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ATMPs and Gene Therapies in Development

Horizon Scanning

Report

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ATMPs and Gene Therapies in Development

Horizon Scanning

Vienna, July 2020

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ZUSAMMENFASSUNG

Hintergrund: Es wird prognostiziert, dass bis 2022 etwa 16 "Arzneimittel für neuartige Therapien (Advanced Therapies Medicinal Products, ATMP) auf dem Markt sein werden (derzeit: 11), etwa 2-4 neue Therapien pro Jahr. Nach Angaben der Europäischen Arzneimittelagentur (EMA) lassen sich ATMPs in drei Haupttypen einteilen: Gentherapeutika und somatisch-zelltherapeutische Arzneimittel sowie Tissue-Engineering Produkte. Laut dem Jahresbericht der "Alliance of Regenerative Medicine (ARM)" untersuchen Ende 2019 weltweit mehr als 1.000 klinische Studien regenerative Therapien für verschiedene Krankheiten, davon 94 in der Phase 3, 591 in der Phase 2. Aufgrund der umfangreichen Forschungsaktivitäten in diesem Bereich und aufgrund der Technologie (ATMP) selbst und ihrer spezifischen Herausforderungen (ethisch, rechtlich, wirtschaftlich) ist es wichtig, diese Entwicklungen frühzeitig zu beobachten. Der vorliegende Bericht soll auf die Fragen eingehen, für welche Indikationen Gentherapien und ATMPs in der Entwicklung sind und bis wann eine Zulassung zu erwarten ist.

Prognose bis 2022: 16 ATMPs, 2-4 p.a.

EMA Einteilung ATMPs: Gentherapeutika somatisch-zelltherapeutische Arzneimittel Tissue-Engineering Produkte

94 Produkte bereits in der Phase 3

Methoden: Zur Beantwortung der Fragen wurde eine systematische Suche in den Studienregistern durchgeführt, um in der Entwicklung befindliche Gentherapien und ATMPs zu identifizieren, gefolgt von der Extraktion von Daten über die identifizierten laufenden klinischen Studien, ergänzt durch eine Suche in der EMA-Datenbank über in Evaluation befindliche Medikamente, um diejenigen Therapien zu identifizieren, die bereits bald zugelassen werden. Schließlich wurden veröffentlichte Informationen über die Produkte, ihre Indikation und die Patientenpopulation gesammelt.

systematische Suche in Studienregistern Datenextraktion Informationen zu Produkten und Indikationen

Ergebnisse: Unsere Suche identifizierte 32 ATMPs und Gentherapien (CAR-T-Zelltherapien und onkologische Indikationen ausgeschlossen) in der späten Entwicklungsphase (Phase 2 oder 3 Studien), die in den kommenden Jahren auf den Markt kommen werden. Die Indikationsgebiete sind eine Vielfalt von genetischen Krankheiten und umfassen acht breite Indikationsgruppen (Hämophilie, Stoffwechsel-, Augen-, Muskel-, Skelett-, Gefäß-, nephrologische, dermatologische und neurologische Erkrankungen). Vier Therapien werden bereits von der EMA evaluiert, fünf werden voraussichtlich Ende 2020 oder 2021 in den Zulassungsprozess eintreten.

32 ATMPs (ohne CAR-T) in Phase 2&3Studien

in 8 Indikations-bereichen
4 bereits in Zulassung
5 Ende 2020/ 2021 erwartet

Schlussfolgerung: Es gibt zahlreiche Herausforderungen bei der Bewertung dieser Therapien. Sie werden oft als "kurative" oder "disruptive" Technologien bezeichnet, obwohl für die wenigen bereits zugelassenen Therapien kaum Langzeitdaten verfügbar sind. Aus diesem Grund ist das Horizon Scanning (HSS) in vielen Ländern zu einer bedeutenden Aktivität geworden. Die vorliegende Arbeit wurde in Zusammenarbeit mit der "Tirol Kliniken GmbH" durchgeführt, um gemeinsam nach neuen und kostenintensiven Therapien zu scannen. Diese HSS in kleinem Maßstab stellt lediglich eine "Momentaufnahme" neuer Technologien dar und ist und kann nicht so zuverlässig sein wie internationale Initiativen (BeNeLuxA, IHSI) und ihre systematischen und dauerhaften Aktivitäten.

zahlreiche Herausforderungen bei Bewertung:

hohe Erwartung, wenig Daten

internationale Kooperation ist wichtig

EXECUTIVE SUMMARY

forecast: 16 ATMPs by 2022, 2-4 p.a.

EMA classification: gene therapy and somatic-cell therapy medicinal products tissue-engineered products

94 products in phase 3

Background: It is forecasted that until 2022 around 16 "Advanced Therapies Medicinal Products (ATMP) will be at the market (as of today: 11), around 2-4 new therapies per year. 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 the annual report of the "Alliance of Regenerative Medicine (ARM)" more than 1,000 clinical trials worldwide are investigating regenerative therapies for various diseases at the end of 2019, of which 94 are in phase 3, 591 in phase 2. Due to the extensive research activities in this area and due to the technology (ATMP) itself and its specific challenges (ethical, legal, economic), it is important to observe these developments at an early stage. 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 dataextraction informationen on products and indications

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, 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, their indication and patient population was collected.

32 ATMPs (without CAR-T) in Phase 2&3 trials

8 fields of indications 4 already in approval process, 5 expected end 2020/21

Results: Our search identified 32 ATMPs and gene therapies (CAR-T cell therapies and oncologic indications excluded) in late-stage development (phase 2 or 3 trials), which will reach the market in the years to come. 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). Four therapies are already under evaluation by the EMA, five are expected to enter the approval process in late 2020 or 2021.

numerous challenges in the evaluation

high expectations, few data

international cooperation necessary

Conclusion: There are numerous challenges in the evaluation of these therapies. They are often referred to as "curative" or "disruptive" technologies, though hardly any long—term data are available for the few therapies already approved. The causes for the advance praise might be found in the high expectations of gene therapies. For these reason Horizon Scanning (HSS) has become an activity in many countries. This report was carried out in collaboration with "Tirol Kliniken GmbH" to scan the Horizon for new and eventually cost-intensive 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 (BeNeLuxA, IHSI) and their systematic and permanent activities.

1 INTRODUCTION

1.1 Definitions: ATMP and Regenerative Medicine

It is forecasted that until 2022 around 16 „Regenerative Medicine Advanced Therapy Designation (RMAT)" (a term often used in the USA by the FDA) or "Advanced Therapies Medicinal Products (ATMP)" (a term used in Europe by EMA) will be at the market, around 2-4 new additional therapies per year [1]. As of July 2020, eleven ATMPs have been approved by the European Medicines Agency (EMA) [2].

jährlich ca 2-4 neue ATMPs

2020: 11 zugelassene
Vorhersage 2022: 16

Both terms are umbrella expressions encompassing a variety of gene- and cell therapies based on methods of replacing or regenerating human cells, tissues or organs to restore or establish normal function [3]. But while regenerative medicine is not a new field (bone marrow or organ transplants are conducted since some decades), the approval of ATMPs by EMA has been regulated only a bit more than ten years ago (2007) and entered into force in December 2008.

Überbegriffe:
USA: Regenerative
Europa: ATMP
Therapien

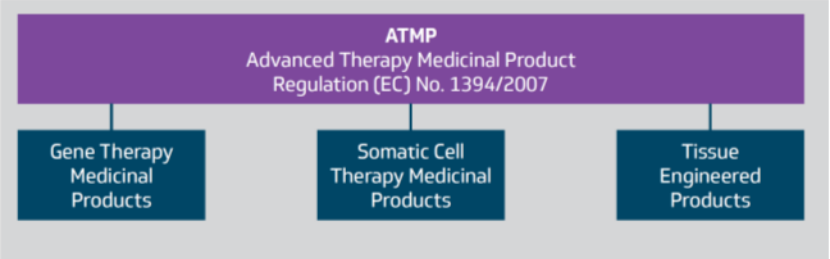


Figure 1-1: Umbrella term „Advanced Therapy Medicinal Product (ATMP)" [4]

According to the EMA ATMPs can be classified into three main types (see Figure 1-1):

EMA Definitionen

ATMP können in 3 Typen klassifiziert werden

- 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;

Gentherapien
Somatische Zelltherapien
Tissue-engineered Produkte

In addition, some ATMPs may contain one or more medical devices as an integral part of the medicine, which is referred to as combined ATMPs. An example of this is cells embedded in a biodegradable matrix or scaffold [5].

manchmal in Kombination mit Medizinprodukten

1.2 Market development

ca. 1.000 laufende klinische Studien in Phase 1-3

fast 60% davon in Onkologie

Problembereiche:
Zulassung
HTA-Frühbewertung
Post-Market Datengenerierung

According to the annual report of the "Alliance of Regenerative Medicine (ARM)" more than 1,000 clinical trials worldwide are investigating regenerative therapies for various diseases at the end of 2019, of which 94 are in phase 3, 591 in phase 2, 381 in phase 1 ([6], see Figure 1-2). Within the last years, there has been a vast increase of early-stage clinical activity in gene-modified and cell-based immune-oncology, which make up to 62% of all trials ([6], see Figure 1-3). These cell-therapies, known as autologous CAR-T cell therapies for haematological malignancies have been approved and expansions of indications will follow. Cell and gene therapies present a challenge not only to regulators but to existing pre-reimbursement assessments (Health Technology Assessments [HTAs]), because the early approvals are based on small studies and short follow-up only. Additional, the cell and gene therapies are challenging the financing and reimbursement itself due to enormous acquisition costs and the necessity for additional data collections to assess the individual benefits to patients [1].

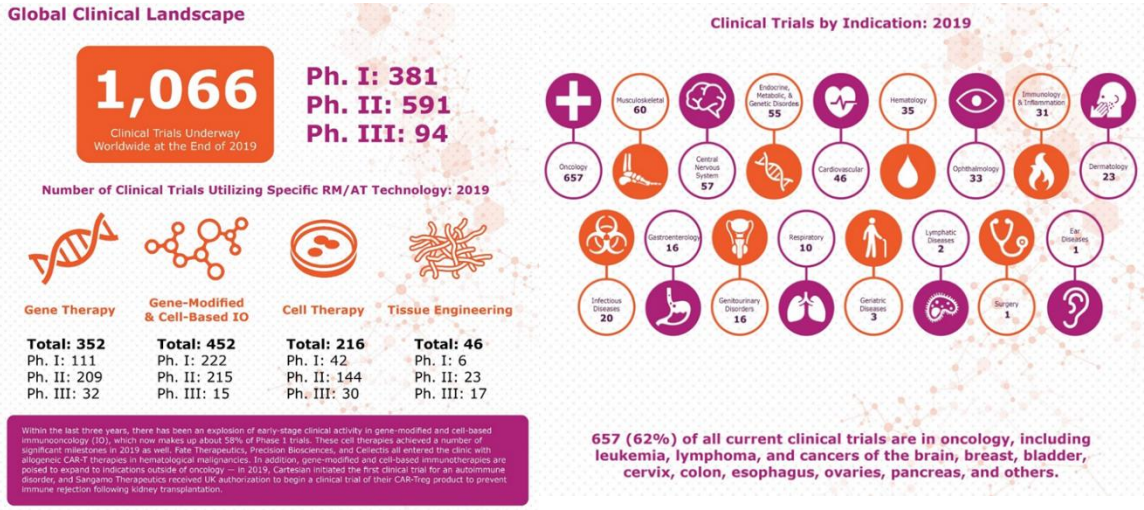
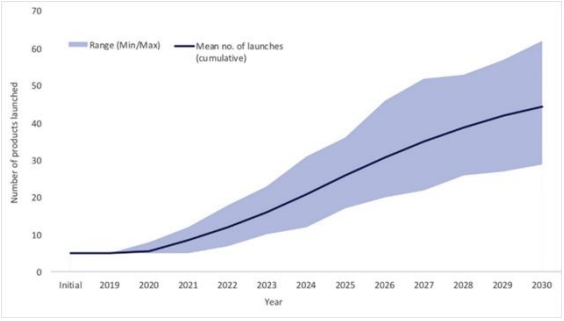


Figure 1-2: Global Landscape of trials on regenerative medicine therapies [6] by numbers
Figure 1-3: Global Landscape of trials on regenerative medicine therapies [6] by indications

Vorhersage: Zunahme der Patient*innen-population

While for now only a few patients with rare or very rare diseases are covered by the approved therapies, it will be additionally challenging when cell and gene therapies are approved for broad indications and many patients (see Figure 1-4 und 1-5).



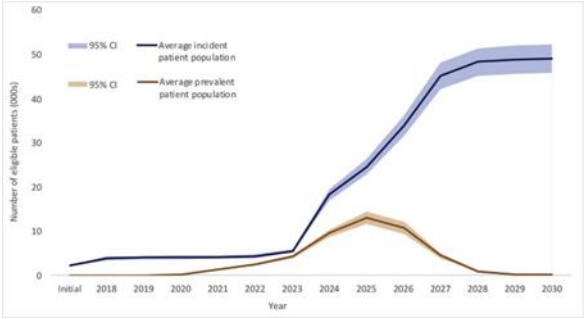


Figure 1-4: Number of products to be launched (forecast) [1]
Figure 1-5: Number of eligible patients for ATMP (forecast for USA) [1]

Abbreviations: CI=confidence interval

Horizon Scanning von ATMP

Due to the extensive research activities in this area and due to the technology (ATMP) itself and its specific challenges (ethical, legal, economic), it is important to observe these developments at an early stage. Horizon Scanning has become a prominent instrument to support health policy [7].

1.3 Horizon Scanning

Ziel von Horizon Scanning:

frühe Identifikation von Therapien zur Vorbereitung von gesundheits-politischen Entscheidungen

A Horizon Scanning System (HSS) (synonyms: Early Awareness & Alert System [EAAS], Early Warning System [EWS]) is a system that aims

- to identify, filter and prioritize new and emerging health technologies, or new uses of existing interventions;
- to assess or predict their impact on health, health services and/or health budgets;
- to facilitate evidence-based reimbursement decisions; and
- to disseminate information early on, i.e. before the routine introduction of these technologies.

1.4 Research Questions

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

Forschungsfragen:

Welche Gen- Und Zelltherapien sind in Entwicklung?

- 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?
- RQ3: For which patients (burden of disease, size of the population) are the new therapies indicated?

Within this report oncologic indications are excluded and are covered in a separate report [8].

2 METHODS

methodisches Vorgehen:

1. Suche in Studienregistern

2. Extraktion der Studieninformationen

3. Handsuche nach vertiefenden Informationen zu Interventionen

Rationale and approach: 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.
3. To answer RQ3 additional information was sought in published information from sponsors, information from medical sources (Medline via Pubmed), specialist medical societies, etc.

The methodologies are described in more detail as follows:

2.1 Search strategy and in-/exclusion criteria

im Detail Suchstrategie

in 1 Studienregister Gentherapien und ATMP

in Phase 2 & 3

Überprüfung in 1 weiteren Register

A search in the following clinical registry was performed between July 6th and 9th.

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

Duplicates with the same trial-ID were removed.

Results were crossed checked with findings in

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

Ein-/Ausschlusskriterien:

keine onkologischen Therapien

Produkt-zentriert

Inclusion criteria:

- (Phase 1/2), Phase 2 to 3 clinical trials.
- All indications (except oncological indications)

Exclusion criteria:

- Phase 1 clinical trials
- Status unknown and/or last updated 2018
- No product, but (in-house/hospital) process

Finally, the identified interventions were cross-checked with the list in “Potential Pipeline Gene Therapies in the Emerging Technologies and Therapeutics Reports Part I and II of the Patient-Centered Outcomes Research Institute (PCORI)” [9, 10]. Further 22 interventions were included in the analyses that were not part of the search in the clinical trial registry.

The inclusion and exclusion criteria for relevant trials and literature are summarized in Table 2-1.

Table 2-1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Application human medicine	Publications on basic research or animal experiments without direct clinical application
All indications (but oncology)	Oncologic indications
Therapeutic indication of gene-therapy or ATMP	Pre-clinical, phase 1 studies, status unknown or last updated in 2018
Clinical trial phase 2, 3 (4 and 1/2) or approved technologies in new indications	Articles in languages other than English or German
Interventional studies	Articles not publicly available

Abbreviations: ATMP= Advanced Therapy Medicinal Product

2.2 Selection of interventions

nach Deduplikation und Ausschlüssen 32 Therapien eingeschlossen

The search in ClinicalTrials.gov yielded 99 hits (84 hits for gene-therapies and 15 for ATMP/tissue-engineered products), 22 additional interventions were identified in the PCORI report. After deduplication and clustering of the same therapies, 39 different gene therapies and seven tissue-engineered products were identified. After the application of the in-/exclusion criteria finally 32 therapies were left for further searches of information and extraction of data (see Figure 2-1).

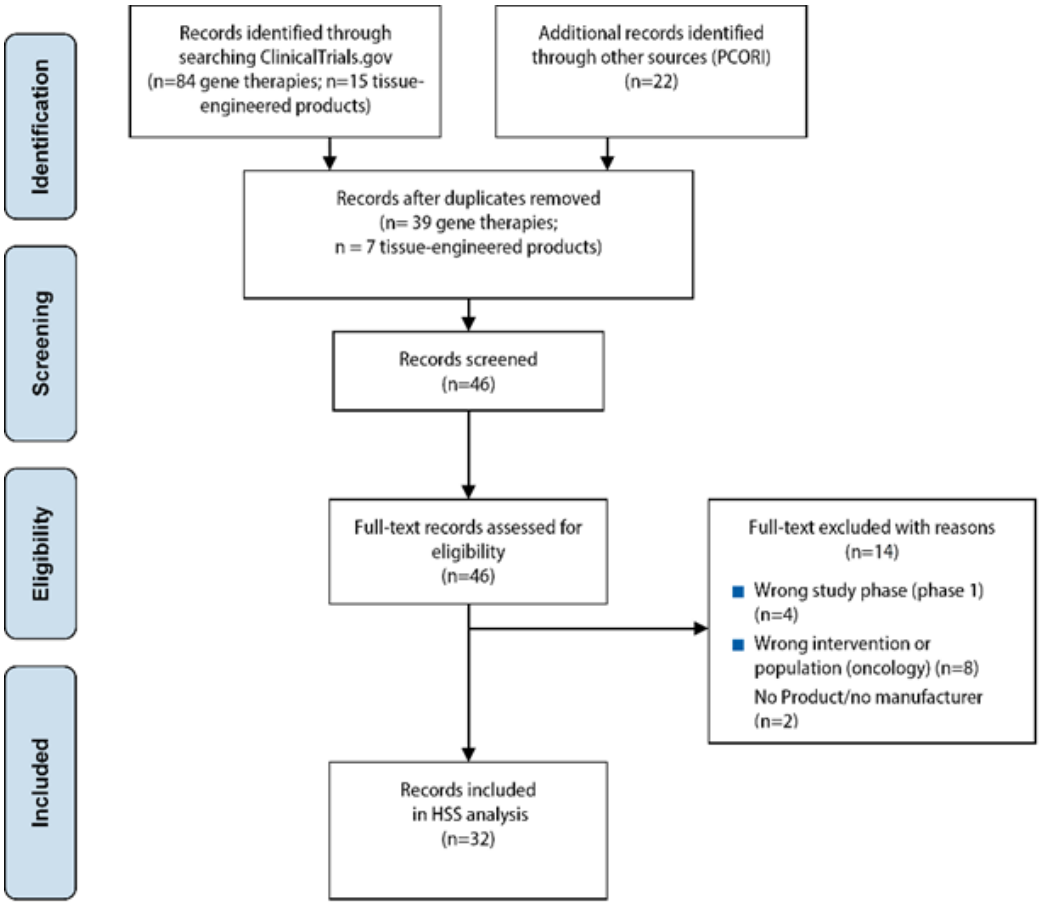


Figure 2-1: Presentation of the selection process (PRISMA Flow Diagram)

Abbreviations: HSS=Horizon Scanning System, PCORI=Patient-Centered Outcomes Research Institute

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 (KW) 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.
- Cross-checked in EudraCT https://eudract.ema.europa.eu/ (see Appendix A-2).

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 und Indikationen

Then, a targeted search in

- Specialist Pharmacy Service (SPS) https://www.sps.nhs.uk/articles/sps-horizon-scanning-service/
- PCORI, Emerging Technologies and Therapeutics Reports: Landscape Review and Evidence Map of Gene Therapy [9, 10]
- Genetics Home Reference Database: https://ghr.nlm.nih.gov/condition/
- Adis Insight: https://adisinsight.springer.com/search

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
- details of indication and condition (patient population, stage of disease, etc.) incl. epidemiological data for Austria and Germany (incidence, prevalence) – if available
- description of the technology

was collected and extracted.

The search in Pubmed was limited to articles published in English between 2015 and 2020 and restricted to clinical trials in humans.

3 RESULTS

As indicated in Figure 2-1, the search in clinical trials registries and the cross-check with a PCORI-report (2019) [9, 10] yielded 32 ATMP /gene therapy candidates 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 and Table A-2, These are two different tables, as only 23 of the technologies identified in clinicaltraisl.gov were also found in EudraCT.). A detailed description is presented in the following text.

32 Therapien in 8 Indikationsfeldern

3.1 Indication Haemophilia

Table 3-1: Haemophilia therapies under development

Indication	Product	Sponsor	Development/ regulatory status
Haemophilia A	**Valoctocogene roxaparvovec (BMN-270)**	**BioMarin**	**Phase 3: 9/2023 (EPCD); FDA: ODD (2016), BTT (2017),** FDA: rejected (8/2020) **EMA: under evaluation, ODD (2016), PRIME (2017)**
Haemophilia A	**Fitusiran**	**Sanofi**	**Phase 3: 6/2021 (EPCD); FDA: ODD (2013) EMA: ODD (2014) FDA/ EMA approval expected in 2021**
Haemophilia B	**Etranacogene dezaparvovec (AMT-06, AAV5-hFIXco-Padua)**	**UniQure**	**Phase 3: 8/2024 (EPCD); FDA: ODD, FTD (2019) EMA: ODD, PRIME (2017) EMA/FDA: approval expected in 2021**
Haemophilia A Haemophilia B	Giroctocogene fitelparvovec (PF-07055480) Fidanacogene elaparvovec (SPK-9001, PF-06838435)	Pfizer	Phase 3: 11/2026 (EPCD); FDA: ODD, BTT (2016) EMA: ODD, PRIME (2017)
Haemophilia B	FLT180a	Freeline	Phase 2/3: 12/2035; (EPCD) FDA: not available EMA: ODD (2018)

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

Proposed Indication and Patients in Austria:

There are two main types of inherited haemophilia: Type A, the most common type, is caused by a deficiency of factor VIII, one of the proteins that help blood to form clots. Type B haemophilia is caused by a deficiency of factor IX.

- **Haemophilia A**: Haemophilia A is the most common, with an incidence of 1: 10.000 newborn [11]. The Austrian Haemophilia Registry covers more than 85% of the assumed total number of haemophilia patients in Austria. It summarizes data on 753 patients whereof 84.3% (635) are suffering from haemophilia A [12].
- **Haemophilia B** has an incidence of around 1 in 50.000 newborn with 118 patients being recorded in the Austrian Haemophilia Registry [11] [12]. The reference level of factor IX is 5 µg/mL, but the normal

Hämophilie A & B
HA & HB

Österreich:
635 Hämophilie A Pts.
118 Hämophilie B Pts.

range is from half to twice that level. Severe disease occurs with a factor IX level below 1% of the reference and accounts for about 50% of cases. Moderate severity occurs with a level of 1-5% and accounts for around 30% of cases [13].

Condition:

Mangel an Faktor VIII (A) oder Faktor IX (B)

Blutgerinnungsstörung

- Haemophilia is a rare bleeding disorder, whereby the blood does not clot properly due to the lack of or dysfunction of factor VIII (haemophilia A) or factor IX (haemophilia B) clotting protein. In severe haemophilia, this causes frequent spontaneous bleeding. The inability of their blood to clot means that patients are at high risk of internal bleeding, increasing their mortality risk. The prognosis for haemophilia is favourable if therapy is administered early. However, compared to patients with milder forms of haemophilia, those with severe disease are prone to spontaneous bleeding, including sub-clinical bleeds. Untreated severe haemophilia can result in 18-47 bleeds per year [14].

3.1.1 Valoctocogene roxaparvovec (Biomarin) - Valrox®

Development/Regulatory Status:

derzeit bei EMA unter Begutachtung, von FDA abgelehnt (Aug. 2020)

- 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.

bei Hämophilie A

- 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).

Pts mit schweren Erkrankungen ohne Antikörper gegen 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.

Companion-AAV5 Antikörper Test

- 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.

Condition: Haemophilia A

Technology:

- 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).

Adeno-assoziierte Viren (AAV) dienen als Vektorviren

erste Gentherapie:

Einmalinfusion zur Normalisierung von Faktor VIII-Werten

3.1.2 Fitusiran (Sanofi)

Development/Regulatory Status:

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

derzeit in Entwicklung

Interimauswertungen von Phase 2

Condition: Haemophilia A

bei Hämophilie A

Technology:

- 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.

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

3.1.3 Etranacogene dezaparvovec (AMT-061, AAV5-hFIXco-Padua) (UniQure)

Development/Regulatory Status:

derzeit in Entwicklung

- 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).

Hämophilie B

Phase 2b
Phase 3 begonnen

- 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.

Einmalinfusion

- In the phase 3 trial (HOPE-B trial, active, not recruiting) 56 severe or moderately severe haemophilia B patients are tested.

Condition: Haemophilia B

AAV-Vektor

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.

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: HA

- 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.

fidanacogene elaparvovec: HB

- 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.

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.

Condition:

- Haemophilia A (giroctocogene fitelparvovec) &
- Haemophilia B (fidanacogene elaparvovec)

Technology:

AAV-Vektoren

- 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 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.
- 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.

giroctocogene fitelparvovec: AVV6

fidanacogene elaparvovec: AVV2

Einmalinfusion zur Normalisierung von Faktor VIII/IX-Werten

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.

derzeit in Entwicklung

Condition: Haemophilia B

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

3.2 Metabolic Disorders

Table 3-2: Metabolic disorders therapies under development

Indication	Product	Sponsor	Development/Regulatory status
ADA Immunodeficiency	**Simoladagene autotemcel (OTL-101)**	**Orchard**	**Phase 2/3: 2/2021** (EPCD); **FDA approval expected in 2020** **FDA: PDD, BTT (2017)** **EMA: ODD (2019)**
Metachromatic Leukodystrophy	**OTL-200**	**Orchard**	**Phase 3: 1/2032** (EPCD); **FDA/EMA under evaluation** **FDA: PDD (2018)** **EMA: AA (2019)**
Cerebral Adrenoleukodystrophy	**Elivaldogene tavalentivec (Lenti-D)**	**Bluebird bio**	**Phase 3: 7/2023 (EPCD),** **FDA: ODD (2012), BTT** **EMA: ODD, PRIME (2018)** **EMA/ FDA approval expected in 2021**
Mucopolysaccharidosis Type 3 A	Olenasufligene relduparvovec (SAF-302)	Lysogene	Phase 2/3: 3/2022 (EPCD) FDA: FTD (2020) EMA: ODD (2014)
Mucopolysaccharidosis Type 3 B Mucopolysaccharidosis 3 A	rAAV9.CMV.hNAGLU (ABO-101) scAAV9.U1a.hSGSH (ABO-102)	Abeona	Phase 1/2: 10/2022 (EPCD) Phase 1/2: 12/2022 (EPCD) FDA: ODD, PDD (2019) EMA: ODD, PRIME (2019)
Alpha 1-Antitrypsin Deficiency	ARO-AAT	Arrowhead	Phase 2/3: 5/2022 (EPCD) FDA: ODD, FTD (2019) EMA: ODD (2018)
(hATTR) Amyloidosis	Vutrisiran (ALN-TTRSC02)	Alnylam	Phase 3: 5/2024 (EPCD) FDA: ODD (2018) EMA: ODD (2018)

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 Simoladagene autotemcel (OTL-101) (Orchard)

derzeit in Entwicklung

Development/Regulatory Status:

- Simoladagene autotemcel is a therapy under development; FDA approval is expected in late 2020.

Phase 2
Beginn Phase 3

- 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 [15].

Proposed Indication and Patients in Austria:

sehr selten:
1 in 200.000 bis
1 Mio Neugeborene

- ADA deficiency is very rare and is estimated to occur in approximately 1 in 200,000 to 1,000,000 newborns worldwide. This disorder is responsible for approximately 15 percent of SCID cases.

Condition:

- ADA deficiency is an inherited disorder that damages the immune system and causes SCID. People with SCID lack virtually all immune protection from bacteria, viruses, and fungi. They are prone to repeat and persistent infections that can be very serious or life-threatening. These infections are often caused by "opportunistic" organisms that ordinarily do not cause illness in people with a normal immune system. The main symptoms of ADA deficiency are pneumonia, chronic diarrhoea, and widespread skin rashes. Affected children also grow much more slowly than healthy children and some have developmental delay. Most individuals with ADA deficiency are diagnosed with SCID in the first six months of life. Without treatment, these babies usually do not survive past age two. In 10 to 15% of cases, the onset of immune deficiency occurs between six and 24 months of age (delayed onset) or in adulthood (late onset) [14].

hereditärer Adenosindesaminase Mangel

schwere kombinierte Immundefizienz (SCID)

ADA ist Ursache für 10-15% von SCID

Technology:

- 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.

autologe Stammzellentherapie

3.2.2 OTL-200 (Orchard)

Development/Regulatory Status:

- OTL-200 is a therapy under development, but – according to Orchard - is under review with the EMA.
- The FDA has granted OTL-200 a Rare Pediatric Disease Designation (May 2018); EMA granted OTL-200 accelerated assessment for the treatment of metachromatic leukodystrophy (MLD) (Nov 2019).
- A phase 3 clinical trial in Metachromatic leukodystrophy (in children, in adults, in the elderly) started in June 2020.

EMA review: accelerated assessment

Phase 2
Beginn Phase 3

Proposed Indication and Patients in Austria:

- Metachromatic leukodystrophy is reported to have a prevalence of 1 in 40,000 to 160,000 individuals worldwide.

1 in 40.000 Bevölkerung

Condition:

- Metachromatic leukodystrophy is an inherited disorder characterized by the accumulation of fats called sulfatides in cells. This accumulation especially affects cells in the nervous system that produce myelin, the substance that insulates and protects nerves. The white matter consists mainly of nerve cells that are covered by myelin (myelinated axons). Sulfatide accumulation in myelin-producing cells causes progressive destruction of white matter (leukodystrophy) throughout the nervous system, including in the brain and spinal cord (the central nervous system) and the nerves connecting the brain and spinal cord to muscles and sensory cells that detect sensations such as touch, pain, heat, and sound (the peripheral nervous system). The most common

metachromatische Leukodystrophie

Arylsulfatase A-Mangel

führt zu ZNS-Degeneration

form of metachromatic leukodystrophy, affecting about 50 to 60 percent of all individuals with this disorder, is called the late infantile form. This form usually appears in the second year of life [14].

Technology:

autologe Stammzellentherapie

- OTL-200 is an autologous stem cell ex-vivo gene therapy. Hematopoietic stem cells are collected, purified and transduced in the same way for both (cryopreserved and fresh) formulations. For the cryopreserved formulation, following transduction, the gene-corrected cells are placed in a specific medium that allows them to be stable.

3.2.3 Elivaldogene tavalentivec (Lenti-D) (BluebirdBio)

Development/Regulatory Status:

derzeit in Entwicklung

- Elivaldogene tavalentivec is a therapy under development.

laufende Phase 3

- FDA and EMA granted Orphan Drug Designation (2012). FDA granted Breakthrough Therapy Designation for the treatment of cerebral adrenoleukodystrophy based on preliminary data from the ongoing phase 2/3 Starbeam Study, EMA grants PRIME status (2018).
- Phase 3 trial (ALD-104) started in 2019: Open-label single group assignment trial enrols 35 patients.
- BluebirdBio plans to launch Elivaldogene tavalentivec for Adrenoleucodystrophy (cerebral adrenoleukodystrophy) (CALD) in 2021/22 for the treatment of patients less than 18 years of age with early CALD for whom a human leukocyte antigen (HLA) – matched sibling haematopoietic stem cell (HSC) donor is not available.

Proposed Indication and Patients in Austria:

1 in 10.000 bis 17.000 Bevölkerung

- Adrenoleukodystrophy (ALD), or Lorenzos Oil disease, is a rare X-linked disorder caused by mutations of ABCD1. The prevalence of ALD is estimated to be between 1 in 10,000 and 1 in 17,000 individuals in the general population.

Condition:

fast ausschließlich bei Buben

meist im Kindesalter
oft schneller neurologischer Verfall

- Cerebral adrenoleukodystrophy - the most severe form of the disease - is a genetic disorder that occurs primarily in males. Symptoms of CALD usually occur in early childhood and progress rapidly if untreated, leading to a severe loss of neurological function and eventual death in most patients.
- It mainly affects the nervous system and the adrenal glands, which are small glands located on the top of each kidney. In this disorder, the fatty covering (myelin) that insulates nerves in the brain and spinal cord is prone to deterioration (demyelination), which reduces the ability of the nerves to relay information to the brain. There are three distinct types of X-linked adrenoleukodystrophy: a childhood cerebral form, an adrenomyeloneuropathy type, and a form called Addison disease only [14].

Technology:

autologe Stammzellentherapie

- Elivaldogene tavalentivec is an autologous stem cell therapy based on lentiviral vector expressing a human ATP-binding cassette, sub-

family D, member 1 (ABCD1) gene, transduced with autologous CD34+ haematopoietic stem cells.

3.2.4 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).

derzeit in Entwicklung

laufende Phase 2/3

Proposed Indication and Patients in Austria:

- Mucopolysaccharidosis is a common disease worldwide. Some forms are more common than others: the frequency also varies greatly in different countries. The number of patients with mucopolysaccharidosis has increased recently as the diagnosis has been improved and the knowledge of doctors is also increasing. For MPS 3 the incidence is estimated to be 1 in 20,000 children in Austria.

MPS 3
1:20.000 Kinder

Condition:

- Mucopolysaccharidoses are a group of metabolic disorders caused by the absence or malfunctioning of lysosomal enzymes needed to break down molecules called glycosaminoglycans (GAGs). Mucopolysaccharidosis type 3 (MPS 3), also known as Sanfilippo syndrome, is a progressive disorder that primarily affects the brain and spinal cord. It is characterized by the deterioration of neurological function (neurodegeneration), resulting in many of the features of the condition. Other body systems can also be involved, although the physical features are usually mild in the early stages. MPS III is divided into types 3A, 3B, 3C, and 3D, which are distinguished by their genetic cause. The different types of MPS 3 have similar signs and symptoms, although the features of MPS 3A typically appear earlier in life and progress more rapidly [14].

Gruppe der lysosomalen Speicherkrankheiten

vererbbaren Störungen des enzymatischen Abbaus der sauren Mukopolysaccharide (Glykosaminoglykane)

Typ MPS 3a, b,c,d

Condition: Mucopolysaccharidosis Type 3 A

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

3.2.5 rAAV9 (ABO-101) and scAAV9 (ABO-102) (Abeona)

Development/Regulatory Status:

derzeit in Entwicklung

- rAAV9 (ABO-101) and scAAV9 (ABO-102) are therapies under development.

laufende Phase 1/2

- 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) [16, 17].
- Efficacy data from the phase 1/2 Transpher A trial in Mucopolysaccharidosis 3 was released in May 2020.

Proposed Indication and Patients in Austria:

- See 3.2.4

Condition: MPS 3A (ABO-102) and MPS 3B (ABO-101)

- See 3.2.4

Technology:

AAV Vektorviren

Einmalinfusion

- 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.
  - 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.

3.2.6 ARO-AAT (Arrowhead)

Development/Regulatory Status:

derzeit in Entwicklung

- 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).
- 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 and Patients in Austria:

1 in 1.500 bis 3.500 Bevölkerung

- Alpha-1 antitrypsin deficiency occurs worldwide, but its prevalence varies by population. This disorder affects about 1 in 1,500 to 3,500 individuals with European ancestry.

Condition:

- Alpha-1 antitrypsin deficiency is an inherited disorder that may cause lung disease and liver disease. The signs and symptoms of the condition and the age at which they appear vary among individuals. People with alpha-1 antitrypsin deficiency usually develop the first signs and symptoms of lung disease between ages 20 and 50. Affected individuals often develop emphysema. About ten percent of infants with alpha-1 antitrypsin deficiency develop liver disease, which often causes yellowing of the skin and whites of the eyes (jaundice). Approximately 15 percent of adults with alpha-1 antitrypsin deficiency develop liver damage (cirrhosis) due to the formation of scar tissue in the liver [14].

Alpha-1 Antitrypsin Mangel

kann zu Leberzirrhose und Lungenemphysem führen

Technology:

- 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.

RNAi zur zielgerichteten Hemmung

3.2.7 Vutrisiran (ALN-TTRSC02) (Alnylam)

Development/Regulatory Status:

- Vutrisiran (ALN-TTRSC02) is a therapy under development.
- Vutrisiran has been granted Orphan Drug designation in the United States (U.S.) (Jun 2018) and the European Union (EU) (May 2018).
- 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.

derzeit in Entwicklung

Phase 3

Proposed Indication and Patients in Austria:

- The exact incidence of transthyretin amyloidosis is unknown. Transthyretin amyloidosis is less common among Americans of European descent, where it is estimated to affect 1 in 100,000 people.

1 in 100.000 Bevölkerung

Condition:

- Transthyretin amyloidosis is a slowly progressive condition characterized by the build-up of abnormal deposits of a protein called amyloid (amyloidosis) in the body's organs and tissues. These protein deposits most frequently occur in the peripheral nervous system, which is made up of nerves connecting the brain and spinal cord to muscles and sensory cells that detect sensations such as touch, pain, heat, and sound. Protein deposits in these nerves result in a loss of sensation in the extremities (peripheral neuropathy). The age at which symptoms begin to develop varies widely among individuals with this condition and is typically between ages 20 and 70 [14].

Amyloidose: Anreicherung von (zum Teil abnorm veränderten) Proteinen in Organen und Geweben

infolge Neuropathien

Technology:

RNAi zur gezielten Hemmung

- 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.

3.3 Ophthalmologic Disorders

Table 3-3: Ophthalmologic disorders therapies under development

Indication	Product	Sponsor	Development/Regulatory status
Choroideremia	Timrepigene emparvovec (AAV2-REP1)	Biogen	Phase 3: 11/2020 (EPCD), FDA: RMAT, FTD, BTT (2018) EMA: ODD (2015)
Leber Hereditary Optic Neuropathy	**Lenadogene nolparvovec (GS010)**	**GenSight Biologics**	**Phase 3: 6/2021 (EPCD), FDA approval expected in 2021 FDA: ODD (2013) EMA: ODD (2011)**
X-Linked Retinitis Pigmentosa	AAV8-RPGR	Biogen	Phase 2/3: 3/2021 (EPCD), FDA: ODD, FTD (2019) EMA: ODD (2018), ATMP, PRIME (2020)
Achromatopsia	AAV - CNGB3	MeiraGTx	Phase 1/2: 1/2022 (EPCD), FDA: ODD, FTD (2018) EMA: ODD, PRIME (2018)
Achromatopsia	ACHM CNGA3	Applied Genetic Tech	Phase 1/2: 6/2023 (EPCD), FDA: ODD (2018) EMA: ODD (2018)

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:

derzeit in Entwicklung

- Timrepigene emparvovec is a potential first-in-class AAV2 gene therapy for the treatment of choroideremia. It is under development.

Phase 3

- 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 and Patients in Austria:

- The prevalence of choroideremia is estimated to be 1 in 50,000 to 100,000 people. However, it is likely that this condition is underdiagnosed because of its similarities to other eye disorders.

1 in 50.000 bis 100.000 Bevölkerung

Condition:

- Choroideremia is a condition characterized by progressive vision loss that mainly affects males. The first symptom of this condition is usually an impairment of night vision (night blindness), which can occur in early childhood. A progressive narrowing of the field of vision (tunnel vision) follows, as well as a decrease in the ability to see details (visual acuity). These vision problems are due to an ongoing loss of cells (atrophy) in the specialized light-sensitive tissue that lines the back of the eye (retina) and a nearby network of blood vessels (the choroid). The vision impairment in choroideremia worsens over time, but the progression varies among affected individuals. However, all individuals with this condition will develop blindness, most commonly in late adulthood [14]. Choroideremia is thought to account for approximately 4 percent of all blindness.

seltene angeborene Erkrankung mit fortschreitender Atrophie der Aderhaut

Technology:

- 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.

AAV2 Vektor

3.3.2 Lenadogene nolparvovec (GS010) (GenSight Biologics)

Development/Regulatory Status:

derzeit in Entwicklung

- Lenadogene nolparvovec is a drug under development. Market launch in the US is planned for 2021.

Phase 3

- Lenadogene nolparvovec was designated Orphan Drug Status for Leber's hereditary optics neuropathy in the EU in 2011 and in the USA in 2013.

USA: Zulassung 2021 geplant

- It is currently in phase 3 clinical trial development.

Proposed Indication and Patients in Austria:

The worldwide prevalence of Leber's hereditary optic neuropathy (LHON) ranges between 1:15,000 and 1:50,000, in Austria about 100 persons are affected. It occurs five to ten times more often in men than in women.

1 in 15.000 bis 50.000, Ö: 100

Condition:

Lebersche Optikusatrophie

seltene, neurodegenerative Erbkrankheit der Ganglienzellen des Sehnervs

- LHON is an inherited form of vision loss. Although this condition usually begins in a person's teens or twenties, rare cases may appear in early childhood or later in adulthood. For unknown reasons, males are affected much more often than females. Blurring and clouding of vision are usually the first symptoms of LHON. These vision problems may begin in one eye or simultaneously in both eyes. In addition to vision loss, the features of LHON can include movement disorders, tremors, and abnormalities of the electrical signals that control the heartbeat (cardiac conduction defects). Some affected individuals develop features similar to multiple sclerosis, which is a chronic disorder characterized by muscle weakness, poor coordination, numbness, and a variety of other health problems [14].

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.

3.3.3 AAV8-RPGR (Biogen)

Development/Regulatory Status:

derzeit in Entwicklung Phase 2/3

- AAV-RPGR is a drug under development.
- 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:

1 in 3.500 bis 4.000

- Retinitis pigmentosa is one of the most common inherited diseases of the retina (retinopathies). It is estimated to affect 1 in 3,500 to 1 in 4,000 people in the United States and Europe.

Condition:

- Retinitis pigmentosa is a group of related eye disorders that cause progressive vision loss. These disorders affect the retina, which is the layer of light-sensitive tissue at the back of the eye. In people with retinitis pigmentosa, vision loss occurs as the light-sensing cells of the retina gradually deteriorate. The first sign of retinitis pigmentosa is usually a loss of night vision, which becomes apparent in childhood. The disease progresses over years or decades to affect central vision, which is needed for detailed tasks such as reading, driving, and recognizing faces. In adulthood, many people with retinitis pigmentosa become legally blind. Several major types of nonsyndromic retinitis pigmentosa distinguished by their pattern of inheritance: autosomal dominant, autosomal recessive, or X-linked (XLRP) [14].

durch Vererbung oder spontane Mutation entstehende Netzhautdegeneration, bei der die Photorezeptoren zerstört werden

Erblindung

Technology:

- 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.

AAV-Vektor

3.3.4 AAV - CNGB3 (MeiraGTx)

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).
- A **phase** 1/2 clinical trial is ongoing.

derzeit in Entwicklung Phase 1/2

Proposed Indication and Patients in Austria:

- Achromatopsia is estimated to affect 1 in 30,000 people worldwide. Complete achromatopsia is more common than incomplete achromatopsia.

1 in 30.000 Bevölkerung

Condition:

- Achromatopsia is a condition characterized by partial or total absence of colour vision. People with complete achromatopsia cannot perceive any colours; they see only black, white, and shades of grey. Incomplete achromatopsia is a milder form of the condition that allows some colour discrimination. Achromatopsia also involves other problems with vision, including an increased sensitivity to light and glare (photophobia), involuntary back-and-forth eye movements (nystagmus), and significantly reduced sharpness of vision (low visual acuity). Affected individuals can also have farsightedness (hyperopia) or, less commonly, nearsightedness (myopia). These vision problems develop in the first few months of life. Achromatopsia is different from the more

Achromatopsie oder Achromasie:

seltene, erbliche Störung der Farbwahrnehmung, nur Kontraste (hell-dunkel)

common forms of colour vision deficiency (also called colour blindness), in which people can perceive colour but have difficulty distinguishing between certain colours, such as red and green [14].

Technology:

AAV Vektor

- 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.

3.3.5 ACHM CNGA3 (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).
- ACHM CNGA3 is being developed in phase 1/2 clinical trials at the moment.

Proposed Indication and Patients in Austria and Condition:

- Achromatopsia (See 3.3.4)

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.

3.4 Musculoskeletal Disorders

Table 3-4: Muscular dystrophy therapies under development

Indication	Product	Sponsor	Development/Regulatory status
Duchenne Muscular Dystrophy (DMD)	SRP-9001 (AAVrh74.MHCK7)	Sarepta	Phase 2: 10/2022 (EPCD), FDA: ODD, FTD (2020) EMA: ODD (2020)
Duchenne Muscular Dystrophy (DMD)	PF-06939926	Pfizer	Phase 3: 6/2027 (EPCD), FDA: ODD (2017) EMA: ODD (2016)

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 (AAVrh74.MHCK7) (Sarepta)

Development/Regulatory Status:

derzeit in Entwicklung
Phase 1/2

- 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 planned.

Proposed Indication and Patients in Austria:

- Duchenne muscular dystrophy (DMD) is a rare muscle disorder but it is one of the most frequent genetic conditions affecting approximately 1 in 3,500 male births worldwide [18]. Estimated numbers for Austria are about 220 patients.

1 in 3.500 neugeborene Buben
Ö: 220

Condition:

- Muscular dystrophies are a group of genetic conditions characterized by progressive muscle weakness and wasting (atrophy). The Duchenne and Becker types of muscular dystrophy are two related conditions that primarily affect skeletal muscles, which are used for movement, and heart (cardiac) muscle. These forms of muscular dystrophy occur almost exclusively in males. Duchenne and Becker muscular dystrophies have similar signs and symptoms and are caused by different mutations in the same gene. The two conditions differ in their severity, age of onset, and rate of progression. In boys with Duchenne muscular dystrophy, muscle weakness tends to appear in early childhood and worsen rapidly. Affected children may have delayed motor skills, such as sitting, standing, and walking. They are usually wheelchair-dependent by adolescence [14].

Duchenne-Muskeldystrophie

häufigste muskuläre Erbkrankheit

Muskelschwäche

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

3.4.2 PF-06939926 (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).
- Updated efficacy and adverse events data from a phase 1b trial in treat DMD was released: a global phase 3 started in May 2020.

derzeit in Entwicklung
Phase 1/2
Beginn Phase 3

Proposed Indication and Patients in Austria & condition:

- Duchenne muscular dystrophy (DMD) (See 3.4.1)

Technology:

AAV Vektor

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

3.5 Vascular Disorders

Table 3-5: Cardiovascular disease therapies under development

Indication	Product	Sponsor	Development/ Regulatory status
Acute Myocardial Infarction (AMI) Painful diabetic peripheral neuropathies (PDPN)	Donaperminogene seltoplasmid (VM202RY)	Helixmith	Phase 2 (AMI): 4/2020 (EPCD), Phase 3 (PDPN): completed FDA: RMAT (2018) EMA: -
Heterozygous & Homozygous FH Atherosclerotic Cardiovascular Disease	**Inclisiran**	**Novartis**	**Phase 3: 9/2021** (EPCD), **FDA: under review** **EMA under evaluation**
Atherosclerotic Cardiovascular Disease	AMG 890	Amgen	Phase 2: 4/2023 (EPCD), FDA: - EMA: -
Critical Limb Ischemia (CLI) in Diabetes Mellitus (DM) (Type 1+2)	REX-001, Rexmyelocel T	Rexgenero	Phase 3: 10/2020 (EPCD), Phase 3: 10/2021 (EPCD), FDA: - EMA: ATMP

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 (VM202RY) (Helixmith)

Development/Regulatory Status:

derzeit in Entwicklung
Phase 3 für PDNP
Phase 2 AMI

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

Status unklar

- Donaperminogene seltoplasmid was granted Regenerative Medicine Advanced Therapy (RMAT) Designation in the U.S. (May 2018), but not by the EMA.
- 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. Helixmith announced plans to work on designing the next phase 3 trial to confirm data in the phase 3b extension study.

Proposed Indication and Patients in Austria:

54 % DM Typ 1
45 % DM Typ 2
entwickeln
Neuropathie

- The estimated annual incidence of peripheral diabetic neuropathy is between 268 and 371 cases per 100,000 inhabitants. The prevalence of people older than 55 years is about 3-5%. About 54 % of type 1 and 45 % of type 2 diabetics develop a neuropathy [19].

AMI: sehr häufig

- Acute Myocardial Infarction is a highly prevalent disease in western countries.

Condition:

Peripheral neuropathies are hereditary or acquired diseases affecting the cell body of peripheral sensory or motor neurons, their axon, or myelin; they are clinically defined as demyelinating and axonal, or neuropathy (when the cell body is affected). Peripheral neuropathies can be classified depending on their time course into acute, subacute or chronic. Diabetic neuropathy is the most common peripheral neuropathy in the western world. However, several other types of painful nerve damage, with different medical history, clinical and neurophysiological examinations can be recognized in diabetic patients [20].

Neuropathie: vererbt oder krankheitsbedingt (Diabetes)

Erkrankungen der peripheren Nerven

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

3.5.2 Inclisiran (Novartis)

Development/Regulatory Status:

- Inclisiran is a drug for (heterozygous and homozygous) Hypercholesterolaemia, but also patients in risk of Atherosclerotic Cardiovascular Disease with elevated LDL-cholesterol (LDL-C) despite maximum tolerated doses of LDL-C lowering therapies. It is under evaluation by EMA since February 2020 and also in the approval process at FDA.
- Updated efficacy data from the phase 3 ORION-11 trial in Hypercholesterolaemia and pooled adverse events and efficacy data from the phase 3 ORION-9, ORION-10 and ORION-11 trial for Hypercholesterolaemia were released in March 2020.
- Analysts predict this will be one of the top ten most-anticipated new US drug launches of 2020 based on estimated global sales in 2024.

bereits im Zulassungsprozess von EMA und FDA

3 Phase 3 Studien
Vorhersage: große Marktnachfrage

Proposed Indication and Patients in Austria:

- Heterozygous (familial) hypercholesterolemia (FH) affects an estimated 1 in 200 to 1 in 250 people in most countries and is thought to be the most common inherited condition affecting the heart and blood vessels (cardiovascular disease). Homozygous patients are rare and have an estimated prevalence of approximately 1:300,000 to 1:400,000.

Heterozygote FH: sehr häufig: 1 in 200 bis 250 Bevölkerung

Condition:

erbliche Hypercholesterinämie: hoher Cholesterinspiegel im Blut

Risikofaktor für Arteriosklerose

aber auch..

- FH is an inherited condition characterized by very high levels of cholesterol in the blood. Cholesterol is a waxy, fat-like substance that is produced in the body and obtained from foods that come from animals (particularly egg yolks, meat, poultry, fish, and dairy products). The body needs this substance to build cell membranes, make certain hormones, and produce compounds that aid in fat digestion. In people with FH, the body is unable to get rid of extra cholesterol, and it builds up in the blood. Too much cholesterol increases a person's risk of developing heart disease. People with FH have a high risk of developing a form of heart disease called coronary artery disease at a young age.

Risikopatient*innen mit KHK

- Atherosclerotic cardiovascular disease is a disease in which plaque builds up inside your arteries. Plaque is made up of fat, cholesterol, calcium, and other substances found in the blood. Over time, plaque hardens and narrows your arteries. Inclisiran is indicated in patients in patients who have failed to achieve optimal benefit or have contraindications or intolerances to first-line therapy.

Technology:

PCSK9 RNAi zur zielgerichteten Hemmung

- Inclisiran is a PCSK9 protein inhibitor; proprotein convertase subtilisin/kexin type 9 (PCSK9) modulates low-density lipoprotein (LDL)-cholesterol (LDL-C) levels through its ability to mediate the LDL receptor (LDLR) protein degradation via RNAi. In contrast to Repatha and Praluent, it works by another mechanism, RNA interference that keeps PCSK9 from being made in the liver. Inclisiran only needs to be injected twice a year to be effective, whereas Repatha and Praluent need to be injected at least once a month. On the plus side for Repatha and Praluent, patients can inject themselves; a clinician needs to inject inclisiran.

3.5.3 AMG-890 (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.
- A phase 2 trial starts in August 2020

Proposed Indication and Patients in Austria:

- Atherosclerotic cardiovascular disease is a highly prevalent disease in western countries. AMG-890 is investigated in patients with Lipoprotein (a) > 150 nmol/L and evidence of atherosclerotic cardiovascular disease.

Condition:

breite und ungenaue Indikation

- Elevated serum lipoprotein(a), also referred to as Lp(a), is a risk factor for atherosclerotic cardiovascular disease (ASCVD). There is a causal relationship between Lp(a) excess and the development of ASCVD and aortic valve stenosis.

- Lipoprotein(a), is a particle in the blood which carries cholesterol, fats and proteins. The amount the body produces is inherited from one or both parent. Atherosclerotic cardiovascular disease is a disease in which plaque builds up inside your arteries. Plaque is made up of fat, cholesterol, calcium, and other substances found in the blood. Over time, plaque hardens and narrows your arteries.

Technology:

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

RNA Interferenz (RNAi)

3.5.4 Rexmyelocel T (REX-001) (Rexgenero)

Development/Regulatory Status:

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

derzeit in Entwicklung: Tissue-engineered Produkt

2 Phase 3 Studien

Proposed Indication and Patients in Austria:

- CLI is the most severe form of peripheral artery disease (PAD) and imposes an increasing burden on health care. The incidence of CLI (stage III and IV according to Fontaine) lies between 0,5-1% of the total population (500–1,000 new cases per 1 million inhabitants). One of the main goals in the treatment of CLI is to prevent major amputation in patients with DM.

Prävalenz: 0,5-1% der Bevölkerung

Condition:

- CLI, the end-stage of PAD, is a severe obstruction of peripheral arteries, markedly reducing blood flow to the limbs. This often results in severe pain, skin ulcers, and gangrene leading to the requirement of limb amputation. Mortality rates can be as high as 40% within a year of diagnosis. DM is a major risk factor for PAD, and patients with diabetes are twice as likely as those without diabetes to develop the condition. PAD also progresses more rapidly in those with diabetes, and these patients are five to ten times more likely to need major amputation than patients without diabetes. PAD in patients with DM is often accompanied by peripheral neuropathy with sensory dysfunction. This means that patients may not be aware of the development of an ischaemic ulcer or gangrene, and the presentation of CLI in patients with diabetes is usually at a later stage than patients without diabetes, with more severe lesions.

kritische Extremitätenischämie resultiert in Schmerzen, Geschwüren

Risiko: Amputationen

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.

3.6 Nephrological Disorders

Table 3-6: Kidney disorder therapies under development

Indication	Product	Sponsor	Development/regulatory status
aHUS, IgA Nephropathy, glomerulonephritis	Cemdisiran (ALN-CC5)	Alnylam	Phase 2: 2/2023 (EPCD), **FDA: -** **EMA: -**
Primary Hyperoxaluria Type 1 (PH1)	**Lumasiran (ALN-GO1)**	**Alnylam**	**Phase 3: 5/2024 (EPCD),** **FDA: BTD, under review** **EMA: PRIME, under evaluation**

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:

derzeit in Entwicklung

- Cemdisiran is a drug under development for atypical hemolytic uremic syndrome (aHUS) and glomerulonephritis.

Phase 2

- A Phase 2 clinical trial in Paroxysmal nocturnal haemoglobinuria has started in 2020, then suspended. Now another phase 2 study is planned as a combination therapy with Eculizumab (Soliris; a recombinant humanized monoclonal antibody against the complement protein C5).

Proposed Indication and Patients in Austria:

1 in 500.000 Bevölkerung

- The incidence of aHUS is estimated to be 1 in 500,000 people per year in the United States. The atypical form is probably about ten times less common than the typical form.

Condition:

- aHUS is an extremely rare disease. aHUS is a disease that primarily affects kidney function. This condition, which can occur at any age, causes abnormal blood clots (thrombi) to form in small blood vessels in the kidneys. These clots can cause serious medical problems if they restrict or block blood flow. Atypical haemolytic-uremic syndrome is characterized by three major features related to abnormal clotting: haemolytic anaemia, thrombocytopenia, and kidney failure. Haemolytic anaemia occurs when red blood cells break down (undergo haemolysis) prematurely. In atypical haemolytic-uremic syndrome, red blood cells can break apart as they squeeze past clots within small blood vessels. Anaemia results if these cells are destroyed faster than they can replace them. As a result of clot formation in small blood vessels, people with atypical haemolytic-uremic syndrome experience kidney damage and acute kidney failure that lead to end-stage renal disease (ESRD) in about half of all cases. These life-threatening complications prevent the kidneys from filtering fluids and waste products from the body effectively [14].

atypisches hämolytisch urämisches Syndrom aHUS

Blutgerinnsel im ganzen Körper

infolge akutes Nierenversagen

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)

3.6.2 Lumasiran (ALN-GO1) (Alnylam)

Development/Regulatory Status:

- Lumasiran is a drug under development for primary Hyperoxaluria Type 1.
- Lumasiran was granted Breakthrough Therapy Designation by the FDA and PRIME status by EMA. Lumasiran received Priority Review status and is under review by the FDA (May 2020) and under evaluation by EMA (Apr 2020).
- A phase 3 trial, the ILLUMINATE-A trial in children, aged six years and older, and adults with primary hyperoxaluria type 1 is still ongoing.

derzeit in Entwicklung Phase 3

Proposed Indication and Patients in Austria:

- Primary hyperoxaluria is estimated to affect 1 in 58,000 individuals worldwide. Type 1 is the most common form, accounting for approximately 80 percent of cases. Types 2 and 3 each account for about ten percent of cases.

1 in 58.000 Bevölkerung

Condition:

Primäre Hyperoxalurie
Anstieg und vermehrte Ausscheidung der Oxalsäure im Urin

resultiert in Nierenfunktions-einschränkung

- Primary hyperoxaluria is a rare condition characterized by recurrent kidney and bladder stones. The condition often results in end-stage renal disease (ESRD), which is a life-threatening condition that prevents the kidneys from filtering fluids and waste products from the body effectively. Primary hyperoxaluria results from the overproduction of a substance called oxalate. Oxalate is filtered through the kidneys and excreted as a waste product in urine, leading to abnormally high levels of this substance in urine (hyperoxaluria). During its excretion, oxalate can combine with calcium to form calcium oxalate, a hard compound that is the main component of kidney and bladder stones. Deposits of calcium oxalate can damage the kidneys and other organs and lead to blood in the urine (haematuria), urinary tract infections, kidney damage, ESRD, and injury to other organs. In primary hyperoxaluria type 1, kidney stones typically begin to appear anytime from childhood to early adulthood [14].

Technology:

RNA Interferenz (RNAi)

- Lumasiran (ALN-GO1) is a subcutaneously administered, investigational RNAi therapeutic targeting glycolate oxidase (GO) in development for the treatment of Primary Hyperoxaluria Type 1. Lumasiran utilizes the Enhanced Stabilization Chemistry (ESC)-GalNAc delivery plat-form developed by Alnylam to enables subcutaneous dosing with increased potency and durability.

3.7 Dermatologic Disorders

Table 3-7: Dermatologic disorder therapies under development

Indication	Product	Sponsor	Development/ regulatory status
Epidermolysis bullosa	EB-101	Abeona	Phase 3: 3/2021 (EPCD), FDA: ODD (2017) EMA: ODD (2017)
Epidermolysis bullosa	FCX-007	Fibrocell	Phase 3: 3/2021 (EPCD), FDA: ODD, PDD (2015), FTD, PDD (2017), RMAT EMA: -

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 EB-101 (Abeona)

Development/Regulatory Status:

derzeit in Entwicklung
Beginn Phase 3

- 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).

- 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 and Patients in Austria:

- Epidermolysis bullosa (EB) is a rare disease with a prevalence of 1: approximately 1 in 53,000 newborn. In Austria, there are about 500 people living with EB [21].

1 in 17.000, 500 in Ö

Condition:

- Inherited EB comprises a clinically and genetically heterogeneous group of rare genetic diseases characterized by skin fragility and blister formation following minor trauma. Patients with RDEB lack a protein called type VII collagen, which is an important component of the anchoring fibrils that attach the epidermis (top layer of the skin) to the dermis (layer of skin below the epidermis). This lack prevents the upper skin layer from binding with the lower, causing symptoms such as chronic skin blistering, and open and painful chronic wounds on skin and mucus membranes. Disease-causing variants in at least 20 different genes account for the genetic heterogeneity of EB [14].

Epidermolysis bullosa

„Schmetterlingskinder“

Technology:

- 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.

autologe Zelltherapie

3.7.2 FCX-007 (Fibrocell)

Development/Regulatory Status:

- 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.

derzeit in Entwicklung Phase 3

Proposed Indication and Patients in Austria & Condition:

- Recessive Dystrophic Epidermolysis Bullosa (See 3.7.1)

Technology:

- 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.

autologe Zelltherapie

3.8 Neurologic Disorders

Table 3-8: Neurologic disorder therapies under development

Indication	Product	Sponsor	Regulatory/ development status
Huntington Disease	Tominersen (RG-6042)	Roche	Phase 3: 7/2022 (EPCD), FDA: ODD (2016), EMA: ODD (2016), PRIME (2018)
Parkinson's Disease	VY-AADC02	Neurocrine Biosciences	Phase 2: 12/2022 (EPCD), FDA: - EMA: -
Acute Traumatic Spinal Cord Injury	NeuroSave (FAB117-HC)	Ferrer	Phase 1/2: 3/2022 (EPCD), FDA: - EMA: -

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:

derzeit in Entwicklung
Beginn Phase 3

- 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.

Proposed Indication and Patients in Austria:

2-7 in 100.000
Bevölkerung
500 in Ö

- Huntington disease affects an estimated 3 to 7 per 100,000 people of European ancestry. In Austria, there are about 500 people living with HD. In studies from Europe, North America and Australia, the prevalence of HD was 5.7 per 100,000.

Condition:

Chorea Huntington
erbliche Erkrankung
des Gehirns

neurodegenerative
Erkrankung

um das 40. Lebensjahr

- HD is a progressive brain disorder that causes uncontrolled movements, emotional problems, and loss of thinking ability (cognition). Adult-onset Huntington disease, the most common form of this disorder, usually appears in a person's thirties or forties. Early signs and symptoms can include irritability, depression, small involuntary movements, poor coordination, and trouble learning new information or making decisions. Many people with Huntington disease develop involuntary jerking or twitching movements known as chorea. As the disease progresses, these movements become more pronounced. Affected individuals may have trouble walking, speaking, and swallowing. People with this disorder also experience changes in personality and a decline in thinking and reasoning abilities. Individuals with the adult-onset form of Huntington disease usually live about 15 to 20 years after signs and symptoms begin. A less common form of Huntington disease known as the juvenile form begins in childhood or adolescence [14].

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 krankheits-fördernder Proteine

3.8.2 VY-AADC02 (Neurocrine Biosciences)

Development/Regulatory Status:

- VY-AADC02 is a treatment under development for Parkinson's disease.

derzeit in Entwicklung
Planung Phase 3

FDA/EMA status is not available.

- A phase 2 RESTORE-1 trial in Parkinson's disease is ongoing, phase 3 RESTORE-2 trial is being planned in patients diagnosed four or more years ago (with motor fluctuations).

Proposed Indication and Patients in Austria:

- The frequency of Parkinson disease (PD) varies depending on the diagnostic criteria, study population, and epidemiologic methods used. With these caveats in mind, the worldwide prevalence of PD was approximately 0.3 percent in the general population 40 years of age and older. Estimates of the incidence of PD range from 8 to 18.6 per 100,000 people.
- The late-onset form is the most common type of Parkinson disease, and the risk of developing this condition increases with age. Because more people are living longer, the number of people with this disease is expected to increase in the coming decades. In Austria, there are about 20.000 people living with Parkinson disease.

13 in 100.000

ca 20.000 in Ö

Condition:

- Parkinson disease is a progressive disorder of the nervous system. The disorder affects several regions of the brain, especially an area called the substantia nigra that controls balance and movement. Often the first symptom of Parkinson disease is trembling or shaking (tremor) of a limb, especially when the body is at rest. Typically, the tremor begins on one side of the body, usually in one hand. Tremors can also affect the arms, legs, feet, and face. Other characteristic symptoms of Parkinson disease include rigidity or stiffness of the limbs and torso, slow movement (bradykinesia) or an inability to move (akinesia), and impaired balance and coordination (postural instability). These symptoms worsen slowly over time. Generally, Parkinson disease that begins after age 50 is called late-onset disease. The condition is described as an early-onset disease if signs and symptoms begin before age 50. Early-onset cases that begin before age 20 are sometimes referred to as juvenile-onset Parkinson disease [14].

Morbus Parkinson

langsam fortschreitender Verlust von Nervenzellen

Technology:

- VY-AADC uses the AAV2 capsid as a vector encoding AADC; expression is driven by a cytomegalovirus promoter. VY-AADC attempts to

AAV Vektor

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.

3.8.3 NeuroSave (FAB117-HC) (Ferrer)

Development/Regulatory Status:

derzeit in Entwicklung Planung Phase 1/2

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

Proposed Indication and Patients in Austria:

2-3 in 100.000 Bevölkerung

- The worldwide incidence of traumatic SCI varies greatly: although a global incidence of 2.3 cases/100,000 inhabitants was estimated in 2007, the figures found in the literature cover a broad range [22]. In the concrete case of Germany, it lists approximately 80,000 cases of a total of 81.1 million inhabitants [23].

Condition:

akute Verletzung von Wirbelsäule und Rückenmark

sekundäre Komplikationen

- Traumatic SCI is a devastating neurological condition. The management of SCI demands the contribution of important healthcare resources since coordinated and multidisciplinary action is required not only for highly specialized care in the acute phase but also for the associated secondary complications that arise over the long term [22]. Traumatic SCI can give rise to a range of neurological problems, including motor and sensory function loss, intestinal and bladder dysfunction, spasticity, neuropathic pain and autonomic dysreflexia. Acute traumatic SCI involves primary and secondary injury mechanisms. The primary mechanism is related to the initial mechanical damage caused by local deformation and energy transformation within the spinal cord at the time of injury, and this damage is irreversible. The secondary mechanisms intervene after the initial traumatic event and lead to tissue destruction during the first hours after injury. These secondary mechanisms include processes such as ischemia, axonal degeneration, vascular dysfunction, oxidative stress, excitotoxicity, demyelination and inflammation leading to cell death, and are potentially avoidable and/or reversible. This concept is crucial for the development of protective strategies aimed at improving the prognosis of patients with acute traumatic SCI [22].

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 [24]. 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 [25].

4 DISCUSSION

4.1 Summary of findings

Fortschritte in den medizinischen Therapien zu „individuelleren“ Therapieansätzen

Recent advancements in biological therapies have initiated a shift from the traditional ‘one-size fits all’ approach towards personalized medicinal strategies. ATMPs are at the forefront of this new tendency. ATMP is the umbrella term for three drug product classes: Somatic cell therapies, gene therapeutics and tissue-engineered products as well as a combination of these technologies with a medicinal product. All ATMP classes contain either living cells or viral vectors and are therefore characterized by a high degree of complexity. Cells are usually derived from a patient or an allogeneic donor, processed in the laboratory (e.g. expanded in vitro or genetically engineered) and (re-) administered to the patient in a hospital. Gene therapy is designed to introduce genetic material into living cells to compensate for abnormal genes or express a beneficial protein [2].

seit 2008 ATMP Zulassungs-Verordnung

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.

10 Jahre später: 2018: 8 ATMPs 2020: 11: ATMPs derzeit 3 im Zulassungsverfahren insg. 32 Therapien identifiziert in 8 Indikationsfeldern

Ten years later, in August 2018 eight ATMPs, and two years later in August 2020 eleven ATMPs are approved and three are under evaluation by the EMA. Our search identified 32 ATMPs and gene therapies (CAR-T cell therapies and oncologic indications excluded) in late-stage development (phase 2 or 3 trials), which will reach the market in the years to come. It is forecasted [6] that until 2022 around such 16 will be approved. The areas of indications are a diversity of genetic diseases and encompass eight broad indication groups (see chapters). Four therapies are already under evaluation by EMA, five are expected to enter the approval process in late 2020 or 2021.

*Table 4-1: Therapies in approval process (n=4) or short before approval process (n=5)**

Indication	Product	Sponsor	FDA/EMA: approval expected in (year)
Haemophilia A	**Valoctocogene roxaparvovec (BMN-270)**	BioMarin	Phase 3: 9/2023 (EPCD); FDA: rejected (8/2020) **EMA: under evaluation**
Haemophilia A	**Fitusiran**	Sanofi	Phase 3: 6/2021 (EPCD); **EMA/FDA approval expected in 2021**
Haemophilia B	**Etranacogene dezaparvovec (AMT-06, AAV5-hFIXco-Padua)**	UniQure	Phase 3: 8/2024 (EPCD); **EMA/FDA approval expected in 2021**
ADA Immunodeficiency	**Simoladagene autotemcel (OTL-101)**	Orchard	Phase 2/3: 2/2021 (EPCD); **FDA approval expected in 2020, EMA 2021**
Metachromatic Leukodystrophy	**OTL-200**	Orchard	Phase 3: 1/2032 (EPCD); **FDA/EMA under evaluation**
Cerebral Adrenoleukodystrophy	Elivaldogene tavalentivec (Lenti-D)	Bluebird bio	Phase 3: 7/2023 (EPCD), **EMA/FDA approval expected in 2021**
Leber Hereditary Optic Neuropathy	**Lenadogene nolparvovec (GS010)**	GenSight Biologics	Phase 3: 6/2021 (EPCD), **EMA/ FDA approval expected in 2021**
Heterozygous & Homozygous FH	**Inclisiran**	Novartis	Phase 3: 9/2021, **EMA under evaluation**
Primary Hyperoxaluria Type 1 (PH1)	**Lumasiran (ALN-GO1)**	Alnylam	Phase 3: 5/2024 (EPCD), FDA: under review, **EMA: under evaluation**

*see also 4.3 limitations of search strategy

4.2 Challenges

oft als kurative Therapien bezeichnet trotzdem keine Langzeit Daten vorliegen

There are numerous challenges in the evaluation of these therapies. They have received advance praise and are often referred to as "curative" or "disruptive" technologies, though hardly any long—term data are available for the few therapies already approved. The causes for the advance praise might be found in the high expectations of gene therapies. These are defined as products that replace or circumvent defective genes by a variety of mechanisms [26]:

hohe Erwartungen an Gentherapien

- Replacing a disease-causing gene with a healthy copy of the gene,
- Repairing, inactivating, or modulating a disease causing gene that is not functioning properly, or
- Introducing a new or modified gene into the body to help treat a disease.

prominente Beispiele für öffentlichen Diskurs (und Erwartungen):

CAR-T SMA-Therapien

The most prominent approved therapies are the CAR-T cell therapies and those for spinal muscular atrophy (SMA) (Nusinersen/Spinraza® and Onasemnogene abeparvovec/Zolgensma®), that have been given extensive public attention mainly due to their exorbitant prices. But the challenges that have to be faced are not only the financial burden, but technological and ethical challenges. Experts and stakeholders are exploring ways to tackle some of the most challenging issues, such as

- modifying the approval and pre-reimbursement assessment process,
- payment and reimbursement strategies, incl. exploring conditions for publicly financed preclinical R&D.

Aufgabe von HTA: enge Beobachtung der echten Effekte

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.

Herausforderungen:

There are still many unknown issues [26] such as

technologische Fragen

- **Technological risks**: The potential of the disruption of the genome by replacing or modulating genes for the individual (adverse outcomes: immune response or organ failure) and for future generations is an open question. Patients´registries to track the long-term effectiveness and long-term risks and harms are proposed. Additional truly informed consent of the risks and provider and patient literacy is demanded.

finanzielle Risken

- **Financial risks**: The potential of disrupting the solidarity-based health care systems by unaffordable and unstainable prices has become a matter of concern. Transparency of price-building, a close observation of the public contribution to the development of the therapies, public manufacturing in centres of excellence (e.g. of CAR-T celltherapies) and alternative public procurement and reimbursement methods are proposed and piloted.

ethische Fragen des Zugangs

- **Ethical risks**: The unequal access to time- and cost-intensive therapies disrupts democratic societies and is perceived as a true danger. Additional the raising of expectations for "curative" therapies without evidential proofs and without the public understanding of the dark sides of gene therapies and their risks is unethical. Health policy is asked to set frameworks for equal access to truly innovative therapies and to set conditions for those not proven to be effective yet.

regulatorische Auflagen

- **Regulatory challenges**: Due to the nature of gene therapies to be truly individualized many of the therapies are approved and come to the

market with little evidence and only short-term follow-up data. Conditional approvals, close monitoring and re-evaluations are therefore demanded with effectual consequences (of e.g. regulatory withdrawals in cases of unbalanced risk-benefit relation).

4.3 Limitations of the searches

Limitationen der Suchstrategien:

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.

nur in 2 Registern, aber unwahrscheinlich dass nicht in EudraCT registriert

aber: wesentliche Limitation

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, were missed. As a prominent example, that was missed-out, is risdiplam (Evrysdi®, Roche, approved on Aug 7th by FDA), the 3rd SMA therapy that will soon be marketed in Europe. It is an investigational survival motor neuron 2 (SMN2) splicing modifier for SMA, which is designed to increase and sustain SMN protein levels in the central nervous system and throughout the body. Five ongoing trials are registered:

Suchbegriffe Gentherapie, ATMP

3. SMA-Therapie von Roche als "chemical drug" registriert

im August von FDA zugelassen

5 laufende Studien

1. FIREFISH: 1-year results on motor function in babies 1-7 months with Type 1 SMA receiving risdiplam (RG7916) (NCT02913482)
2. FIREFISH: Survival, ventilation and swallowing ability in infants with Type 1 SMA receiving risdiplam (RG7916)
3. Update from SUNFISH: Safety, tolerability and PK/PD from the dose-finding study, including exploratory efficacy data in patients with Type 2 or 3 SMA (children and young adults/adolescents: 2-25 years) treated with risdiplam (RG7916) (NCT02908685)
4. JEWELFISH: exploratory, non-comparative, and open-label study to investigate the safety, tolerability, PK, and PK/PD relationship of risdiplam in adults, children and infants with SMA previously enrolled in Study BP29420 (Moonfish) with the splicing modifier RO6885247 or previously treated with nusinersen, olesoxime or AVXS-101. (NCT03032172)
5. RAINBOWFISH: in infants with genetically diagnosed and pre-symptomatic SMA (NCT03779334)

For the above mentioned reasons this report might not be comprehensive covering all upcoming therapies based on genetic knowledge.

4.4 Learnings and Recommendation

Horizon Scanning als Blick in die Zukunft

wird immer wichtiger

hochaufwändig (Zeit- und Kosten intensiv)

Horizon Scanning (HSS) has become an activity in many countries, meaning "keeping an eye on the future for upcoming change; understanding future medicines, devices and diagnostics, helping to shape policy, regulation, approvals and stimulating research activity" [27].

Examples for HSS in Oncology and other Medicines are

- AT - LBI-HTA/AIHTA Horizon Scanning in Oncology: https://aihta.at/page/horizon-scanning-in-der-onkologie-berichte/en
- SCO – SCO: Scottish Medicines Consortium: https://www.scottish-medicines.org.uk/about-us/horizon-scanning/
- UK – SPS: Specialist Pharmacy Service: https://www.sps.nhs.uk/articles/sps-horizon-scanning-service/
- Etc.

Examples for HSS for a broad range of interventions (also, but not only medicines)

- UK - NIHR Innovation Observatory: new drugs, devices and diagnostics: http://www.io.nihr.ac.uk/
- CA- CADTH: Emerging Health Technologies: https://www.cadth.ca/about-cadth/what-we-do/products-services/horizon-scanning
- AUS & NZ – ANZHSN: Australia and New Zealand Horizon Scanning Network: http://www.horizonscanning.gov.au/
- Etc.

EMA: PRIME Designation

40% der PRIME-Medikamente sind ATMPs

Additionally, the EMA launched the PRIME scheme in March 2016. The scheme provides early and enhanced scientific and regulatory support to medicines that have the potential to significantly address patients' unmet medical needs. Most ATMPs (including gene therapies) and most therapies with Orphan Drug Designation receive also PRIME designation. Monitoring PRIME can therefore be a short-cut to the identification of novel ATMPs and gene therapies in the pipeline of the EMA. The same is true for FDA´s "Breakthrough Designation" [28, 29].

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 [8] 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!

It is strongly recommended

- to join forces in supranational centres of activity, such as the BeNeLuxA initiative on Horizon Scanning: https://beneluxa.org/horizonscanning and the associated International Horizon Scanning Initiative (IHSI): https://ihsi-health.org/ in favour of fair pricing of medicines.

From the perspective of decision-makers (e.g. in centres of expertise, university hospitals) on the implementation of new health technologies it is not only of interest

- which new interventions and medicines are upcoming (Horizon Scanning), but
- how they perform (early assessment)
- in comparison to established interventions (assessment of comparative effectiveness),
- national access schemes (national recommendations for exact indications) for expert- und cost-intensive therapies,
- national price negotiations, and
- finally patient data collections to generate evidence on the true effects and ev. harms of these cost-intensive therapies.

Teilnahme an BeNeLuxA(IR) HSS resp. IHSI

nationale Zugangsbestimmungen und Preisverhandlungen

sind wichtig

außerdem: Patientenregister zum langfristigen Nutzen (und Schaden) der Therapien

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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	NCT03549871	A Study of **Fitusiran** in Severe Haemophilia A and B Patients Previously Receiving Factor or Bypassing Agent Prophylaxis	Recruiting	Haemophilia	Fitusiran	Genzyme (Sanofi)	Phase 3	70	July 30, 2018	March 2022	**FDA/EMA: 2021?**
	NCT03974113	**Fitusiran** Prophylaxis in Male Paediatric Subjects Aged 1 to Less Than 12 Years With Haemophilia A or B	Recruiting				Phase 2, Phase 3	12	January 28, 2020	February 2025	
	NCT03754790	Long-term Safety and Efficacy Study of **Fitusiran** in Patients With Haemophilia A or B, With or Without Inhibitory Antibodies to Factor VIII or IX	Recruiting				Phase 3	244	January 9, 2019	January 2026	
	NCT03417102	A Study of **Fitusiran** (ALN-AT3SC) in Severe Haemophilia A and B Patients With Inhibitors	Active, not recruiting	Haemophilia A, Haemophilia B			Phase 3	54	February 14, 2018	June 2021	
	NCT03417245	A Study of **Fitusiran** (ALN-AT3SC) in Severe Haemophilia A and B Patients Without Inhibitors	Active, not recruiting				Phase 3	120	March 1, 2018	August 2021	
2	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	June 2020	December 2025	**EMA: under evaluation**
	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					40	March 14, 2018	March 1, 2024	
	NCT03370913	Single-Arm Study To Evaluate The Efficacy and Safety of **Valoctocogene**	Active, not recruiting					134	December 19, 2017	September 2023	

Rank	Trial-ID	Title	Status	Conditions	Interventions	Lead Sponsor	Phase	N of Patients	Start date	Completion date	Approval Status
		Roxaparvovec in Haemophilia A Patients									
3	NCT04370054	Study to Evaluate the Efficacy and Safety of PF-07055480 in Moderately Severe to Severe Haemophilia A Adults	Not yet recruiting	Haemophilia A	Recombinant AAV2/6 (giroctocogene fitelparvovec)	Pfizer	Phase 3	63	July 15, 2020	November 5, 2026	
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 Haemophilia B	Recruiting	Haemophilia B	PF-0683843 (fidanacogene elaparvovec)	Pfizer	Phase 3	55	July 29, 2019	November 24, 2026	
5	NCT03641703	A Long-Term Follow-Up Study of Haemophilia B Patients Who Have Undergone Gene Therapy	Recruiting	Haemophilia B	FLT180a	Freeline Therapeutics	Phase 2, Phase 3	50	July 10, 2018	December 31, 2035	
6	NCT03569891	HOPE-B: Trial of AMT-061 in Severe or Moderately Severe Haemophilia B Patients	Active, not recruiting	Haemophilia B	AAV5-hFIXco-Padua	UniQure Biopharma	Phase 3	56	June 27, 2018	August 2024	
	NCT03489291	Dose Confirmation Trial of **AAV5-hFIXco**-Padua	Active, not recruiting				Phase 2	3	July 24, 2018	September 20, 2023	
	Metabolic Disorders										
7	NCT03315182	Gene Transfer Clinical Trial for Mucopolysaccharidosis (MPS) IIIB	Recruiting	Mucopolysaccharidosis Type 3 B	rAAV9.CMV.hNAGLU (ABO-101)	Abeona Therapeutics	Phase 1, Phase 2	15	October 16, 2017	October 2022	
	NCT02716246	Phase I/II Gene Transfer Clinical Trial of **scAAV9.U1a.hSGSH**	Recruiting	Mucopolysaccharidosis 3A	scAAV9.U1a.hSGSH (ABO-102)		Phase 1, Phase 2	22	March 2016	December 2022	
9	NCT01474343	Intracerebral Gene Therapy for Sanfilippo Type A Syndrome	Completed	Mucopolysaccharidosis Type 3 A	SAF-301	Lysogene	Phase 1, Phase 2	4	August 2011	May 2013	June 2020: FDA issues Clinical hold
	NCT03612869 EudraCT2018-000195-15	Study of **AAVrh10-h.SGSH** Gene Therapy in Patients With Mucopolysaccharidosis Type IIIA (MPS IIIA) (AAVance)	Active, not recruiting		SAF-302		Phase 2, Phase 3	20	December 17, 2018	March 2022	
10	NCT03759379	HELIOS-A: A Study of **Vutrisiran** (ALN-TTRSC02) in Patients With Hereditary	Active, not recruiting	(hATTR) amyloidosis	Vutrisiran (ALN-TTRSC02)	Alnylam Pharmaceuticals	Phase 3	164	January 18, 2019	May 2024	

Rank	Trial-ID	Title	Status	Conditions	Interventions	Lead Sponsor	Phase	N of Patients	Start date	Completion date	Approval Status
		Transthyretin Amyloidosis (hATTR Amyloidosis)									
	NCT04153149	HELIOS-B: A Study to Evaluate **Vutrisiran** in Patients With Transthyretin Amyloidosis With Cardiomyopathy	Recruiting	(hATTR) amyloidosis			Phase 3	600	November 26, 2019	June 2025	
11	NCT03946449	Assessment of Changes in a Novel Histological Activity Scale in Response to **ARO-AAT**	Recruiting	Alpha 1-Antitrypsin Deficiency	ARO-AAT	Arrowhead Pharmaceuticals	Phase 2	12	December 19, 2019	November 15, 2021	
	NCT03945292	Safety, Tolerability and Effect on Liver Histologic Parameters of ARO-AAT Alpha 1-Antitrypsin Deficiency	Recruiting				Phase 2, Phase 3	120	August 7, 2019	May 1, 2023	
12	NCT04283227	**OTL-200** in Patients With Late Juvenile Metachromatic Leukodystrophy (MLD)	Recruiting	Lysosomal Storage Disease, Metachromatic Leukodystrophy	OTL-200	Orchard Therapeutics	Phase 3	6	June 2020	January 2032	
	NCT03392987	A Safety and Efficacy Study of Cryopreserved **OTL-200** for Treatment of Metachromatic Leukodystrophy (MLD)	Active, not recruiting				Phase 2	10	January 25, 2018	August 23, 2028	
13	NCT04140539	A Clinical Study to Enable Process Validation of Commercial Grade **OTL-101**	Recruiting	Severe Combined Immunodeficiency Due to ADA Deficiency	OTL-101 (Simoladagene autotemcel)	Orchard Therapeutics	Phase 2, Phase 3	3	October 15, 2019	February 28, 2021	
14	NCT03852498	Clinical Study to Assess the Efficacy and Safety of Gene Therapy for the Treatment of Cerebral Adrenoleukodystrophy (CALD)	Recruiting	Cerebral Adrenoleukodystrophy (CALD)	Lenti-D (Elivaldogene tavalentivec)	Bluebird bio	Phase 3	35	January 24, 2019	July 2023	
	Ophthalmologic disorders										
	NCT02407678	REP1 Gene Replacement Therapy for Choroideremia	Active, not recruiting	Choroideremia	AAV-mediated REP1 gene replacement	University of Oxford	Phase 2	30	Aug.16	August 2021	
	NCT03496012	Efficacy and Safety of **AAV2-REP1** for the Treatment of Choroideremia	Active, not recruiting	Choroideremia	AAV2-REP1	NightstaRx (Biogen)	Phase 3	169	December 11, 2017	November 30, 2020	
15	NCT03507686	A Safety Study of Retinal Gene Therapy for Choroideremia	Active, not recruiting				Phase 2	60	November 6, 2017	February 28, 2022	

Rank	Trial-ID	Title	Status	Conditions	Interventions	Lead Sponsor	Phase	N of Patients	Start date	Completion date	Approval Status
	NCT02553135	Choroideremia Gene Therapy Clinical Trial	Completed/ Has results			Byron Lam	Phase 2	6	Sep.15	February 2018	
	NCT02671539	THOR - Tübingen Choroideremia Gene Therapy Trial	Active, not recruiting			STZ Eyetrial	Phase 2	6	January 2016	March 2021	
16	NCT03001310	Gene Therapy for Achromatopsia (**CNGB3**)	Completed	Achromatopsia	AAV - CNGB3	MeiraGTx	Phase 1, Phase 2	23	January 16, 2017	October 25, 2019	
	NCT03278873	Long-Term Follow-Up Gene Therapy Study for Achromatopsia **CNGB3** and **CNGA3**	Recruiting		or CNGA3		Phase 1, Phase 2	72	June 27, 2017	August 7, 2024	
	NCT03758404	Gene Therapy for Achromatopsia (**CNGA3**)	Recruiting		AAV- CNGA3		Phase 1, Phase 2	18	July 18, 2019	January 2022	
17	NCT02599922	Safety and Efficacy Trial of AAV Gene Therapy in Patients With **CNGB3** Achromatopsia	Recruiting	Achromatopsia	rAAV2tYF-PR1.7-hCNGB3 (ACHM CNGB3)	Applied Genetic Technologies	Phase 1, Phase 2	24	February 2016	June 2024	
	NCT02935517	Safety and Efficacy Trial of AAV Gene Therapy in Patients With **CNGA3** Achromatopsia	Recruiting		rAAV2tYF-PR.1-hCNGA3 (ACHM CNGA3, AGTC-402)		Phase 1, Phase 2	24	May 1, 2017	June 2023	
18	NCT03116113	A Clinical Trial of Retinal Gene Therapy for X-linked Retinitis Pigmentosa	Recruiting	X-Linked Retinitis Pigmentosa	AAV8-RPGR	NightstaRx (Biogen)	Phase 2, Phase 3	63	March 16, 2017	March 2021	
19	NCT03406104	RESCUE and REVERSE Long-term Follow-up	Recruiting	Leber Hereditary Optic Neuropathy	GS010 (Lenadogene nolparvovec)	GenSight Biologics	-	74	January 9, 2018	August 2022	**EMA pre-submission meeting**
	NCT02652767	Efficacy Study of **GS010** for the Treatment of Vision Loss up to 6 Months From Onset in LHON Due to the ND4 Mutation	Completed				Phase 3	39	February 23, 2016	July 4, 2019	
	NCT02652780	Efficacy Study of **GS010** for Treatment of Vision Loss From 7 Months to 1 Year From Onset in LHON Due to the ND4 Mutation (REVERSE)	Completed				Phase 3	37	January 2016	December 2018	
	NCT03293524	Efficacy & Safety Study of Bilateral IVT Injection of **GS010** in LHON Subjects Due to the ND4 Mutation for up to 1 Year	Active, not recruiting				Phase 3	90	March 12, 2018	June 30, 2021	

Rank	Trial-ID	Title	Status	Conditions	Interventions	Lead Sponsor	Phase	N of Patients	Start date	Completion date	Approval Status
	Musculoskeletal disorder										
20	NCT04281485	A Phase 3 Study to Evaluate the Safety and Efficacy of **PF-06939926** for the Treatment of Duchenne Muscular Dystrophy	Not yet recruiting	Duchenne Muscular Dystrophy	PF-06939926	Pfizer	Phase 3	99	July 16, 2020	June 9, 2027	
21	NCT03769116	A Randomized, Double-blind, Placebo-controlled Study of SRP-9001 for Duchenne Muscular Dystrophy (DMD)	Active, not recruiting	Duchenne Muscular Dystrophy	SRP-9001 /AAVrh74.MHCK7.micro dystrophin	Sarepta	Phase 2	41	December 22, 2018	October 10, 2022	
	Vascular disorder										
22	NCT03404024	Safety and Efficacy Study of Gene Therapy for Acute Myocardial Infarction in Korea	Recruiting	Acute Myocardial Infarction	VM202RY (Donaperminogene seltoplasmid)	Helixmith	Phase 2	108	January 25, 2018	April 2020	
	NCT02427464	Phase 3 Gene Therapy for Painful Diabetic Neuropathy	Completed	Painful diabetic peripheral neuropathies (PDPN)			Phase 3	507	April 2016	July 2019	
23	NCT03814187	Trial to Assess the Effect of Long Term Dosing of **Inclisiran** in Subjects With High CV Risk and Elevated LDL-C	Active, not recruiting	Heterozygous FH, Homozygous FH	Inclisiran	The Medicines Company	Phase 3	2991	April 16, 2019	December 2023	**EMA: under evaluation**
	NCT03851705	A Study of **Inclisiran** in Participants With Homozygous Familial Hypercholesterolemia (HoFH)	Active, not recruiting	Homozygous FH			Phase 3	56	February 6, 2019	September 2021	
	NCT03400800	**Inclisiran** for Subjects With ACSVD or ACSVD-Risk Equivalents and Elevated Low-density Lipoprotein Cholesterol	Completed	Atherosclerotic Cardiovascular Disease			Phase 3	1617	November 1, 2017	August 27, 2019	
	NCT03705234	A Randomized Trial Assessing the Effects of **Inclisiran** on Clinical Outcomes Among People With Cardiovascular Disease	Recruiting	Atherosclerotic Cardiovascular Disease		University of Oxford	Phase 3	15000	October 30, 2018	December 2049	

Rank	Trial-ID	Title	Status	Conditions	Interventions	Lead Sponsor	Phase	N of Patients	Start date	Completion date	Approval Status
	NCT02963311	A Study of ALN-PCSSC in Participants With Homozygous Familial Hypercholesterolemia (HoFH)	Completed/ Has results	Homozygous FH		The Medicines Company	Phase 2	9	December 13, 2016	October 8, 2018	
24	NCT04270760	Randomized Study to Evaluate Efficacy, Safety, and Tolerability of **AMG 890** in Subjects With Elevated Lipoprotein(a)	Not yet recruiting	Atherosclerotic Cardiovascular Disease	AMG 890	Amgen	Phase 2	240	August 4, 2020	April 7, 2023	
25	NCT03174522	The Efficacy and Safety of **REX-001** to Treat Ischemic Ulcers in Subjects With CLI Rutherford Category 5 and DM	Recruiting	Peripheral Arterial Disease (PAD), Diabetes Mellitus (DM) (Type 1+2) Cardiovascular Disease, Critical Limb Ischemia (CLI)	REX-001 (Rexmyelocel T)	Rexgenero	Phase 3	78	April 25, 2017	October 2021	
	NCT03111238	The Efficacy and Safety of **REX-001** to Treat Ischemic Rest Pain in Subjects With CLI Rutherford Category 4 and DM						60	April 25, 2017	October 2020	
	Nephrological disorders										
26	NCT03999840	Eculizumab to Cemdisiran Switch in aHUS	Not yet recruiting	Atypical Hemolytic Uremic Syndrome	Cemdisiran	Mario Negri Institute	Phase 2	12	February 2020	February 2023	
	NCT03841448	A Study of Cemdisiran in Adults With Immunoglobulin A Nephropathy (IgAN)	Recruiting	IgA Nephropathy (IgAN), Berger Disease, Glomerulonephritis, IgA		Alnylam Pharmaceuticals	Phase 2	30	April 24, 2019	February 14, 2023	
27	NCT03905694	A Study of **Lumasiran** in Infants and Young Children With Primary Hyperoxaluria Type 1	Active, not recruiting	Primary Hyperoxaluria Type 1 (PH1)	Lumasiran	Alnylam Pharmaceuticals	Phase 3	18	April 22, 2019	September 2024	**EMA: under evaluation**
	NCT04152200	A Study to Evaluate **Lumasiran** in Patients With Advanced Primary Hyperoxaluria Type 1	Recruiting				Phase 3	20	January 21, 2020	August 2025	
	NCT03681184	A Study to Evaluate **Lumasiran** in Children and Adults With Primary Hyperoxaluria Type 1	Active, not recruiting				Phase 3	30	November 27, 2018	May 2024	

Rank	Trial-ID	Title	Status	Conditions	Interventions	Lead Sponsor	Phase	N of Patients	Start date	Completion date	Approval Status
	Dermatologic disorders										
28	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 Therapeutics	Phase 3	15	January 10, 2020	March 2021	
29	NCT04213261	A Study of **FCX-007** for Recessive Dystrophic Epidermolysis Bullosa	Recruiting	Epidermolysis bullosa	FCX-007	Fibrocell Technologies	Phase 3	20	March 30, 2020	March 2021	
	Neurologic disorders										
30	NCT03562494	**VY-AADC02** for Parkinson's Disease With Motor Fluctuations (RESTORE-1)	Recruiting	Parkinson's Disease	VY-AADC02	Neurocrine Biosciences	Phase 2	85	June 28, 2018	December 2022	
31	NCT03842969	An Open-Label Extension Study to Evaluate Long-Term Safety and Tolerability of **RO7234292** (RG6042) in Huntington's Disease Patients Who Participated in Prior Roche and Genentech Sponsored Studies	Recruiting	Huntington Disease	RO7234292 (RG6042) Tominersen	Roche	Phase 3	1050	April 23, 2019	June 19, 2024	
	NCT03761849	A Study to Evaluate the Efficacy and Safety of Intrathecally Administered **RO7234292** (RG6042) in Patients With Manifest Huntington's Disease	Active, not recruiting				Phase 3	909	January 23, 2019	July 9, 2022	
	NCT03342053	A Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of RO7234292 (ISIS 443139) in Huntington's Disease Patients Who Participated in Prior Investigational Studies of **RO7234292** (ISIS 443139)	Completed				Phase 2	46	November 27, 2017	October 8, 2019	
32	NCT02917291	Safety and Preliminary Efficacy of **FAB117-HC** in Patients With Acute Traumatic Spinal Cord Injury	Recruiting	Acute Traumatic Spinal Cord Injury	FAB117-HC (NeuroSave)	Ferrer Internacional	Phase 1, Phase 2	48	December 2016	March 2022	

Legend: colour blue: no equivalent entry in EudraCT

Abbreviations: AAV=adeno-associated virus, EMA=European Medicines Agency, FDA=US Food and Drug Administration

Table A-6-2: Ongoing trials of ATMPs and Gene Therapies – sorted by indication (https://eudract.ema.europa.eu/) (n=23)

Rank	EudraCT Number	Sponsor Protocol Number	Sponsor Name	Full Title	Start Date	Medical condition	Population Age	Gender	Trial protocol	Searchterm/ Intervention
Haemophilia										
1	2018-002880-25	LTE15174	Genzyme Corporation	ATLAS-OLE: An Open-label, 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	Information not available in EudraCT	Hemophilia A or Hemophilia B	Adolescents, Under 18, Adults, Elderly	Male	IE (Ongoing) GB (Ongoing) DE (Ongoing) PT (Completed) HU (Ongoing) ES (Ongoing) FR (Ongoing) DK (Ongoing) Outside EU/EEA	Fitusiran
	2015-001395-21	ALN-AT3SC-002	Genzyme Corporation	An Open-label Extension Study of Subcutaneously Administered Fitusiran in Patients with Moderate or Severe Hemophilia A or B who have Participated in a Previous Clinical Study with Fitusiran	2015-07-22	Hemophilia A or Hemophilia B	Adults, Elderly	Male	GB (Ongoing) BG (Temporarily Halted)	Fitusiran
	2019-000679-18	EFC15467	Genzyme Corporation	ATLAS-PEDS: An open-label, multinational study of fitusiran prophylaxis in male pediatric subjects aged 1 to less than 12 years with hemophilia A or B	2019-07-23	Hemophilia A or B	Infants and toddlers, Children, Under 18	Male	ES (Ongoing) Outside EU/EEA	Fitusiran
	2016-004087-19	ALN-AT3SC-009	Alnylam Pharmaceuticals, Inc.	ATLAS-PPX trial: an open-label, multinational, switching study to describe the efficacy and safety of fitusiran prophylaxis in hemophilia A and B patients previously receiving factor or bypassing a...	2017-08-25	Hemophilia A or Hemophilia B	Adolescents, Under 18, Adults, Elderly	Male	ES (Temporarily Halted) IE (Ongoing) GB (Ongoing) DE (Completed) DK (Ongoing) NL (Not Authorised) IT (Ongoing)	Fitusiran
	2016-001463-36	EFC14768	Genzyme Corporation	ATLAS-INH: A Phase 3 Study to Evaluate the Efficacy and Safety of Fitusiran in Patients with Hemophilia A or B, with Inhibitory Antibodies to Factor VIII or IX	2018-07-25	Hemophilia A or Hemophilia B	Adolescents, Under 18, Adults, Elderly	Male	GB (Ongoing) BG (Completed) HU (Ongoing) ES (Prematurely Ended) PT (Completed) DE (Completed) DK (Completed) NL (Not Authorised) IT (Ongoing)	Fitusiran
	2016-001464-11	ALN-AT3SC-004	Alnylam Pharmaceuticals, Inc.	ATLAS-A/B: A Phase 3 study to evaluate the efficacy and safety of fitusiran in patients with hemophilia A or B, without inhibitory antibodies to factor VIII or IX	Information not available in EudraCT	Hemophilia A or Hemophilia B	Adolescents, Under 18, Adults, Elderly	Male	IE (Prematurely Ended) BG (Completed) HU (Ongoing) ES (Ongoing) PT (Completed) FR (Ongoing) GB (Ongoing) DE (Completed)	Fitusiran

Rank	EudraCT Number	Sponsor Protocol Number	Sponsor Name	Full Title	Start Date	Medical condition	Population Age	Gender	Trial protocol	Searchterm/ Intervention
									DK (Ongoing) NL (Not Authorised) IT (Ongoing)	
2	2017-003573-34	270-302	BioMarin Pharmaceutical Inc.	Phase 3 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 4E13 vg/kg in Hemoph...	2018-02-23	Haemophilia A	Adults, Elderly	Male	GB (Ongoing) ES (Prematurely Ended) FR (Completed)	Valoctocogene roxaparvovec
	2017-000662-29	270-203	BioMarin Pharmaceutical Inc.	A Phase 1/2 Safety, Tolerability, and Efficacy Study of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Hemophilia A Patients with Residual FVIII Levels ≤ 1...	2018-02-01	Haemophilia A	Adults	Male	GB (Ongoing) FR (Ongoing)	Valoctocogene roxaparvovec
	2017-003215-19	270-301	BioMarin Pharmaceutical Inc.	A Phase 3 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 Res...	2017-11-25	Haemophilia A	Adults, Elderly	Male	GB (Ongoing) DE (Ongoing) ES (Ongoing) FR (Ongoing)	Valoctocogene roxaparvovec
3	2018-003086-33	C0371002	Pfizer Inc.	Phase 3, open label, single arm study to evaluate efficacy and safety of FIX gene transfer with PF-06838435 (rAAV-Spark100-hFIX-Padua) in adult male participants with moderately severe to severe he...	2020-01-28	severe to moderately severe hemophilia B <=2%	Adults	Male	GB (Ongoing) FR (Ongoing)	PF-06838435
4	2017-005080-40	FLT180a-04	Freeline Therapeutics Limited	An Open-Label, Multicentre, Long-Term Follow-Up Study to Investigate the Safety and Durability of Response Following Dosing of a Novel Adeno-Associated Viral Vector (FLT180a) in Patients with Haemo...	2018-05-15	Haemophilia B	Adults, Elderly	Male	GB (Ongoing)	FLT180a
	2017-000852-24	15/0552	University College London (UCL)	A Phase I/II, Open label, Multicentre, Ascending Single Dose, Safety Study of a Novel Adeno-associated Viral Vector (FLT180a) in Patients With Haemophilia B	2017-08-23	Haemophilia B	Adults, Elderly	Male	GB (Ongoing)	FLT180a

Rank	EudraCT Number	Sponsor Protocol Number	Sponsor Name	Full Title	Start Date	Medical condition	Population Age	Gender	Trial protocol	Searchterm/ Intervention
5	2017-004305-40	CT-AMT-061-02	uniQure biopharma B.V.	Phase III, open-label, single-dose, multi-center multinational trial investigating a serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene ...	2018-10-12	Hemophilia B	Adults, Elderly	Male	DK (Ongoing) GB (Ongoing) IE (Ongoing) NL (Ongoing) DE (Ongoing) BE (Ongoing) SE (Ongoing)	AAV5-hFIXco-Padua
	2013-005579-42	CT-AMT-060-01	uniQure biopharma B.V.	A phase I/II, open-label, uncontrolled, single-dose, dose-ascending, multi-centre trial investigating an adeno-associated viral vector containing a codon-optimized human factor IX gene (AAV5-hFIX) ...	2015-03-20	Haemophilia B	Adults, Elderly	Male	DE (Ongoing) DK (Ongoing) NL (Ongoing)	AAV5-hFIXco-Padua
	Metabolic Disorders									
6	2019-002936-97	LTFU-ABO-101	Abeona Therapeutics Europe SL.	A Long-term Follow-up Study of Patients with MPS IIIB from Gene Therapy Clinical Trials Involving the Administration of ABO-101 (rAAV9.CMV.hNAGLU)	Information not available in EudraCT	Mucopolysaccharidosis IIIB	Children, Adolescents, Under 18	Male, Female	DE (Ongoing)	rAAV9.CMV.hNAGLU (ABO-101)
	2014-001411-39	ABT-002	Abeona Therapeutics Inc	Phase I/II gene transfer clinical trial of rAAV9.CMV.hNAGLU for Mucopolysaccharidosis (MPS) IIIB	2018-09-04	Mucopolysaccharidosis IIIB	Infants and toddlers, Children, Adolescents, Under 18, Adults	Male, Female	ES (Ongoing) DE (Ongoing) GB (Ongoing)	rAAV9.CMV.hNAGLU (ABO-101)
	2019-002979-34	LTFU-ABO-102	Abeona Therapeutics Inc	A Long-term Follow-up Study of Patients with MPS IIIA from Gene Therapy Clinical Trials Involving the Administration of ABO-102 (scAAV9.U1a.hSGSH)	2020-05-18	Mucopolysaccharidosis IIIA	Children, Adolescents, Under 18	Male, Female	ES (Ongoing)	scAAV9.U1a.hSGSH (ABO-102)
	2015-003904-21	ABT-001	Abeona Therapeutics Inc	Phase I/II gene transfer clinical trial of scAAV9.U1a.hSGSH for Mucopolysaccharidosis (MPS) IIIA	2016-08-01	Mucopolysaccharidosis IIIA	Infants and toddlers, Children, Adolescents, Under 18, Adults	Male, Female	ES (Ongoing) FR (Ongoing)	scAAV9.U1a.hSGSH (ABO-102)
	2018-000504-42	ABT-003	Abeona Therapeutics Inc	A Phase I/II Open Label, Single-dose, Gene Transfer Study of	2019-05-21	Mucopolysaccharidosis IIIA	Children, Adolescents, Under 18	Male, Female	ES (Ongoing)	scAAV9.U1a.hSGSH (ABO-102)

Rank	EudraCT Number	Sponsor Protocol Number	Sponsor Name	Full Title	Start Date	Medical condition	Population Age	Gender	Trial protocol	Searchterm/ Intervention
				scAAV9.U1a.hSGSH (ABO-102) in Patients with Middle and Advanced Phases of MPS IIIA Disease						
7	2010-019962-10	P1-SAF301	SANFILIPPO Therapeutics SAS	An open-label, single arm, monocentric, phase i/ii clinical study of intracerebral administration of adeno-associated viral vectors serotype 10 carrying the human sgsh and sumf1 cdnas for the treat...	Information not available in EudraCT	Sanfilippo type A syndrome (also named Mucopolysaccharidosis Type A)	Infants and toddlers, Children, Under 18	Male, Female	FR (Completed)	SAF-301
	2018-000195-15	P4-SAF-302	Lysogene SA	An Open-Label, Single-Arm, Multicenter Study of Intracerebral Administration of Adeno-Associated Viral Vectors Serotype rh10 Carrying the Human N-sulfoglucosamine sulfohydrolase (SGSH) cDNA for the... Start Date: 2018-12-27	2018-12-27	Mucopolysaccharidosis IIIA	Infants and toddlers, Children, Under 18	Male, Female	FR (Ongoing) GB (Ongoing) NL (Temporarily Halted) DE (Temporarily Halted)	SAF-302
8	2018-002098-23	ALN-TTRSC02-002	Alnylam Pharmaceuticals, Inc.	HELIOS-A: A Phase 3 Global, Randomized, Open-label Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients with Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis)	2019-05-09	Hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis)	Adults, Elderly	Male, Female	DE (Ongoing) PT (Ongoing) GB (Ongoing) BG (Ongoing) ES (Ongoing) BE (Ongoing) GR (Ongoing) NL (Ongoing)	Vutrisiran (ALN-TTRSC02)
	2019-003153-28	ALN-TTRSC02-003	Alnylam Pharmaceuticals, Inc.	HELIOS-B: A Phase 3 Global, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Clinical Outcomes, Efficacy and Safety of Vutrisiran in Patients with Transthyretin Amyloidosis with C...	2019-12-23	Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)	Adults, Elderly	Male, Female	LV (Ongoing) PT (Ongoing) HU (Ongoing) SI (Ongoing) NO (Ongoing) LT (Ongoing) ES (Ongoing) DE (Ongoing) GB (Ongoing) NL (Ongoing)	Vutrisiran (ALN-TTRSC02)
9	2018-003385-14	AROAAT2001	Arrowhead Pharmaceuticals, Inc.	A Placebo-Controlled, Multi-dose, Phase 2/3 Study to Determine the Safety, Tolerability and Effect on Liver Histologic Parameters in Response to ARO-AAT in Patients with Alpha-1 Antitrypsin Deficie...	2019-08-06	alpha-1 antitrypsin deficiency (AATD)-associated liver disease	Adults, Elderly	Male, Female	IE (Ongoing) SE (Ongoing) ES (Restarted) PT (Ongoing)	ARO-AAT
	2019-000068-86	AROAAT2002	Arrowhead Pharmaceuticals, Inc.	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	2019-07-01	alpha-1 antitrypsin deficiency (AATD)-associated liver disease	Adults, Elderly	Male, Female	GB (Ongoing) DE (Restarted) AT (Ongoing)	ARO-AAT

Rank	EudraCT Number	Sponsor Protocol Number	Sponsor Name	Full Title	Start Date	Medical condition	Population Age	Gender	Trial protocol	Searchterm/ Intervention
				with Alpha-1 Antitrypsin Deficiency Associated Liver Diseas...						
10	2019-002636-82	OTL-200-07	Orchard Therapeutics (Europe) Limited	An open label, non-randomised trial to evaluate the safety and efficacy of a single infusion of OTL-200 in patients with Late Juvenile (LJ) Metachromatic Leukodystrophy (MLD)	Information not available in EudraCT	Metachromatic Leukodystrophy	Children, Under 18	Male, Female	IT (Ongoing)	OTL-200
	2017-001730-26	205756	GLAXOSMITHKLINE RESEARCH AND DEVELOPMENT	A single arm, open label, clinical study of cryopreserved autologous CD34+ cells transduced with lentiviral vector containing human ARSA cDNA (GSK2696274), for the treatment of early onset Metachro...	2017-11-30	Metachromatic Leukodystrophy	Infants and toddlers, Children, Under 18	Male, Female	IT (Ongoing)	OTL-200
11	2017-001275-23	OTL-101-5(17IC04)	Great Ormond Street Hospital for Children NHS Trust	Efficacy and safety of a cryopreserved formulation of autologous CD34+ haematopoietic stem cells transduced ex vivo with EFS lentiviral vector encoding for human ADA gene in subjects with Severe Co...	2017-09-21	Adenosine deaminase (ADA) deficiency	Infants and toddlers, Children, Adolescents, Under 18	Male, Female	GB (Ongoing)	OTL-101
12	2018-001145-14	ALD-104	bluebird bio, Inc.	A Phase 3 Study of Lenti-D Drug Product After Myeloablative Conditioning Using Busulfan and Fludarabine in Subjects ≤17 Years of Age With Cerebral Adrenoleukodystrophy (CALD)	2019-04-17	Cerebral Adrenoleukodystrophy (CALD)	Children, Adolescents, Under 18	Male	GB (Ongoing) FR (Ongoing) DE (Temporarily Halted) NL (Ongoing)	Lenti-D
	2015-002805-13	LTF-304	bluebird bio, Inc	Longterm Follow-up of Subjects With Cerebral Adrenoleukodystrophy Who Were Treated With Lenti-D Drug Product	2015-11-27	Cerebral Adrenoleukodystrophy (CALD)	Children, Adolescents, Under 18	Male	GB (Ongoing) FR (Ongoing)	Lenti-D
	2011-001953-10	ALD-102	bluebird bio, Inc.	A phase 2/3 study of the efficacy and safety of hematopoietic stem cells transduced with Lenti D lentiviral vector for the treatment of cerebral adrenoleukodystrophy (CALD)	2013-12-13	Cerebral Adrenoleukodystrophy (CALD)	Children, Adolescents, Under 18	Male	GB (Ongoing) FR (Completed) DE (Ongoing) Outside EU/EEA	Lenti-D
	Ophthalmologic disorders									
13	2015-001383-18		University of Oxford	An open label Phase 2 clinical trial of retinal gene therapy for choroideremia using an adeno-associated viral	2015-11-30	Choroideremia (CHM)	Adults	Male	GB (Ongoing)	AAV-mediated REP1 gene replacement

Rank	EudraCT Number	Sponsor Protocol Number	Sponsor Name	Full Title	Start Date	Medical condition	Population Age	Gender	Trial protocol	Searchterm/ Intervention
				vector (AAV2) encoding Rab-escort protein 1 (REP1)						
	2017-003104-42	NSR-CHM-OS2	NightstaRx Ltd	A 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 Prot...	2018-01-05	Choroideremia (CHM)	Adults	Male	DE (Ongoing) GB (Ongoing) FI (Ongoing)	AAV2-REP1
	2017-002395-75	NSR-REP-02	NightstaRx Ltd	An Open-Label Safety Study of Retinal Gene Therapy for Choroideremia with Bilateral, Sequential Administration of Adeno-Associated Viral Vector (AAV2) Encoding Rab Escort Protein 1 (REP1)	2018-01-17	Choroideremia (CHM)	Adults, Elderly	Male	DE (Temporarily Halted)	AAV2-REP1
	2015-003958-41	NSR-REP-01	NightstaRx Ltd	A Randomised, 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 (...	2016-10-31	Choroideremia (CHM)	Adults	Male	DE (Ongoing) FI (Ongoing) DK (Ongoing) NL (Ongoing)	AAV2-REP1
	2014-005004-21	THOR-TUE-01	Universitätsklinikum Tübingen, STZ eyetrial am Department für Augenheilkunde	THOR - Tübingen Choroideremia gene therapy trial open label Phase 2 clinical trial using an adeno-associated viral vector (AAV2) encoding Rab-escort protein 1 (REP1)	2015-12-23	Choroideremia (CHM)	Adults, Elderly	Male	DE (Ongoing)	AAV2-REP1
14	2016-002290-35	MGT006	MeiraGTx UK II Limited	An open label, multi-centre, Phase I/II dose escalation trial of a recombinant adeno-associated virus vector (AAV2/8-hCARp.hCNGB3) for gene therapy of adults and children with achromatopsia owing t...	2016-12-20	Achromatopsia caused by mutations in the CNGB3 gene	Children, Adolescents, Under 18, Adults	Male, Female	GB (Completed)	AAV - CNGB3
	2016-003856-59	MGT007	MeiraGTX UK II Ltd	Long-term follow-up study of participants following an open label, multi-centre, Phase I/II dose escalation trial of a recombinant adeno-associated	2017-04-12	Achromatopsia caused by mutations in the CNGB3 gene	Children, Adolescents, Under 18, Adults	Male, Female	GB (Ongoing)	CNGA3

Rank	EudraCT Number	Sponsor Protocol Number	Sponsor Name	Full Title	Start Date	Medical condition	Population Age	Gender	Trial protocol	Searchterm/ Intervention
				virus vector (AAV2/8-hCARp.hCNGB3) for gene thera...						
	2018-003431-29	MGT012	MeiraGTx UK II Limited	An open label, multi-centre, Phase I/II dose escalation trial of an adeno-associated virus vector (AAV2/8-hG1.7p.coCNGA3) for gene therapy of children with achromatopsia owing to defects in CNGA3	2019-06-24	Achromatopsia caused by mutations in the CNGA3 gene	Children, Adolescents, Under 18	Male, Female	GB (Ongoing)	CNGA3
15	2016-003852-60	NSR-RPGR-01	NightstaRx Limited	A Dose Escalation (Phase 1), and Dose Expansion (Phase 2/3) Clinical Trial of Retinal Gene Therapy for X-linked Retinitis Pigmentosa Using an Adeno-Associated Viral Vector (AAV8) Encoding Retinitis...	2017-01-09	X-Linked retinitis pigmentosa (XLRP)	Children, Adolescents, Under 18, Adults	Male	GB (Ongoing)	AAV8-RPGR
16	2017-002153-11	GS-LHON-CLIN-06	GENSIGHT BIOLOGICS	Long-term Follow-up of ND4 LHON Subjects Treated With GS010 Ocular Gene Therapy in the RESCUE or REVERSE Phase III Clinical Trials	2018-02-12	Leber Hereditary Optic Neuropathy due to mutations in the mitochondrial NADH Dehydrogenase 4 gene	Adults	Male, Female	DE (Ongoing) GB (Ongoing) IT (Ongoing) FR (Ongoing)	RESCUE and REVERSE Long-term Follow-up
17	2017-002187-40	GS-LHON-CLIN-05	GENSIGHT BIOLOGICS	Efficacy and Safety of Bilateral Intravitreal Injection of GS010: A Randomized, Double-Masked, Placebo-Controlled Trial in Subjects Affected with G11778A ND4 Leber Hereditary Optic Neuropathy for U...	2018-03-15	Leber Hereditary Optic Neuropathy due to mutations in the mitochondrial NADH Dehydrogenase 4 gene	Adolescents, Under 18, Adults, Elderly	Male, Female	BE (Ongoing) FR (Ongoing) GB (Ongoing) ES (Ongoing) NL (Ongoing)	GS010
	2015-001266-26	GS-LHON-CLIN-03B	GENSIGHT-BIOLOGICS	A Randomized, Double-Masked, Sham-Controlled, Pivotal Clinical Trial to Evaluate the Efficacy of a Single Intravitreal Injection of GS010 (rAAV2/2-ND4) in Subjects Affected for more than 6 months	2016-01-21	Leber Hereditary Optic Neuropathy due to mutations in the mitochondrial NADH Dehydrogenase 4 gene	Adolescents, Under 18, Adults, Elderly	Male, Female	DE (Completed) GB (Completed) IT (Completed)	GS010
	2015-001265-11	GS-LHON-CLIN-03A	GENSIGHT-BIOLOGICS	A Randomized, Double-Masked, Sham-Controlled, Pivotal Clinical Trial to Evaluate the Efficacy of a Single Intravitreal Injection of GS010	2016-01-21	Leber Hereditary Optic Neuropathy due to muta-	Adolescents, Under 18, Adults, Elderly	Male, Female	DE (Completed) GB (Completed)	GS010

Rank	EudraCT Number	Sponsor Protocol Number	Sponsor Name	Full Title	Start Date	Medical condition	Population Age	Gender	Trial protocol	Searchterm/ Intervention
				(rAAV2/2-ND4) in Subjects Affected for 6 Months or Less by...		tions in the mitochondrial NADH Dehydrogenase 4 gene				
	2013-001405-90	GS-LHON/CLIN/01	GENSIGHT-BIOLOGICS	A phase I/IIa, non randomized, escalating dose, open-label study to evaluate safety and efficacy of GS010 (rAAV2/2-ND4) in patients suffering from Leber Hereditary Optic Neuropathy due to mutations...	2013-12-26	Leber Hereditary Optic Neuropathy due to mutations in the mitochondrial NADH Dehydrogenase 4 gene	Adults	Male, Female	FR (Ongoing)	GS010
Vascular disorder										
18	2016-003815-37	MDCO-PCS-16-01	The Medicines Company	An open label, active comparator extension trial to assess the effect of long term dosing of inclisiran and evolocumab given as subcutaneous injections in subjects with high cardiovascular risk and...	2017-02-24	Hypercholesterolemia	Adults, Elderly	Male, Female	GB (Ongoing) DE (Ongoing) NL (Ongoing)	Inclisiran
	2017-003092-55	MDCO-PCS-17-05	The Medicines Company	A long term extension trial of the Phase III lipid-lowering trials to assess the effect of long term dosing of inclisiran given as subcutaneous injections in subjects with high cardiovascular risk ...	2019-02-05	Hypercholesterolemia	Adults, Elderly	Male, Female	GB (Ongoing) CZ (Ongoing) DE (Ongoing) SE (Ongoing) DK (Ongoing) HU (Ongoing) NL (Ongoing)	Inclisiran
	2017-005066-22	CTSU_MDCO-PCS-17-01	University of Oxford	HPS-4/TIMI 65/ORION-4: A double-blind randomized placebo-controlled trial assessing the effects of inclisiran on clinical outcomes among people with atherosclerotic cardiovascular disease	2018-06-11	Atherosclerotic cardiovascular disease	Adults, Elderly	Male, Female	GB (Ongoing)	Inclisiran
	2017-002472-30	MDCO-PCS-17-03	The Medicines Company	A placebo-controlled, double-blind, randomized trial to evaluate the effect of 300 mg of inclisiran sodium given as subcutaneous injections in subjects with heterozygous familial hypercholesterolem...	2018-01-04	Hypercholesterolemia	Adults, Elderly	Male, Female	GB (Ongoing) ES (Completed) CZ (Completed) SE (Completed) DK (Completed)	Inclisiran

Rank	EudraCT Number	Sponsor Protocol Number	Sponsor Name	Full Title	Start Date	Medical condition	Population Age	Gender	Trial protocol	Searchterm/ Intervention
	2017-001846-90	MDCO-PCS-17-08	The Medicines Company	A placebo-controlled, double-blind, randomized trial to evaluate the effect of 300 mg of inclisiran sodium given as subcutaneous injections in subjects with atherosclerotic cardiovascular disease (...	2017-12-12	Hypercholesterolemia	Adults, Elderly	Male, Female	DE (Completed) HU (Completed) GB (Completed) CZ (Completed) NL (Prematurely Ended)	Inclisiran
	2016-003376-49	MDCO-PCS-16-02	The Medicines Company	An Open-Label, Single-Arm, Multicenter Pilot Study to Evaluate Safety, Tolerability, and Efficacy of ALN-PCSSC in Subjects with Homozygous Familial Hypercholesterolemia	2017-06-20	Homozygous Familial Hypercholesterolemia	Adolescents, Under 18, Adults	Male, Female	NL (Completed)	Inclisiran
19	2016-003980-21	REX-001-004	Rexgenero Limited	The Efficacy and Safety of Intra-Arterial Administration of Rexmyelocel T to treat Critical Limb Ischemia in Subjects with Diabetes Mellitus: Two Pivotal, Placebo Controlled, Double-Blind, Parallel...	2017-03-17	Critical Limb Ischemia in patients with Diabetes Mellitus	Adults, Elderly	Male, Female	ES (Restarted) AT (Restarted) NL (Ongoing) HU (Ongoing) PL (Ongoing) CZ (Ongoing) PT (Ongoing) GB (Ongoing) LV (Ongoing) LT (Ongoing)	REX-001 (Rexmyelocel T)
	2016-000240-34	REX-001-004	Rexgenero Limited	The Efficacy and Safety of Intra-Arterial Administration of Rexmyelocel T to treat Critical Limb Ischemia in Subjects with Diabetes Mellitus: A Multicenter, Randomized, Double-Blind, Placebo Contro...	2016-07-07	Critical Limb Ischemia in patients with Diabetes Mellitus	Adults, Elderly	Male, Female	ES (Restarted) AT (Restarted) NL (Ongoing) HU (Ongoing) PL (Temporarily Halted) PT (Ongoing)	REX-001 (Rexmyelocel T)
Nephrological disorders										
20	2018-002716-27	ALN-CC5-005	Alnylam Pharmaceuticals Inc	A Phase 2, Randomized, Double-blind, Placebo-controlled Study of Cemdisiran in Adult Patients with IgA Nephropathy	2019-06-11	Immunoglobulin A nephropathy (IgAN)	Adults	Male, Female	GB (Ongoing) SE (Ongoing) ES (Ongoing)	Cemdisiran
	2017-001082-24	ALN-CC5-004	Alnylam Pharmaceuticals, Inc.	A Phase 2, Open Label, Multicenter Study of ALN-CC5 Administered Subcutaneously in Adult Patients with Atypical Hemolytic Uremic Syndrome	2017-08-18	Atypical Hemolytic Uremic Syndrome	Adults, Elderly	Male, Female	LV (Prematurely Ended) LT (Prematurely Ended) EE (Prematurely Ended) SE (Prematurely Ended)	Cemdisiran
21	2019-001346-17	ALN-GO1-005	Alnylam Pharmaceuticals, Inc.	ILLUMINATE-C: A Single Arm Study to Evaluate Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics	Information not available in EudraCT	Primary Hyperoxaluria Type 1 (PH1)	Infants and toddlers, Children, Adolescents, Under 18, Adults	Male, Female	FR (Ongoing) DE (Ongoing) GB (Ongoing) BE (Ongoing) NL (Ongoing) Outside EU/EEA	Lumasiran

Rank	EudraCT Number	Sponsor Protocol Number	Sponsor Name	Full Title	Start Date	Medical condition	Population Age	Gender	Trial protocol	Searchterm/ Intervention
				of Lumasiran in Patients with Advanced Primary Hyperoxaluria Type 1 (PH1)						
	2018-004014-17	ALN-GO1-004	Alnylam Pharmaceuticals, Inc.	ILLUMINATE-B: An Open-Label Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Lumasiran in Infants and Young Children with Primary Hyperoxaluria Type 1	2019-03-01	Primary Hyperoxaluria Type 1 (PH1)	Newborns, Infants and toddlers, Children, Under 18	Male, Female	GB (Ongoing) FR (Ongoing) DE (Ongoing)	Lumasiran
	2018-001981-40	ALN-GO1-003	Alnylam Pharmaceuticals, Inc.	ILLUMINATE-A: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study with an Extended Dosing Period to Evaluate the Efficacy and Safety of Lumasiran in Children and Adults with Primary Hypero...	2018-11-20	Primary Hyperoxaluria Type 1 (PH1)	Children, Adolescents, Under 18, Adults	Male, Female	GB (Ongoing) FR (Ongoing) DE (Ongoing) NL (Ongoing)	Lumasiran
	2016-003134-24	ALN-GO1-002	Alnylam Pharmaceuticals, Inc.	A Phase 2, Multicenter, Open-Label, Extension Study to Evaluate the Long-Term Administration of ALN-GO1 in Patients with Primary Hyperoxaluria Type 1	2017-12-28	Primary Hyperoxaluria Type 1 (PH1)	Children, Adolescents, Under 18, Adults	Male, Female	DE (Ongoing) GB (Ongoing) NL (Ongoing) FR (Ongoing)	Lumasiran
Neurologic disorders										
22	2018-002987-14	BN40423	F.Hoffmann La-Roche Ltd	A randomized, multicenter, double-blind, placebo-controlled, phase iii clinical study to evaluate the efficacy and safety of intrathecally administered ro7234292 (rg6042) in patients with manifest ...	2019-02-13	Huntington's disease (HD)	Adults, Elderly	Male, Female	GB (Ongoing) DK (Restarted) NL (Ongoing) AT (Ongoing)	RO7234292
	2017-002471-25	BN40697(ISIS443139-CS2)	F.Hoffmann La-Roche Ltd	An open-label extension study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of ro7234292 (isis 443139) in huntington's disease patients who participated in prior inves...	2018-10-18	Early Manifest Huntington's Disease	Adults, Elderly	Male, Female	GB (Completed) DE (Completed)	RO7234292
	2018-003898-94	BN40955	F.Hoffmann La-Roche Ltd	An open-label extension study to evaluate the long term safety and tolerability of intrathecally administered ro7234292 (rg6042) in patients with huntington's disease	2019-03-07	Huntington's disease (HD)	Adults, Elderly	Male, Female	GB (Ongoing) ES (Ongoing)	RO7234292

Rank	EudraCT Number	Sponsor Protocol Number	Sponsor Name	Full Title	Start Date	Medical condition	Population Age	Gender	Trial protocol	Searchterm/ Intervention
23	2015-005717-80	FAB117-CT-01	Ferrer Internacional S.A	Clinical trial of phase 1/2 to evaluate the feasibility, safety, tolerability and preliminary efficacy of the administration of FAB117-HC, a drug whose active ingredient is HC016, allogeneic adipos...	2016-05-29	Patients with acute traumatic spinal cord injury	Adults	Male, Female	ES (Ongoing)	FAB117-HC

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