EFPIA Pipeline Innovation Review

Pipeline Overview

August 2022

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The 2022 report will cover 8 innovation areas for review, updating 4 areas identified in 2021 and introducing 4 new platforms

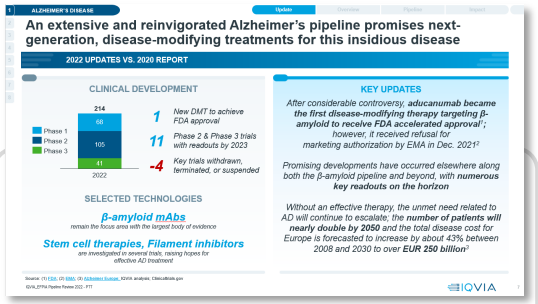
1	**Alzheimer's therapies**	High unmet need means even a moderate efficacy would have a high impact on patients/HC system
2	**Stem cells for CNS**	Promising candidate to treat central nervous system disorders with a potential profound health and economic impact
3	**Psychoplastogens**	Emerging paradigm to tackle the multi-generational mental health pandemic with profound impact on health loss and quality of life, as well as global economy
4	**Gene therapy (e.g., haemophilia, IRD)**	Offers symptomatic relief and potential cure within rare indications with poor prognosis and QoL, to include overview of delivery systems
5	**CRISPR gene editing**	Sophisticated clinical advances and a robust pipeline is translating CRISPR technology as a disruptive treatment option for multiple TAs, including SCD
6	**mRNA personalized vaccines**	mRNA vaccines established efficacy, safety, and success in COVID-19 and herald a new era in personalised vaccines, including cancer vaccines
7	**BiTEs**	A new avenue in personalised cancer therapy, BiTEs overcome significant treatment gaps like access and flexibility with current CAR-T therapy
8	**Remyelinating CNS therapies**	By reversing or improving disability, remyelination promises to improve lives of patients and bring benefits to broader society

○ = *included in previous reports* ○ = *new for 2022*

4 areas deprioritised in 2022: *Checkpoint inhibitor combinations, cell therapy with a focus on CAR-Ts, NASH, and Curative therapies for hepatitis B and HIV*

Our assessment framework investigates the areas for a specified indication under 4 categories – Update, Overview, Pipeline, and Impact

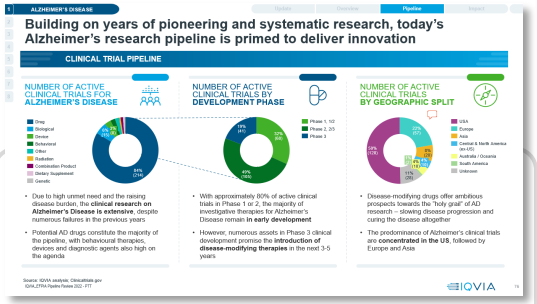
REPORT FRAMEWORK



Update

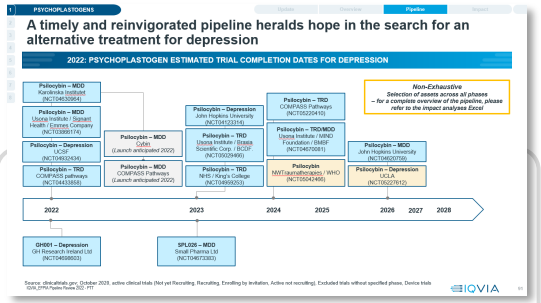
A complete review and reassessment of the selected 2020 innovation areas, including revision of epidemiology estimates, patients, healthcare and societal burden and future projections.

For newly identified areas, a pipeline assessment and review of selected indications for deep-dive



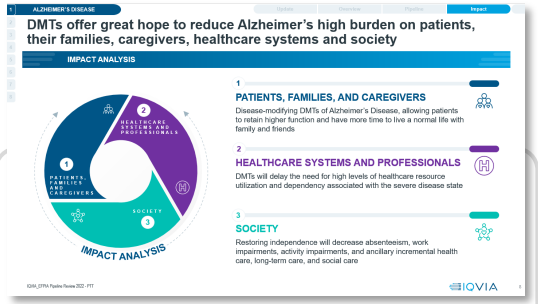
Overview

A detailed overview of the highlighted therapeutic area and clinical trial activity from three perspectives; Phases, Indications and Geographical Locations



Pipeline

A complete pipeline review of the current treatments and therapies being developed for the selected indication is provided, highlighting key trial updates and estimated completion timelines



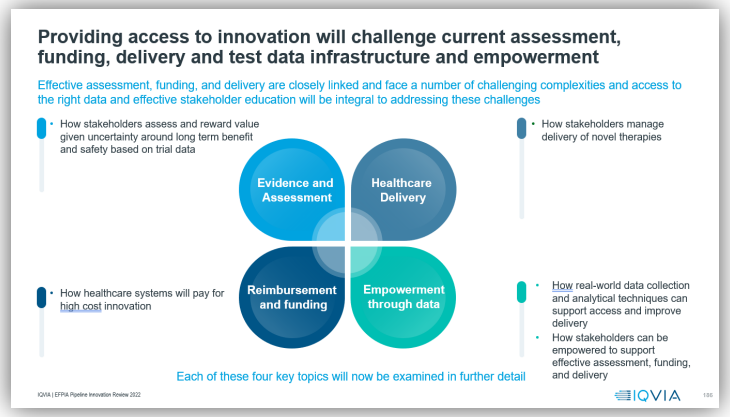
Impact

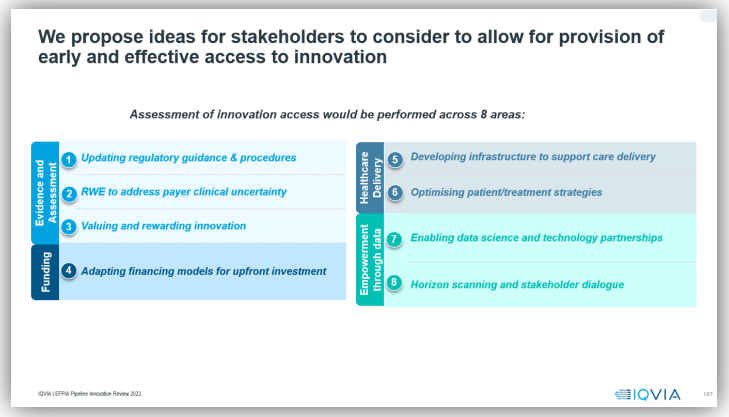
A detailed analysis of the potential impact that a therapy will have on the chosen indication is undertaken and broken down into three key area; the impact on patients, healthcare systems and society

Abbreviations *- Link to Glossary*

This is followed by the final segment comprising an overview of access challenges expected before the launch of these innovations

REPORT FRAMEWORK





A review of potential access challenges across four pillars: Evidence and Assessment, Reimbursement and funding, Delivery, and Data collection

Each of the pillars are analysed through different lenses to assess the readiness of European market before the launch of the selected innovations

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2021 witnessed the EMA marketing authorization of 92 medicines, 54 of which were new active substances

Oncology
Infectious Disease
Neurology
Haematology
Endocrinology
Immunology
Cardiovascular
Dermatology
Reproductive
Metabolic Disease
Ophthalmology
Gastroenterology

Conditional approval, exceptional circumstances, and/or accelerated approval, n = 20

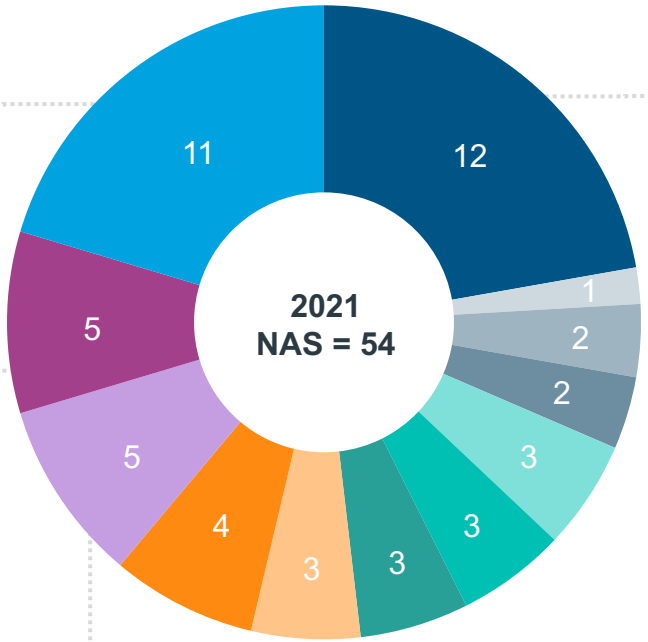
Orphan designated products, n = 9

Infectious Disease*

- COVID-19 vaccine Janssen (COVID-19)
- nuvaxovid (COVID-19)
- regdanvimab (COVID-19)
- casirivimab / imdevimab (COVID-19)
- elasomeran (COVID-19)
- Vaxzevria (COVID-19)
- sotrovimab (COVID-19)
- Apexxnar (Pneumonia)
- Vaxneuvance (Pneumonia)
- artesunate (Malaria)
- tecovirimat monohydrate (Orthopox viruses)

Neurology

- remimazolam (Sedation)
- risdiplam (Spinal Muscular Atrophy)
- selumetinib (Neurofibromatosis Type I)
- elivaldogene autotemcel (CALD)
- eptinezuman (Migraines)



Oncology

- idecabtagene vicleucel (Multiple Myeloma)
- pralsetinib (RET+ NSCLC)
- dostarlimab (dMMR EC)
- sotorasib (KRAS+ NSCLC)
- selinexor (Multiple Myeloma)
- enfortumab vedotin (Bladder Cancer)
- pemigatinib (Cholangiocarcinoma)
- ripretinib (GIST)
- amivantamab (EGFR+ NSCLC)
- tepotinib (METex14+ NSCLC)
- sacituzumab govitecan-hziy (TNBC)
- glucarpidase (Methotrexate toxicity)

Hematology

- zanubrutinib (WM)
- dubelisib (CLL/SLL & FL)
- roxadustat (Anaemia/CKD)
- tafasitamab (r/r DLBCL)
- voxelotor (Anaemia/SCD)

Note: * Infectious diseases includes COVID-19, vaccines, and infection therapeutics; **Abbreviations**: Coronavirus Disease (COVID-19); Spinal Muscular Atrophy (SMA), Cerebral Adrenoleukodystrophy (CALD); Non-Small Cell Lung Cancer (NSCLC); Gastrointestinal Stromal Tumor (GIST); Tumour-Negative Breast Cancer (TNBC); Waldenström's Macroglobulinemia (WM); Chronic/ Slow-Growing Lymphocytic Leukemia (CLL/SLL); Follicular Lymphoma (FL); Chronic Kidney Disease (CKD); Diffuse Large B-Cell Lymphoma (DLBCL); Sickle Cell Disease (SCD)

The number of new active substances approved by EMA in 2021 increased by ~30% compared to 2020

Oncology
Infectious Disease
Neurology
Haematology
Endocrinology
Immunology
Cardiovascular
Dermatology
Reproductive
Metabolic Disease
Ophthalmology
Gastroenterology

Across TAs:

- **6** PRIME designations (vs. 8 in 2020)
- **9** orphan designations (vs 7 in 2020)
- **20** conditional approvals / exceptional circumstances, and/or accelerated approvals (vs 24 in 2020)

Between 2020 and 2021, **infectious disease and cancer continued to represent the majority of NAS approvals by EMA,** providing continued developmental support, expedited reviews, and early access to new medicines with outstanding contributions to public health

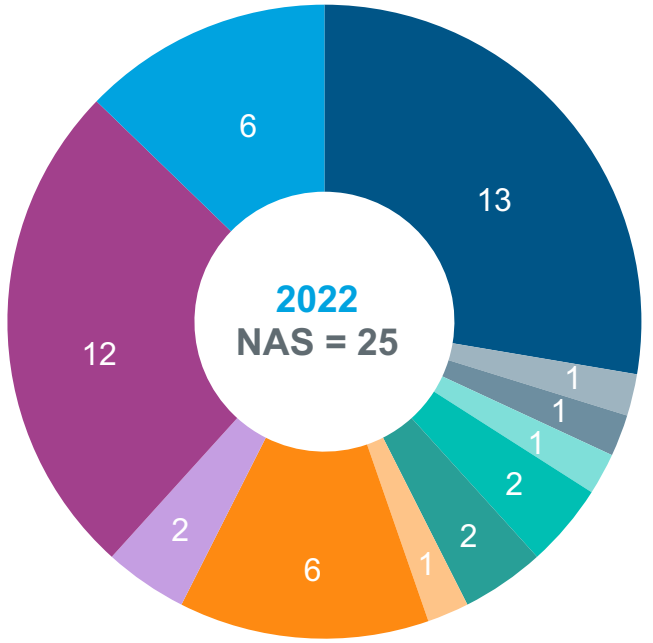
Note: **Abbreviations**: New active substance (NAS), Therapy Area (TA); Source: EMA European public assessment reports; Human Medicines highlights 2020

Abbreviations *- Link to Glossary*

To date, EMA's CHMP has recommended 58 medicines for approval in 2022, with a continued focus on new and orphan medicines

Oncology
Infectious Disease
Neurology
Haematology
Endocrinology
Immunology
Cardiovascular
Dermatology
Reproductive
Metabolic Disease
Ophthalmology
Gastroenterology

CATEGORY	JAN. 2022	FEB. 2022	MAR. 2022	APR. 2022	MAY 2022	JUN. 2022	JUL. 2022
New Medicines [non-orphan]	1	5	1	1	1	3	7
Orphan Medicines	1	1	1	2	4	4	3
Biosimilars	2	2	0	0	0	2	0
Generics / Hybrids / Informed Consent	3	5	3	1	4	0	1
TOTAL							58

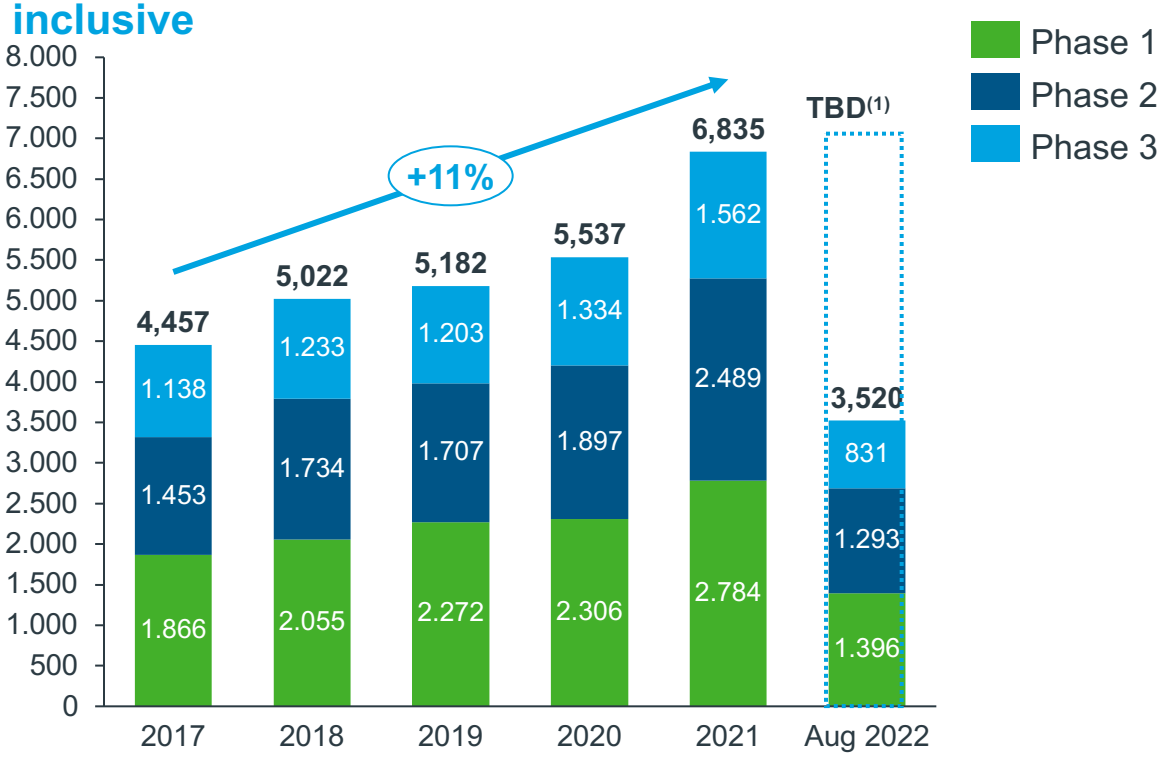


Note: **Abbreviations**: European Medicines Agency (EMA); Committee for Medicinal Products for Human Use (CHMP);
Source: EMA CHMP Meeting Highlights

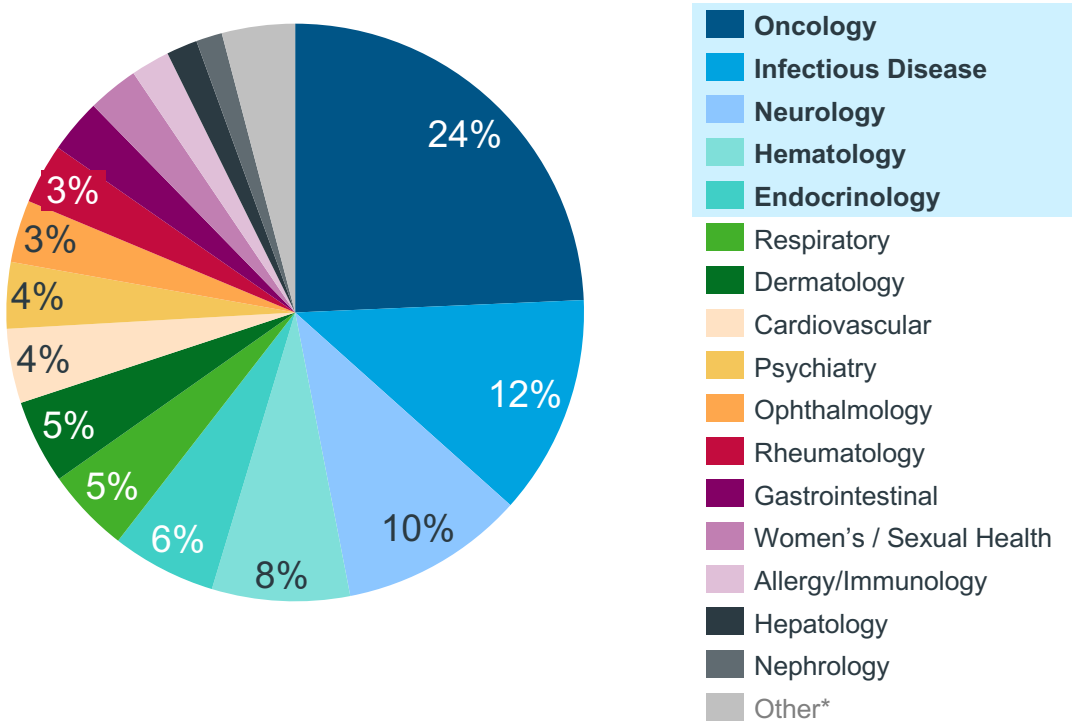
Abbreviations *- Link to Glossary*

The number of newly initiated clinical trials is growing steadily, with oncology remaining the most active therapy area with an extensive pipeline

FULL PIPELINE – No. of trials started from 2017-2022 inclusive



PIPELINE SUMMARY – Key Therapy Areas (% of trials started from 2017 – 2022 inclusive)



Since 2017, the **volume of pipeline activity has increased steadily year-on-year**, with new records reached in 2021 with the resumption of clinical activity following the COVID-19 pandemic

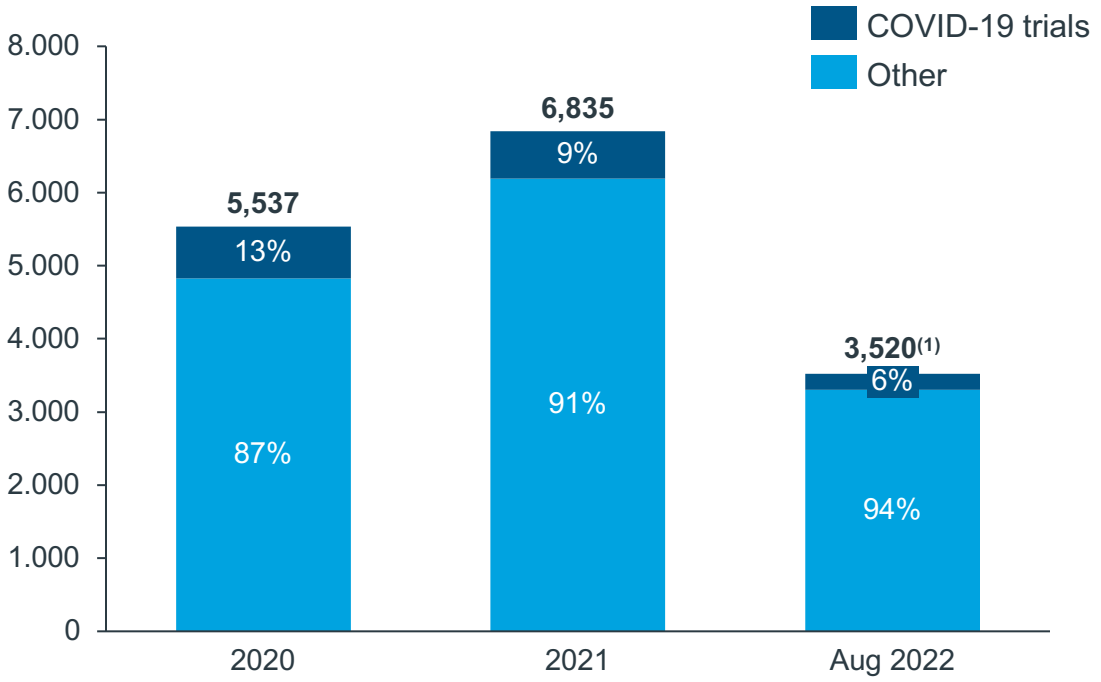
Oncology dominates the pipeline, representing approximately 26% of ongoing trials

Note: (1) Total number of trials started in 2022 to be defined – final number will be available in the beginning of 2023; **Other includes Medical Genetics, Acute Care, Orthopedics, Transplantation and Miscellaneous and represents ~4% of the pipeline*
Source: Clarivate Analytics Cortellis, **Year to Aug 2022**; Phase 2 includes Phases 1/2, 2, 2a, 2b. Phase 3 includes Phase 2/3 and 3. Trials were industry sponsored; Terminated trials & medical devices were excluded from analysis

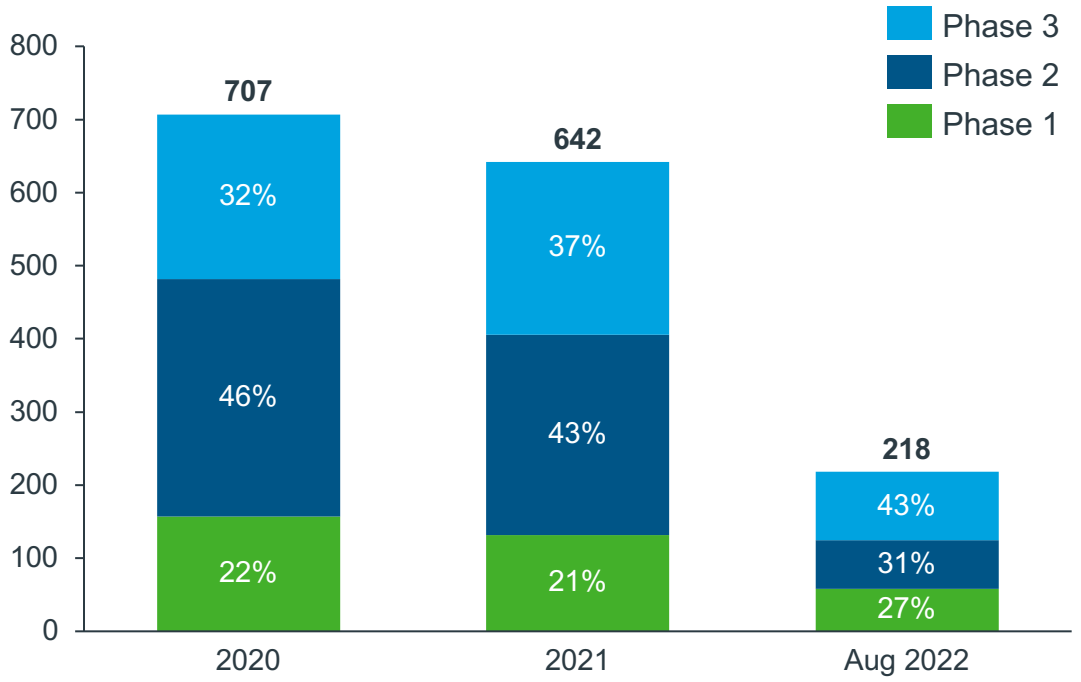
***Abbreviations** – Link to Glossary*

In 2021, clinical trial number rebounded from the slight dip in new trials due to the pandemic; this is exclusive of trials related to COVID-19

FULL PIPELINE – No. of trials started in 2020-2022



COVID-19 PIPELINE – Trial phase split 2020-2022

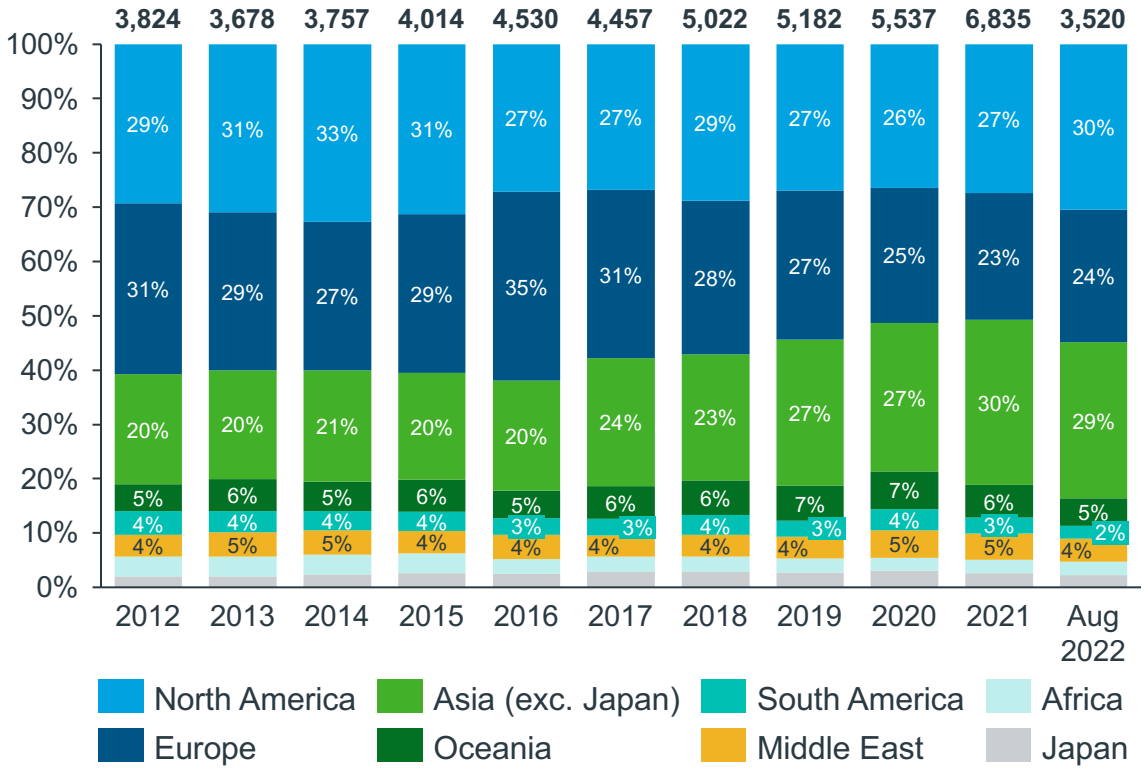


Analyses indicate that the **COVID-19 pandemic affected both the initiation of clinical trials overall and the initiation of non-COVID-19 trials**. In Europe, the decrease was less pronounced, but trial numbers mainly remained below the 2019 average until February 2021. Indeed, a significant recovery was observed ensuing the pandemic in 2021, with ~24% growth in the total number of trials, a trend anticipated to continue as we successfully mitigate the effect of the COVID-19 pandemic on clinical disruption.

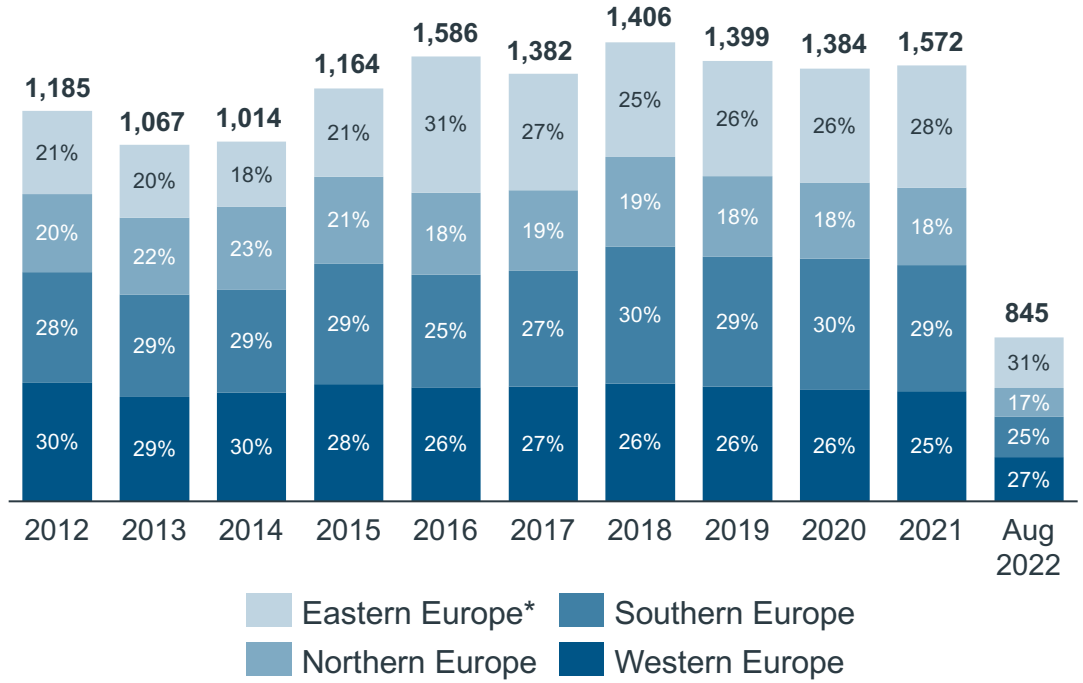
Note: (1) Total number of trials started in 2022 to be defined – final number will be available in the beginning of 2023
Source: Clarivate Analytics Cortellis, **Year to Aug 2022**; Phase 2 includes Phases 1/2, 2, 2a, 2b. Phase 3 includes Phase 2/3 and 3. Terminated trials were excluded from the analysis. Trials not industry sponsored, and device trials were excluded

The impact of COVID-19 on trials' geographic split remains negligible; Meanwhile, Asia plays an increasing role in clinical development

FULL PIPELINE – No. of trials started per region[1]



EU PIPELINE – No. of trials started per sub-region[1]



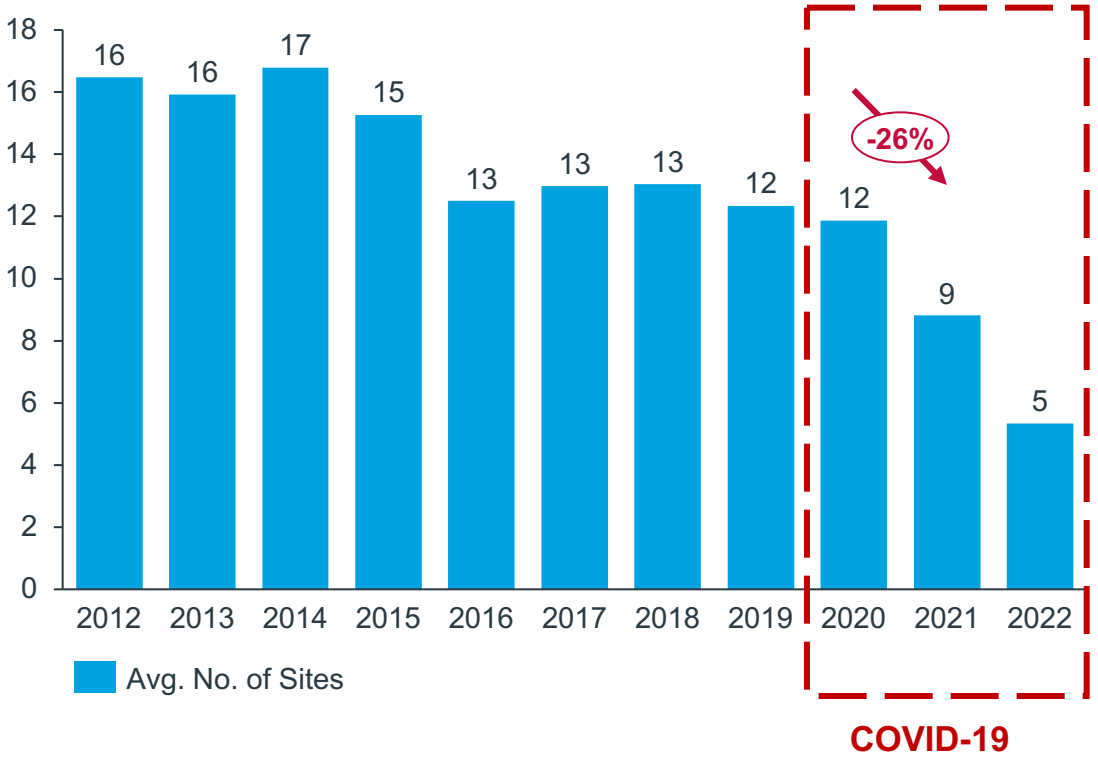
The geographic distribution of clinical trial location has not changed significantly compared to previous years, which indicates that the COVID-19 pandemic has not forced pharmaceutical companies to move their development activities**.** The long-term trend observed is the increasing share of clinical trials conducted in Asia (mainly China, South Korea), which has grown by over 10% in the last decade.

Source: Clarivate Analytics Cortellis, **Year to Aug 2022**; Phase 2 includes Phases 1/2, 2, 2a, 2b. Phase 3 includes Phase 2/3 and 3. Terminated trials were excluded from the analysis. Trials were industry sponsored and device trials were excluded; (*) Including Georgia; (1) *Figures represent number of trials with region listed as a location (of potentially multiple locations)*

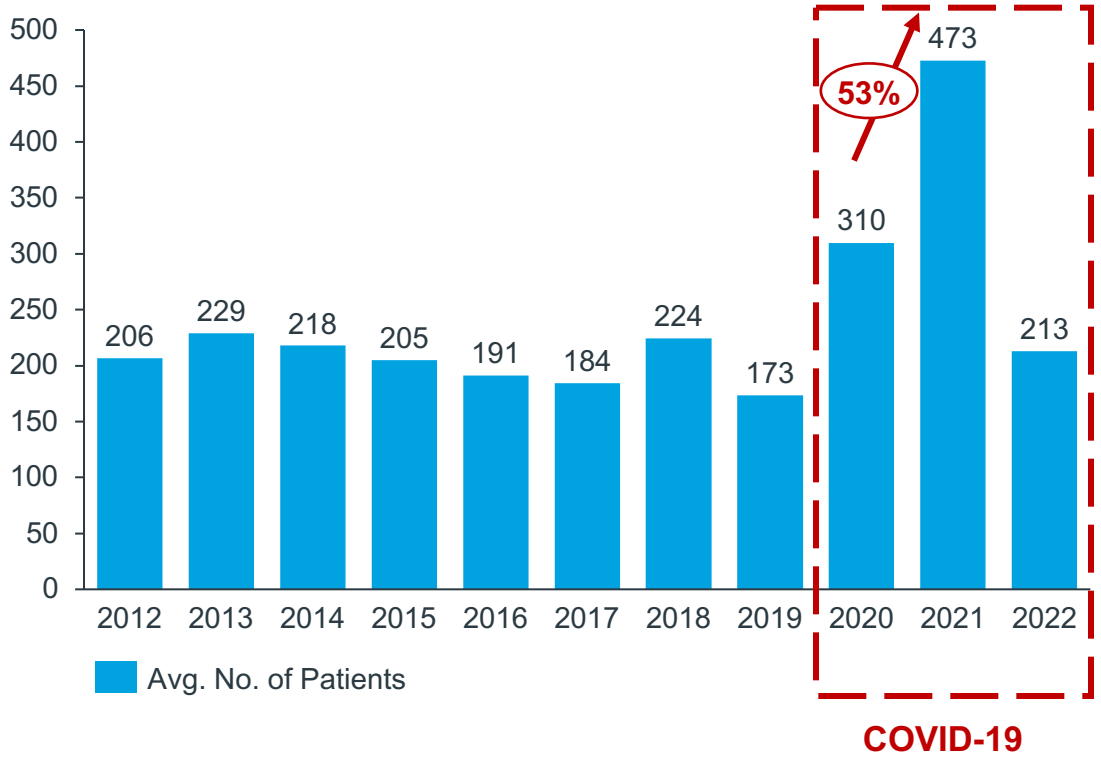
Abbreviations *- Link to Glossary*

The COVID-19 pandemic continues to influence the average number of sites and patients per clinical trial; albeit in opposite directions

FULL PIPELINE – Average No. of sites per trial



FULL PIPELINE – Average No. of patients per trial



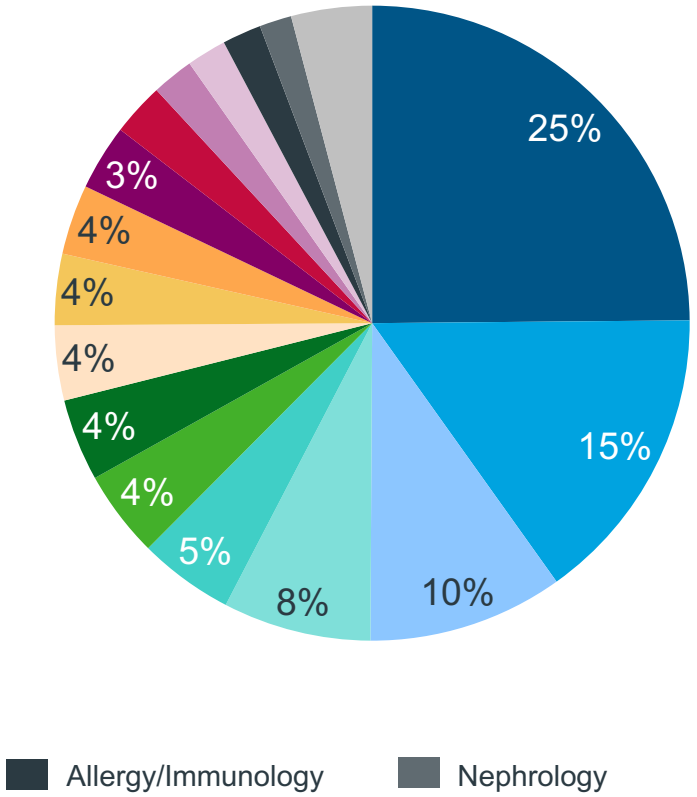
The analysis shows that the **effects of the COVID-19 pandemic** on the average number of sites per clinical trials **continue to ensue**. Specifically, we observe 26% reduction in the average number of sites per clinical trials from 2020 to 2022. That said, the opposite effect was observed in the average number of subjects per clinical trials during the pandemic, increasing by 53% between the same time period (2020 - 2021), before restabilizing in 2022.

Source: Clarivate Analytics Cortellis **Year to Aug 2022**; Phase 2 includes Phases 1/2, 2, 2a, 2b. Phase 3 includes Phase 2/3 and 3. Terminated trials were excluded from the analysis. Trials were industry sponsored and device trials were excluded

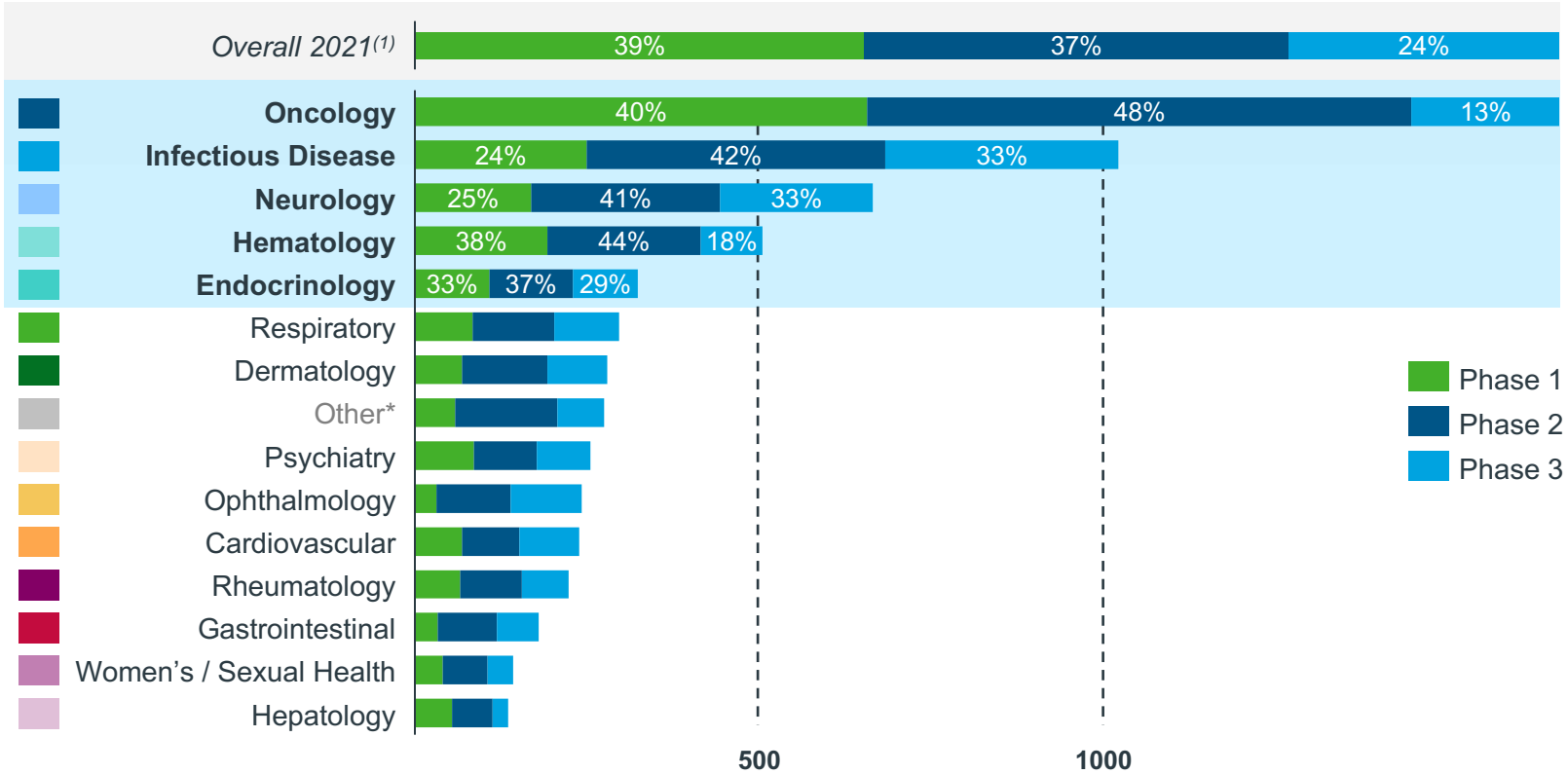
Abbreviations *- Link to Glossary*

In 2021, oncology dominated the clinical pipeline, representing approximately 25% of all new trials

PIPELINE SUMMARY – Key TAs [% of trials, 2021]



PIPELINE SUMMARY – Split per clinical trial phase

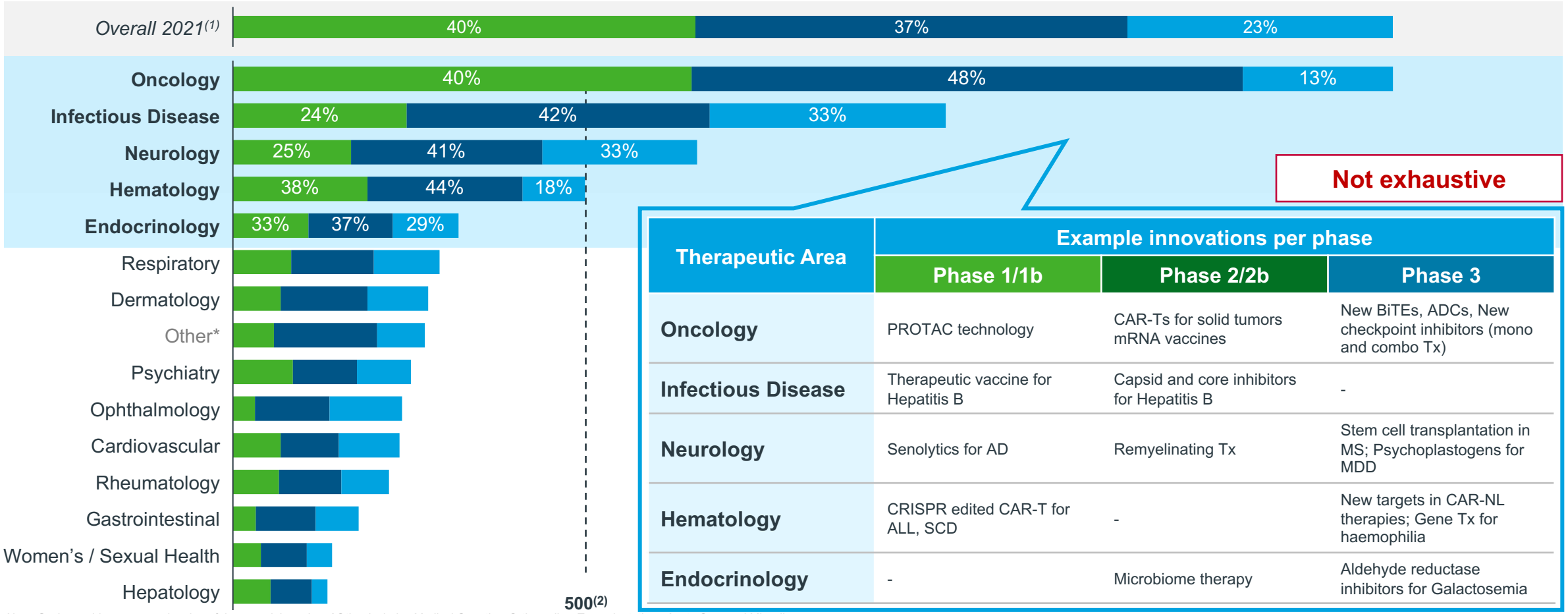


- The top **5 key TAs accounted for ~46% of all trials**, with oncology accounting for ~3x more trials than the next largest TA – Infectious Disease
- Overall Phase 1 trials represented the largest proportion of the 6,835 newly initiated clinical trials in 2021, however **for each of the top 5 TAs in terms of number of clinical trials initiated, Phase 2 trials dominated the pipeline**

Note (1) Scale provides an approximation of the true trial number, **Other includes Medical Genetics, Orthopedics, Transplantation , Acute Care and Miscellaneous - representing ~4% of the pipeline;* **Abbreviations**: Therapy Area (TA)
Source: Clarivate Analytics Cortelis, **Year to Aug 2022** Phase 2 includes Phases 1/2, 2, 2a, 2b. Phase 3 includes Phase 2/3 and 3. Trials were industry sponsored; Terminated trials & medical devices were excluded from analysis.

With 40% of the 2021 oncology pipeline still in Phase 1, further innovation is anticipated over the next 3-5 years for the TA

FULL PIPELINE – Split per clinical trial phase [share in No. of trials in 2021]



Not exhaustive

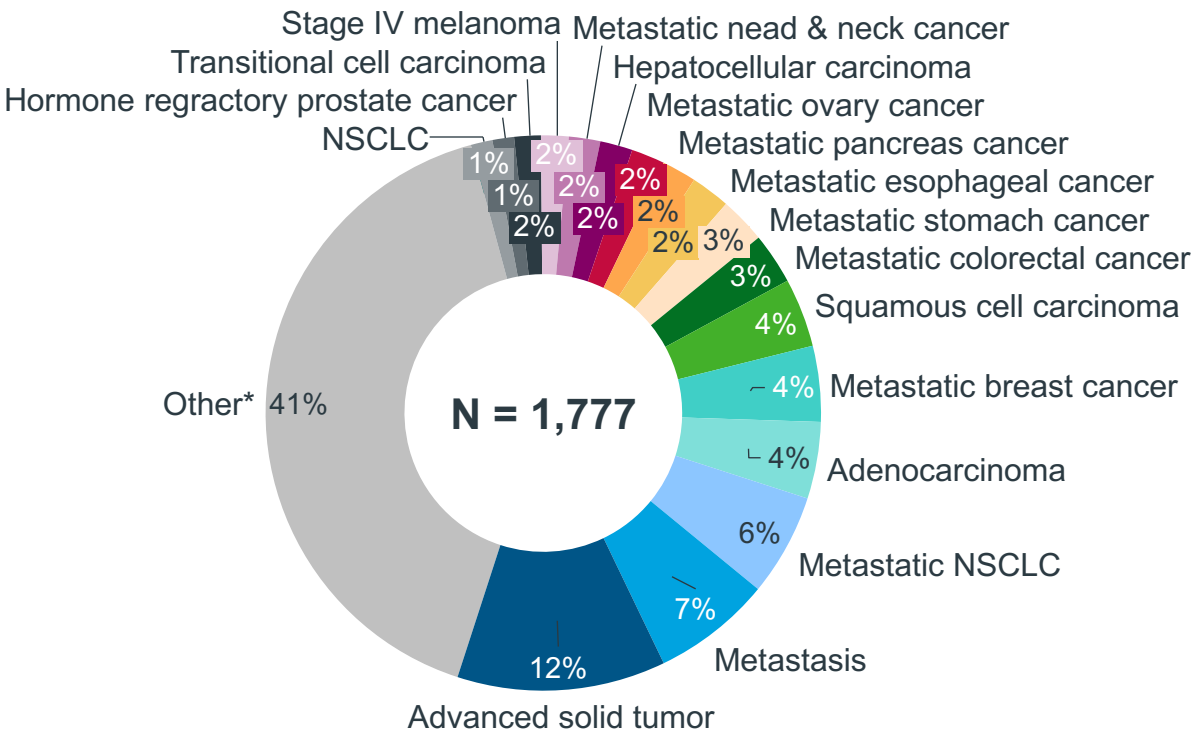
Therapeutic Area	Example innovations per phase		
	Phase 1/1b	Phase 2/2b	Phase 3
Oncology	PROTAC technology	CAR-Ts for solid tumors mRNA vaccines	New BiTEs, ADCs, New checkpoint inhibitors (mono and combo Tx)
Infectious Disease	Therapeutic vaccine for Hepatitis B	Capsid and core inhibitors for Hepatitis B	-
Neurology	Senolytics for AD	Remyelinating Tx	Stem cell transplantation in MS; Psychoplastogens for MDD
Hematology	CRISPR edited CAR-T for ALL, SCD	-	New targets in CAR-NL therapies; Gene Tx for haemophilia
Endocrinology	-	Microbiome therapy	Aldehyde reductase inhibitors for Galactosemia

Note: Scale provides an approximation of the true trial number, **Other includes Medical Genetics, Orthopedics, Transplantation , Acute Care and Miscellaneous*
Abbreviations: Alzheimer's Disease (AD), Multiple Sclerosis (MD), Major Depressive Disorder (MDD), Acute Lymphoblastic Leukemia (ALL), Sickle Cell Disease (SCD), Therapy Area (TA)
Source: Clarivate Analytics Cortelis, **Year to Aug 2022** Phase 2 includes Phases 1/2, 2, 2a, 2b. Phase 3 includes Phase 2/3 and 3. Trials were industry sponsored; Terminated trials & medical devices were excluded from analysis.

***Abbreviations** – Link to Glossary*

Within Oncology, clinical activity focuses primarily on metastatic or advanced tumours

ONCOLOGY PIPELINE – Key indications [% of trials in 2021]



*Other includes Cytotoxics, Hormonal therapy and Radiotherapeutics

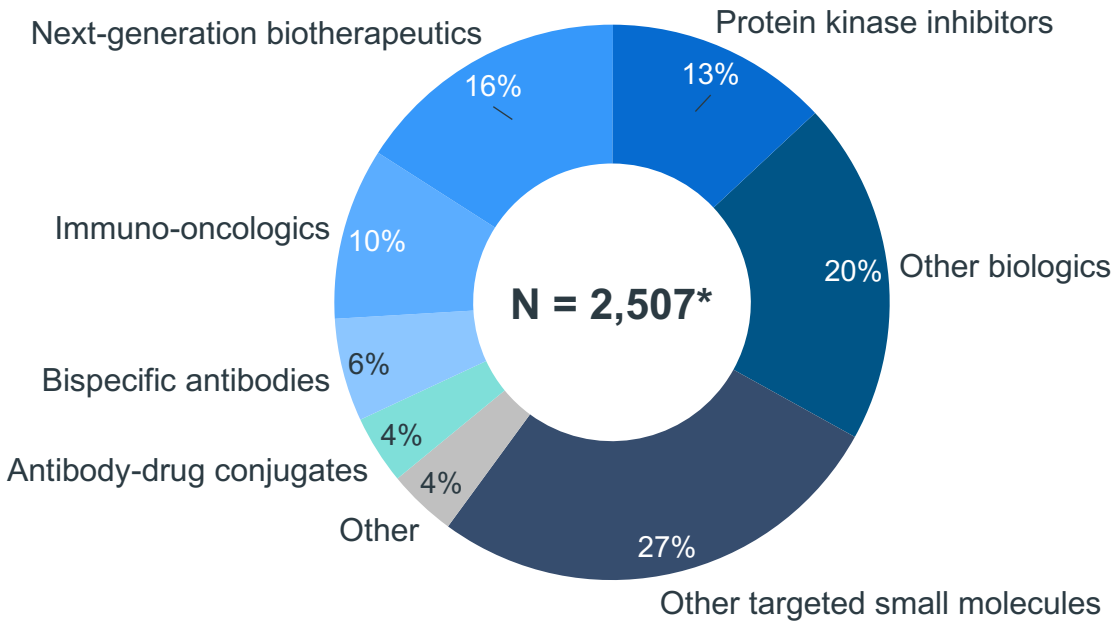
KEY HIGHLIGHTS

- The 2021 oncology pipeline represents a focus on **metastatic cancers** and **high prevalence indications** such as NSCLC, breast cancer and solid tumours
- Research focused on cancers in early stages is challenging because patients are rarely diagnosed sufficiently early to be enrolled in a dedicated trial for early disease
- However, trials for **early cancer therapies** have **made significant recent progress**, with number of trials more than doubling in last 10 years

Note: * Other includes Cytotoxics, Hormonal Therapy and Radiotherapeutics; **Abbreviations**: Non-Small Cell Lung Cancer (NSCLC)
Source: Clarivate Analytics Cortellis, **Aug 2022**; Phase 2 includes Phases 1/2, 2, 2a, 2b. Phase 3 includes Phase 2/3 and 3. Terminated trials were excluded from the analysis. Trials were industry sponsored and device trials were excluded

Overall, the global oncology pipeline in 2021 represented robust development across a broad spectrum of innovative technologies

ONCOLOGY R&D PIPELINE – *Phase 1 to regulatory submission by type, Ongoing trials in 2021*



KEY HIGHLIGHTS

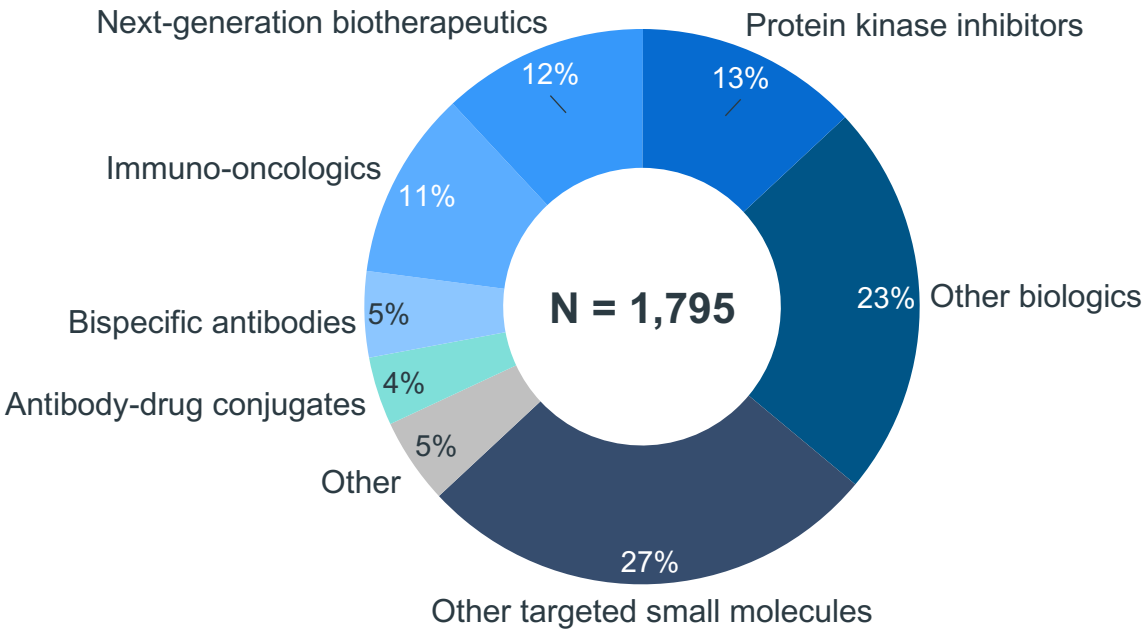
- An increased focus on targeted therapies with innovative mechanisms of actions can be observed in the oncology pipeline with **next-generation biotherapeutics already accounting for ~16% of the total oncology pipeline**
- **Immuno-oncologics, which saw significant growth in the last decade can been seen to be tapering off** (accounting for only ~10% of the overall pipeline), making room for novel therapies
- Despite being first developed in 1960s, **bispecific antibody** development for cancer treatment has began growing in recent years due to the **ability of these molecules to act on multiple targets**

Note: Other includes Cytotoxics, Hormonal therapy and Radiotherapeutics; * represents the number of ongoing oncology trials from Phase 1 to regulatory submission and will hence differ from the number of oncology trials initiated in 2021
Source: IQVIA Global Oncology Trends 2022 (1) Key technologies in the 2021 oncology pipeline; 2022 figures released beginning of 2023

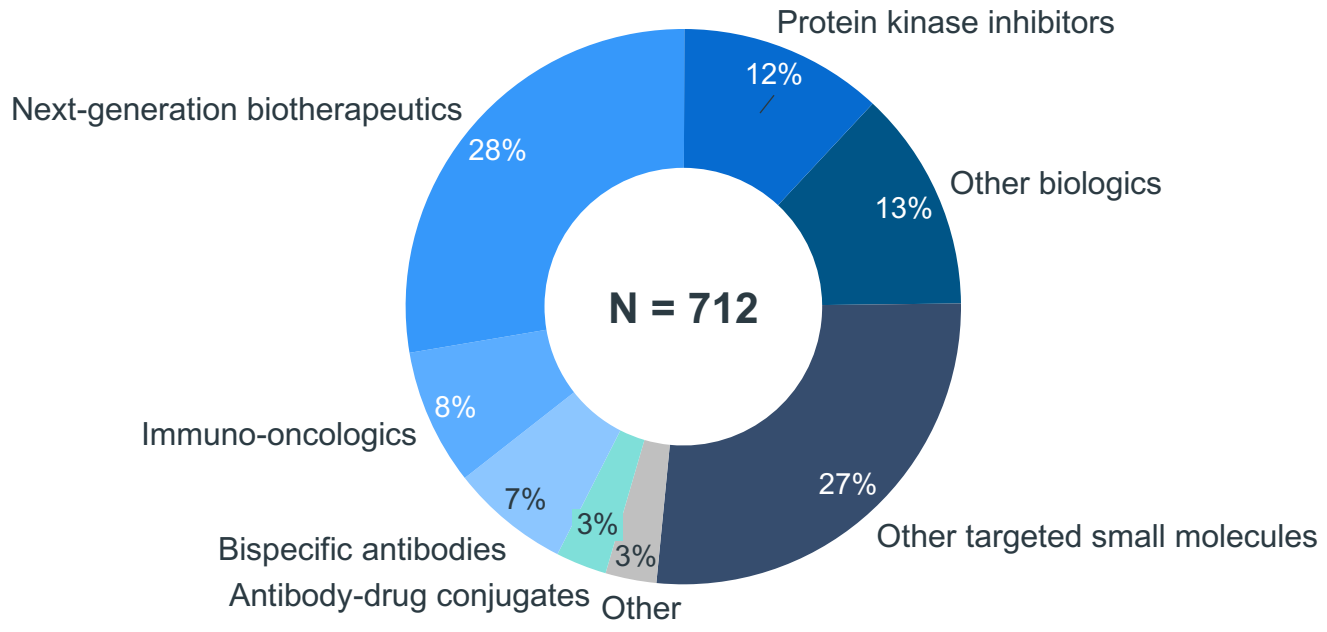
Abbreviations *- Link to Glossary*

The 2021 oncology pipeline broken down by cancer type highlights key differences between the use of biologics and next-gen. biotherapeutics

SOLID CANCERS R&D PIPELINE – *Phase 1 to regulatory submission by type, Ongoing trials in 2021*



HAEMATOLOGICAL CANCERS R&D PIPELINE – *Phase 1 to regulatory submission by type, Ongoing trials in 2021*



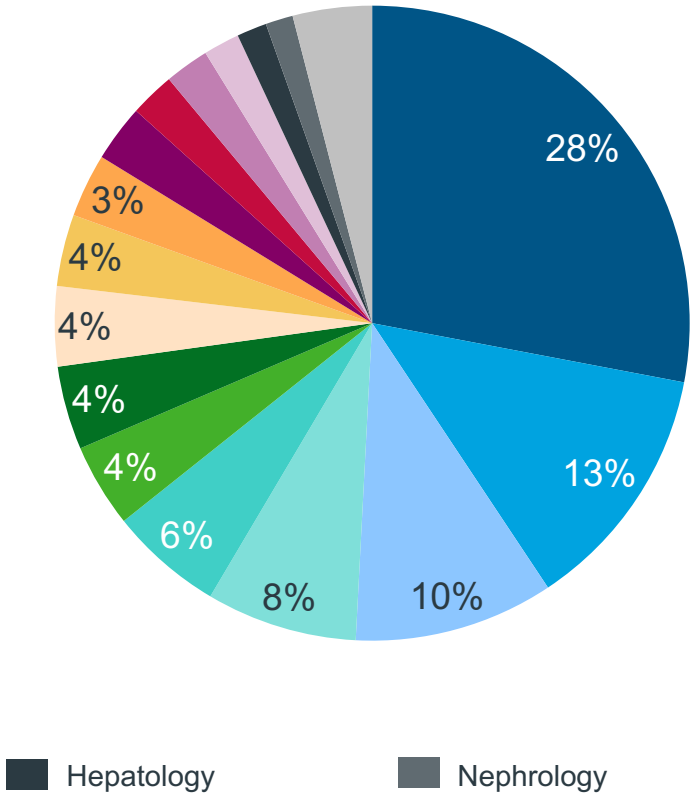
Within the solid tumour cancers development pipeline, a significant increase in the share of next-generation biotherapeutics is observed compared to the haematological cancers pipeline. On the other hand, a significant increase in the share of biologics is observed in the haematological pipeline compared to the solid tumours cancers pipeline. The share of other technologies remains fairly consistent within the two pipelines.

Note: Other includes Cytotoxics, Hormonal therapy and Radiotherapeutics
Source: IQVIA Global Oncology Trends 2022 (1) Key technologies in the 2021 haematological cancers pipeline; 2022 figures released beginning of 2023

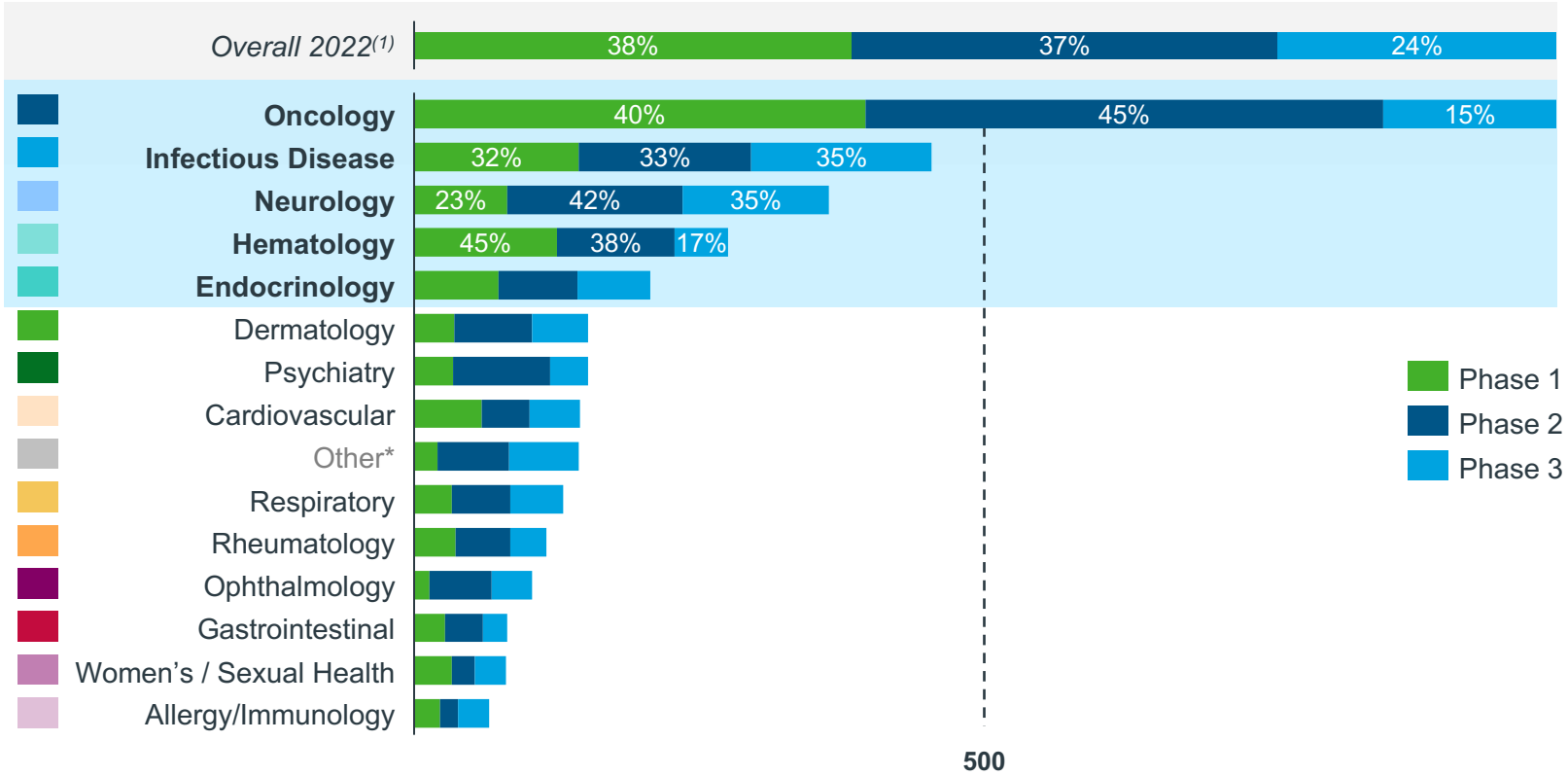
Abbreviations *- Link to Glossary*

To date in 2022, oncology continues to dominate the clinical pipeline, with an increased representation from 25% to 28% of all newly initiated trials

PIPELINE SUMMARY – Key TAs [% of trials, 2022]



PIPELINE SUMMARY – Split per clinical trial phase



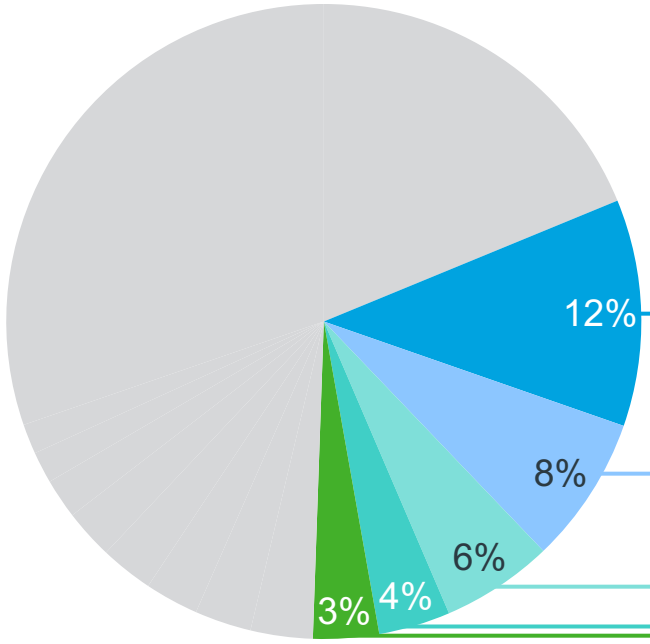
- **Oncology increased its majority share** in the clinical trial pipeline from **25% in 2021 to 28% so far in 2022**
- Excluding the unverified Phase 1 trials, **Phase 2 trials continue to represent the largest proportion** of the newly initiated clinical trials in 2022

Note: **Other includes Medical Genetics, Orthopedics, Transplantation , Acute Care and Miscellaneous - representing ~4% of the pipeline; ;* **Abbreviations:** Therapy Area (TA)
Source: Clarivate Analytics Cortelis, **Year to Aug 2022**; Phase 2 includes Phases 1/2, 2, 2a, 2b. Phase 3 includes Phase 2/3 and 3. Trials were industry sponsored; Terminated trials & medical devices were excluded from analysis.

Outside oncology, trials in diseases with high societal impact (COVID-19, HIV, Alzheimer's Disease, MM, Asthma) dominate clinical activity

FULL PIPELINE 2021 – Key TAs [% of active trials, share]

- Oncology
- **Infectious Disease**
- **Neurology**
- **Hematology**
- **Endocrinology**
- **Respiratory**
- Dermatology
- Psychiatry
- Ophthalmology
- Cardiovascular
- Rheumatology
- Gastrointestinal
- Women's / Sexual Health
- Hepatology
- Other



TOP 5 INDICATIONS PER SELECTED TAs

Infectious diseases: **COVID-19 (49%), Viral Pneumonia (4%),** Hepatitis B (3%), Influenza Infection (3%), RSV (2%)

Neurology: **Pain (9%), Alzheimer's Disease (8%),** MND (5%), Parkinson's Disease (4%), Multiple Sclerosis (4%)

Hematology: **Multiple Myeloma (6%), Non-Hodgkin Lymphoma (6%),** Diffuse Large B-Cell Lymphoma (5%), Hematological Neoplasm (4%), Chronic Lymphocytic Leukemia (4%)

Endocrinology: **Diabetes* (31%), Obesity (14%),** Hyperuricemia (4%), Iron Deficiency Anemia (4%), Gout (3%)

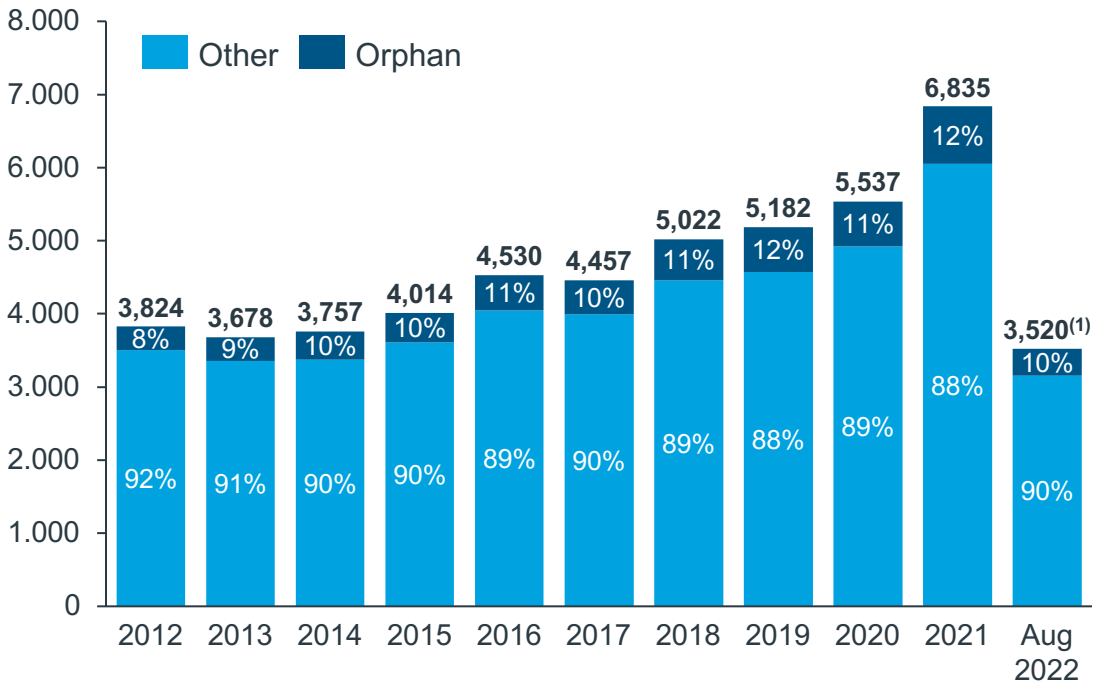
Respiratory: **COVID-19 (17%), Asthma (10%),** Viral Pneumonia (9%), Idiopathic Pulmonary Fibrosis (6%), Respiratory Distress Syndrome (6%)

Indications in bold are of high importance for European (and global) society due to high incidence rates and large burdens on HCS.
They are also key focus areas in the current clinical development.

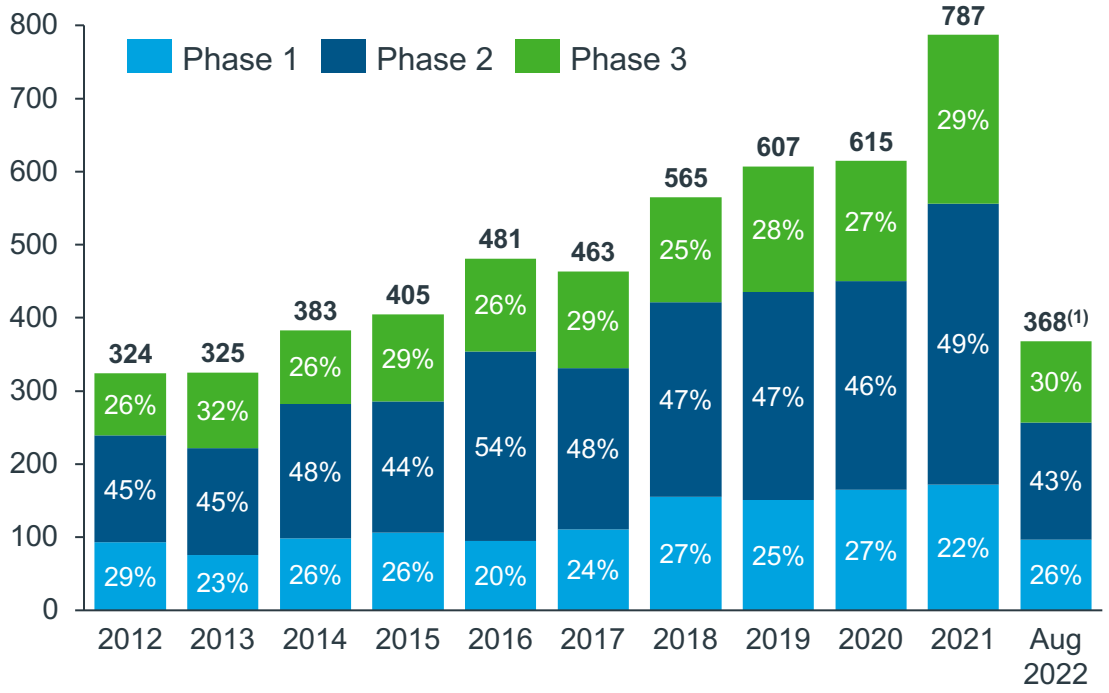
Note: * The share of the diabetes pipeline for insulin-dependent diabetes is approximately 4%
Abbreviations: Multiple Myeloma (MM), Motor Neuron Disease (MND), Health Care Systems (HCS), Therapy Area (TA)
Source: Clarivate Analytics Cortellis, **Year to Aug 2022** Phase 2 includes Phases 1/2, 2, 2a, 2b. Phase 3 includes Phase 2/3 and 3. Trials were industry sponsored; Terminated trials & medical devices were excluded from analysis.

A steady increase in the number of newly initiated orphan disease clinical trials is observed over the past decade

FULL PIPELINE – No. of trials started in 2012-2022



ORPHAN PIPELINE – No. of trials started in 2012-2022



Share of orphan indications in the clinical activity has **stabilised between 10-12%** since 2014; however, **share of therapies advancing to later phases i.e. Phase 2 and 3 has increased indicating increased success and a maturing pipeline for orphan indications**

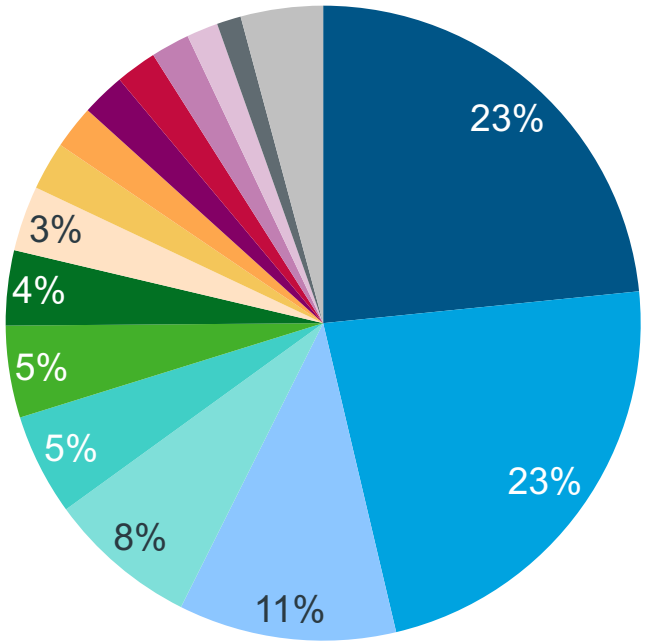
Note: (1) Total number of trials started in 2022 to be defined – final number will be available in the beginning of 2023

Source: Clarivate Analytics Cortellis, **Year to Aug 2022**; Phase 2 includes Phases 1/2, 2, 2a, 2b. Phase 3 includes Phase 2/3 and 3. Terminated trials were excluded from the analysis. Trials not industry sponsored, and device trials were excluded

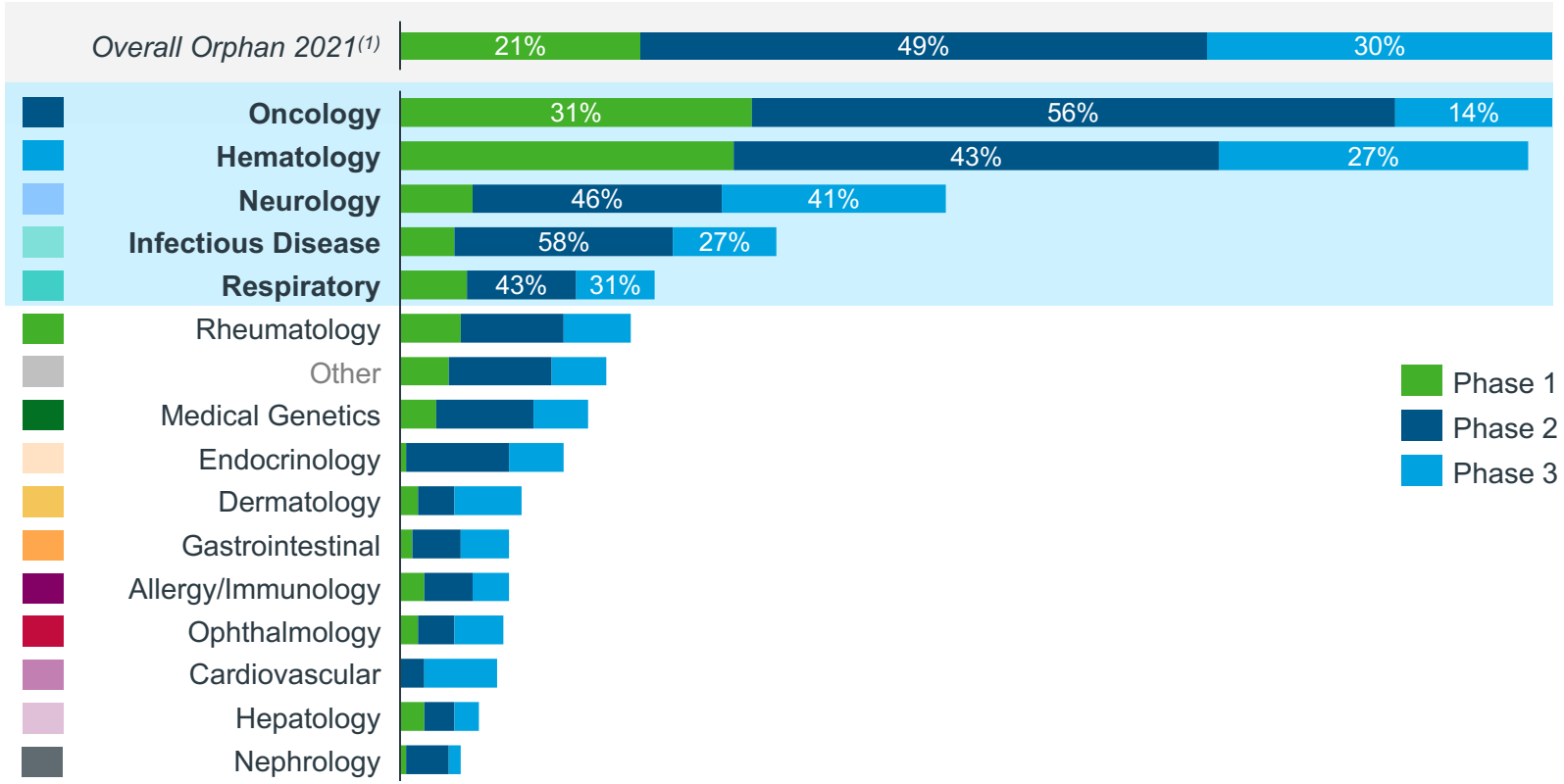
Abbreviations *- Link to Glossary*

Oncology and hematology together represent almost half of newly initiated trials in rare diseases

PIPELINE SUMMARY – Key TAs [% of trials, 2021]



PIPELINE SUMMARY – Split per clinical trial phase

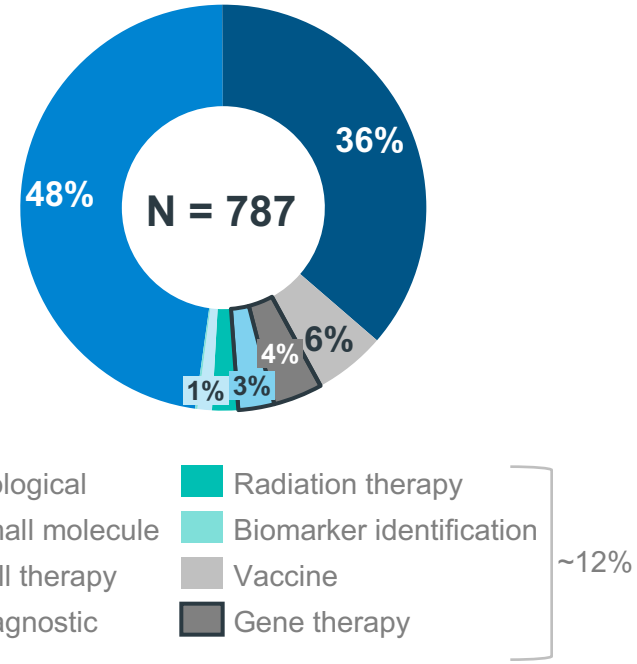


- **Oncology and hematology together dominate the rare disease pipeline**
- **Phase 2 trials represented the largest proportion (approximately half)** of the 823 newly initiated orphan disease clinical trials

Note: **Other includes Orthopedics, Women's / Sexual Health, Transplantation, Psychiatry, and Acute Care - representing ~4% of the pipeline;* **Abbreviations:** Therapy Area (TA)
Source: Clarivate Analytics Cortellis, **Year to Aug 2022** Phase 2 includes Phases 1/2, 2, 2a, 2b. Phase 3 includes Phase 2/3 and 3. Trials were industry sponsored; Terminated trials & medical devices were excluded from analysis.

Oncology remains the key therapy area in Orphan indication pipeline; innovative therapies like cell and gene therapy are gaining importance

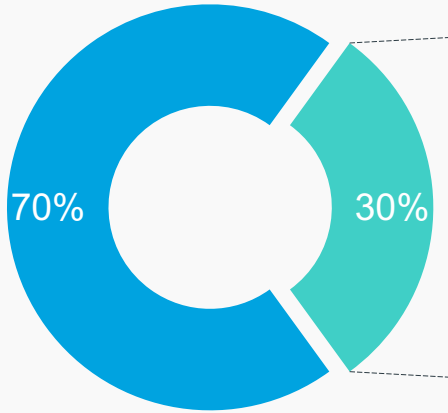
KEY PIPELINE CATEGORIES FOR ORPHAN THERAPY AREAS



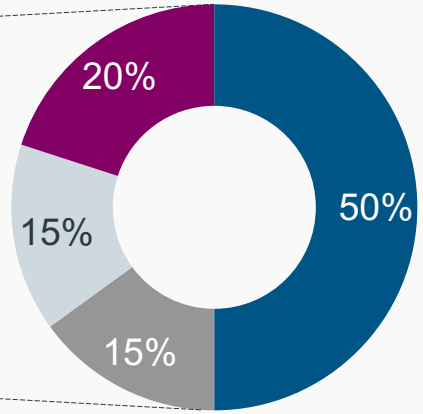
Source: Clarivate Analytics Cortellis, **Aug 22**

Although the majority of clinical activity focuses on biologics and small molecules, innovative technologies like cell and gene therapies constitute 7% of trials initiated for orphan indications in 2021

ORPHAN VS. NON-OPRHAN DRUGS IN R&D



KEY ORPHAN DRUGS BY THERAPY AREAS



Source: IQVIA Institute report on R & D trends 2022; Drugs in development from pre-clinical to Pre-registration globally

- From pre-clinical to pre-registration, there are **~1,800 products (30% of the total) under development for rare diseases.** 50% of these are in rare oncology, followed by rare neurological treatments and rare gastrointestinal disorders
- Phase 2 makes up a significant portion of the pipeline, reflective of a high Phase 1 success rate of **~68% for rare diseases** over the last five years

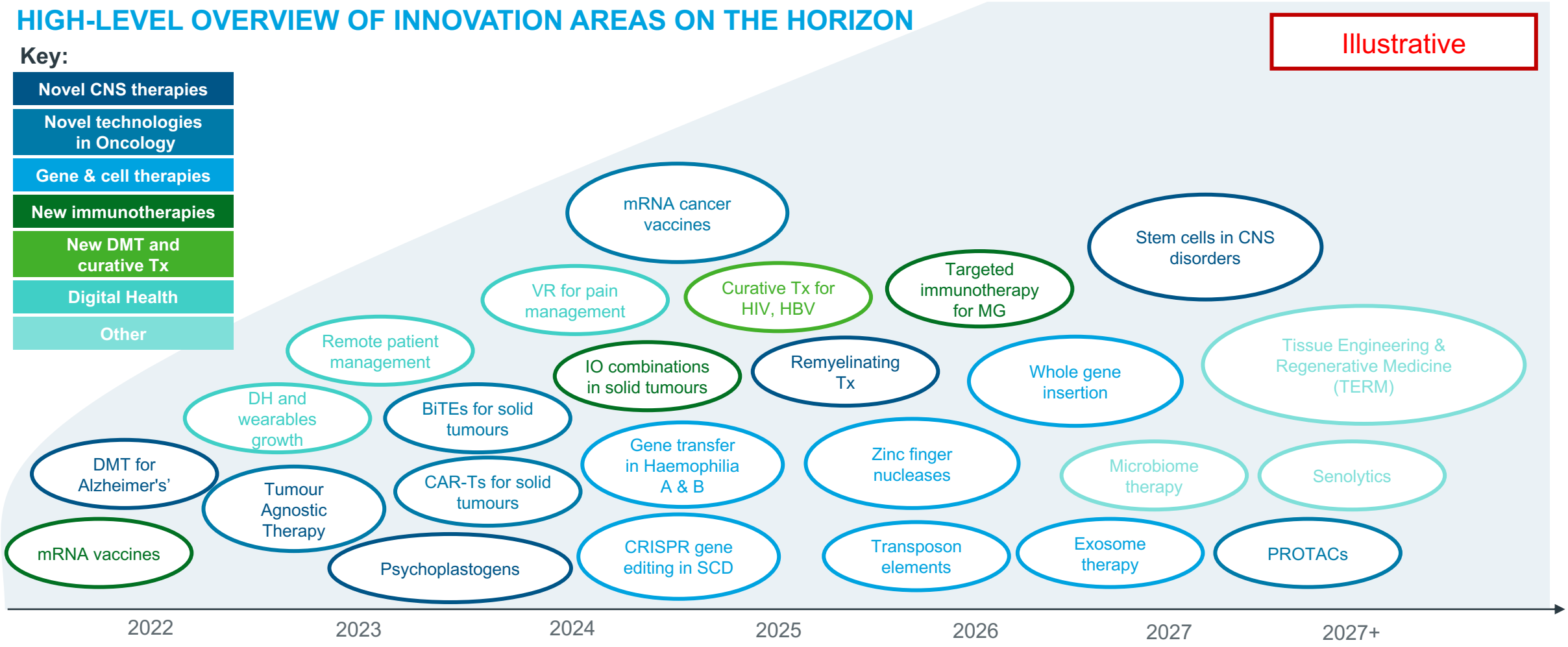
Sources: (1) IQVIA Institute, Jan 2022

Abbreviations *- Link to Glossary*

Recently several innovation areas have appeared on the horizon, with the potential to gain importance in the coming years

HIGH-LEVEL OVERVIEW OF INNOVATION AREAS ON THE HORIZON

Illustrative



Abbreviations: Disease modifying therapies (DMTs), therapies (Tx), Digital health (DH), virtual reality (VR), central nervous system (CNS), human immunodeficiency virus (HIV, hepatitis B virus (HBV), Proteolysis Targeting Chimeras (PROTAC), Chimeric antigen receptor T cells (CAR-Ts), antibody drug conjugate (ADC), Myasthenia Gravis (MG)

Indeed, multiple innovation areas are appearing on the horizon with the potential to reach the market in the short- to mid-term (1/2)..

Remyelinating therapies
(Multiple Sclerosis, PD)

Psychoplastogens
(Major depressive disorder)

CAR-T/NKs for solid tumors

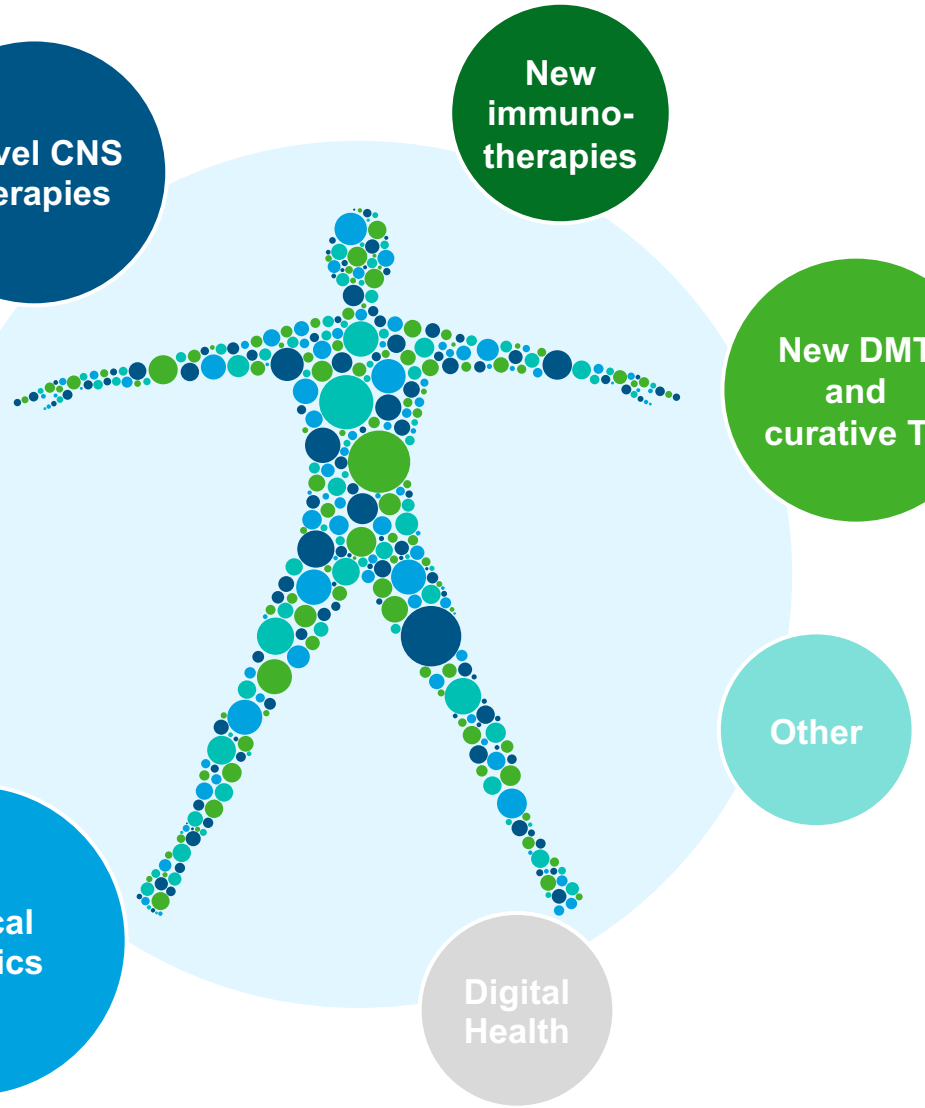
PROTACs

BiTEs for solid tumors

Gene delivery systems
(Transposon elements, AAV, LNP)

Gene editing technologies
(CRISPR-CAS9, ZFNs, TALENs)

Gene therapies



Novel vaccines
(mRNA vaccines)

Novel immunotherapies
New targets

Curative Tx for infectious disease
(HIV, Hepatitis B)

Disease Modifying Treatments
for AD, DMD, Osteoporosis

Tissue engineering & regenerative medicine

Senolytics for age-related diseases

Gut microbiome

Remote patient management

VR for pain management

Wearables growth and new applications

Abbreviations *– Link to Glossary*

Some of these therapies are expected to reach the market in short- to mid-term (2/2)…

Novel CNS therapies

Remyelinating therapies
Hold potential not only to prevent further myelin damage caused by CNS disorders (Multiple Sclerosis, PD), but also reverse disease effects

Psychoplastogens
New technologies bring rapid improvement to patients with ADHD and depression; novel drugs for schizophrenia in the pipeline

Novel technologies in Oncology

Tumour agnostic Tx
First therapies approved present challenges for HTAs to assess added benefit versus SoC linked to a tumour location

CAR-Ts/NKs for solid tumours
CAR-Ts have brought improved treatment outcomes to patients with blood cancers and now are further investigated in solid tumours (e.g. ovarian, GI)

BiTEs for solid tumors
BiTE platform provides significant advantages over current innovative CAR-T therapies, as off-the-shelf products with high safety profile

Gene & cell therapies

Gene delivery systems (Transposon elements, AAV, LNP)
Used across most gene technologies as delivery vehicles for genetic cargo

Gene editing technologies (CRISPR-CAS9, ZFNs, TALENs)
Most advanced genetic editing includes CRISPR-cas9, being evaluated across rare diseases & oncology

Gene transfer therapies
Introduction of an additional gene into specific cells to compensate for abnormal genes or to make a beneficial protein

New immunotherapies

mRNA vaccines
may be leveraged to boost immunity against cancer, infectious diseases, and more

Novel immunotherapies
Significant research is investigating 21 new immune checkpoints and inhibitory targets across solid tumors and hematologic malignancies

New DMT and curative Tx

Curative Tx for infectious disease
Currently no curative therapy is available for chronic HepB and HIV infections; several investigative Tx are in the pipeline with high degree of novelty and diversity

Disease modifying therapies
New DMT approved for Alzheimer's disease

Other

Senolytics
Telehealthcare and wearable medical devices driving growth of this market

Gut Microbiome
Recent research has delineated the role of the gut microbiome in the pathogenesis of various common disorders, including obesity, type 2 diabetes, non-alcoholic liver, cardiovascular disease, and mental health disorders

Note: Short- to mid-term = up to 3-5 years

Abbreviations *- Link to Glossary*

…whereas other interesting technologies are further on the horizon, their active developments merit continued monitoring

SELECTED TECHNOLOGIES ON THE HORIZON

PROTACs

- PROTAC (proteolysis-targeting chimera) substances have been developed as a useful technology to **degrade and dispose of targeted proteins that support cancers**
- New therapies could target different cancer types, potentially offering higher efficiency with lower toxicity and side effects[1]

ZFNs

- Engineered Zinc Finger Nucleases (ZFNs) are powerful base editing platforms to specifically target genome cleavage enabling modification and manipulation of disease-causing genes[2]
- Early clinical trials are underway to translate the gene editing tool to clinical practice[3]

EXOSOMES

- Exosomes are nano-vesicles released by nearly every cell in the body, which may be used as a diagnostic/therapeutic agents
- Exosomes may offer an improved safety profile for stem cell therapy, and may reduced side effects and scar tissue[4,5]

WHOLE GENE INSERTION

- Precision insertion technique to enable gene-sized insertions of longer DNA sequence, up to ~5 kb and ~36 kb, using DNA recombinases or integrases in conjunction with prime editors[3]
- Offers promise of safe, durable, and efficient integration of large DNA sequences into genes

SENOLYTICS

- New class of drugs that can induce death of senescent cells responsible for aging and age-related diseases[6]
- Targeting aging itself might be a novel strategy to prevent several neurodegenerative disorders, with first-in-human trials recently launched

MICROBIOME THERAPY

- Microbiome therapy aims to restore healthy gut microbiota to control a variety of local and distant pathologies including obesity, type 2 diabetes, and mental health disorders[7]
- Coupled with diagnostic advances and sophisticated AIML, microbiome research is poised for growth and clinical application

Sources: (1) ScienceDirect; (2) Nature; (3) Broker reports; (4) NCBI; (5) Exopharm; (6) NCBI; (7) Nature

Abbreviations – *Link to Glossary*

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Immune checkpoint inhibitors (ICIs) remain a vital and promising tool in the fight against cancer and have become an established SoC in NSCLC

01 | Tx Landscape Update

NSCLC

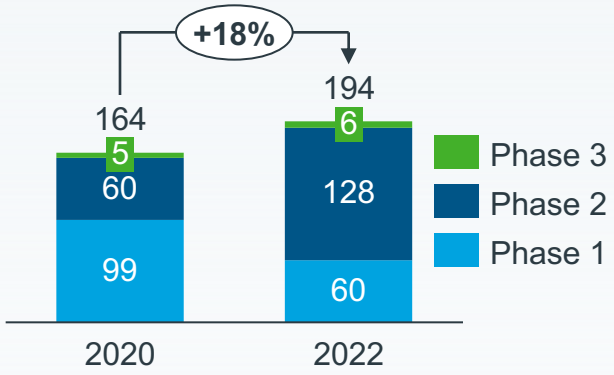
- Transformed NSCLC care affording deep, durable responses and sustained long-term efficacy replacing SoC, with several ICIs becoming entrenched in guidelines, including **pembrolizumab**, **atezolizumab**, **nivolumab** & **ipilimumab**
- In 2018, **pembrolizumab** and **pemetrexed** was the first EMA approved ICI + chemo combo for NSCLC[1]
- In Mar. 2022, EMA validated **nivolumab** in combination with chemotherapy for the neoadjuvant treatment NSCLC[2]
- In Apr. 2022, EMA validated MAA for **tislelizumab** following positive Phase 3 RATIONALE readout[3]

OTHER CANCERS

- Checkpoint inhibitor combinations are expected to become SoC in BC, with **pembrolizumab** and **atezolizumab** approved in 1L
- In Mar. 2022, CHMP adopted a positive opinion recommending multiple indication expansions for **pembrolizumab**[4]

02 | Pipeline Update

Number of active clinical trials



- Total number of **trials increased by 18%** with number of Phase 2 studies almost doubling, implying high rate of trial progression from Phase 1 to 2

- There are **~70 Ph 3 trials** running for ICI combos in cancers inc. melanoma, glioblastoma, colorectal, breast, ovarian, liver, kidney & prostate
- In addition to 3 approved checkpoints, significant research is investigating 21 new checkpoints and inhibitory targets

03 | Impact Update

Health outcomes

- Mounting randomized clinical trials have proven that ICIs improve OS, PFS, and ORR vs. chemotherapy
- Indeed, in its pivotal Phase 3 KEYNOTE-189 study, **pembrolizumab** + **pemetrexed** demonstrated significant OS and PFS improvement as 1L treatment in advanced NSCLC, with risk of progression or death reduced by approximately half[1]

Economic outcomes

- For those NSCLC patients diagnosed in 2020, an estimated €717m could be generated in GDP each year through the use of novel ICI combinations[5]

Health outcomes

- **Pembrolizumab** + chemotherapy reduced risk of death by 27% vs chemo as 1L treatment for patients with metastatic triple-negative BC, including an OS increase of 6.9 months compared to chemo alone[6]

Note: NSCLC: Non-Small Cell Lung Cancer; SoC: Standard of Care; 1L: First Line; EMA: European Medicines Agency; CHMP: Committee for Medicinal Products for Human Use; ICI: Immune Checkpoint Inhibitors; BC: Breast Cancer; OS: Overall Survival, PFS: Progression-Free Survival; ORR: Overall Response Rate; GDP: Gross Domestic Product

Source: 1. Merck; 2. BMS; 3. Novartis; 4. EMA; 5. As per 2020 EFPIA-IQVIA report; 6. Merck

Abbreviations – Link to Glossary

CAR-Ts have achieved remarkable results against hematological cancers with sustained tumor regression and long-term anti-neoplastic effects

B-CELL MALIGNANCIES

MULTIPLE MYELOMA

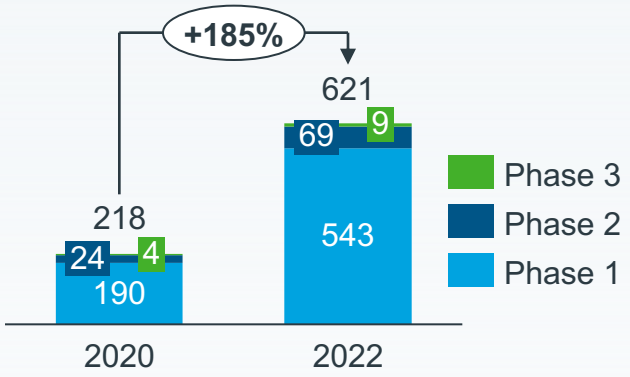
01 | Tx Landscape Update

- Well established in EHA-ESMO clinical guidelines for the treatment of relapsed and refractory B-Cell malignancies
- In Dec. 2020, **Brexucabtagene autoleucel** received CMA for 3L treatment of r/r MCL[1]
- In Jan. 2022, **lisocabtagene maraleucel** received approval to treat r/r DLBCL, PMLBCL, and FL3B in 3L+ therapy[2]
- In Mar. 2022, **Tisagenlecleucel** received a new indication expansion for r/r FL after 2L+ of systemic therapy[3]
- In Apr. 2022, **axicabtagene ciloleucel** was approved to expand to 2L therapy, receiving the first NCCN Treatment Guideline Category 1 recommendation and improvement upon SoC in 30 years[4]

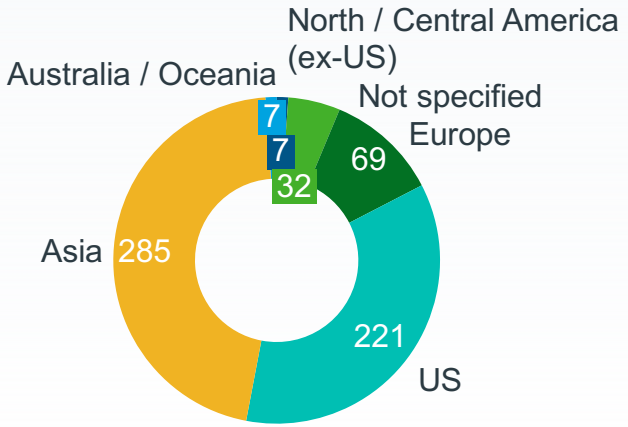
- Recognized in latest 2021 EHA-ESMO clinical practice guidelines for MM[5]
- In Aug. 2021, **Idecabtagene vicleucel** received the first anti-BCMA CAR-T approval in MM[6]
- In May 2022, **ciltacabtagene autoleucel** received conditional approval for 4L treatment[7]

02 | Pipeline Update

Number of active clinical trials



Active clinical trials by geographic location



03 | Impact Update

Health outcomes

- Consistently high ORR of 52-83% in DLBCL, including 40-55% CR
- Landmark ZUMA-7 demonstrated patients on **axicabtagene ciloleucel** were 2.5x more likely to be alive at 2 years without progression or need for additional cancer treatment[4]
- Several emerging agents have improved the prognosis of patients with MM, with the 5-year OS rate rising from ~30% to ~70% vs. comparators selinexor & pomalidomide
- Both **Idecabtagene vicleucel** and **ciltacabtagene autoleucel** have reported deep and durable responses in treatment of MM, with an ORR of 85% and 95%, and stringent CR of 45% and 83%, respectively

Economic outcomes

- Current price-setting of CAR-Ts has encouraged EU member states to adopt innovative agreements to ensure access to patients, including CED in France and UK, outcomes-based staged payment agreements in Italy and Spain, and rebates in Germany

Note: CAR-T: Chimeric Antigen Receptor T-Cells; EHA-ESMO: European Hematological Association-European Society of Medical Oncology: CMA: Conditional Marketing Authorisation; NCCN: National Comprehensive Cancer Network; MM: Multiple Myeloma; ORR: Overall Response Rate; CR: Complete Response; OS: Overall Survival; CED: Coverage with Evidence Development; Source: 1. EMA; 2. EMA; 3. Novartis; 4. Gilead; 5. Pfizer; 6.BMS; 7. EMA

Abbreviations – Link to Glossary

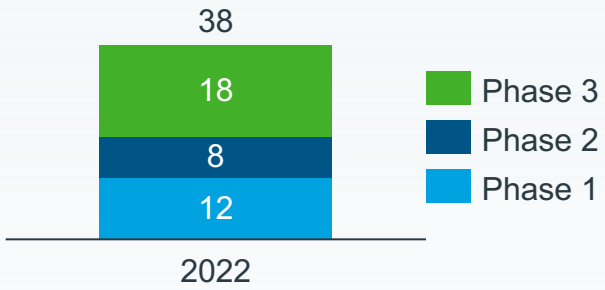
Calcitonin gene-related peptide (CGRP) inhibitors are increasingly contesting the SoC for preventative and acute treatments for migraines

01 | Tx Landscape Update

- CGRP antagonists are the first class of drugs developed exclusively for treating patients with frequent, episodic, and/or chronic migraine headaches
- **Erenumab**, **Fremanezumab**, and **Galcanezumab** have since been integrated into the EHF guidelines as effective 3L+ treatment[1]
- In Jan. 2022, **eptinezumab** was the 4th preventative mAb treatment to be approved by EMA[2]
- In addition, 3 new gepants have been approved in the US, marking the first treatments that appear to be both beneficial for treatment and prevention
  - **Ubrogepant** Dec. 2019[3]
  - **Rimegepant** Feb. 2020[4]; Positive CHMP opinion Feb. 2022[5]
  - **Atogepant** Sep. 2021[6]

02 | Pipeline Update

Number of active clinical trials



- Several new CGRP inhibitor drugs are currently in the pipeline, including:
  - **BHV-3500**
  - **HTL 0022562**
- In addition, several new drug MoAs are being investigated, including **STS-101, ALLOD 2, TRV-250**, and **Lasmiditan**; FDA approved in 2019[7]

03 | Impact Update

Health outcomes

- CGRP inhibitors have demonstrated robust efficacy signals in numerous randomized clinical trials[8], and an improvement in adherence over SoC[9]
- **Eptinezumab** reported a 1-day reduction in migraine prevalence by ~50% in its pivotal PROMISE chronic migraine trials[10]
- Estimations of **Erenumab** in Germany conclude a potential reduction of ~166 million migraines per year[11]
- In Mar. 2022, reported positive Phase 3 **atogepant** data[12] for the preventive treatment of chronic migraines

Economic outcomes

- Data from the Eurolight project estimated indirect costs associated with migraines accounted for more than 90% of total, reaching €1,222 per patient per year[13]
- Specifically, it is estimated that £9.7Bn per year is lost in the U.K. due to migraines[14], and as high as €27Bn in Germany[11]

Note: EHF: European Headache Federation; mAb: Monoclonal Antibody; CHMP: Committee for Medicinal Products for Human Use; MoAs: Mechanisms of Action; SoC: Standard of Care. Source: 1. EHF; 2. EMA; 3. U.S. FDA (ubrogepant); 4. AHS(rimegepant); 5. Pfizer; 6. AHS(atogepant); 7. U.S. FDA (lasmiditan); 8. Journal of Headache & Pain; 9. Patient Preference & Adherence; 10. Cephalalgia; 11. Value in Health; 12. AbbVie; 13. Journal of Headache & Pain; 14. NICE

Abbreviations – Link to Glossary

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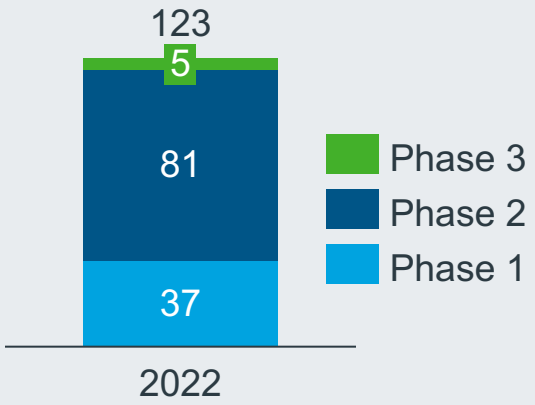
The search for mAbs for lower respiratory tract infections (LRTI) yielded an unpopulated late stage clinical trial development pipeline

CLINICAL DEVELOPMENT



KEY MoAs ADDED

Gram +/- bacteria monoclonal antibodies

True Human Monoclonal antibody (IgG3, IgG1, & IgM)

KEY UPDATES

1. The number of new treatments in the later stages of clinical trial development is minimal following several negative clinical readouts
2. **Nirsevimab** is the first investigational long-acting antibody designed to protect all infants against LRTI for RSV
   - In Feb. 2022, the EMA's Committee for Medicinal Products for Human Use (CHMP) granted **nirsevimab** accelerated assessment as it was deemed of major interest for public health and therapeutic innovation[1]
   - Regulatory decision is anticipated as early as Q3 2022 following positive MELODY and MEDLEY Phase 3 trials demonstrating 74.5% efficacy[1,2]
3. **AR-301** pivotal Phase 3 mAb program is being developed as a therapeutic treatment of S. aureus pneumonia with anticipated topline results in 2022[3]
4. Despite a negative readout of pivotal SAATELLITE phase 2 trial[4], **AR-320** (in-licensed **suvratuxomab**) will be investigated in the first ever Phase 3 clinical study evaluating a fully human mAb to treat pneumonia in the ICU setting in 2022 as an adjunctive treatment to SoC antibiotics[5]

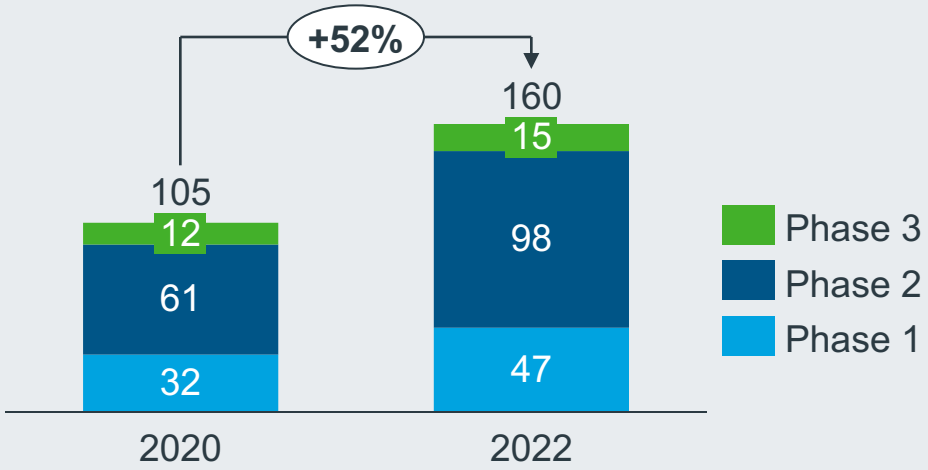
Note: 2019 clinical development estimates not available; LRTI: Lower Respiratory Tract Infections; RSV: Respiratory Syncytial Virus; mAb: Monoclonal antibody; ICU: Intensive Care Unit

Source: 1. AstraZeneca; 2. AstraZeneca; 3. Aridis Pharmaceuticals; 4. The Lancet Infectious Disease; 5. Aridis Pharmaceuticals

Abbreviations *- Link to Glossary*

Despite a significant and urgent unmet need, the NASH clinical pipeline shows minor prospective innovation

CLINICAL DEVELOPMENT



KEY MoAs ADDED

Combination of FXR agonist + THR beta agonist

FXR agonist/CCR2 + 5 inhibitor

FXR agonist + ACC inhibitor

FXR agonist + DGAT2 inhibitor

KEY UPDATES

1. Most advanced drug **obeticholic acid**, a synthetic bile acid analog and FXR agonist, received a CRL from FDA in Jun. 2020 despite positive Phase 3 results, and withdrew its EU marketing authorization application (MAA) with potential resubmission in 2022/23[1]
2. Other notable clinical development updates include:
   - **lanifibranor** progression to Phase 3, a pan-PPAR agonist that modulates NASH pathogenesis[2]
   - **K-877** discontinued in Apr. 2022 having failed to meet primary endpoint[3]
   - Positive topline results for both **TERN-101**[4] and **EYP001**[5], respectively
   - Recent expanded clinical collaboration and Phase 2 launch between **cilofexor, firsocostat, semaglutide** investigating triple combination regimen in a Phase 2 trial for NASH Patients[6]
3. Interest in combination therapy is growing, consistent with the complexity of the disease and multi-system involvement; yet it remains to be seen how effective these treatments prove to be as lifestyle modifications remain the most effective intervention for NASH

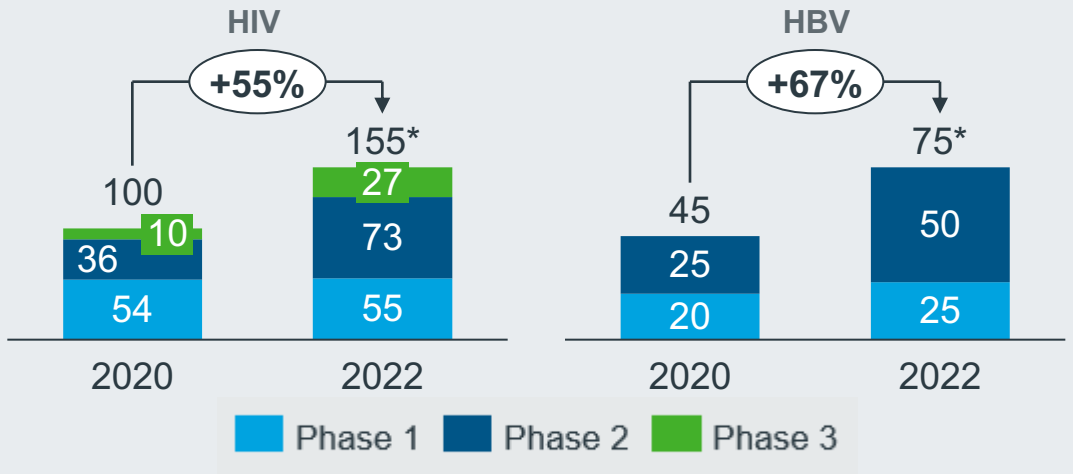
Note: PPAR: Peroxisome proliferator-activated receptor; FXR: Farnesoid X receptor; CRL: Complete Response Letter; MAA: Marketing Autorisation; MoA: Mechanism of Action

Source: 1. Cowen Report; 2. Clinicaltrials.gov; 3. PRNews; 4. News; 5. Enyo Pharma; 6. Gilead

Abbreviations *- Link to Glossary*

Since the previous report, the pipeline for curative therapies for HBV and HIV remains crowded without significant updates

CLINICAL DEVELOPMENT



*Includes few non-curative therapies as well. Detailed analysis of pipeline was out-of-scope. Phase 2 also includes Phase 1 / 2 studies

KEY MoAs ADDED

CRISPR gene editing (Trial approved in Sep '21)

KEY UPDATES

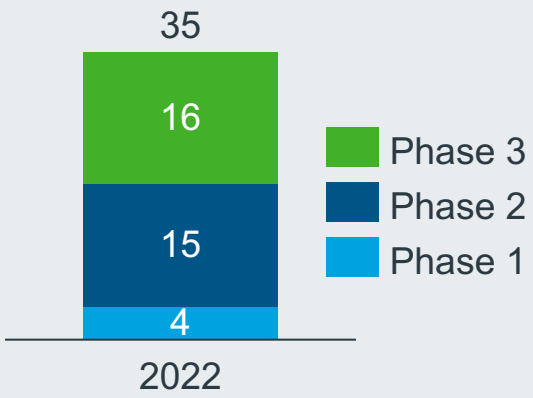
1. Several approaches are being investigated to cure Hepatitis B and HIV; However, a curative treatment is still far from the clinic
2. **HBV:** Key mechanisms of action evaluated in 2020/21 included Small interfering RNA (siRNA), therapeutic vaccine and Core/Capsid inhibitors
   - Innovative treatments continue in development, with the majority of investigations currently in Phase 2 without major trial readouts or progressions
3. **HIV:** Key MoAs evaluated in 2020/21 included broad neutralizing antibodies, CGTs, DNA-based therapeutic vaccines, dual CARTs, gene editing and monoclonal antibodies, for which several notable updates have been identified:
   - In Feb. 2022, a clinical trial of **AGT103-T** demonstrated positive Phase 1 results, confirming substantial increases in virus-specific T cells consistent with improved immunity against HIV[1]
   - The innovative monoclonal antibody **UB-421** has since progressed to Phase 3[2]
   - No major updates have been reported for the other previously identified agents evaluated in 2020/21 report

Note: HIV: Human immunodeficiency virus; HBV: Hepatitis B virus
Source: 1. News; 2. Clinicaltrials.gov

Abbreviations *- Link to Glossary*

Despite several positive late-stage clinical trial readouts, we have yet to see the promised wave of microbiome therapeutics for CDI management

CLINICAL DEVELOPMENT



KEY MoAs ADDED

Toxoid vaccines

Recombinant protein vaccines

Complex biologic cocktails

Oral formulation of NTCD-M3 spores

Small molecule antibiotics

KEY UPDATES

1. The growing literature on *Clostridioides difficile* infection (CDI) and novel treatment approaches prompted the ESCMID to publish a 2021 treatment guidance document update[1]
2. Several biotech companies are aiming to supply first-in-class treatments to restore gut microbiota, reduce the risk of recurrent CDI, and prevent CDI altogether, in indications including severe diarrhea and colitis, including:
   - **SER-109** ECOSPOR Phase 3 achieved high rates of sustained clinical responses with a favorable safety profile vs. placebo; Open-label study SERES-013 ECOSPOR IV expected to support FDA BLA[2]
   - **RBX2660** microbiota-based biotherapeutic proven effective in PUNCH CD3 phase 3 clinical trial and open-label real-world study that enrolled patients with co-morbid conditions[3]; Oral version **RBX7455** completed Phase 1[4]
   - **VE303** and **VE202** candidate achieved positive Phase 1; Phase 2 readouts anticipated in May 2022[5]
3. The microbiome field continues to garner interest from the pharmaceutical industry with multiple collaborations announced

Note: 2020 clinical development estimates not available CDI: Clostridioides difficile infection; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; FDA: Food & Drug Administration; BLA: Biologics License Application

Source: 1. CMI ESCMID; 2. Seres Therapeutics; 3. Rebiotix; 4. Clinical Infectious Diseases; 5. Vedanta Biosciences; 6. BusinessWire

Abbreviations *- Link to Glossary*

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Alzheimer's is one of Europe's largest public health crises, with a serious impact upon quality of life for patients, families, and caregivers

EXECUTIVE SUMMARY

01 TECHNOLOGY & PIPELINE ASSESSMENT

- Building on years of systematic research, today's **AD research pipeline is large and diverse**. With hopes of slowing progression and curing AD altogether, over **115 potential treatments** are currently in clinical development, of which **~75% are new DMTs**
- In Jun. 2021, aducanumab became the first DMT targeting β-amyloid to receive FDA approval, however, it was not recommended for marketing authorization by EMA in Dec. 2021
- There is much uncertainty about the future of the AD pipeline

02 INDICATION ASSESSMENT

- Although Alzheimer Europe research indicates a **reduction in the prevalence of AD**, the rapid growth of the over-65 segment of the population is expected to fuel a **doubling in patients with dementia** by 2050, afflicting ~18.8 Mn in the wider European region
- In parallel, the **economic burden of AD** is anticipated to increase 3-fold by 2050 to ~€633 Bn

03 IMPACT ANALYSIS

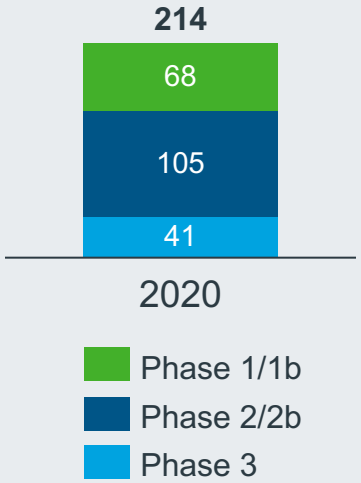
- Disease-modifying therapies offer hope in reducing **Alzheimer's high burden** on patients, families, caregivers, healthcare systems and society
- **Patients, families and caregivers:** Treatment would allow cognitive and functional capabilities and personality to be sustained for longer, safeguarding autonomy and quality of relationships
- **Healthcare systems:** Reduced and delayed need and dependence on health care resources
- **Society:** Delaying onset of AD will ease its considerable and rising socioeconomic burden, and relieve the financial, social, and psychological stress faced by caregivers and associated costs

Note: AD: Alzheimer's Disease; DMT: Disease-Modifying Therapy; FDA: Food & Drug Administration; EMA: European Medicines Agency

An extensive Alzheimer's pipeline could deliver next-generation, disease-modifying treatments for the insidious disease, but uncertainties remain

2022 UPDATES VS. 2020 REPORT

CLINICAL DEVELOPMENT



1 new disease-modifying therapy to achieve FDA approval

11 phase 2 and 3 trials with anticipated readouts by 2023

-4 key trials withdrawn*

SELECTED TECHNOLOGIES

β-amyloid mAbs

remain the predominant hypothesis and largest focus area

Stem cell therapies, Filament inhibitors

are investigated in several trials as alternative MoAs for effective AD treatment

KEY UPDATES

Aducanumab became the first disease-modifying therapy targeting β-amyloid to receive FDA accelerated approval[1]; however, it received refusal for marketing authorization by EMA in Dec. 2021[2]

*Promising clinical development are occurring across both the β-amyloid pipeline and beyond, with **numerous key readouts on the horizon** highlighting the diversity of ongoing research*

*Without an effective therapy, the unmet need related to AD will continue to escalate; the **number of patients will nearly double by 2050** with a resulting total disease cost in Europe forecasted at over **€633 billion** by 2050[3]*

Note: (*) Includes withdrawn, terminated, and suspended trials; FDA: Food & Drug Agency; EMA: European Medicines Agency;
Source: (1) FDA; (2) EMA; (3) Alzheimer Europe; IQVIA analysis; Clinicaltrials.gov

Abbreviations – *Link to Glossary*

Alzheimer's is one of Europe's largest public health crises, severely impacting all quality of life facets for patients, families, and caregivers

Alzheimer's Disease

A progressive, insidious, and irreversible neurological disease, Alzheimer's disease (AD) is the leading cause of cognitive impairment and dementia globally, and a severe cause of morbidity and mortality with substantial economic costs and burdens to healthcare provision

18.8 Million
AD patients in EU by 2050 (+90% since 2019)

149 Million
Increase in # of 65+ at risk in EU by 50% by 2050[1]

Highly impacted QoL
Significant impact on ADL and risk of co-morbidities, life expectancy

€232 billion+
Total healthcare and social care costs, not including informal costs

Lack of effective Tx
Significant disease burden with no approved DMT

- Alzheimer's is one of EU's **largest public health crises** and the most common cause of dementia
- It is estimated that today **~7.9 Mn patients suffer from AD across the EU27** and ~9.8 Mn in European countries represented by Alzheimer Europe[1]
- Although Alzheimer Europe research indicates **a reduction in the prevalence of AD**, the rapid growth of the over-65 segment is expected to fuel a **doubling in patients with dementia by 2050**, afflicting ~14.3 Mn in the EU and ~18.8 Mn in the wider European region
  - While Alzheimer's does shorten life expectancy, its **greatest impact is upon quality of life**
  - Dementia leads to **gradual loss of memory/intellect** and a change in mental stability (e.g., aggression, hallucinations, psychosis), diminishing independence
- The **significant total societal economic burden of AD** includes direct costs (medical and non-medical) and indirect costs (largely informal care costs, loss of productivity, and intangible); **total economic burden of AD is anticipated to increase 3-fold by 2050** to ~€633 Bn from ~€250 Bn[2]
- Since 1998, **over 150 AD drugs have failed** in clinical testing[4]; Current treatments are palliative by nature, addressing the worsening of symptoms with minimal efficacy in patients over a limited duration; Hence, there is a clear and **significant unmet need** for Disease-Modifying Therapies (DMT) to prevent, cure or slow the progression of AD
- In 2021, aducanumab became the **first DMT targeting β-amyloid** to receive FDA approval for AD[5], however, It subsequently received refusal for marketing authorization by EMA[6]

Source: (1) Alzheimer Europe; (2) Neurology & Therapy; (3) Alzheimer Europe Yearbook 2019; (4) Bright Focus Foundation, 2020; (5) FDA; (6) EMA

Abbreviations *- Link to Glossary*

Designed to target the underlying pathophysiology of AD, DMTs hope to provide an enduring beneficial effect on the clinical course of the disease

INTRODUCTION TO DISEASE MODIFYING THERAPY (DMTs) FOR AD

Introduction to Disease-Modifying Therapy in Alzheimer's Disease

- Over the past several decades, a share of research efforts has concentrated on the clinical development of agents targeting the characteristic features of AD: the appearance of extracellular β-Amyloid plaques and intracellular neurofibrillary tangles
- Building on increasingly sophisticated neurobiological understanding, DMTs aim to breakdown or inhibit the formation of these 'plaques' in the brain to mitigate cell death and general disease progression, for which only symptomatic treatment is available in Europe

Headways in the Clinical Development of DMTs

- Investigative clinical research has traditionally concentrated on three key categories of DMTs:
  - **β-Amyloid Immunotherapies** (antibodies) which disrupt established plaques and promote plaque clearance in the brain
  - **Active Immunotherapy** (vaccines) to stimulate the production of neutralizing antibodies against the plaque-causing β-Amyloid
  - **Passive, targeted monoclonal antibody therapy** directed towards plaque-causing β-Amyloid
- In 2021, aducanumab became the first DMT targeting β-amyloid to receive FDA approval for AD. However, it received refusal for marketing authorization by EMA in the same year

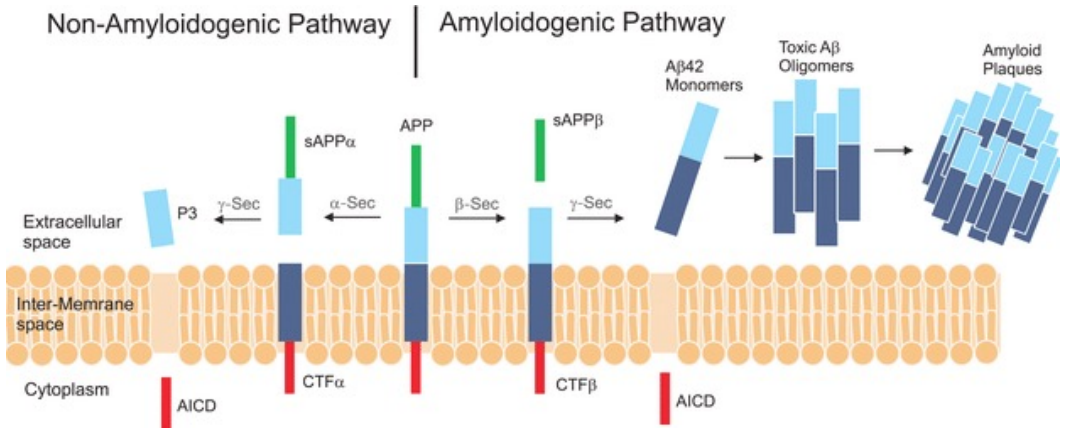


Figure 1. *Illustration of the β-Amyloid pathway.*

Abbreviations *- Link to Glossary*

Beyond β-Amyloid, new research efforts are diversifying and exploring novel hypotheses and MoAs

SELECT APPROACHES TO CURATIVE TREATMENT FOR ALZHEIMER'S DISEASE

β-Amyloid & Anti-Tau Monoclonal Antibodies

β-Amyloid peptide and pathological forms of the **tau protein** are known to "co-operate" in causing AD genotypes, with build up of both β-Amyloid peptides and tau proteins in the brain believed to lead to nerve cell damage and neuronal death. Better understanding of this link will support development of effective therapeutics for AD[1]. β-Amyloid Immunotherapies (antibodies) disrupt established plaques and encourage plaques to move out of the brain. Anti-tau monoclonal antibodies are designed to block or slow down this process[1,2]. Tau protein is not only directly toxic to cells but is also a mediator of β-amyloid toxicity[3].

Stem Cell Therapy

Stem cell therapies, e.g., Mesenchymal Stem Cells, **aim to replace the brain cells damaged by AD with healthy cells**, supporting neuron regeneration and potentially resulting in the improvement of functional memory and overall functional recovery. [4,5]

Combination & Beyond-the-Pill Solutions

As AD is characterised by multiple complex pathways, and a number of possible targets within these pathways, researchers are paying closer attention to potential combination therapies targeting multiple disease pathways[6,7]. In parallel, beyond-the-pill solutions are under development offering combined service and treatment solutions to reduce the medical and care burden of AD.

Vaccine Treatments

Other interesting technologies in development include Axon's **AD vaccine which stimulates immune system to attack a specific part of tau**, responsible for pathological interaction between the proteins[8], or **preventative combination vaccines** which target both amyloid beta plaques and tau protein aggregates linked to Alzheimer's - AV-1959R and AV-1980R[9].

Note: (*) AMBAR - Alzheimer Management by Albumin Replacement
Source: References 0-9 available in speaker notes

The success of any Alzheimer's therapy will depend on the ability to identify and target patients at early disease stages

THE NEED FOR SCALABLE ALZHEIMER'S DISEASE BIOMARKERS

Targeting Appropriate Patient Populations

- Clinical research and development efforts are increasingly shifting towards preclinical and early AD therapy where benefit is hoped and estimated to be most meaningful
- Indeed, key success factors include **identifying appropriate molecular therapeutic targets** and establishing universal and **corroborated biomarkers** in order to detect disease in early preclinical and pre-dementia stages and initiate personalised treatment protocols for the right patient or patient population[1,2]

β-Amyloid Pathway

- Doubts regarding the validity of β-amyloid hypothesis have been raised. It has been suggested that this is **most likely the right pathway and wrong therapeutic target**[3]. New drug candidates selectively targeting soluble AβOs (β-amyloid oligomers) in development may demonstrate greater efficacy and improved AE profiles compared to first-generation Aβ-based drugs[4].

Tau Pathway

- Tau pathway is being investigated as **an alternative to β-amyloid hypothesis**, as tau tangles can be observed in the brains of patients without Aβ pathologies and with very mild dementia. Tau pathology also correlates more closely with disease severity and progression. Nevertheless, this hypothesis remains unconfirmed, as a number of anti-tau therapies have failed in clinical trials[5].

The development of **reliable and accessible biomarkers** to identify the most **effective treatment course for a patient** or patient population remains paramount in **preparing healthcare systems** for DMTs in AD

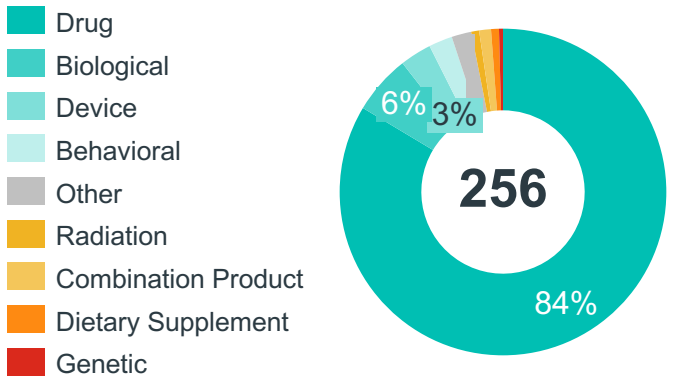
Source: (1) Change in trial entry criteria based on results for mild/moderate vs advanced patients: SciElo; NCBI; Alzheimer's Association (2) BioSpace; (3) Genetic Engineering & Biotechnology News; (4) Frontiers in Neurology; (5) Medical News

Abbreviations *- Link to Glossary*

Previous failures have not discouraged the industry from studying new therapies, with a number of new technologies are on the horizon

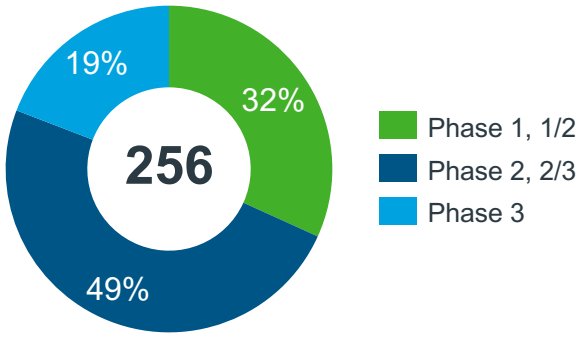
CLINICAL TRIAL PIPELINE

Number of Alzheimer's **Active Clinical Trials**



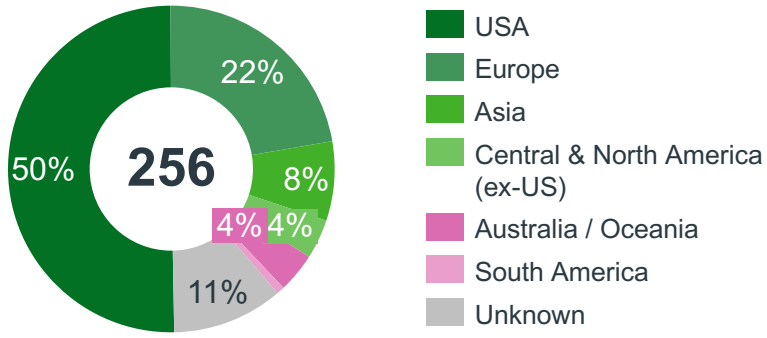
- Due to high unmet need and the raising disease burden, the **clinical research on Alzheimer's Disease is extensive**, despite numerous failures in the previous years
- Potential AD drugs constitute the majority of the pipeline, with behavioural therapies, devices and diagnostic agents also high on the agenda

Number of Clinical Trials By **Development Phase**



- With approximately 80% of active clinical trials in Phase 1 or 2, the majority of investigative therapies for Alzheimer's Disease remain **in early development**
- However, numerous assets in Phase 3 clinical development promise the **introduction of disease-modifying therapies** in the next 3-5 years

Number of Clinical Trials By **Geographic Split**



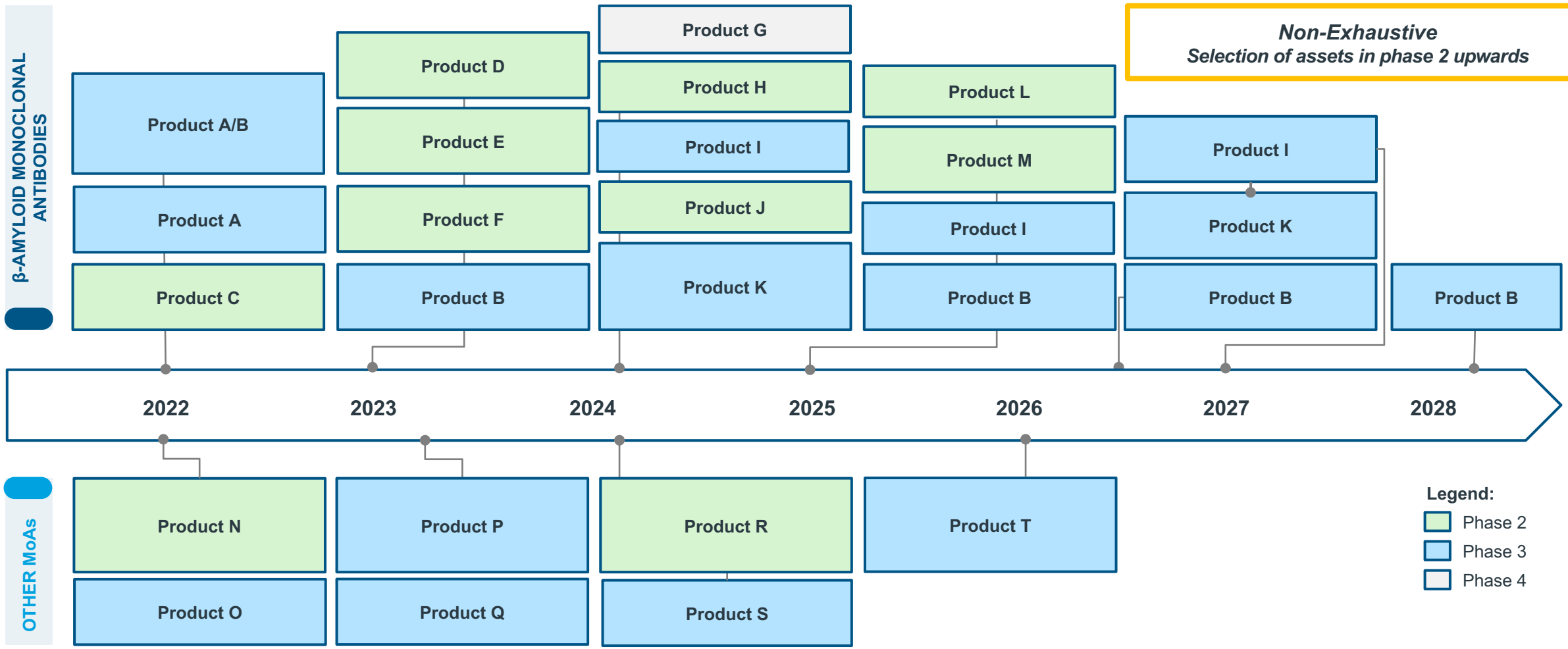
- Disease-modifying drugs offer ambitious prospects towards the "holy grail" of AD research – slowing disease progression and curing the disease altogether
- The predominance of Alzheimer's clinical trials are **concentrated in the US**, followed by Europe and Asia

Source: IQVIA analysis; Clinicaltrials.gov

Abbreviations – *Link to Glossary*

Since 2020, one pipeline product has materialised and received FDA approval, none EMA, with another 10+ progressing to late stage trials

2022 AD THERAPY PIPELINE: ESTIMATED TRIAL COMPLETION DATES

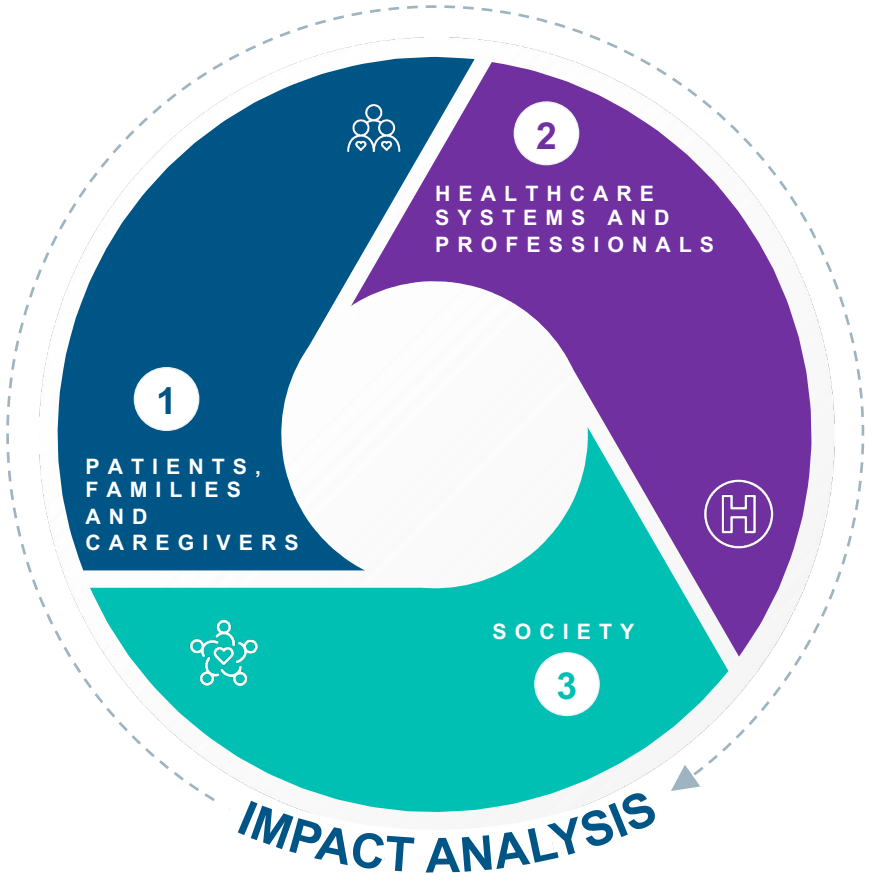


Source: Clinicaltrials.gov; June 2022, active clinical trials (Not yet Recruiting, Recruiting, Enrolling by invitation, Active not recruiting), Excluded trials without specified phase, Device trials

Abbreviations *- Link to Glossary*

DMTs would offer great hope in reducing Alzheimer's high burden on patients, families, caregivers, healthcare systems and society at large

IMPACT ANALYSIS



1 PATIENTS, FAMILIES, AND CAREGIVERS

Disease-modifying therapies for Alzheimer's Disease could preserve and restore cognitive functions whilst preserving precious family time and higher quality of life

2 HEALTHCARE SYSTEMS AND PROFESSIONALS

DMTs will delay the need for high levels of healthcare resource utilization and dependency associated with the severe disease state

3 SOCIETY

Restoring independence will decrease absenteeism, work impairments, activity impairments, and ancillary incremental health care, long-term care, and social care

Delaying disease progression will safeguard activities of daily living and extend precious time with friends and family prior to severe disease onset

1

PATIENTS	CURRENT STATE	FUTURE STATE
ECONOMIC INDEPENDENCE 	• With the age of retirement typically 65 or over across Europe, Alzheimer's Disease significantly **hinders a patients' economic independence** and ability to **naturally continue a professional career**	• Delaying disease progression will allow patients to **continue working** and remain **fully engaged in social and professional lives**, whilst **preserving financial autonomy** and **independence**
EMOTIONAL WELLBEING 	• **Distressing loss of cognitive functions**, memory and sleep • **Behavioral and psychological conditions** (e.g., aggression, hallucinations, psychosis) prevent patients from being a part of their family	• Allows for **cognitive and functional capabilities and personality to be sustained for longer**, in turn conserving high quality of relationships with friends/family • DMTs offer added time to carefully prepare for any later decline in cognitive functionality
PHYSICAL WELLBEING 	• **Immobility** due to muscle rigidity and tremors • **Incontinence** due to memory loss and/or poor bladder control • **Decline in physical health** and **undiagnosed co-morbidities** that are often life-threatening	• **Delayed physical decline** and **increased ability to communicate problems**, consequently enhancing collaboration with multi-disciplinary care, co-morbidity diagnosis and personalized treatment

Delaying disease progression will safeguard activities of daily living and extend precious time with friends and family prior to severe disease onset

1

PATIENTS	CURRENT STATE	FUTURE STATE
SOCIAL CARE	• Moderate-to-severe patients require **care within residential/nursing homes**	• Allows patients to **spend more time at home**, rather than being relocated, *potentially against their will*
CAREGIVER WELLBEING	• Impact of Alzheimer's on **caregivers' quality of life** often unrecognised • Caregivers experience higher rates of depression/fatigue due to pressure and emotional distress of care	• Delay in onset/progression of disease places **less pressure on caregivers** following diagnosis, enables and supports **enhanced caregiver planning and active collaboration** with the patient

Treatment	Total number of hours spent by AD family members on care (per year)	Average care giver health care costs (per patient per year)	Total care giver health care costs (per year)
Current Therapy	~1,825 hours	€3,215	€ 26.9 Bn

Source: IQVIA analysis; Clinicaltrials.gov

DMTs for AD will delay the need for attentive care and reduce the high healthcare system utilisation typically observed in a severe disease state

2

HC SYSTEMS	CURRENT STATE	FUTURE STATE
HOSPITAL UTILISATION	• As severity increases, patients spend more **nights in hospital** and **visit emergency rooms or outpatient clinics more frequently** • Severe patients are estimated to cost healthcare systems ~€7.300 per year, amounting to **~€26,6 billion across the EU**	• **Reduced pressure** on hospital services • Shorter waiting times for healthcare consultations • Increased bed space and ICU coverage
DRUG EXPENDITURE	• As severity increases, patients become increasingly dependent on **symptomatic regimens** (AChEi + memantine) • In addition, severe disease states demand **increasing treatment of co-morbidities**	• Although DMTs will be more costly than the standard of care, there is the potential for **reduced expenditure on symptomatic therapy** and **medication for co-morbidities** (e.g. urinary tract disorders, epilepsy, depression, etc.)
CAREGIVER COSTS	• Caregivers report **higher rates of morbidity** (e.g., depression) and **mortality** placing further pressure on healthcare systems • In 2019, caregivers spent on average **five hours a day providing support** for daily living	• Potential for **reduced dependency of patients** on caregivers leading to better overall health and wellbeing

Source: IQVIA analysis; Clinicaltrials.gov
IQVIA | EFPIA Pipeline Innovation Review 2022

Abbreviations – *Link to Glossary*

Disease-modifying therapies promise to alleviate the social care costs of AD, improving productivity and QoL benefit to society

3

SOCIETY	CURRENT STATE	FUTURE STATE
SOCIETAL COSTS	• **Informal and social care are the greatest direct costs of Alzheimer's**, representing approximately 40% of the global cost • However, two thirds of this cost is borne by patients and their families	• Delays disease progression and payment for social care, **relieving the financial, social, and psychological stress faced by carers** • The total cost of social care in severe cases across the EU is estimated at **~€32bn**[1]; even incremental savings would be substantial
OPPORTUNITY COSTS	• **Decline in economic productivity**/tax revenue due to: - Loss of productivity/tax revenue from caregivers - Caregivers mortality, depression and fatigue - Patients are often forced into early retirement	• Delaying the onset of the disease could see less people of working age care for patients, **improving QoL, decreasing absenteeism, and overall healthcare use** • Delaying the onset of the disease could see **patients working longer and retiring later**

Treatment	Average patient social care costs (per patient per year)	Average patient informal care costs (per year)	Total patient social care costs (per year)	Total patient informal care costs (per year)	Total social and informal care costs (per year)
Current Therapy	€6,800	€20,151	€56.7 Billion	€169.6 Billion	€225.3 Billion

Source: IQVIA analysis; Clinicaltrials.gov

Abbreviations – *Link to Glossary*

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A promising candidate to treat central nervous system disorders, stem cells may offer a renewable source of replacement cells and tissues

EXECUTIVE SUMMARY

01 TECHNOLOGY & PIPELINE ASSESSMENT

- A **nascent field**, clinical development of stem cells remains in the early stages of investigation, aiming to **establish proof-of-efficacy** and offer hope in **replacing cells and tissues** damaged or lost to disease
- In ALS specifically, stem cells are emerging as a leading candidate to **help regulate harmful immune responses** and produce growth factors that help **protect, support and repair neurons**

02 INDICATION ASSESSMENT

- **ALS** is a rare, **late-onset neurodegenerative disease** characterized by the degeneration of both lower and upper motor neurons estimated to affect ~32,000 patients in Europe[1]
- An overwhelming, **high burden disease** associated with **significant quality of life depreciation,** estimating to have a total cost of illness of ~€78,000 per patient per year[2]

03 IMPACT ANALYSIS

- ALS neurodegeneration incurs **high healthcare resource utilization**, manifesting as progressive motor weakness leading to severe disability and early mortality
- **Patients, families and caregivers:** Allows for cognitive and functional capabilities to be sustained for longer, safeguarding autonomy, survival, and quality of relationships
- **Healthcare systems:** Reduced expenditure on symptomatic therapy and mitigate high healthcare resource use
- **Society:** Ease large socioeconomic burden, reducing need for daily care and dependence and enabling vibrant contribution to society

Sources: (1) Neuroepidemiology; (2) Orphanet J. Rare Dis.; IQVIA | EFPIA Pipeline Innovation Review 2022

Abbreviations – Link to Glossary

ALS is a rare, late-onset neurodegenerative disease characterized by the degeneration of both upper and lower motor neurons

Amyotrophic Lateral Sclerosis

A rare neurodegenerative disease characterized by the progressive degeneration and eventual death of nerve cells in the brain, brainstem and spinal cord, requiring extensive multi-disciplinary care and healthcare provision

32,000 Patients[1]

in EU; with an **increasing reported incidence** worldwide

60 years of age

Mean age of onset for sporadic ALS; slight preponderance in males[3]

Highly impacted QoL

Significant somatization and **poorer psychological well-being**[4]

€78,000 COI/Patient[6]

Annual estimated cost, half of which attributable to informal care

High disease burden

Rapidly **debilitating physical decline**, severely impairing all ADLs[5]

- **ALS results in the loss of the ability to initiate and control voluntary movement**, affecting the muscles needed to move the arms and legs, speak and swallow, support the neck and trunk, and breathe
- As a result of **progressive upper and lower motor neuron degeneration** and signaling disruption, muscles gradually weaken and waste away
  - Upper motor neurons in the brain send messages to lower motor neurons in the spinal cord and brainstem, which then relay the message to various muscles
- As symptoms worsen over time, individuals **lose muscle control and coordination** throughout the body, in the chest and diaphragm leading to ventilatory failure
- Indeed, death frequently results from respiratory failure within 2 to 10 years of symptom onset
- **ALS is predominantly sporadic** (~90%), yet 5-10% of cases are familial
  - Of these, 20% involve a mutation of the SOD1 gene, 2-5% involve mutations of the TARDBP gene, and 1-2% involve mutations of the VCP gene
- **With no cure,** management of ALS is **supportive, palliative and multidisciplinary,** frequently involving non-invasive ventilation which prolongs survival and moderately improves QoL
  - EMA approved in 1996, riluzole is the only drug that has been shown to extend survival by several months[7]

Source: IQVIA analysis; (1) Neuroepidemiology; (2) Curr Opin Neurol; (3) Gender Medicine; (4) Neurotherapeutics; (5) Front. Neurol; (6) Orphanet J. Rare Dis.; (7) EMA

Abbreviations - *Link to Glossary*

Stem cells may offer an attractive avenue to treat ALS by virtue of their intrinsic multi-directional differentiation and modulatory capacities

AN INTRODUCTION TO STEM CELLS

The Promise

- **Degenerative Central Nervous System (CNS) disorders** are a group of neurological disorders that affect the **structure and function of the brain and spinal cord.** Many currently lack effective treatment, often resulting in significant morbidity, disability and early fatality
- A foundational building-block of regenerative medicine and tissue engineering, **stem cell transplantation** is being investigated as a potential therapeutic approach for CNS disorders based on their potential **regenerative** and **self-renewal capacity**, **multi-differential ability** to a wide-variety of functional cells, **neurotrophic** properties, and **immune modulation** effects
- By targeting multiple pathogenic mechanisms, **cellular therapy via stem cells** hopes to mitigate or even reverse CNS disease and offer significant clinical and healthcare system respite

Stem Cell Treatments for Amyotrophic Lateral Sclerosis

- Stem cell therapy is one of the most promising new approaches in the treatment of ALS by **addressing the complex pathogenetic etiology** through multiple potential mechanisms
- The premise of stem cell therapy is based on a **"neighbourhood theory",** where transplanted stem cells home to the affected sites to provide a supportive, nurturing, neuroprotective micro-environment via differentiation into non-diseased neuronal and non-neuronal modulatory cells
- The viability of stem cells as a treatment strategy for ALS will require **diligent, well-designed, and appropriately powered clinical trials**, of which early-stage clinical trials are presently evaluating the applicability of stem cell sources, cell doses, and methods of delivery

Key Classifications of Stem Cells

- To appreciate the potential applications of stem cell technology to CNS disorders, it is important to understand the characteristics of the various stem cell types available and the potential impact of cellular therapies on disease mechanisms:

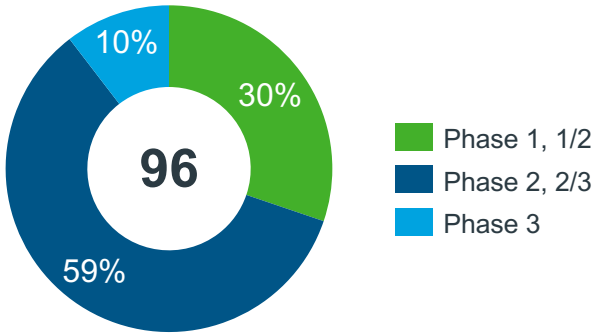
Embryonic Stem Cells (ESCs)	• Pluripotent stem cells with unlimited differentiation capacity and remarkable plasticity, long-term proliferative and self-renewal potential
Mesenchymal Stem Cells (MSCs)	• Ubiquitous, multi-potent stem cells that can differentiate into a variety of skeletal cell types including osteoblasts, myocytes and adipocytes
Neural Progenitor Cells (NPCs)	• Immature neural precursors that give rise to all cell types that populate the CNS, potentially renewing, restoring and promoting brain self-repair
Induced Pluripotent Stem Cells (iPSCs)	• Reprogrammed adult somatic cells to a pluripotent ESC-like state through the forced expression of genes and factors for an unlimited source of cells

Abbreviations – Link to Glossary

A promising candidate to treat central nervous system disorders, stem cells may offer a renewable source of replacement cells and tissues

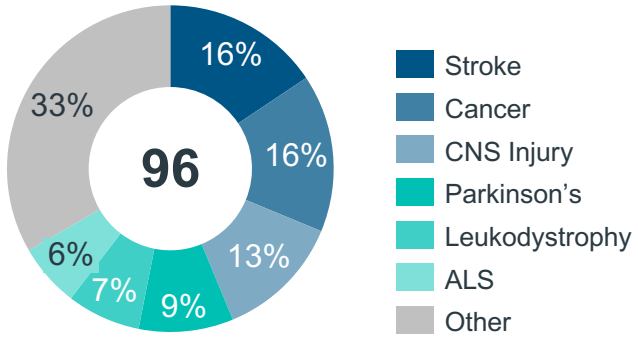
CLINICAL TRIAL PIPELINE

Number of Clinical Trials By **Development Phase**



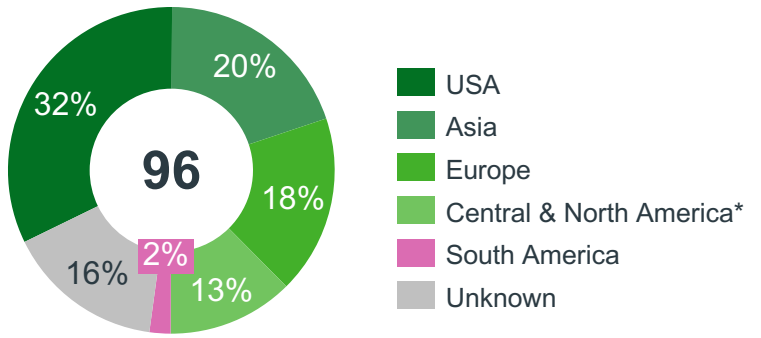
- CNS disorders, including age-related diseases, spinal cord injury, stroke, cerebral palsy, and others, are **typically irreversible** as a result of limited regeneration of the CNS
- The majority of clinical trials remain in **early stages of development**, attempting to establish proof-of-efficacy and bridge the gap to clinical implementation

Number of Clinical Trials By **Indication**



- Characterized by their **renewal capacity, multi-directional differentiation, neurotrophic properties,** and **immune modulation effects**, stem cells offer an attractive avenue to treat CNS disorders, including Parkinson's disease and ALS, where the leading cause of disability is linked to a defined, localised degeneration of neurons

Number of Clinical Trials By **Geographic Split**



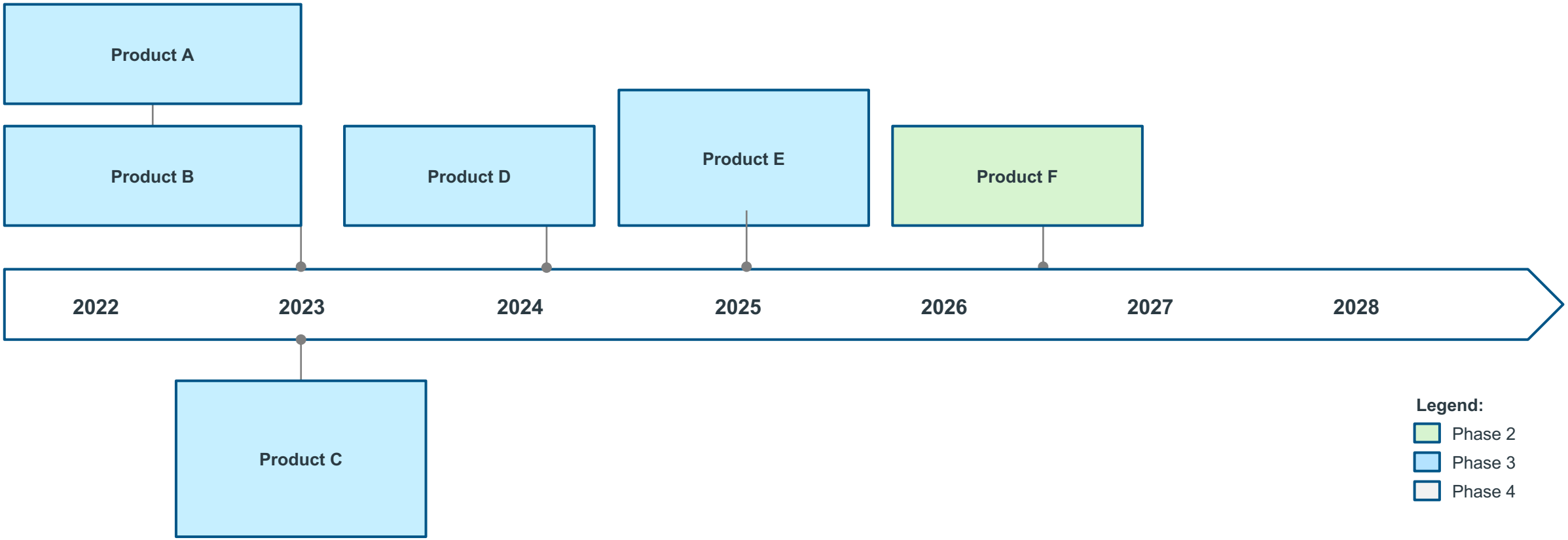
- **Pioneering research** is currently being driven by the US, followed by Europe in second and Asia in third

Note: Excluding the USA
Source: IQVIA analysis; Clinicaltrials.gov

Abbreviations *– Link to Glossary*

Several stem cells are currently in mid- and late- stage clinical development for ALS, hoping to establish safety and efficacy

2022 ALS STEM CELL THERAPY PIPELINE: ESTIMATED TRIAL COMPLETION DATES

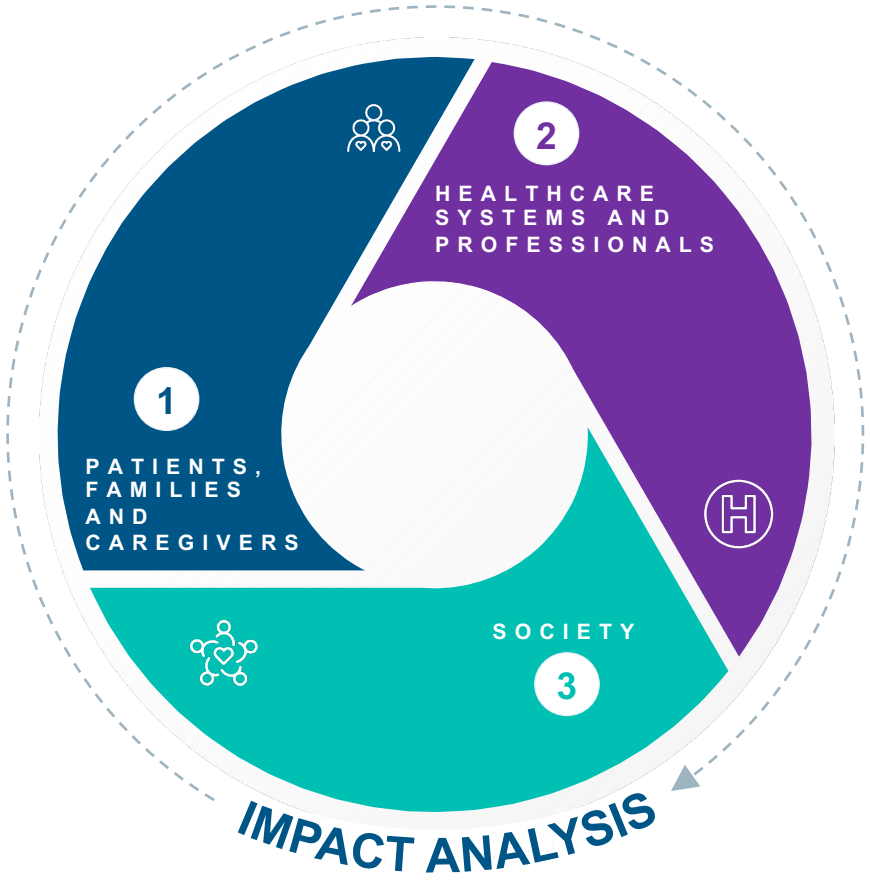


Source: clinicaltrials.gov; June 2022, active clinical trials (Not yet Recruiting, Recruiting, Enrolling by invitation, Active not recruiting), Excluded trials without specified phase, Device trials

Abbreviations *- Link to Glossary*

ALS neurodegeneration manifests as motor weakness leading to severe disability and mortality, incurring high healthcare resource utilization

IMPACT ANALYSIS



1 PATIENTS, FAMILIES, AND CAREGIVERS

Remarkable regeneration of neuronal tissue, stabilization of neuronal networks, neurotrophic support, and neurodegeneration reversal restoring cognitive and functional capabilities

2 HEALTHCARE SYSTEMS AND PROFESSIONALS

Reduced visits and associated elevated costs in every aspect of healthcare, including expenditure on daily, chronic, symptomatic medication with limited efficacy

3 SOCIETY

Significant socioeconomic contribution by mitigating rapid neurodegeneration, disability and early mortality, avoiding loss of workforce and early retirement

The unmet need for ALS is extremely high, it is usually associated with fatal neurodegeneration within 3-5 years of symptom onset

1

PATIENTS	CURRENT STATE	FUTURE STATE
MORTALITY COST	• **High mortality cost** experienced in ALS due to a significantly **reduced life expectancy** of 59 years of age, and low 3-to-5-year year survival following diagnosis	• Stem cells promise to **extend lifespans** of patients with the fatal neurodegenerative disease, reducing the large mortality cost
EMOTIONAL WELLBEING	• Severe **disruption of relationships** with family and friends • **Loss of curiosity, cognitive functions, and memory**, and consistently **poorer health** status in human-reported quality of life indicators • **Lack of economic independence** affecting mood and personal happiness	• The goal is for profound and enduring **restoration of cognitive capabilities** resulting in increased independence of ALS patients, thus positively impacting their **emotional wellbeing** • Enables quality of the relationships with friends/family to be maintained for longer
PHYSICAL WELLBEING	• Rapid neurodegeneration leading to **physical disability and dependence** on caregivers	• **Course correction** necessary to positively affect treatment outcomes for health/comorbid conditions

Abbreviations *– Link to Glossary*

Confronted with short-term changes and long-term adjustments, ALS affects the physical and emotional well-being of caregivers

1

PATIENTS	CURRENT STATE	FUTURE STATE
SOCIAL CARE	• Need for formal, **dedicated professional care** incumbent on multi-disciplinary care team to provide appropriate support and counseling as the patient transitions through stages of disease	• **Diminished burden on social care** following regeneration of neuronal cells • Enables **increased patient autonomy**
CAREGIVER WELLBEING	• Patient physical, cognitive and behavioral impairments can contribute substantially to the **psychological and physical morbidity of the caregiver** due to limitations and restrictions • Indeed, caregivers experience significantly and consistently higher rates of **depression/fatigue** due to pressure, exhaustion, **psychological and emotional distress**	• **Comfort, repose, and time to caregivers**, improving all aspects of quality of life, such as physical and emotional distress due to anxiety, pressure, stress, depression, and fatigue

Lack of truly disease modifying treatments in ALS results is a high healthcare resource use, indirect burden and excessive mortality costs

2

HC SYSTEMS	CURRENT STATE	FUTURE STATE
HOSPITAL UTILISATION 	• The vast majority of **direct costs** are attributed to hospitalizations, medical professional visits and procedures, with ALS patients typically visiting their neurologists on a monthly basis, with other specialties quarterly • All patients receive some form of **rehabilitation**: occupational, physical or speech therapy	• **Reduction in healthcare system visits** following sustained regeneration of the CNS • **Increased treatment adherence** and reduced costs in managing serious adverse effects
DRUG EXPENDITURE 	• Solely **palliative and low efficacy treatments** which only marginally increase life expectancy are available; This is correlated with **higher indirect costs and increased mortality costs** • Drug expenditure is estimate to cost €2,190 per patient per year	• Potential for **reduced expenditure on symptomatic therapy** and **medication for co-morbidities** given long-lasting outcomes of regenerative therapy
CAREGIVER COSTS 	• High and frequent need for **nursing home care** • **Non-medical equipment and home modifications** are essential to facilitate and accommodate patient needs	• Potential for **reduced dependency** of patients on caregivers for activities of daily living, leading to **independence and significant financial relief**

Abbreviations – *Link to Glossary*

By protecting, supporting, and repairing neurons, stem cells will have a profound direct and indirect impact on society

3

SOCIETY	CURRENT STATE	FUTURE STATE
SOCIETAL COSTS	• ALS forces **early retirement** on all patients upon diagnosis, causing significant **patient productivity loss** of ~€10,000 per patient per year, which, alongside caregiver burden, accounts for ~20% of total indirect costs	• The re-establishing of functional capabilities will have a profound effect on the **long-term economic contribution** to society
OPPORTUNITY COSTS	• **Decline in economic productivity**/tax revenue due to: - Friends and family often provide care at the expense of work; leading to a loss of productivity/tax revenue - Caregivers depression, distress and fatigue	• Enabling vibrant return to normal lives will have a profound impact on productivity of economies • **Improving caregiver quality of life** could see lower absenteeism and better overall health of carers, reducing healthcare resource utilization

Treatment	Average direct medical costs (per patient per year)	Average direct social and informal costs (per patient per year)	Average indirect costs (per patient per year)	Total cost of illness (per patient per year / total)
Current Therapy	€28,087	€38,412	€11,757	€78,526 / ~€2.5 Bn

Abbreviations – Link to Glossary

Table of Contents

Recent revival in Psychoplastogen research presents a potential paradigm shift in our approach to treating some psychiatric disorders

EXECUTIVE SUMMARY

01 TECHNOLOGY & PIPELINE ASSESSMENT

- **COVID-19 has exacerbated the high unmet need** and devastating disease burden of psychiatric disorders, affecting the therapeutic area and psychoplastogen clinical trial pipeline
- With hopes of offering a potential **change** in our approach to treating psychiatric disorders, the first Phase 3 clinical trials of psychoplastogens are expected to launch in 2022

02 INDICATION ASSESSMENT

- Psychoplastogens are emerging as **feasible, efficacious, and toxicologically safe** treatments for Major Depressive Disorder (MDD) and Treatment Resistant Depression (TRD)
- In particular, psilocybin and DMT hope to **circumvent historical challenges** of tolerance development and abuse in psychiatry, manifesting **profound experiences** with **minimal addiction** liabilities and long-term perceptual, cognitive, or neurological dysfunctions

03 IMPACT ANALYSIS

- Psychoplastogens offer a novel approach to MDD care, which may replace the chronic use of anti-depressants and healthcare system resources
- **Patients, families and caregivers:** By liberating the mind of depression, psychoplastogens may have profound and enduring impact on patients' quality of life, as well as families and caregivers
- **Healthcare systems:** Curb chronic use of anti-depressants, reduce need for informal care, and mitigate chronic healthcare system resource use through enduring benefit of therapy sessions
- **Society:** Psychoplastogens may nurture enduring equity-oriented care, deepen cultural connections, and decrease socioeconomic costs

MDD is a common psychiatric disorder associated with considerable suffering for individuals and their families, affecting ~6% of the population

Major Depressive Disorder (MDD)

A debilitating disease that is characterized by diminished interest, impaired cognitive function, persistent and pervasive low mood, despondency and vegetative symptoms, such as disturbed sleep or appetite, with an overwhelming impact on everyday quality of life

31.2 Million[1,2]
Patients in EU per year, equating to 6% of the population

25 years of age
Mean age of onset, occurring x2 as often in women after puberty[3]

Highly impacted QoL
20-fold more likely to commit suicide than the general population

€4,200 COI/Patient[6]
Annual estimated HCS cost per patient; €6,100 for TRD patients

High disease burden
Second leading **contributor to chronic disease burden** by YLD

- **MDD is a debilitating disease** characterized by at least **one discrete depressive episode** lasting 2 weeks or more and involving clear-cut changes in mood, interests, ability for pleasure, cognition, and onset or worsening of psychomotor impairment or slowness in movement
- **MDD is a multifactorial disorder**, with an estimated heritability of approximately 40%[1]
  - Moreover, external and environmental factors, such as sexual, physical or emotional abuse during childhood, are strongly associated with an increased risk of developing MDD
- A common complication of chronic illness, patients with MDD are themselves at an **increased risk of developing chronic diseases**, such as diabetes mellitus, heart disease, and stroke, further increasing the risk of functional impairment, morbidity, and mortality[2,3]
- The **COVID-19 pandemic triggered a 25% increase in prevalence**, with young people and women affected the most[6]
  - It is estimated that lifetime risk of suicide among people with MDD ranges between 2 and 15%, with up to 60% of people who commit suicide reporting MDD[7,8]
- Currently, **treatment options for management of depression** can be broadly be divided into antidepressants, electroconvulsive therapy and psychosocial interventions, yet are often correlated with poor treatment cooperation and compliance
  - Indeed, **Treatment Resistant Depression** (TRD), the failure to respond to ≥2 treatments, manifests in ~20% of patients with MDD[9,10]

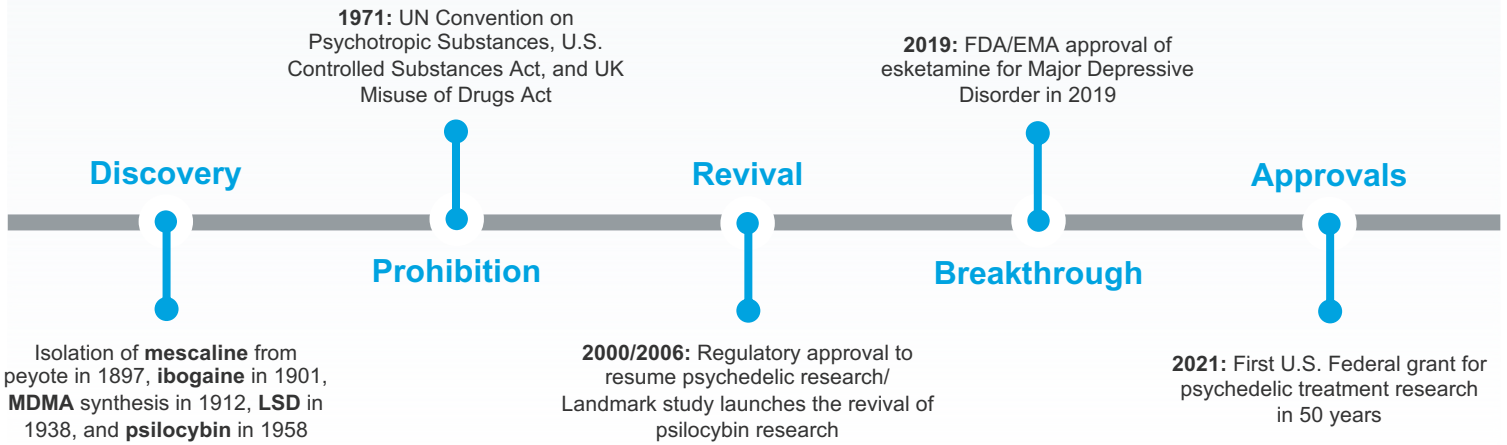
Note: QoL: Quality of Life; SoC: Standard of Care
Source: (1) Nature; Nat Rev Dis Primers, (2) Arch Gen Psychiatry, (3) BMC Medicine (6) WHO (9) J Affect Disord (10) J Affect Disord - abbreviations - link to glossary
IQVIA | EFPIA Pipeline Innovation Review 2022
Abbreviations - Link to Glossary

Psychoplastogens are an emerging paradigm that may have the potential to revolutionise treatment of psychiatric disorders

AN INTRODUCTION TO PSYCHOPLASTOGENS

The Renaissance

- Psychoplastogens are a class of **plasticity-promoting therapeutics** capable of rapidly and robustly promoting neural plasticity to promote **beneficial, enduring behaviours**[1]
- A recently defined class, psychoplastogens include **classical psychedelics** (e.g., LSD, psilocybin, DMT), **dissociatives** (e.g., ketamine), and **empathogens** (e.g., MDMA)
- Unlike traditional anti-depressants that target "chemical imbalances", psychoplastogens may offer **timely, sustained, broad therapeutic effects** following a single administration, placing emphases on long-lasting selective modulation of neural circuits
- Indeed, psychoplastogens represents a potential **paradigm shift** in our approach to treating the ongoing mental health crises, including mood and substance-abuse disorders



Psychedelic-Assisted Therapy

- A **neuroplasticity-based approach to systems, not disease**, psychedelic-assisted therapy is a modality aimed at facilitating a **positive and meaningful altered conscious experience** by cultivating introspection via psychoplastogens
- Sandwiched between "preparatory" and "integrative" drug-free sessions to provide a holding structure and consolidate insights, respectively, patients are continuously **monitored and supported during the experience**, and are typically accompanied by rich, evocative music

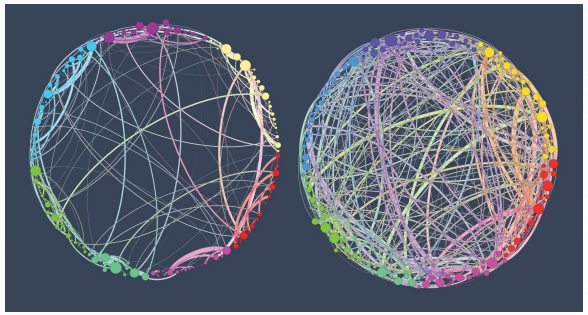


Figure 1. *Hyperconnectivity of the brain's neural pathways before and after psilocybin use**

Source: (1) Journal of Experimental Neuroscience; (2) PNAS
IQVIA | EFPIA Pipeline Innovation Review 2022

Abbreviations – *Link to Glossary*

Compounds like psilocybin, DMT and MDMA are increasingly being explored in clinical research, rapidly progressing through early trials

PSYCHOPLASTOGENS OVERVIEW

1 CLASSIC HALLUCINOGENICS

Psilocybin

- A naturally occurring tryptamine known for its psychedelic properties, **psilocybin** is a prodrug compound produced by more than 200 species of fungi, or 'magic mushrooms'
- Historically used as an agent for religious and spiritual ceremonies, a **new age of research** is heralding psilocybin's potential across several psychiatric conditions, notably depression and anxiety resistant to conventional therapy

LSD

- First synthesized by Albert Hoffmann in 1938, **Lysergic Acid Diethylamide (LSD)**, or "acid", is a potent hallucinogenic drug derived from ergot that imparts an **altered state of consciousness**
- Recent resurgence in its evaluation in small doses to **treat behavioral and personality changes**, with increasingly interesting potential use cases in substance-abuse disorders

DMT

- Also known as the "spirit molecule", **N,N-Dimethyltryptamine (DMT)** is a natural substance produced by multiple plants, animals, and humans, used in traditional hallucinogenic ayahuasca rituals
- Clinical research has demonstrated **potent neurogenic and synaptic plasticity-inducing effects**, holding therapeutic potential for a range of psychiatric disorders

2 DISSOCIATIVES

Ketamine

- Widely employed as an anesthetic agent, **ketamine** is a synthetic, non-selective NMDA receptor antagonist that has emerged as an exciting therapeutic for several psychiatric disorders
- Ketamine is purported to **modify and mediate key neural pathways** disrupted in depression, including glutaminergic, dopaminergic, and serotonergic neurotransmissions

3 EMPATHOGENS

MDMA

- A synthetic drug known colloquially as "ecstasy", **MDMA** is a triple monoamine reuptake inhibitor that produces distortions in time and perception and an enhanced sensory experience
- Some promising evidence supports MDMA as a **safe, effective, and durable therapeutic alongside psycho- therapy** in the treatment of PTSD, as well as depression, bipolar, and anxiety

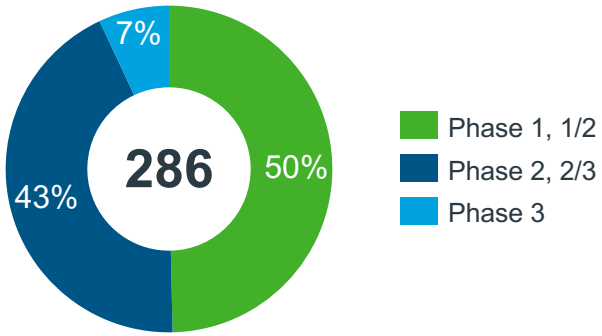
Source: (1) Journal of Experimental Neuroscience; (2) PNAS

Abbreviations – Link to Glossary

Recent revival in psychoplastogen research presents a potential paradigm shift in our approach to treating psychiatric disorders

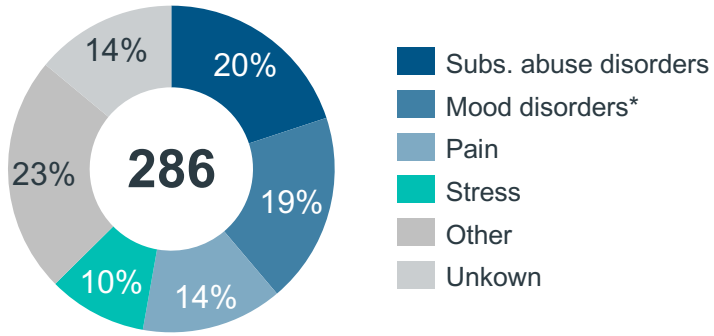
CLINICAL TRIAL PIPELINE

Number of Clinical Trials By **Development Phase**



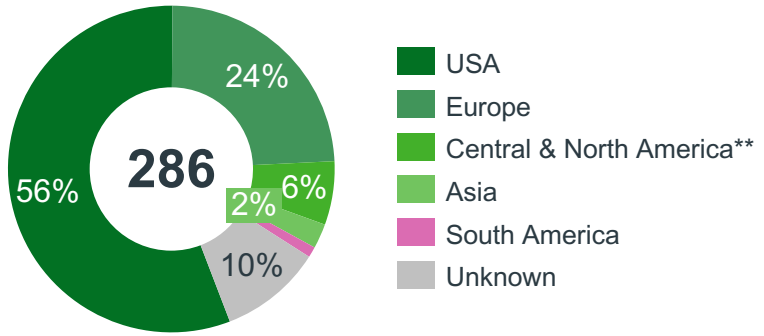
- The **high unmet need** and devastating **disease burden** of psychiatric disorders has rapidly revived the psychoplastogens clinical trial pipeline
- The majority of clinical trials remain in the **early stages of development**, however multiple pivotal readouts are anticipated in the next 5 years

Number of Clinical Trials By **Indication**



- With **promise of broad therapeutic potential**, today over 280 clinical trials are being investigated across a wide range of indications
- Substance abuse disorders, mood disorders including depression and anxiety, pain, and stress disorders concentrate the majority of psychoplastogen research

Number of Clinical Trials By **Geographic Split**



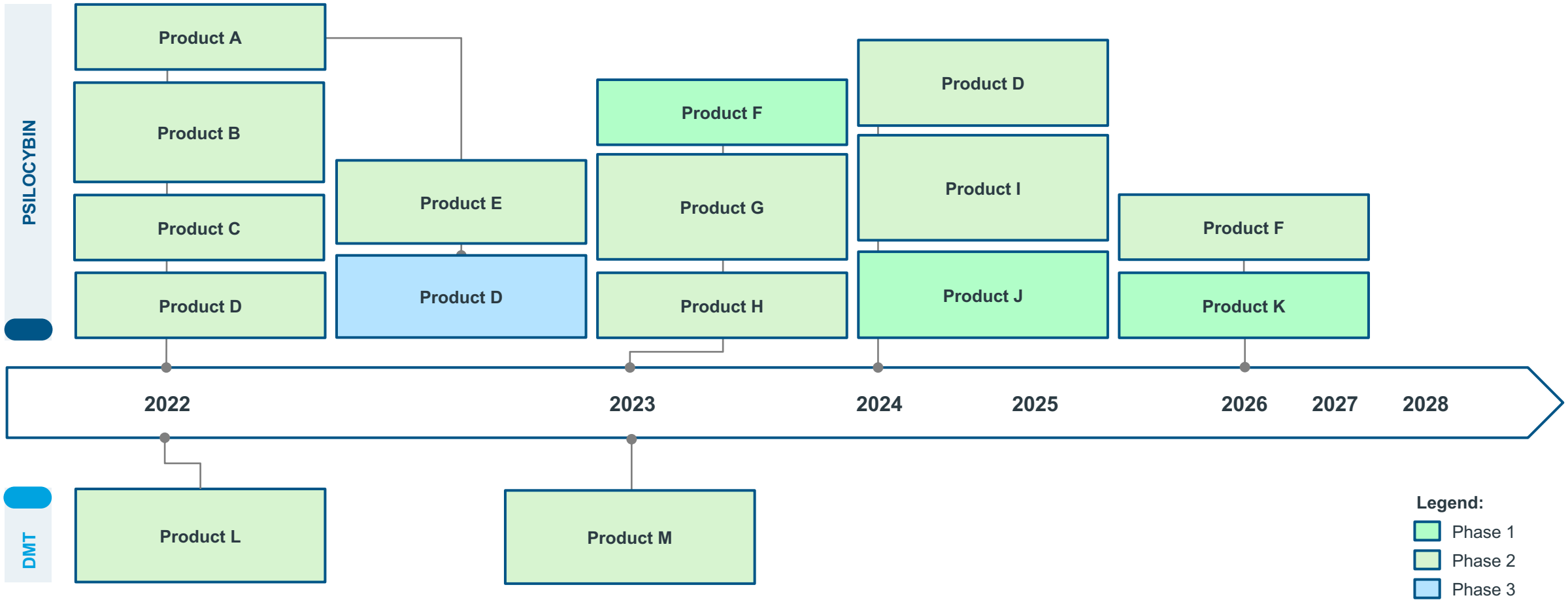
- The psychoplastogens revival and revolution has been primarily driven by North American efforts, particularly in the US
- However, significant **knowledge transfer** and trial expansion is occurring as Europe and the rest of the world tackles the ongoing mental health crises; In Europe, Switzerland, the U.K., and the Netherlands lead the charge

Note: Subs. (Substance), * including Depression and Anxiety, ** Excluding the USA
Source: IQVIA analysis; Clinicaltrials.gov

Abbreviations – *Link to Glossary*

A timely and reinvigorated pipeline heralds hope in the search for an alternative treatment for depression

2022 PSYCHOPLASTOGEN THERAPY PIPELINE: ESTIMATED TRIAL COMPLETION DATES

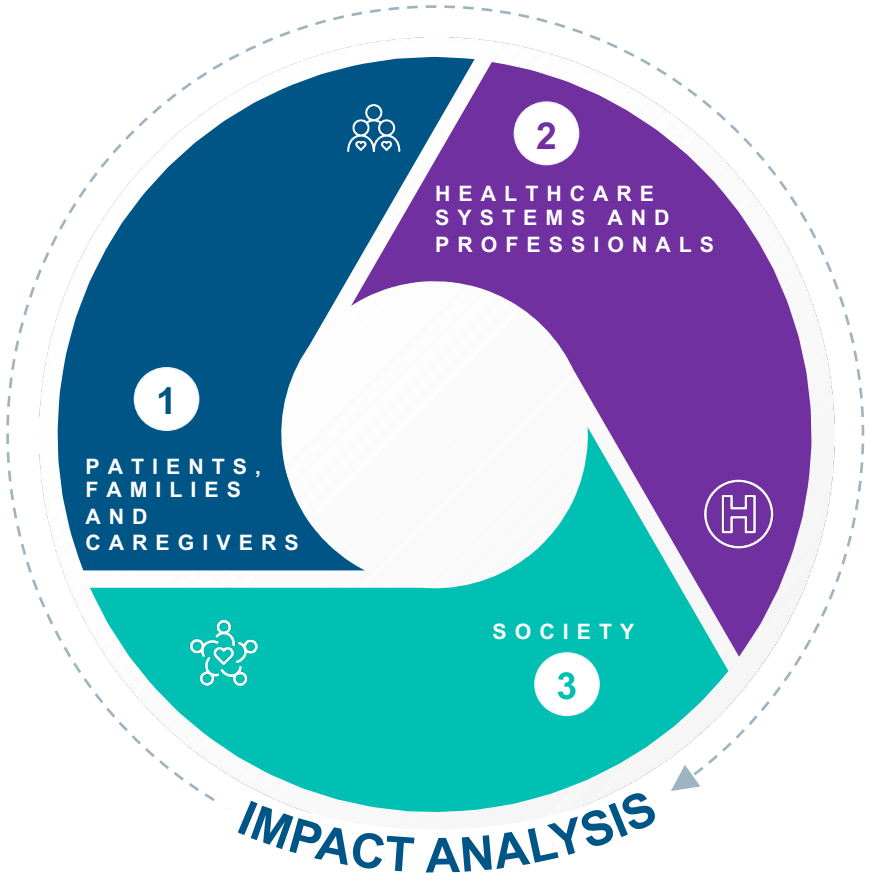


Source: clinicaltrials.gov; June 2022, active clinical trials (Not yet Recruiting, Recruiting, Enrolling by invitation, Active not recruiting), Excluded trials without specified phase, Device trials

Abbreviations *- Link to Glossary*

Feasible, efficacious, and safe, Psychoplastogens may offer promise of lasting changes to overcome the significant burden of depression

IMPACT ANALYSIS



1

PATIENTS, FAMILIES, AND CAREGIVERS

Profound and enduring system changes in cognitive and functional capabilities liberate patients from patterns of relapse and remission enhancing psycho-social wellbeing

2

HEALTHCARE SYSTEMS AND PROFESSIONALS

Reduced visits and associated elevated costs in every aspect of healthcare, including expenditure on daily, chronic medication with limited efficacy and serious adverse effects

3

SOCIETY

Despite large upfront costs to implement psychedelic-assisted therapy, psychoplastogens nurture equity-oriented, personalized care, deepened cultural connections and decreasing socioeconomic costs over the long-term

An overwhelming remitting and recurring disorder without effective treatment, TRD has a profound impact on a patient's quality of life…

1

PATIENTS	CURRENT STATE	FUTURE STATE
ECONOMIC INDEPENDENCE 	• **Overwhelming disorder** limiting ability to engage in social and professional activities due to feeling fatigued, detached, distracted or abstracted • Estimated **one in 5 people affected** by depression never fully recover	• **Systems change** liberating patients from depressive and repressive episodes • **Enable individuals** to participate and engage in daily lives, reestablishing control and sense of meaning in the present to achieve independence
EMOTIONAL WELLBEING 	• **Severe disruption of relationship** with family and friends • Loss of curiosity, intellect, and memory • Chronic and recurrent feelings of distress and discomfort **diminishing quality of life** marked as poorer health status in reported EQ-5D-5L, EQ-VAS, and all subdomains of SF-12	• Profound and enduring **restoration of cognitive and functional capabilities and personality**, cultivating introspection and awareness of thoughts feelings, and memories • Enables quality of the relationships with friends/family to be maintained for longer • Disrupts patterns of remission and relapse
PHYSICAL WELLBEING 	• **Exacerbates health conditions** and affects sleep, focus, and general physical care, with **physical impairments** of a similar magnitude as those found in chronic diseases such as diabetes and cancer	• **Course correction** necessary to positively affect treatment outcomes for health / comorbid conditions

Abbreviations *– Link to Glossary*

… and requires prudent, enduring management often leading to significant caregiver burden, exhaustion, and emotional distress

1

PATIENTS	CURRENT STATE	FUTURE STATE
SOCIAL CARE	• **Stigmatization** and self-stigmatization preventing proper care and conversations • Indirect care typically falls on **pressure of immediate relatives and friends** who may lack the appropriate education and understanding of the condition to best support loved one's with depression	• Psychoplastogen-assisted Psychotherapy may offer a **safe, trusted, monitored, and supported environment** for introspection and care, that additionally encourages the therapeutic conversation and relationship • Patients will indirectly benefit from PAP as a buffer against stressful circumstances
CAREGIVER WELLBEING	• Impact of caregivers' quality of life often unrecognised and under-reported • Caregivers experience **higher rates of depression/fatigue** due to pressure, exhaustion, psychological and emotional distress including fear, powerlessness, guilt, and anxiety for their loved one's depression	• By circumventing patterns of recurrence and remission, psychoplastogens may **lessen the direct and indirect burden** placed on caregivers, eliminating the added pressure and belief of having to "fix" the problem

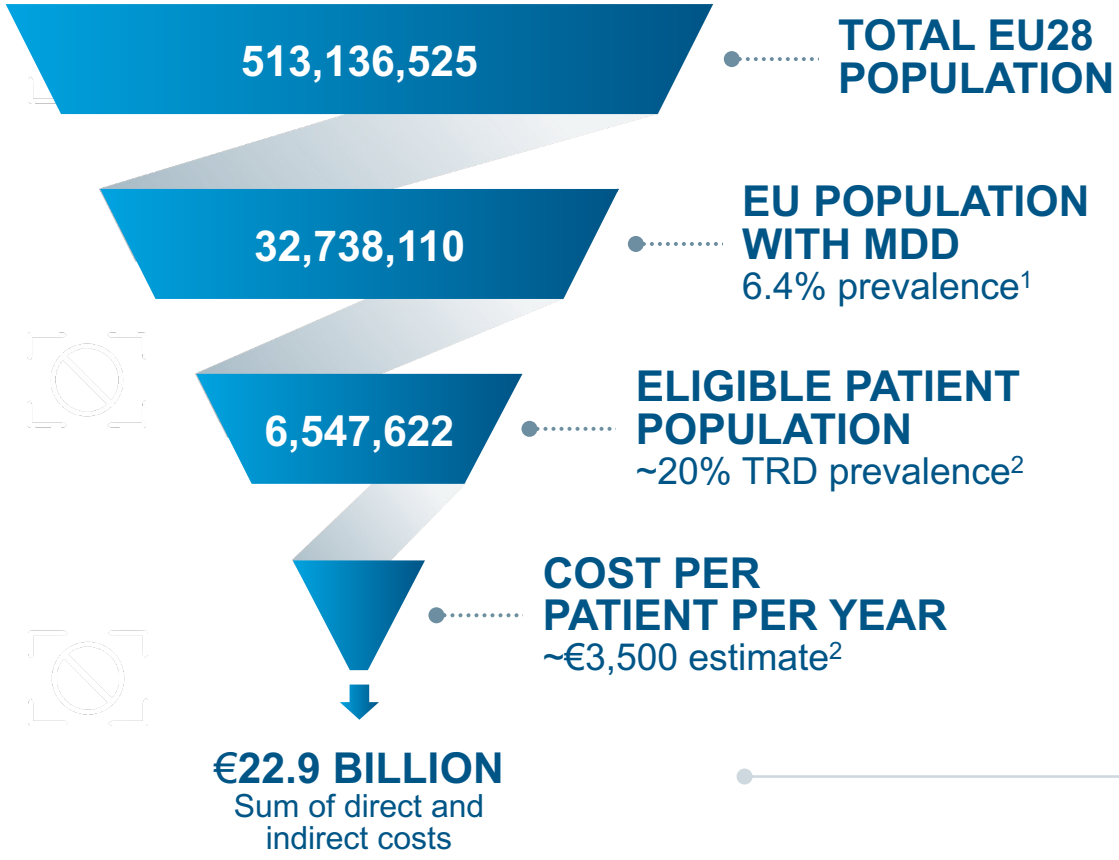
Psychoplastogens may offer a novel approach to care, replacing chronic use of anti-depressants and elevated healthcare system resources

2

HC SYSTEMS	CURRENT STATE	FUTURE STATE
HOSPITAL UTILISATION	• Amplified perceptions of the need for medical care and **significant increase in utilization** of health services and likelihood of ER admission • Research indicates that depression is associated with **higher costs in every aspect of healthcare**, not simply due to need for specialist mental health services or additional costs of antidepressants	• **Reduction in healthcare system visits** with need for only one or two sessions due to rapid and enduring effects of psychoplastogens therapy • **Increased treatment adherence** and reduced costs in managing serious adverse effects • Clear path to specialised resources and care
DRUG EXPENDITURE	• Daily use of antidepressants and higher mean number of medications vs. non-depressed patients, including need for additional symptomatic regiments and treatment of co-morbidities	• Potential for **reduced expenditure on symptomatic therapy** and medication for co-morbidities given long-lasting outcomes of psychoplastogens therapy
CAREGIVER COSTS	• Caregivers report **higher rates of morbidity and mortality** placing further pressure on healthcare systems	• Potential for **reduced dependency** of patients on caregivers for activities of daily living, leading to better overall health and wellbeing

Indeed, patients with MDD report significantly and consistently higher healthcare resource utilisation than the general population

2 HEALTHCARE SYSTEMS



HCP visits

GP visits

Hospital visits

ER visits

- With an average of **13 visits per year vs. 4 for general population**, TRD patients frequently interact with general practitioners, psychiatrists, psychologists, mental health counselors, social workers, and psychiatric-mental health nurses
- Exacerbated by the COVID-19 pandemic, GP **mental health consultations continue to rise**, with a significantly higher number registered for TRD patients (4 vs. 1.5)
- Profound **disparities in hospital visits** including ICU admission between all MDD patients and the general population 2.7 vs 0.15
- Depression has consistency been found as a significant **predictor of prospective emergency hospital admissions**, with the odds of visiting an ER ~3-fold higher

Source: IQVIA analysis; (1) Journal of Affective Disorders; (2) Journal of Affective Disorders

Abbreviations – *Link to Glossary*

Psychoplastogens nurture enduring equity-oriented care, deepen cultural connections, and decrease socioeconomic costs

3

SOCIETY	CURRENT STATE	FUTURE STATE
SOCIETAL COSTS	• The **mental health pandemic** knows no borders, permeates demographics, socioeconomics, and cultures, afflicting the **economic vitality of societies** • Long-term **recurring nature of depression** magnifies the economic burden • Patients report significantly and consistently higher rates of **absenteeism** (4.4-fold increase), **presenteeism** (2.5-fold increase), **work impairment** (2.7-fold increase), and **activity impairment** (2.5-fold increase)[1] • Patients with depression are twice as likely to be unemployed as the general population[2]	• The re-establishing of functional capabilities will have a profound and beneficial effect on the **long-term economic contribution** to society • Any risk of tolerance development and abuse potential must be monitored at an individual and societal level
OPPORTUNITY COSTS	• Decline in **economic productivity**/tax revenue due to: - Friends and family often provide care at the expense of work; leading to a loss of productivity/tax revenue - Caregivers depression, distress and fatigue	• Curbing the mental health pandemic will have significant impact on **productivity** of afflicted patients and those closes to them • **Improving caregiver quality of life** could see lower absenteeism and better overall health of carers, reducing healthcare resource utilization

Source: IQVIA analysis; (1) BMC Psychiatry; (2) OECD

Table of Contents

Gene therapy treats or prevents disease by correcting the underlying genetic problems instead of through drugs or surgery

Gene therapy-based approaches can be broken down into:

Gene transfer

- Introduction of an additional gene into specific cells which may stay as an extra piece of DNA in the cell or be inserted into the cell's own chromosomes to become part of the cell's own DNA, to compensate for abnormal genes or to make a beneficial protein
- For e.g., Luxturna for inherited retinal dystrophy which provides a working copy of the RPE65 gene to retinal cells

Gene editing

- Technologies such as CRISPR / cas9, that can target and cut a specific piece of DNA. If delivered with some healthy donor DNA, this healthy donor DNA will be copied into the patient's own chromosomes. This can be thought of as a find and replace system for a faulty gene
- For e.g., CRISPR-based gene editing for sickle cell disease and beta-thalassemia (CTX001)

Nucleic acid therapeutics

- Non-coding small pieces of RNA and DNA such as small interfering RNAs (siRNA) or antisense oligonucleotides (ASO) can treat disease by altering how the genetic code is read to produce protein
- Coding mRNA are also nucleic acid therapies, but they function differently than non-coding RNA and are covered under mRNA vaccines
- For e.g., Spinraza (ASO) for spinal muscular atrophy

Gene Delivery: Process of delivering genetic material into the cell can be common across all three categories and is often achieved by using 2 classes of vectors: viral and non-viral. For e.g., Adeno-associated viruses and Lipid nanoparticles are gene delivery vehicles

Note: Cell-based gene therapies i.e., CAR T are covered separately; Abbreviations: ASO: Anti-sense oligonucleotide; mRNA: messenger RNA; RNAi: RNA interference
Source: (1) MedlinePlus; (2) FDA website

Gene therapy is being applied to various rare diseases to restore the missing functions of damaged genes…

Therapeutic area	Indication	Modalities: Viral vectors	Gene editing	RNA therapeutics: ASO	RNA therapeutics: mRNA	RNA therapeutics: RNAi	Other (1)
Haematological (blood)	Haemophilia (A+ B)	zynteglo					
	Beta thalassemia						
	Sickle cell disease						
Ophthalmic (eye)	RPE65-mutation assoc. retinal dystrophy	LUXTURNA					
	Choroideremia						
	Achromatopsia						
	Leber congenital amaurosis						
	Retinitis pigmentosa						

Disease prevalence in EU:

- <500
- 1k-50k
- 50k – 500k
- 1,000,000+
- Marketed products

Description

Hemophilia (A+ B):	Group of inherited bleeding disorders that cause abnormal or exaggerated bleeding and poor blood clotting
Beta thalassemia	A blood disorder that reduces the production of hemoglobin, the iron-containing protein in the red blood cell
Sickle cell disease	Inherited blood disorder in which patients have crescent/sickle-shaped RBCs which do not bend and move easily
Retinal dystrophy	Causes progressive and severe loss of vision by altering the anatomy and/or function of the retina, ultimately progressing to complete blindness
Choroideremia	A condition characterized by progressive vision loss that mainly affects males
Achromatopsia	A condition characterized by a partial or total absence of color vision
Leber congenital amaurosis	Most severe retinal dystrophy causing blindness or severe visual impairment before the age of 1 year
Retinitis pigmentosa	Makes cells in the retina break down slowly over time, causing vision loss

Abbreviations: ASO: Anti-sense oligonucleotide; mRNA: messenger RNA; RNAi: RNA interference; (1) Others includes plasmids etc.
Source: Chardan report on Gene therapy overview and secondary research.

…with clinical studies ongoing across several therapy areas and seven gene-therapy related treatments already available in EU

Therapeutic area	Indication	Modalities: Viral vectors	Gene editing	RNA therapeutics: ASO	RNA therapeutics: mRNA	RNA therapeutics: RNAi	Other (1)
Musculo-skeletal	X-linked myotubular myopathy						
	Duchenne muscular dystrophy						
Neurological	Spinal muscular atrophy	zolgensma		SPINRAZA			
	Huntington's disease						
	Giant axonal neuropathy						
Dermatological	Dystrophic epidermolysis bullosa						
Hepatological (liver)	Acute porphyria						
	Hereditary Angioedema						

Disease prevalence in EU:

- <500
- 1k-50k
- 50k – 500k
- 1,000,000+
- Marketed products

Description

X-linked myotubular myopathy	Neuromuscular disorder characterized by muscle weakness, diminished muscle tone and potentially severe breathing complications
Duchenne muscular dystrophy	Involves progressive muscle degeneration & weakness due to the alterations of a protein called dystrophin that helps keep muscle cells intact
Spinal muscular atrophy	Characterized by weakness and wasting (atrophy) in muscles used for movement (skeletal muscles)
Huntington's disease	Causes the progressive breakdown (degeneration) of nerve cells in the brain
Giant axonal neuropathy	Characterized by low muscle tone, muscle weakness, decreased reflexes, impaired muscle coordination, seizures & intellectual disability
Dystrophic epidermolysis bullosa	Causes the skin to be very fragile and to blister easily
Acute porphyria	Causes acute attacks of severe abdominal pain, a rapid heartbeat etc. due to deficiency of a metabolic enzyme along with other factors
Hereditary Angioedema	Characterized by recurrent episodes of severe swelling of limbs, face intestinal tract and airway, caused by low level of a protein

Abbreviations: ASO: Anti-sense oligonucleotide; mRNA: messenger RNA; RNAi: RNA interference; (1) Others includes plasmids etc.
Source: Chardan report on Gene therapy overview and secondary research.

Recent scientific advancements have facilitated the rapid rise of RNA therapeutics that have the potential to treat high prevalence indications

Therapeutic area	Indication	Modalities: Viral vectors	Gene editing	RNA therapeutics: ASO	RNA therapeutics: mRNA	RNA therapeutics: RNAi	Other(1)
Oncology	Ovarian cancer						
	Glioblastoma						
	CD19+ malignancies (NHL & B-ALL)						
	Multiple Myeloma						
	Clear cell renal cell carcinoma						
	Melanoma	IMLYGIC					
Metabolic	Familial hyper-cholesterolemia					LEQVIO	
	Hereditary ATTR amyloidosis					onpattro	
	Glycogen storage disease Type IIb (Danon)						
	Hypertension						
	Meta-chromatic leuko-dystrophy	libmeldy					
	Adenosine deaminase deficiency	Strimvelis					

Disease prevalence in EU:

- <500
- 1k-50k
- 50k – 500k
- 1,000,000+
- Marketed products

Desc.

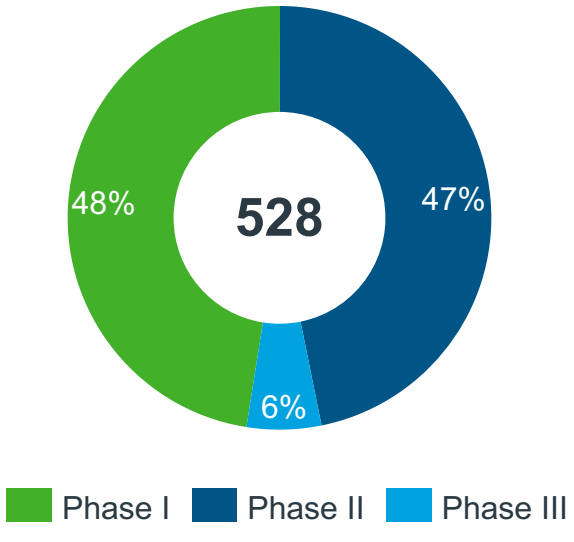
Hereditary ATTR amyloidosis	Caused by a fault in transthyretin gene that results in abnormal protein which forms aggregates that deposit as amyloids in organs & tissues
Danon disease	Lysosomal and glycogen storage disorder associated with hypertrophic cardiomyopathy, skeletal muscle weakness, and intellectual disability
Meta-chromatic leuko-dystrophy	Causes fatty substances (lipids) to build up in cells, particularly in the brain, caused by deficiency of an enzyme that helps break down lipids

Abbreviations: ASO: Anti-sense oligonucleotide; mRNA: messenger RNA; RNAi: RNA interference; (1) Others includes plasmids etc.
Source: Chardan report on Gene therapy overview and secondary research.

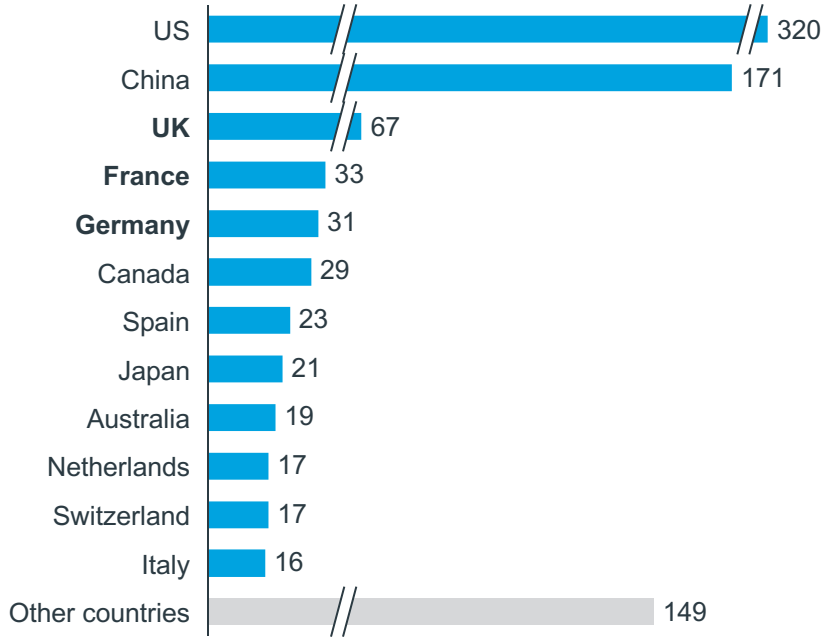
Abbreviations - *Link to Glossary*

Europe continues to excel in the development of gene and cell therapies (CGT) offering ample opportunity for more investment in this area

Active Cell and Gene Therapy Clinical Trials



Geographic Split of Cell and Gene Active Clinical Trials



*Includes **528** drugs being tested in **1,203** trials involving **~4k investigators** globally*

Key Takeaways

- Globally, there are 500+ drugs being tested across most therapy areas inc. oncology and rare diseases
- US reports the highest clinical activity, which is measured by # drugs in trials in this case
- Other key regions include EU with key markets like UK, France and Germany being three of the top 5 countries for CGT development globally
- US is leading the way in gene therapy R&D propelled by high investment of $16B in 2021, compared with $3B invested in EU
- China has emerged as an important hub for development of CGT supported by favorable government policies and increased capital inflows

Notes: Above counts include cell therapies as well and split between gene and cell therapies was not availablele. Excludes vaccines for infectious diseases.
Source: (1) Alliance of Regenerative Medicine (2) Labiotech.EU (3) Internal pipeline database

There are significant challenges for Cell & Gene Therapy access, including high upfront cost, long term uncertainty & limited HTA provisions

Misalignment between MNF costs and market ability to pay

Due to high development and manufacturing costs associated, these therapies are **priced at a much higher premium** compared with traditional therapies

Payer 3–5-year budgetary cycles cannot handle high upfront cost

Uncertain long-term clinical benefit

Payers sceptical of **long-term clinical** efficacy due to lack of statistically significant, head-to-head trials and limited long term follow-up data

Gap between regulatory (offering incentives to accelerate approval) and HTA bodies (consider **clinical data immature** and weak for reimbursement)

Systems not set up for CGTs

Challenging to **quantify** and fully **capture** the benefits of CGTs in the absence of long-term data

Settings of care **less likely** to be **familiar** and able to **cope** with new and complex technology

Source: IQVIA analysis

Abbreviations *- Link to Glossary*

There is an increased acceptability of innovative reimbursement schemes amongst EU payers, but challenges remain

EXAMPLES OF INNOVATIVE OUTCOMES-BASED AGREEMENTS (OBAs)

Outcome-based Payment

- Partial payment upfront (50-75% of full price), followed by additional payments if certain outcomes are met
- For e.g., After initial partial reimbursement further payments triggered for Luxturna after 30 days, 90 days and 30 months (US) and CAR T therapies Kymriah and Yescarta in Italy and Spain

Outcome-based Annuity

- Payer makes annuity payments, contingent upon continued duration of therapy efficacy
- For e.g., Zynteglo was reimbursed with 5 equal annual payments in Germany

Outcome-based Rebates

- Full price upfront but manufacturer agrees to rebates if certain outcomes are not met
- For e.g., rebate for Holoclar is agreed upfront if the drug fails within 12 months if treatment in Italy and CAR T therapies Kymriah and Yescarta in Germany

Fallout between DE Payers and Bluebird Bio: Despite increasing acceptance of innovative reimbursement mechanisms, Bluebird Bio withdrew its gene therapy Zynteglo, approved for the treatment of ß-thalassemia, from German market in 2021 after unsuccessful pricing negotiations with payors

Source: (1) EMA, (2) EMA, (3) Spark press release;
IQVIA | EFPIA Pipeline Innovation Review 2022

Abbreviations - Link to Glossary

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Gene therapy offers a potential life change for patients with Haemophilia A and their families, with additional benefits for HCS and societies

EXECUTIVE SUMMARY

01 TECHNOLOGY & PIPELINE ASSESSMENT

- Gene therapy refers to introduction of genetic material into cells to compensate for abnormal genes or to make a beneficial protein
- Pipeline for gene therapies within Haemophilia is crowded and has advanced with 5 products in Phase 3 and 6 products in Phase 2

02 INDICATION ASSESSMENT

- Haemophilia A affects ~31,000 patients in EU, with 60%+ suffering from severe form of the disease. Patients are mainly undergoing prophylactic therapy, causing great burden
- Patients with Haemophilia A often bleed more and longer than other people – where bleeding can occur internally into joints and muscles, or externally from minor cuts or trauma

03 IMPACT ANALYSIS

- Gene therapy offers a potential life change for Haemophilia A patients and families, with considerable long-term direct and indirect benefits for healthcare systems and society
- **Patients, families and caregivers:** An improvement inpatient QoL will result from reduction in treatment burden and incidence of haemorrhages
- **Healthcare systems:** Less frequent/severe haemorrhages are also expected to result in a reduction in hospital utilisation and drug expenditure
- **Society:** Expected to shift in severity from moderate-to-severe to mild, along with elimination of hidden costs of €121 million associated with the loss in productivity

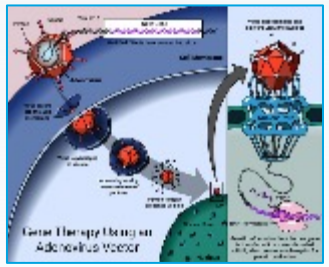
Gene therapy is being applied to various orphan diseases to restore the missing functions of damaged genes

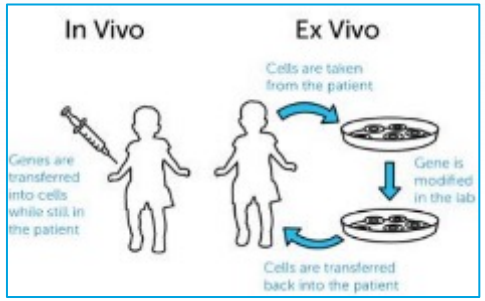
- **Gene therapy** delivers a gene or repairs a defective one as treatment, where the damaged genes could: encourage the cell to multiply (oncogenes), stop the cell multiplying (tumour suppressor genes), or repair other damaged genes[1,2]
- **Genes** are coded messages that tell cells how to make proteins, which are molecules that control cell behavior[1,4]
- **Applicable** to single-gene, polygenic and infectious diseases, where hematopoietic stem cell transplantation (HSCT) with chemotherapy is performed for **haematological malignancies,** autologous HSCT is performed in some diseases efficiently & safely[3]
- **Gene editing is another mechanism under development**: the defective gene can be corrected with a molecular mechanism[3,4]

Mechanism of Action[1]

- Genetic material is introduced into cells to **compensate for abnormal genes,** replace an **dysfunctional protein,** and/or **introduce a beneficial protein** and **restore function**
- A gene carrier (**vector)** is genetically engineered to deliver the gene – certain modified viruses are often used as vectors to deliver the new gene by infecting the cell
- Some types of viruses (**retroviruses**) integrate genetic material into a human **chromosome,** while other viruses (**adenoviruses**) introduce their DNA into the **nucleus** of the cell

Gene Therapy Administration[1,3]





***In vivo*:** therapy administered directly to patient where genes are changed in cells while still in the body. Types of vectors: integrating and episomal

***Ex vivo*:** cells (e.g. blood) extracted from the patient's body and grown in the laboratory, genes are changed in the lab, then the cells are returned to the body

Notes: HSCT - hematopoietic stem cell transplantation
Source: (1) FDA, (2) Cancer Research UK, (3) Medlineplus, (4) Center for Molecule Medicine

There are ~31,000 patients with Haemophilia A in Europe, who are mainly undergoing prophylactic therapy, causing great burden

Haemophilia A

An orphan disease caused by a faulty gene that is unable to produce a key protein needed for blood clotting, if left untreated leads to haemorrhages

31,200 (2)
Patients diagnosed in EU
(6 per 100,000 population)

60% severe form[1]
More than half of patients are living with a severe form of Haemophilia A

Low Quality of Life

Leads to haemorrhages in response to mild trauma or spontaneously in moderate-to-severe cases

€122,000
Annual HC cost / patient
and further social and economic costs

High Burden Disease
Patients must receive an IV infusion as part of prophylaxis therapy every 3-7 days causing great discomfort

- Caused by a faulty gene that is unable to produce a **key protein needed for blood clotting** (factor VIII), with more than half of A patients suffering from a severe form
  - **Severe** (factor levels less than 1%) represent approximately 60% of cases
  - **Moderate** (factor levels of 1-5%) represent approximately 15% of cases
  - **Mild** (factor levels of 6%-30%) represent approximately 25% of cases
- Although it is passed down from **parents to children**, about 1/3 of cases are caused by a **spontaneous mutation** (a change in a gene)
- Patients with Haemophilia A often **bleed more and longer than other people** – where bleeding can occur internally - into joints and muscles, or externally - from minor cuts, dental procedures or trauma
- Current treatment for Haemophilia A includes Hemlibra, a monoclonal antibody, and concentrated factor VIII, referred to as clotting factors; **~75% of the patient community** is currently treated with such factors, which are administered intravenously every 3-7 days causing great discomfort
- Severe patients (and children) are often on these treatments as a **prophylaxis regimen**, to **maintain a sufficient level of clotting factors** to prevent bleeds

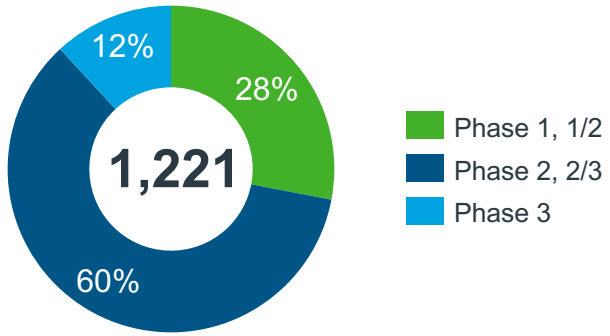
Source: (1) Hemophilia.org; (2) EMA; (2) EUHANET; (3) Chess Study
IQVIA | EFPIA Pipeline Innovation Review 2022

Abbreviations *- Link to Glossary*

The cell and gene therapy pipeline is becoming increasingly crowded; focus remains on rare indications, oncology and infectious diseases

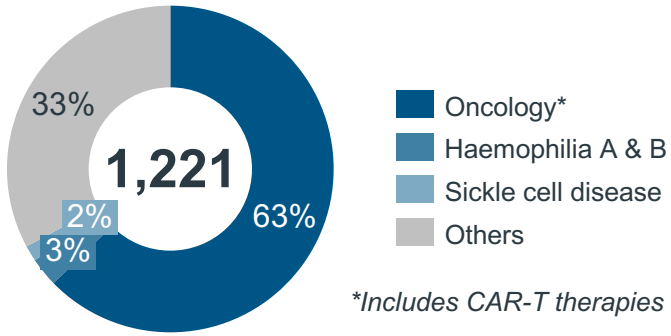
CLINICAL TRIAL PIPELINE FOR CELL AND GENE THERAPIES

Number of Clinical Trials By **Development Phase**



- There are 1,200+ clinical studies ongoing for cell and gene therapies with 60% studies being in Phase 2 and ~10% in Phase 3
- Phase 3 studies include rare indications such as Sickle cell disease, Thalassemia, haemophilia, Duchenne Muscular Dystrophy and Retinal dystrophy, along with certain cancers in which cells therapies are being evaluated

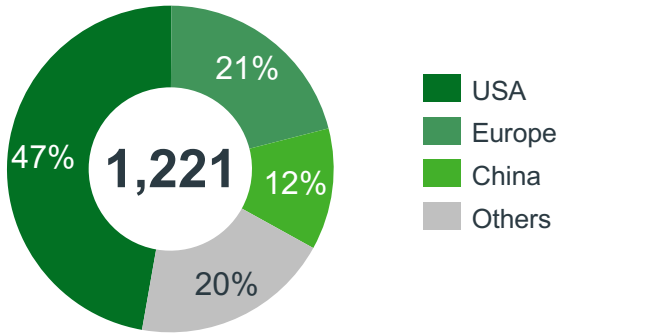
Number of Clinical Trials By **Indication**



**Includes CAR-T therapies*

- More than 60% of studies are attributed to oncology which primarily includes CAR T therapies. However, CRISPR edited T cell immunotherapies also take a minority share of oncology studies
- Within rare indications, Haemophilia A & B and Sickle cell disease are two most crowded and advanced, taking 5% share of total studies

Number of Clinical Trials By **Geographic Split**



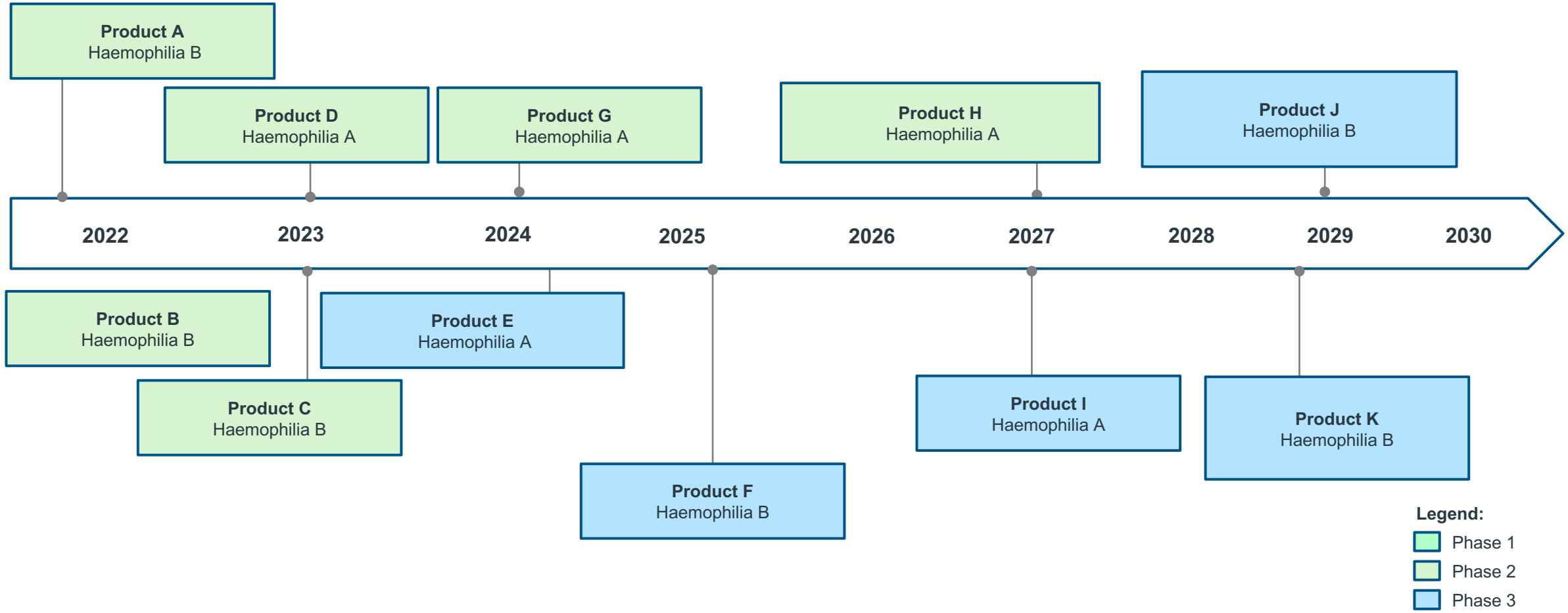
- The US is leading the way with highest number of clinical studies, followed by Europe and China
- Overall, ~70% studies are focused across US and Europe implying the high focus on cutting edge healthcare innovation across these two regions

Source: IQVIA analysis; Clinicaltrials.gov

Abbreviations *– Link to Glossary*

2 products for Haemophilia A are set to launch in the next 3 years, with additional therapies in the pipeline for Haemophilia B

2022 GENE THERAPY PIPELINE: ESTIMATED TRIAL COMPLETION DATES

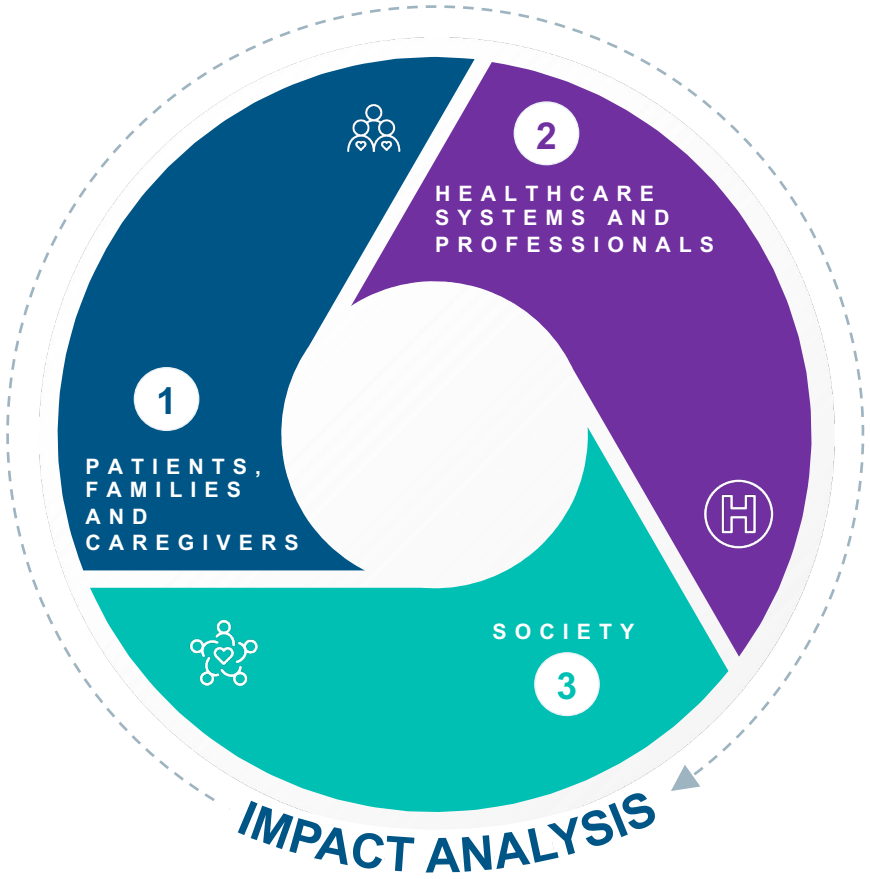


Source: clinicaltrials.gov; May 2022, active clinical trials (Not yet Recruiting, Recruiting, Enrolling by invitation, Active not recruiting), Excluded trials without specified phase, Device trials

Abbreviations *- Link to Glossary*

Gene therapy offers a potential life change for Haemophilia A patients and families; additional benefits for HCS and societies

IMPACT ANALYSIS



1 PATIENTS, FAMILIES, AND CAREGIVERS

Gene therapy may improve patient quality of life for patients with Haemophilia A by reducing disease management burden, the stress of spontaneous hemorrhages and the long-term disabilities, specifically arthritis, that they cause

2 HEALTHCARE SYSTEMS AND PROFESSIONALS

Hospital utilisation and drug expenditure could be reduced with gene therapy, due to a decline in the use of cost intensive replacement (factor VIII) therapy and treatment of co-morbidities associated with frequent hemorrhages

3 SOCIETY

Gene therapy offers a potential life change for patients with Haemophilia A and their families, thereby reducing absenteeism and increasing economic productivity

Source: IQVIA internal expertise

An improvement in patient QoL will result from reduction in treatment burden and incidence of haemorrhages

1

PATIENTS	CURRENT STATE	FUTURE STATE
SOCIAL CARE	• Moderate-to-severe cases (~75% patients) require prophylactic replacement (factor VIII) therapy every 3-7 days • Administered intravenously at great discomfort to patients	• Offers a one time rather than chronic treatment option • Reduction in need for prophylactic replacement (factor VIII) therapy in moderate-to-severe patients; evidence indicates complete prophylactic replacement therapy cessation for moderate-severe patients
CAREGIVER WELLBEING	• Moderate-to-severe patients experience approx. 14 haemorrhages per year • Patients must alter the timing and degree of physical activity to match the peaks and troughs of factor VIII levels	• Substitutional reduction in risk of spontaneous haemorrhages (due to stable factor VIII levels) • Offers patients opportunity to live a more active lifestyle due to lower severity of trauma-related haemorrhages

Source: Cost of severe haemophilia in Europe, IQVIA internal expertise

Less frequent/severe haemorrhages are also expected to result in a reduction in hospital utilisation and drug expenditure

2

HC SYSTEMS	CURRENT STATE	FUTURE STATE
HOSPITAL UTILISATION 	• Care provided at specialised clinics by multi-disciplinary teams including haematologists, physiotherapists, dentists and orthopaedists • Severe intracranial haemorrhages require hospitalisation	• Decline in consultation expenditure (due to decline in use of prophylactic therapy + treatment of internal haemorrhages) and clinic overhead costs (e.g. imaging, laboratory tests, hospital beds) • Improved access to specialist care • Reduction in hospitalisation and associated costs (due to decline in severe haemorrhages)
DRUG EXPENDITURE 	• Factor VIII replacement therapy represents the greatest cost of Haemophilia A	• Significant decline in expenditure on prophylactic therapy, by up to ~90%

Treatment for moderate-to-severe patients	Management Cost (per patient per year)	Drug Cost (per patient per year)	Total Cost (per patient per year)	Total EU Annual Cost	Total EU lifetime Cost
Current Therapy	€8,600 (1)	€113,000 (1)	€122,000	**€1.30 bn**	**€99bn**

Source: (1) Cost of haemophilia treatment; IQVIA internal expertise

Gene therapy offers a potential treatment for a disease that negatively impacts patients and their families for their entire lives

3

SOCIETY	CURRENT STATE	FUTURE STATE
AGE OF DIAGNOSIS	• Afflicts many children; median age of diagnosis is 8 months • Lifetime disease with no cure	• Shift in severity from moderate-to-severe to mild *(assuming the science will evolve to be applicable for children)*
PRODUCTIVITY COST	• Patient absenteeism due to haemorrhages, hospitalisation, physician appointments and distant travel to specialised centres • Family absenteeism due to care of elderly/children	• Decline in missed days of work from patients and families due to reduced risk of haemorrhage and long-term complications

Calculated using research report economic burden of haemophilia

Treatment	Days of work lost (per patient per year)	GDP per capita in EU	# hours missed by all patients (per year)	Total loss of Nominal GDP (per year)
Current Therapy	~35 days	€36,653 (1)	606 k (2)	€121 million

Source: (1) World Bank estimate, (2) Calculated using research report economic burden of haemophilia; IQVIA internal expertise

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Duchenne muscular dystrophy is a rare muscle disorder and one of the most frequent genetic conditions, affecting approx. 1 in 3,500 male births

Duchenne Muscular Dystrophy (DMD)

A rare, genetic, muscular dystrophy primarily affecting males. It is characterized by rapidly progressive muscle weakness and wasting due to degeneration of skeletal, smooth and cardiac muscle

26,000[1]
Patients in EU (0.5:10,000)
Increasing due improvements in diagnostics

Patient type
Usually affects boys in early childhood, onset is usually between 3-5 years of age

Quality of Life
Delays in early-childhood muscle use, learning and speech difficulties, patients are wheelchair bound by 12 years of age

€49,000[2]
Annual COI* / patient
Substantial economic burden that becomes larger around the time ambulation is lost (age 10)

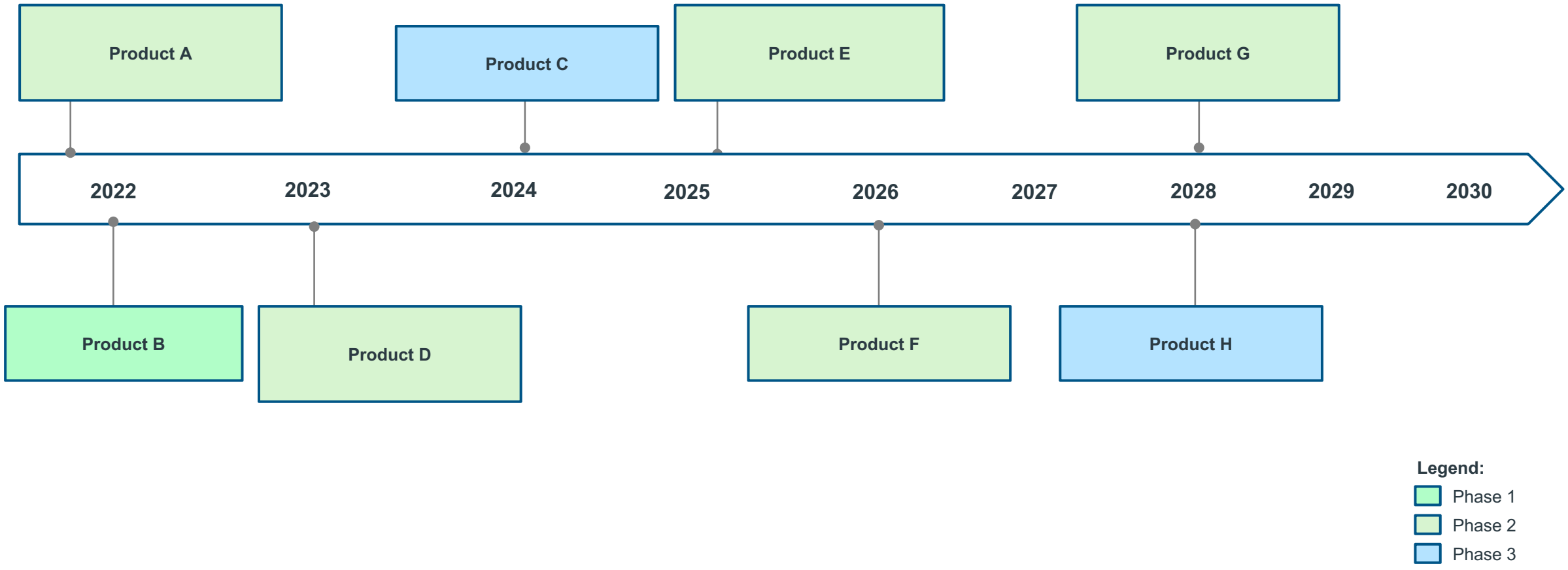
High Burden Disease
People with the condition will usually only live into their 20s or 30s

- Duchenne muscular dystrophy (DMD) is a genetic disorder characterized by **progressive muscle degeneration and weakness** due to the alterations of a protein called **dystrophin** that helps keep muscle cells intact
- DMD is the most **severe** and common type of muscular dystrophy, it affects males at a rate of 1 in 3,500 births
- Diagnosis in boys usually occurs between 16 months and 8 years - parents are usually the first to notice its symptoms
- By the late teens, DMD may also be characterized by complications including weakness and deterioration of the heart muscle (**cardiomyopathy**), impairing the ability of the heart to pump blood, causing irregular heartbeats (arrhythmias) and heart failure.
- Death from DMD usually occurs by age of 30, with dilated cardiomyopathy as the leading cause
- No cure exists for DMD, and treatments are aimed at the specific symptoms. Corticosteroids (prednisone, deflazacort) are used as SoC to slow the progression of muscle weakness and delay the loss of ambulation by 2-3 years.
- Currently, there is an ongoing **Phase 3** trial of a **gene therapy**[3] for ambulatory patients with DMD in 11 countries

Note: *COI refers to Cost of Illness; Source: (1) EMA, (2) PMID 34604937, (3) NCT04281485;

For Duchenne MD, currently two gene therapies are in their Phase 3 with potential upcoming regulatory milestones

EXPECTED COMPLETION YEAR FOR KEY TRIALS



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CRISPR related gene editing therapy has the potential to cure Sickle Cell Disease (SCD), positively impacting ~52,000 patients across EU

EXECUTIVE SUMMARY

01 TEHCNOLOGY & PIPELINE ASSESSMENT

- CRISPR related gene editing enables researchers to edit parts of the genome by removing, adding or altering sections of the DNA sequence
- The pipeline is taking form with applications across oncology and rare indications; 2 CRISPR based gene editing therapies for sickle cell disease are in advanced clinical studies currently

02 INDICATION ASSESSMENT

- Sickle cell disease is one of the most prevalent genetic diseases in the EU, affecting ~52,000 patients, reducing their life expectancy by ~30 years compared with general population
- Patients with SCD have sickle-shaped red blood cells which do not bend and move easily, potentially blocking blood flow to the rest of the body causing multiple complications like severe anemia, silent brain injury, heart disease and acute chest syndrome

03 IMPACT ANALYSIS

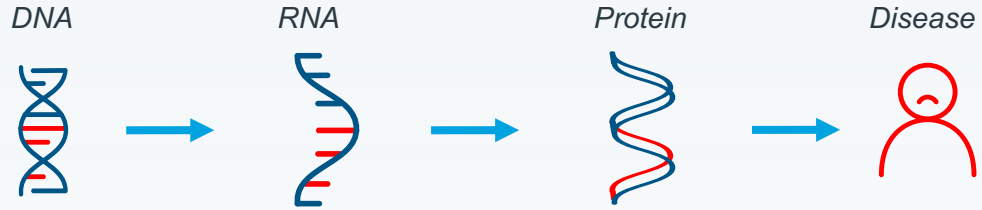
- Gene therapy offers a potential cure for a disease that negatively and chronically impacts patients and families, with a large economic burden driven by treatment cost and productivity loss
- **Patients, families and caregivers:** Can eliminate all serious complications associated with the disease, enabling patients to lead a normal life
- **Healthcare systems:** Potential to circumvent majority of SCD cost due to frequent hospitalizations with one-time treatment
- **Society:** Expected to increase overall survival and productivity in patients, eliminating the hidden costs associated with current Standard of Care, leading to a lifetime addition of €11.3 bn to the EU GDP

Abbreviations – Link to Glossary

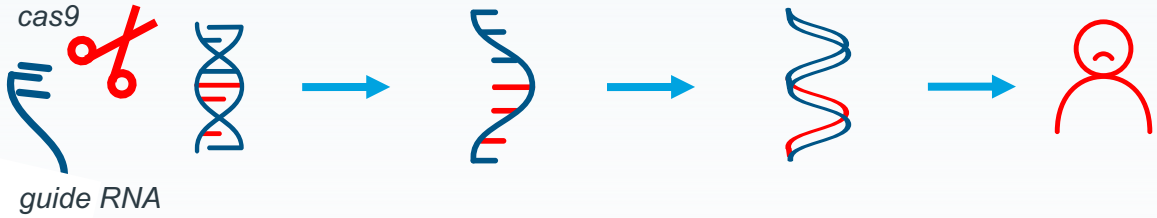
CRISPR related gene editing enables researchers to edit parts of the genome by removing, adding or altering sections of the DNA sequence

AN OVERVIEW OF CRISPR GENE EDITING

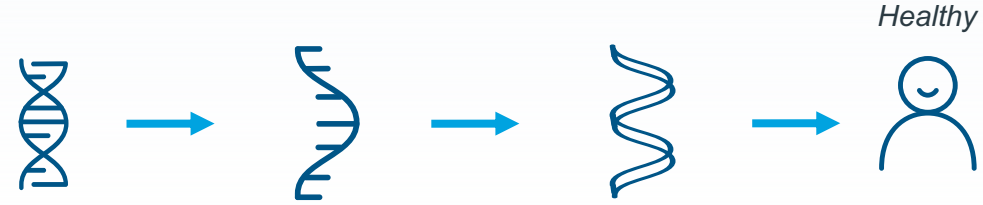
Errors in genetic code are decoded in wrong RNA which gives rise to a mutated protein



Small guide RNA brings 'molecular scissors protein' Cas9 to a target location in genome



The incorrect gene can be either turned off or fixed with the correct DNA code



NOBEL PRIZE FOR CRISPR GENE EDITING

In 2020, **Emmanuelle Charpentier** and **Jennifer A. Doudna** shared the Nobel Prize in Chemistry in 2020 for the development of a method for genome editing using CRISPR

Source: (1) Nature article

Abbreviations *- Link to Glossary*

Sickle cell disease is one of the most prevalent genetic diseases in Europe, with a life expectancy 30 years below the general population

Sickle cell disease (SCD)

A group of inherited rare diseases that produce unusually shaped red blood cells (RBCs) that can cause problems because they do not live as long as healthy RBCs and can block blood vessels. The most serious type is called sickle cell anaemia

52,000[1]

Patients in EU (1:10,000)

Increasing due to immigration and new births

Patient type

Predominantly affects people of African, Mediterranean and South Asian descent – although mutation is found across all ethnicities

Poor Quality of Life[2]

Leads to haemolytic anaemia and vascular occlusion (VO), causing painful episodes, neuro-cognitive deficits and organ failures

€6,000[3]

Annual HCS cost / patient

Ranging up to €84,000/patient, driven mostly by hospitalisation associated VO events

High Burden Disease[4]

Premature death (median age 36 years), higher number of hospitalisations, ER and outpatient visits than the general population

- Affects **haemoglobin,** the **protein that carries oxygen** through the body inside of RBCs. Normal RBCs are disc shaped and flexible to move easily through blood vessels
- Patients with SCD have crescent/sickle-shaped RBCs which do not bend and move easily - potentially **blocking blood flow** to the rest of the body causing multiple complications (e.g., severe anaemia, silent brain injury, lung disease, hearth disease and chest syndrome)
- A **lifelong illness,** most patients with SCD have a **30-year gap in life expectancy** compared to the general population
- Patients with SCD inherit two abnormal haemoglobin genes, one from each parent
- Depending on the mutation there are several types: **SS** (referred to as **sickle cell anaemia**, most common and severe), **SC** (2nd most common, less severe), **Sβ+** thalassemia (milder), **Sβ0** thalassemia (severe, poorer prognosis) and **SD/SE/SO** (rare types, usually no severe symptoms)
- Current treatments that aim to reduce symptoms, improve QoL and prolong life include hydroxyurea, penicillin, **crizanlizumab-tmca** (EMA, 2020) and **voxelotor** (EMA, 2022). Acute and regular **transfusions** are also used to treat and prevent SCD complications
- The only cures for SCD are bone marrow or stem cell transplants - mostly in children and require a related and matched donor. FDA has recently approved (2021) the first test of CRISPR[5] and a clinical trial[6] (CRISPR_SCD001) to directly to correct the gene mutation

Source: (1) EMA, (2) PMID 25125865 33496753, (3) 32672889, (4) 34242255, (5) UC Berkeley, (6) NCT04774536 ; abbreviations - link to glossary

CRISPR-related gene editing proceeds to take root as a dominant modality in biotechnology

APPLICATION OF CRISPR RELATED GENE EDITING

LNP-CRISPR editing

- *In vivo* gene-editing therapeutic agent that comprises a lipid nanoparticle (LNP) encapsulating messenger RNA for Cas9 protein and a single guide RNA targeting TTR
- Has reported positive first evidence by reducing the levels of bad protein i.e., TTR that causes the deadly condition by over 80% within 4 weeks (1) (2021)

NTLA-2001 for **hATTR**
(Intellia Therapeutics)

Ex vivo CRISPR editing

- CTX001 is an autologous, ex vivo CRISPR/Cas9 gene-edited therapy in which a patient's hematopoietic stem cells are edited to produce high levels of fetal hemoglobin in red blood cells
- CRISPR Therapeutics is on track to submit global regulatory filings in late 2022
- Company has reported positive results from Phase 1 / 2 in severe Sickle Cell Disease (SCD) patients preventing VOCs for up to 2 years; currently ongoing Phase 3

CTX001 for **Sickle cell disease** and **ß thalassemia**
(**CRISPR** and **Vertex Pharma**)

CRISPR/cas12a-edited HSC

- EDIT-301 consists of patient-derived CD34+ hematopoietic stem and progenitor cells edited at the gamma globin gene (HBG1 and HBG2) promoters, where naturally occurring fetal hemoglobin (HbF) inducing mutations reside, by a **highly specific** and **efficient** CRISPR/Cas12a ribonucleoprotein (RNP) (3)

EDIT-301 for **Sickle Cell Disease**
(Editas)

CRISPR CAR T

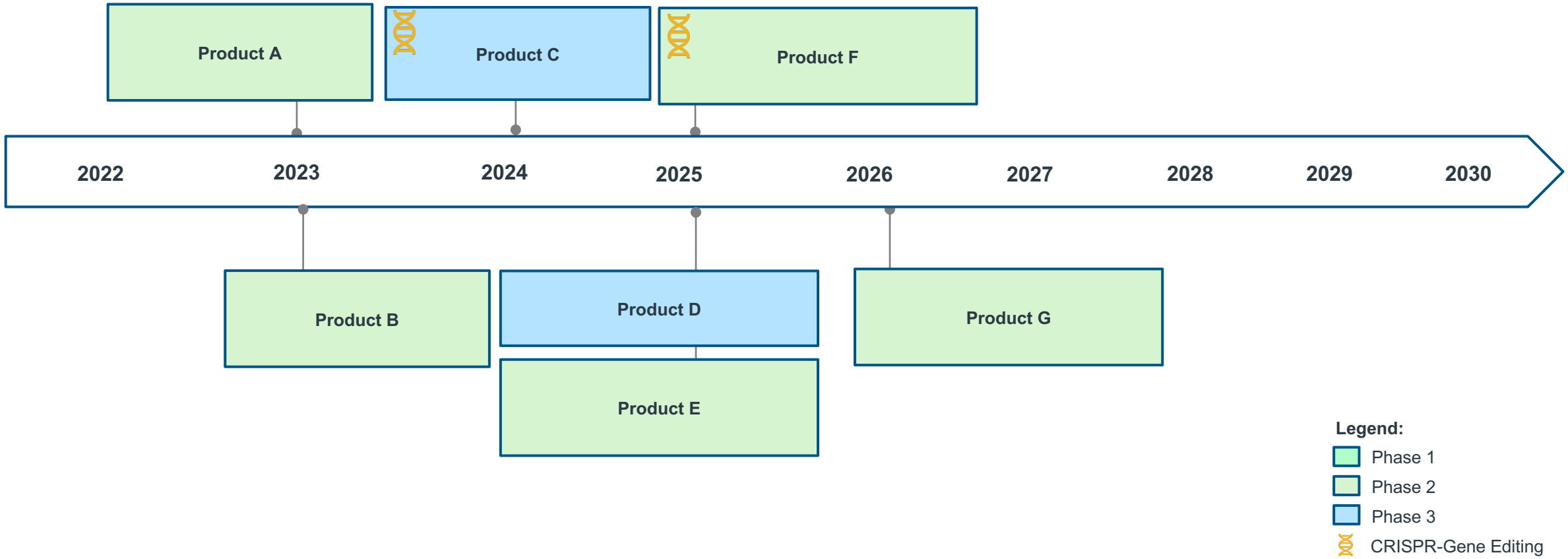
- Off-the-shelf (allogeneic) CAR T cells that uses CRISPR-cas9 to make 3 modifications to healthy donor T cells to allow for off-the-shelf usage:
- For insertion of CAR construct precisely, to eliminate the T cell receptor with high efficiency (reducing the risk of Graft Vs Host Disease (GvHD)) and eliminate class I major histocompatibility complex (reducing risk of rejection) (4)

CTX110 for **CD19+ malignancies**
(CRISPR Therapeutics)

Source: (1) Intellia press release (2) Sickle cell anemia news (3) Editas press release (4) CRISPR Therapeutics. VOC: Painful vaso-occlusive crisis (VOC)

There are multiple gene therapies in trial for Sickle Cell Disease; however CRISPR gene editing is most advanced with Phase 3 trial ongoing

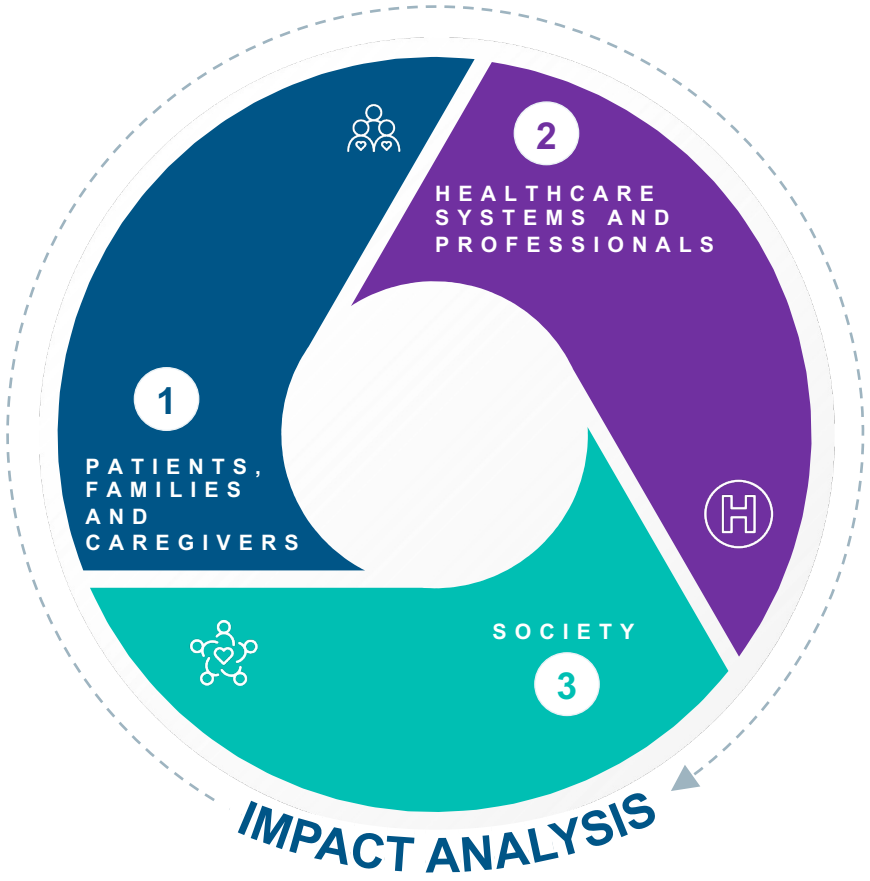
EXPECTED COMPLETION YEAR FOR KEY TRIALS



Abbreviations - *Link to* Glossary

Gene therapy offers a potential treatment for a disease that negatively impacts patients and their families for their entire lives

IMPACT ANALYSIS



1

PATIENTS, FAMILIES, AND CAREGIVERS

Gene therapy has the potential to cure this chronic disease that shows acute symptoms throughout the patient's life and also increases the risk of stroke

2

HEALTHCARE SYSTEMS AND PROFESSIONALS

Hospital utilisation could be reduced with gene therapy, due to a decline in acute symptoms that potentially require hospitalisation. However, it is still uncertain how the lifetime treatment cost of gene therapy would compare with current SoC

3

SOCIETY

Large upfront costs of a single administration cure are offset by significant downstream gains in health for patients treated early in life, along with increasing the life expectancy of SCD patients

Source: IQVIA internal expertise

Abbreviations – *Link to Glossary*

Gene therapy can eliminate all serious complications associated with Sickle Cell Disease, enabling patients to lead a normal life

1

PATIENTS	CURRENT STATE	FUTURE STATE
TREATMENT BURDEN	• Require lifelong treatment, resulting in high personal and financial burden on individuals and their families	• A study of an investigational gene therapy for sickle cell disease has found that a single dose restored blood cells to their normal shape and eliminated the most serious complication of the disease for at least three years in some patients
LIFESTYLE	• Patients with Moderate-to-severe disease experience some level of pain daily and must be absent from work to undergo blood transfusion • Patients experience frequent Vaso-occlusive (VOC) crises leading them to the emergency department about 1-5 times per year	• Can offer quality of life improvements including improved function, reduced or eliminated pain and suffering, and a psychological sense of well-being

Source: Company Research, IQVIA internal expertise

Abbreviations – *Link to Glossary*

Majority of treatment burden is contributed by frequent patient hospitalisations, which can potentially be reduced or eliminated

2

HC SYSTEMS	CURRENT STATE	FUTURE STATE
HOSPITAL UTILISATION	• Majority of the treatment burden can be attributed to **hospitalization** and **lab testing** • Hospitalisation is essential to manage acute symptoms including VOC crises acute chest syndrome, acute anaemia and fever episodes • VOC is the most frequent acute symptoms that requires hospitalisation for intravenous hyperhydration and the administration of analgesics such as nitrous oxide, a sedative gas treatment by inhalation	• Decline in consultation expenditure • Decline in clinic overhead costs (e.g. imaging, laboratory tests, hospital beds) • Reduction in hospitalisation and associated costs (due to decline in VOC crises) • Improved access to specialist care

Disease burden of SCD

Treatment	Avg. total cost of treatment / patient / year	# SCD patients in EU	Total EU Annual Cost for all patients	Total Lifetime Cost for all SCD patients in EU
Current Therapy	€6,086 (1)	~52,000	€316 Mn	**€17 Bn** *Direct cost associated with current treatment*

Source: (1) Disease burden of SCD, IQVIA internal expertise

Abbreviations – *Link to Glossary*

Gene therapy is expected to increase overall survival and productivity of patients, eliminating the hidden costs associated with current SoC

3

SOCIETY	CURRENT STATE	FUTURE STATE
SURVIVAL	• Currently, the average life expectancy of SCD patients is ~55 years compared with 80 years for a healthy individual	• Gene therapy is expected to increase survival of SCD patients by ~25 years by addressing and correcting its underlying genetic cause
PRODUCTIVITY LOSS Implied from SCD life expectancy research	• Patient absenteeism due to vaso-occlusive crisis, hospitalisation, physician appointments and distant travel to specialised centres • As per a US study, SCD patients reported missing 7 weeks per year because of pain from the disease	• Decline in missed days of work from patients and families due to reduced risk of VOC and long term complications

Treatment	Avg. # of working years reduced from life of employed patients (60%)	GDP per capita in EU	Cumulative loss in nominal GDP across lifetime of all employed SCD patients	Loss in productivity of employed SCD patients after cure	Overall loss due to decreased life span and productivity
Current Therapy	~10 years (1)	€36,653	€11bn	€3 M (10 M hours)	**€11.3bn** *Hidden cost associated with current treatment*

Source: (1) Implied from SCD life expectancy research, IQVIA internal expertise

Abbreviations – *Link to Glossary*

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mRNA vaccines have the potential to change the current paradigm in the treatment of Glioblastoma

EXECUTIVE SUMMARY

01 TECHNOLOGY & PIPELINE ASSESSMENT

- The introduction of an mRNA sequence from the vaccine instructs the body's cells on how to temporarily replicate proteins – **stimulating an immune response** against these same proteins when they are found in tumour cells (i.e Glioblastoma cells)
- The **pandemic has reinvigorated the mRNA clinical pipeline** with a substantial increase in the number of clinical trials, with robust activity in infectious diseases and oncology

02 INDICATION ASSESSMENT

- **Glioblastoma is an aggressive cancer** that predominantly occurs in the brain and given its location, treatment is difficult, with full recovery often not possible (1 year survival rate is ~25%)
- Tumours often grow quickly and invade neighbouring brain tissue causing **severe deterioration in quality of life** for suffering patients

03 IMPACT ANALYSIS

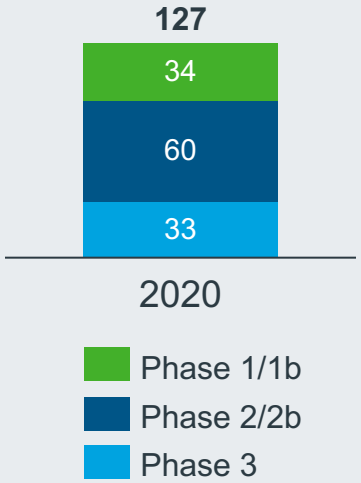
- mRNA offers a promising platform to develop long-term treatment options for glioblastoma, improving survival outlook and healthcare system sustainability with vast socioeconomic benefits
- **Patients, families and caregivers:** Potential to dramatically improve long-term survival, allowing patients more time to spend time with loved ones and a reduction in emotional distress and care load on caregivers
- **Healthcare systems:** Current Glioblastoma treatment places a large burden on healthcare resources - a curative mRNA vaccine would help alleviate some of this burden
- **Society:** Expected to increase overall survival which would allow patients to return to their normal lives as productive members of society – adding an estimated €46 million in GDP / year

Abbreviations – Link to Glossary

The COVID-19 pandemic animated the mRNA landscape, promising next generation treatments for a broad range of indications

2022 UPDATES VS. 2020 REPORT

CLINICAL DEVELOPMENT



+93 new trials started

29 trials with anticipated readouts by the end of 2023

-1 trial suspended

SELECTED INDICATION(S)

Glioblastoma

remain the focus area of the 2022 report as the indication with the greatest unmet need

Respiratory Syncytial Virus (RSV)

RSV was also identified as an indication with a large unmet need and as a result a snapshot is provided

KEY UPDATES

*The COVID-19 pandemic invigorated the clinical trial pipeline for mRNA vaccines with the number of clinical trials **increasing from ~34 in 2020 to ~127 in 2022***

*Without an effective treatment, Glioblastoma continues to be the indication with the **greatest unmet need and potential to gain** with very poor patient prognosis and severe associated financial burdens*

*Promising developments have occurred across the mRNA pipeline, with **3 mRNA vaccine focussed clinical trials completed for Glioblastoma since 2020** with more on the horizon*

Source: IQVIA analysis; Clinicaltrials.gov

Abbreviations – *Link to Glossary*

mRNA vaccines train the body to fight a real antigen, by training the immune system using an engineered antigen produced via a specific mRNA code

AN OVERVIEW OF mRNA VACCINES

mRNA vaccines

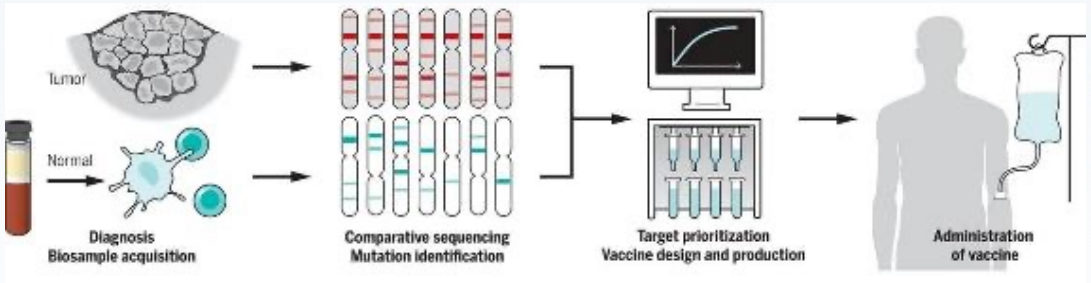
- mRNA vaccines for **both prevention *and* therapy** work by **introducing an mRNA sequence** (messenger RNA, the molecule which tells cells what to build) which is **coded for a disease specific antigen**, once produced within the body, the **antigen is recognised** by the immune system, **preparing it to fight the disease**[1]
- mRNA vaccines are **faster and cheaper to produce** than traditional vaccines, and an mRNA based vaccine may also **safer for the patient**, as they are not produced using infectious elements[1]
- The **success** of Moderna and Pfizer-BioNTech's mRNA vaccines in combatting the COVID-19 pandemic has animated the mRNA vaccine landscape and has attracted a lot of **new investment and research**

Mechanism of Action[1]

Types of RNA vaccines:

- **Non-replicating:** simplest type, mRNA strand is packaged and delivered to the body, where it is taken up by the body's cells to make the antigen
- ***In vivo* self-replicating:** pathogen-mRNA strand is packaged with additional RNA strands that ensure it will be copied once the vaccine is inside a cell
- ***In vitro* dendritic cell non-replicating**: dendritic cells extracted from the patient's blood, transfected with the RNA vaccine, then given back to the patient to stimulate an immune reaction

Gene Therapy Administration[1,3]



A patient's **healthy and cancerous tissues are compared**, where tumor-specific nucleotide **variations can then be identified**

These "**mutant" variations are assessed** (based on a specific predicted affinity) for an **optimal vaccine target**, after which the **vaccine is produced and administered** to the patient

Source: (1) PHG foundation, (2) ScienceMag, (3) Pfizer press release

Abbreviations - *Link to Glossary*

Glioblastoma is an aggressive cancer affecting the brain, with many patients eventually relapsing

Glioblastoma (GBM)

An **aggressive type of cancer** that occurs **predominantly in the brain**, but can also appear in the brain stem, cerebellum and spinal cord[1,2]

22.100[3]
Incidence in the EU*
(3.2 per 100,000 population)

47% Of all brain and other CNS tumours[3]

Quality of Life
Lowered physical ability, as well as psychological health resulting from seizures, fatigue, insomnia, and treatment

€47,000*
Annual HC cost / patient
and further social and economic costs

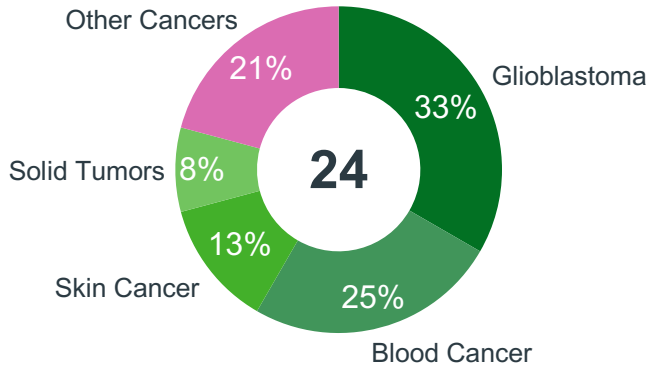
High Mortality
Following diagnosis, 25% of patients survive more than 1 year and only 3% to 5% of patients survive more than 5 years

- **Glioblastomas are malignant grade 4 brain tumours**, are fast growing, and diffuse – meaning they have tentacles that infiltrate the brain rendering them particularly difficult to control and remove completely
- Diagnoses are as either **IDH-wildtype or IDH-mutant**: IDH-wildtype glioblastomas are more common, tend to be more aggressive, and have worse prognosis than IDH-mutant glioblastomas
- **Patients develop symptoms rapidly**, including nausea, vomiting, and severe headaches (due to increased pressure in the brain) and/or weakness or sensory changes, balance difficulties, seizures (dependent on the tumour location)
- The first step in treating glioblastoma is a **surgical procedure** to make a diagnosis, to relieve pressure on the brain, and to safely remove as much tumour as possible
- **Radiation and chemotherapy** are used for tumour that cannot be removed with surgery (for diffuse cases) and to slow down the growth of residual tumour after surgery
- **Tumour Treating Fields** (TTFields) may be also be offered in combination with chemotherapy
- Treatment for newly diagnosed GBM also depends on a variety of factors, including molecular biomarkers (MGMT status & IDH mutation) and age

Note: (*) based on an EU population of 690,712,271, Total calculates using approximate 1st of June 2018 USD to GBP exchange rate
Source: (1) The Brain Tumour Charity, (2) ABTA, (3) American Association of Neurological Surgeons, (4) HRQoL in glioma patients, (5) NIH

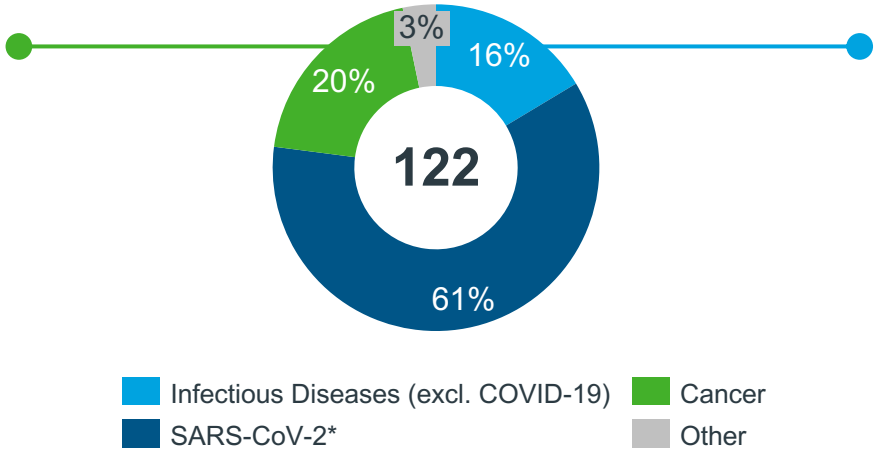
Due to their large unmet need and burden on society, we focus on mRNA vaccines for Glioblastoma and infectious disease (excluding COVID-19)

Number of Clinical Trials for **Cancer**

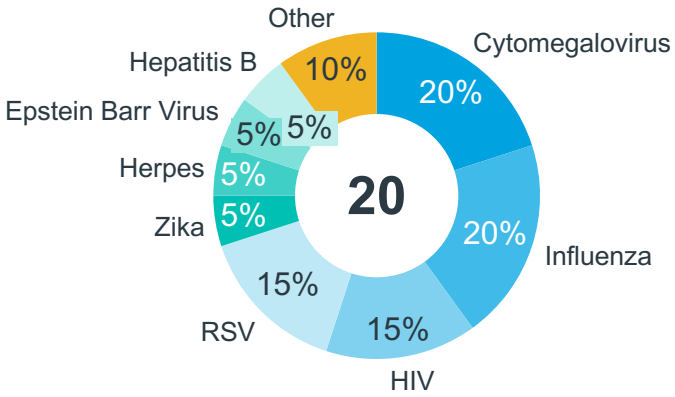


- Glioblastoma **represents 100%** of brain cancer indications currently being studied
- Indeed, Glioblastoma is the most common malignant brain and other CNS tumours accounting for **47.7% of all cases**[2]
- Further, the **5 year survival rate for GBM is as low as 3% in the EU**[3]

Current active mRNA clinical trials



Number of Clinical Trials for **Infectious Disease**



- RSV currently represents the **greatest unmet need** and the greatest potential area of impact
- Specifically RSV as the **second most common reason for infant mortality** and places a large burden on society
- Further, currently there are **no available curative acute or preventative treatments for RSV**

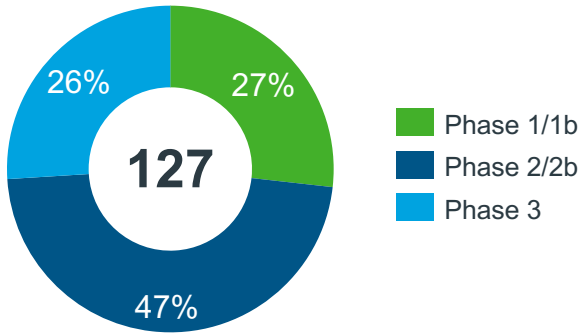
Note: * SARS-CoV-2 has been extracted from infectious diseases as they are discussed in the Pipeline Overview chapter and to allow for a closer examination of other infectious diseases in the mRNA vaccine pipeline
Source: (1) IQVIA Data Analysis, (2) CORDIS EU research results, (3) American Cancer Society

Abbreviations - *Link to Glossary*

mRNA vaccines represent a highly innovative area, currently being explored broadly for viral infections and cancers

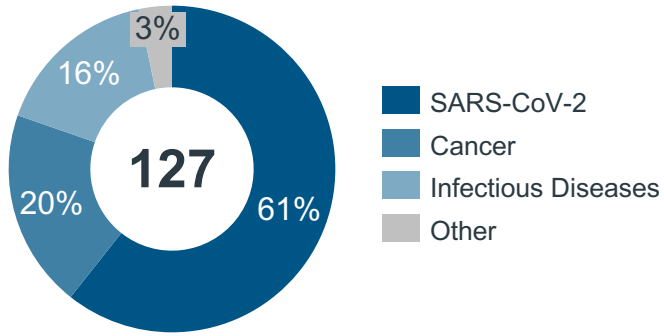
CLINICAL TRIAL PIPELINE

Number of Clinical Trials By **Development Phase**



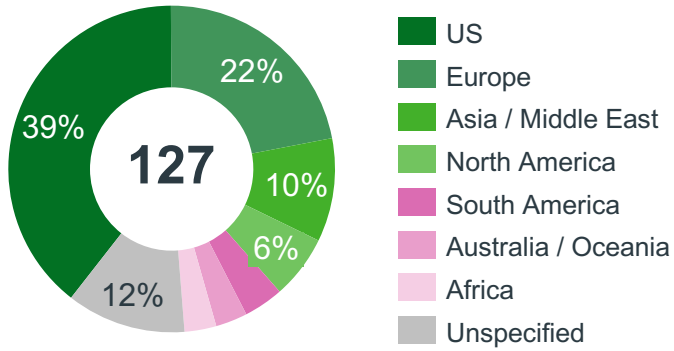
- There are currently **~127 trials** studying the possible use of mRNA vaccines, representing **a 273% increase** in the total number of trials studying this technology since 2020
- Due to the COVID-19 pandemic animating this landscape, **13 of the 19 Phase 3** clinical trials are investigating **COVID-19 vaccinations**

Number of Clinical Trials By **Indication**



- Due to the COVID-19 pandemic, the number of active clinical trials in phases 2 & 3 investigating mRNA for **SARS-CoV-2** has increased **~1'867% from 3 to 59**
- Infectious diseases and cancers are **key areas of public concern and therapeutic innovation**

Number of Clinical Trials By **Geographic Split**



- Trials for mRNA vaccines are also **happening globally**, across all continents, with the majority of trials happening **in the US and Europe**

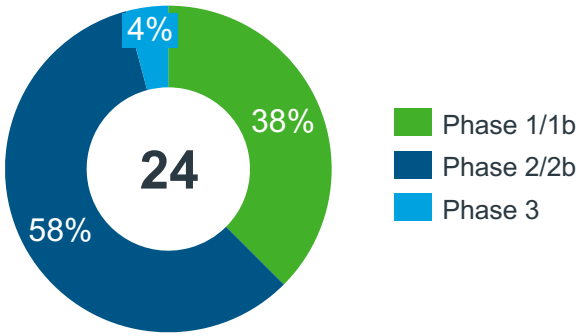
Source: IQVIA Data Analysis, clinicaltrials.gov

Abbreviations *– Link to Glossary*

Within cancer research, mRNA vaccines offer promise as a treatment for Glioblastoma

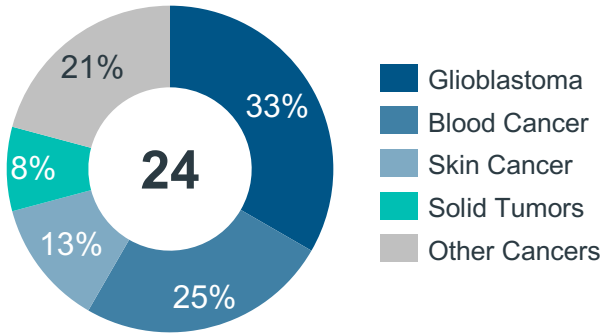
CLINICAL TRIAL PIPELINE

Number of Clinical Trials By **Development Phase**



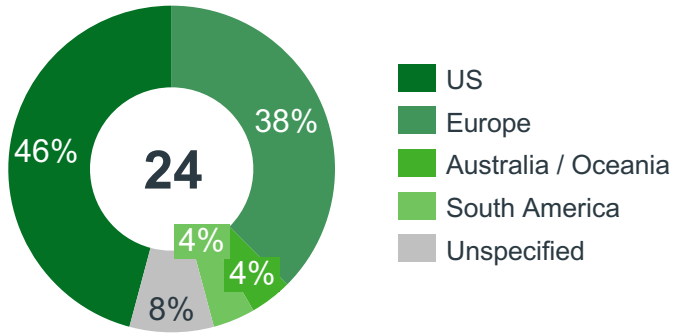
- There are currently **~24 trials** studying the possible use of mRNA vaccines as preventative and acute cancer treatments
- As it remains a **highly innovative** and **new** area, the **majority of these trials are in Phase 1 and Phase 2**

Number of Clinical Trials By **Indication**



- mRNA vaccines are being developed for a broad range of different cancers
- **Glioblastoma and blood cancers** are the two areas with the highest activity
- Glioblastoma represents **100% of brain cancer studies** and will be of primary focus in this review

Number of Clinical Trials By **Geographic Split**



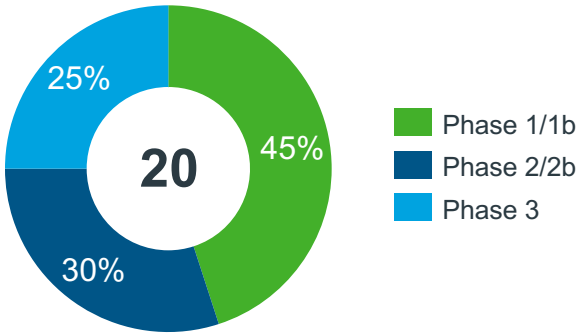
- Trials for mRNA vaccines being developed for cancers are **happening predominantly in the US and Europe**

Note: Active trials refers only to active mRNA vaccine for cancer trials and Phase 1|Phase 2 are categorised as Phase 2 trials, and Phase 2| Phase 3 trials are categorised as Phase 3 trials
Source: IQVIA Data Analysis, clinicaltrials.gov

The landscape for infectious diseases is also very rich with a broad range of indications being investigated

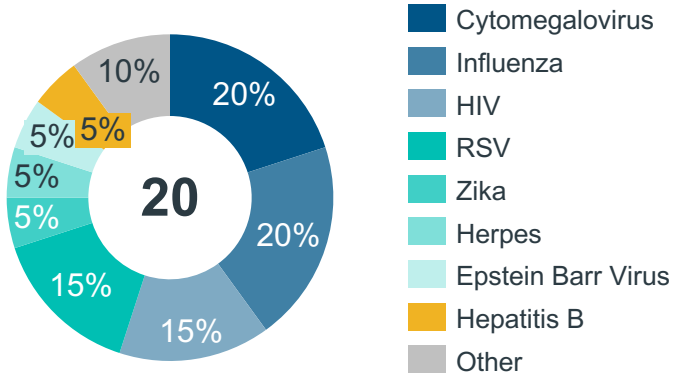
CLINICAL TRIAL PIPELINE

Number of Clinical Trials By **Development Phase**



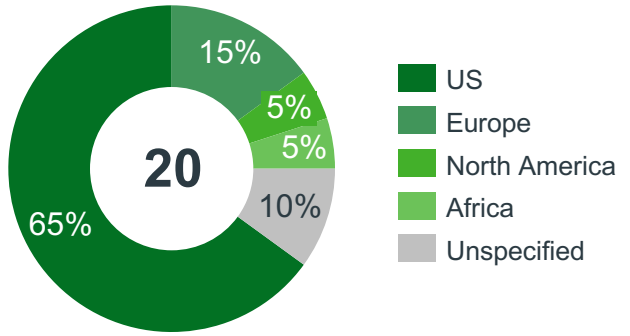
- There are currently **~21 trials** studying the possible use of mRNA vaccines as preventative and acute treatments for infection diseases
- Given the success of the COVID-19 vaccines there are already some Phase 3 trials for other indications

Number of Clinical Trials By **Indication**



- mRNA vaccines are being developed for a broad range of different infectious diseases
- **RSV, Cytomegalovirus, HIV and Influenza** are currently the areas with the highest activity
- A snapshot updated is included for RSV in this review

Number of Clinical Trials By **Geographic Split**

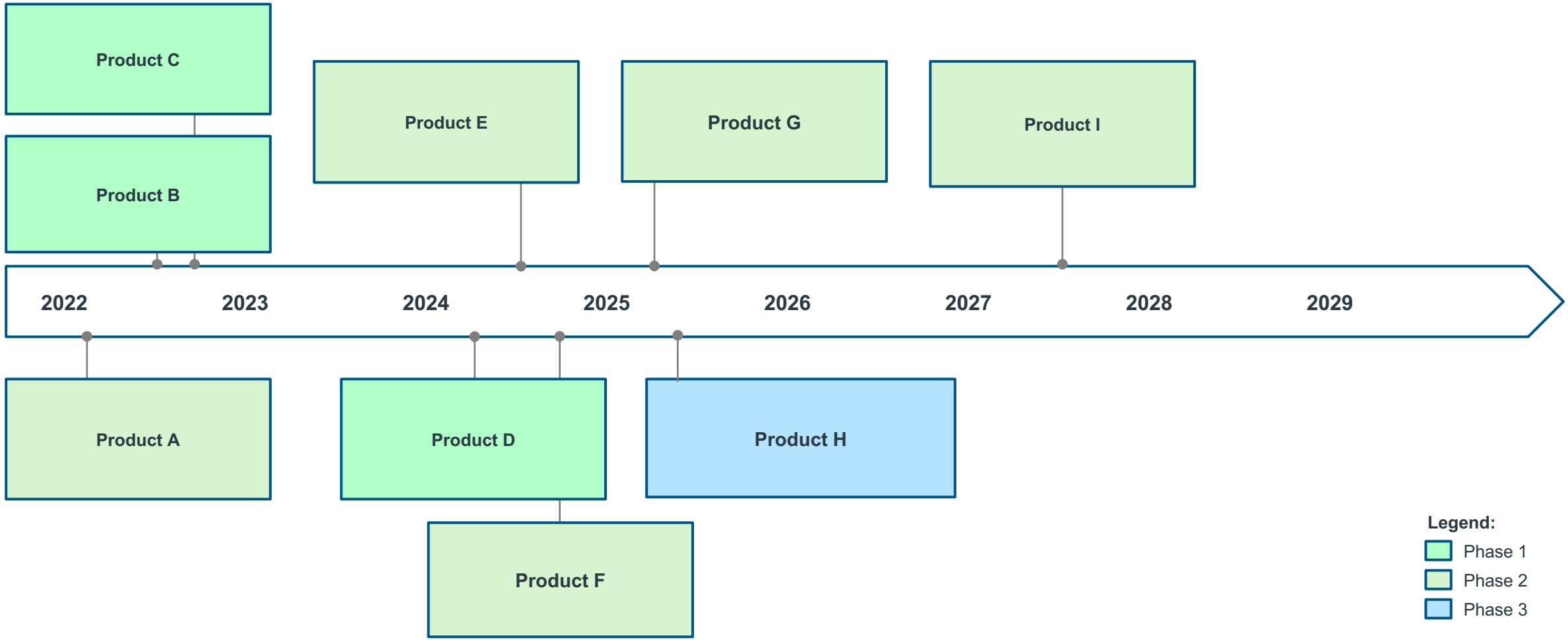


- Trials for mRNA vaccines being developed for infectious diseases are principally happening **in the US**

Note: This analysis excludes COVID-19 trial sas they are discussed in the Pipeline Overview chapter and to allow for a closer examination of other infectious diseases in the mRNA vaccine pipeline
Note: Active trials refers only to active mRNA vaccine for infectious diseases trials and Phase 1|Phase 2 are categorised as Phase 1 trials, and Phase 2| Phase 3 trials are categorised as Phase 2 trials
Source: IQVIA Data Analysis, clinicaltrials.gov

mRNA vaccines for Glioblastoma remain a highly innovative area of research with a definitive cure a long way ahead

2022 mRNA GBM VACCINE PIPELINE: ESTIMATED TRIAL COMPLETION DATES

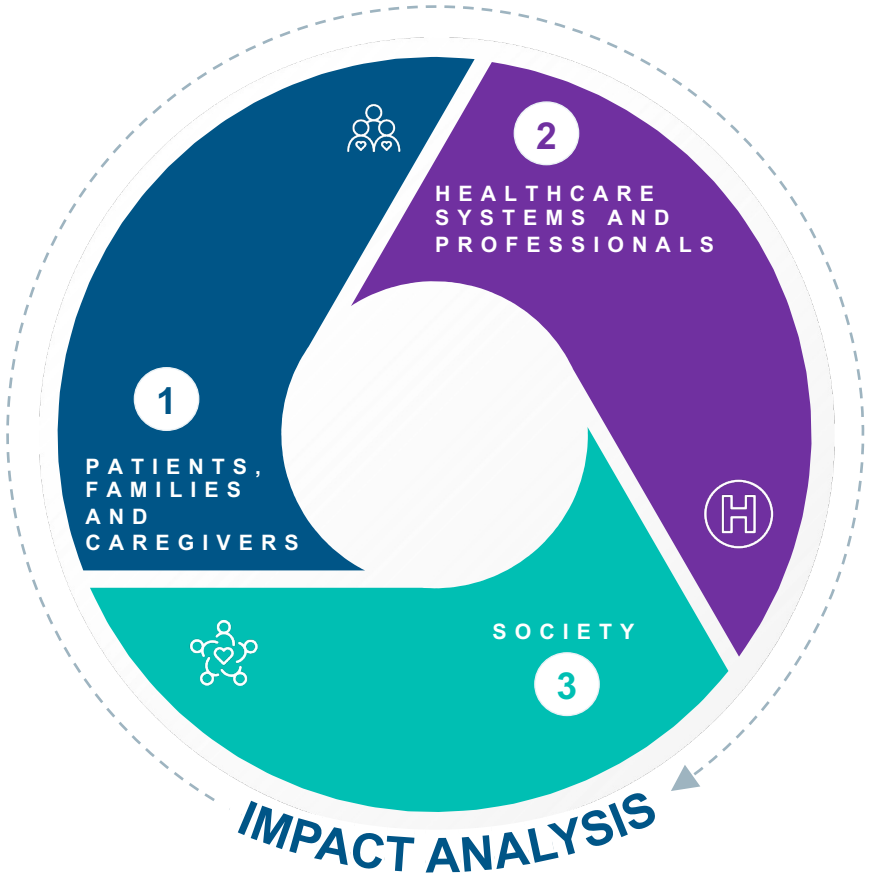


Source: Clinicaltrials.gov; October 2022, active clinical trials (Not yet Recruiting, Recruiting, Enrolling by invitation, Active not recruiting), Excluded trials without specified phase, Device trials

Abbreviations *- Link to Glossary*

An mRNA vaccine for glioblastoma would offer patients longer term survival, impacting healthcare systems and society

IMPACT ANALYSIS



1

PATIENTS, FAMILIES, AND CAREGIVERS

Significant improvements in expected survival translates into longer and healthier lives, sparing families and patients from the emotional and physical distresses of current therapy

2

HEALTHCARE SYSTEMS AND PROFESSIONALS

Alleviating hospital based healthcare burdens by reducing the need for palliative and surgical care from oncologists freeing up resources that can be used to diagnose and treat more patients faster and more effectively

3

SOCIETY

Patients survive long term allowing them to return to work reducing the care burden on families and friends, who will also need to take less time off from their work or other responsibilities

Longer term survival would spare patients and families the emotional distress endured from current therapy

1

PATIENTS	CURRENT STATE	FUTURE STATE
Life Expectancy	• Glioblastoma patients have **low survival rates** – following diagnosis, 25% of patients survive more than 1 year and only 3% to 5% of patients survive more than 5 years • **Surgery, radiation therapy, and chemotherapy with temozolomide** remain the SoC for majority of patients	• Potential for **larger proportion of patients to experience long term survival** will allow patients **more time with friends and family** (see following slide) • Based on KOL opinion a **35% OS rate** could be achievable with mRNA vaccines
Quality of Life	• Current therapeutic options are known to **significantly impact QoL given invasiveness (surgery) and toxicity** • Patients and their families often experience **depression upon diagnosis**	• **Reduction in emotional distress for patients and families** and fewer patients relying on toxic chemotherapy
Financial Pressure	• The mean overall **indirect cost** of Glioblastoma care for patients in Europe was **€20,588 per year** causing financial pressure and emotional stress due to financial burden[2]	• Potentially curative effect / prevention of progression of certain mRNA vaccines could dramatically **reduce treatment-related costs** and even see patients returning to work

Note: SoC: Standard of Care, QoL: Quality of Life, KOL: Key Opinion Leader, OS: Overall Survival
Source:; (1) PubMed; (2) Journal of Neuro-Oncology, American Cancer Society, Neuro Oncol., European Journal of Cancer, CORDIS, Front Pharmacol., Value in Health Journal, Journal of Medical Economics,

Healthcare systems would also benefit due to the reduced burden patients place on inpatient services

2

HC SYSTEMS

HOSPITAL UTILISATION

CURRENT STATE

- Surgery for glioblastoma can greatly **improve a patient's prognosis and quality of life**
- However, this requirement for **comprehensive neurosurgical treatment** places a **large burden on healthcare resources**
- The mean overall cost of Glioblastoma care for patients in Europe treated with surgery and/or chemotherapy was **€ 50,389 per year**

FUTURE STATE

- Increased number of patients experiencing long term survival would see **fewer patients requiring surgical care, palliative care, or overnight stays**
- **Longer OS of mRNA vaccines** vs. the standard of care could result in reduced hospital visits for glioblastoma patients, and thus – a **reduction in waiting times for hospital beds** and **increased availability of healthcare practitioners**

Treatment	Avg. total cost of treatment / patient / year	Total cost of treatment per year for all GBM patients in EU	Total lifetime surgery cost for all GBM patients in EU	Total Lifetime Cost for all GBM patients in EU
Current Therapy (chemo + surgery)	€ 45,165	~€ 288 million	~€ 72 million	**~€ 360 million**

Direct cost associated with current treatment

Note: OS: Overall Survival, GBM: Glioblastoma
Source: American Cancer Society, Neuro Oncol., European Journal of Cancer, CORDIS, Front Pharmacol., Value in Health Journal, Journal of Medical Economics,
IQVIA | EFPIA Pipeline Innovation Review 2022

Abbreviations – *Link to Glossary*

By providing a long-term treatment option for the disease, more patients could return as productive members of society

3

SOCIETY	CURRENT STATE	FUTURE STATE
PRODUCTIVITY LOSS	• **Poor long-term survival** and **high risk of progression** means that many patients do not return to work following a diagnosis* • The total mean indirect cost (the cost associated with a loss of productivity due to the disease) is estimated to be **€ 111,926 per patient**[1]	• More patients could survive-long term **allowing patients to return to work, pay taxes and actively contribute towards society** • *E.g. for glioblastoma patients diagnosed in 2022; an **estimated €46m could be generated in GDP each year***
OPPORTUNITY COST	• **Decline in economic productivity/tax revenue** from friends/family due to time taken off work due to - **Care for or time spent with patients** following a terminal diagnosis - Depression associated with impending or subsequent **death of a loved one**	• By **improving long term survival**, the number of families taking time off to care for a loved one, and the associated impact on economic productivity, will decline

Note: (*) assumes ~29% of patients are diagnosed under the age of 65 based on KOL estimates in NSCLC (Non-Small Cell Lung Cancer), GDP (Gross Domestic Product)
Source : (1) Neurología (English Edition), American Cancer Society, Neuro Oncol., European Journal of Cancer, CORDIS, Front Pharmacol., Value in Health Journal, Journal of Medical Economics,

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BiTEs promise to extend healthier, more productive lifespan for patients, with significant downstream impacts on healthcare systems and society

EXECUTIVE SUMMARY

01 TECHNOLOGY & PIPELINE ASSESSMENT

- **Bispecific T-cell engagers (BiTEs)** are a new class of **cancer immunotherapy** that enhance a patient's immune response to cancer tumours by triggering the programmed cell death of cancer cells (apoptosis)
- A **nascent field of research**, the clinical trial pipeline of BiTEs in Multiple Myeloma is largely concentrated in early stages of development, with no Phase 3 trials currently underway

02 INDICATION ASSESSMENT

- **Multiple Myeloma** is a rare cancer of the plasma cells in bone marrow tissue, that affects approximately **125,000 patients in EU** with a 10-year survival rate of 29%
- The cancer often affects **multiple areas of the body** such as the skull and spine, and eventually causes a deterioration of a patient's immune response resulting in recurring infections

03 IMPACT ANALYSIS

- The curative potential of BiTEs may allow people to live longer, healthier, more productive lives, with significant downstream impacts on healthcare systems and society
- **Patients, families and caregivers:** Demonstrated improvements on patients' survival above the current therapy improving lives and reducing emotional distress
- **Healthcare systems:** As "off-the-shelf" treatments, BiTEs have proven to also be cheaper than next generation therapy, reducing the cost of treatment for healthcare systems
- **Society:** With the promise of extending survival rate of patients and enabling them to return to work, BiTEs for RRMM could result in a +€ 500 million of annual GDP saved per year in Europe

Abbreviations – Link to Glossary

BiTEs show promising signs of being an effective off-the-shelf treatment for cancers by triggering an immune response to tumour cells

AN OVERVIEW OF BI-SPECIFIC T-CELL ENGAGERS (BiTEs)

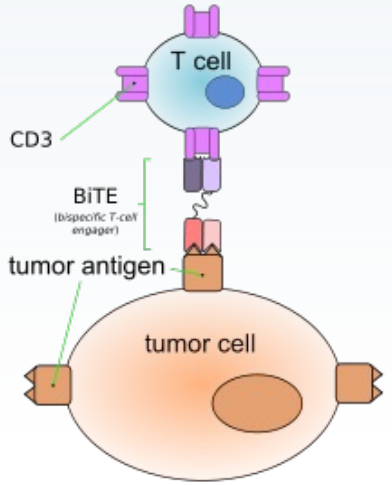
BiTEs

- New class of artificial bispecific monoclonal antibodies used in cancer immunotherapy that **engage a patient's immune response** to target tumour specific cancer cells **by forming a link between a patient's T cells and tumour cells** - triggering tumour cell apoptosis (programmed cell death)
- **No need for *ex vivo* specific engineering** of a patients T cells (as is needed for CAR T therapy) and as a result could be **deployed quickly** as "*off-the-shelf*" treatment without any delays
- Currently being investigated in preclinical and clinical trials across oncology with Blinatumomab being the first **FDA approved** therapy for adults with RRALL being a good portend

Mechanism of Action

- BiTEs link tumour cells and T-cells by leveraging two variable domains (one to target tumour specific antigens and the other on the surface of T-cells)
- By leveraging these domains, BiTEs are **designed to find cancer specific antigens** on the surface of cancer cells eliminating the need for antigen processing, presentation & recognition by T-cells
- Once binded, **T-cells in close proximity to the BiTE associated cancer cells are recruited** through the other binding arm of the BiTE molecule
- Subsequent, **T-cell activation resulting in cytotoxic activity on tumour cells** by releasing proteins that enter the tumour cell and initiate the cell's apoptosis

BiTEs link T-cells and cancer cells(5)



Note: BiTEs (Bi-specific T-cell Engagers), RRALL (Relapsed or Refractory Acute Lymphoblastic Leukaemia)
Source: (1) Targeted Oncology, (2) Journal of Hematology & Oncology, (3) blood advances, (4) AMGEN, (5) Diagram

Multiple myeloma is a rare disease, it is the second most common blood cancer, with a significant morbidity due to end-organ destruction

Multiple Myeloma (MM) and Relapsing/Refractory MM (RRMM)

A rare type of bone marrow cancer. Bone marrow is the spongy tissue at the centre of some bones that produces the body's blood cells. This cancer also often affects several areas of the body, such as the spine, skull, pelvis and ribs.

125,000[1]

Patients in EU (2.4:10,000)

1% of all cancers and 15% blood cancers

Patient type

Affect adults of any age, but it is much more common in people aged over 65 years, and in men rather than women[2]

Quality of Life

Continuous administration of maintenance medication involves long-term side effects, both physical and emotional[3]

€31,500[4,5]

Annual COI / patient

Drug costs are the main contributor[5]

High Burden Disease

Associated with significant morbidity due to end-organ destruction

- MM is characterized by the **malignant transformation and proliferation of plasma cells** that accumulate in the bone marrow and overcrowd normal cells, leading to bone lysis and fractures
- Myeloma cells produce M protein instead of antibodies. The accumulation of M protein can make blood more viscous and can be deposited in organs such as kidney nerves and immune systems
- 30% of patients are diagnosed incidentally while being evaluated for unrelated problems, having 1) clonal bone marrow plasma cells >10 % and 2) signs of end-organ damage
- The success and approval of Blinatumomab, a targeted immunotherapy treatment for ALL, in Europe is encouraging for other BiTEs in the pipeline focusing on the relapsing form RRMM

Staging

- **Smouldering Melanoma:** increased plasma cells in bone marrow and the presence of M protein, without the presence of symptoms. Treatment is a 'watch and wait' approach
- **Stage 1** (Average survival 62 months): Relatively small number of myeloma cells with slightly elevated beta-2 macroglobulin levels (indicates renal filtration disorders) and albumin may have decreased (indicates liver damage and/or inflammatory disease)
- **Stage 2** (Average survival: 44 months): Intermediate stage if levels fall between Stage 1 and 2
- **Stage 3** (Average survival: 29 months): Number of myeloma cells is high, high levels of beta-2 macroglobulin and low albumin

Note: COI (Cost of Illness)

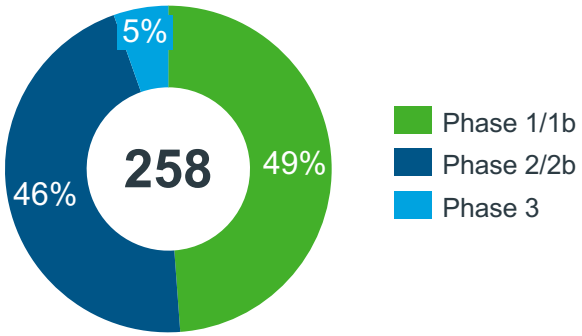
Source : (1) The brain tumour charity; (2) Mofitt Cancer Center; (3) Long Term Survival in Glioblastoma; (4) Vaccination in the immunotherapy of GBM; (5) Journal of Neuro-Oncology

Abbreviations *- Link to Glossary*

BiTEs are a novel and highly innovative mechanism of action currently being research predominantly for cancer globally

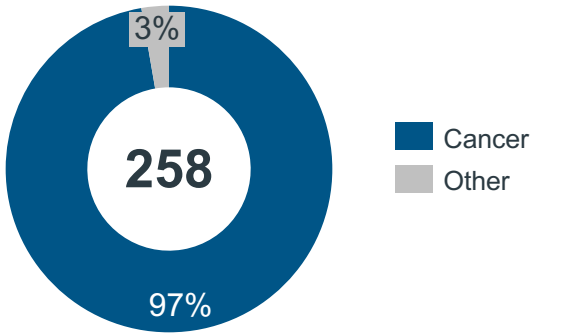
CLINICAL TRIAL PIPELINE

Number of Clinical Trials By **Development Phase**



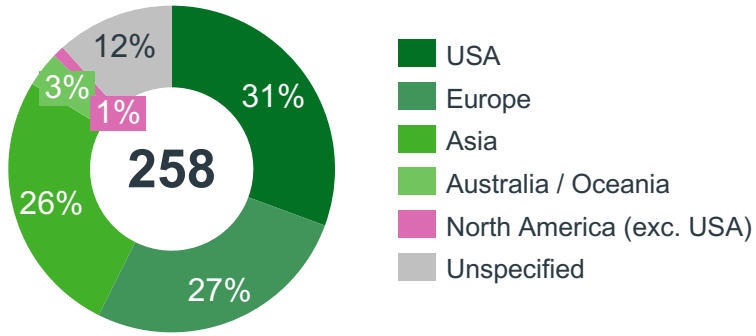
- There are currently **~258 trials** studying the possible uses of BiTEs
- The majority of the clinical trials are currently evenly split between **Phase 1 (~49%) and Phase 2 trials (~46%) with only 14 Phase 1 trials (~5%)** – this is in part due to the fact that BiTEs are a novel technology

Number of Clinical Trials By **Indication**



- Cancer dominates the BiTEs clinical trial pipeline – accounting for approximately **97% of all trials**
- BiTEs are **key areas of research for cancers** due to their **potential as a *off-the-shelf* curative therapy**

Number of Clinical Trials By **Geographic Split**



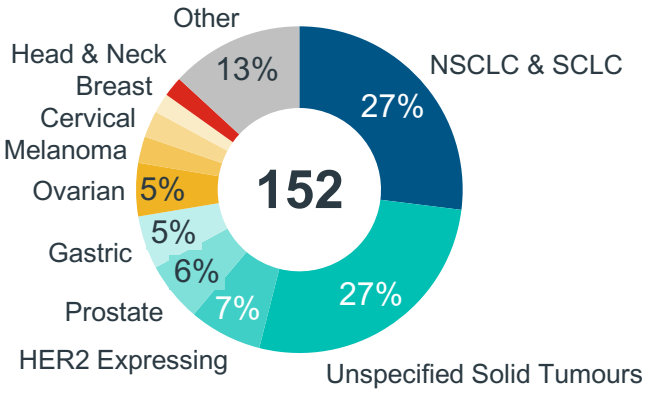
- Trials for mRNA vaccines are also **happening globally**, across all continents, with the majority of trials happening **in the USA followed closely by Europe and Asia**

Note: (1) Infectious Diseases include Mycosis Fungoides and HIV, (2) Disorders include Down Syndrome
Source: IQVIA Data Analysis, clinicaltrials.gov

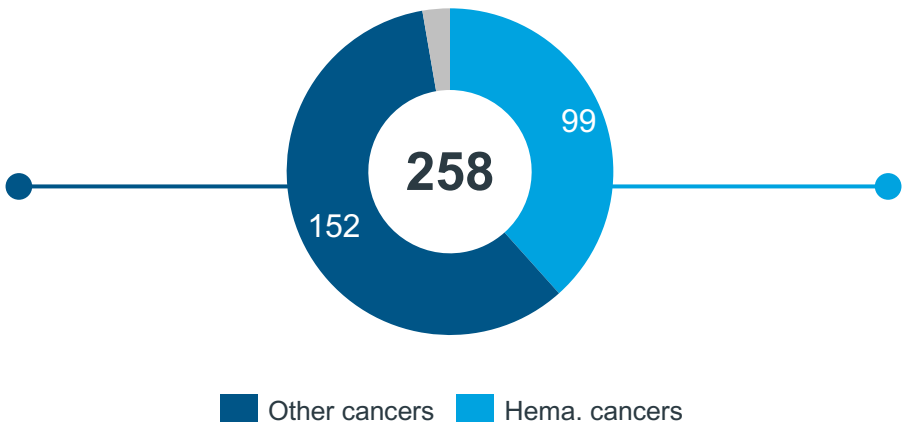
Abbreviations *– Link to Glossary*

Hematological cancers are among the most researched in the BiTE pipeline accounting for approximately 40% of all cancer specific trials

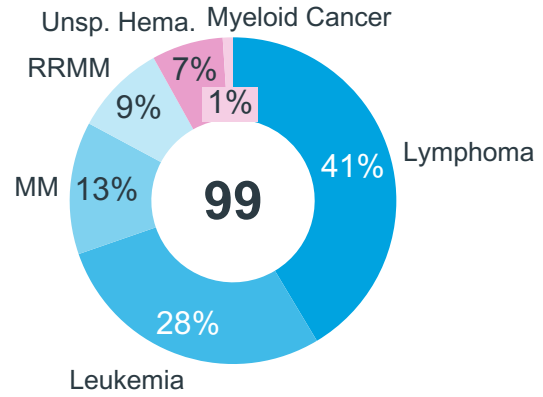
Number of Clinical Trials for **Other Cancers**



Current active BiTE clinical trials



Number of Clinical Trials for **Hematological Cancers**



- **Excluding hematological cancers, trials in NSCLC & SCLC** account for the largest share of clinical trials – **approximately 27% of all trials**
- Beyond NSCLC & SCLC, BiTEs are being researched for **a broad range of other solid tumours**

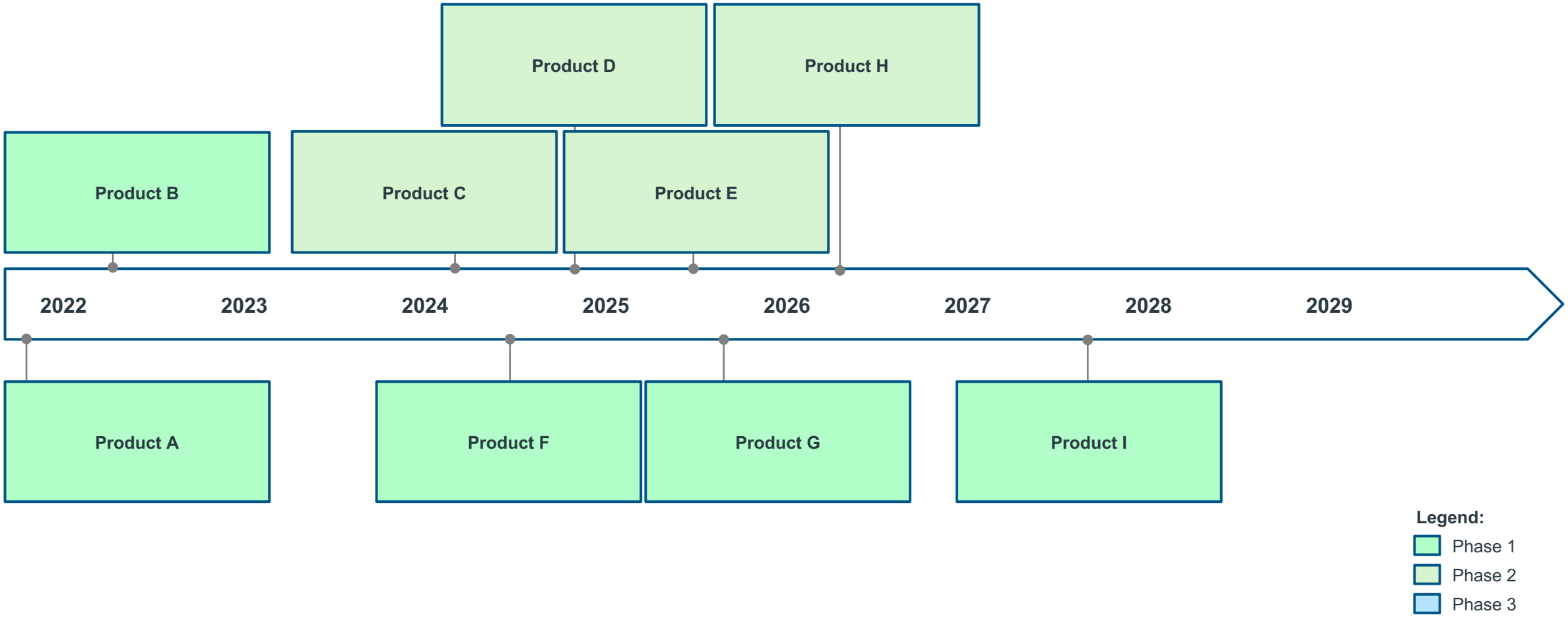
- **Blinatumomab** (BiTE) has been **approved for the treatment of ALL**(1) and demonstrated a clinical response for Lymphoma patients(2)
- MM / RRMM currently has a **large unmet need** and boasts a **robust research pipeline**

Note: MM (Multiple Myeloma), RRMM (Relapsed / Refractory Multiple Myeloma), Unsp. (Unspecified), Hema. (Haematological)
Source: IQVIA Data Analysis, (1) Journal of Hematology & Oncology, (2) Journal of Hematology & Oncology

Abbreviations *- Link to Glossary*

BiTES vaccines for Relapsing/Refractory Multiple Myeloma remains a highly innovative area of research with a definitive cure a long way ahead

2022 BiTEs THERAPY PIPELINE: ESTIMATED TRIAL COMPLETION DATES

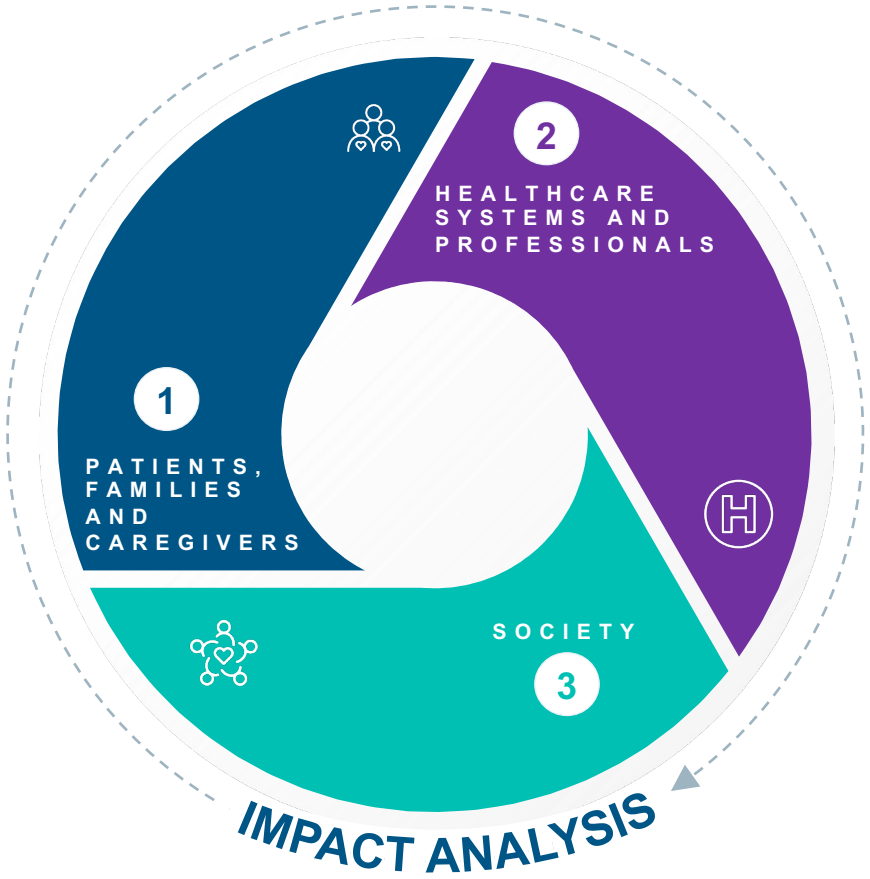


Source: clinicaltrials.gov; October 2022, active clinical trials (Not yet Recruiting, Recruiting, Enrolling by invitation, Active not recruiting), Excluded trials without specified phase, Device trials

Abbreviations *- Link to Glossary*

The potential BiTEs offer as a treatment holds great promise for patients, healthcare systems and society

IMPACT ANALYSIS



1 PATIENTS, FAMILIES, AND CAREGIVERS

BiTEs have the potential to become a life saving therapy for patients suffering from Multiple Myeloma, ensuring longer term survival and a reducing in emotion distress for patients and families as a result of the reduce exposure to current toxic treatments

2 HEALTHCARE SYSTEMS AND PROFESSIONALS

Hospitalisation costs could decline, as patients will no longer require lengthy burdensome stays in hospital, clinician attendances or stem cell transplants – benefits that could further be enhanced with future generation BiTEs (including combination therapy)

3 SOCIETY

The curative potential of BiTEs may allow people to live longer, healthier, more productive lives; rather than dying early or suffering from a debilitating disease treated patients can work, pay taxes and contribute to GDP

Note: BiTE (Bispecific T-cell Engager), GDP (Gross Domestic Product)
Source : IQVIA internal expertise, NCBI paper

Compared to CAR Ts and the Standard of Care, BiTEs have already delivered on their potential

1

PATIENTS

BiTEs (AMG-701 & AMG-420) vs. CAR T (Abecma) vs. 1L SoC (Bortezomib) in Multiple Myeloma

83% vs. 73% vs. 67%

Overall Response Rate

The response rate was 83%[1] for patients treated with AMG-701 in the most recent cohort, compared to 73% for Abecma[2] and 67% for Bortezomib[3]

23.5 vs. 8.6 vs. 6.5 months

Progression Free Survival

The PFS was 23.5 months for patients receiving 7 cycles of AMG420[4] as compared to 8.7 months[2] for patients treated with Abecma and 6.5[5] for patients treated with Bortezomib monotherapy

Notes : Comparison is not based on a head to head trial. Instead figures are based on clinical trial readout of BiTE for Multiple Myeloma (MM), and Birstol Myers Squibb (BMS)'s approved CAR T for MM - Abecma
Source : (1) AMGEN, (2) BMS, (3) PubMed, (4) ASH Publications, (5) PubMed

BiTEs have proven to be as effective and more cost efficient than current ground-breaking CAR T therapy

2

HEALTHCARE SYSTEMS

HEALTHCARE SYSTEM BENEFITS

- In contrast to CAR Ts, BiTEs are “off the shelf” treatments that can be manufactures in large quantities without patient specific considerations, and as a result, they are **rapidly deployed**[1]
- For the aforementioned reasons, **BiTEs compare favourable to CAR Ts** once the costs of production, logistics, treatment, days of hospitalization and short- and long-terms adverse events are considered[1]
- Therefore, in line with CAR T predictions, **current expenditure on targeted therapy could decline by more than ~55-100%** following displacement of high-cost salvage and maintenance treatment paradigms in the relapsed/refractory setting
- **Expenditure on Sarcococcygeal Teratomas (SCTs) could also decline significantly**
- **Hospitalisation costs may also decline** as a patient survives longer; depending on required setting for long term follow ups

Assessment criteria	RRMM (BiTE)	RRMM (CAR T)
Expenditure Estimates	€ 225,904	€ 350,000
% increase treatment expenditure with CAR Ts	+55%	
Number of patients cured	12,092	7,613
% increase in number of patients cured with BiTEs	+59%	

Notes : RRMM (Relapsed/Refractory Multiple Myeloma), ALL (Acute lymphoblastic leukaemia) , SCTs (Sarcococcygeal Teratoma)
Source : (1) NIH, NICE, cancernet, Journal of Medical Economics, EMA, NICE

Abbreviations – *Link to Glossary*

The knock-on effect of an approved BiTE for RRMM would be seen in increased participation in society, and an increase in annual nominal GDP

3

SOCIETY

IMPACT ON SOCIETY

- The success BiTEs have had in treating ALL (a haematological cancer comparable to Multiple Myeloma), with an estimated 2-year survival rate of over 90% is a good portend for the opportunity of BiTEs in treating Multiple Myeloma with the consequence of more people being able to actively contribute to economic productivity
- In ALL this would result in an additional annual contribution of ~€200 million to nominal GDP[1] across the EU for all patients diagnosed in 2020 *(EU GDP in 2013 was €13,07 trillion)* and an estimate **~€1 billion if the same results are seem for Multiple Myeloma**
- BiTEs will also reduce the burden patients themselves place upon relatives and welfare systems
  - Relatives will have to take less leave to care for loved ones allowing them in turn to contribute further to economic productivity
  - Patients that do experience a complete response will no longer require welfare support following debilitating chronic treatment

Assessment criteria	RRMM (BiTE)	RRMM (CAR T)
Total Life Years gained (across EU)	36,275	22,840
EU nominal GDP saved per year	+€ 500 million	+€ 300 million
increase in saved GDP per year with BiTEs	+33.3%	

Notes : Relapsing/Refractory Multiple Myeloma (RRMM), MM (Multiple Myeloma), ALL (Acute lymphoblastic leukaemia)
Source : (1) NIH, NICE, cancernet, Journal of Medical Economics, EMA, NICE

Table of Contents

Remyelinating therapies have the potential to delay, prevent or reverse/improve disability in Multiple Sclerosis (MS)

EXECUTIVE SUMMARY

01 TECHNOLOGY & PIPELINE ASSESSMENT

- Remyelinating treatments in development have the potential to delay, prevent or reverse/improve disability in MS by restoring function to nerve cells affected by the disease
- There are several remyelinating therapies in Phase 2 most focusing on Relapsing Multiple Sclerosis (RMS) / Relapsing-Remitting Multiple Sclerosis (RRMS); key trial results are expected in 2022 / 23

02 INDICATION ASSESSMENT

- Multiple Sclerosis affects more than 700,000 patients in Europe, placing a heavy burden on patients, caregivers and HC systems
- RRMS is the most common course of the disease characterized by relapses and remission, the severity and frequency of which varies significantly between patients

03 IMPACT ANALYSIS

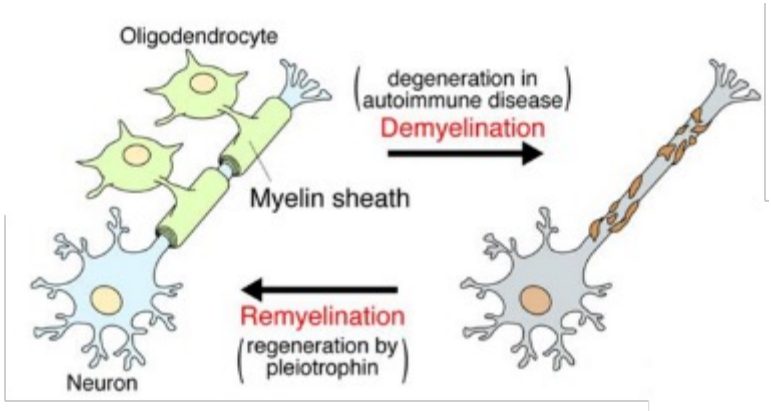
- By reversing or improving disability, remyelination promises to improve the lives of patients and bring benefits to broader society
- **Patient, families and caregivers:** Remyelinating therapies have the potential to increase the quality of life of MS patients by reducing or improving their levels of mobility, cognition, and vision
- **Healthcare systems:** As remyelinating therapies are likely to be used as add-on treatments or in combination with other therapies they may generate incremental costs for healthcare systems
- **Society:** Disability and functional improvements will reduce social costs related to home care, transportation, etc., along with increase workforce participation rate among MS patients

Remyelinating therapies have the potential to delay, prevent or reverse/improve disability in Multiple Sclerosis

Introduction to Remyelinating Therapies

- **Multiple Sclerosis is a demyelinating disease - demyelination** is damage caused by the immune system to myelin, the protective covering around nerve fibres. When myelin sheaths are damaged, the conduction of electrical impulses along the nerve cells is impaired, which negatively affects a number of downstream neurological functions
- **Remyelinating treatments in development have the potential to delay, prevent or reverse/improve disability in MS** by repairing demyelinated lesions in the brain and spinal cord and restoring function to nerve cells affected by the disease[1];
  Remyelination not only leads to formation of new myelin sheath around axons (and restoration of electric conduction along them), but also reduces neurodegeneration, which directly impacts clinical disability[2]
- There is significant pre-clinical activity, as well as a number of ongoing clinical studies, assessing potential remyelinating therapies which **hold promise for the first MS treatment to partially reverse the disease's effects** on patients[2]
- **Some of the remyelinating therapies are also being investigated in Parkinson's Disease and Amyotrophic Lateral Sclerosis;** however, in these cases the proposed mechanism of action is different. As these diseases are caused by degeneration and death of neurons, the therapies focus on preventing the loss of mitochondria and improving the survival of dopaminergic (PD) and motor (ALS) neurons[3]

Demyelination and Remyelination



Source: Multiple Sclerosis News Today (4)

Current therapies only reduce CNS inflammation, decreasing the frequency of attacks and preventing further damage; remyelination has the potential to repair the damage made to myelin sheaths protecting axons

Note: MS; Multiple Sclerosis; ALS; Amyotrophic lateral sclerosis; PD: Parkinson's Disease

Multiple Sclerosis (MS) affects more than 700,000 patients in Europe, placing a heavy burden on patients, caregivers and HC systems

Multiple Sclerosis

Multiple Sclerosis is a chronic demyelinating disease, in which the immune system attacks and damages the myelin sheath on nerve fibers in the brain and spinal cord causing fatigue, vision problems, muscle spasms, stiffness and weakness, mobility problems and pain[1].

750,000

Patients diagnosed in EU

(108 per 100,000 population)

Patient type

Often diagnosed in people in their 20s and 30s (average of 29), 3:2 more common in women than men

Quality of Life

Significant negative impact on mental and physical HRQoL*

€7.9 billion

Annual HC cost

and further social and economic costs

High Burden Disease

Relatively young age at diagnosis, with half of patients usually not able to work after first three years

- MS is one of the most common neurological conditions in Europe and the **leading cause of non-traumatic disability in young adults**, with symptoms ranging from fatigue and depression, to severe mobility problems and blindness in extreme cases[2]
- **Relapsing-remitting MS** is the most common course of the disease (80% of patients), characterised by periods of new or worsening symptoms (relapses) followed by periods of stability or recovery (remission); the severity and frequency of relapses varies significantly between patients, but on average occur once or twice per year[3]
- **MS diminishes patients' QoL** by interfering with their physical and occupational functions, psychological state, as well as social interactions[4]; workforce participation of MS patients decreases from ~80% in the initial disease stages to less than 10% in the late stages[2]
- In addition to the high therapy costs (drugs for MS and co-morbidities), **social costs associated with MS are high** because of lifetime duration, early loss of productivity, the need for assistance in daily activities and multidisciplinary health care[5]
- There are a number of available **disease modifying drugs** for the treatment of active** relapsing-remitting multiple sclerosis that focus on reducing the risk of relapse, with less options available for secondary progressive and primary progressive disease[6]

(*) HRQoL – Health Related Quality of Life; (**) At least two clinically significant relapses within the last 2 years

Source: (1) NHS (2) EMSP (3) NICE (4) AJMC (5) PubMed (6) NICE

IQVIA | EFPIA Pipeline Innovation Review 2022

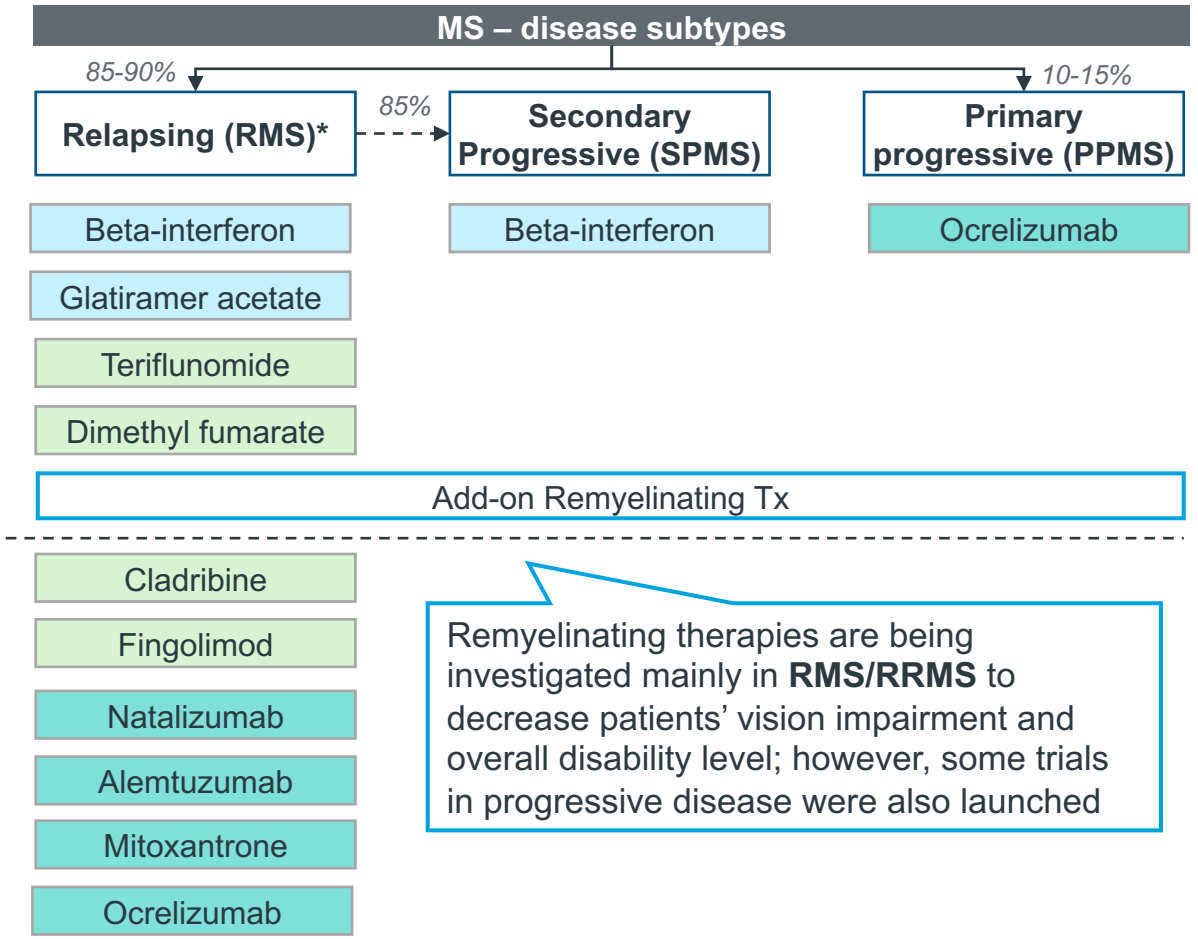
Abbreviations *- Link to Glossary*

Remyelinating therapies will likely be added-on to current anti-inflammatory disease modifying therapies

Promise of remyelinating therapies vs. anti-inflammatory DMTs

- **Current MS treatments** focus on preventing relapses, supporting patients' recovery after the attacks and, in general, slowing disease progression[1]
- Anti-inflammatory disease modifying therapies (ocrelizumab for PPMS and numerous options for RMS/RRMS) can slow down disease progression and prevent future damage; **however, they are not able to effectively reverse this damage**[2]
- The key promise of remyelinating therapies is their potential to **repair the myelin sheath damaged by MS and therefore restore some of the patients' key functions**, such as mobility, cognition or vision
- Currently ongoing trials are investigating potential remyelinating agents in multiple sclerosis, mainly as **combination and add-on therapies** for RMS/RRMS and vision disorders related to MS
- In summary, **remyelinating drugs are not likely to displace** the currently used disease modifying therapies, but will rather bring additional value on top of the existing standard of care

Current vs. 'Future' Treatment Paradigm



Abbreviations: RMS covering CIS (Clinically Isolated Syndrome), RRMS (relapsing-remitting), active SPMS; DMT – disease modifying therapy, RR – relapsing-remitting, SP – secondary progressive, PP – primary progressive

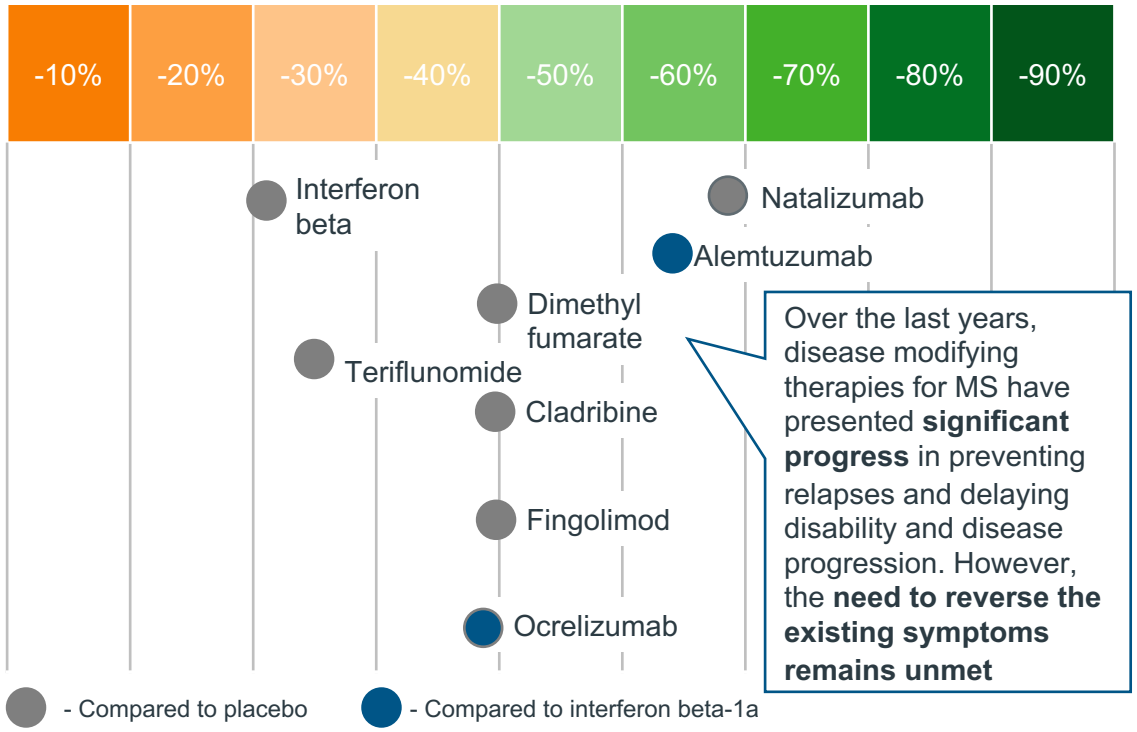
Source: (1) Multiple Sclerosis News Today (2) Nature.com (3) Parkinson's News Today

While disease-modifying therapies focus on delaying progression, remyelination promises to restore mobility, cognition and vision

Efficacy of current therapies

The efficacy of current disease modifying therapies is focused on preventing relapses and delaying disability and disease progression …

Efficacy of current selected DMTs –
% decrease in annualized relapse rates



Over the last years, disease modifying therapies for MS have presented **significant progress** in preventing relapses and delaying disability and disease progression. However, the **need to reverse the existing symptoms remains unmet**

Added value of remyelinating therapies in development

…whereas the potential value of remyelinating therapies lies primarily in reversing disability, thereby improving the quality of life of MS patients

Improvement in visual impairment related to MS (chronic optic neuropathy)

- Positive preliminary results in low-contrast vision improvement as determined by LCLA test (low-contrast letter acuity)
- Based on phase 2 VISIONARY-MS trial for CNM-Au

Improvement in functional ability, as per Multiple Sclerosis Functional Composite (MSFC) sub-scales:

- Cognition, upper extremity function, gait
- Based on phase 2 VISIONARY-MS trial for CNM-Au

Overall disability improvement

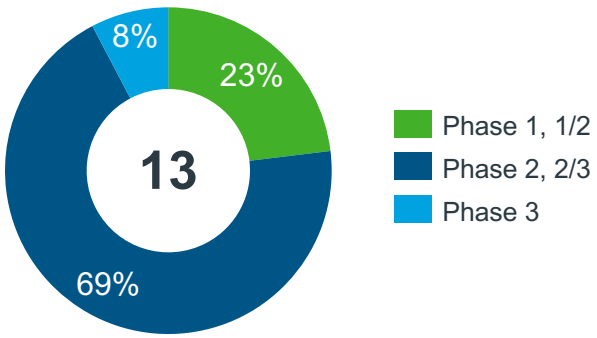
- Measured with Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk, Nine-Hole Peg Test and the three-second Paced Auditory Serial Addition Test
- Based on phase 2 SYNERGY trial for opicinumab (results not conclusive) and AFFINITY trial results

Abbreviations *- Link to Glossary*

With several remyelinating therapies in phase 2 (most focusing on RMS / RRMS), key trial results are expected in 2022 / 23

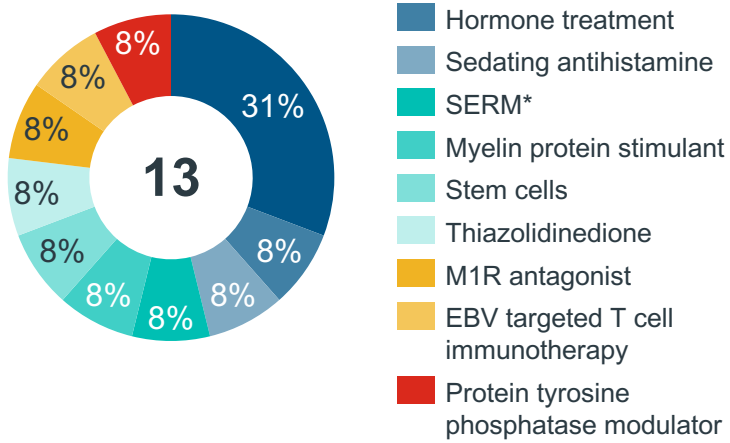
CLINICAL TRIAL PIPELINE

Number of Clinical Trials By **Development Phase**



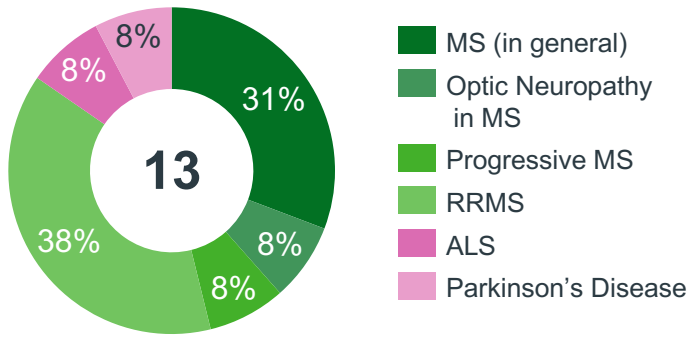
- More than 90% of active clinical trials investigating remyelinating agents are currently in **phase 2 and 3**
- In addition to these agents in-human trials, there are several additional candidates being investigated in **pre-clinical studies**

Number of Clinical Trials By **Mechanism of Action**



- Multiple technologies in development offer remyelination potential – based on some interim clinical results the most promising ones are: **gold nanocrystal suspension, LINGO-1 antibodies, concentrated biotins and hormone treatments** (see next slide for more details)

Number of Clinical Trials By **Indication**



- Almost **85%** of currently ongoing trials focus on the remyelination effect in **multiple sclerosis**, out of which 45% target **relapsing-remitting** disease (RRMS)
- **Different mechanism of gold nanocrystal suspensions is** also tested in ALS and in Parkinson's Disease

Source: IQVIA analysis; clinicaltrials.gov (data accessed April 2022), IQVIA analysis; (*) SERM - Selective estrogen receptor modulator

Abbreviations *– Link to Glossary*

Different remyelination strategies are being investigated to repair the myelin sheath damaged by Multiple Sclerosis

APPROACH TO REMYELINATION IN MS

- **Current approaches to remyelination include:** (a) blocking inhibitors of remyelination, (b) increasing the number of oligodendrocyte precursor cells (OPCs) that mature into oligodendrocytes, which are responsible for myelin production and (c) clearing debris left over from myelin damage that inhibit remyelination.
- To achieve more robust remyelination, future development activities will likely involve a **combination** of these mechanistic strategies

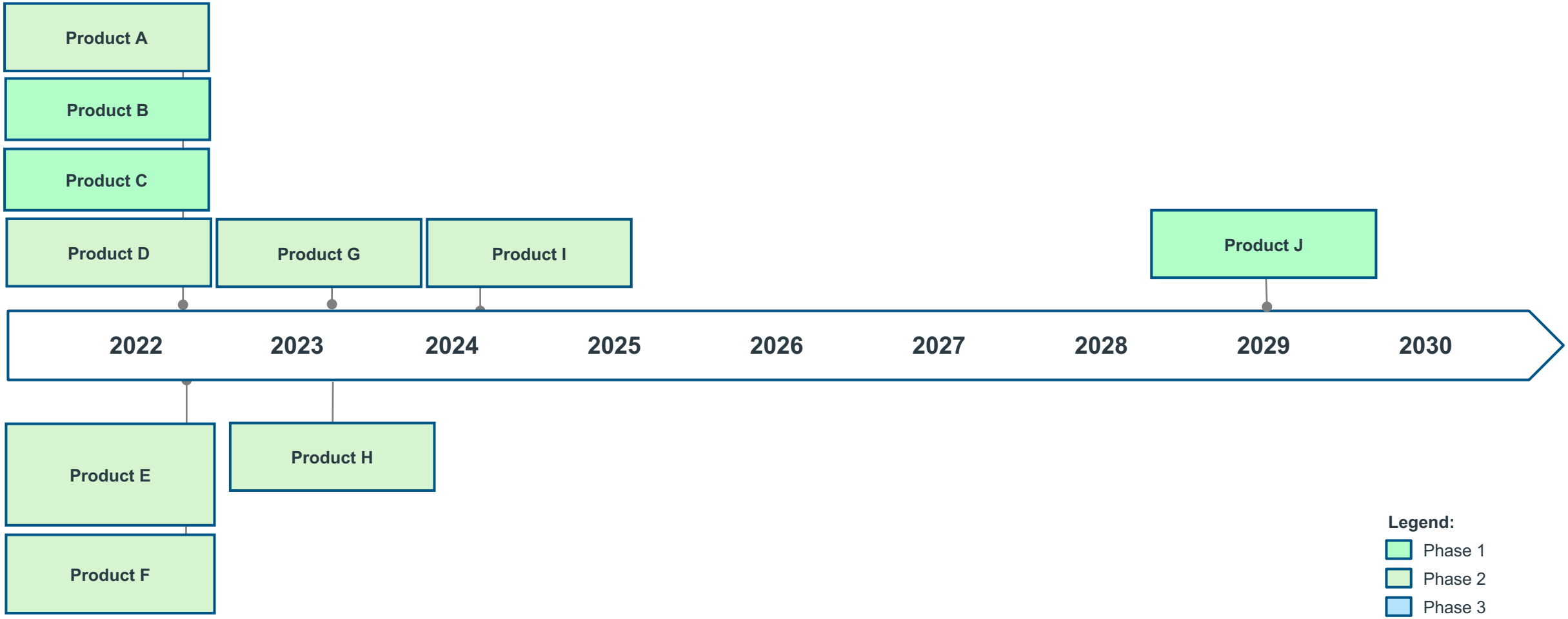
Selected mechanisms of action investigated

Gold nanocrystal suspension	Protein tyrosine phosphatase modulator	Myelin protein stimulant	EBV targeted T-cell immunotherapy
Nanocrystalline gold can be used as a biocatalyst to support various intracellular reactions that generate energy. One of applications is the improvement in differentiation and maturation of OPCs into oligodendrocytes, responsible for myelination process[3]	NVG-291 is a potent inhibitor of protein tyrosine phosphatase sigma (PTPσ). The activation of PTPσ inhibits remyelination, plasticity, and neural repair in MS	There is an oral small molecule under investigation by Biogen that induces growth of the cells that make myelin*, potentially allowing for the re-myelination and restoration of nerve communication of MS patients. *by blocking mechanisms that prevent differentiation of OPCs[5]	It has now been established that EBV is the primary driver of the development of MS. ATA188 is a T-cell immunotherapy targeting EBV antigens as a potential treatment for multiple sclerosis
CNM-Au8 (Clene Nanomedicine)	**NVG-291** (Nervgen)	**BIIB061** (Biogen)	**ATA188** (Atara)

Abbreviations - Link to Glossary

2022 / 23 are important years for MS treatment with multiple expected Phase 2 read-outs

EXPECTED COMPLETION YEAR FOR KEY TRIALS

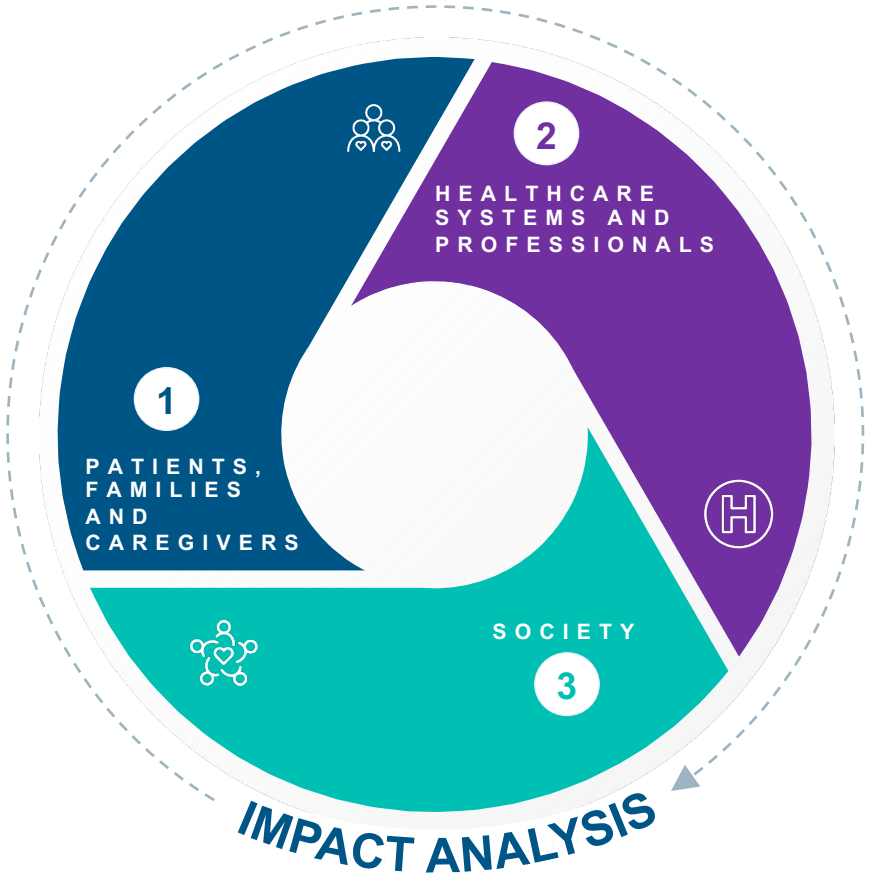


Source: clinicaltrials.gov; April 2022, active clinical trials (Not yet Recruiting, Recruiting, Enrolling by invitation, Active not recruiting), Excluded trials without specified phase, Device trials

Abbreviations *- Link to Glossary*

By reversing or improving disability, remyelination promises to improve the lives of patients and bring benefits to broader society

IMPACT ANALYSIS



1

PATIENTS, FAMILIES, AND CAREGIVERS

Remyelinating therapies have the potential to increase the quality of life of MS patients by reducing or improving their levels of mobility, cognition, and vision, positively impacting the well-being of patients, families, and caregivers alike

2

HEALTHCARE SYSTEMS AND PROFESSIONALS

As remyelinating therapies are likely to be used as add-on treatments or in combination with other existing therapies (not likely to replace current DMTs or other symptomatic MS therapies), they may generate incremental costs for healthcare systems

3

SOCIETY

Disability and functional improvements will reduce social costs related to home care, transportation, amongst others, along with increase workforce participation rate among MS population and their families and caregivers bestowing profound socioeconomic benefits

Source: IQVIA internal expertise

Remyelination may improve physical and cognitive functions of MS patients, and have a positive impact on their psychological health

PATIENTS	CURRENT STATE	FUTURE STATE
REDUCE OR IMPROVE PATIENTS' DISABILITY LEVEL	• Multiple sclerosis puts a heavy burden on patients' lives by **affecting their physical and cognitive functions** - causing problems with mobility, fatigue, vision impairment, issues with concentration and memory • Existing treatments, including DMTs, are only able` to prevent or slow disease progression, but cannot reverse the disease effects	• Remyelinating therapies will be able to reverse some of the effects of Multiple Sclerosis, **improving patients' mobility, vision and cognition** and therefore significantly improve their quality of life
POSITIVELY IMPACT PSYCHOLOGIC AL HEALTH	• Due to physical impairment, moderate and severe MS patients require **support in daily activities** and are often **excluded from regular social and professional lives**, which in turn has negative impact on their psychological health • **Depression and anxiety** are common co-morbidities in MS patients	• Reduced disability will result in increased independence of MS patients, thus positively impacting their **psychological condition**
LIMIT REQUIRED INFORMAL SUPPORT FROM PATIENTS' FAMILIES	• Multiple sclerosis impacts not only the lives of patients, but also of their families - **~70% of MS patients regularly use the help of their family members**, and the extent of this support increases significantly with disease progression	• The improved independence of MS patients resulting from disability level reduction by remyelinating drugs will **limit the time required for supportive care** provided informally by patients' families

Remyelination might improve MS-related fatigue that is experienced by more than 80% patients

PATIENTS	CURRENT STATE	FUTURE STATE
REDUCE PATIENTS' FATIGUE LEVEL	• More than 80% of MS patients suffer from acute or chronic fatigue that can prevent them from functioning normally and severely impact quality of life • Causes of MS related fatigue are uncertain and could be either muscle weakness associated with MS or constant activation of immune system	• Reduced disability might lead to lower fatigue experienced by MS patients; however since exact cause of MS-related fatigue are uncertain, it is difficult to establish how remyelinating therapies can improve this aspect of MS patients' life

As remyelinating drugs will likely be used as add-ons to current MS treatments, they will create incremental costs for HCS

2

HC SYSTEMS	CURRENT STATE	FUTURE STATE

INCREASE COST OF MEDICATIONS FOR MS PATIENTS	• On average, healthcare cost per MS patient amounts to **~€6,100** per year and remains similar for different disease stages, though the key components of this cost differ:
	  • For mild and moderate patients HC cost is driven by **Disease Modifying Therapies** (used by 47% and 32% of patients, respectively)
	  • For severe patients **inpatient care** becomes the key driver of HC costs
		• Remyelinating drugs will likely be used as an add-on treatment to current DMTs and other symptomatic MS medications, creating an **incremental cost** for healthcare systems (the height of which is not yet known)
		• They are **not expected to decrease the overall HC cost** per MS patient

Abbreviations *– Link to Glossary*

Remyelinating therapies are expected to reduce costs of social services and increase work participation of MS patients

3

SOCIETY	CURRENT STATE	FUTURE STATE
DECREASE COSTS OF SOCIAL SERVICES	• **Social services** (not healthcare related, such as home help, transportation etc.) are another important cost component related to MS management • While for mild patient average annual cost of social services is **~€520** per year, it raises to **~€2,800** for moderate patients and **~€9,300** for severe patients (1)	• Through improving physical condition of MS patients, **remyelinating therapies** will reduce their need for social services, thus bringing savings to healthcare systems • Assuming remyelinating drugs will reduce the disability by 25% in 15% of MS patients[1], they will generate **~€124 million savings** across the European area
INCREASE WORK PARTICIPATION	• Work participation of MS patients deteriorates following the disease progression – whereas ~80% of mild patients continue to work, **this share drops to only 35% for moderate and 8% for severe patients**	• Remyelinating therapies may reverse or improve disability caused by MS, having twofold impact – enabling more patients to keep their jobs and reducing the time off work for their family members, bringing overall positive impact on GDP generation across Europe of ~800 million per year (2)

Treatment	Workforce participation of MS Patients (weighted average)	Loss of Nominal GDP for MS Patients (per year)	Total number of hours spent by MS family members on informal care (per year)	Loss of Nominal GDP for MS Patients' families (per year)	Total loss of Nominal GDP (per year)
Current Therapy	35%	€17.7 billion	~580 thousand*	€3.7 billion	**€21.4 billion** *Hidden cost associated with current treatment*

(1) 15% of patients based on clinical trials for MD1003 (and previously Opicinumab and Avonex combination); 25% reduction in disability is an expert assumption, as not much information on efficacy is available now (2) Calculation based on the previous assumptions: impacting 15% of eligible patients, decreasing disability by 25% ; Source: (1) Disease burden of Multiple Sclerosis

Abbreviations *– Link to Glossary*

Social services account for >40% of total HCS costs related to MS; even a slight decrease in their use will bring significant savings

3 SOCIETY

Social services costs related to MS

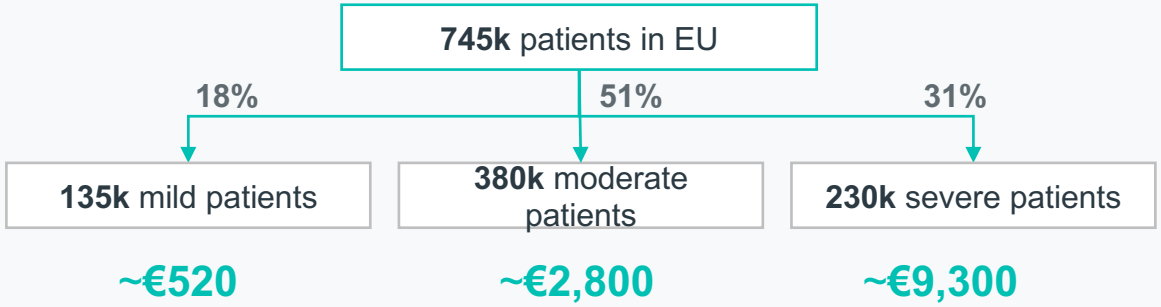
€3.3bilion **total cost** of social services provided to MS Patients across Europe

42% **share of social services cost** in total cost of MS disease management born by HCS

22% **average share of MS patients** using social services (home help, transportation services)

18x **increase in** the social care cost for patients with severe MS as compared to patients with mild disease

Impact of remyelinating therapies



Depending on the efficacy of remyelinating therapies, they will bring savings in social services cost to MS patients of more than ~€124 million

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Enabling accessible, affordable, and integrated access to novel technologies propels the next wave of innovation

Each innovation wave advances closer towards new cures and discoveries

NOT EXHUASTIVE

Novel innovations

		Before 2000	2000-2020	2022 onwards		
Therapy type	**Major Technology / Platform**	**Chemicals**	**Biologics**	**Cell replacement Tx**	**Gene therapy**	**Gene modified cell Tx**
	Target population	Large population	Smaller populations / rare disease	Personalised		
Evidence	**Generation**	RCT with placebo	RCT w/ active comparator, static RWE	Novel RCT, dynamic RCT/RWE		
	Endpoints	Traditional, biomarkers, discrete	Traditional, biomarkers, discrete	Traditional, biomarkers, genomics, digital, PCEs, longitudinal		
	Data ownership	Pharma	Pharma	Pharma + Payer + Provider + Patient		
Rate of change	**Innovation rate**	Many new classes, many me-toos	More new classes, fewer me-toos	Many new classes and combinations		
	SoC change	Slow	Moderate	**Fast**		
Business model	**Price/year**	Hundreds to thousands	Tens of thousands	Hundreds of thousands		
	Longevity	10-15 years	10 years	5-10 years		
	Model	Volume maximisation	Price-volume optimisation	**Outcome-based / personalised**		

Source: IQVIA material - Funding Innovative, High-Budget New Medicines

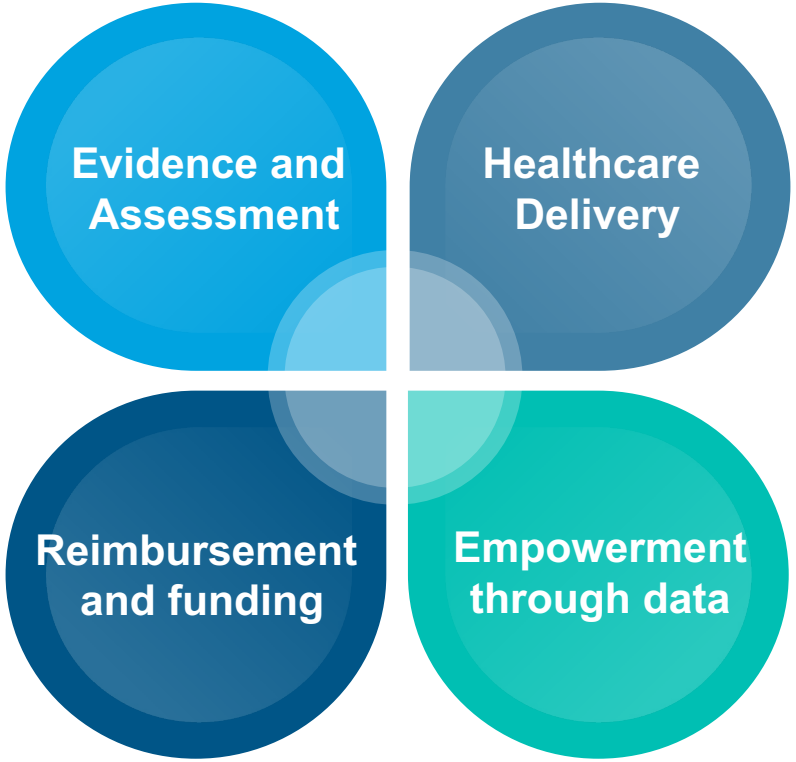
Abbreviations *- Link to Glossary*

Providing access to innovation will challenge current assessment, funding, delivery and test data infrastructure and empowerment

Effective stakeholder education is paramount to ensure effective assessment, funding, and delivery of novel innovations

How stakeholders **assess and reward value** given uncertainty around long-term benefit and safety based on trial data

How healthcare systems will **pay for high-cost innovation**



How stakeholders **manage delivery** of novel therapies

How **real-world data collection** and analytical techniques can **support access and improve delivery**

How stakeholders can be **empowered** to support effective assessment, funding, and delivery

Each of these four key topics will now be examined in further detail

We have identified 8 key areas for stakeholder consideration to diligently ensure the provision of early and effective access to innovation

Assessment of innovation access will be performed across 8 areas:

Evidence and Assessment

1. *Updating regulatory guidance & procedures*
2. *Real World Evidence (RWE) to address payer clinical uncertainty*
3. *Valuing and rewarding innovation*

Funding

4. *Adapting financing models for upfront investment*

Healthcare Delivery

5. *Developing infrastructure to support care delivery*
6. *Optimising patient/treatment strategies*

Empowerment through data

7. *Enabling data science and technology partnerships*
8. *Horizon scanning and stakeholder dialogue*

We have mapped these 8 key areas to our 8 prioritised innovation areas to highlight where they are best applicable

	1 Alzheimer's Disease	2 Stem cells for CNS	3 Psycho plastogens	4 & 5 Gene Therapy & CRISPR gene editing	6 mRNA vaccines	7 BiTEs	8 Remyelinating therapies
Updating regulatory guidance & procedures	✓	✓	✓	✓	✓	✗	✓
RWE to address payer clinical uncertainty	✓	✓	✓	✓	✓	✓	✓
Valuing and rewarding innovation	✓	✓	✓	✓	✓	✓	✓
Adapting financing models	✗	✓	✗	✓	✗	✗	✓
Developing infrastructure to support care delivery	✗	✓	✓	✓	✓	✓	✗
Optimising patient management/ treatment strategies	✓	✓	✓	✓	✓	✓	✓
Enabling data science and technology partnerships	✓	✓	✓	✓	✓	✓	✓
Horizon scanning and stakeholder dialogue	✓	✓	✓	✓	✓	✓	✓

Abbreviations *- Link to Glossary*

Updating regulatory guidance & procedures

Revised regulation will guide trial design and support access despite challenges to meet evidence requirements for certain innovations

Challenges in collecting sufficient evidence *often leads to* ***delayed access*** *for patients and* ***increased costs*** *to manufacturers discouraging entry and stifling innovation, requiring dedicated strategies to address uncertainties:*

Timely & Harmonized Consultation

- **Proactive engagement** with EMA through working groups with multiple manufacturers to receive guidance on broader methodological or policy /regulatory issues
- Direct interaction with EMA for specific **guidance and scientific advice** to establish reliable and relevant endpoints and ensure appropriate trial design
- **Iterative development of manufacturing standards** to mitigate challenges in process control, material quality and contamination
- **Harmonized, timely, and streamlined** clinical benefit assessments of novel innovation areas within a sustainable network across Europe

Adaptive Pathways & Living Labels

- **Broader use of adaptive pathways** to encourage conditional access to new treatments expected to benefit patients with no current treatment options for their disease, or offer a major therapeutic advantage over existing treatments
- Expanding criteria to **satisfy "high unmet need" demands** to include societal perspective and indications that do not qualify under conditions
- A greater emphasis on inclusion of **RWE to enable a 'living label'**, encouraging label evolution for novel indications and patient sub-groups as products gain early regulatory approval with limited data and likely restrictions

Novel Evidence Generation

- **Expanding the type of evidence accepted** for regulatory approval beyond the traditional "randomized controlled trial" to **balance the value of innovative medicines** with difficulties in generating evidence from limited size of trial/ orphan populations, lack of individual patient data on appropriate comparators, and uncertainties in long-term efficacy, durability, and safety (e.g., basket trials, RWD/RWE, synthetic comparator arms, digital platforms, etc.)
- **Empower manufacturers** to generate real-world evidence that demonstrates the **benefit/risk profile** of a product in a more reflective, efficient and pragmatic manner for clinical practice and uptake

Note: RWE: Real World Evidence; RWD: Real World Data; Source: EFPIA – Regulatory road to Innovation; EFPIA – Evidence – MIX report

Abbreviations *– Link to Glossary*

Access-relevant regulatory features are rewarding innovation to improve access to novel life-saving medicines in high unmet need areas

Timely and iterative dialogue, dynamic regulatory and expertise-drive assessments, and agile centralized authorization to optimize the development pathway, accelerating path to market for new innovations

Timely & Harmonized Consultation | Adaptive Pathways & Living Labels | Novel Evidence Generation

Ongoing Developments & Trends

- At the EU level, regulators are taking steps to **harmonize and streamline the clinical benefit assessment** of health technologies with the the EUnetHTA consultations and initiative (in-depth case study here)
- **Growing appreciation for novel innovative medicines** has lead to to new avenues for early dialogue, and broad and integrated policy efforts to improve access to novel therapies in high unmet need TAs to address underserved patient populations, including:
  - EMA Innovation Network and Innovation Task Force
  - Provision of the EMA PRIority MEdicines (PRIME) or ATMP designations to innovative therapies
  - EMA technical regulatory and product development guidance, such as the EMA guidance document for ATMPs containing genetically modified cells
  - Supranational EU-member collaborations to support timely, equal and synchronized access to innovative products through joint clinical assessments building on EUnetHTA, to improve knowledge sharing on innovative products, and standardize methodologies and evidence requirements to increase efficiency and leverage resources to increase price negotiation power
  - Member state specific developments, such as the French National Plan on Rare Disease

Note: EU: European Union; EMA: European Medicines Agency; ATMP: Advanced Therapy Medicinal Products

EMA's PRIME scheme facilitates, rewards, and fast-tracks development of promising innovations of major public health interest

CASE STUDY: EMA PRIME SCHEME

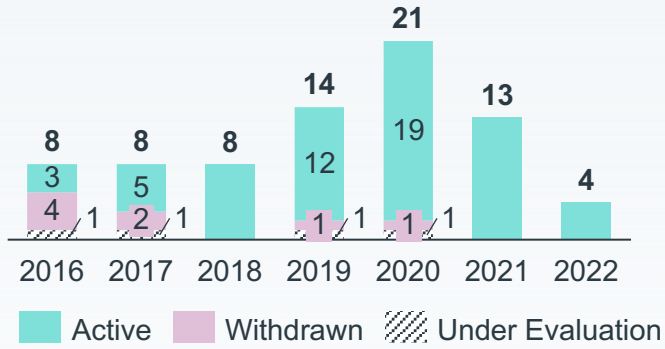
A Pivotal Tool in the Regulatory Eco-System

- PRIME is a scheme launched by the EMA to drive enhanced interaction and early dialogue with developers of promising medicines that target an unmet medical need
- PRIME builds on existing regulatory frameworks to foster early dialogue with EMA to obtain guidance at key development milestones, including clinical trial design to ensure suitable data generation, in turn increasing likelihood of accelerated approval
- Products with a PRIME designation are very likely to qualify for an accelerated assessment*, which shortens the market authorization application timeframe from 210 to 150 days

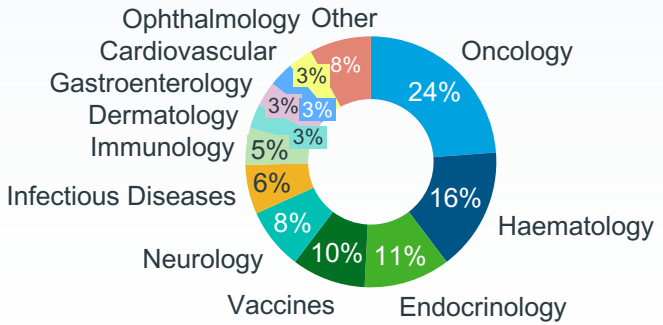
A Positive Impact on Drug Development: PRIME's 5-Year Review

- From March 2016 to June 2021, a total of 18 medicines that had PRIME support were approved in the EU, 7 of which were advanced therapy medicinal products (ATMPs) and 16 of which targeted rare diseases
- In 2021, six medicines with PRIME designation were recommended for approval (Abecma, Bylvay, Evrysdi, Imcivree, Oxbryta and Skysona), and 14 medicines under development were included in the scheme in 2021 in five medical specialties, oncology, neurology, hematology, immunology/rheumatology, and endocrinology

Yearly Number of PRIME Designations



Active PRIME Designations per TA



Source: Clarivate Analytics Cortellis, **Year to Aug 2022**
IQVIA | EFPIA Pipeline Innovation Review 2022

Abbreviations – *Link to Glossary*

EMA has now revised the guidance on advanced therapies, including Cell and Gene therapies, to reflect their increasing importance in healthcare

CASE STUDY: EMA GUIDANCE FOR ATMPS CONTAINING GENETICALLY MODIFIED CELLS

Timely Provision of Regulatory Guidance

- Effective Jun. 2021, EMA finalised revised **guidance for advanced therapy medicinal products** containing genetically modified cells, including chimeric antigen receptor (CAR) T cell therapies
- The updates to the guidance reflect, among others, the increase in clinical experience with CAR Ts and cover new categories of products, such as induced pluripotent stem cells
- New tools for genetic modification of cells, such as genome editing technologies will be also considered
- Guidelines also included more specific requirements, adjusted to the specificity of ATMPs, e.g., regarding trial design or 15-year monitoring period after marketing authorisation

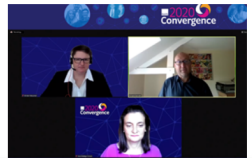
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Convergence: EMA close to finalizing guidance for advanced therapies

Regulatory News | 17 September 2020 | By Mary Ellen Schneider

The European Medicines Agency is on the verge of releasing revised guidance for advanced therapy medicinal products containing genetically modified cells, which includes chimeric antigen receptor (CAR)-T cell therapies.

The "Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells" was originally issued in 2012 but underwent revision and consultation from July 2018-July 2019. The revised version is expected to be adopted in October and published in November, according to Ana Hidalgo-Simon, MD, PhD, head of advanced therapies at EMA. She previewed the major changes at RAPS Convergence 2020.



There were an "enormous" number of comments on t
The agency is also working on a Q&A document on pr
starting material. There will likely be consultation on
the EU, *Regulatory Focus*, 16 July 2020.)

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Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells Share

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- Current effective version
- Revision 1 (effective from 1/06/2021)
- First version

The original guideline was developed in 2010-2011, before the first gene therapy medicinal product based on genetically modified cells was authorised. The revision of the guideline reflects the experience gained since then with the approval of this type of gene therapy products. Additionally, science has moved on rapidly, and novel technologies that were not yet at the horizon in 2010 are now commonplace: these include CAR-T cells, induced pluripotent stem cells and genome editing. The revision does also incorporate guidance of genetically modified cells developed using these novel technologies.

Note: ATMP: Advanced Therapy Medicinal Products

Targeted reforms and the establishment of dedicated early access pathways will streamline the road to market for innovative new medicines

Embedding expedited and adaptive regulatory pathways that support conditional marketing authorizations and consolidate the concept of "unmet medical need" will equitably deliver on the promise of innovation in the pipeline

Early & Ongoing Consultation | **Adaptive Pathways & Living Labels** | Novel Evidence Generation

Ongoing Developments & Trends

- Indeed, Targeted reforms to shorten time to and **facilitate the path to market** for novel ATMPs in high unmet need TAs, including:
  - EMA conditional marketing approval
  - Innovative Licensing and Access Pathway (ILAP) in the UK established to accelerate the development and approval of innovative medicines
  - Reform and streamlining of France's early access program to facilitate access while awaiting the standard HAS HTA process
  - For example, FR's ATU pathway and IT's Law 648 significantly expedite access to novel innovative medicines (potentially even prior to EMA approval and the completion of P&R negotiations)

2021: Conditional Marketing Approvals

- Thirteen medicines received a recommendation for a conditional marketing authorization in 2021, one of the possibilities in the EU to give patients **early access to new medicines**
- Key products that received conditional approval in 2021 include:
  - **Idecabtagene vicleucel** (Abecma) for Multiple Myeloma
  - **Sacituzumab govitecan** (Trodelvy) for breast cancer
  - **Selumetinib** (Koselugo) for Neurofibromatosis

Note: ATMPS: Advanced Therapy Medicinal Product; EMA: European Medicines Agency; HAS: Haute Autorité de Santé

Regulatory convergence on RWD/RWE to support decision making can mitigate increasingly complex and evolving evidence requirements

Establishing clear principles and frameworks fostering data quality, accountability, interoperability, access, analysis and regulatory acceptance is crucial in supporting HTA decisions

Early & Ongoing Consultation | Adaptive Pathways & Living Labels | **Novel Evidence Generation**

Ongoing Developments & Trends

- Evidence requirements from regulators are **evolving** to account for **new data collection capabilities** and difficulties in conducting "gold-standard" RCTs in areas of high unmet need
- Growing willingness of regulators to engage on RWE with submission of robust RWE generation proposal
- EFPIA has published a recommendation to **establish a regulatory framework** to foster the use of Real World Data (RWD) while respecting data privacy concerns and providing accountability to patients, outlining:
  - Need to establish appropriate tools and methods for fit-for-purpose data generations
  - Timely engagement and dedicated resources at key development milestones
  - Educational training and knowledge sharing of National and Local expertise

Initiatives to Improve Data Collection

- Through new initiatives, e.g., **EMA Patient Registries initiative**, **EMA Regulatory Science to 2025 Strategy**, the EMA is encouraging registry custodians to partner with patient groups and industry
- The objective is to **anticipate the evolving needs** of industry and regulators, and develop models of research access that allow the registry data to be more effectively utilised[3]

Note: EMA: European Medicines Agency; EU: European Union; HTA: Health Technology Assessment; RWE: Real-World Evidence; RWD: Real World Data

EMA launched the DARWIN EU Coordination Center to promote the use of Real World Data (RWD) in regulatory and HTA reviews of medicines

CASE STUDY: DARWIN EU

EMA Established Coordination Center for The Data analysis and Real-World Interrogation Network (DARWIN EU®)

- EMA is establishing a coordination center in collaboration with Erasmus University Medical Center Rotterdam to provide **timely and reliable evidence** on the use, safety and effectiveness of medicines for human use, including vaccines, from real world healthcare databases across the EU

Support Decision Making and Syndicate Access to Validate RWE

- The overarching objective is to develop and manage a **network of real-world healthcare data sources** across the EU and to conduct scientific studies to answer research questions raised during the evaluation of medicines
- DARWIN EU aims to leverage valid and trustworthy real-world evidence on diseases, patient populations, and the use, safety and effectiveness of medicines for regulators, HTA bodies, healthcare professionals, and patients
- DARWIN EU will also **support decision-making** by establishing a metadata catalogue for use in regulatory decisions, developing scientific protocols, interrogating relevant data sources and interpreting study results, reinforcing collaboration between EMA and national HTA bodies, and improving data sharing
- The first DARWIN EU pilot studies will be delivered in 2022

Key Insights

- DARWIN EU represents another step toward **greater acceptability of RWE** in Europe
- RWE has been central to past advanced therapy submissions, and its broader use in regulatory reviews and HTAs will likely be advantageous for these products
- This step also provides the promise of **clearer guidelines for RWE requirements** that are applicable across regulatory and HTA, enabling future advanced therapies supported by RWE to have a higher likelihood of meeting regulatory and payer expectations
- A further advantage is the availability of more RWD sources with a wider coverage, including patients with rare diseases

Note: EMA: European Medicines Agency; EU: European Union; HTA: Health Technology Assessment; RWE: Real-World Evidence; RWD: Real World Data

Real World Evidence (RWE) to address payer uncertainty

Real World Evidence (RWE) will help mitigate several recurring uncertainties with establishing efficacy and durability in new innovation areas

CONTROLLED TRIAL DATA

Limitations in conducting gold-standard RCTs due to small patient populations and ethical consideration with placebo or double-arm studies

SHORT TRIAL DURATIONS

Limited follow-ups and and use of surrogate endpoints will limit ability to **establish efficacy and durability**; investment is required to validate these endpoints

SMALL PATIENT POPULATIONS

Breakthroughs occurring in advanced therapies often have very **small patient populations** leading to poor statistical significance, and difficulty identifying which sub-populations could benefit most

VARIED CLINICAL ENDPOINTS

Endpoints are often based on qualitative scoring systems and **unstandardised**. The actual benefit of a specific % increase in these scores is uncertain when applied to the real world

UNKOWN TECHNOLOGY

No standards currently exist for many new products due to the novel technologies they are based on, raising **uncertainty over long-term safety**

*Generation of reliable RWE data requires **transparent, harmonized collaboration** between all stakeholders, including payers, manufacturers, and academic institutions*

Imatinib (Glivec), the first tyrosine kinase inhibitor, was approved based on limited data and has since established positive long-term data

CASE STUDY: IMATINIB (GLIVEC)

Generating RWE to Support Decision Making

- Imatinib (Glivec), the first tyrosine kinase inhibitor, launched in 2001 for treatment of Ph+ CML
- Prior to imatinib, 5-year survival was 50% and treatment options were limited (IFN + chemotherapy or SCT)
- Imatinib launched with the **promise of extending survival** but had **limited data** and **a high cost**:
  - Marketing authorisation granted based on results from three single arm studies (Phase 1 and 2 Phase 2)
  - Increased healthcare systems budget impact of CML by 120% in the UK and 73% in Germany
- Yet, most EU markets **recognised the added value** of imatinib and, despite incidences of delayed/restricted entry, patients were granted access
- Since, the investment in imatinib has been rewarded with the collection of long-term RWD:
  - Longer-term data has illustrated event free survival of ~81%of patients were event free, ~92% progression free survival, at 8 years
  - Imatinib has since been granted six indication expansions

Continued adoption of national early access schemes will allow for validation of effectiveness in the real world

RWE GENERATION THROUGH TEMPORARY ACCESS SCHEMES

Generating RWE to Support Decision Making

- **Temporary access** based on conditional approval/reimbursement is heavily dependent upon high quality real world clinical and pharmacoeconomic data to assess the impact on patient outcomes
- RWE allows for **temporary treatment access** to patients while generating clearer **evidence of benefit** to be used to inform final pricing and market access decisions

Real world data collection/evidence generation

- Pivotal trial readout
- Marketing authorisation (MA)
- **Launch:** P&MA negotiations
- Final clinical benefit assessments

For Example:

Pre-marketing authorisation/launch: allows access to unlicensed promising phase 2/3 products to patients with life threatening or debilitating disease

- Established ***ATU (temporary market authorisation) in France***
- ***UK's Early Access to Medicines Scheme (EAMS)*** (introduced in Mar 2015)

Temporary post launch: UK Cancer Drugs Fund (CDF) requires data collection as part of managed entry (ME); this data is re-appraised by NICE at end of ME, to inform reimbursement decision

RWE generation through temporary access schemes would account for and inform benefit assessments, and aid in getting potentially life saving therapies to patients quickly and efficiently

Abbreviations *- Link to Glossary*

Real world evidence has played a critical role in terms of supporting the initial regulatory decision or post marketing obligations

CASE STUDY: EMA USE OF RWE

Generating RWE to Support Decision Making

- **EMA has accepted real world data** "where available evidence of efficacy required contextualization" or where uncertainties existed around "long-term safety and efficacy":
  - Helped provide an external control arm, as was the case for Zalmoxis specifically, the European Bone Marrow Transplantation (EBMT) patient registry was used to compile an appropriate control group selected on the same criteria as the control arm of the ongoing Phase 3 trial and a specific set of matching parameters
  - For Yescarta, RWE was used for a retrospective patient-level pooled analysis of two Phase 3 randomized control trials (RCTs), and two observational studies were developed as a companion study to contextualize the results of an open label, single arm study (ZUMA 1)
  - For Kymriah, efficacy results were compared against three external data sets to contextualize the results of a single arm trial
  - Provided data to extend an indication as was the case for Soliris, where an RCT was unfeasible. For this, a global paroxysmal nocturnal haemoglobinuria (PNH) registry has been established for a prospective, observational, noninterventional study
  - The registry was established to support Soliris' authorization to evaluate safety data specific to the use of the drug and to characterize the progression of PNH as well as clinical outcomes, and morbidities and mortality in Soliris and non-Soliris treated patients
- Other examples where RWE played a major role include Biogen Inc.'s antisense oligonucleotide nusinersen (Spinraza) and Orchard Therapeutics Ltd.'s stem cell gene therapy Strimvelis

Enabling flexible pricing and market access in Europe would allow manufacturers to address real-world clinical uncertainty of innovation

IMPACT OF RWE ON PRICE AND MARKET ACCESS

AT LAUNCH – "UNBRANDED RWE"

- In Europe, evidence available at launch tends to be critical in **shaping the price and access** levels achievable for a certain medicinal products
- Today, RWE is actively taken into decision-making if available; However, it currently has limited benefit in shaping the price and market access potential of a drug on top of evidence from conventional Randomised Controlled Trials (RCTs) given the strict criteria and inflexibility of national clinical benefit assessments

Current Applications of RWE
LOW – *limited benefit; used to "support" RCT data*

RWE

POST-LAUNCH – "UNBRANDED RWE"

- On the contrary, evidence available post-launch holds less leverage and is used typically used to **'course correct'** (e.g., net-price erosion)
- There are more applications for RWE generated post-launch, yet the impact varies significantly across and within markets, e.g.,:
  - In France, RWE is utilized as a powerful tool to validate the added value of a medicinal product during the 5-year re-evaluation post-launch, with significant potential implications on price-volume or net price agreements
  - In Spain, RWE acceptance is currently low with limited trust in data sourcing and applicability

Current Applications of RWE
MODERATE – *"course correction" in certain markets only*

Note: EMA: RWE: Real World Evidence; RCT: Randomised Controlled Trial
IQVIA | EFPIA Pipeline Innovation Review 2022

Abbreviations - Link to Glossary

European HTAs are gradually becoming more open to including RWE in their assessments

CASE STUDY: INCLUSION OF RWE BY GERMAN AND UK HTA AUTHORITIES

Increasing Acceptance for RWE in Germany

- Enacted by the German legislative process (*GSAV**) in 2019, the new bill can oblige manufacturers of **orphan drugs, exceptional use products and conditionally approved medicines to submit real world data** from registry-based studies that would impact pricing[1]
- G-BA** will determine the parameters of data collection, with manufacturers responsible for conducting or financing studies[2]
- For now, only RWE from registry-based studies would be allowed for early benefit assessment - electronic patient records and claims data from health insurance funds will not be included due to insufficient quality and reliability
- Apart from improving drug safety, this **law is likely to provide additional opportunities for pharma companies related to RWE**, opening the door to wider acceptance and use; to date, RWE has been viewed less favourably than clinical data in Germany[3]

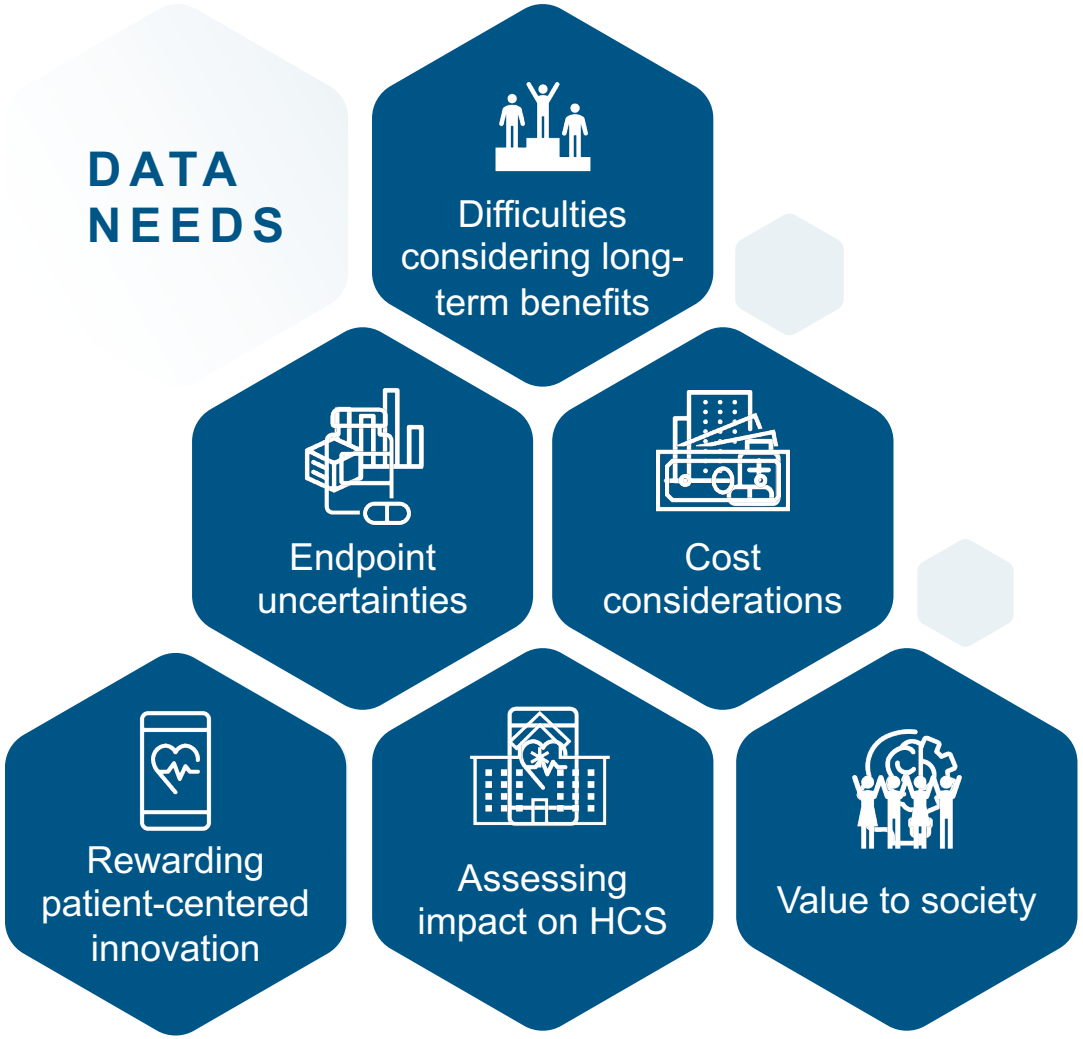
EHR and RWD Included by Nice in Future Guidance Development Process

- In February 2020, NICE released a statement of intent detailing additional data sources to include in guidance evaluation and development:
  - Electronic health record (EHR) data
  - Real-world data (RWD)
  - Relevant data collected outside of the context of traditional trials[4]
- The intent is, among others, to allow for more **rapid guidance updating and decision making**
- Following NICE statement: “We acknowledge that there are challenges in expanding our use of data and analytics, but we believe that the potential benefits to health and social care providers and users of their services outweigh the risks”[5]

Note: *GSAV - Act for Greater Security in the Pharmaceutical Supply System; (**) G-BA – The Federal Joint Committee
Source: 1. Informa Pharma Intelligence; 2. Partners4Access; 3. Vitaccess; 4. NICE; 5. The Evidence Base

Valuing and rewarding innovation

Current payer systems struggle to evaluate innovations and award appropriate prices; oncology combinations are a key example



Barriers to Assessing Value

- Economic benefits promised by many innovations are long-term and will impact healthcare systems and broader society
- However, current HTAs struggle to effectively evaluate innovations and therefore cannot reward through appropriate pricing
- The data packages generated for innovations may be deemed insufficient to fully assess value at launch for HTA bodies (especially if targeting rare diseases, or indications with high unmet need)
    - Trials in rare diseases can struggle to recruit sufficient patients
    - Diseases with high unmet need may gain marketing authorisation with Phase 2 data
    - Difficultly rewarding patient centered innovation from value added medicines (i.e., improvements in administration)

Abbreviations *- Link to Glossary*

However, systems are starting to adapt current processes to fairly and transparently assess the economic value of innovation

POTENTIAL SOLUTIONS: HTA ADAPTATIONS FOR HIGH-COST INNOVATIONS

Capturing and Integrating Value into HTA Assessments

- Healthcare systems should continue to objectively review HTA limitations in order to address issues surrounding 'non-traditional' products
- Any review should ensure that value is effectively captured; this will allow for accelerated access and incentivise future investment in R&D
- Assessing the long-term impact of innovation on healthcare systems and society could provide HTAs the means to effectively capture value
- However, systems need to ensure continued fairness and transparency throughout the process

Examples of Frequently Discussed HTA Adaptations

Flexible Thresholds in Cost-Effectiveness Analysis

- Payers and manufacturers can further define flexible thresholds and adapted criteria that transparently and fairly account for innovation across specific indications
- Flexible thresholds are already in use for orphan drugs (e.g. Soliris for paroxysmal nocturnal haemoglobinuria)

Consider Flexible Criteria

- Multiple-criteria decision analysis (MCDA) can be used as a tool to create a fair and transparent decision-making process as it allows adaptation to take into consideration nuances of different technologies
- Furthermore, HTA providers could work with regulators to validate surrogate endpoints to allow flexibility and enable shorter trials

There are examples of HTA bodies adjusting their assessments to conform to changing market dynamics…

CASE STUDY: HAS AND pCODR – NEW HTA ELEMENTS

Inclusion of an Economic Impact HTA

- In 2013, the Commission d' Evaluation Economique et de Sante Publique (CEESP) – (a sub-committee of Haute Autorité de santé (HAS), the French National Authority for Health) began conducting economic evaluations for innovative medicines expected to have a budget impact of >€20m / year, as a discussion point during reimbursement negotiations with manufacturers
- In doing so they hoped to improve access to drugs that could have a high impact on healthcare efficiency and financial sustainability
- HAS is considering future discussions with the Ministry of Health to reinforce the importance of the economic evaluation with the aim of making it mandatory not only for pricing decisions but also for access to reimbursement

HAS

CADTH's pan-Canadian Oncology Drug Review (pCODR)

- Process is designed for consistency and clarity in the cancer drug review process; makes evidence-based recommendations to Canadian provinces and territories (excl. Quebec) to guide their drug funding decisions
- Expert review committee focuses on:
  - Clinical Benefit
  - Patient Based Value
  - Economic Evaluation
  - Adoption Feasibility
- Review completed within 100-150 working days
- Final recommendation is either: positive without conditions, conditional, or negative

pCODR

… Such as in the UK, where NICE has adjusted the ICER threshold to enable access to higher cost drugs

CASE STUDY: NICE REVISIONS

NICE: Adaptive ICER Thresholds

- On 1st April 2017, the National Institute for Health and Care Excellence (NICE) and the National Health Service (NHS) England introduced a new Incremental Cost-Effectiveness Ratio (ICER) threshold for innovative technologies indicated for very rare diseases[1], which can find these new therapies cost effective on a sliding scale between £100,000-£300,000/Quality-Adjusted Life Year (QALY)
  - This is in contrast to the typical ICER threshold of £30,000/QALY
- The very rare diseases threshold is introduced on top of the end-of-life threshold that has been active since 2009, which allows NICE to find end-of-life therapies to be cost effective up to £50,000/QALY

NICE National Institute for Health and Care Excellence

NICE: HTA Evaluation Revision

NICE is in the process of reviewing their approach towards technology appraisals, highly specialised technologies, medical technologies, and diagnostics assessment programmes.

Some topics to be considered in this review cover:

- Using **data analytics and real-world evidence** to reduce uncertainty in HTA economic modelling
- **Incorporating quality of life into economic analyses** and considerations by committees
- Technology-specific issues (e.g. evaluating the new generation of **treatments that target tumours according to their genetic make-up** rather than where they originate in the body)
- Methods needed to assess the clinical and cost-effectiveness of the position of technologies in the care pathway

IQWiG changed their approach to PRO data assessment, potentially driving novel evaluations to QoL across Europe

CASE STUDY: G-BA REVISIONS

IQWiG adjusted their assessment method relating to Patient Reported Outcome (PRO) data evaluation, implementing:

01 ***Responder analyses of PRO***

- Responders should be defined as patients with an improvement or deterioration of at least 15% of the range of the PRO instrument (or scale), regardless of the minimal important difference (MID)

02 ***Threshold for missing data***

- Data will not be considered if based on <70% of the ITT population or there is a >15% difference between arms

03 ***Different follow-up durations between arms***

- If median follow-up durations for AE and PRO endpoints differ between arms, data will be rejected unless they are based on analyses that take this difference into account, such as survival analyses

Implications for QoL data use in Germany…

While imposing new requirements, these changes in HTA approach may eventually **improve the limited trust in QoL data and increase their relevance in future HTA evaluations in Germany**

…and potential next steps across Europe

In late 2021, the European Commission adopted its regulation on **Joint Clinical Assessments (JCA),** which mandates a single assessment of clinical data that must be taken into account in pricing and reimbursement decisions by each EU member state. As the process matures, it will be important to monitor **how QoL data is considered and integrated into JCAs**

The first JCAs will be published in **2025** as a requirement for cancer therapies and ATMPs and expand to orphan drugs by 2027. By then, every member state will need to **implement regulations** on how JCA will be considered at **national level**

Note: IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen: PRO: Patient-Reported Outcome; QoL: Quality of Life; MID: Minimal Important Difference; ITT: Intention-To-Treat; AE: Adverse Event; Source: 1. https://www.iqwig.de/en/methods/methods-paper.3020.html; 2. Spain

Perceptions of PROs are evolving; further work is needed to ensure patient-centric endpoints are adequately valued by HTA bodies

PROs WILL BE VITAL WHERE PATIETN QoL IS IMPROVED

Patient-reported outcomes (PROs) are evaluated directly by the patient and are therefore **valuable** and, in some conditions, **critical**, to capturing the **patients' perspective** and significantly demonstrating the **value** of a new health technology

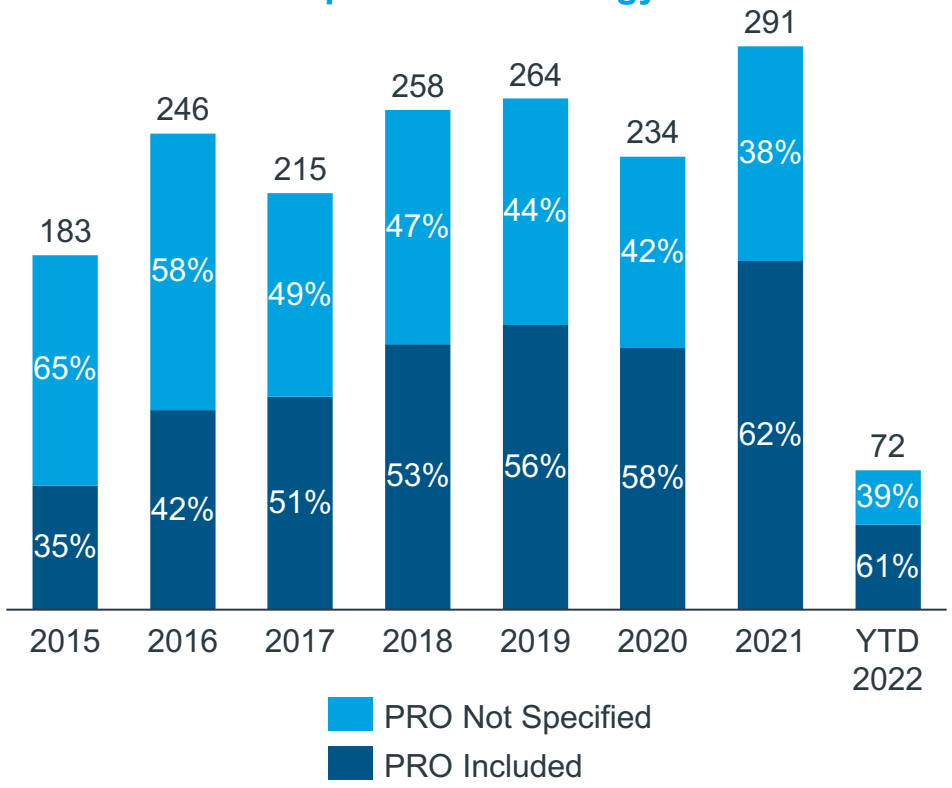
The actual **influence** of PRO data on HTA bodies varies, but use is generally **increasing** over time

In **Germany, England, Scotland**, **70-80%** of HTA reports include PRO data

In France, PRO data is included in <60% of HTA reports and only has a very minor impact on ASMR1 rating

Consistent evaluation of PROs by HTA bodies, alongside pro-active planning of PRO endpoint development by manufacturers, will be paramount in **capturing patient perspective** in future innovation assessments

Increasing use of PROs mentioned in HTA reports for Oncology



Agencies include CADTH, G-BA, HAS, NICE, PBAC, SMC, TLV, ZIN

Note: PRO: Patient-Reported Outcomes; ASMR: Amélioration du Service Médical Rendu (Actual Medical Benefit). HTA: Health Technology Assessments; MS: Multiple Sclerosis; French authorities assess drugs on an ASMR scale of 1-5; ASMR 1 is highest medical benefit; ASMR 5 is lowest
Source: HTA Accelerator

Abbreviations *- Link to Glossary*

Certain therapies have already benefited from increasing PRO acceptance by HTA bodies, and have additionally scored FDA label expansions

CASE STUDY: PRO ACCEPTANCE IN EU AND US

HAS, G-BA and SMC accepted crizotinib (Xalkori) in NSCLC considering improvement in PFS and strong QoL data

- Crizotinib (Xalkori) failed to demonstrate an improvement in OS, but did show clinically meaningful improvement in PFS
- Crizotinib also measured QoL using the general instrument EQ-5D, disease-specific instruments and median time to deterioration of patient-reported chest pain, dyspnoea or cough
- Time to deterioration of symptoms was **significantly longer in the crizotinib arm (5.6 months)** than in the standard chemotherapy arm (1.4 months)
- This significant improvement in QoL was a driver of acceptance by HTA bodies

Ruxolitinib (Jakafi) FDA label expanded to include improvement in fatigue PRO

- Ruxolitinib (Jakafi) (manufactured by Incyte) is indicated for the treatment of myelofibrosis
- One of the major symptoms of myelofibrosis is fatigue, which significantly disrupts patient day-to-day quality of life
- IQVIA recently developed several **new PRO assessment instruments** in collaboration with Incyte to adequately and comprehensively capture PRO improvement
- These new instruments were able to demonstrate improvement in one PRO symptom, fatigue, which has subsequently been included in the US ruxolitinib label
- This is the first ever PRO-measurement information system-based label extension by the FDA and demonstrates the increasing importance of patient-centred endpoints

Note: HAS: Haute Autorite de Sante; G-BA: Der Gemeinsame Bundesausschuss; SMC: Scottish Medical Council; NSCLC: Non-Small Cell Lung Cancer; PFS: Progression-Free Survival; QoL: Quality of Life; FDA: Food and Drug Agency
Source: 1. NICE, July 2019; 2. NICE, Review timeline

Abbreviations – Link to Glossary

In order to facilitate innovation, new payment models will need to be evaluated on a case-by-case basis

POTENTIAL SOLUTIONS: INNOVAITVE MODELS TO FACILIATATE INNOVATION

Pricing By Country Income

- Different countries have a **different ability to pay**
- Differential prices based on country income would avoid the problem of different access scenarios and **ensure access** to the greatest number of patients
- However, price would have to be confidential or International Reference Pricing (IRP) inactive in order to maintain a tiered pricing system

Indication & Combination Pricing

- In pricing by indication, **evaluating a product for each indication** would allow for a more **transparent pricing** process better **reflecting the added-value** a product imparts
- In parallel, **pricing by combination indication** overcomes the complexities in assigning value and negotiating prices when separate medicines are used in novel combinations, reflecting value beyond just the sum of its parts

Pricing By Performance

- Enable list price to be **adjusted over time** based on real-world evidence
- Yet, pricing by performance will be difficult to achieve in the short-term, where paying *for* performance is viewed as a potential intermediate alternative
- Paying *for* performance involves **modulating net price based on individual patient outcomes**; rebates or discounts are provided if a patient does not meet certain outcomes

Pricing by performance, or outcomes-based agreements, have been implemented for high cost / budget impact therapies

CASE STUDY: INNOVATIVE PAYMENT MODELS

- Sofosbuvir (Sovaldi) and ADA gene therapy* (Strimvelis) achieved **novel pricing models** in Europe
- Sofosbuvir list price is **~€60,000 per course** in large population; ADA gene therapy list price is **~€650,000 per treatment**

Sofosbuvir (Sovaldi)	CEPS secured a money-back guarantee as an MEA for Sovaldi in case of treatment failure, improving patient access to the high cost drug
ADA Gene Therapy* (Strimvelis)	AIFA negotiated price and outcomes-based agreement on behalf of other countries to enable cross-border funding

- US payers are starting to discuss new models to **manage high-cost upfront payments** of cell and gene therapies
- Voretigene neparvovec (Luxturna) list price is **$425,000 per eye**; Tisagenlecleucel (Kymriah) list price is **$475,000 per treatment**

Voretigene neparvovec (Luxturna)	Case studies provided on page 214
Tisagenle-cleucel (Kymriah)	

*However, these innovative models are more suited to small patient populations, and where **robust monitoring systems** are in place and occur in the same setting of care, making outcomes tracking easier. As patient tracking improves, there is potential to increase the number of products using these models (e.g., tracking readmission and recurrence in microbiome)*

*Strimvelis INN = autologous CD34+ cells transduced with a lentiviral vector containing the human adenosine deaminase (ADA) gene (shortened here to ADA gene)

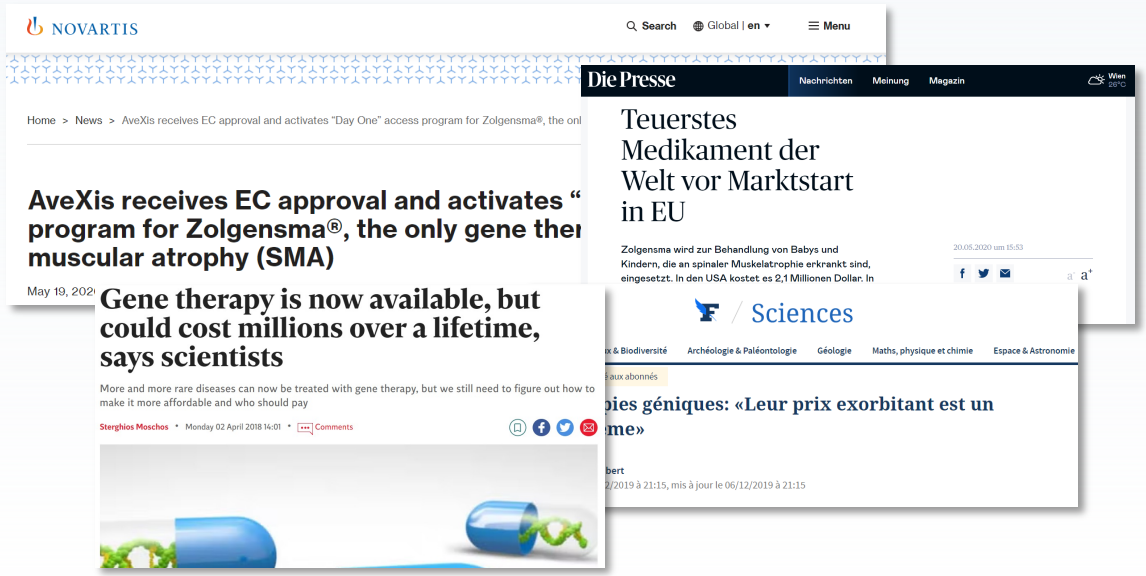
Pricing by performance, or outcomes-based agreements, have been implemented for high cost / budget impact therapies

CASE STUDY: RISK-SHARING SCHEME FOR HIGH-PRICED GENE THERAPY

Onasemnogene abeparvovec (Zolgensma) for Spinal Muscular Atrophy

€2 Mn

The ~€2 Mn price tag of Zoglensma highlights the importance of **innovative payment models** for high & high budget impact therapies to ensure and facilitate access for patients



Onasemnogene abeparvovec (Zolgensma) for Spinal Muscular Atrophy

- Zolgensma, a one-time intravenous infusion, is indicated to treat a **rare patient population** with a **high unmet need** currently underserved by one high-cost alternative
- In EU, Zolgensma received both **Orphan drug** and **PRIME / Priority Review regulatory designations**, streamlining development, assessment, and regulatory approval
- In Europe, Novartis used a "Day One" access scheme to enable access for Zolgensma upon approval under which it guaranteed rebates in line with the later negotiated net price
  - Early paid access via imports from US in DE, Cohort ATU designation in FR, and Law 648 in Italy, amongst others, additionally **facilitated early access in EU**
- Although every HTA body required **registry data collection** to gather long-term data on durability, efficacy, and safety, Novartis achieved **outcomes-based deals** based on individual patient data in several EU markets

Abbreviations *- Link to Glossary*

Some therapies have benefited from increasing PRO acceptance, with PRO importance recognised by HTAs, and an FDA label expansion

CASE STUDY: OUTCOMES-BASED PRICING

Voretigene neparvovec (Luxturna)

- **Voretigene neparvovec (Luxturna),** a gene therapy, is the first approved treatment for patients with **Inherited Retinal Disease** and has a current price tag of **~€350k per eye**
- Due to a **high degree of efficacy** vs the standard of care in an area of high unmet need, Luxturna was able to achieve **positive HTA outcomes** despite a lack of long-term data
- **Innovative contracts, such as outcomes-based deals, were not used in most EU markets** to offset long-term uncertainty as it was biologically reasonable to assume long-term efficacy
- Yet, **in the US,** certain private payers (e.g., Harvard Pilgrim) **entered into outcomes-based deals** (e.g., payment over multiple years based on performance) for Luxturna to enhance patient access and minimize risk and financial burden

Axicabtagene ciloleucel (Yescarta)

- **Axicabtagene ciloleucel (Yescarta)**, an innovative medicine used to treat two types of non-Hodgkin lymphoma**,** was approved in Aug 2018 by EMA with a price of **~€350k**
- Yescarta received generally favourable HTA outcomes based on a **high degree of efficacy vs. Best Supportive Care (BSC)**, despite a lack of long-term data
- In certain EU markets, such as in Germany and Italy, Yescarta saw the use of **outcomes-based agreements** as a means to **mitigate against uncertainty** regarding long-term efficacy
- In the UK, CAR Ts such as Yescarta have been reimbursed via the **Cancer Drugs Fund**, a tailored pathway to faster (temporary) reimbursement for cancer therapies whilst data on real world effectiveness is collected

Adapting financing models

Current Healthcare budgets are constrained to “silos” and are unable to adapt to finance new high cost / high-budget impact innovations

CHALLENGES WITH HEALTHCARE BUDGETS

New innovations

- **High cost/budget impact -** *e.g.,*
  - Upfront cost for one time treatments
  - Budget impact of treatment where none existed *(patient ‘warehousing’ effect)*
- **Financial benefits beyond healthcare**
  - Greater efficacy means people living longer and requiring less social care, etc.

Challenges

Siloed Budgets	**Siloed healthcare budgets** can prevent benefits of savings for either HC systems or society being shared between both areas; siloed budgets also prevent HTAs from assessing full value of innovations
Funding Delays	**Patient outcomes suffer as a result of delaying patient access in countries where treatments are covered by Diagnosis-related group systems (DRGs)*.** Updating DRGs is a lengthy process between stakeholders at multiple levels; interim funding is often limited
Inequality of Access	Inequality within countries in terms of access to innovative therapies arises from **local budgets which vary in size, formulary inclusion** and **availability of treatment centres;** national budgets would help to alleviate this inequality
Upfront payments	Providing reimbursement upfront may not be feasible under annual funding cycles or when the cost-savings/benefits are only realized long-term
Risk exposure	**Current finance models provide upfront reimbursement, exposing healthcare budgets to risk** with little evidence of lasting benefit

Potential Solutions

- National Funding Schemes
- Annuity payments, Outcomes - based payment models, Subscription models

* Under DRGs patients are classified into a limited number clinically meaningful and relatively homogenous groups in their resource consumption patterns; means of reimbursing hospitals in many EU countries

Abbreviations *- Link to Glossary*

Innovative financing models *e.g.* national funding schemes can enable more equal and sustainable funding for expensive therapies

POTENTIAL SOLUTIONS: NATIONAL FUNDING SCHEMES

National Funding Schemes/Centralised Budgets: Schemes / budgets that are not influenced by existing silos should be adopted

- **Consolidation of siloed budgets** would enable the consideration of wider societal benefits and provide stakeholders with sufficient resources to pay for treatment without delay

National / centralised budgets

Integrated therapy area funds
Funds to cover a whole therapy area, including HC system and social care budgets

Pan-insurance schemes
Funding provided by multiple insurers to spread risk

Drug Innovation funds
Funds devoted to new therapies qualifying as innovative

Health care bonds
Private investors providing funding for a service which gov't pays a return on investment, which is time and or outcome-based

Public health taxes
Using taxes on harmful products to part-fund healthcare

- National-level funding can alleviate the **regional and local inequality** of access to innovative, high cost, treatments
  - Sub-national budget holders may not be required to prioritise services and treatments, enabling less disparate funding
- Schemes with pan-insurance cooperation could spread the risk of high innovation across stakeholder
- **Health savings accounts** into which individuals, families and governments contribute tax free, to be used for future personal or immediate family's illness, e.g. Singapore's Medisave system
- Some countries earmark funds from taxes on products which adversely affect health (e.g. tobacco) for public health and healthcare

Across the EU, innovative national financing mechanisms have started responding to the need to fund innovative treatments

EXAMPLES OF NATIONAL FUNDING SCHEMES

Innovative Medicines Fund (2021)

- Building on the success of UK Cancer Drugs Fund (CDF) established in 2016, NHS has launched a new fund to improve access to innovative treatments
- The setup of the NHS Innovative Medicines Fund (IMF) in 202 1 (£340mm) offers the prospect of early access and reimbursement to Cell and Gene therapies (CGT) especially with rare disease indications, subject to the collection of further data to support final NICE recommendations around routine use
- However, there is limited guidance on selection criteria for products to achieve funding via the IMF and on how IMF funding may impact price negotiations for a CGT once it is no longer funded through the IMF

Cures Within Reach, Social Impact Bond

- Social Impact Bonds (SIB) are an arrangement between an investor and one or more governmental organisations
  - The governmental organisation pre-specifies an outcome and agrees to pay the investor a sum upon accomplishment of this outcome
- This model has been used in US by Cures Within Reach
  - It repurposed the generic sirolimus (immunosuppressant for organ transplants), to be developed and used for a rare childhood disease ALPS[1]
- A similar model could be used to fund high cost therapies

ALPS = Autoimmune Lymphoproliferative Syndrome

Spreading the cost over time reduces the initial budget impact of treating all prevalent patients in the first-year post-launch, while ensuring access

POTENTIAL SOLUTIONS: ANNUITY BASED AGREEMENSTS

Annuity-based agreements or over time payments: Can enable HC systems to pay for innovations that either have a very high one-off cost, and allows them to manage risk of clinical uncertainty by linking payments to outcomes

ANNUITY-BASED AGREEMENTS OR OVER TIME PAYMENTS

- Includes three mechanisms currently adopted within EU:
  1. **Outcome based payment:** Partial payment upfront (50-75% of full price), followed by additional payments if certain outcomes are met
  2. **Outcome based rebate:** Full price upfront but manufacturer agrees to rebates if certain outcomes are not met
  3. **Outcome based annuity:** Payer makes annuity payments, contingent upon continued duration of therapy efficacy
- Allows the **risk of failure to be shared** with manufacturers and upfront payments to be reduced

EXAMPLES

1. Luxturna for Inherited retinal dystrophy: After initial partial reimbursement further payments triggered for Luxturna after 30 days, 90 days and 30 months (US)
   - CAR T therapies Kymriah and Yescarta in Italy and Spain
2. Rebate for Holoclar is agreed upfront if the drug fails within 12 months if treatment in Italy
   - CAR T therapies Kymriah and Yescarta in Germany
3. Zynteglo was reimbursed with 5 equal annual payments in Germany

Sources: (1) EFPIA, Shifting the paradigm for ATMPs: Adapting reimbursement and value frameworks to improve patient access in Europe

Abbreviations *- Link to Glossary*

Subscription payments offer payers increased budget predictability and therefore financial stability, but currently are least commonly used

POTENTIAL SOLUTIONS: SUBSCRIPTION PAYMENTS

Subscription payments[1]: can help payers anticipate budget impact by decoupling payment for a treatment from the number of patients that receive the therapy; may be particularly applicable in disease areas where the expected number of patients is high, though uncertain

SUBSCRIPTION PAYMENTS

- Involves a lump-sum payment to manufacturers who then provide an unlimited supply of drugs for determined time period
- This model has been referred to as the “Netflix model” and contrasts with payment based on the volume of actual drugs sold
- May help payers predict the budget impact associated with treating patients in each disease area and ensure its sustainability in the long run1
- Model differs from lump-sum payments, where a fixed amount is paid for a given volume

EXAMPLES

- Vertex Pharmaceuticals signed portfolio-based subscription deals in Denmark and the UK, offering an **unlimited access to their existing and future cystic fibrosis therapies**
- Previously this model has been successful in US with Washington, leveraging a package of services that includes outreach and testing to identify patients as well as the drugs to treat Hepatitis C (2)

The impact of innovative payment models is greatest when multiple are used in parallel; together they allow healthcare systems to benefit from economies of scale and greater bargaining power

Sources: (1) EFPIA, Novel Pricing and Payment Models: New solutions to improve patient access (2) Seattle Times

Abbreviations *- Link to Glossary*

Through introducing subscription-based model for antibiotics, the UK NHS aims to make the development of novel products more attractive

EXAMPLES OF SUBSCRIPTION BASED MODELS

Case Study: NHS' subscription-based model to combat antimicrobial resistance[1]

- Originally, the commercial attractiveness of developing antibiotics is lower than for other products due to relatively higher cost and lower returns[2]
- To address this issue, in June 2020 NHS has launched world's first subscription-based payment model for antibiotics, with the first two drugs to be selected and evaluated next year
- Scheme's objective is to incentivise investment in researching and developing new antibiotics in the face of growing antibiotic resistance[3]
- Selected pharmaceutical companies will receive upfront payments for their products, based on the value it provides to the NHS and not based on the uptake[3]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UK launches world's first 'subscription-style' payment model for antibiotics

18th June 2020


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UK launches subscription-style payment pilot to incentivise pharma antibiotics R&D

Pilot much more to industry liking, but devil will be in detail

Article by Andrew McConaghie

9th July 2019

From: Research

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GLOBAL A failure to address the problem of antibiotic resistance could result in:

10m deaths by 2050

Costing £66 trillion

Print Friendly

Sources: (1) Pfizer; (2) Pharma Times; (3) BMJ;
IQVIA | EFPIA Pipeline Innovation Review 2022

Abbreviations *- Link to Glossary*

In order to implement these models there are several logistical and regulatory challenges that will need to be addressed

CHALLENGES FACED BY INNOVATIVE FINANCIAL MODELS

National Funding Schemes

- **New regulation would be required to establish remit and responsibility** of stakeholders managing national funding schemes
- **Limited incentive for regional/local stakeholders to participate** within schemes unless savings are passed on and inequality addressed
- **Regional/local stakeholder unwilling to devolve budget responsibility** to a centralised authority could limit the negotiating power and remit of such a fund

Annuity or outcome-based agreements

- **New regulation would be required to establish in which situations annuity-based agreements are possible**
  - *For example, in US, legislation prevents staggered payments due to current government price reporting requirements*
- **Development of a framework to allow financial institutions to take on risk of failure** and provide the full payment upfront for a fee to ensure access to capital for R&D and shareholder dividends
- **Development of a robust third party patient monitoring system** to ensure both manufacturers and healthcare systems have confidence in pay-by-performance agreements

Subscription Payments

- Main challenge would be to define governance around product use beyond the agreed contract, which will require accurate tracking of utilisation and/or application of reimbursement criteria
- Additionally, it could be difficult to define terms and conditions that account for uncertainties around uptake/ usage of innovation treatments and are beneficial for both parties; regular reviews and adjustments would be needed
- Manufacturer should receive a payment on par with expected revenue and the payer should be able to manage uncertain budget impact more effectively[1]

Implementing innovative financial models requires country-specific tailoring to overcome specific regulatory and procedural barriers

Sources: (1) USC Schaeffer;
IQVIA | EFPIA Pipeline Innovation Review 2022

Abbreviations *- Link to Glossary*

We have summarised pricing and reimbursement mechanisms for currently available innovative therapies across key EU markets

	Product	Innovative Agreements			
					
SC*	Alofisel	• Approved but not reimbursed by the Italian NHS (SSN) • Agreement achieved with the region of Lombardy on a contractual price	• No Temporary Authorization for Use (ATU) • Funded through the supplementary list of costly medicines (liste-en-sus)	• Value-based pricing: Reimbursement of part or of the entire drug cost depending on patient outcomes (in the private market)	• Price structuring model *(details were never disclosed)*
In vivo	Luxturna	• A spending cap of €21.6 Mn over 24 months was implemented, which included all previous spending on the gene therapy (even costs incurred during the early access scheme), and if this threshold is crossed within this timeframe, net of any discounts achieved through negotiation, the excess needs to be refunded	• ATU and coverage with evidence development (annual re-assessment) • Transited from post-ATU funding to funding through the supplementary list of costly medicines (liste-en-sus)	• Novartis offered a significant discount on Luxturna's list price of £613,140, as that list price would have broken NHS budget rules. • NHS agreed to fund Luxturna, but discounts were not disclosed	• Billed by a NUB procedure (NUB Status-1), until end of 2021, and is now part of a DRG
In vivo	Zolgensma	• MEA - Outcomes-based agreement that is valid for 24 m and has no option for renewal **(payment at result);** Includes checkpoints for results at 12, 24, 36, & 48 mths • As part of the deal, an obligatory discount on the ex-factory price was applied at public health facilities, including those accredited by Italy's national health service (SSN) • An agreement for patients between 13.5 and 21 kg in order to acquire additional efficacy and safety data (Zolgensma was given free of charge to patients in this group who were part of a clinical trial)[3]	• ATU and coverage with evidence development (annual re-assessment within three years)	• NICE and Novartis agreed on a simple but "substantial" discount to the list price • The amount of the discount was not disclosed	• OBR linked to several patient outcomes was agreed with GWQ Service Plus AG, an insurance provider • AveXis assumed the risk of repaying up to 100% of costs
Ex vivo	Libmeldy	• Reimbursement valuation from AIFA is ongoing (as of March 2022)	• No ATU granted as of today • Received *accès précoce* as an RTU by the ANSM to cover off-label prescriptions • Negotiations are ongoing (delayed by COVID-19)	• Libmeldy was discounted twice (details undisclosed) in order to achieve a deal with NHS because it was considered as too expensive and yet to be proven in the long term	• Negotiations are still in progress
Ex vivo	Strimvelis	• MEA - Outcomes-based agreement linked to patient outcomes **(payment by result)** • Payment arrangement with AIFA, covering all European patients treated in Italy. Includes staggered payments, as well as refunds if patients have to receive another therapy or did not receive the expected benefit	• Cross-border agreements in the EU for Strimvelis with the Italian government • The French government covers treatment costs and other expenses such as travel and accommodation	• The cost of €594,000 per person plus Italian travel and hospitalization costs are covered by NHS	• Never assessed in Germany and only reimbursed in one hospital in Italy

* SC stands for Stem Cells

Developing infrastructure to support care delivery

Collaboration between stakeholders and industry is needed to ensure the delivery of cell and gene and Alzheimer's therapies

LOGISTICS AND INFRASTRUCTURE ARE CRITICAL ACCESS CONSIDERATIONS

Communication and organisation between stakeholders and manufacturers would allow for the optimal delivery innovation as not all aspects of delivery fit the traditional pharmaceutical delivery pathway and therefore require the development of new infrastructure

	Manufacturing Plants	Logistics	Specialist Centres

CELL & GENE THERAPY	• In the case of autologous CAR Ts, each treatment must be personalised
	  - Efficiency will be vital for patient's suffering from aggressive cancer
	• For all cell and gene therapies, Good Manufacturing Practices (GMP) facility guidelines result in long, high cost builds
		• Samples need to be transported to plant and back to patient
		• Per patient distribution must be:
		  - Time sensitive
		  - Temp. controlled
		  - Competently tracked
		• Contingency planning will need to be prepared in advance
			• Access is needed to specialist centres with trained staff to:
			  - Prepare patients
			  - Infuse or insert devices and observe (e.g. for CRS*)
			  - Conduct follow-ups
			• Barriers to specialist access or low patient numbers may lead to cross-border treatment, creating issues *e.g.,* reimbursement and pricing differentials, patient travel burden, QC concerns
			• Cross-border collaboration may also be needed (e.g. for ADA gene therapy (Strimvelis))

ALZHEIMERS	• N/A	• Even if an early diagnostic were available the infrastructure to screen everyone does not currently exist	• As with other mental health disorders such as Schizophrenia, Alzheimer's would require specialist early diagnosis clinics to be created

*CRS – cytokine release syndrome;

For upcoming Alzheimer's therapies to be effective, reliable patient screening infrastructure is required

EARLY DETECTION IS THE KEY TO EFFECTIVE ALZHEIMER'S TREATMENT

Alzheimer's Disease – The need for early disease diagnosis

- The burden of Alzheimer's disease (AD) in Europe is expected to nearly double by 2050[1]
- Recent clinical development gives hope that disease modifying therapies might become available in the near future; based on previous trial results, these therapies will likely provide **greatest benefits to early stage AD patients through preventing or delaying disease progression**[2]
- With this preventive treatment paradigm, it will be crucial to screen and diagnose large numbers of patients with mild dementia[2]
- **The first step** in preparing the healthcare systems for DMTs in Alzheimer's is **development of a reliable and accessible marker to identify the right patient population for the treatment** (e.g. blood test)
- **And the second step** is to provide **large-scale capacity for patient diagnosis and treatment delivery,** especially in short-term, to avoid long wait lists and patients progressing from early to late stage, where the treatment may rend ineffective[3]

Alzheimer's Disease Health System Readiness – The Time to Act is Now[3]

- Current **AD diagnostic pathway involves several medical assessment steps**: medical history verification, physical and neurological exams, mental status and mood testing
- If MCI* is confirmed in initial evaluation and no alternative explanation is found, patients are referred to biomarker testing
- **Confirmatory biomarker testing** is an important step in accurate diagnosis of Alzheimer's Disease. At the moment available tests include a lumbar puncture (Cerebrospinal Fluid - CSF) and neuroimaging (amyloid PET scan)
- However, **at the moment these solutions are not widely used in clinical practice** – due to barriers related to CSF/amyloid beta testing reimbursement, as well as high price and limited scalability of PET scans
- This results in significant delays in the current Alzheimer's Disease diagnosing; **therefore HCS should focus on increasing the access to diagnostic tests before the DMTs become available**

(*) MCI – Mild cognitive impairment

Sources: (1) Alzheimer Europe Yearbook 2019; (2) NCBI; (3) EFPIA - Alzheimer's Disease Health System Readiness – The Time to Act is Now

Joint investment in centres of integrated care would ensure the highest quality of care for patients

POTENTIAL SOLUTION: JOINT INVESTMENT IN CENTRES OF CARE

Manufacturing

- In order to limit logistical difficulties, manufacturing facilities of CAR Ts and cell therapies could occur at centers of excellence
- The potentially high cost of building such facilities could be shared by manufacturers and public to reduce the risk to either stakeholder
- Quality control could also take place in the center of excellence

Both Govt. and Private parties can collaborate from early on and reduce the burden of each aspect of care delivery

Integrated Care

- Centres of care could provide the newly developed services for CAR T and Cell and Gene therapy patients
- Facilities would also be able to train specialists
- Considering the low prevalence of patients with single-gene mutation diseases, countries may group together to invest in centres which would address inequality of access
- Focus on specialist procedures would maximise efficiencies and effectiveness

Some centres of excellence have already been set up to increase expertise and efficiency in delivering innovative care

Centers of Excellence: Cell and Gene Therapy Manufacturing

Catapult, UK

- Catapult centres are a network of world-leading centres designed to transform the UK's capability for innovation in specific areas
- The Cell and Gene Therapy Catapult provides the infrastructure and a team of onsite specialists across the cell and gene therapy life cycle, to help companies to perfect their manufacturing processes and scale up quickly
- In 2020, UK government invested £100 Mn into the expansion of this facility for large scale production of COVID-19 vaccines
- Has worked with 30+ national and international companies across Europe, US, South Korea, Japan and Brazil, along with key regulatory agencies including European Commission and FDA

Centers of Excellence: Alzheimer's Disease Early Detection

Karolinska Hospital, Sweden

- At the Karolinska Hospital, a new Highly Specialised Cognitive Reception (HSCR) has been set up, which aims to improve speed of Alzheimer's diagnosis
  - It can provide a result within five days, compared to standard investigation time of three months
- The HSCR aims to identify the fastest and most accurate way to diagnose patients
  - The assessment uses a multi-professional team, including neuropsychologists and occupational health, and requires both lumbar puncture and MRI scanning

Source: Fierce Pharma, Karolinska Institute website

Abbreviations *- Link to Glossary*

Possible solutions for CAR Ts include the development of large treatment facilities or the distribution of cell-processing services

EXAMPLE OF POSSIBLE CAR T INFRASTRUCTURE

Large Treatment Facility

- Co-location of **trained staff and manufacturing facilities** will eliminate need for transportation of modified cellular material, ensure access to highest care standards, and result in savings from economies of scale
  - ADA gene therapy (Strimvelis) *(for ADA-SCID)* has adopted this model, being manufactured **and** administered in Milan
- However will require patient travel burden and **large investment from industry**
  - Governments/providers can **encourage investment in large, cross-manufacturer facilities** to reduce the required investment
  - This will reduce potential variation between individual plants and services
  - For cross-market facilities legislation is needed to allow for differential pricing

Distribution of cell processing services

- Larger specialist centres could use a **scaled-down cell-processing device**
- **Manufacturers would supply** disposable reagents, such as tumour antigens
- This **resembles more traditional delivery pathway** as product does not need to be personalised until reaching the hospital
- However **further research into feasibility** of device/manufacturing GMP **and cost** is required

"In terms of adaptation to delivery, it is not going to be as difficult as people fear. The infrastructure exists in specialist centres with SCT facilities" – ***Haematology KOL***

Risk management plans were adopted to lower risk related to CAR T administration; now, interest in outpatient therapy is on the rise

CURRENT REQUIREMENTS TO CAR TS ADMINISTRATION AND POTENTIAL FUTURE SHIFTS

Current Settings

Examples from Europe show strict requirements for CAR Ts administration from accredited centers[1,2]

EMA: Kymriah and Yescarta have agreed to risk management plan with EMA to monitor and mitigate safety concerns related to the therapies' administration; plan covers among others:

- Requirements regarding **treatment centre qualification** (e.g. JACIE accreditation*)
- Requirements regarding **qualifications and training of healthcare professionals** supervising the treatment; **patient education program** is also mandatory
- **Availability of tocilizumab** to manage cytokine release syndrome (CRS), common systemic response to the activation and proliferation of CAR T cells

- **National authorities** across EU markets have published additional specifications, *e.g.* Germany requires centres to have extensive experience in given TA and in stem transplants, an established tumour board and an ICU** in the vicinity

Future Potential

The question for the future is: is outpatient use for CAR TS feasible?

Currently, the **interest in potential CAR Ts administration in outpatient setting is growing**

- Recent analyses show that the move to outpatient setting — specifically the community oncology outpatient setting — could be favorable for reimbursement (through lowering the procedure costs) as well as for patients[3,4,5]
- **However, there are major challenges to overcome before this change will be possible**
- One of the major issues is related to commonly observed toxicities resulting from the treatment, with CRS as a primary concern; outpatient setting would require close patient monitoring for potential CRS or neurotoxicity[6]
- Potential way to address this issue is to investigate outpatient treatment in patients with lower tumour burden and therefore lower risk of adverse events; **however, for this to be possible, CAR Ts would need to be available in earlier therapy lines[6]**

(*) Joint Accreditation Committee ISCT-Europe & EBMT; (**) Intensive Care Unit
Sources: (1) CAR T Treatment dynamics and funding, IQVIA November 2019; (2) EMA; (3) AJMC; (4) Cancer Therapy Advisor; (5) Med City News; (6) Healio

Abbreviations *- Link to Glossary*

Complex procurement and supply process set up for distribution of COVID-19 vaccines can be leveraged for delivery of other mRNA vaccines

Rapid deployment of billions of COVID-19 vaccines was made possible by collaboration among key stakeholders, led by UNICEF

Understanding the demand

Vaccine demand and studies on cold chain equipment and safe injection devices were used by UNICEF to develop procurement strategies ensuring demand met supply

Long term contracts and procurement of non-vaccine material

- UNICEF aligned with manufacturers for long term contracts
- Brought 1 billon syringes, 10 million safety boxes and necessary cold chain equipment

Ensuring authenticity and traceability of vaccines

Labelling of vaccines with GS1 barcodes to enable the traceability

Transport and delivery

In December 2020, UNICEF, through the World Economic Forum, signed a charter with major logistics operators to collectively support this mammoth global undertaking.

Preparing countries to receive and rollout vaccines

UNICEF, along with WHO, has mapped out existing cold chain equipment and storage capacity in the private as well as public sector and prepared guidance for countries to receive the vaccines. Since 2017, 84,000 cold-chain fridges, including solar fridges, have been installed across health facilities

Vaccination received by COVID patients

Waste Management

Medical waste produced by vaccination programs requires safe collection and final disposal to eliminate potential health risks to health care workers and the public

Public information and vaccines dashboard

In December 2020, UNICEF launched the COVID-19 Vaccine Market Dashboard – an interactive tool for countries, partners, and industry

Sources: (1) UNICEF.org
IQVIA | EFPIA Pipeline Innovation Review 2022

Abbreviations - Link to Glossary

Optimising patient management/ treatment strategies

Collaboration and early discussions around integration into current treatment paradigms will be vital for optimal patient access

POTENTIAL SOLUTIONS: COLLABORATION BETWEEN STAKEHOLDERS AND MANUFACTURERS

Through early collaboration throughout the drug and patient journey, manufacturers, healthcare system payers and clinical guideline authors will be able to achieve the best outcomes for patients

Drug and Patient Journey

Clinical Trial Design

- Collaborate to **design clinical trials** to ensure outcomes will be accepted as satisfactory evidence of safety and efficacy
- Furthermore, if the treatment paradigm shifts, **adequate powering of trials** and **patient stratification** will be required to support **which** patients and **when** patients should receive the new technology

Drug and Biomarker Development

- Payers support the **development of biomarkers or diagnostics** for targeted treatment by providing clear development guidelines
- Early collaboration to understand the **impact on healthcare systems** and value the innovation accordingly will be important to ensure swift access

Patient Management

- Collaborate to develop new approaches to patient management in order to **optimise patient outcomes** and **reduce the risk of adverse events**
- **Periodically review the management strategy** through **real world data collection** and **evidence generation** to ensure efficiencies are made and **patient management is optimised**

Throughout, develop clear understanding of which stakeholder is responsible for which action

Abbreviations *- Link to Glossary*

New innovations present a challenge as they are disruptive to current treatment paradigms and require guideline revision (1/2)

IN ORDER TO OPTIMISE THE BENEFITS OF INNOVATION, CHANGES TO CURRENT TREATMENT WILL BE REQUIRED

Patient Management

Disease Modifying Therapies for Alzheimer's

- Clinical trials only occur in moderate or severe patients, whereas benefit could be seen in mild disease
- There is still need for reliable and **more accessible biomarkers** to reach high patient populations and identify patients who are going to develop Alzheimer's
- If a DMT becomes available, **wide-spread screening** would need to be implemented
- The trials to determine benefit in early and pre-dementia patients requires a long timeframe and many patients
- Guidelines will have to reflect upon which **patients will benefit most** based on the evidence available

Treatment Strategy

Oncology Combinations

- Since the number of oncology combination therapies is growing rapidly, guidelines have not been able to keep up with the pace of launches
- Physicians will need to have **reliable and accurate methods of choosing combination treatments** for patients
- Manufacturers will therefore need to **identify sub-groups of patients** with optimal efficacy profiles
- Additionally, advances in biomarker research and development will enable optimisation of patient treatment strategy

New innovations present a challenge as they are disruptive to current treatment paradigms and require guideline revision (2/2)

IN ORDER TO OPTIMISE THE BENEFITS OF INNOVATION, CHANGES TO CURRENT TREATMENT WILL BE REQUIRED

Treatment Strategy

Remyelinating therapies for MS

- Remyelinating therapies for Multiple Sclerosis hold the promise to reverse some of the disease effects on patients' disability (mobility, vision, cognition)
- They will likely be used as add-ons to the Disease modifying therapies already in use
- Therefore, it will be **crucial to define the role of remyelinating drugs in current treatment paradigm** next to existing therapies
- As well as **establish guidelines to prioritise novel treatment** for patients who will benefit most based on the evidence available

Guideline Revision

mRNA vaccines

- Both preventative and therapeutic mRNA vaccines are in the clinical development
- Therapeutic vaccines in oncology can potentially be life saving for certain patient groups, allowing them to live longer, healthier lives
- Preventative vaccines for SARS-CoV-2 (COVID-19) were the first mRNA vaccines to reach the market
- Relevant guidelines should be established to **facilitate the development and authorisation of mRNA vaccines in other TAs** after the pandemic

Advances in biomarker development are critical to reap the benefits of innovative cancer treatment therapies

CASE STUDY: ENABLING DIALOGUE TO BETTER INTEGRATE BIOMARKER DEVELOPMENT IN DRUG DEVELOPMENT

Innovations and Biomarkers in Cancer Drug Development Conference (IBCD) 2022 is expected to take place in Spain to tackle key questions including:

1. **Does Whole Genome Sequencing have real value for health care settings?**
2. **Will Real-World data challenge classical trial designs?**
3. **Are biased biomarker-statistics an issue in biomarker-driven trials?**
4. **Are Laboratory-Developed tests a good alternative to regulatory-approved assays?**

THE IMPORTANCE OF BIOMARKERS IN DECISION-MAKING DURING DRUG DEVELOPMENT CONTINUES TO INCREASE

- Biomarkers can improve clinical trial efficacy and reduce uncertainty in regulatory decision making
- Biomarker based strategies enable:
  - Identification of patient sub-groups that can potentially benefit most out of a therapy
  - Help in monitoring safety and efficacy of a drug
  - Determine if the treatment is having the desired effect
  - Potentially enable time and cost savings in clinical trials
- Focus of the IBCD convention is to explore how biomarker assay development could be more effectively integrated into drug development and regulatory approval processes to drive further progress in cancer-related precision medicine

Source: IBCD, EPFIA - Unlocking the potential of precision medicine in Europe – Improving cancer care through broader access to quality biomarker testing
IQVIA | EFPIA Pipeline Innovation Review 2022

Abbreviations *- Link to Glossary*

Manufacturers are developing approaches to support and improve informed HCP decision making using registry patient data

CASE STUDY: USING RWD TO TAILOR TREATMENT PLANS TO PATIENT NEEDS

TAKEDA INSIGHT-MM: Informed decision making with RWE[1,2]

- Rare diseases, such as Multiple Melanoma (MM), **often lack large data sets due to the scarcity of patients**
- Hence, HCP decision making is **based on limited evidence**, compromising the quality of care for rare disease patients
- **INSIGHT-MM** is the largest, pharmaceutical-company-sponsored global observational study of its kind, with the purpose to describe "real world patterns of patient characteristics, clinical disease presentation, therapeutic regimen chosen, and clinical outcomes in participants with newly diagnosed MM and with relapsed/refractory MM"[2]
- **~4,200 patients were enrolled** between 2016-2019, and are **followed up over 5 years** – the study spans across the globe, with 150 trial sites and expected to complete in July 2024

Payer / physician's perspective[1,2]:

Designed to be collaborative, **INSIGHT-MM remains open for the MM community** to **propose analyses** and **request data** to better understand MM and improve on current treatment practices

Guidelines for Registry-based studies: EMA

- In 2020, EMA developed guidance for RWE to validate the importance of these studies and provide additional structure for their implementation
- The guideline focuses on studies using disease registries as a data source

PHARMA

Takeda takes collaborative, open-source path to gather data on multiple myeloma

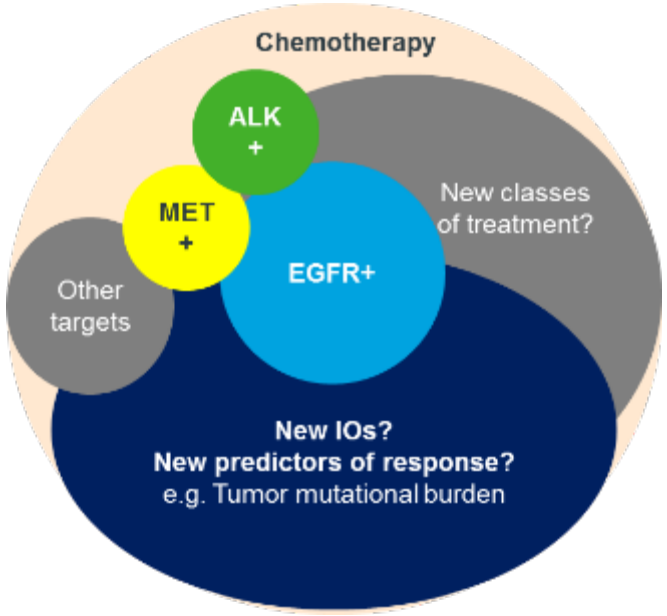
Takeda Pharmaceuticals launches what it bills as the largest pharma company-sponsored observational study in mutiple myeloma that aims to enroll up to 5,000 patients worldwide and follow them for a minimum of five years.

Source: (1) Takeda, (2) ClinicalTrials.gov; (3) EMA

Abbreviations *- Link to Glossary*

At least in oncology, treatment is becoming increasingly complicated; paradigms may need to shift to being more holistic

CASE STUDY: EVOLUTION OF TREATMENT PARADIGM IN NON-SMALL CELL LUNG CANCER (NSCLC)



For NSCLC treatment, focus is moving away from site-specific mutations / biomarkers towards tumour mutational burden[1] and treatment of non-site specific tumours with a single type of mutation

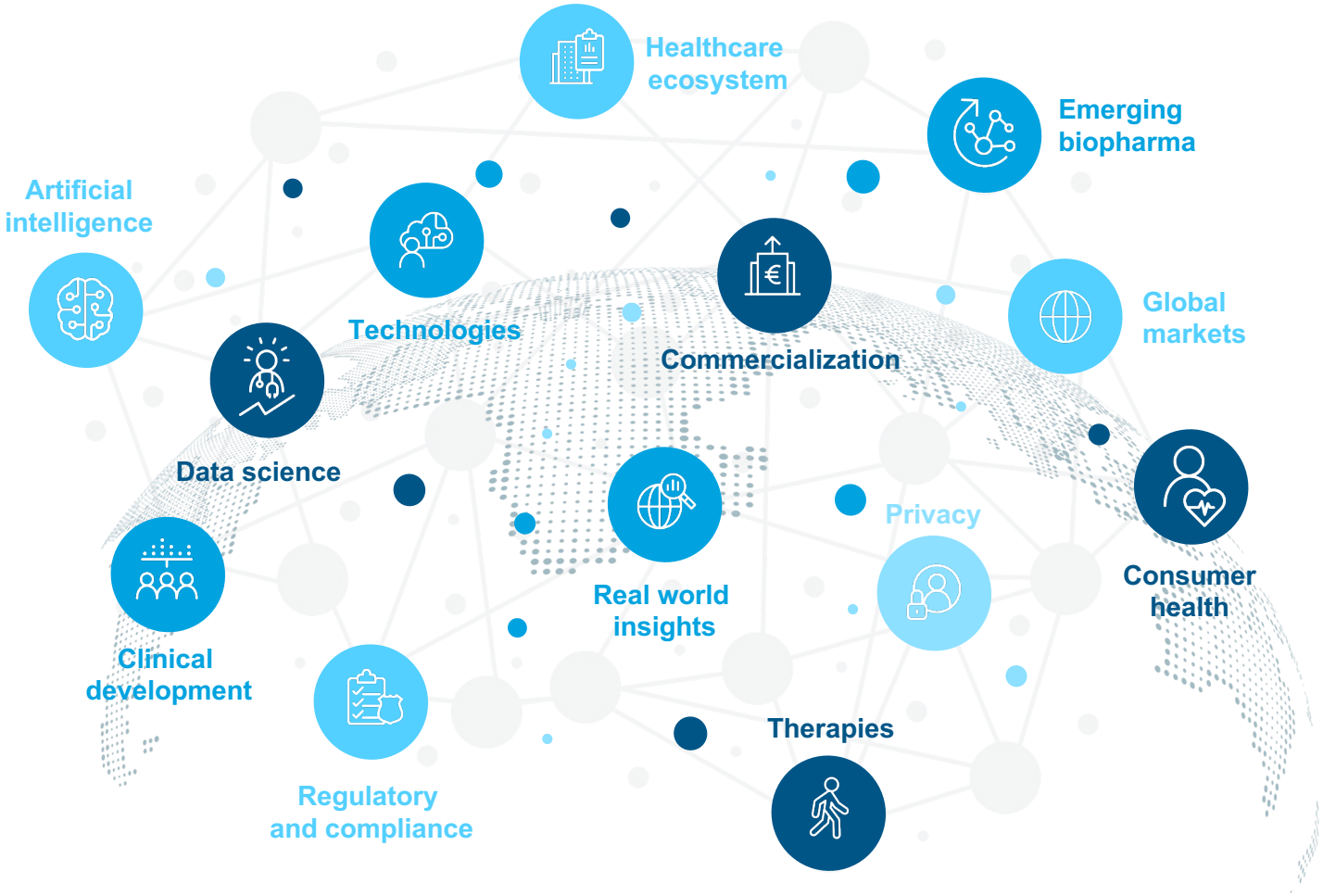
- Pembrolizumab (Keytruda) was the first product to gain approval by the FDA for a pan tumour indication
  - It received authorisation in unresectable or metastatic solid tumours that have been identified as having MSI-H or dMMR biomarker
- Although data was sufficient in US, clearer evidence for biomarker specific efficacy is needed in EU
  - EU payers have faced challenges assessing the first EMA approved pan tumour product Vitraki (larotrectinib) due to unclear comparative benefit across populations and uncertain budget impact of the product upon expansion
- The ability of next generation sequencing (NGS) to identify multiple biomarkers or mutations can facilitate this shift in the treatment paradigm

Note: A tumour is not made up of all cells with the same types of mutations. A single tumour can have cells with several different types of mutations
MSI-H = Microsatellite instability-high; **dMMR** = deficient DNA mismatch repair

Enabling data science and technology partnerships

With increasing importance placed on outcomes, leveraging technological advances for RWD can be the key to delivering impacts

ADVANCED ANALYTICS ARE UNLOCKING NEW WAYS TO LEVERAGE RWD AND RWE



- The focus is shifting from traditional measures to demonstrate value such as randomized clinical trials and traditional uses of Real World Evidence (RWE)
- More emphasis is now being placed on leveraging digital advances and advanced analytics to find new innovative uses of RWE
- In this changing climate, the insights generated from RWE is taking an increasingly pivotal role in understanding of the effect of patient centric data on health outcomes
- For example;
  - Predicting disease progression
  - Predicting patient response
  - Predicting risk of adverse events
- Ultimately, to enable RWE to fulfil its potential, the right framework needs to be established

Source: McKinsey & Co

Regulatory acceptance and rising demand from stakeholders has already begun to pay dividends

EXAMPLES OF STAKEHOLDER ACROSS THE INDUSTRY THAT HAVE SUCCESSFULLY LEVERAGE RWE

CASE STUDY 1: SALFORD LUNG STUDIES

- Sponsored by GSK, the Salford Lung Study was a first of its kind combining the gold standard of a Randomised Controlled Trial (RCT) with RWD observed from patients
- The study bridged the gap between the lack of real world setting in RCTs and the bias of gathering RWD from observational studies by combining the robust methodology of an RCT with the benefits of an observational study
- The study proved effective in demonstrating the value of the treatment in a *real world setting*
- Ultimately, the study sparked interest in the commercial world for more “real world” methodologies

CASE STUDY 2: AVELUMAB APPROVAL

- Avelumab is a mAb developed for the treatment of metastatic Merkel cell carcinoma (MCC) which received orphan designation from the FDA
- Lacking a Standard of Care for mMCC, investigators leveraged RWD from historical observed clinical outcomes in patients with mMCC treated with chemotherapy to establish a benchmark efficacy in a real world setting
- As a result, investigators were able to use Real World Evidence (RWE) to demonstrate the efficacy of avelumab compared to the benchmarked data
- The effort proved effective leading the accelerated approval for avelumab from the FDA

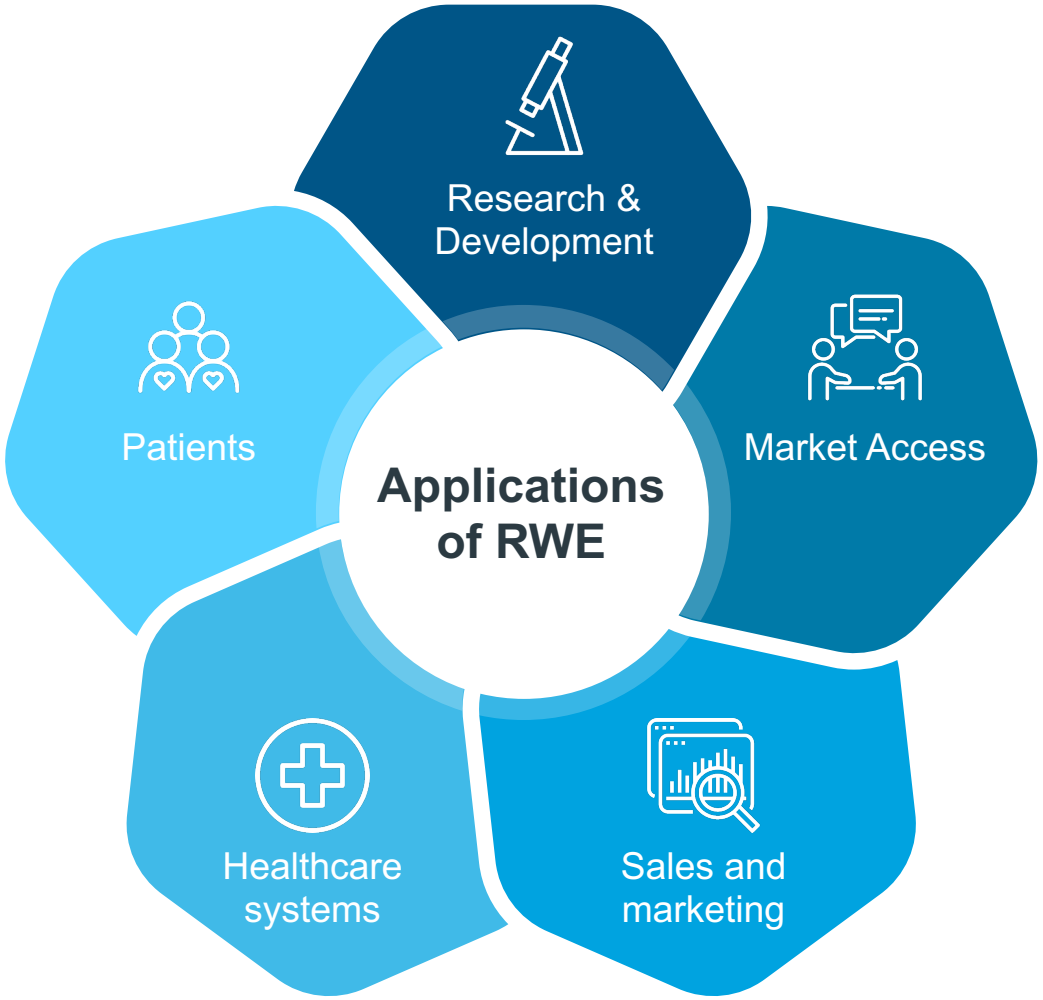
CASE STUDY 3: PATIENTSLIKEME & ALS

- PatientLikeMe is a data patient-centric platform enabling patients with similar conditions to share personal health data with each other, enabling data aggregation and support
- For ALS, researchers leveraged data from this platform to find that 9% of patients with ALS in the community used lithium carbonate in their treatment basket, but did not have regulatory approval
- As a result, this motivated a larger observational study investigating the use of lithium carbonate in ALS patients

Source: (1) Clinical & Medical Affairs, (2) Pragmat Obs Res, (3) The New England Journal of Medicine, (4) SagePub

Abbreviations – *Link to Glossary*

As the RWE transformation continues, we can expect more sophisticated information extraction and deeper insights across five fronts



Research & Development

- Accelerate treatment development and drug discovery
- Predicting patient response
- Optimizing clinical trial design
- Predicting adverse events of different treatment options

Market Access

- Demonstrate treatment values
- Support hybrid approach between observational studies and RCTs
- Enable outcome-based pricing
- Generate stronger evidence of efficacy and value

Sales and Marketing

- Identify greatest unmet need
- Screen for patients with the greatest propensity to switch treatments
- Predict regulatory success

Healthcare Systems

- Accelerate patient diagnosis
- Shift paradigm from treatment to prevention
- Facilitate treatment selection and optimize effects

Patients

- Optimize treatment line
- Identify and mitigate predispositions to diseases
- Accelerate access to treatments

Source: McKinsey & Co
IQVIA | EFPIA Pipeline Innovation Review 2022

Abbreviations *- Link to Glossary*

Such developments only represent the tip of the iceberg, with many more opportunities and applications of RWE to be explored

CONTINUOUS RWE INNOVATION WILL PAVE THE WAY FOR INCREASINGLY SOPHISTICATED APPLICATIONS

01 Artificial Intelligence & Data Science

- As the Artificial Intelligence landscape continues to thrive, the continuous innovations spills over into healthcare unlocking many novel applications of RWD yielding limitless possibilities
- Model evaluation and explainable Artificial Intelligence (AI) will enable practitioners to gain increasingly further insights into their fields by leverage RWD - leading to AI assisted innovations
- As the Data Science (DS) and AI talent pool continues to grow, stakeholders will be able to pursue larger RWD initiatives accelerating its widespread adoption

02 Digital health platforms

- Increasing innovation and adoption of AI & DS technologies within the pharmaceutical industry promotes entrepreneurial initiatives leveraging and generating RWD for patients, practitioners and healthcare systems
- For example, Babylon Health is a digital care company that combines an AI powered platform with virtual clinical operation for patients and Benevolent AI that is using AI to accelerate drug discovery

03 Personal health technologies

- Increasing provision and adoption of digital health platforms is empowering individuals to generate, track and share health data in platforms such as PatientsLikeMe
- As patients become increasingly willing to share personal health data, the need for more AI & DS initiatives will grow, perpetuating the cycle

However, to take advantage of data-centric innovations, stakeholders will need to continue to confront several hurdles

SOLVING THESE HURDLES WILL BE CRITICAL FOR THE SUCCESS OF RWD INITIATIVES

1 Framework

- To fully integrate RWD applications in the pipeline, stakeholders will need to invest in a robust framework on 5 fronts; RWD integration, Expertise, Partnerships, Data, Capabilities
- Specifically, data pipelines will be required contributing to an extensive ecosystem across groups of mutually reinforcing

2 Regulations

- Current regulation and policy at national and international level on these new data technologies is generally limited or unclear
  - Clinical data requirements are not well defined
  - Exact standards defining quality are limited

3 Guidelines

- New data technologies often struggle to generate meaningful data through clinical trials, as meaningful outcomes are not defined
- Guidelines generally cannot integrate new technologies into guidelines without strong evidence
- Yet RWE cannot easily be generated without incorporation into clinical guidelines

4 Awareness

- Due to the relatively new concept of these data technologies, and relatively slow change in payer views, EU payers are generally not aware of new data technologies and their benefits
  - Uptake and use is generally low across Europe

Establishing a robust framework is critical for the success of any RWE initiative and can be broken down into 5 key areas

ESTABLISHING ROBUST SETTING FOR EACH AREA IS KEY FOR THE SUCCESS OF RWE APPLICATIONS

1 Governance

- Capability groups are needed to oversee RWE initiatives, and ensure integration of evidence generation
- Collaboration between RWE initiatives and other key business function to identify opportunities and align on approach

2 Expertise & Capabilities

- To deliver at scale, a code of practice needs to be established and followed
- Standardized pipeline capabilities are required to handle automated evidence generation
- Understanding of evidence generation across functions

3 Collaboration

- Collaboration with innovative RWD centric start ups
- Collaboration between manufactures, payers and regulators ensures that initiative have real impact and value
- Collaboration with academic guarantees optimal application

4 Data

- Building robust relationships with data providers ensured proprietary access enabling robust data applications and impact
- Collaborating with patients to access patient-centric data
- Data storage is also key to guarantee capture and access for all stakeholders

5 Ecosystem

- In house environment for data exploration and experimentation for various use cases and models
- Automated pipelines across business functions for data ingestion
- Platform provision for data generation across indications and therapies

National and international regulations are needed to set clearer targets and guidelines for all stakeholders

REGULATION IS NEEDED TO ENSURE QUALITY AND ACCESS

STANDARDISED DEFINTIONS

- *Although General Data Protection Regulation (GDPR) legislation has provided a governance framework – harmonization and implementation mechanism are lacking*
- Better defining data types and analysis platforms will help to improve transparency and harmonization
  - The FDA published guidance to further define what is meant by clinical and patient decision support software
- It will be vital the EMA and national policy makers follow suit, to ensure standardisation, lowering hurdles for industry and confronting the obstacle of interoperability
- The EU has begun to address the problem of interoperability with its Data Act that aims to create a robust framework to encourage data sharing across borders

DATA COLLECTION

- *On top of a standard definition, a standard policy is needed to ensure data is gathered homogeneously; cooperation or joint research ventures between registries and/or EU policy makers is key*
- Electronic patient health records throughout Europe would ensure quality and access to homogenised data for decision makers
- Real world data (RWD) is often classified, captured, stored and reported differently across different registries, markets and databases due to different standards
- This prevents many data sources from being aggregated or compared with one another without the use of expensive natural language algorithms

Improvements in quality and access of data via clear guidelines will improve strength of analyses and accelerate developments on innovations

CLEAR GUIDELINES WILL ALLOW INSIGHTS TO BE MORE ACCURATE AND RELEVANT

DATA GENERATION & QUALITY

- *Involving a third party to collect and anonymise data or approaching patients directly would address concerns of healthcare practitioners regarding privacy*
  - It could also assure HTA/market access stakeholders of quality and reliability
- Current attempts to collect data are often hampered by the reluctance of practitioners or patients to provide personal information to an organisation they do not trust

DATA ACCESS

- *Buying existing data, collaborating with academic partners or accessing public funded databases remain the most common forms of gathering data; guidelines and innovative* intellectual property *(IP) agreements are need to encourage the distribution of data*
- *Legal frameworks are also needed to ensure data can be shared between EU and non-EU markets*
- With introduction of GDPR, there is a need for clear harmonised rules on the primary and secondary use of data
- There is currently discussion over IP rights and the legality of sharing information between data centres

Collaboration between key stakeholders is key to ensure the innovations are converted into large scale impacts

COLLABORATION WILL ENSURE THE RWD INNOVATION HAVE REAL IMPACTS

PHYSICIANS

- *Physicians need to adopt new technologies consistently; whether it be electronic medical record systems used by themselves or encouraging patients to use eHealth/mHealth platforms*
- Data is increasingly collected in the primary care/community setting but physician time and training is often lacking to enable this

MARKET ACCESS

- *Payers can take advantage of data collection initiatives for reporting and analysis by proactively incorporating them into existing value assessment processes and financing models*
- To date, stakeholders have been cautious to embrace novel analytical techniques or encourage collection of RWD

MANUFACTURERS

- *Collaboration between healthcare systems and manufacturers at an early stage in the development of data capture tools is necessary to ensure that they capture relevant RWD and conduct informative analyses to help inform HCSs make decisions*
  - *The introduction of GDPR in May 2018 has improved data governance and legislation, but implementation mechanisms are still lacking further increasing the importance of relevant data collection initiatives*
- The systems required to capture RWD vary depending upon the setting in which they are offered and the variables under observation

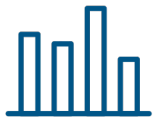
Further, increased payer engagement, manufacturer investment and academic involvement will also be vital for the uptake of new technologies

FURTHER COLLABORATION AND INVOLVENT IS CRITICAL TO OVERCOMING IMPLEMENTATION HURDLES

PAYER ENGAGEMENT

- **There is heterogeneous** and **unclear funding pathways** across markets for new clinical decision support software
- Building **payer engagement** is vital to gain national or regional recommendations (e.g. inclusion in NICE guidance for OncotypeDx, QRISK)
- Payer engagement will:
  - Generate a clear **reimbursement** pathway, or
  - Increase **likelihood** of **available funding**
  - Drive **physician uptake**

MANUFACTURER INVESTMENT



- Healthcare systems often lack the capacity or capability to set up this infrastructure independently
- Manufacturers could support healthcare systems to set up initiatives
- Many have already invested in these initiatives and have experience handling real world data, large data sets, and predictive analytic suites

ACADEMIC INVOLVEMENT

- Academic stakeholders, including thought leaders and disease /technology experts will be vital in driving forward the adoption of technology
- Already, physicians with a professional interest in clinical decision algorithms are starting to adopt these algorithms into clinical practice
  - Further use and advocacy by these leading physicians, will be vital to drive further acceptance and uptake

Abbreviations – Link to Glossary

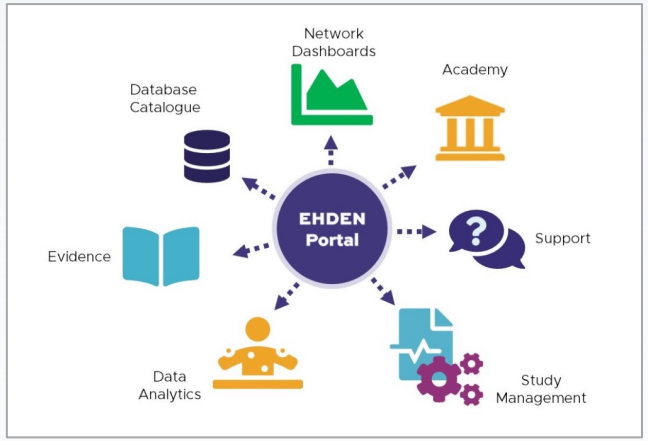
Cross-industry initiatives that were put in place to ensure that data is used in an optimal and efficient way are already beginning to pay dividends

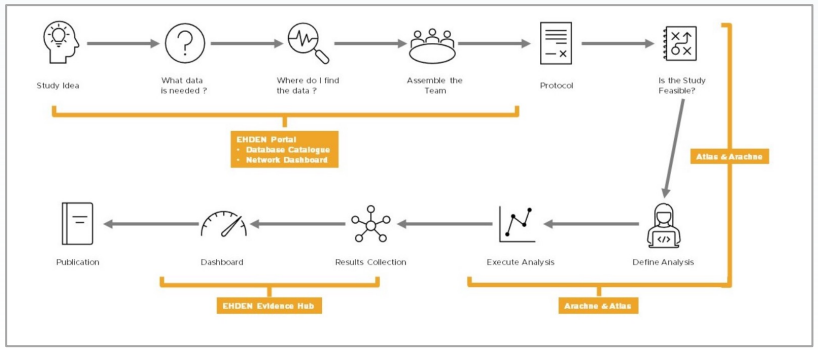
EHDEN IF FACILITATING COOPERATION FROM EUROPEAN HI* THROUGH DATA EXCHANGE AND ANALYSIS

Case Study: EHDEN (European Health Data and Evidence Network)

- EHDEN is a cross-industry initiative of 22 partners who are working together until 2024 to **create a large-scale, standardized network of data sources** to harmonise around **Electronic Health Records** across multiple data sources such as hospitals and primary care networks
- This will enable streamlined collection and analysis of real-world clinical and **generating insights based on this data**, to support patients, clinicians, payers, regulators, governments, and the pharmaceutical industry in providing better health decisions, outcomes and care
- In 2022 the EHDEN Portal was launched providing free **access to over 500 million unidentified patient records** to the research community.
- The launch of the platform represented the first successful steps in **a wider imitative to facilitate research and study workflow to analytical results**.

EHDEN
EUROPEAN HEALTH DATA & EVIDENCE NETWORK





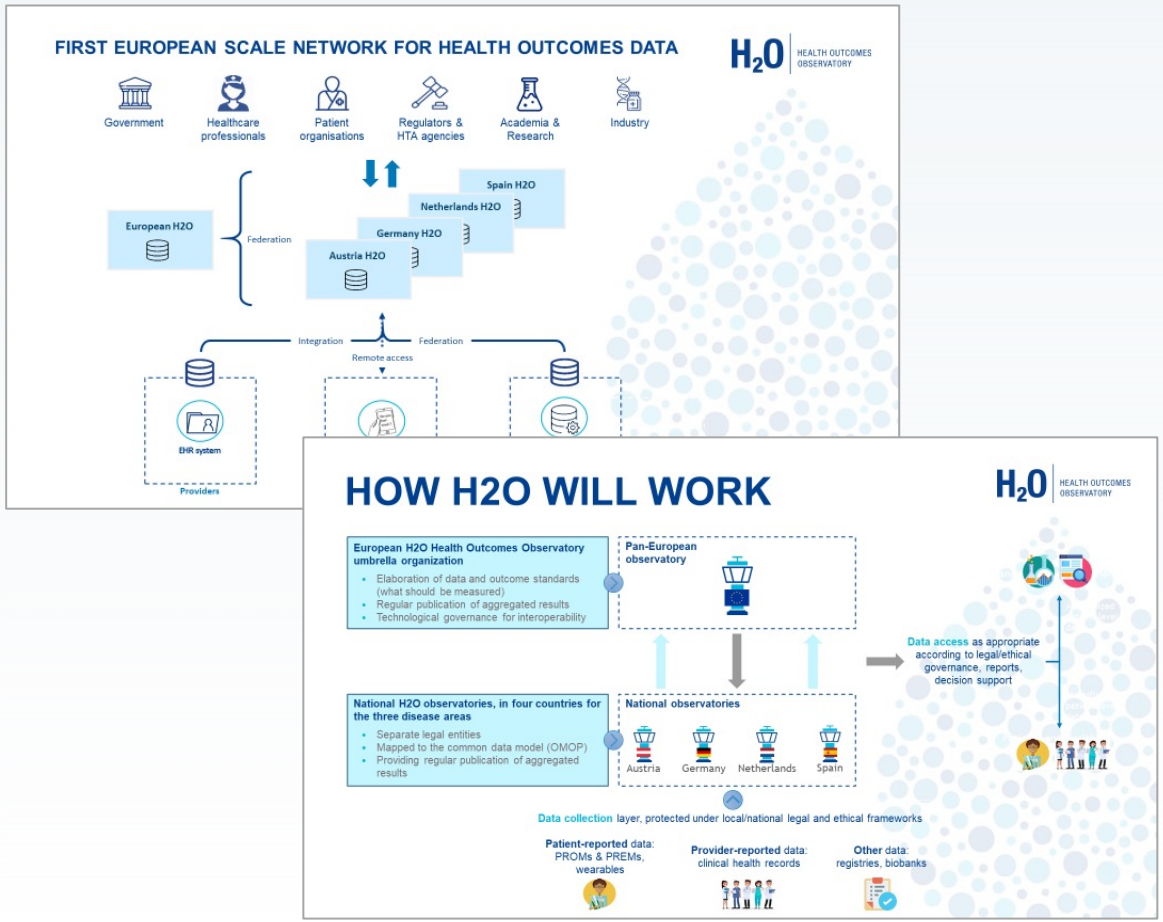
Abbreviations – *Link to Glossary*

The IMI H2O project sets up "outcomes observatories" in EU countries to collect standardised patient reported outcomes

H2O IS COLLECTING PATIENT REPORTED OUTCOMES IN SELECTED DISEASE ARES

Case Study: H2O (Health Outcomes Observatory)

- Today, many measures of disease (and disease outcomes) are based largely on input from clinicians. As such they **do not fully capture patients' own experiences** of the disease and its impact on their lives
- The aim of H2O is to create 'health outcomes observatories' that will **amplify the patient voice** by **providing patients with digital tools**, to report their health outcomes which **will then be anonymised and tracked** so that clinicians can compare their progress with other patients with similar health issues
- In February 2022 H2O announced it would be collaborating with public health partners to lead and advise the **first pan-European Observatory**
- The Pan-European H2O Health Outcomes Observatory will be a **virtual "hub" for the collation and sharing of Patient Reported Outcomes (PROs)** with patients, providers, regulators and healthcare decision makers



Abbreviations – *Link to Glossary*

EFPIA is committed to working with all stakeholders to revolutionise healthcare into an integrated, people-centric and outcomes-based system

The Issue

- Fragmentation and lack of interoperability is holding back the digitalisation of the health sector
  - According to EFPIA's POWERUP report, approximately 80% of health data remains untapped(1)
- There is a need to move towards more outcomes-based decision making
  - Here, healthcare systems will focus on paying specifically for realised improvement in patient outcomes, rather than for an intervention with putative effect

The Solution

- Such a digital transformation would require an EU-wide collaboration between key stakeholders
- A clear and transparent governance framework is needed to ensure accountability, and availability of health data
  - Focus on people-centricity and societal benefit which will incentivise health actors to improve health outcomes
  - Patient ownership of data and harmonisation of consent across Europe is essential for uptake of digitalisation
- Ultimately data needs to be FAIR* to ensure the success of the digital transformation of healthcare

The Cause

- There are a number of obstacles to overcome before the full power of a digitalised health sector can be harnessed:
  1) Data collection systems need to become interoperable
  2) The collection, format and quality of the data needs to be homogenised across systems and countries
  3) Infrastructure and a robust legislative framework needs to be established for sharing data – especially across borders

The Outcome

- Better stakeholder engagement with health services and researchers
- Improved decision making about patient care
- More efficient allocation of resources for payers
- Better value and unmet need identification for manufacturers
- Overall - a more resilient healthcare system that is able to learn and adapt

Source: EFPIA Power Up Health System; Note: * Findable, Accessible, Interoperable, Re-usable

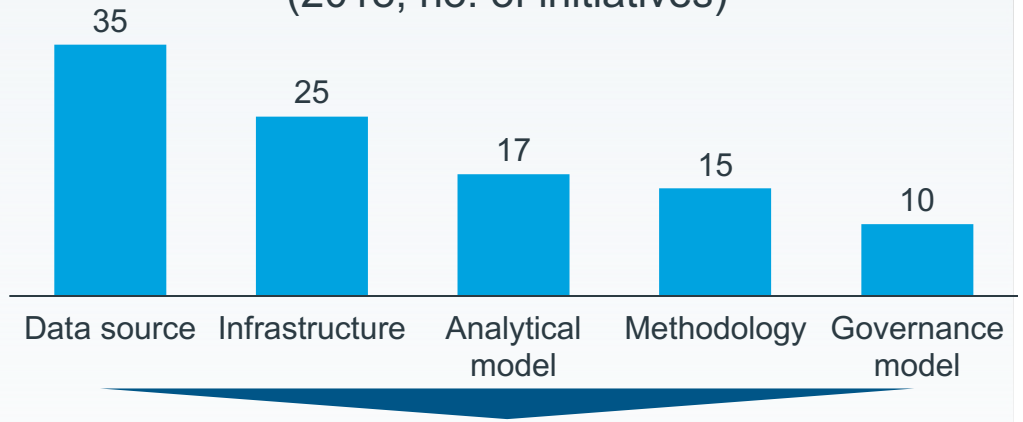
Abbreviations *- Link to Glossary*

In addition, there are numerous EU-funded initiatives aimed at supporting the generation and collection of real-world data

THE EU INVESTS HIGHLY INTO COLLECTION OF REAL WORLD EVIDENCE (RWE)

- The **EU has launched and funded** multiple initiatives to generate and collect RWE as part of various **health-related programs** including: sixth and seventh Framework Programmes (FP6/FP7), Horizon 2020 (H2020), the Innovative Medicines Initiative (IMI), DARWIN EU, EU4Health, etc
- Of these initiatives, **5 key topic areas were identified**:
  - **Data source**: database linkage, patent identifier or paediatric data
  - **Infrastructure**: development of platforms or websites to share, extract and store data, cloud-based technologies
  - **Analytical models**: machine learning, natural language programming, data mining
  - **Methodologies**: guidance on protocol design, management of bias/confounders, and use of electronic health records
  - **Governance models**: confidentiality and data protection
- However, currently the use of the outputs from these initiatives is often limited, mainly due to not **enough information captured** and restricted sustainability
- Future programs will be expected to ensure delivery of stated objectives, data availability, sustainability and reflection of areas of medical need

Topic areas of RWE initiatives
(2018, no. of initiatives)



€734 million in funding

The EU approach now places RWE in the wider context of big data and is guided by the priority recommendations of the Big Data Task Force. These recommendations are being implemented through the Big Data Steering Group and the second multi-annual work plan was published in August 2021(1)

Source: BMJ Open (1) Clinical Pharmacology & Therapeutics
IQVIA | EFPIA Pipeline Innovation Review 2022

Abbreviations – *Link to Glossary*

The AIFA and DAWN patient registries collect patient, to allow tracking of prescriptions, test scores, appointments and outcomes

ACCESS & DEVLIVERY CASE STUDIES

Case Study: Access

AIFA Patient Registry

- AIFA, the Italian medicines agency, often controls spending on expensive and innovative drugs through various managed entry agreements e.g. payment by results, cost-sharing and risk-sharing schemes
- In order to monitor the agreements it set up a nation wide patient registry (*Registri Farmaci sottoposti a monitoraggio*) to track prescriptions and patient outcomes
- AIFA leveraged RWE to perform a nationwide, registry-based study on Italian hospitalized patients with COVID-19 treated with remdesivir to assess the impact of major confounders on crude 15-day and 29-day mortality

Case Study: Delivery

4s DAWN Patient Sample Monitoring System

- The 4s DAWN Patient Sample Monitoring System is a commercial offering that can help healthcare systems manage large numbers of patient information
- It provides monitoring of patient data for patients on anti-coagulants, biologics and other high-risk medications
- It can also effectively manage Congestive Heart Failure patients through collating patient health data, flagging out-of-line tests or scores, and enabling easy patient tracking
- Its ease of integration into primary care settings, and the collation of data and automatic processing, enables healthcare systems to more efficiently manage patients through their patient journey
  - Several Clinical Commissioning Groups* have already procured 4s DAWN, to aid in anti-TNF and multiple sclerosis patient monitoring

* CCGs were established by the Heal and Social Care Act 2021 to organise the delivery of NHS services in each of their local areas in England

EUResist and the Rare Diseases Registries Programme collect patient disease data to increase access for research and treatment

DELIVERY CASES STUDIES

Case Study: Delivery

EUResist HIV Database

- EUResist is among the largest available databases of HIV genotypes and clinical response to antiretroviral therapy
- The project Integrates biomedical information from multiple databases and predictive analytics to support healthcare practitioners identify the optimal treatment for HIV patients based on their HIV genotype
- The service is freely available online providing open access to practitioners
- It evolved from the international collaboration between manufacturers, healthcare systems and research groups (e.g. Max Planck Institute)
- The service is able to outperform international experts in terms of identifying treatment that can improve patient outcomes

Case Study: Delivery

Sanofi Genzyme Rare Disease Registries Programme

- Sanofi Genzyme actively sponsor and manage the rare disease registries programme, which collects data on Gaucher's, Fabry, MPS I and Pompe Diseases
- The registry contains patient medical data that can be analysed and used by physicians; this is especially valuable in rare diseases
- Following launch of Cerdelga, Genzyme collaborated with the International Collaborative Gaucher Group (ICGG) Registry to collect and report long-term efficacy data from Q4 2016 to Q4 2020
  - The ICGG Registry is part of the wider Rare Disease Registries programme and is the largest co-operative observational database on Gaucher disease in the world
  - Data from over 5,000 patients in over 60 countries is used to maximise knowledge and optimise outcomes for patients

The increasing number of digital health projects will reshape the clinical discovery, development and healthcare delivery

Across-industry digital health initiatives as change catalyst for European healthcare systems

Engagement of policymakers, regulators and healthcare providers in digital health transformation is required to ensure that full potential of this change is being leveraged[1]

Digital Health area	Blockchain initiatives for clinical discovery	Innovations in clinical development	Patient monitoring solutions	Leveraging Big Data	Other
Examples	**Melloddy** – using predictive Machine Learning models on decentralised data of 10 PharmaCos to increase efficiencies in drug discovery[2] **PharmaLedger** - scalable blockchain platform to serves as a single source of truth for the healthcare ecosystem for efficient decentralised governance[3]	**Mobilise-D** - comprehensive system to monitor and evaluate patients' mobility with digital technologies, including wearables (focus on COPD, PD, MS, other)[4] **EU-PEARL** – strategic alliance to set up and coordinate multi-company platform trials in any disease area to accelerate drug development[5]	**RADAR-AD** (Remote Assessment of Disease And Relapse – Alzheimer's Disease) - using mobile technologies and devices to transform patient care through remote assessment. Developing technology to identify which digital biomarkers can be measured remotely to predict deterioration[6]	**PIONEER** - single integrated system with medicine data and knowledge platform for prostate cancer, transforming the field of prostate cancer care with focus on improving: prostate cancer-related outcomes; health system efficiency; the quality of health and social care across Europe[7]	Other initiatives related to connected data, patient empowerment, remote engagement and others…

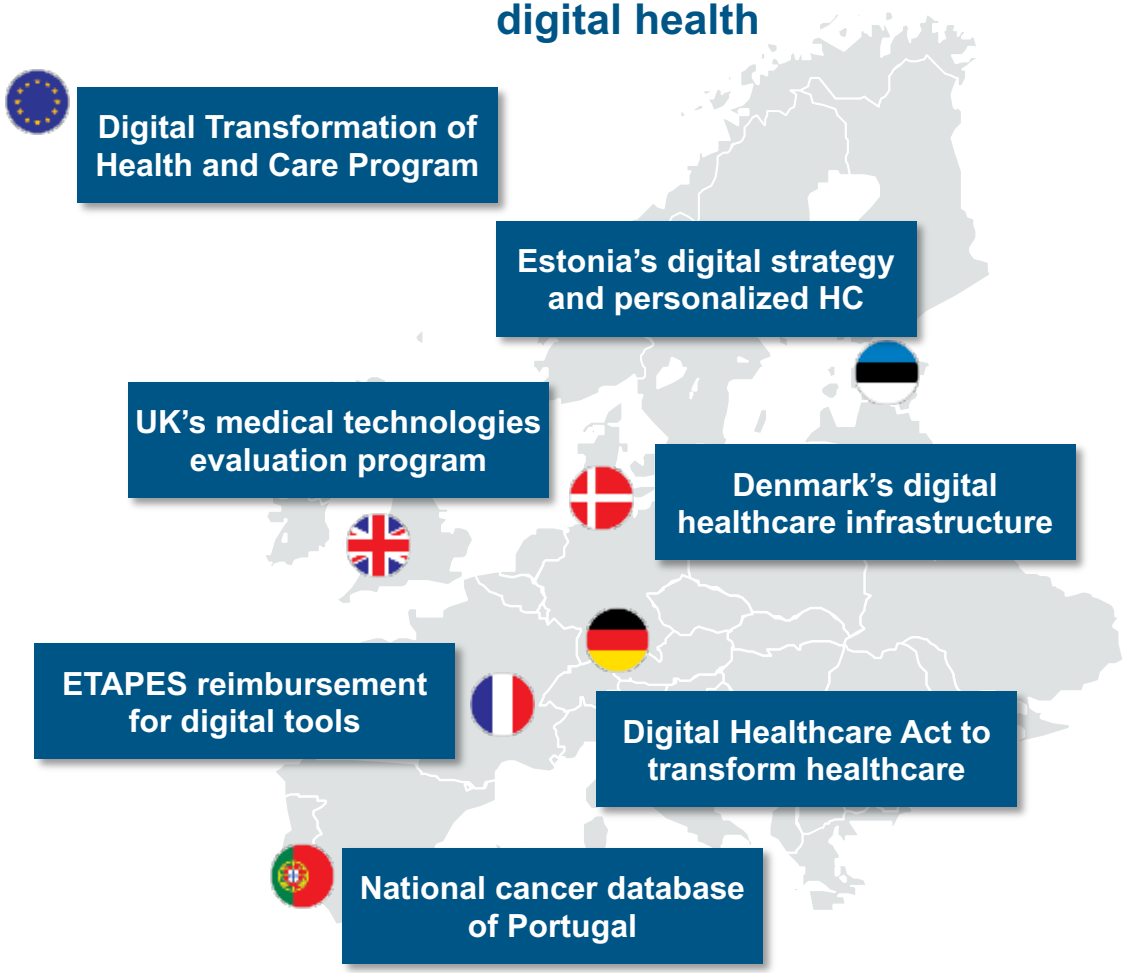
Not exhaustive

Source: EFPIA material - Selected IMI projects on Digital Health; (1) EFPIA; (2) Melloddy; (3) PharmaLedger; (4) Mobilise-D; (5) EU-Pearl; (6) Radar-AD

Abbreviations *- Link to Glossary*

Payers have also recognized the value of digital health and have implemented initiatives to facilitate their adoption

Overview of payer-led initiatives to support digital health



Payers are recognizing the potential of digital solutions and are facilitating their implementation

- **Reimbursing and incentivizing** the use of digital and technology
- Believe that digital health will **decrease spending over time** on healthcare
- Digital health encourages the transition from a 'fee for service' to a **value-based model**

Note: description of initiatives in speaker notes
Source: IQVIA internal expertise, IQVIA analysis

Abbreviations *- Link to Glossary*

Horizon scanning and stakeholder dialogue

Horizon scanning is pivotal for ensuring that new innovations are planned for in advance and successfully assimilated into the market

HORIZON SCANNING IS PIVOTAL FOR THE SUCCESSFUL ASSIMILATION OF NEW INNOVATIONS

THE PROBLEM

- For new innovations entering the market, budgets need to be planned effectively, new services / re-designing existing one to support the innovations, incorporation into treatment guidelines, staffing and training and finally financial assessments need to be undertaken
- The success of the introduction of these new innovations into the market depends on the timely exchange of information between stakeholders
- However, disruptive innovations have the tendency to catch healthcare systems off guard such as the Hepatitis C drug – sofosbuvir and immunotherapies such as pembrolizumab
- Prices for these treatments were not adjusted to cover their impact causing affordability concerns

THE SOLUTION

- Horizon Scanning (HS) is the systematic process of identifying emerging innovations that are in development before they reach market
- HS allows for better predictions of potential impacts and supports resource planning
- **Payers:** Robust HS will facilitate; informed negotiations, estimation of budgetary impacts and informed policy-making
- **Assessment bodies:** Robust HS will also facilitate assessment prioritization which subsequently reduces access delay for patients and allows for early dialogue between stakeholders

EXAMPLE: BeneLuxA

Beneluxa Initiative on Pharmaceutical Policy

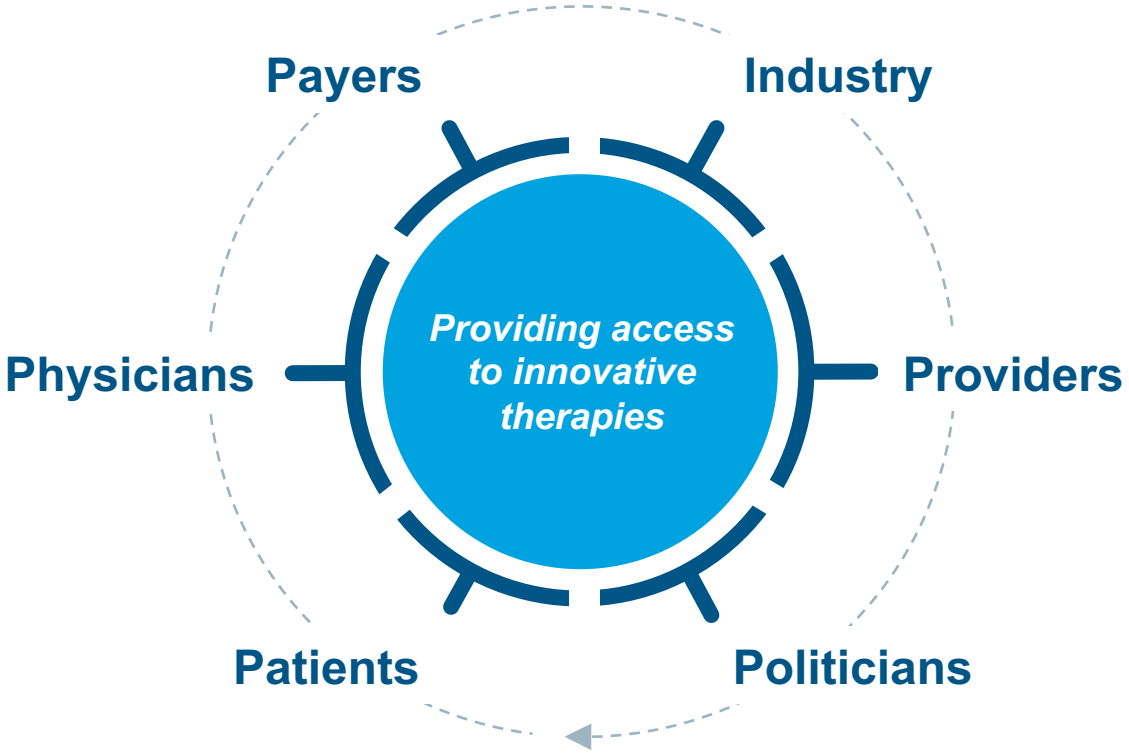
- BeneLuxA is an initiative involving health services in Belgium, The Netherlands, Luxembourg, Austria and Ireland in part as a joint horizon scanning initiative
- By leveraging collaboration, the participating health services work together to identify the innovations that are on the verge of becoming available
- Successful projects have included:
  - Jan 2022 report on *Pharmaceutical Developments on Alzeimer's Disease*[1] which provides an overview of new pharmaceutical developments within Alzeihmer's
  - Apr 2020 report on *Covid-19 : HSS*[2] to inform European health policy makers early on which treatments are currently undergoing clinical trials and monitor them to provide support evidence-based purchasing

Sources: (1) Alzheimer Report, (2) Covid-19:HSS

Abbreviations – *Link to Glossary*

Cross-stakeholder dialogue will ensure that stakeholders cooperate to increase efficiency and support optimal patient access

CROSS-STAKEHOLDER DIALOGUE IS REQUIRED FOR OPTIMAL ACCESS



Empowering stakeholders through early and continued dialogue sets clear expectations and is the best way to ensure long-term partnerships

This helps ensure that innovation potential is fully realised

- Informed **physicians** are aware of the benefits of upcoming innovation and can advise payers about access and are aware about how to maximise benefit for patients
- Informed **patients** will be a more empowered partner for introducing innovation and shaping their own care
- Informed **payers** understand the upcoming horizon of innovation entering the market and can prepare accordingly to ensure swift access for patients
- **Providers** can prepare for upcoming innovation and plan for training and financing to coincide with innovation launch
- Engaged **politicians** are able to set a comprehensive and actionable agenda addressing the concerns associated with innovative treatments and can drive lasting change
- The **industry** are able to drive the empowerment of all stakeholders, and also learn what is the best way of helping to ensure access to innovation now and in the future e.g. through early engagement with payers *(as seen between Swedish TLV and industry since 2011)*

Abbreviations *- Link to Glossary*

Table of Contents

Glossary A, A - C (1/5)

Abbreviation	Explanation
#	Number
AA	Accelerated Approval
AAV	Adeno-associated virus
AD	Alzheimer's Disease
ADA	Adenosine Deaminase
ADA-SCID	Adenosine Deaminase -Deficient Severe Combined Immunodeficiency
ADAS-cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
ADC	antibody drug conjugates
ADLs	Activities of Daily Living
AE	Adverse Event
AI	Artificial Intelligence
AIFA	Italian Medicines Agency
AIML	Artificial Intelligence / Machine Learning
ALL	Acute Lymphoblastic Leukaemia
ALS	Amyotrophic lateral sclerosis
ANSM	French National Agency of Medicine
ASO	Antisense Oligonucleotide
ATMP	Advanced Therapy Medicinal Product
ATTR	Transthyretin Amyloidosis
ATU	Temporary Authorization for Use
Avg.	Average

Abbreviation	Explanation
Aβ	β-Amyloid
AβO	β-Amyloid Oligomers
BACE	β-site amyloid precursor protein cleaving enzyme
B-ALL	B-Cell Acute Lymphoblastic Leukemia
BiTE	Bispecific T-cell Engager
BMS	Bristol Myers Squibb
Bn	Billion
BTD	Breakthrough Therapy Designation
CALD	Cerebral Adrenoleukodystrophy
CAR	Chimeric antigen receptor
CAR T	Chimeric Antigen Receptor T cell
CHMP	Committee for Medicinal Products for Human Use
CKD	Chronic Kidney Disease
CLL	Chronic Lymphocytic Leukemia
CML	Chronic Myelogenous Leukemia
CMV	Cytomegalovirus
CNS	Central Nervous System
COI	Cost of Illness
COVID-19	Coronavirus Disease
CR	Complete Response
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats

Glossary C - E, E - H (2/5)

Abbreviation	Explanation
CRISPR-CAS9	CRISPR-associated protein 9
CRS	Cytokine Release Syndrome
DARWIN	Data Analysis and Real-World Interrogation Network
DC	Dendritic Cell
DH	Digital Health
DIPG	Diffuse Intrinsic Pontine Glioma
DLBCL	Diffuse Large B-Cell Lymphoma
dMMR	deficient DNA Mismatch Repair
DMT	Disease-Modifying Therapy
DNA	Deoxyribonucleic Acid
DOR	Duration of response
DS	Data Science
EBV	Epstein-Barr Virus
EDSS	Expanded Disability Status Scale
EGFR	Epidermal Growth Factor Receptror
EHDEN	European Health Data and Evidence Network
EMA	European Medicines Agency
EQ-5D-5L	European Quality of life Descriptive system (5 dimensions & 5 severity levels)
EQ-VAS	European Quality of life Vertical Visual Analogue Scale
ER	Emergency Room
ESC	Embryonic Stem Cell

Abbreviation	Explanation
EU	European Union
EU27	The 27 European Union countries after the UK left the EU
FAIR	Findable, Accessible, Interoperable, Re-usable
FDA	Food and Drug Administration
FL	Follicular Lymphoma
FP6/FP7	sixth and seventh Framework Programmes
GDP	Gross Domestic Product
GDPR	General Data Protection Regulation
gen.	Generation
GI	Gastrointestinal
GIST	Gastrointestinal Stromal Tumor
GLP-1 ARs	Glucagon-like-peptide-1 Receptor Agonists
GMB	Glioblastoma
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
GMP	Good manufacturing Practice
GP	General Practitioner
GSC	Glioma Stem Cells
GvHD	Graft-versus-Host Disease
H2020	Horizon 2020
H2O	Health Outcomes Observatory
hATTR	Hereditary Transthyretin Amyloidosis

Glossary H - K, L - M (3/5)

Abbreviation	Explanation
HBV	Hepatitis B Virus
HC	Health Care
HCP	Health Care Practitioner
HCS	Health Care Systems
HGG	High Grade Glioma
HIV	Human immunodeficiency virus
HRQoL	Health Related Quality of Life
HS	Horizon Scanning
HTA	Health Technology Assessment
iADRS	integrated Alzheimer's Disease Rating Scale
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
IFN	Interferon
IMF	International Monetary Fund
IMI	Innovative Medicines Initiative
IO	Immuno-oncology
IP	Intellectual Property
JNJ	Johnson & Johnson
kb	Kilobase
KOL	Key Opinion Leader

Abbreviation	Explanation
LAMP	Lysosomal Associated Membrane Protein
LCLA	Low Contrast Letter Acuity
LNP	Lipid Nanoparticle
LSD	Pyschedlic Drug
mAbs	Monoclonal Antibodies
MCC	Merkel Cell Carcinoma
MDD	Major Depressive Disorder
MDMA	Empathogen Drug
MEA	Managed Entry Agreements
METex14	Hepatocyte Growth Factor Receptor (MET) exon 14
MG	Myasthenia Gravis
MM	Multiple Myeloma
Mn	Million
MND	Motor Neuron Disease
MoA	Mechanism of Action
mPFC	medial Prefrontal Cortex
MRD	Multi-Drug Resistance
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MS	Multiple Sclerosis
MSI-H	Microsatellite Instability-high

Glossary M - P, P - R (4/5)

Abbreviation	Explanation
MTD	Maximum Tolerated Dose
MTR	Matt's TraceRoute
NAS	New Active Substance
NASH	Nonalcoholic Steatohepatitis
NCI	National Cancer Insititue
NHL	Non-Hodgkin Lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NK	Natural Killer
NMDA	N-Methyl-D-Aspartate
No.	Number
NSCLC	Non-Small Cell Lung Cancer
NUB	Innovation funding in Germany
OBR	Outcomes-based Reimbursement
OPC	Oligodendrocyte Precursor Cells
ORR	Overall Response Rate
OS	Overall Survival
P&R	Pricing and Reimburesemnt
PAP	Psychoplastogen Assisted Pyschotherapy
PCE	Patient Centered Endpoints
PD	Peritoneal Dialysis

Abbreviation	Explanation
PD	Parkinson's Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PPMS	Primary - Progressive Multiple Sclerosis
PRIME	PRIority MEdicines
PRO	Patient Reported Outcome
PROTAC	Proteolysis targeting chimeric
PTPσ	Protein Tyrosine Phosphatase Sigma
PTSD	Post-Traumatic Stress Disorder
QALY	Quality-adjusted Life-Year
QC	Quality Check
QoL	Quality of Life
QRISK	Cardiovascular Risk Score
R&D	Research & Development
r/r	Relapsed / Refractory
RBC	Red Blood Cells
RCT	Randomised Controlled Trials
RET	Rearranged during Transfection
RMS	Relapsing Multiple Sclerosis
RNA	Ribonucleic Acid
RNA-LP	RNA-Lipid Particle

Glossary R - T, T - Z (5/5)

Abbreviation	Explanation
RP2D	Recommended Phase 2 Dose
RRALL	Relapsed / Refractory Acute Lymphoblastic Leukaemia
RRMM	Relapsed / Refractory Multiple Myeloma
RRMS	Relapsing / Remitting Multiple Sclerosis
RSV	Respiratory Syncytial Virus
RTU	Temporary Recommendation for Use
RWD	Real World Data
RWE	Real World Evidence
SCD	Sickle Cell Disease
SCT	Sacrococcygeal Teratoma
SERM	Selective Estrogen Receptor Modulator
SF-12	12-Item Short Form Health Survey
siRNA	Small interfering RNA
SLL	Slow-Growing Lymphocytic Leukemia
SMA	Spinal Muscular Atrophy
SoC	Standard of Care
SPMS	Secondary - Progressive Multiple Sclerosis
SSN	Italian National Health Service
SSRI	Selective Serotonin Reuptake Inhibitor
TA	Therapy Area
TALEN	Transcription activator-like effector nuclease

Abbreviation	Explanation
TBD	To Be Determined
TERM	Tissue Engineering & Regenerative Medicine
TMZ	Temozolomide
TNBC	Tumour-Negative Breast Cancer
TRD	Treatment Resistant Depression
TTR	Transthyretin protein
Tx	Therapy / Treatment
VGPR	Very Good Partial Response
VOC	Vaso-Occlusive Crisis
VR	Virtual Reality
WM	Waldenström's Macroglobulinemia
YLD	Years of healthy Life lost due to Disability
ZFN	Zinc finger nucleases