (restricted to phase 2/3 and 3), complemented by a search in the EMA-database on medicines under evaluation to identify those therapies closest to approval. Finally published information on the products and the current stage of development/regulation was collected and subsequently transformed into short „vignettes“.

58 new trials on 34 ATMPs (without CAR-T) identified in 8 fields of indications

Results: The search in ClinicalTrials.gov yielded 58 hits (Phase 2/3, 3), of which 34 were new studies. After deduplication and clustering of the same therapies, 34 different ATMPs (without CAR-T) were identified. The areas of indications are a diversity of genetic diseases and encompass eight broad indication groups (Haemophilia, Metabolic -, Ophthalmologic -, Musculoskeletal -, Vascular -, Nephrologic -, Dermatologic - and Neurologic disorders). Since August 2020 six new ATMPs have been approved by EMA (2020: 3, 2021: 1, 2022: 2) and upon another five will be decided until 2023.

gene therapies and ATMPs are often referred to as curative therapies: but promises still need to be fulfilled

Conclusion: There are many challenges in evaluating these therapies. They have received advance praise and are often referred to as "curative" or "disruptive" technologies, although there is little long-term data for the few therapies already approved. The challenge now is that the potential promise of gene therapies must live up to expectations, and it is the role of HTA to closely monitor the actual effectiveness of the respective therapies.

Horizon scanning is time-consuming and therefore international Austria joins IHSI in 2022: big win!

This HS report only represents a "snapshot" and is not as reliable as international initiatives and their systematic and permanent activities, as horizon scanning is time-consuming: in 2022, Austria will join the International Horizon Scanning Initiative (IHSI), which is a major step forward in the efforts to identify new therapies at an early stage that could have an impact on health and budget in the future.

1 Introduction

1.1 Definition: ATMP

EMA Definitionen von ATMP

ATMP können in 3 Typen klassifiziert werden

Gentherapien. Somatische Zelltherapien. Tissue-Engineering Produkte

According to the EMA, Advanced Therapy Medicinal Products (ATMPs) can be classified into three main types (see Figure 1-1):

- Gene therapy medicinal products: these contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources;
- Somatic-cell therapy medicinal products: these contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases;
- Tissue-engineered products: these contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue;

Figure 1-1: Umbrella term „Advanced Therapy Medicinal Product (ATMP)" [1]

1.2 Market development

ca. 535 laufende klinische Studien in Phase 1-3

häufigste nicht-onkologische Indikation: Hämophilie

According to the ASGCT Pharma Intelligence Quarterly Report Q1 2022 [2] 535 ATMPs are investigated in Phase 1 to 3 trials, another 1451 are in preclinical stages (see Figure 1-2). Coagulation factor VIII ((haemophilia A) remains the most common target for non-oncology indications and coagulation factor IX (haemophilia B) has risen to second most common indication [2] (see Figure 4-1 in the discussion). Due to the extensive research activities in this indication, the BeNeLuxA initiave on Horizon Scanning has conducted a short overview on upcoming Haemophilia therapies [3].

Global Status	Q1 2021	Q2 2021	Q3 2021	Q4 2022	Q1 2022
Preclinical	1,190	1,296	1,353	1,412	1,451
Phase I	225	269	264	248	248
Phase II	231	236	239	244	250
Phase III	27	27	29	32	31
Pre-registration	8	7	5	5	6
Total	**1,711**	**1,835**	**1,890**	**1,941**	**1,986**

Figure 1-2: Ongoing clinical trials on Gene, Cell & RNA Therapies [2]

Update des Horizon Scanning Berichts zu ATMPs 2020

seitdem 6 ATMPs zugelassen

This report is an update of an earlier Horizon Scanning report from 2020 [4], in which 32 ATMPs were identified. Since August 2020 six of these new ATMPs have been approved by EMA

- XENPOZYME® (olipudase alfa) for the treatment of non-central nervous system (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) (05/2022)

  https://www.ema.europa.eu/en/news/first-therapy-treat-two-types-niemann-pick-disease-rare-genetic-metabolic-disorder
- UPSTAZA ® (eladocagene exuparvovec, PTC-AADC) for severe aromatic L-amino acid decarboxylase (AADC) deficiency (PTC Therapeutics International Limited) (05/2022)

  https://www.ema.europa.eu/en/news/first-therapy-treat-rare-genetic-nervous-system-disorder-aadc-deficiency
- SKYSONA® (elivaldogene autotemcel, Lenti-D) for Cerebral Adrenoleukodystrophy (Bluebird bio) (07/2021)

  https://www.ema.europa.eu/en/medicines/human/EPAR/skysona
- LIBMELDY® (Atidarsagen autotemcel, OTL-200) for metachromatic leukodystrophy (MLD) (Orchard Therapeutics) (12/ 2020)

  https://www.ema.europa.eu/en/medicines/human/EPAR/libmeldy
- LEQVIO® (Inclisiran) for Heterozygous & Homozygous FH Atherosclerotic Cardiovascular Disease (Novartis) (12/ 2020)

  https://www.ema.europa.eu/en/medicines/human/EPAR/leqvio
- OXLUMO® (Lumasiran) for Primary Hyperoxaluria Type 1 (PH1) (Alnylam) (11/ 2020)

  https://www.ema.europa.eu/en/medicines/human/EPAR/oxlumo

die Zulassung von weiteren 5 ATMPs wird für 2022/23 vorausgesagt

According to the annual report of the "Alliance of Regenerative Medicine (ARM)" 2021 [5] regulatory decisions on the following therapies for 2022 and 2023 (of which some are CAR-T cell therapies covered in the recent AIHTA-report [6]) are forecasted. Based on the ARM-forecast two ATMPs (other than CAR-T cells) will be decided upon by EMA in 2022, three more in 2023 (as of knowledge from 2021) [5] (see Figure 1-3):

2022

- Etranacogene dezaparvovec (AMT-061, AAV5-hFIXco-Padua, CSL222, EtranaDez®) for Haemophilia B
- Valoctocogene roxaparvovec (BMN-270, Valrox®, Roctavian) for Haemophlia A

2023

- Lenadogene nolparvovec (GS010, LUMEVOQ®) for Leber Hereditary Optic Neuropathy
- Beremagene geperpavec (B-VEC, Vyjuvek®) for Dystrophic Epidermolysis Bullosa
- OTL-103 (GSK 2696275) for Wiskott–Aldrich syndrome (WAS)

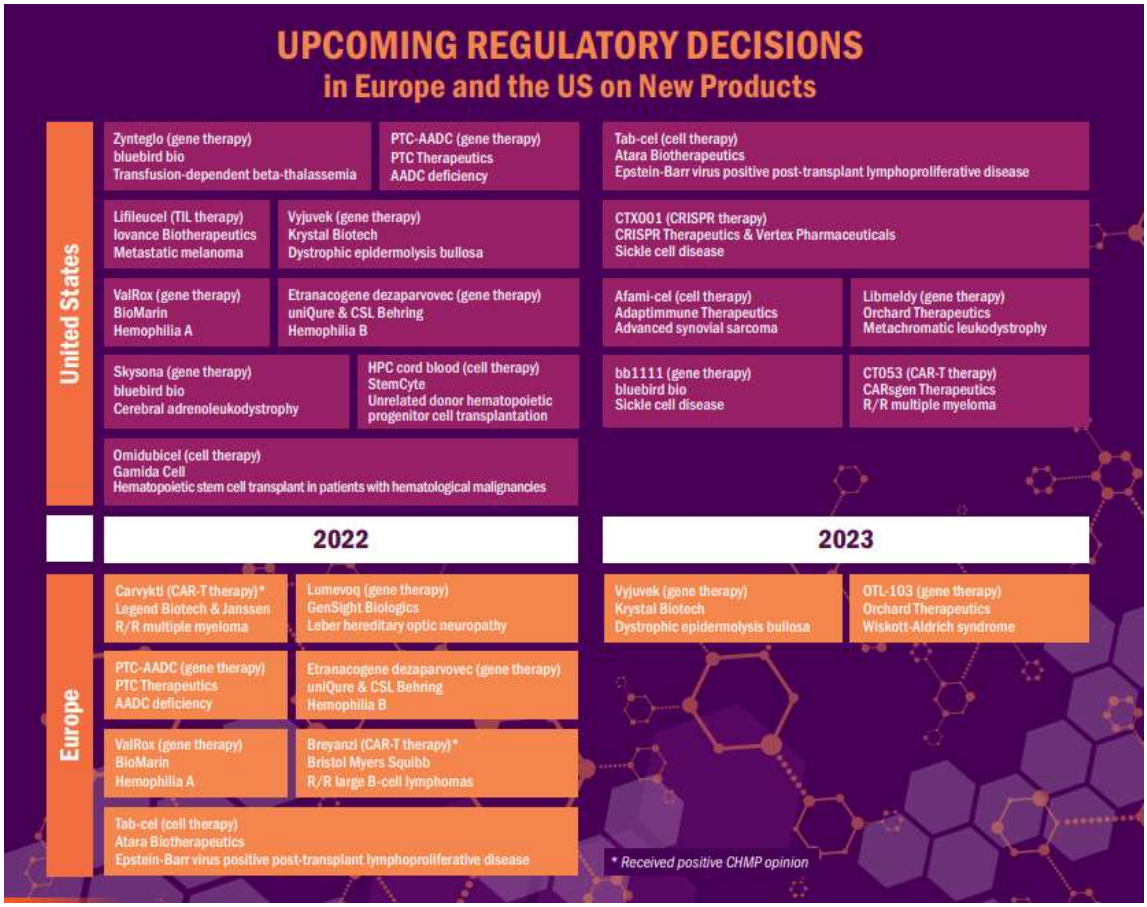

Figure 1-3: Alliance of Regenerative Medicine (ARM) annual report 2021 - forecast of upcoming regulatory decisions [5]

2 Methods

2.1 Research Questions

This report aims to address the following research questions (RQ):

- RQ1: For which indications are gene-therapies and ATMPs under development?
- RQ2: What is the status of development and by when can an approval be expected?

Forschungsfragen:

Welche Gen- Und Zelltherapien sind in Entwicklung?

The following methods will be applied to answer the research questions:

1. To answer RQ1, a systematic search in trial registries was conducted to identify gene-therapies and ATMPs under development.
2. To answer RQ2, data on the identified ongoing clinical trials was extracted from the registry, esp. on status of trials and complemented by a search in the EMA-database on medicines under evaluation to identify those therapies closest to approval.

The methodologies are described in more detail as follows:

2.2 Search strategy and in-/exclusion criteria

A search in the following clinical trials registry was performed between March 28th and 30th 2022.

Suchstrategie im Detail

- ClinicalTrials.gov https://clinicaltrials.gov/
- Search terms used were „gene therapy“ AND “biological” AND “phase 2/3 or 3”, „Advanced therapy* medicinal product*” AND “phase 2/3 or 3”.

in 1 Studienregister Gentherapien und ATMP

in Phase 2/3 & 3

Duplicates with the same trial-ID were removed.

Results were crossed checked with findings in

Überprüfung in 1 weiteren Register

- EudraCT https://eudract.ema.europa.eu/
- EMA https://www.ema.europa.eu/en/medicines/medicines-under-evaluation

Inclusion criteria:

Ein-/Ausschlusskriterien:

- Phase 2/3 to Phase 3 clinical trials.
- All indications (except oncological indications)

keine onkologischen Therapien

Exclusion criteria:

Produkt-zentriert

- Phase 1, 2 clinical trials
- No product, but (in-house/hospital) process
- No EMA or FDA Status (only China)
- Oncological indications

Selection of interventions: The search in ClinicalTrials.gov yielded 58 hits (Phase 2/3, 3), of which 34 were new studies. After deduplication and clustering of the same therapies, 34 different ATMPs were identified.

nach Deduplikation und Clustering: 34 ATMPs identifiziert

2.3 Data extraction

Extraktion der Daten aus Studienregister

ergänzt durch Suche in EMA-Datenbank

After selection of interventions, data were extracted by one person (OS) and controlled by a second researcher (CW). The following relevant clinical trial data was extracted from ClinicalTrials.gov (https://clinicaltrials.gov/) (see Appendix A-1):

- Trial-ID, title, status (e.g. recruiting, active not recruiting etc.), condition, intervention, name of the sponsor, phase, number of patients enrolled, start date, completion date, the status of the application process for centralised marketing authorization. The detailed extraction tables are presented in the Appendix.
- Complemented by a search in

  https://www.ema.europa.eu/en/medicines/medicines-under-evaluation#2020 to identify those therapies closest to approval.

Moreover, the yielded results from the search in the clinical trial registry were analysed by conditions, forming eight indication clusters.

Handsuche in Pubmed und auf Hersteller-Websites nach Detailinformationen zu den Therapien

Then, a targeted search in

- Specialist Pharmacy Service (SPS)

  https://www.sps.nhs.uk/articles/sps-horizon-scanning-service/

was conducted and the respective sponsors´/manufacturer´ websites were visited for additional information for the short “vignettes”.

Publicly available information in English and German language on

- the current stage of development/regulation
- description of the technology

was collected and extracted.

3 Results

As indicated, the search in clinical trials registries yielded 34 ATMPs in phase 2 or phase 3 trials in eight areas of indications. The longlist sorted by indication can be found in the Appendix (Table A-1). A detailed description is presented in the following text.

34 Therapien in 8 Indikationsfeldern

3.1 Indication haemophilia

Table 3-1 is providing information on gene- (incl. RNA) therapies for haemophilia. Further upcoming therapeutics for haemophilia are reported in the BeNeLuxA Report [3]. It is expected that the entire Hemophilia market will grow to $18.88 billion by 2028.[7].

Hämophilie: riesiger Wachstumsmarkt auch BeneluxA-Bericht

3.1.1 Valoctocogene roxaparvovec (BMN-270, Roctavian, Valrox®) (Biomarin)

Development/Regulatory Status:

- The application for **valoctocogene roxaparvovec**, for centralised marketing authorization is currently reviewed under EMA´s accelerated assessment program. It was rejected by FDA in 8/2020. The FDA has given regenerative medicine advanced therapy (RMAT) designation after re-application in 2021. In August 2021, the FDA decided to delay its decision on the approval until two-year data from the company's Phase 3 GENEr8-1 clinical trial (NCT03370913) were available. A similar decision was taken by the European Medicines Agency (EMA), which asked for one more year of data. BioMarin plans to resubmit to FDA in June 2022, followed by an expected six-month review.
- Valoctocogene roxaparvovec was granted US Orphan Drug Designation (February 2016) and US Breakthrough Therapy (October 2017) status by the US Food and Drug Administration (FDA), EU Orphan Drug Designation (March 2016) and EU PRIME (PRIority MEdicines) Designation (February 2017) by the EMA. It is indicated for the treatment of adults with severe haemophilia A (congenital factor VIII deficiency) without detectable antibodies to adeno-associated virus (AAV) serotype 5 (AAV5).
- This submission is based on an interim analysis of study participants treated in an ongoing phase 3 study with result from the updated three-year Phase 1/2 data.
- In addition, the FDA has accepted the premarket approval (PMA) application for an AAV5 total antibody assay intended as a companion diagnostic test for valoctocogene roxaparvovec.

derzeit bei EMA unter Begutachtung, von FDA abgelehnt (08/2020)

bei Hämophilie A

Pts mit schweren Erkrankungen ohne Antikörper gegen AAV5

Companion-AAV5 Antikörper Test

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Table 3-1: Haemophilia therapies under development - overview

Indication	Product	Sponsor	Development/ regulatory status	Phase; Study-ID: primary completion date, location(s)
Haemophilia A	Valoctocogene roxaparvovec (BMN-270, Valrox, Roctavian)	BioMarin	NEW FDA: ODD (2016), BTT (2017), FDA: rejected (8/2020), FDA: RMAT (2021) FDA/EMA: Delayed decision until results of NCT03370913 (2022) EMA: Withdrawn MAA, ODD (2016), PRIME (2017) BioMarin plans to resubmit to FDA in June 2022, followed by an expected six-month review [8]	NEW Results Phase 3: NCT03392974 (Active, not recruiting, 05/2019, US) Phase 3: NCT03370913 (Active, not recruiting, 11/2020, US/Australia/Brazil/EU/Israel/Korea/South Africa/Taiwan/UK) Phase 3: NCT04323098 (Active, not recruiting, 01/2023, US/Australia/Brazil/Taiwan)
Haemophilia B	Etranacogene dezaparvovec (AMT-06,1 AAV5-hFIXco-Padua, CSL222, EtranaDez)	UniQure/CSL	NEW FDA: ODD, FTD (2019) EMA: ODD, PRIME (2017) EMA: Accelerated CHMP Assessment (12/2021) FDA/ EMA approval expected in 2022 [9]	Phase 3: NCT03569891 (Active, not recruiting, 09/2021, US/EU/UK)
Haemophilia A/B	Fitusiran	Sanofi	NEW: Postponed FDA: ODD (2013) EMA: ODD (2014) FDA/ EMA filing for approval postponed to 2024 [10]	NEW completed studies: Phase 3: NCT03417102 (Completed 06/2021, US/Australia/Canada/China/EU/India/Japan/Korea/Malaysia/South Africa/ Taiwan/Turkey/Ukraine/UK) Phase 3: NCT03417245 (Completed 07/2021, US/EU/India/Israel/Japan/Malaysia/South Africa/Taiwan/Turkey/Ukraine/UK) Phase 3: NCT03549871 (Active, not recruiting, 03/2022, US/Australia/Canada/China/EU/Japan/Korea/Malaysia/Turkey/Ukraine/UK) Phase 2/3: NCT03974113 (Recruiting, 08/2023, US/Canada/EU/India/Turkey) Phase 3: NCT03754790 (Recruiting, 10/2026, US/Australia/Canada/China/EU/India/Israel/Japan/Korea/Malaysia/South Africa/Taiwan/Turkey/Ukraine/UK)

Indication	Product	Sponsor	Development/ regulatory status	Phase; Study-ID: primary completion date, location(s)
Haemophilia A Haemophilia B	Giroctocogene fitelparvovec (PF-07055480) Fidanacogene elaparvovec (SPK-9001, PF-06838435)	Pfizer	NEW FDA: ODD, BTT (2016) EMA: ODD, PRIME (2017) EMA 09/2020: agreement of a paediatric investigation plan and on the granting of a deferral [11, 12]	NEW Study Phase 3: NCT04370054 (Active, not recruiting, 09/2023, US/Australia/Brazil/Canada/EU/Japan/Korea/Saudi Arabia/Taiwan/Turkey/UK) Phase 3: NCT03861273 (Active, not recruiting, 11/2022, US/Australia/Brazil/Canada/EU/Japan/Korea/Saudi Arabia/Taiwan/Turkey/UK) Phase 3: NCT03587116 (Recruiting, 05/2023, US/Australia/Brazil/Canada/EU/Japan/Korea/Saudi Arabia/Taiwan/Turkey/UK) SPK-9001: No Phase 3 studies
Haemophilia B	FLT180a	Freeline	FDA: not available EMA: ODD (2018)	No Phase 3 studies 03/22: expected to begin the start-up activities for the Phase III trial in the first half of 2023.[13]

Abbreviations: BTT = Breakthrough Therapy, EMA=European Medicines Agency, EPCD=Estimated Primary Completion Date, FDA= US Food and Drug Administration, FTD= Fast Track Designation; ODD = Orphan Drug Designation, PRIME = PRIority Medicines, RMAT = regenerative medicine advanced therapy

Technology:

Adeno-assoziierte Viren (AAV) dienen als Vektorviren

erste Gentherapie:

Einmalinfusion zur Normalisierung von Faktor VIII-Werten

- Valoctocogene roxapavovec (BMN-270) is a recombinant codon-optimised AAV5 vector that encodes a B-domain-deleted human factor VIII (AAV5-hFVIII-SQ), which is a clotting factor that is an essential part of the coagulation cascade and therefore blood clotting – with a hybrid liver-specific transcription promoter. Thus, it restores factor VIII plasma concentrations to levels which are adequate for normal clotting in haemophilia A. If licensed, valoctocogene roxaparvovec would be the first gene therapy for severe haemophilia A. Valoctocogene roxaparvovec administered as a single treatment would be sufficient to maintain normal levels of factor VIII in adult males with severe haemophilia A, and might reduce the need for regular factor VIII prophylaxis (preventative treatment).

Approval Status:

- Not yet approved by EMA/FDA

Clinical investigations:

3 Phase 3 Studien

NCT03392974 (**BMN270-302**, Phase 3, US, 1 Pt., 03/2018 – 05/2019)

- Open-label, single-arm study to evaluate the efficacy and safety of BMN 270, an adeno-associated virus vector-mediated gene transfer of human factor VIII at a dose of 4e13vg/kg in hemophilia a patients with residual VIII levels ≤1IU/dL receiving prophylactic fVIII infusions)
- Status: Active, not recruiting (Last Update: 10/2021)

NCT03370913 (**BMN270-301**, Phase 3, US/Australia/Brazil/EU/Israel/Korea/South Africa/Taiwan/UK, 137 Pts., 12/2017-11/2020)

- Open-label, single-arm study to evaluate the efficacy and safety of BMN 270, an adeno-associated virus vector-mediated gene transfer of human factor VIII in hemophilia a patients with residual f VIII levels ≤ 1IU/dL receiving prophylactic fVIII infusions
- Status: Active, not recruiting (Last Update: 10/2021

NCT04323098 (**GENEr8-3**, Phase 3, US/Australia/Brazil/Taiwan, 20 Pts., 12/2017-01/2023)

- Open-label, single arm study to evaluate the efficacy and safety of BMN 270, an adeno-associated virus vector-mediated gene transfer of human factor VIII, with prophylactic corticosteroids in hemophilia a patients
- Status: Active, not recruiting (Last Update: 02/2022)

3.1.2 Etranacogene dezaparvovec (AMT-061, AAV5-hFIXco-Padua, CSL222, Etranadez®) (UniQure/CSL)

Development/Regulatory Status:

- Etranacogene dezaparvovec is a therapy in development.
- Etranacogene dezaparvovec received Orphan Drug (2019) and Fast Track Designations (2019) from the FDA. Etranacogene dezaparvovec has been Orphan Drug Designation (2017) and access to PRIME regulatory initiative by the EMA (2017).
- A phase 2b study was conducted to confirm that a single dose of 2 × 1013 genome copies per kilogram of etranacogene dezaparvovec will result in factor IX activity ≥5% six weeks after dosing. Etranacogene dezaparvovec was administered as a single IV infusion to three adults with severe to moderately severe haemophilia B.
- In the phase 3 trial (HOPE-B trial, active, not recruiting) 56 severe or moderately severe haemophilia B patients are included.
- The European Medicines Agency (EMA) has approved an accelerated assessment request for etranacogene dezaparvovec. The decision means that, once an application is submitted seeking approval for marketing authorization of etranacogene dezaparvovec, it will be reviewed more quickly than normal.[14]
- Marketing applications for etranacogene dezaparvovec for the treatment of patients with Hemophilia B will be submitted in both the U.S. and EU in the 1st half of 2022.

Wird in Q2 2022 zur Zulassung eingereicht

Hämophilie B

Phase 2b
Phase 3 begonnen

Einmalinfusion

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

- Etranacogene dezaparvovec (AMT-061) is a recombinant AAV5 vector including a gene cassette containing the factor IX (FIX) Padua variant under the control of a liver-specific promoter.

AAV-Vektor

Approval Status:

- Not yet approved by EMA/FDA, approval expected in 2022.

Clinical investigations:

1 Phase 3 Studie

NCT03569891 (**HOPE-B**, Phase 3, US/EU/UK, 56 Pts., 06/2018-09/2021)

- Open-label, randomized parallel study to evaluate the efficacy and safety of Fitusiran in patients with hemophilia A or B, with inhibitory antibodies to factor VIII or IX
- Status: Active, not recruiting (Last Update: 03/2022)

3.1.3 Fitusiran (Sanofi)

Development/Regulatory Status:

derzeit in Entwicklung

- Fitusiran, a novel RNA interference (RNAi) therapy in development.

Interimauswertungen von Phase 2 Studie bei Hämophilie A

- Fitusiran holds Orphan Drug Designation by the US FDA (2013) and by EMA (2014) for haemophilia.
- Sanofi announces positive long-term efficacy and safety data for fitusiran from an interim analysis of phase 2 (open-label) extension study in people with haemophilia A and B, with or without inhibitors. This data evaluated 34 enrolled patients who received monthly fixed 50 mg or 80 mg doses of fitusiran and were followed for a period up to 4.7 years, with a median exposure of 2.6 years.
- In 2017, the developer Alnylam halted fitusiran trials after a patient with haemophilia died, suffering fatal blood clots before resuming the trials. After a clinical hold by the FDA the trial was restarted.

FDA/ EMA filing for approval postponed to 2024 [10]

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

RNA Interferenz (RNAi) zur zielgerichteten Abschaltung von Genen monatliche subkutane Verabreichung

- Fitusiran is a synthetic double-stranded siRNA oligonucleotide directed against antithrombin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues for the treatment of haemophilia. Fitusiran is a once-monthly subcutaneously administered investigational RNAi therapeutic targeting antithrombin (AT) to enhance thrombin generation (TG) and rebalance hemostasis in patients with haemophilia A (HA) or haemophilia B (HB) with or without inhibitors.

Approval Status:

- Not yet approved by EMA/FDA

Clinical investigations:

4 Phase 3 Studien
1 Phase 2/3 Studie

NCT03417102 (**ATLAS-INH**, Phase 3, US/Australia/Canada/China/EU/India/Japan/Korea/Malaysia/South Africa/ Tai-wan/Turkey/Ukraine/UK, 60 Pts., 02/2018-11/2020)

- Open-label, randomized parallel study to evaluate the efficacy and safety of Fitusiran in patients with hemophilia a or b, with inhibitory antibodies to factor VIII or IX
- Status: Completed 06/2021 (Last Update: 12/2021)

NCT03417245 (**ALN-AT3SC**, Completed 07/2021, Phase 3, US/EU/India/Israel/Japan/Malaysia/South Africa/Taiwan/Turkey/Ukraine/UK, 120 Pts., 03/2018 – 01/2021)

- Open-label, randomized parallel study to evaluate the efficacy and safety of Fitusiran in patients with hemophilia a or b, with inhibitory antibodies to factor VIII or IX
- Status: Completed 07/2021 (Last Update: 02/2022)

NCT03549871 (**ATLAS-PPX**, Phase 3, US/Australia/Canada/China/EU/Israel/Japan/Korea/Malaysia/Turkey/Ukraine/UK, 80 Pts., 07/2018 - 03/2022)

- Open-label, single arm, multinational, switching study to describe the efficacy and safety of Fitusiran prophylaxis in patients with he-

mophilia a and b previously receiving factor or bypassing agent prophylaxis

- Status: Active, not recruiting (Last Update: 03/2022)

NCT03974113 (**ATLAS-PEDS**, Phase 2/3, US/Canada/EU/India/Turkey, 25 Pts., 01/2020 - 08/2023)

- Open-label, single arm, multinational study of Fitusiran prophylaxis in male pediatric subjects aged 1 to less than 12 years with hemophilia A or B
- Status: Recruiting (Last Update: 09/2021)

NCT03754790 (**ATLAS-OLE**, Phase 3, US/Australia/Canada/China/EU/India/Israel/Japan/Korea/Malaysia/South Africa/Taiwan/Turkey/Ukraine/UK, 244 Pts., 01/2019 - 08/2026)

- Open-label, single arm, multinational, long-term safety and efficacy study of Fitusiran in patients with hemophilia A or B, with or without inhibitory antibodies to factor VIII or IX
- Status: Recruiting (Last Update: 12/2021)

3.1.4 Giroctocogene fitelparvovec (PF-07055480) and fidanacogene elaparvovec (PF-06838435) (Pfizer)

Development/Regulatory Status:

derzeit in Entwicklung
Phase 1/2
Beginn Phase 3

- Giroctocogene fitelparvovec and fidanacogene elaparvovec are therapies in development. **Giroctocogene fitelparvovec** is being developed as part of a collaboration agreement for the global development and commercialization of gene therapies for Hemophilia A between **Sangamo and Pfizer**. In late 2019, Sangamo transferred the manufacturing technology and the Investigational New Drug (IND) application to Pfizer. The US FDA granted Orphan Drug, Fast Track, and regenerative medicine advanced therapy (RMAT) designations to giroctocogene fitelparvovec, which also received Orphan Medicinal Product Designation from the European Medicines Agency [15].

giroctocogene fitelparvovec: Hämophilie A

fidanacogene elaparvovec: Hämophilie B

- Giroctocogene fitelparvovec as well as fidanacogene elaparvovec were granted Orphan Drug Designation (Nov 2016), US Breakthrough Therapy (Jul 2016) status by the FDA and Orphan Drug Designation and PRIME Designation (Mar 2017) by the EMA.
- The phase 1/2 Alta study is an open-label, dose-ranging, multicenter clinical trial designed to assess the safety and tolerability of giroctocogene fitelparvovec in patients with severe haemophilia A. The mean age of the eleven patients assessed across four dose cohorts is 30 years (range 18-47 years). Pfizer announced Updated phase 1/2 results showing sustained Factor VIII Activity Levels and no bleeding events or factor usage in 3e13 vg/kg Cohort following giroctocogene fitelparvovec (SB-525) Gene Therapy in June 2020. Pfizer is now enrolling patients in the phase 3 study. Although the clinical hold has now been lifted, the company said it will pause the trial until “all necessary conditions are met,” which include the FDA approving updated study protocols.[16]

Phase 1/2
Phase 3 laufend

- Data from 15 patients participating in the phase 1/2 study designed to treat severe or moderately severe haemophilia B (FIX levels under 2% of normal concentrations) were the basis for the phase 3 open-

label, multi-centre, lead-in study to evaluate the efficacy and safety of current factor IX prophylaxis replacement therapy.

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

AAV-Vektoren

Technology:

giroctocogene fitelparvovec: AVV6

- Giroctocogene fitelparvovec comprises an AAV serotype 6 vector (AAV6) encoding the complementary deoxyribonucleic acid for B domain deleted human FVIII. The giroctocogene fitelparvovec expression cassette was designed for optimal liver-specific expression of FVIII protein and supports the production of high yields of the vector.

fidanacogene elaparvovec: AVV2

- Fidanacogene elaparvovec comprises an AAV serotype 2 (AAV2) expressing the Padua variant (R338L) of human coagulation factor IX (F9, Factor IX, FIX), under the control of the liver-specific apolipoprotein E (Apo E). Is a novel, investigational vector that contains a bio-engineered AAV capsid (protein shell) and a high-activity human coagulation factor IX gene.

Einmalinfusion zur Normalisierung von Faktor VIII/IX-Werten

- Both are single infusions of a gene therapy that uses an adeno-associated viral vector to deliver a codon-optimised, high-activity gene for human Factor IX or VIII to liver cells.

Approval Status:

- Not yet approved by EMA/FDA

Clinical investigations:

3 Phase 3 Studien

NCT04370054 (**AFFINE**, Phase 3, US/Australia/Brazil/Canada/EU/Japan/Korea/Saudi Arabia/Taiwan/Turkey/UK, 63 Pts., 08/2020-09/2023)

- Open-label, single-arm study to evaluate the efficacy and safety of PF-07055480 (recombinant AAV2/6 human factor VIII gene therapy) in adult male participants with moderately severe to severe hemophilia A (FVIII:C≤1%)
- Status: Active, not recruiting (Last Update: 01/2022)

NCT03861273 (**BENEGENE-2**, Phase 3, US/Australia/Brazil/Canada/EU/Japan/Korea/Saudi Arabia/Taiwan/Turkey/UK, 43 Pts., 08/2020-11/2022)

- Non-randomized, open-label, single-arm study to evaluate the efficacy and safety of of fix gene transfer with PF-06838435 (RAAV-SPARK100-HFIX-PADUA) in adult male participants with moderately severe to severe hemophilia B (FIX:C <=2%)
- Status: Active, not recruiting (Last Update: 03/2022)

NCT03587116 (Phase 3, Recruiting, US/Australia/Brazil/Canada/EU/Japan/Korea/Saudi Arabia/Taiwan/Turkey/UK, 250 Pts., 07/2018-05/2023)

- Open-label, single-arm non-investigational product, multi-center, lead-in study to evaluate at least 6 months of prospective efficacy and selected safety data of current factor IX (FIX) or factor VIII (FVIII) prophylaxis replacement therapy in the usual care setting of moderately severe to severe adult hemophilia b subjects (FIX: c≤2%) who are negative for neutralizing antibodies to adeno-associated virus vector-spark100 (benegene-1) and moderately severe to severe hemophilia a adult subjects (FVIII: c≤1%) who are negative for neutralizing antibodies to adeno-associated virus vector SB-

525 CAPSID (AAV6), prior to the respective therapeutic phase 3 gene therapy studies

- Status: Recruiting (Last Update: 03/2022)

3.1.5 FLT180a (Freeline)

Development/Regulatory Status:

- FLT180a is a therapy in development
- FLT180a was granted Orphan Drug Designation by the EMA (Oct 2018). FDA-Status is not available.
- It is currently investigated in patients with severe haemophilia B, in a phase 1/2 clinical trial. The results support the start of a pivotal phase 3 trial of FLT180a.
- 03/22: expected to begin the start-up activities for the Phase III trial in the first half of next year [13].

derzeit in Entwicklung

Haemophilia B

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

- FLT180a a next-generation, AAV gene therapy consists of a single-stranded, replication incompetent adenovirus vector, in which a codon optimised variant FIX transgene is encapsidated in a novel synthetic capsid (AAVS3). It is investigated as a single-dose infusion.

AAVS3 Vektor

Approval Status:

- Not approved by EMA/FDA

Clinical investigations:

- No Phase 3 studies
- Phase 3 study planned for first half of 2023 [17]

Phase 3 Studien ab 2023

3.2 Metabolic disorders

Table 3-2: Metabolic disorders therapies under development

Indication	Product	Sponsor	Development/Regulatory status	Phase; Study-ID: primary completion date, location(s)
(hATTR) Amyloidosis	Vutrisiran (ALN-TTRSC02)	Alnylam	FDA: ODD (2018) FDA: FTD (2020) EMA: ODD (2018) EMA: MAA submitted (2021) 04/2022: Alnylam Announces 3-Month Extension of Review Period for New Drug Application for Vutrisiran [18-20]	Phase 3: NCT03759379 (HELIOS-A, Active, not recruiting, 11/2020, US/Australia/Canada/Argentina/Brazil/Bulgaria/EU/Japan/Korea/Malaysia/Mexico/Taiwan/UK) Phase 3: NCT04153149 (HELIOS-B, 06/2024, Active, not recruiting, US/Australia/Canada/Argentina/Brazil/Bulgaria/Colombia//EU/Israel/Japan/Korea/Lebanon/Malaysia/Mexico/Moldova/Peru/Thailand/UK)
ADA Immunodeficiency	Simoladagene autotemcel (OTL-101)	Orchard	FDA: PDD, BTT (2017) EMA: ODD (2019) 06/21: Despite positive outcome data, Orchard have officially abandoned development of OTL-101 [21]	Terminated Study Phase 2/3: NCT04140539 (Terminated, Phase 2/3, US) 11/2021: Orchard Therapeutics terminates a phase II/III trial for Adenosine deaminase deficiency in USA, due to business reasons [22]
Mucopolysaccharidosis Type 3 A	Olenasufligene relduparvovec (SAF-302)	Lysogene	FDA: Discussion about updated evidence Q4/2022 [23] FDA: FTD (2020) FDA: PDD (2020) EMA: ODD (2014) [24]	Phase 2/3: NCT03612869 (Active, not recruiting, 08/2021, US/EU/UK) 05/2022: Efficacy data from a phase III AAVance trial in Mucopolysaccharidosis III presented at the 25th Annual Meeting of the American Society for Gene & Cell Ther-apy (ASGCT-2022) [25]
Mucopolysaccharidosis Type 3 B Mucopolysaccharidosis 3 A	rAAV9.CMV.hNAGLU (ABO-101) scAAV9.U1a.hSGSH (Rebisufligene etisparvovec, ABO-102)	Abeona	FDA: ODD, PDD (2019) EMA: ODD, PRIME (2019) ABO-101: Discontinued (2022) [26] ABO-102: Abeona announces it will pursue a strategic partner to take over development activities for ABO-102 for MPS IIIA [27]	No Phase 3 studies
Alpha 1-Antitrypsin Deficiency	ARO-AAT	Arrowhead	FDA: ODD, FTD (2019) EMA: ODD (2018)	No Phase 3 studies Phase 2: NCT03946449 Phase 2: NCT03945292
Glycogen Storage Disease Type IA	Pariglasgene brecaparvovec (DTX401)	Ultragenyx Pharmaceutical Inc	FDA: FTD (2018), ODD, RMAT EMA: ODD (2016) [28]	Phase 3: NCT05139316 (Active, not recruiting, 04/2023, US/Canada/EU/Brazil/Japan/Korea)
Wiskott-Aldrich Syndrome	OTL-103 (GSK-2696275)	Orchard Therapeutics	FDA: Application expected in 2022 [29, 30]	Phase 3: NCT03837483 (Recruiting, 07/2023, US/Italy)

Abbreviations: AA= Accelerated Assessment, ADA= adenosine deaminase, BTT= Breakthrough Therapy, EMA=European Medicines Agency, EPCD=Estimated Primary Completion Date, FDA= US Food and Drug Administration, FTD = Fast Track Designation, hATTR= Hereditary Transthyretin Amyloidosis, ODD= Orphan Drug Designation, PDD = Paediatric Disease Designation, PRIME = PRIority Medicines

3.2.1 Vutrisiran (ALN-TTRSC02) (Alnylam)

Development/Regulatory Status:

- Vutrisiran (ALN-TTRSC02) is an investigational RNAi therapeutic for the treatment of hereditary transthyretin-mediated (hATTR) amyloidosis in adult patients with polyneuropathy. Alnylam filed Vutrisiran for authorization by EMA in 09/2021 [31].
- Vutrisiran has been granted Orphan Drug designation in the United States (U.S.) (Jun 2018) and the European Union (EU) (May 2018). Vutrisiran has also been granted Fast Track designation in the United States (U.S.) (Apr 2020). Alnylam submitted Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) for vutrisiran for the treatment of hereditary transthyretin-mediated (hATTR) amyloidosis in adult patients with polyneuropathy in September 2021. Vutrisiran is considered by analysts to have blockbuster potential.
- The safety and efficacy of vutrisiran are being evaluated in the HELIOS Phase 3 clinical trial. HELIOS-A is a randomized, open-label, global multi-centre Phase 3 study of 160 patients with Hereditary Transthyretin Amyloidosis (hATTR) with polyneuropathy. Results are expected in late 2020. Alnylam also plans to initiate HELIOS-B, a phase 3 trial evaluating vutrisiran in patients with ATTR amyloidosis with cardiomyopathy.

zur Zulassung bei EMA eingereicht

Polyneuropathie

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

- Vutrisiran (ALN-TTRSC02) is an investigational RNAi therapeutic being evaluated for the treatment of ATTR amyloidosis, which encompasses both hereditary (hATTR) and wild-type (wt) amyloidosis. Vutrisiran works by inhibiting the production of disease-causing TTR proteins, leading to a reduction in the levels of TTR in a patient's bloodstream. Vutrisiran is subcutaneously administered.

RNAi zur gezielten Hemmung

Approval Status:

- Not approved by EMA/FDA

Clinical investigations:

2 Phase 3 Studien

NCT03759379 (**HELIOS-A**, Phase 3, US/Australia/Canada/Argentina/Brazil/Bulgaria/EU/Japan/Korea/Malaysia/Mexico/Taiwan/UK, 164 Pts., 02/2019-11/2020)

- Global, randomized, two-arm, open-label study to evaluate the efficacy and safety of ALN-TTRSC02 in patients with hereditary transthyretin amyloidosis
- Status: Active, not recruiting (Last Update: 04/2022)

NCT04153149 (**HELIOS-B**, Phase 3, US/Australia/Canada/Argentina/Brazil/Bulgaria/Colombia//EU/Israel/Japan/Korea/Lebanon/Malaysia/Mexico/Moldova/Peru/Thailand/UK, 655 Pts., 11/2019 – 06/2024)

- Randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy (attr amyloidosis with cardiomyopathy)
- Status: Active, not recruiting (Last Update: 04/2022)

3.2.2 Simoladagene autotemcel (OTL-101) (Orchard)

Entwicklung vorerst abgebrochen

Phase 2
Beginn Phase 3

Development/Regulatory Status:

- Simoladagene autotemcel was a therapy under development; Orchard abandoned development in 2021 [32].
- Simoladagene autotemcel was granted rare Paediatric Disease Designation by the FDA (Jul 2017) and also has Breakthrough Therapy status as well as an Orphan Drug Designation from EMA (Feb 2019).
- A phase 2 prospective, non-randomised, single-cohort, longitudinal clinical study designed to assess the efficacy and safety of OTL-101 cryopreserved formulation administered in adenosine deaminase-severe combined immunodeficiency (ADA-SCID) subjects is ongoing and basis for the phase 3 investigation. In clinical trials comparing the use of simoladagene to allogeneic hematopoietic stem cell transplantation (HSCT) in ADA-SCID patients [33].

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

autologe Stammzellentherapie

- Simoladagene autotemcel (OTL-101) is an autologous stem cells ex-vivo lentiviral adenosine deaminase gene therapy in which cryopreserved EFS-ADA LV CD34+ hematopoietic stem/progenitor cells (HSPCs) are introduced into a functional copy of the human ADA gene.

Approval Status:

- Not approved by EMA/FDA

1 Phase 2/3 Studie (abgebrochen)

Clinical investigations:

NCT04140539 (Terminated, Recruitment on hold for business reasons, Phase 2/3, US, 3 Pts., 10/2019 – 08/2021)

- Single arm, open label clinical study to enable process validation of commercial grade ex vivo hematopoietic stem cell gene therapy (OTL-101) in subjects with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID)
- Status: Terminated (Recruitment on hold for business reasons) (Last Update: 11/2021)

3.2.3 Olenasufligene relduparvovec (LYS-SAF-302) (Lysogene)

Development/Regulatory Status:

- Olenasufligene relduparvovec is a therapy under development.
- Olenasufligene relduparvovec receives Fast Track Designation for Mucopolysaccharidosis III [Intracerebral,Injection] (in adolescents, in children, in the elderly, in adults) in USA in February 2020, but in June 2020 FDA puts hold on a phase 2/3 clinical trial in Mucopolysaccharidosis III (NCT03612869; EudraCT2018-000195-15). EMA granted Orphan Drug Designation (Dec 2014). Since January 2021 LYS-SAF-302 also holds rare paediatric disease designation in the US. Registrational trial is fully recruited with top-line data expected in H2/22. Lysogene has reported positive LYS-SAF302 biomarkers demonstrating biological activity [34].

in Entwicklung

laufende Phase 2/3 Mucopolysaccharidosis (MPS) Type 3 A

positive Ergebnisse

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

- Olenasufligene relduparvovec is an AAV-mediated gene therapy, the goal of which is to replace the faulty SGSH gene with a healthy copy of the gene. It employs the AAVrh10 virus, chosen for its ability to target the central nervous system.

AAV Vektorviren

Approval Status:

- Not approved by EMA/FDA

1 Phase 2/3 Studie

Clinical investigations:

NCT03612869 (**AAVance**, Phase 2/3, US/EU/UK, 20 Pts., 12/2018-03/2022)

- Open-label, single-arm, multi-center study of intracerebral administration of adeno-associated viral (AAV) serotype rh.10 carrying human N-sulfoglucosamine Sulfohydrolase (SGSH) cDNA for treatment of mucopolysaccharidosis type IIIA
- Status: Active, not recruiting, (Last Update: 08/2021)

3.2.4 RAAV9 (ABO-101) and SCAAV9 (ABO-102) (Abeona)

Development/Regulatory Status:

- rAAV9 (ABO-101) was discontinued in March 2022. Abeona announces it will focus its R&D resources primarily on VITAL data readout while actively pursuing potential commercialization partner for EB-101, and maintain focus on preclinical eye gene therapy programs. In addition, it will pursue a strategic partner to take over development activities for ABO-102 for MPS IIIA, while discontinuing development of ABO-101 for MPS IIIB.
- rAAV9 (ABO-101) and scAAV9 (ABO-102) received Orphan Drug Designation by FDA and EMA as well as Fast Track Designation and Rare Paediatric Disease Designation by the FDA (Apr 2019) and PRIME status by EMA (Dec 2019) [35, 36].
- Efficacy data from the phase 1/2 Transpher A trial in Mucopolysaccharidosis 3 was released in May 2020.

Entwicklung vorerst abgebrochen

laufende Phase 1/2 Mucopolysaccharidosis (MPS) Type 3 A

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

AAV Vektorviren

- The therapy is designed to address the underlying enzyme deficiency responsible for the abnormal accumulation of glycosaminoglycans in the brain and throughout the body that results in progressive cell damage and neurodevelopmental and physical decline.

Einmalinfusion

  - ABO-101: AAV serotype (AAV9) carrying the human NAGLU gene under the control of a CMV enhancer/promoter (rAAV9.CMV.hNAGLU) will be delivered one-time through a venous catheter inserted into a peripheral limb vein.
  - ABO-102: AAV9 carrying the human SGSH gene under the control of a U1a promoter (scAAV9.U1a.hSGSH) will be delivered one time through a venous catheter inserted into a peripheral limb vein.

Approval Status:

- Not approved by EMA/FDA

keine Phase 3 Studie

Clinical investigations:

- No Phase 3 studies

Phase 1/2 Study terminated NCT04088734: 1.3.2022 Abeona Therapeutics terminates the phase I/II ABT-003 trial in Mucopolysaccharidosis III (In children, In adolescents) in Australia, Spain and USA (IV), due to lack of efficacy seen in patients (NCT04088734)

3.2.5 ARO-AAT (Arrowhead)

derzeit in Entwicklung

Development/Regulatory Status:

- ARO-AAT is a therapy under development.

laufende Phase 2
Beginn Phase 2/3

- ARO-AAT holds Orphan Drug Designation by EMA (2018) and the FDA; the FDA granted a Fast Track Designation (2019).

Alpha-1-Antitrypsinmangelerkrankung

- A Pilot open label, multi-dose, phase 2 study to assess changes in a novel histological activity scale in response to ARO-AAT in patients with Alpha-1 antitrypsin deficiency associated liver disease (AATD) is ongoing; another phase 2/3 study is initiated.

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4]

Technology:

RNAi zur zielgerichteten Hemmung

- ARO-AAT is being developed to treat the liver disease associated with alpha-1 antitrypsin deficiency (AATD): ARO-AAT is a second-generation, subcutaneously administered RNAi therapeutic that inhibits alpha 1-antitrypsin.

Approval Status:

- Not approved by EMA/FDA

keine Phase 3 Studie

Clinical investigations:

- No Phase 3 studies

3.2.6 DTX401 (Pariglasgene brecaparvovec) (Ultragenyx)

Development/Regulatory Status: **in Entwicklung ODD seit 2016**

- DTX401 is a gene therapy in development. DTX401 has orphan drug designation in the US and EU (2016) and holds Regenerative Medicine Advanced Therapy (RMAT) and Fast Track designation (FTD) in the US since 2018.

Condition: **Glykogenspeicherkrankheit Typ I (GSD I)**

- Glycogen storage disease type I (GSD I) is an inherited disease that results in the liver being unable to properly break down stored glycogen. This impairment disrupts the liver's ability to break down stored glycogen that is necessary to maintain adequate blood sugar levels.

Technology: **AAV Vektorviren**

- DTX401 is an adeno-associated virus serotype 8 (AAV8) vectored gene therapy designed to deliver stable expression and activity of glucose-6-phosphatase-α using a single intravenous infusion. DTX401 consists of a virus that has been modified to contain a gene that produces normal glucose 6-phosphatase. When given to patients, the virus is expected to carry this gene into liver cells. This would enable these cells to produce glucose 6-phosphatase so that glycogen can be broken down to glucose. This is expected to reduce symptoms of the condition. The virus used (adeno-associated virus) does not cause disease in humans [37].

Approval Status:

- Not approved by EMA/FDA

Clinical investigations: **1 Phase 3 Studie**

NCT05139316 (Phase 3, US/Canada/EU/Brazil/Japan/Korea, 50 Pts., 11/2021-04/2023)

- Randomized, multi-center, double-blind, placebo-controlled study to determine the efficacy and confirm the safety of DTX401 in patients 8 years and older with Glycogen Storage Disease Type IA (GSDIA). Participants will be randomized 1:1 to DTX401 or placebo group, and followed closely for 48 weeks. At week 48 eligible participants will cross over and receive DTX401 if they had previously received placebo or placebo if they had previously received DTX401, and will be followed closely for an additional 48 weeks. After completion of week 96 or early withdrawal, participants will be offered enrollment into a Disease Monitoring Program (DMP) where they will be followed for at least 10 years post DTX401 infusion
- Status: Active, not recruiting (Last Update: 03/2022)

3.2.7 OTL-103 (Orchard)

Development/Regulatory Status: **in Entwicklung**

- OTL-103 is currently in clinical development for the treatment of Wiskott-Aldrich Syndrome (WAS). In 2012, OTL-103 was granted orphan designation in the EU for the treatment of Wiskott-Aldrich syndrome. Orchard is preparing for a Marketing Authorization Ap- **EMA Zulassung In Vorbereitung**

plication (MAA) submission for OTL-103 in Europe in mid-2022. In the U.S., Orchard is planning to interact with FDA in early 2022 to discuss elements of a potential BLA filing package, including development work on a functional potency assay and the clinical dataset [38].

Wiskott-Aldrich Syndrome (WAS)

Condition:

- WAS is a rare disease with immunological deficiency and reduced ability to form blood clots. This syndrome is caused by an abnormality in the gene found on the X chromosome that codes for WAS protein (WASP). This WAS gene defect and the severity of the condition varies widely between individuals. Severe cases may be present soon after birth or develop in the first year of life. WAS affects the functions of white blood cells and platelets, making people affected susceptible to serious infections and bleeding events. WAS occur almost exclusively in males. It is life-threatening and long-term debilitating disease due to recurrent infections that can lead to sepsis, bleeding episodes and cancer. Stem cell transplantation is the only treatment currently available to stabilize WAS [39].

Technology:

CD34+ Zelltherapie

- OTL-103 is administered intravenously. It is made up of immature bone marrow cells (called CD34+ cells) taken from the patient. It works by correcting cells using a modified virus that contains the correct gene for the WAS protein. When these corrected cells are transplanted back into the patient, they populate the bone marrow and produce healthy platelets and immune cells that produce the WAS protein, thereby relieving the symptoms of the disease. If licensed, OTL-103 will provide a treatment option for patients with WAS [39].

Approval Status:

- Not approved by EMA/FDA

1 Phase 3 Studie

Clinical investigations:

NCT03837483 (Phase 3, US/Italy, 10 Pts., 01/2019-07/2023)

- Multi-center, open-label, single arm study to evaluate the cryopreserved formulation of OTL-103 Gene Therapy. OTL-103 consists of autologous CD34+ hematopoietic stem cells in which the gene encoding for the Wiskott-Aldrich Syndrome is introduced by means of a third generation lentiviral vector.
- Status: Recruiting (Last Update: 02/2022)

3.3 Ophthalmologic disorders

Table 3-3: Ophthalmologic disorders therapies under development

Indication	Product	Sponsor	Development/Regulatory status	Phase; Study-ID: primary completion date, location(s)
Choroideremia	Timrepigene emparvovec (AAV2-REP1, BIIB111)	Biogen	FDA: RMAT, FTD, BTT (2018) EMA: ODD (2015) 07/2021: Development discontinued [40]	STUDY Completed Phase 3: NCT03496012 (Completed 12/2020, US/Canada/EU/UK) Phase 3: NCT03584165 (Enrolling by invitation, 03/2027, US/Canada/EU/UK)
Leber Hereditary Optic Neuropathy	NR082 (rAAV2-ND4)	Neurophth Therapeutics	FDA: ODD (2020) [41] EMA: ODD (2022) [42]	Phase 2/3: NCT03153293 (Active, not recruiting, 01/2020, China)
Leber Hereditary Optic Neuropathy	Lenadogene nolparvovec (GS010, LUMEVOQ®)	GenSight Biologics	FDA: ODD (2013) EMA: ODD (2011) FDA recommends additional trial (2022) [43] EMA: Delay in MAA application (2022) [44] Committee for Medicinal Products for Human Use (CHMP) opinion expected by Q3 2023 [45]	Phase 3: NCT03293524 (Active, not recruiting, 06/2023, US/EU/Taiwan/UK) Phase 3: NCT03406104 (Active, not recruiting, 07/2022, US/EU/Taiwan/UK)
Age-related macular degeneration	RGX-314	Regenxbio Inc.	FDA: Submission expected in 2024 [46] EMA: n.a.	Phase 2/3: NCT04704921 (ATMOSPHERE, Recruiting, 03/2023, US)
X-Linked Retinitis Pigmentosa	AAV5-RPGR (MGT009, botaretigene sparoparvovec)	MeiraGTx UK II Ltd/Janssen	FDA: ODD, FTD EMA: ODD, ATMP, PRIME [47]	Phase 3: NCT04794101 (Recruiting, 07/2023, US) Phase 3: NCT04671433 (Recruiting, 07/2022, US)
X-Linked Retinitis Pigmentosa	AAV8-RPGR (BIIB112)	Biogen	FDA: ODD, FTD (2019) EMA: ODD (2018), ATMP, PRIME (2020)	NEW STUDY: Phase 3: NCT03584165 (SOLSTICE, Enrolling by invitation, 03/2027, US/Canada/EU/UK)
X-Linked Retinitis Pigmentosa	AGTC-501 (laruparetigene zosaparvovec , rAAV2tYF-GRK1-hRPGRco)	Applied Genetic Technologies Corp	FDA: ODD (2017) EMA: ODD (2016) [48, 49]	Phase 3: NCT04850118 (Not yet recruiting, 01/2024)
Achromatopsia	Entacingene turiparvovec (AAV - CNGB3)	MeiraGTx	FDA: ODD (2016), FTD (2018) EMA: ODD (2015), PRIME (2018) Not listed in Janssen planned filings, so do not expect data to be available for filing before 2024 [50]	No Phase 3 studies
Achromatopsia	AGTC-402 (ACHM CNGA3, rAAV2tYF-PR.1-hCNGA3)	Applied Genetic Tech	FDA: ODD (2018) EMA: ODD (2018)	No Phase 3 studies

Abbreviations: ATMP = Advanced Therapy Medicinal Product, BTT= Breakthrough Therapy, EMA=European Medicines Agency, EPCD=Estimated Primary Completion Date, FDA= US Food and Drug Administration, FTD = Fast Track Designation, ODD= Orphan Drug Designation, PRIME = PRIority Medicines, RMAT = Regenerative Medicine Advanced Therapy

3.3.1 Timrepigene emparvovec (AAV2-REP1) (Biogen)

Development/Regulatory Status:

in Entwicklung (abgebrochen?)

- Timrepigene emparvovec is a first-in-class AAV2 gene therapy for the treatment of choroideremia. It seems likely to be discontinued in June 2021 [51]. Biogen has announced that a late-stage trial did not meet its primary and key secondary endpoints in patients with the rare inherited eye disease choroideremia [52, 53].

Phase 3

Choroideremie

- Timrepigene emparvovec has received Regenerative Medicine Advanced Therapy (RMAT) Designation from the FDA (Jun 2018), including Fast Track and Breakthrough Therapy Designation and Orphan Drug Designations by the EMA (Jan 2015).
- Phase 1/2 study published and phase 3 ongoing: enrolment in the STAR trial (180 patients) for Choroideraemia in USA, Canada, Finland, Germany, Netherlands, United Kingdom and Denmark.

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

AAV2 Vektor

- Timrepigene emparvovec is an AAV2 vector administered by subretinal injection, which aims to provide a functioning CHM gene and expression of the REP-1 protein to restore membrane trafficking and thereby slow, stop or potentially reverse a decline in vision. The procedure involves an injection of AAV under the retina with a very narrow needle under local anaesthetic by a retinal surgeon.

Approval Status:

- Not approved by EMA/FDA

2 Phase 3 Studien

Clinical investigations:

NCT03496012 (Phase 3 Completed 12/2020, US/Canada/EU/UK, 170 Pts., 12/2017-12/2020))

- Randomised, multi-center, open label, outcomes-assessor masked, prospective, parallel controlled group, phase 3 clinical trial of retinal gene therapy for choroideremia using an adeno-associated viral vector (AAV2) encoding rab escort protein 1 (REP1).
- Status: Completed (12/2020, Last Update: 12/2021)

NCT03584165 (**SOLSTICE**, Phase 3, US/Canada/EU/UK, 440 Pts., 06/2018-03/2027)

- Non-randomized, multi-center outcomes-assessor masked, long-term follow-up study to evaluate the safety and efficacy of retinal gene therapy in subjects with choroideremia previously treated with adeno-associated viral vector encoding rab escort protein-1 (AAV2-REP1) and in subjects with x-linked retinitis pigmentosa previously treated with adeno-associated viral vector encoding RPGR (AAV8-RPGR) in an antecedent study.
- Status: Enrolling by invitation (Last Update: 04/2022)

3.3.3 NR082 (NFS-01, RAAV2-ND4) (Neurophth therapeutics)

Development/Regulatory Status:

- NR082 is an ophthalmic gene therapy in development for the treatment of Leber's Hereditary Optic Neuropathy (LHON) associated with ND4 mutation. NR082 received orphan drug designation (ODD) from the FDA (2020) and EMA (2022) [54].

in Entwicklung
ODD seit 2022

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Lebersche hereditäre Optikus-Neuropathie (LHON)

Technology:

- LHON disease is caused by mutations in mitochondrial DNA 11778, 14484 or 3460. ND4 gene of 11778 G>A mutation is the main pathological factor, which exists in 55-70% of European and American patients and 90% of Chinese patients. NR082 (NFS-01 project) is an candidate drug for ophthalmic AAV-based gene therapy. It uses AAV2 vector to express human ND4 gene in the retinal ganglion cells to repair optic neuropathy caused by 11778 G>A mutation.

AAV Vektoren

Approval Status:

- Not approved by EMA/FDA

Clinical investigations:

1 Phase 2/3 Studie

NCT03153293 (Phase 2/3, China, 159 Pts., 12/2017-01/2020)

- A single-arm, open label study of a single intravitreal injection of rAAV2-ND4 for the treatment of leber's hereditary optic neuropathy
- Status: Active, not recruiting (Last Update: 09/2020)

3.3.4 Lenadogene nolparvovec (LUMEVOQ®, GS010) (GenSight Biologics)

Development/Regulatory Status:

- Lenadogene nolparvovec is a drug under development. Market launch in the US was planned for 2021. The FDA provided feedback in January 2022 recommending that the company conduct an additional placebo-controlled trial to bolster the demonstration of Lumevoq efficacy in view of the unexpected bilateral effect observed in unilaterally treated patients in the RESCUE, REVERSE and REFLECT trials. GenSight says it is engaging with the FDA on the design of such a trial and aims to initiate it as soon as possible in 2022 [43]. EMA licence application also was delayed due to manufactoring issues [44]. In April 2022 the Committee for Advanced Therapies (CAT) of the European Medicines Agency (EMA) has granted the company a six-month extension for submitting its responses to the Day 120 questions in the regulatory review of LUMEVOQ®, GenSight's gene therapy for the treatment of Leber Hereditary Optic Neuropathy (LHON) [45].

in Entwicklung
ODD (seit 20213)

Zulassung 2022 geplant

Lebersche hereditäre Optikus-Neuropathie (LHON)

- Lenadogene nolparvovec was designated Orphan Drug Status for Leber's hereditary optics neuropathy in the EU in 2011 and in the USA in 2013.
- It is currently in phase 3 clinical trial development.

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

AAV Vektor

- Lenadogene nolparvovec is a recombinant AAV vector serotype. It delivers the nicotinamide adenine dinucleotide dehydrogenase subunit (ND4) gene directly to the mitochondrial membrane of the retinal ganglion cells. Lenadogene nolparvovec shows allotropic expression and proteins involved in the respiratory chain can be directly integrated into the mitochondrial membrane during the translation process, thus checking the progression of the disease.

Approval Status:

- Not approved by EMA/FDA

2 Phase 3 Studien

Clinical investigations:

NCT03293524 (**GS-LHON-CLIN-05,** Phase 3, US/EU/Taiwan/UK, 90 Pts., 03/2018-06/2023)

- Global, multi-center randomized, double-masked for the primary analysis, placebo-controlled, clinical study. As LHON is a neurodegenerative disease, the goal is to administer GS010 as soon as possible upon confirmation of the LHON diagnosis and the causative mutation.
- Status: Active, not recruiting (Last Update: 02/2021)

NCT03406104 (**RESCUE/REVERSE**, Phase 3, US/EU/Taiwan/UK, 61 Pts., 01/2018-07/2022)

- Long-term, randomized, open-label, sham-controlled, double-masked follow-up of ND4 LHON subjects treated with GS010 ocular gene therapy in the RESCUE or REVERSE phase III clinical trials.
- Status: Active, not recruiting (Last Update: 02/2021)

3.3.5 RGX-314

Development/Regulatory Status:

in Entwicklung
Zulassung 2024?
AMD, Diabetische Retinopathie

- RGX-314 is being developed as a potential one-time treatment for wet AMD, diabetic retinopathy and other additional chronic retinal conditions treated with anti-VEGF. Biological license application (BLA) is expected to be submitted to FDA in 2024 based on tow pivotal trials, ASCENT and the ongoing ATMOSPHERE trial.

Condition: wet age-related macular degeneration, diabetic retinopathy

Technology:

AAV Vektor

- AAV8 vector carries gene encoding for monoclonal antibody fragment, ranibizumab, which binds to & neutralises activity of vascular endothelial growth factor (VEGF), modifying the pathway new leaky blood vessel formation and retinal fluid accumulation [55].

Approval Status:

- Not approved by EMA/FDA

Clinical investigations: **1 Phase 2/3 Studie**

NCT04704921 (**ATMOSPHERE**, Phase 2/3, US, 300 Pts., 12/2020-03/2023)

- Randomized, quadruple masked, controlled clinical study to evaluate the efficacy and safety of RGX-314 gene therapy in participants with nAMD
- Status: Recruiting (Last Update: 09/2021)

3.3.6 AAV5-RPGR (MGT009, botaretigene sparoparvovec) (Janssen/MEIRAGT)

Development/Regulatory Status:

- AAV5-RPGR is an investigational gene therapy product for RPGR-Associated X-Linked Retinitis Pigmentosa developed by Janssen (Johnson & Johnson) & MEIRAGTx. AAV5-RPGR received Fast Track and Orphan designation from the FDA. EMA granted PRIME (PRIority MEdicines) and Advanced Therapy Medicinal Product (ATMP) and Orphan designations to AAV-RPGR. **in Entwicklung PRIME**

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

- AAV-RPGR is designed to deliver functional copies of the RPGR gene to the subretinal space in order to improve and preserve visual function [56]. **AAV Vektoren**

Approval Status:

- Not approved by EMA/FDA

Clinical investigations: **2 Phase 3 Studien**

NCT04794101 (Phase 3, US, 66 Pts., 03/2021-07/2023)

- Follow-up, randomized, outcome-assessor masked, controlled study of AAV5-RPGR for the treatment of X-linked retinitis pigmentosa associated with variants in the RPGR gene
- Status: Recruiting (Last Update: 09/2021)

NCT04671433 (Phase 3, US, 66 Pts., 03/2021-07/2023)

- Randomized, outcome-assessor masked, controlled study of AAV5-RPGR for the treatment of X-linked retinitis pigmentosa associated with variants in the RPGR gene
- Status: Recruiting (Last Update: 04/2022)

3.3.8 AAV8-RPGR (BIIB-112, Biogen)

Development/Regulatory Status:

Entwicklung vorerst abgebrochen?

- 10/2021: Biogen has suspended further development of BIIB-112 as part of its strategic review process and it is no longer listed in its pipe-line; consider development (at least for now) is discontinued [57]. The experimental treatment, BIIB112, did not show significant improvement in a mid-to-late stage study in retinal sensitivity in patients with X-linked retinitis pigmentosa [58].
- AAV-RPGR has received Fast Track (Apr 2018) and Orphan Drug Designations from the FDA (Apr 2019) and PRIME, ATMP (Feb 2020) and Orphan Medicinal Product Designations from the EMA (Feb 2018).
- Phase 1/2 data from the dose-escalation portion of the XIRIUS trial for NSR-RPGR demonstrated an increase in central retinal sensitivity. The phase 2/3 dose-expansion portion of the XIRIUS trial is currently ongoing.

Proposed Indication and Patients in Austria: see AIHTA Report 2020 [4].

Technology:

AAV-Vektor

- AAV-RPGR is comprised of an AAV vector administered by subretinal injection which provides a functioning RPGR gene and thus an expression of the RPGR protein, which is critical for protein transport in photoreceptors. The restoration of photoreceptor function is intended to slow, stop or potentially reverse the decline in vision.

Approval Status:

- Not approved by EMA/FDA

1 Phase 3 Studie

Clinical investigations:

NCT03584165 (Phase 3, US/Canada/EU/UK, 440 Pts., 06/2018-03/2027)

- Non-randomized, multi-center outcomes-assessor masked, long-term follow-up study to evaluate the safety and efficacy of retinal gene therapy in subjects with choroideremia previously treated with adeno-associated viral vector encoding rab escort protein-1 (AAV2-REP1) and in subjects with x-linked retinitis pigmentosa previously treated with adeno-associated viral vector encoding RPGR (AAV8-RPGR) in an antecedent study.
- Status: Enrolling by invitation (Last Update: 04/2022)

3.3.9 AGTC-501 (Iaruparetigene zosaparvovec, rAAV2tYF -- hRPGRco)

Development/Regulatory Status:

in Entwicklung ODD seit 2016

Retinitis pigmentosa

- AGTC-501 is a recombinant AAV vector-based gene therapy for the treatment of X-linked retinitis pigmentosa in development. AGTC was granted FDA orphan drug designation in 2017, as well as European orphan medicinal product designation in 2016, for its gene

therapy product candidate to treat XLRP caused by mutations in the RPGR gene [59].

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

- AGTC-501 (laruparetigene zosaparvovec) uses an engineered AAV vector to insert a stabilized and functional copy of the Retinitis Pigmentosa GTSase Regulator (RPGR) gene into a patient's photoreceptor cells. AGTC-501 is comprised of that stabilized RPGR gene and a promoter that was specifically selected due to its ability to drive efficient gene expression in rods and cones, maintain photoreceptor function and delay disease progression in large animal, naturally occurring preclinical models of XLRP [48, 60].

AAV Vektor

Approval Status:

- Not approved by EMA/FDA

Clinical investigations:

1 Phase 3 Studie

NCT04850118 (Phase 3, 63 Pts., 08/2021-01/2024)

- Randomized, controlled, masked, multi-center study to evaluate the efficacy, safety and tolerability of two doses of AGTC-501, a recombinant adeno-associated virus vector expressing RPGR (rAAV2tYF-GRK1-RPGR), compared to an untreated control group in male subjects with X-linked retinitis pigmentosa confirmed by a pathogenic variant in the RPGR gene.
- Status: Not yet recruiting (Last Update: 05/2021)

3.3.10 AAV – CNGB3 (entacingene turiparvovec) (MEIRAGT)

Development/Regulatory Status:

- AAV - CNGB3 is currently under development.
- AAV - CNGB3 was granted Orphan Drug status by FDA and EMA and received Fast Track Status by FDA and PRIME status by EMA (2018).
- Data for filing not expected before 2024 [61].

derzeit in Entwicklung
PRIME 2018

Achromatopsie oder Achromasie

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

- AAV - CNGB3 is an AAV gene therapy, designed to rescue retinal cone cell function and increase survival by delivering a codon-optimised CNGB 3 cDNA under the control of the cone arrestin (CAR) promoter to photoreceptor cells.

AAV Vektor

Approval Status:

- Not approved by EMA/FDA

Clinical investigations:

keine Phase 3 Studie

- No Phase 3 studies

3.3.11 AGTC-402 (ACHM CNGA3, rAAV2tYF - PR.1-hCNGA3 (applied genetic technologies)

Development/Regulatory Status:

derzeit in Entwicklung Phase 1/2

- ACHM CNGA3 is a drug under development.
- ACHM CNGA3 was granted Orphan Drug Designation in the U.S. (Aug 2018) and EU (Jun 2018) [62].
- ACHM CNGA3 is being developed in phase 1/2 clinical trials at the moment. [63]

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

AAV Vektor

- ACHM CNGA3 is an AAV gene therapy meaning that the virus infects patient cells to deliver a healthy copy of a gene so that it will be properly expressed, thereby curing the disease.[63]

Approval Status:

- Not approved by EMA/FDA

keine Phase 3 Studie

Clinical investigations:

- No Phase 3 studies

3.4 Musculoskeletal disorders

Table 3-4: Muscular dystrophy therapies under development

Indication	Product	Sponsor	Development/ Regulatory status	Phase; Study-ID: primary completion date, location(s)
Duchenne Muscular Dystrophy (DMD)	SRP-9001 (Delandistrogene moxeparvovec, AAVrh74.MHCK7)	Sarepta	FDA: ODD, FTD (2020) EMA: ODD (2020) 12:2019: Roche to pay Sarepta $1B upfront for DMD gene therapy rights [64]. 04/2022: Roche now plans to file in EU & US in 2024 [65]	New study: Phase 3: NCT05096221 (Recruiting, 10/2023, US/Spain)
Duchenne Muscular Dystrophy (DMD)	PF-06939926 (Fordadistrogene movaparvovec)	Pfizer	FDA: ODD (2017), FTD EMA: ODD (2016) [66]	Phase 3: NCT04281485 (Active, not recruiting, 09/2023, Canada/EU/Israel/Japan/Korea/ Russia/Switzerland/ Taiwan/UK)

Abbreviations: EMA=European Medicines Agency, EPCD=Estimated Primary Completion Date, FDA= US Food and Drug Administration, FTD = Fast Track Designation, ODD= Orphan Drug Designation

3.4.1 SRP-9001 (Delandistrogene moxeparvovec, AAVrh74.MHCK7) (Sarepta)

Development/Regulatory Status:

- SRP-9001 is a treatment against Duchenne muscular dystrophy (DMD) under development.
- SRP-9001 was granted Orphan Drug Designation by EMA and FDA (2020) and Fast Track Designation by FDA (2020).
- In the open-label phase 1/2a trial, known as Study 101, four ambulatory participants between the ages of four and seven were treated with an infusion of SRP-9001. A phase 3 study is running since October 2021.

derzeit in Entwicklung
ODD seit 2020

Duchenne-Muskeldystrophie

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4]

Technology:

- SRP-9001 is an investigational gene transfer therapy intended to deliver its micro-dystrophin-encoding gene to muscle tissue for the targeted production of micro-dystrophin protein. It is a recombinant AVV carrying a truncated "micro" dystrophin transgene under control of a muscle-specific MCK promoter.

AAV Vektor

Approval Status:

- Not approved by EMA/FDA

Clinical investigations:

1 Phase 3 Studie

NCT05096221 (**EMBARK**, Phase 3, US/Spain, 120 Pts., 10/2021-10/2023)

- Multinational, randomized, double-blind, placebo-controlled systemic gene delivery study to evaluate the safety and efficacy of SRP-9001 in patients with Duchenne Muscular Dystrophy (EMBARK)
- Status: Recruiting (Last Update: 04/2022)

3.4.2 PF-06939926 (Fordadistrogene movaparvovec) (Pfizer)

Development/Regulatory Status:

- PF-06939926 is a treatment against DMD under development.
- PF-06939926 was granted Orphan Drug Designation by EMA (2016) and by FDA (2017). PF-06939926 received FDA's Fast Track designation in 2020[66].
- Updated efficacy and adverse events data from a phase 1b trial in treat DMD was released: a global phase 3 started in May 2020. [67]

derzeit in Entwicklung
ODD seit 2016

Duchenne-Muskeldystrophie

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

- PF-06939926 is an investigational, recombinant AAV9 capsid carrying a shortened version of the human dystrophin gene (mini-dystrophin) under the control of a human muscle specific promotor.

AAV Vektor

The AAV9 capsid was chosen as the delivery vector because of its potential to target muscle tissue. [67]

Approval Status:

- Not approved by EMA/FDA

1 Phase 3 Studie

Clinical investigations:

NCT04281485 (Phase 3, 99 Pts., Canada/EU/Israel/Japan/Korea/Russia/Switzerland/Taiwan/UK, 11/2020-09/2023)

- Multicenter, randomized, double-blind, placebo controlled study to evaluate the safety and efficacy of PF 06939926 for the treatment of duchenne muscular dystrophy
- Status: Active, not recruiting (Last Update: 03/2022)

3.5 Vascular disorders

Table 3-5: Cardiovascular disease therapies under development

Indication	Product	Sponsor	Development/ Regulatory status	Phase; Study-ID: primary completion date, location(s)
Acute Myocardial Infarction (AMI) Painful diabetic peripheral neuropathies (PDPN)	Engensis (Dona-perminogene seltoplasmid, VM202RY)	Helixmith	FDA: RMAT (2018) EMA: -	Phase 3: NCT04469270 (Recruiting, 12/2022, US) Phase 3: NCT04873232 (Recruiting, 03/2022, US)
Atherosclerotic Cardiovascular Disease	AMG 890 (Olpasiran)	Amgen	FDA: FTD (2020) [68] EMA: -	No Phase 3 studies
Critical Limb Ischemia (CLI) in Diabetes Mellitus (DM) (Type 1+2)	REX-001, Rexmyelocel T	Ixaca (formerly Rexgenero)	FDA: - EMA: ATMP (2015) [69]	NEW study (but terminated) Phase 3: NCT03174522 (Recruiting, 04/2022, EU/UK) Phase 3: NCT03111238 (Terminated, 03/2021, EU)
Arterial Occlusive Disease Ischemia Ulcers Peripheral Vascular Disease	NL003	Viromed/ Beijing Northland Biotech. Co., Ltd.	FDA: - EMA: -	Phase 3: NCT04275323 (NL003-CLI-III-1, Recruiting, 10/2023, China) Phase 3: NCT04274049 (NL003-CLI-III-2, Recruiting, 10/2023, China)

Abbreviations: AMI= Acute Myocardial Infarction, ATMP= Advanced Therapy Medicinal Product, EMA=European Medicines Agency, EPCD=Estimated Primary Completion Date, FDA= US Food and Drug Administration, FH=familial hypercholesterolemia, PDPN= Painful Diabetic Peripheral Neuropathy, RMAT = Regenerative Medicine Advanced Therapy

3.5.1 Donaperminogene seltoplasmid (Engensis, VM202RY) (Helixmith)

Development/Regulatory Status:

- Donaperminogene seltoplasmid for painful diabetic peripheral neuropathies (PDPN) and acute myocardial infarction (AMI) is under development.

derzeit in Entwicklung Phase 3 für PDNP Phase 2 AMI

- Donaperminogene seltoplasmid was granted Regenerative Medicine Advanced Therapy (RMAT) Designation in the U.S. (May 2018), but not by the EMA.

Status unklar

- Currently under development in a phase 3 extension study (DPN 3-1b) for painful diabetic peripheral neuropathies (PDPN). Though the trial is completed, no publications are available. Currently two phase 3 trials are running.

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4]

Technology:

- Donaperminogene seltoplasmid (VM202) is a first-in-class non-viral plasmid DNA gene therapy which aims to restore blood flow to affected areas through regenerative angiogenesis. It aids the formation of new microvasculature and re-myelination and regeneration of damaged nerves. Donaperminogene seltoplasmid is a DNA-based drug, consisting of a plasmid DNA vector encoding modified hepatocyte growth factor (HGF) that is designed to produce two isoforms of HGF, HGF728 and HGF723. When VM202 is delivered to the affected area by a single intramuscular injection, the drug enters a small portion of the surrounding muscle cells.

DNA-Vektor

Approval Status:

- Not approved by EMA/FDA

Clinical investigations:

2 Phase 3 Studien

NCT04469270 (**REGAiN-1A**, Phase 3, US, 152 Pts., 10/2020-12/2022)

- Adaptive, double-blind, randomized, placebo-controlled, multicenter study to assess the safety and efficacy of Engensis in participants with painful diabetic peripheral neuropathy.
- Status: Recruiting (Last Update: 11/2021)

NCT04873232 (Phase 3, US, 250 Pts., 05/2021-03/2022)

- A 6-Month extension study following protocol VMDN-003-2 - an adaptive, phase 3, double-blind, randomized, placebo-controlled, multicenter study to assess Engensis in participants with painful diabetic peripheral neuropathy.
- Status: Recruiting (Last Update: 02/2022)

3.5.3 AMG-890 (olparisan) (Amgen)

Development/Regulatory Status:

derzeit in früher Entwicklung Beginn Phase 2

- AMG-890 is a drug for patients with atherosclerotic cardiovascular disease and elevated Lipoprotein under early development. Fast Track designation (FTD) was granted by FDA in 2020 [68].
- A phase 2 trial starts in August 2020

atherosklerotische Herz-Kreislauf-Erkrankung

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

RNA Interferenz (RNAi)

- AMG 890 is a small interfering RNA (siRNA) that lowers lipoprotein(a), also known as Lp(a).

Approval Status:

- Not approved by EMA/FDA

keine Phase 3 Studien

Clinical investigations:

- No phase 3 studies.

3.5.4 Rexmyelocel T (REX-001) (ixaca, formerly Rexgenero)

Development/Regulatory Status:

Entwicklung abgebrochen?

- Rexmyelocel T is a treatment under development.
- Rexmyelocel T is classified as a tissue-engineered product (ATMP) by the EMA (2015).

tissue engineered product

periphere Ischämie

- Rexmyelocel T, is currently in phase 3 clinical trials as a treatment for Critical limb ischaemia (CLI) in patients with diabetes mellitus (DM) and ischemic ulcers (CLI Rutherford category 5) who are unsuitable for endovascular or surgical vascularisation as well as treatment for ischemic rest pain in patients with CLI Rutherford category 4. One phase 3 trial was terminated due to inactivity [70].

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

autologe Stammzellentherapie

- Rexmyelocel T (REX 001), an autologous bone marrow-derived stem cell therapy, for the treatment of peripheral ischaemia: REX-001 is a novel cell therapy that consists of autologous bone marrow-derived mononuclear cells (BM-MNCs) which, following administration to CLI patients, migrate to the ischaemic tissue.

Approval Status:

- Not approved by EMA/FDA

2 Phase 3 Studien

Clinical investigations:

NCT03174522 (Phase 3, EU/UK, 78 Pts., 04/2017-04/2022)

- Randomized, pivotal, placebo-controlled, double-blind, parallel-group, adaptive trial assessing the efficacy and safety of intra-arterial administration of REX-001 to treat ischemic ulcers in sub-

jects with critical limb ischemia (CLI) Rutherford Category 5 and diabetes mellitus (DM).

- Status: Recruiting (Last Update: 05/2021)

NCT03111238 (Terminated, Phase 3, EU, 3 Pts. 04/2017-03/2021,)

- Randomized, pivotal, placebo-controlled, double-blind, parallel-group, adaptive trial asssessing efficacy and safety of intra-arterial administration of REX-001 to treat ischemic rest pain in subjects with critical limb ischemia (CLI) Rutherford Category 4 and diabetes mellitus (DM).
- Status: Terminated (Last Update: 05/2021)

3.6 Nephrological disorders

Table 3-6: Kidney disorder therapies under development

Indication	Product	Sponsor	Development/ regulatory status	Phase; Study-ID: primary completion date, location(s)
aHUS, IgA Nephropathy, glomerulonephritis	Cemdisiran (ALN-CC5)	Alnylam	EMA: ODD (2021) [71] FDA: -	No Phase 3 studies (only as combination therapy); as combination therapy: Phase 3 NCT05131204, NCT05133531

Abbreviations: BTD= Breakthrough Therapy, EMA=European Medicines Agency, EPCD=Estimated Primary Completion Date, FDA=US Food and Drug Administration, PRIME= PRIority Medicines

3.6.1 Cemdisiran (ALN-CC5) (Alnylam)

Development/Regulatory Status:

- Cemdisiran is a drug under development for atypical hemolytic uremic syndrome (aHUS) and glomerulonephritis.
- A Phase 2 clinical trial in Paroxysmal nocturnal haemoglobinuria has started in 2020, then suspended. A Phase 3 Combination of Pozelimab and Cemdisiran Versus Continued Eculizumab or Ravulizumab is recruiting.

RNA Interferenz (RNAi)

atypisches hämolytisch urämisches Syndrom aHUS

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

- Cemdisiran has been designed to reduce the level of C5 mRNA in the liver. Cemdisiran (ALN-CC5) is a subcutaneously administered, RNAi (interference) therapeutic targeting the C5 component of the complement pathway in development for the treatment of complement-mediated diseases. Cemdisiran utilizes the Enhanced Stabilization Chemistry (ESC)-GalNAc delivery platform developed by Alnylam to enables subcutaneous dosing with increased potency and durability.

RNA Interferenz (RNAi)

Approval Status:

- Not approved by EMA/FDA

2 Phase 3 Studien: Kombnationstherapie

Clinical investigations:

NCT05131204 (**ACCESS-2**, Phase 3, US, 140 Pts., 03/2022 – 06/2025)

- Randomized, open-label, eculizumab and ravulizumab controlled study to evaluate the efficacy and safety of pozelimab and cemdisiran combination therapy in patients with paroxysmal nocturnal hemoglobinuria who are currently treated with eculizumab or ravulizumab
- Status: Recruiting (Last Update: 02/2022)

NCT05133531 (**ACCESS-1**, Phase 3, US, 124 Pts., 07/2022 – 05/2026)

- Randomized, open-label, ravulizumab-controlled study to evaluate the efficacy and safety of pozelimab and cemdisiran combination therapy in patients with paroxysmal nocturnal hemoglobinuria who are complement inhibitor treatment-naive or have not recently received complement inhibitor therapy
- Status: Recruiting (Last Update: 05/2022)

3.7 Dermatologic disorders

Table 3-7: Dermatologic disorder therapies under development

Indication	Product	Sponsor	Development/ regulatory status	Phase; Study-ID: primary completion date, location(s)
Epidermolysis bullosa	Beremagene geperpavec (B-VEC, Vyjuvek®, Bercolagene telserpavec)	Krystal Biotech	FDA: PDD (2016), ODD (2017), FTD (2018), RMAT (2019), EMA: ODD (2018), PRIME (2019) EMA/FDA: Application for market approval expected in 2022 [72]	Phase 3: NCT04491604 (Active, not recruiting, 09/2021, US) Phase 3: NCT04917874 (Recruiting, 12/2022, US)
Epidermolysis bullosa	EB-101	Abeona	FDA: ODD (2017), PDD (2020), RMAT (2020), FTD (2021) EMA: ODD (2017) [73]	Phase 3: NCT04227106 (Recruiting, 03/2022, US)
Epidermolysis bullosa	FCX-007	Fibrocell	FDA: ODD, PDD (2015), FTD (2017), RMAT (2019) EMA : -	Phase 3: NCT04213261 (Recruiting, 04/2023, US)
Burns	denovoSkin™ (EHSG-KF STSG)	University of Zurich/ Cutiss AG	FDA: ODD EMA: ODD EMA: Application for market approval in 2022 [74, 75]	Phase 2/3: NCT03229564 (Recruiting, 12/2022, Italy/Netherlands/CH) Phase 2/3: NCT03227146 (Recruiting, 01/2022, Italy /Netherlands/CH)

Abbreviations: EMA=European Medicines Agency, FDA=US Food and Drug Administration, EPCD=Estimated Primary Completion Date, FTD= Fast Track Designation, ODD= Orphan Drug Designation, PDD= Paediatric Disease Designation, RMAT=Regenerative Medicine Advanced Therapy

3.7.1 Beremagene geperpavec (B-VEC, Vyjuvek®, (Krystal Biotech)

Development/Regulatory Status:

in Entwicklung

- Beremagene geperpavec is a gene therapy delivers currently in development for the treatment of Dystrophic Epidermolysis Bullosa DEB)
- Currently there are two Phase 3 studies running in the US with results expected in 2022.

Epidermolysis bullosa

„Schmetterlingskinder“

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

COL7A1-Gen zur Zellteilung

- Beremagene geperpavec gene therapy delivers the functional COL7A1 gene directly to dividing and non-dividing skin cells.
- Beremagene geperpavec, made into a topical gel formulation to be applied to the skin, transduces keratinocytes and fibroblasts. After entering the cell nucleus, the vector genome is episomally deposited. Next, COL7A1 transcripts are generated, allowing the cells to produce and secrete the functional protein COL7. The latter assembles into anchoring fibrils that hold the epidermis and dermis together.
- Beremagene geperpavec is built on the proprietary Skin TARgeted Delivery (STAR-D) gene therapy platform, which carries out viral vector transfer of copies of working genes based on herpes simplex virus type 1 (HSV-1) for the treatment of dermatological diseases. The HSV-1 used has no replication capability, is not capable of being inserted into the human genome, and allows multiple administrations into the body [76].

Approval Status:

- Not approved by EMA/FDA

Clinical investigations:

2 Phase 3 Studien

NCT04491604 (Phase 3, US, 31 Pts., 08/2020-09/2021)

- Randomiezd, double blinded, placebo-controlled, efficacy and safety study of Beremagene Geperpavec (B-VEC, Previously "KB103") for the treatment of Dystrophic Epidermolysis Bullosa (DEB)
- Status: Active, not recruiting (Last Update: 09/2021)

NCT04917874 (Phase 3, US, 30 Pts., 05/2021-12/2022)

- Open-label, long-term single-arm, extension study of Beremagene Geperpavec (B-VEC), for participants aged 6 months and older, who have been diagnosed with Dystrophic Epidermolysis Bullosa (DEB).
- Status: Recruiting (Last Update: 06/2021)

3.7.3 EB-101 (Abeona)

Development/Regulatory Status:

derzeit in Entwicklung
ODD seit 2017
Epidermolysis bullosa „Schmetterlingskinder“

- EB-101 is a treatment under development for recessive dystrophic Epidermolysis bullosa (RDEB).
- EB-101 was granted Orphan Drug Designation by FDA (May 2017) and by EMA (Feb 2017). FDA also granted Paediatric Disease Designation (PDD) and Regenerative Medicine Advanced Therapy (RMAT) in 2020 and Fast Track Designation (FTD) in 2021.
- Updated efficacy data from a phase 1/2a trial in Epidermolysis bullosa was released in July 2020. The phase 3 (VIITAL) trial in RDEB (adolescents, adults, children, elderly) started in January 2020.

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

autologe Zelltherapie

- EB-101 is an autologous gene-corrected cell therapy for RDEB. EB-101 has been designed to deliver the corrected version of this gene to patients' skin cells cultured in a lab dish. These cells are then transplanted back to the patients so that their skin regains the ability to generate COL7. EB-101 Cell Therapy aims at continuous production of COL7 in skin cells.

Approval Status:

- Not approved by EMA/FDA

1 Phase 3 Studie

Clinical investigations:

NCT04227106 (**VIITA**L, Phase 3, US, 15 Pts., 01/2020-03/2022)

- Open-label, single-arm study of EB-101 for the treatment of recessive dystrophic epidermolysis bullosa (RDEB).
- Status: Recruiting (Last Update: 04/2022)

3.7.4 FCX-007 (Fibrocell)

Development/Regulatory Status:

derzeit in Entwicklung
Phase 3

Epidermolysis bullosa

„Schmetterlingskinder“

- FCX-007 is a treatment under development for Recessive Dystrophic Epidermolysis Bullosa
- FCX-007 was granted Orphan Drug Designation, Fast Track and Paediatric Disease Designation by FDA (2017).
- Efficacy data from a phase 1/2 trial in RDEB was released in January 2020. A Phase 3 study of FCX-007 for the treatment of persistent non-healing wounds in approximately 20 RDEB subjects started.

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

autologe Zelltherapie

- FCX 007 is an autologous dermal fibroblast genetically modified to express functional type VII collagen (COL7). For FCX-007 skin cells (fibroblasts) are collected from a patient, then modifies them. The

alteration involves using a healthy gene to supersede the defective one that produces faulty COL7 protein.

Approval Status:

- Not approved by EMA/FDA

Clinical investigations:

1 Phase 3 Studie

NCT04213261 (Phase 3, US, 24 Pts., 06/2020-04/2023)

- A pivotal, randomized, intra-patient, controlled, open-label, multi-center study of FCX-007 for recessive dystrophic epidermolysis bullosa.
- Status: Recruiting (Last Update: 12/2021)

3.7.5 Denovoskin™ (Cutiss)

Development/Regulatory Status:

- DenovoSkin™ holds Orphan Drug Designation (ODD) by FDA and EMA.

In Entwicklung
ODD

Technology:

- To bio-engineer denovoSkin™, a small biopsy of healthy skin is harvested from the patient. The biopsy is processed to isolate epidermal and dermal cells. The cells are expanded in vitro, and thereafter used in combination with a hydrogel to create a dermo-epidermal skin graft. denovoSkin™ is now ready to be transplanted on the patient's wounds. The safety trials for denovoSkin™ have been completed. The efficacy trials are currently being conducted at various hospitals in Switzerland and the EU and are supported by Wyss Zurich [77].

Transplantat menschlicher Haut

Approval Status:

- Not approved by EMA/FDA
- Positive Opinion from the Paediatric Committee of the European Medicines Agency (EMA) (2020) [75]

Clinical investigations:

2 Phase 2/3 Studien

NCT03229564 (Phase 2/3, Italy/Netherlands/CH, 12 Pts., 10/2017-12/2022)

- A single-arm, open-label, prospective, intra-patient randomised controlled, multicentre study to evaluate the safety and efficacy of an autologous bio-engineered dermo-epidermal skin substitute (EHSG-KF) for the treatment of partial deep dermal and full thickness burns in children in comparison to autologous split-thickness skin grafts (STSG).
- Status: Recruiting (Last Update 09/2021)

NCT03227146 (Phase 2/3, Italy/Netherlands/CH, 12 Pts., 10/2017-01/2022)

- A single arm, open-label, prospective, intra-patient randomised controlled, multicentre study to evaluate the safety and efficacy of an autologous bio-engineered dermo-epidermal skin substitute (EHSG-KF) for the treatment of partial deep dermal and full thickness burns in adults and adolescents in comparison to autologous split-thickness skin grafts (STSG).

- Status: Recruiting (Last Update: 09/2021)

3.8 Neurologic disorders

Table 3-8: Neurologic disorder therapies under development

Indication	Product	Sponsor	Regulatory/ development status	Phase; Study-ID: primary completion date, location(s)
Huntington Disease	Tominersen (RG-6042)	Roche	FDA: ODD (2016), EMA: ODD (2016), PRIME (2018) 01/2022: Roche is designing a new Phase 2 trial of Tominersen in Huntington Disease [78].	Phase 3: NCT03761849 (Active, not recruiting, 03/2022, US/Australia/Argentina/Canada/EU/Chile/Japan/ New Zeland/Russia/ Switzerland/UK) Phase 3: NCT03842969 (Active, not recruiting, 03/2022, US/Australia/Canada/EU/UK)
Parkinson's Disease	VY-AADC02	Voyager Therapeutics/ Neurocrine Biosciences	FDA: - EMA: - 02/2021: VY-AADC Parkinson Disease Gene Therapy Program Terminated [79]	No Phase 3 studies
Acute Traumatic Spinal Cord Injury	NeuroSave (FAB117-HC)	Ferrer	FDA: - EMA: -	No Phase 3 studies

Abbreviations: EMA=European Medicines Agency, FDA=US Food and Drug Administration, EPCD=Estimated Primary Completion Date, ODD= Orphan Drug Designation, PRIME = PRIority Medicines

3.8.1 Tominersen (RG-6042) (Roche)

Development/Regulatory Status:

Entwicklung abgebrochen

PRIME seit 2018

Chorea Huntington

- Tominersen is a treatment under development for Huntington disease (HD).
- Tominersen was granted Orphan Drug Designation by the FDA (2016) and by EMA as well as PRIME status by EMA (2018).
- An exploratory phase 1/2a trial was released and a phase 3 trial is ongoing. The trial is fully enrolled, with data expected in 2022.
- In March 2021 Roche announces that it will discontinue the study. This decision was based on results of a pre-planned review of the data conducted by an unblinded Independent Data Monitoring Committee [80]. In 01/2022 a new Phase 2 study is planned.

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

- RG6042 is a second-generation modified antisense oligonucleotide (ASO) designed to reduce the production and levels of mHTT protein by targeting human HTT mRNA. Mutant huntingtin protein (mHTT), which is believed to be the underlying cause of HD.

Antisense-Oligonukleotide zur gezielten Hemmung krankheitsfördernder Proteine

Approval Status:

- Not approved by EMA/FDA

Clinical investigations:

2 Phase 3 Studien

NCT03761849 (Phase 3, US/Australia/Argentina/Canada/EU/Chile/Japan/New Zealand/Russia/Switzerland/UK, 791 Pts., 01/2019 - 03/2022)

- Randomized, multicenter, double-blind, placebo-controlled clinical study to evaluate the efficacy and safety of intrathecally administered RO7234292 (RG6042) in patients with manifest Huntington's Disease.
- Status: Active, not recruiting (Last Update: 03/2022)

NCT03842969 (Phase 3, US/Australia/Canada/EU/UK, 236 Pts., 04/2019 - 03/2022)

- Randomized, open-label extension study to evaluate the long-term safety and tolerability of intrathecally administered RO7234292 (RG6042) in patients with Huntington's Disease.
- Status: Active, not recruiting (Last Update: 03/2022)

3.8.2 VY-AADC02 (Neurocrine Biosciences)

Development/Regulatory Status:

- VY-AADC02 is a treatment under development for Parkinson's disease. Neurocrine Biosciences provided notice of ter ıination of the Parkinson’s disease investigation in August 2021[81].

Entwicklung abgebrochen

FDA/EMA status is not available.

Planung Phase 3

- Neurocrine has placed a clinical hold on the RESTORE-1 clinical trial of NBIb-1817 (VY-AADC) due to abnormalities observed in trial participants.

Parkinson

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

- VY-AADC uses the AAV2 capsid as a vector encoding AADC; expression is driven by a cytomegalovirus promoter. VY-AADC attempts to supply transgenic L-amino acid decarboxylase (AADC), the enzyme that converts levodopa to dopamine, directly into the putamen area of the brain. The treatment rationale is that local expression of transgenic AADC will boost dopamine levels in the putamen, reducing motor "off" time and prolonging "on" time for the patient.

AAV Vektor

Approval Status:

- Not approved by EMA/FDA

Clinical investigations:

keine Phase 3 Studien

- No Phase 3 studies.

3.8.3 Neurosave (FAB117-HC) (Ferrer)

Development/Regulatory Status:

derzeit in Entwicklung laufende Phase 1/2

- FAB117-HC (NeuroSave) is a drug under development for acute traumatic spinal cord injury (SCI).
- A Phase1/2 (NCT02917291) trial is ongoing. The status is recruiting (09/21).

akute Verletzung von Wirbelsäule und Rückenmark

Proposed Indication, condition and patients in Austria: see AIHTA Report 2020 [4].

Technology:

allogene Stammzellentherapie

- FAB117-HC is allogeneic cell therapy for the acute treatment of traumatic spinal cord injuries, whose active substance is HC016, allogeneic adipose-derived adult mesenchymal stem cells expanded and pulsed with H2O2 [82]. HC016 cells modulate the inflammatory process by releasing specific enzymes and growth factors. FAB-117 reduces neuronal death in the first few days after injury and so aims to improve the patient´s long-term condition, significantly reducing levels of dependence. AP-117 may also be useful in traumatic brain injury and other non-cancer spinal cord conditions [83].

Approval Status:

- Not approved by EMA/FDA

keine Phase 3 Studien

Clinical investigations:

- No Phase 3 studies

4 Discussion

4.1 Summary of findings

2008 ATMP Verordnung
2018: 8 ATMPs
2020: 11 ATMPs
2022: 17 ATMPs (ohne CAR-T Zelltehrapien)
insg. 35 Therapien identifiziert in 8 Indikationsfeldern

derzeit 5 ATMPs nahe einer Zulassung

On 30 December 2008, the Regulation (EC) No. 1394/2007 amending Directive 2001/83/EC on Advanced Therapy Medicinal Products entered into force and the first EU wide regulatory framework for ATMPs was established [1]. This framework changed the code of regulatory practices, as a central marketing authorisation issued by the EMA was required from now on.

Ten years later, in August 2018 eight ATMPs, and two years later in August 2020 eleven ATMPs were approved and three were under evaluation by the EMA. In 2022 17 ATMPs (excluding CAR-T cell therapies and other therapies for oncological indications) have been approved. This Update of the 2020 report identified further 34 ATMPs of which five are expected to be approved in 2022 and 2023.

Additional, our search identified 25 further ATMPs and gene therapies (CAR-T cell therapies and oncological indications excluded) in late-stage development (phase 2 or 3 trials), which will reach the market in the years to come.

The main indication areas are (see Figure 4-1):

- Haemophilia (5 ATMPs in development or before approval)
- Muscular dystrophy (2 ATMPs)
- Ophtalmogical Indications (Retinits Pigmentosa -3 ATMPs- and Leber Hereditary Optic Neuopathy- 2 ATMPs)
- Epidermolysis bullosa (3 ATMPs)

Figure 4-1: Most common targets in non-oncology indications [2]

On the other hand in some areas of public health needs there is little development and the effort seems to be discontinued in three indications

- Choroideremia Timrepigene emparvovec (AAV2-REP1, BIIB111)
- Chorea Huntington (TOMINERSEN (RG-6042)
- Parkinson´s disease (VY-AADC02).

4.2 Real World evidence

oft als kurative Therapien bezeichnet trotzdem keine Langzeit Daten vorliegen

Datensammlungen (RWE) sollen Gewissheit bringen

There are numerous challenges in the development and the evaluation of these therapies. They have received advance praise and are often referred to as “curative” or “disruptive” technologies, though hardly any longterm data are available for the few therapies already approved. The challenge now is that the potential promise of gene therapies have to live up with the expectations and it is the role of HTA to observe closely the true effectiveness of the respective therapies. The establishement of data collections for monitoring the long term effects of those therapies in the real world setting has become a prominent topic [84].

4.3 Limitations

Limitationen der Suchstrategien: nur in 2 Registern, aber unwahrscheinlich, dass nicht in EudraCT registriert

There are limitations to the applied searches: Firstly, search and extractions were based on the search terms ATMP and gene therapies. The searches were conducted in one database (clinicaltrials.gov) controlled for duplications by a search in another trials registry (EudraCT). We might have missed studies registered in the International Clinical Trials Registry Platform (ICTRP). Since all therapies approved in Europe must be registered in EudraCT the missed studies will be a minority.

aber: wesentliche Limitation Suchbegriffe

Secondly, as our search covered ATMPs and gene therapies, all trials investigating technologies not registered as ATMP or gene therapies, but targeting the functioning of genes, such as enzymes and proteins, might be missed.

4.4 Outlook

HSS nur in nationaler und/oder internationaler Kooperation möglich

This exercise was carried out in collaboration with “Tirol Kliniken GmbH” to scan the Horizon for new and eventually cost-intensive CAR-T [85] and ATMPs/gene therapies. This small scale HSS only represents a “snapshot in time” of new and emerging technologies and is not and cannot be as reliable as international initiatives and their systematic and permanent activities: Horizon Scanning is time-consuming and inefficient as a one-time activity!

Österreich beteiligt sich an IHSI

By mid 2022 Austria will join the International Horizon Scanning Initiative (IHSI) representing a huge step forward in the effort of early identification of new therapies that might have health and budget impact in the future.

Table 4-1: Most advanced ATMP therapies close to aproval

Indication	Product	Sponsor	Development/ regulatory status	Phase; Study-ID: primary completion date, location(s)
Haemophilia A	Valoctocogene roxaparvovec (BMN-270, Valrox, Roctavian)	BioMarin	FDA: ODD (2016), BTT (2017), FDA: rejected (8/2020), FDA: RMAT (2021) FDA/EMA: Delayed decision until results of NCT03370913 (2022) EMA: Withdrawn MAA, ODD (2016), PRIME (2017) BioMarin plans to resubmit to FDA in June, followed by an expected six-month review [8]	Phase 3: NCT03392974 (Active, not recruiting, 05/2019, US) Phase 3: NCT03370913 (Active, not recruiting, 11/2020, US/Australia/Brazil/EU/Israel/Korea/South Africa/Taiwan/UK) Phase 3: NCT04323098 (Active, not recruiting, 01/2023, US/Australia/Brazil/Taiwan)
Haemophilia B	Etranacogene dezaparvovec (AMT-06, AAV5-hFIXco-Padua, CSL222, EtranaDez , previously known as AMT-061)	UniQure/CSL	FDA: ODD, FTD (2019) EMA: ODD, PRIME (2017) EMA: Accelerated CHMP Assessment (12/2021) FDA/ EMA approval expected in 2022 [9]	Phase 3: NCT03569891 (Active, not recruiting, 09/2021, US/EU/UK)
(hATTR) Amyloidosis	Vutrisiran (ALN-TTRSC02)	Alnylam	FDA: ODD (2018) FDA: FTD (2020) EMA: ODD (2018) EMA: MAA submitted (2021) [20]	Phase 3: NCT03759379 (HELIOS-A, Active, not recruiting, 11/2020, US/Australia/Canada/Argentina/Brazil/Bulgaria/EU/Japan/Korea/Malaysia/Mexico/Taiwan/UK) Phase 3: NCT04153149 (HELIOS-B, 06/2024, Active, not recruiting, US/Australia/Canada/Argentina/Brazil/Bulgaria/Colombia//EU/Israel/Japan/Korea/Lebanon/Malaysia/Mexico/Moldova/Peru/Thailand/UK)
Wiskott-Aldrich Syndrome	OTL-103 (GSK-2696275)	Orchard Therapeutics	FDA: Application expected in 2022 [30]	Phase 3: NCT03837483 (Recruiting, 07/2023, US/Italy)
Leber Hereditary Optic Neuropathy	Lenadogene nolparvovec (GS010, LUMEVOQ®)	GenSight Biologics	FDA recommends additional trial (2022) [43] FDA: ODD (2013) EMA: ODD (2011) EMA: Delay in MAA application (2022) [44]	Phase 3: NCT03293524 (Active, not recruiting, 06/2023, US/EU/Taiwan/UK) Phase 3: NCT03406104 (Active, not recruiting, 07/2022, US/EU/Taiwan/UK)
Epidermolysis bullosa	Beremagene geperpavec (B-VEC, Vyjuvek®, Bercolagene telserpavec)	Krystal Biotech	FDA: PDD (2016), ODD (2017), FTD (2018), RMAT (2019), EMA: ODD (2018), PRIME (2019) EMA/FDA: Application for market approval expected in 2022	Phase 3: NCT04491604 (Active, not recruiting, 09/2021, US) Phase 3: NCT04917874 (Recruiting, 12/2022, US)

5 References

[1] Techniker Krankenkasse. Wie bleiben Arzneimittel in Zukunft bezahlbar? 2019. Available from: https://www.tk.de/resource/blob/2058972/a8987eb00a324467763e0b91d744284b/drug-future-report-data.pdf.

[2] American Society of Gene & Cell Therapy (ASGCT)/Pharma Intelligence. Gene, Cell, & RNA Therapy Landscape. Q1 2022 Quarterly Data Report. 2022. Available from: https://pharmaintelligence.informa.com/asgct-report.

[3] Taskforce Horizon Scanning (Taskforce of the Beneluxa Initiative). Pharmaceutical Developments on Haemophilia. 2022. Available from: https://beneluxa.org/sites/beneluxa.org/files/2022-02/Haemophilia_report_DTF%20HS%20final.pdf.

[4] Austrian Institute for Health Technology Assessment (AIHTA). CAR-T Zelltherapien, ATMP- und Gentherapien in Entwicklung, Horizon Scanning: ATMPs und Gentherapien. AIHTA Policy Brief 006b. 2020. Available from: https://eprints.aihta.at/1269/.

[5] Alliance for Regenerative Medicine (ARM). Regenerative Medicine: Disrupting the Status Quo. 2021. Available from: http://alliancerm.org/wp-content/uploads/2022/03/ARM_AR2021_FINAL-singles.pdf.

[6] Austrian Institute for Health Technology Assessment (AIHTA). CAR-T Zell-Therapien in Entwicklung, Update 2022. AIHTA Policy Brief 006a/ 1. Update. 2022. Available from: https://eprints.aihta.at/1368/.

[7] uniQure N.V.: Worth A Look Based On Hemophilia B Marketing Applications. 2022. Available from: https://seekingalpha.com/article/4500489-uniqure-nv-a-biotech-worth-a-look-based-on-hemophilia-b-marketing-applications.

[8] Specialist Pharmacy Service (SPS). Valoctocogene roxaparvovec. 2022. Available from: https://www.sps.nhs.uk/medicines/valoctocogene-roxaparvovec/#:~:text=Valoctocogene%20roxaparvovec.

[9] Specialist Pharmacy Service (SPS). Etranacogene dezaparvovec. 2022. Available from: https://www.sps.nhs.uk/medicines/etranacogene-dezaparvovec/#:~:text=Etranacogene%20dezaparvovec.

[10] Positive Phase III results for fitusiran in hemophilia 2021. Available from: https://www.thepharmaletter.com/article/positive-phase-iii-results-for-fitusiran-in-hemophilia.

[11] Specialist Pharmacy Service (SPS). Giroctocogene fitelparvovec. 2022. Available from: https://www.sps.nhs.uk/medicines/giroctocogene-fitelparvovec/#:~:text=Giroctocogene%20fitelparvovec.

[12] Specialist Pharmacy Service (SPS). Fidanacogene elaparvovec. 2022. Available from: https://www.sps.nhs.uk/medicines/fidanacogene-elaparvovec/#:~:text=Fidanacogene%20elaparvovec.

[13] Freeline Therapeutics doses first subject in haemophilia B therapy trial. 2022. Available from: https://www.clinicaltrialsarena.com/news/freeline-doses-first-subject-hemophilia-b-therapy-trial/.

[14] EMA Speeds Approval Process for Hemophilia B Gene Therapy. 2022. Available from: https://hemophilianewstoday.com/2021/12/17/hemophilia-b-gene-therapy-granted-accelerated-assessment-ema/

[15] Global Hemophilia A Pipeline Insights. Clinical Trials Evaluation Research Report 2022 by DelveInsight. 2022. Available from: https://www.globenewswire.com/news-release/2022/03/29/2412245/0/en/Global-Hemophilia-A-Pipeline-Insights-Clinical-Trials-Evaluation-Research-Report-2022-by-DelveInsight.html.

[16] FDA Lifts Clinical Hold on Pfizer Hemophilia A Gene Therapy Trial. 2022. Available from: https://www.fdanews.com/articles/207688-fda-lifts-clinical-hold-on-pfizer-hemophilia-a-gene-therapy-trial

[17] Dose-confirmation Study Launched for Hem B Gene Therapy FLT180a. 2022. Available from: https://hemophilianewstoday.com/2022/03/11/freeline-launches-dose-confirmation-study-hemophilia-b-gene-therapy-flt180a/.

[18] FDA Extends Review of Vutrisiran for ATTR Amyloidosis 3 Months, Now Expected in July 2022. 2022. Available from: https://www.neurologylive.com/view/fda-extends-nda-review-vutrisiran-attr-amyloidosis-3-months-july-2022

[19] Alnylam Announces 3-Month Extension of Review Period for New Drug Application for Vutrisiran. 2022. Available from: https://www.businesswire.com/news/home/20220404005293/en/Alnylam-Announces-3-Month-Extension-of-Review-Period-for-New-Drug-Application-for-Vutrisiran.

[20] Specialist Pharmacy Service (SPS). Vutrisiran. 2022. Available from: https://www.sps.nhs.uk/medicines/vutrisiran/#:~:text=Vutrisiran.

[21] Specialist Pharmacy Service (SPS). Simoladagene autotemcel. 2022. Available from: https://www.sps.nhs.uk/medicines/simoladagene-autotemcel/#:~:text=Simoladagene%20autotemcel.

[22] Adis Insight. Simoladagene autotemcel - Orchard Therapeutics. 2022. Available from: https://adisinsight.springer.com/drugs/800048069.

[23] Lysogene Provides Update on Efficacy, Safety and Timelines of the AAVance Phase 2/3 Clinical Trial with Gene Therapy LYS-SAF302 for the Treatment of MPSIIIA. 2022. Available from: https://www.businesswire.com/news/home/20220223006276/en/Lysogene-Provides-Update-on-Efficacy-Safety-and-Timelines-of-the-AAVance-Phase-23-Clinical-Trial-with-Gene-Therapy-LYS-SAF302-for-the-Treatment-of-MPSIIIA.

[24] Specialist Pharmacy Service (SPS). Olenasufligene relduparvovec. 2022. Available from: https://www.sps.nhs.uk/medicines/olenasufligene-relduparvovec/#:~:text=Olenasufligene%20relduparvovec.

[25] Lysogene Provides Clinical Update on AAVance Phase 2/3 Clinical Trial with Gene Therapy LYS-SAF302 for the Treatment of MPS IIIA at the 25th Annual ASGCT Meeting. 2022. Available from: https://finance.yahoo.com/news/lysogene-provides-clinical-aavance-phase-060000012.html?guccounter=1&guce_referrer=aHR0cHM6Ly93d3cuZ29vZ2xlLmNvbS8&guce_referrer_sig=AQAAAHSaYqMdrbG1ZW9kNMddQlBIYHCPomR1j8yfrgSPgzMojCthwVd7W6hREeLhlby60TGFNzGiBuXkx7kMkhBbmnYuAYwqRWabEHdvcIQ2cawVHkNUuDRlkbWJmAvKyyVBhtv50F81KSA3Nq7wIDCj6kywKaMdh5u5GWJOqc0-F_Je.

[26] Specialist Pharmacy Service (SPS). ABO-101. 2022. Available from: https://www.sps.nhs.uk/medicines/abo-101/.

[27] Specialist Pharmacy Service (SPS). Rebisufligene etisparvovec. 2022. Available from: https://www.sps.nhs.uk/medicines/rebisufligene-etisparvovec/.

[28] Specialist Pharmacy Service (SPS). Pariglasgene brecaparvovec. 2022. Available from: https://www.sps.nhs.uk/medicines/pariglasgene-brecaparvovec/#:~:text=Pariglasgene%20brecaparvovec.

[29] Adis Insight. OTL 103. 2022. Available from: https://adisinsight.springer.com/drugs/800042616.

[30] Orchard Therapeutics' OTL-103 US application for immunodeficiency disorder, pushed to 2022. 2022. Available from: https://seekingalpha.com/news/3650836-orchard-therapeutics-otlminus-103-us-application-for-immunodeficiency-disorder-pushed-to-2022.

[31] Alnylam Submits Marketing Authorization Application to the European Medicines Agency for Investigational Vutrisiran for the Treatment of Hereditary ATTR Amyloidosis with Polyneuropathy. 2021. Available from: https://www.businesswire.com/news/home/20210913005174/en/Alnylam-Submits-Marketing-Authorization-Application-to-the-European-Medicines-Agency-for-Investigational-Vutrisiran-for-the-Treatment-of-Hereditary-ATTR-Amyloidosis-with-Polyneuropathy.

[32] Orchard abandons promising gene therapy for rare immune disorder 2021. Available from: https://www.biopharmadive.com/news/orchard-abandon-gene-therapy-ada-scid/601232/.

[33] Optum® Health Technology Pipeline. Simoladagene autotemcel (OTL-101). Optum® Health Technology Pipeline. 2020;17(2).

[34] Specialist Pharmacy Service (SPS). Olenasufligene relduparvovec. 2021. Available from: https://www.sps.nhs.uk/medicines/olenasufligene-relduparvovec/#:~:text=Olenasufligene%20relduparvovec.

[35] Specialist Pharmacy Service. ABO-101. 2019 [cited 15.07.2020]. Available from: https://www.sps.nhs.uk/medicines/abo-101/.

[36] Abeona Therapeutics. Abeona Therapeutics Announces Positive Interim Data from MPS III Gene Therapy Programs Presented at WORLDSymposium™. 2020 [cited 15.07.2020]. Available from: https://investors.abeonatherapeutics.com/press-releases/detail/174/abeona-therapeutics-announces-positive-interim-data-from.

[37] European Medicines Agency (EMA). EU/3/16/1771: Orphan designation for the treatment of glycogen storage disease type Ia. 2016. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3161771.

[38] Orchard Therapeutics Announces Recent Commercial and Regulatory Progress for Late-stage HSC Gene Therapy Programs and Outlines Key 2022 Milestones. 2022. Available from: https://www.biospace.com/article/releases/orchard-therapeutics-announces-recent-commercial-and-regulatory-progress-for-late-stage-hsc-gene-therapy-programs-and-outlines-key-2022-milestones/

[39] National Institute for Health and Care Research Innovation Observatory (NIHRIO). OTL-103 for Wiskott-Aldrich syndrome. Health Technology Briefing August 2020. NIHRIO ID 7993. Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/7993-OTL-103-for-Wiskott-Aldrich-Syndrome-V1.0-AUG2020-NON-CONF-2020.pdf.

[40] Specialist Pharmacy Service (SPS). Timrepigene emparvovec. 2021. Available from: https://www.sps.nhs.uk/medicines/timrepigene-emparvovec/#:~:text=Timrepigene%20emparvovec.

[41] Neurophth Therapeutics Receives IND Clearance to Initiate Clinical Trial for China AAV-ND4 Gene Therapy NR082 in Leber Hereditary Optic Neuropathy. 2022. Available from: https://www.biospace.com/article/releases/neurophth-therapeutics-receives-ind-clearance-to-initiate-clinical-trial-for-china-aav-nd4-gene-therapy-nr082-in-leber-hereditary-optic-neuropathy/.

[42] Neurophth Therapeutics' Treatment of Leber's Hereditary Optic Neuropathy Gene Therapy NR082 was Granted Orphan Drug Designation by EMA 2022. Available from: https://www.prnewswire.com/news-releases/neurophth-therapeutics-treatment-of-lebers-hereditary-optic-neuropathy-gene-therapy-nr082-was-granted-orphan-drug-designation-by-ema-301467123.html.

[43] BRIEF—FDA setback for GenSight's Lumevoq. 2022. Available from: https://www.thepharmaletter.com/in-brief/brief-fda-setback-for-gensight-s-lumevoq.

[44] Specialist Pharmacy Service (SPS). Lenadogene nolparvovec. 2022.

[45] GenSight Biologics Granted Six-Month Extension in LUMEVOQ® European Regulatory Review. 2022. Available from: https://www.gensight-biologics.com/2022/04/14/gensight-biologics-granted-six-month-extension-in-lumevoq-european-regulatory-review/.

[46] RGX-314 clinical program: second pivotal trial to begin. 2022. Available from: https://www.optometrytimes.com/view/rgx-314-clinical-program-second-pivotal-trial-to-begin.

[47] AAV5-RPGR Gene Therapy for RPGR-Associated X-Linked Retinitis Pigmentosa- Janssen (Johnson & Johnson) & MEIRAGTx 2020. Available from: https://www.medicalbiochemist.com/2020/11/aav5-rpgr-gene-therapy-for-rpgr.html.

[48] How AGTC-501 Gene Therapy Provides Vision Gains for X-Linked RP. 2022. Available from: https://ophthalmologybreakingnews.com/how-agtc-501-gene-therapy-provides-vision-gains-for-x-linked-rp.

[49] Specialist Pharmacy Service (SPS). AGTC 501. 2021.

[50] Specialist Pharmacy Service (SPS). Entacingene turiparvovec. 2021. Available from: https://www.sps.nhs.uk/medicines/entacingene-turiparvovec/#:~:text=Entacingene%20turiparvovec.

[51] Biogen's ambitions in gene therapy hit by another failed pivotal trial. 2021. Available from: https://pharmaphorum.com/news/biogens-ambitions-in-gene-therapy-are-hit-by-a-second-failed-phase-3-trial/.

[52] Biogen's inherited eye disease gene therapy misses the mark in late-stage trial. 2021. Available from: https://www.pharmatimes.com/news/biogens_inherited_eye_disease_gene_therapy_misses_the_mark_in_late-stage_trial_1371654.

[53] Timrepigene Emparvovec Fails to Demonstrate Efficacy in Choroideremia. 2021. Available from: https://www.cgtlive.com/view/timrepigene-emparvovec-fails-to-demonstrate-efficacy-choroideremia.

[54] Neurophth Therapeutics' Treatment of Leber's Hereditary Optic Neuropathy Gene Therapy NR082 was Granted Orphan Drug Designation by EMA. 2022. Available from: https://www.prnewswire.com/news-releases/neurophth-therapeutics-treatment-of-lebers-hereditary-optic-neuropathy-gene-therapy-nr082-was-granted-orphan-drug-designation-by-ema-301467123.html

[55] Specialist Pharmacy Service (SPS). RGX-314. 2022. Available from: https://www.sps.nhs.uk/medicines/rgx-314/.

[56] MeiraGTx Announces Data from Ongoing Clinical Trial of AAV-RPGR for the Treatment of X-Linked Retinitis Pigmentosa to be Presented at EURETINA 2020 Virtual Meeting. 2020. Available from: https://investors.meiragtx.com/news-releases/news-release-details/meiragtx-announces-data-ongoing-clinical-trial-aav-rpgr/.

[57] Specialist Pharmacy Service (SPS). Cotoretigene toliparvovec. 2021. Available from: https://www.sps.nhs.uk/medicines/cotoretigene-toliparvovec/#:~:text=cotoretigene%20toliparvovec.

[58] Biogen's experimental eye treatment fails to meet study goal. 2021. Available from: https://www.reuters.com/business/healthcare-pharmaceuticals/biogens-experimental-eye-treatment-fails-meet-study-goal-2021-05-14/.

[59] Aurion BioTech presents cell therapy findings with published clinical data. 2022. Available from: https://www.ophthalmologytimes.com/view/aurion-biotech-presents-cell-therapy-findings-with-published-clinical-data

[60] Applied Genetic Technologies exceeds enrollment target for SKYLINE trial of AGTC-501. 2022. Available from: https://www.ophthalmologytimes.com/view/applied-genetic-technologies-exceeds-enrollment-target-for-skyline-trial-of-agtc-501

[61] Specialist Pharmacy Service (SPS). Entacingene turiparvovec. 2021.

[62] Specialist Pharmacy Service (SPS). ACHM CNGA3. 2021. Available from: https://www.sps.nhs.uk/medicines/achm-cnga3/.

[63] AGTC Announces Robust Improvements in Visual Sensitivity in Adult and Pediatric Patients, and Plans to Continue Clinical Development of AGTC-401 in Patients with CNGB3 Achromatopsia. 2022. Available from: https://ir.agtc.com/news-releases/news-release-details/agtc-announces-robust-improvements-visual-sensitivity-adult-and.

[64] Roche to pay Sarepta $1B upfront for DMD gene therapy rights. 2019. Available from: https://www.fiercebiotech.com/biotech/roche-to-pay-sarepta-1b-upfront-for-dmd-gene-therapy-rights.

[65] Adis Insight. Delandistrogene moxeparvovec - Roche/Sarepta Therapeutics. 2022. Available from: https://adisinsight.springer.com/drugs/800050822.

[66] Specialist Pharmacy Service (SPS). Fordadistrogene movaparvovec. 2021. Available from: https://www.sps.nhs.uk/medicines/fordadistrogene-movaparvovec/#:~:text=fordadistrogene%20movaparvovec.

[67] Pfizer to Open First U.S. Sites in Phase 3 Trial of Investigational Gene Therapy for Ambulatory Patients with Duchenne Muscular Dystrophy. 2022. Available from:

https://www.pfizer.com/news/press-release/press-release-detail/pfizer-open-first-us-sites-phase-3-trial-investigational.

[68] Amgen. Q3 '20 EARNINGS CALL. 2020. Available from: https://investors.amgen.com/static-files/a9a9fb50-3b5e-4858-a3a6-86504bdc93b7.

[69] Specialist Pharmacy Service (SPS). Rexmyelocel-T. 2021. Available from: https://www.sps.nhs.uk/medicines/rexmyelocel-t/.

[70] NCT03111238. The Efficacy and Safety of REX-001 to Treat Ischemic Rest Pain in Subjects With CLI Rutherford Category 4 and DM. 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT03111238.

[71] European Medicines Agency (EMA). EU/3/21/2489: Orphan designation for the treatment of primary IgA nephropathy. 2021. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu-3-21-2489.

[72] Vyjuvek (Beremagene Geperpavec). 2022. Available from: https://epidermolysisbullosanews.com/kb103/.

[73] Specialist Pharmacy Service (SPS). EB101. 2021. Available from: https://www.sps.nhs.uk/medicines/eb101/.

[74] CUTISS starts onsite denovoSkin™ production and successfully exits Wyss Zurich accelerator. 2022. Available from: https://cutiss.swiss/cutiss-starts-onsite-denovoskin-production-and-successfully-exits-wyss-zurich-accelerator/.

[75] Cutiss' bio-engineered skin approved to save children's lives. 2020. Available from: https://www.startupticker.ch/en/news/august-2020/cutiss-bio-engineered-skin-approved-to-save-children-s-lives.

[76] Vyjuvek: Effective Treatment for Dystrophic Epidermolysis Bullosa. 2021. Available from: https://biopharma.media/vyjuvek-effective-treatment-for-dystrophic-epidermolysis-bullosa-2318/

[77] Our solution – Personalized, bio-engineered, dermo-epidermal skin grafts. 2022. Available from: https://cutiss.swiss/our-solution/

[78] Roche Designing New Phase 2 Trial of Tominersen in Huntington Disease. 2022. Available from: https://www.neurologylive.com/view/roche-designing-new-phase-2-trial-tominersen-huntington-disease.

[79] VY-AADC Parkinson Disease Gene Therapy Program Terminated. 2021. Available from: https://www.neurologylive.com/view/vy-aadc-parkinson-disease-gene-therapy-program-terminated.

[80] Tominersen. 2021. Available from: https://www.sps.nhs.uk/medicines/tominersen/.

[81] Voyager Therapeutics Provides Update on NBIb-1817 (VY-AADC) Gene Therapy Program. 2021. Available from: https://ir.voyagertherapeutics.com/news-releases/news-release-details/voyager-therapeutics-provides-update-nbib-1817-vy-aadc-gene-0.

[82] Ferrer Internacional S.A. Safety and Preliminary Efficacy of FAB117-HC in Patients With Acute Traumatic Spinal Cord Injury (SPINE). ClinicalTrials.gov2016.

[83] Ferrer Internacional S.A. Ferrer Worldwide. Innovation. Ferrer advanced biotherapeutics. n.d. [cited 17.07.2020]. Available from: https://www.ferrer.com/innovation/key-development-projects.

[84] Wohlhöfner K. (Gute) Praxis Organisationsmodelle für die öffentliche Finanzierung von hochpreisigen Therapien unter Verwendung von Anwendungsevidenz. HTA-Projektbericht 138. 2021. Available from: https://eprints.aihta.at/1329/.

[85] Geiger-Gritsch S. CAR-T cells - Horizon Scanning. AIHTA Policy Brief No. 6a. 2020. Available from: https://eprints.aihta.at/1268/.

6 Appendix

Table A-6-1: Ongoing trials of ATMPs and Gene Therapies – sorted by indication (https://clinicaltrials.gov/)

Rank	Trial-ID	Title	Status	Conditions	Interventions	Lead Sponsor	Phase	N of Patients	Start date	Completion date	Approval Status
Haemophilia											
1	NCT04323098	Study to Evaluate the Efficacy and Safety of Valoctocogene Roxaparvovec, With Prophylactic Steroids in Haemophilia A	Not yet recruiting	Haemophilia A	Valoctocogene roxaparvovec	BioMarin	Phase 3	20	November 10, 2020	January 2027	FDA/EMA: Re-submission in 2022 expected
	NCT03392974	Single-Arm Study To Evaluate The Efficacy and Safety of Valoctocogene Roxaparvovec in Haemophilia A Patients at a Dose of 4E13 vg/kg	Active, not recruiting					1	March 14, 2018	May 2023	
	NCT03370913	Single-Arm Study To Evaluate The Efficacy and Safety of Valoctocogene Roxaparvovec in Haemophilia A Patients	Active, not recruiting					137	December 19, 2017	November 2024	
2	NCT03417102	A Study of Fitusiran (ALN-AT3SC) in Severe Haemophilia A and B Patients With Inhibitors	Completed	Haemophilia A, Haemophilia B	Fitusiran	Sanofi	Phase 3	60	February 14, 2018	June 23, 2021	FDA/ EMA filing for approval postponed to 2024
	NCT03417245	A Study of Fitusiran (ALN-AT3SC) in Severe Haemophilia A and B Patients Without Inhibitors	Completed				Phase 3	120	March 1, 2018	July 14, 2021	
	NCT03549871	A Study of Fitusiran in Severe Hemophilia A and B Patients Previously Receiving Factor or Bypassing Agent Prophylaxis (ATLAS-PPX)	Completed				Phase 3	80	July 25, 2018	March 25, 2022	
	NCT03974113	Fitusiran Prophylaxis in Male Pediatric Subjects Aged 1 to Less Than 12 Years With Hemophilia A or B (ATLAS-PEDS)	Recruiting				Phase 2/3	25	January 28, 2020	December 2026	
	NCT03754790	Long-term Safety and Efficacy Study of Fitusiran in Patients With Hemophilia A or B, With or Without Inhibitory Antibodies to Factor VIII or IX (ATLAS-OLE)	Recruiting				Phase 3	244	January 9, 2019	October 19, 2026	

Rank	Trial-ID	Title	Status	Conditions	Interventions	Lead Sponsor	Phase	N of Patients	Start date	Completion date	Approval Status
3	NCT03569891	HOPE-B: Trial of AMT-061 in Severe or Moderately Severe Haemophilia B Patients	Active, not recruiting	Haemophilia B	Etranacogene dezapar-vovec (AMT-06, AAV5-hFIXco-Padua)	UniQure/CSL	Phase 3	56	June 27, 2018	March 2025	FDA/ EMA approval ' expected in 2022
4	NCT03861273	A Study to Evaluate the Efficacy and Safety of Factor IX Gene Therapy With PF-06838435 in Adult Males With Moderately Severe to Severe Hemophilia B (BENEGENE-2)	Active, not recruiting	Haemophilia A	Giroctocogene fitelparvovec (PF-07055480)	Pfizer	Phase 3	43	July 29, 2019	December 14, 2029	
	NCT03587116	Six Month lead-in Study to Evaluate Prospective Efficacy and Safety Data of Current FIX Prophylaxis Replacement Therapy in Adult Hemophilia B Subjects (FIX:C≤2%) or Current FVIII Prophylaxis Replacement Therapy in Adult Hemophilia A Subjects (FVIII:C≤1%)	Recruiting				Phase 3	250	July 26, 2018	May 14, 2023	
	NCT04370054	Phase 3, Open-Label, Single-Arm Study to Evaluate the Efficacy and Safety of PF-07055480 (Recombinant AAV2/6 Human Factor VIII Gene Therapy) in Adult Male Participants With Moderately Severe to Severe Hemophilia A(FVIII:C≤1%)	Active, not recruiting				Phase 3	63	August 18, 2020	September 16, 2027	
Metabolic Disorders											
5	NCT03759379	HELIOS-A: A Study of Vutrisiran (ALN-TTRSC02) in Patients With Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis)	Active, not recruiting	(hATTR) Amyloidosis	Vutrisiran (ALN-TTRSC02)	Alnylam	Phase 3	164	February 14, 2019	October 2026	EMA: MAA submitted
	NCT04153149	HELIOS-B: A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy	Active, not recruiting				Phase 3	655	November 26, 2019	June 2025	
6	NCT04140539	A Clinical Study to Enable Process Validation of Commercial Grade OTL-101	Terminated	ADA Immunodeficiency	Simoladagene autotemcel (OTL-101)	Orchard	Phase 2/3	3	October 15, 2019	August 30, 2021	Abandoned development
7	NCT03612869	Study of AAVrh10-h.SGSH Gene Therapy in Patients With Mucopolysaccharidosis Type IIIA (MPS IIIA) (AAVance)	Active, not recruiting	Mucopolysaccharidosis Type 3 A	Olenasufligene relduparvovec (SAF-302)	Lysogene	Phase 2/3	20	December 17, 2018	March 2022	

Rank	Trial-ID	Title	Status	Conditions	Interventions	Lead Sponsor	Phase	N of Patients	Start date	Completion date	Approval Status
8	NCT05139316	A Study of Adeno-Associated Virus Serotype 8-Mediated Gene Transfer of Glucose-6-Phosphatase in Patients With Glycogen Storage Disease Type Ia (GSDIa)	Active, not recruiting	Glycogen Storage Disease Type IA	Pariglasgene brecaparvovec (DTX401)	Ultragenyx Pharmaceutical Inc	Phase 3	50	November 8, 2021	April 2024	
9	NCT03837483	A Clinical Study to Evaluate the Use of a Cryopreserved Formulation of OTL-103 in Subjects With Wiskott-Aldrich Syndrome	Recruiting	Wiskott-Aldrich Syndrome	OTL-103 (GSK-2696275)	Orchard Therapeutics	Phase 3	10	January 21, 2019	January 2024	FDA submission expected in 2022
Ophthalmologic disorders											
10	NCT03496012	Efficacy and Safety of BIIB111 for the Treatment of Choroideremia (STAR)	Completed	Choroideremia	Timrepigene emparvovec (AAV2-REP1, BIIB111)	Biogen	Phase 3	170	December 11, 2017	December 1, 2020	
	NCT03584165	Long-term Safety and Efficacy Follow-up of BIIB111 for the Treatment of Choroideremia and BIIB112 for the Treatment of X-Linked Retinitis Pigmentosa (SOLSTICE)	Enrolling by invitation				Phase 3	440	June 4, 2018	March 23, 2027	
11	NCT03153293	A Single Intravitreal Injection of rAAV2-ND4 for the Treatment of Leber's Hereditary Optic Neuropathy	Active, not recruiting	Leber Hereditary Optic Neuropathy	NR082 (rAAV2-ND4)	Neurophth Therapeutics	Phase 2/3	159	December 27, 2017	January 15, 2025	
12	NCT03293524	Efficacy & Safety Study of Bilateral IVT Injection of GS010 in LHON Subjects Due to the ND4 Mutation for up to 1 Year (REFLECT)	Active, not recruiting	Leber Hereditary Optic Neuropathy	Lenadogene nolparvovec (GS010, LUMEVOQ®)	GenSight Biologics	Phase 3	90	March 12, 2018	June 30, 2024	
	NCT03406104	RESCUE and REVERSE Long-term Follow-up (RESCUE/REVERSE)	Active, not recruiting				Phase 3	61	January 9, 2018	August 2022	
13	NCT04704921	Pivotal 1 Study of RGX-314 Gene Therapy in Participants With nAMD (ATMOSPHERE)	Recruiting	Age-related macular degeneration	RGX-314	Regenxbio Inc.	Phase 2/3	300	December 29, 2020	March 2024	FDA submission expected in 2022
14	NCT04794101	Follow-up Gene Therapy Trial for the Treatment of X-linked Retinitis Pigmentosa Associated With Variants in the RPGR Gene	Recruiting	X-Linked Retinitis Pigmentosa	AAV5-RPGR (MGT009, botaretigene sparoparvovec)	MeiraGTx /Janssen	Phase 3	66	March 16, 2021	July 5, 2027	
	NCT04671433	Gene Therapy Trial for the Treatment of X-linked Retinitis Pigmentosa Associated With Variants in the RPGR Gene	Recruiting	X-Linked Retinitis Pigmentosa	AAV5-RPGR (MGT009, botaretigene sparo-	MeiraGTx /Janssen	Phase 3	66	March 16, 2021	July 5, 2022	

Rank	Trial-ID	Title	Status	Conditions	Interventions	Lead Sponsor	Phase	N of Patients	Start date	Completion date	Approval Status
					parvovec)						
15	NCT03584165	Long-term Safety and Efficacy Follow-up of BIIB111 for the Treatment of Choroideremia and BIIB112 for the Treatment of X-Linked Retinitis Pigmentosa (SOLSTICE)	Enrolling by invitation	X-Linked Retinitis Pigmentosa	AAV8-RPGR	Biogen	Phase 3	440	June 4, 2018	March 23, 2027	
16	NCT04850118	A Clinical Trial Evaluating the Safety and Efficacy of a Single Subretinal Injection of AGTC-501 in Participants With X-linked Retinitis Pigmentosa Caused by RPGR Mutations	Not yet recruiting	X-Linked Retinitis Pigmentosa	AGTC-501 (laruparetigene zosaparvovec , rAAV2tYF-GRK1-hRPGRco)	Applied Genetic Technologies Corp	Phase 3	63	August 2021	March 2029	
Musculoskeletal disorders											
17	NCT05096221	A Gene Transfer Therapy Study to Evaluate the Safety and Efficacy of SRP-9001 in Participants With Duchenne Muscular Dystrophy (DMD) (EMBARK)	Recruiting	Duchenne Muscular Dystrophy (DMD)	SRP-9001(Delandistrogene moxeparvovec, AA-Vrh74.MHCK7)	Sarepta	Phase 3	120	October 27, 2021	November 30, 2024	FDA/EMA submission expected in 2023
18	NCT04281485	A Phase 3 Study to Evaluate the Safety and Efficacy of PF-06939926 for the Treatment of Duchenne Muscular Dystrophy	Active, not recruiting	Duchenne Muscular Dystrophy (DMD)	PF-06939926 (Fordadistrogene movaparvovec)	Pfizer	Phase 3	99	November 5, 2020	September 28, 2028	
Vascular disorders											
19	NCT04469270	Study to Assess Safety and Efficacy of Engensis in Painful Diabetic Peripheral Neuropathy (REGAiN-1A)	Recruiting	Acute Myocardial Infarction (AMI) Painful diabetic peripheral neuropathies (PDPN)	Engensis (Donaperminogene seltoplasmid, VM202RY)	Helixmith	Phase 3	152	October 9, 2020	December 31, 2022	
	NCT04873232	A 6-Month Extension Study of VMDN-003-2 to Assess Engensis in Participants With Painful Diabetic Peripheral Neuropathy (REGAiN-1B)	Recruiting				Phase 3	250	May 17, 2021	March 2022	
20	NCT03174522	The Efficacy and Safety of REX-001 to Treat Ischemic Ulcers in Subjects With CLI Rutherford Category 5 and DM	Recruiting	Critical Limb Ischemia (CLI) in Diabetes Mellitus (DM) (Type 1+2)	REX-001, Rexmyelocel T	Ixaca (formerly Rexgenero)	Phase 3	78	April 25, 2017	July 31, 2023	
	NCT03111238	The Efficacy and Safety of REX-001 to Treat Ischemic Rest Pain in Subjects With CLI Rutherford Category 4 and DM	Terminated				Phase 3	3	April 5, 2017	March 31, 2021	

Rank	Trial-ID	Title	Status	Conditions	Interventions	Lead Sponsor	Phase	N of Patients	Start date	Completion date	Approval Status
21	NCT04275323	Safety and Efficacy Study Using Gene Therapy for Critical Limb Ischemia (NL003-CLI-III-1)	Recruiting	Arterial Occlusive Disease Ischemia Ulcers Peripheral Vascular Disease	NL003	Viromed/ Beijing Northland Biotech. Co., Ltd.	Phase 3	300	August 2, 2019	December 31, 2023	
	NCT04274049	Safety and Efficacy Study Using Gene Therapy for Critical Limb Ischemia (NL003-CLI-III-2)	Recruiting				Phase 3	240	August 18, 2019	December 31, 2023	
Dermatologic disorders											
22	NCT04491604	A Phase III Double Blinded, Placebo-Controlled, Efficacy and Safety Study of Beremagene Geperpavec (B-VEC, Previously "KB103") for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)	Active, not recruiting	Epidermolysis bullosa	Beremagene Geperpavec (B-VEC)	Krystal Biotech, Inc.	Phase 3	31	August 17, 2020	October 2021	
	NCT04917874	A Long-term Treatment With B-VEC for Dystrophic Epidermolysis Bullosa	Recruiting				Phase 3	30	May 25, 2021	December 31, 2022	
23	NCT04227106	Phase 3, Open-label Clinical Trial of EB-101 for the Treatment of Recessive Dystrophic Epidermolysis Bullosa (RDEB)	Recruiting	Epidermolysis bullosa	EB-101	Abeona	Phase 3	15	January 10, 2020	September 2022	
24	NCT04213261	A Study of FCX-007 for Recessive Dystrophic Epidermolysis Bullosa (DEFI-RDEB)	Recruiting	Epidermolysis bullosa	FCX-007	Fibrocell	Phase 3	24	June 9, 2020	July 2037	
25	NCT03229564	Study With an Autologous Dermo-epidermal Skin Substitute for the Treatment of Burns in Children	Recruiting	Burns	denovoSkin™ (EHSG-KF STSG)	Cutiss AG	Phase 2/3	12	October 25, 2017	December 2025	
	NCT03227146	Study With an Autologous Dermo-epidermal Skin Substitute for the Treatment of Burns in Adults	Recruiting				Phase 2/3	12	October 25, 2017	January 2025	
Neurologic disorders											
26	NCT03761849	A Study to Evaluate the Efficacy and Safety of Intrathecally Administered RO7234292 (RG6042) in Participants With Manifest Huntington's Disease	Active, not recruiting	Huntington Disease	Tominersen (RG-6042)	Roche	Phase 3	791	January 23, 2019	March 17, 2022	

Rank	Trial-ID	Title	Status	Conditions	Interventions	Lead Sponsor	Phase	N of Patients	Start date	Completion date	Approval Status
	NCT03842969	An Open-Label Extension Study to Evaluate Long-Term Safety and Tolerability of RO7234292 (RG6042) in Huntington's Disease Participants Who Participated in Prior Roche And Genentech Sponsored Studies	Active, not recruiting					236	April 23, 2019	March 25, 2022	
Hematology											
27	NCT05133531	Ravulizumab-Controlled Study to Evaluate the Efficacy and Safety of Pozelimab and Cemdisiran Combination Therapy in Adult Patients With Paroxysmal Nocturnal Hemoglobinuria Who Are Complement Inhibitor Treatment-Naive or Have Not Recently Received Complement Inhibitor Therapy (ACCESS-1)	Recruiting	Paroxysmal Nocturnal Hemoglobinuria	Ravulizumab/ Pozelimab/ Cemdisiran	Regeneron Pharmaceuticals	Phase 3	124	July 31, 2022	July 16, 2027	
	NCT05131204	Efficacy and Safety of the Combination of Pozelimab and Cemdisiran Versus Continued Eculizumab or Ravulizumab Treatment in Adult Patients With Paroxysmal Nocturnal Hemoglobinuria (ACCESS 2)	Recruiting				Phase 3	140	March 31, 2022	September 18, 2026	

HTA Austria
Austrian Institute for
Health Technology Assessment
GesmbH