EFPIA Pipeline Review 2021 Update

Project Report

February 2021

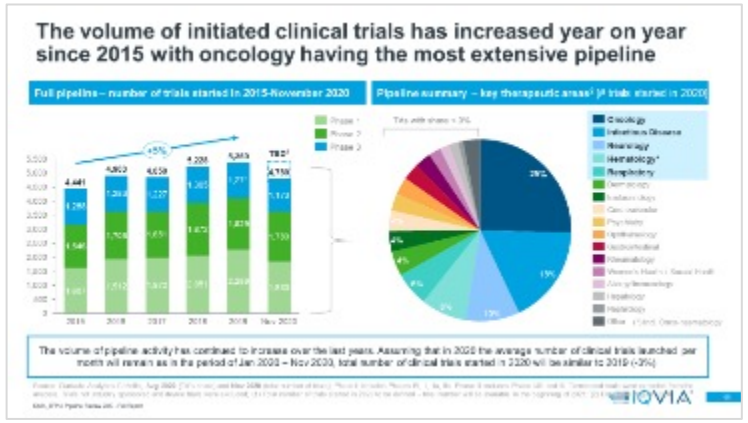
Disclaimer

- Information contained within this document is based on publicly available information and Primary Market Research
- Findings and recommendations are based on the views of IQVIA, and do not necessarily represent those of EFPIA
- **Please note**: the research to inform this report was conducted between August and Nov 2020

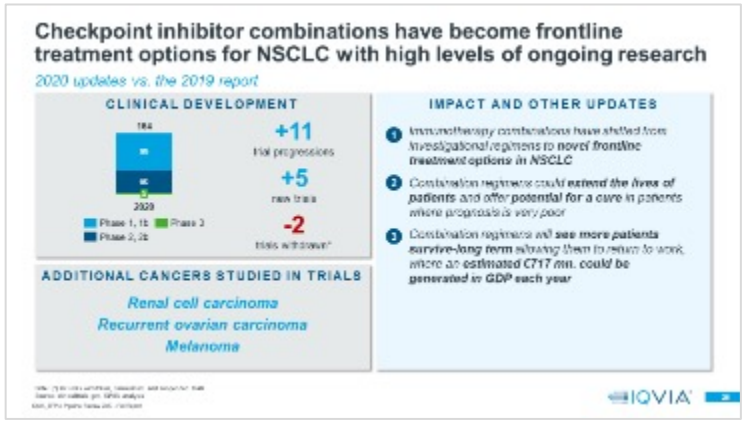
This document contains a pipeline overview, deep dives of the eight areas, as well as considerations for innovation access

Hyperlinks for Content Navigation

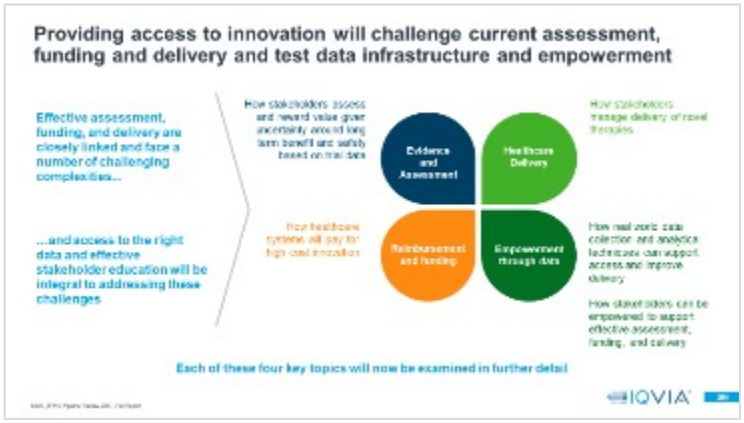
Pipeline overview



Benefit of Innovation



From Innovation to Access



Hyperlinks to detailed content allow for easy reference and navigation of the document

Contents

2020 has witnessed the EMA approval of 55 new active substances, mainly in infectious diseases, immunology and haematology

Cardiovascular disease
Dermatology
Gastrointestinal
Immunology
Infectious disease
Neurology
Oncology / Onco-haematology
Ophtalmology
Rare diseases
Haematology
Other

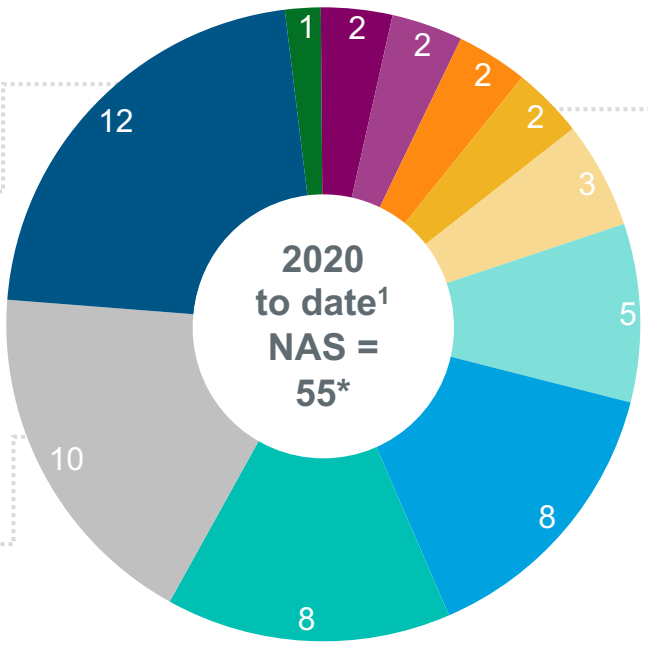
Conditional approval, exceptional circumstances, and/or accelerated approval, n = 11
Orphan designated products, n = 12

Oncology & onco-haematology

darolutamide (prostatic neoplasms)
entrectinib (non small cell lung cancer)
larotrectinib sulfate (abdominal neoplasms)
trametinib (melanoma)
isatuximab (MM)
polatuzumab vedotin (B-cell lymphoma)
gilteritinib fumarate (AML)
belantamab mafodotin (multiple myeloma)
glasdegib maleate (AML)
luspatercept (Myelodysplastic syndrome)
avapritinib (GI stromal tumours)
acalabrutinib (CLL)
melphalan (multiple onco-haem indications)

Infectious diseases

relebactam (Gram negative bacterial infections)
imipenem monohydrate (Gram negative bacterial infections)
Zabdeno, vaccine (Ebola)
Mvabea, vaccine (Ebola)
Ervebo, vaccine (Ebola, hemorrhagic fever)



Vaxchora, vaccine (Cholera)
Pretomanid (Tuberculosis)
MenQuadfi, vaccine (Meningococcal Meningitis)
Obiltoxaximab (Anthrax)

Rare diseases

onasemnogene abeparvovec (SMA)
osilodrostat phosphate (Cushing's syndrome)

Immunology

glycopyrronium bromide (asthma)
indacaterol (asthma)
indacaterol acetate (asthma)
budesonide / formoterol (asthma)
indacaterol, glycopyrronium bromide, mometasone (asthma)
ozanimod hydrochloride (MS)
ivacaftor /tezacaftor / elexacaftor (cystic fibrosis)
upadacitinib (rheumatoid arthritis)
filgotinib (rheumatoid arthritis)

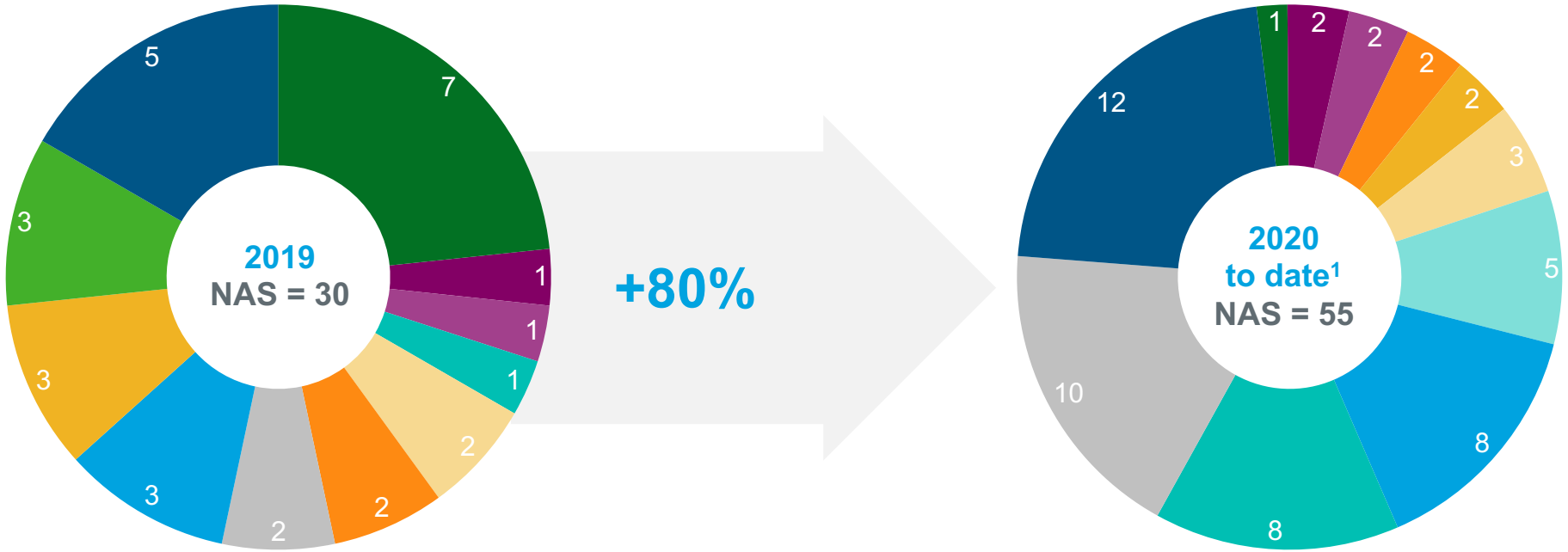
Note: (1) **As of 11.2020, (*) innovative products only** excludes biosimilars, generics, influenza vaccines, indication expansions, and non-human products; **Abbreviations**: Spinal Muscular Atrophy (SMA), Acute Promyelocytic Leukemia (APL), Myeloid Leukaemia (AML), Chronic Lymphocytic Leukaemia, Multiple Sclerosis (MS) – link to glossary; Source: EMA European public assessment reports

The number of new active substances approved by EMA this year increased by ~80% as compared to 2019

Cardiovascular disease
Dermatology
Gastrointestinal
Immunology
Infectious disease
Neurology
Oncology
Ophtalmology
Rare diseases
Haematology
Endocrynology
Other

Across TAs:

- **7** orphan designations (vs 7 in 2020 to date)
- **12** conditional approvals / exceptional circumstances, and/or accelerated approvals (vs 9 in 2020 to date)

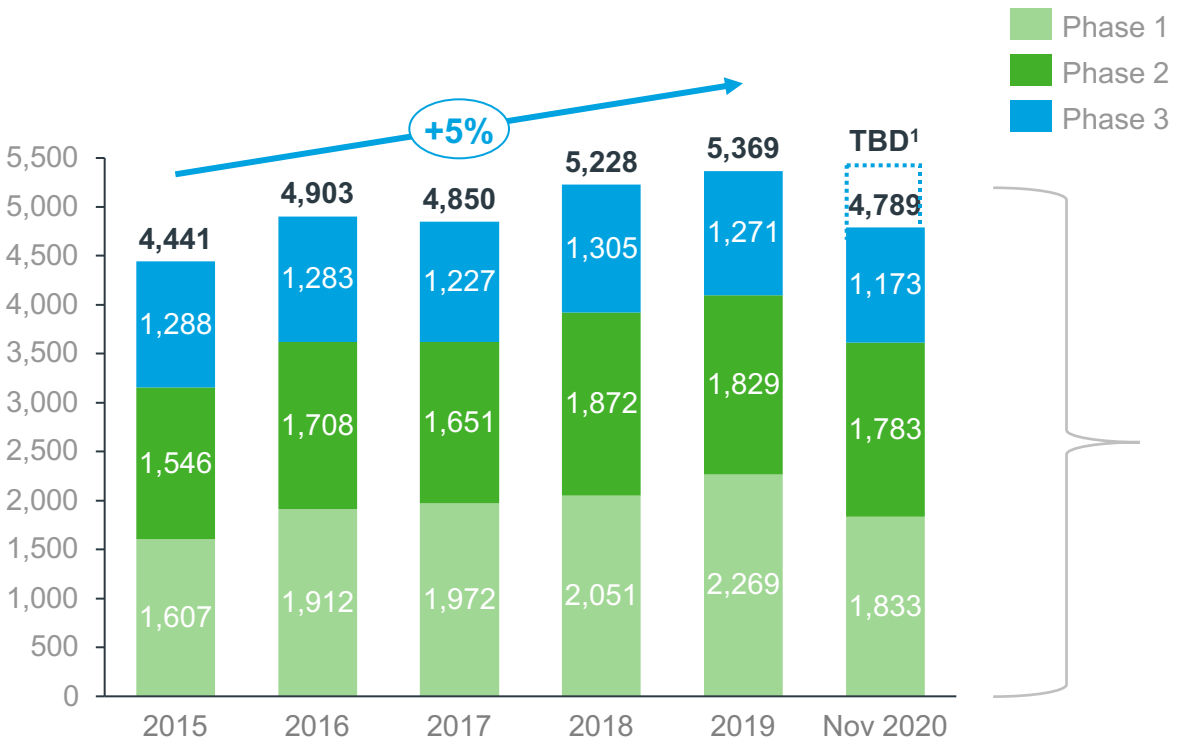


For comparison, 30 new active substances were approved by EMA in 2019, mainly for haematology, infectious diseases and cancer. This indicates that the COVID-19 pandemic has not negatively impacted the approval process for innovations coming to the market so far.

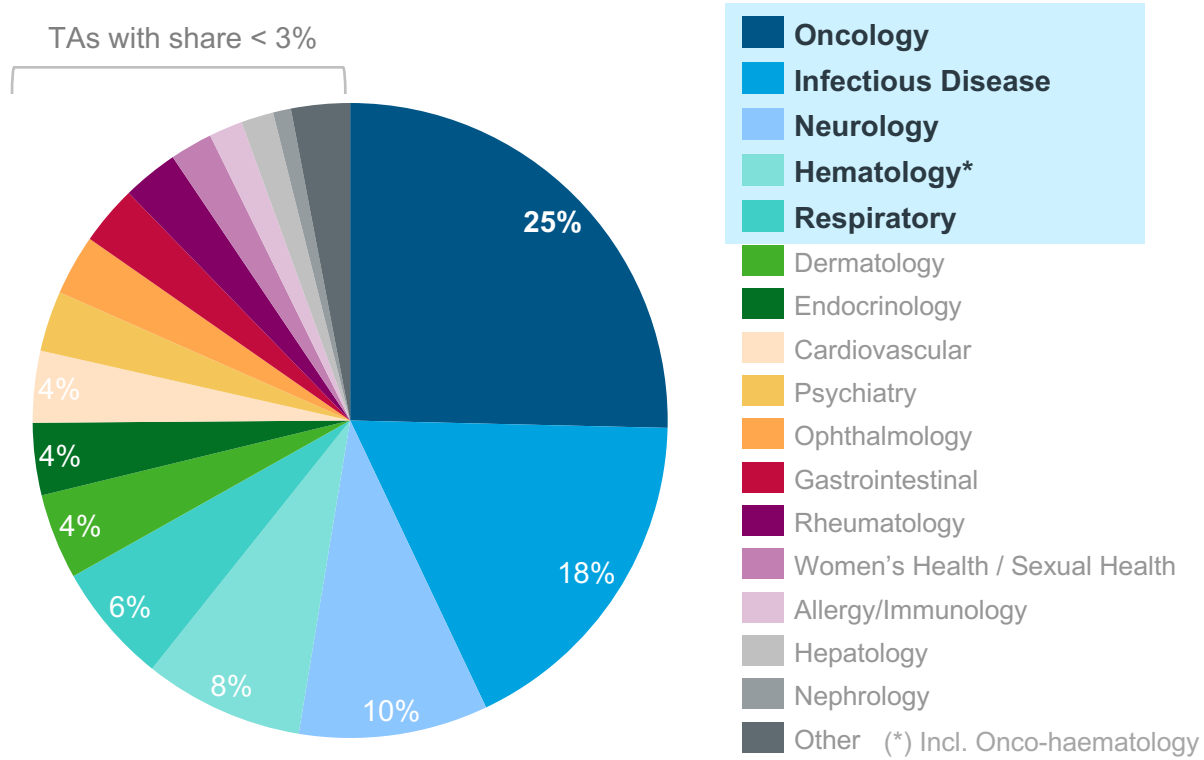
Note: (1) As of **21.09.2020**; **Abbreviations**: New active substance (NAS) - link to glossary; Source: EMA European public assessment reports; Human medicines highlights 2019

The volume of initiated clinical trials has increased year on year since 2015 with oncology having the most extensive pipeline

Full pipeline – number of trials started in 2015-November 2020



Pipeline summary – key therapeutic areas[2] [# trials started in 2020]

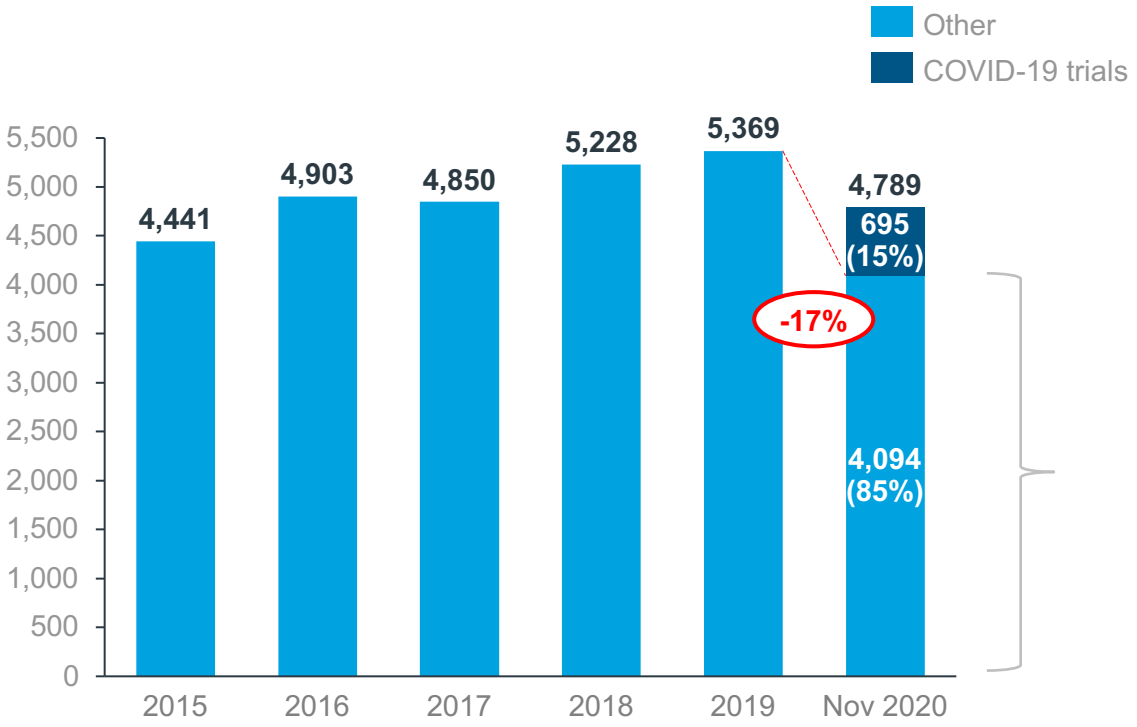


The volume of pipeline activity has continued to increase over the last years. Assuming that in 2020 the average number of clinical trials launched per month will remain as in the period of Jan 2020 – Nov 2020, total number of clinical trials started in 2020 will be similar to 2019 (-3%).

Source: Clarivate Analytics Cortellis, **Aug 2020** (TA's share) and **Nov 2020** (total number of trials); Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. Terminated trials were excluded from the analysis. Trials not industry sponsored and device trials were excluded; (1) Total number of trials started in 2020 to be defined – final number will be available in the beginning of 2021; (2) Data from August 2020

However, if we exclude trials related to COVID-19, the clinical activity in other areas has decreased as compared to 2019

Full pipeline – number of trials started in 2015-November 2020[1]



Change in the number of trials excluding COVID-19 studies

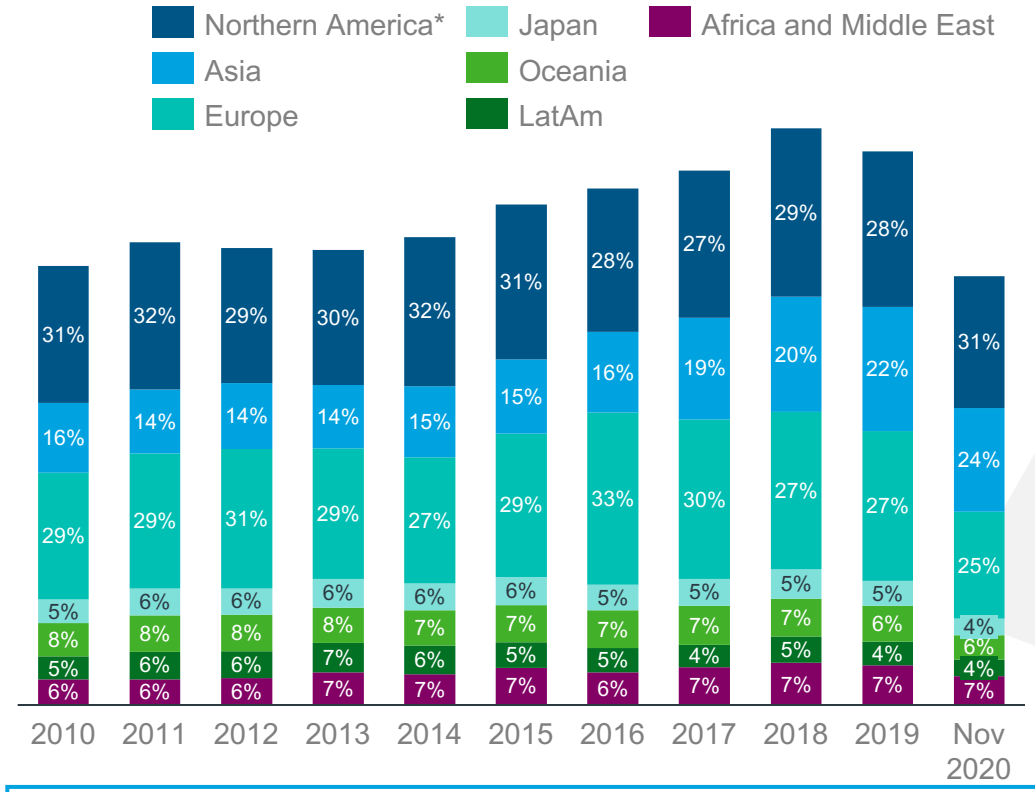
- When we exclude the clinical trials related to COVID-19, constituting ~15% of the clinical pipeline in 2020, we observe that the total number of studies launched in other therapeutic areas has decreased as compared to 2019
- The average number of trials launched per month in 2020 *(excluding COVID-19 trials)* is ~372, whereas the average monthly number in 2019 was ~447 (17% decrease)
- Average monthly number is used in comparison due to unavailability of full-year data for 2020

The final effect of COVID-19 on the clinical development in other therapeutic areas is still to be confirmed – full 2020 data expected early 2021.

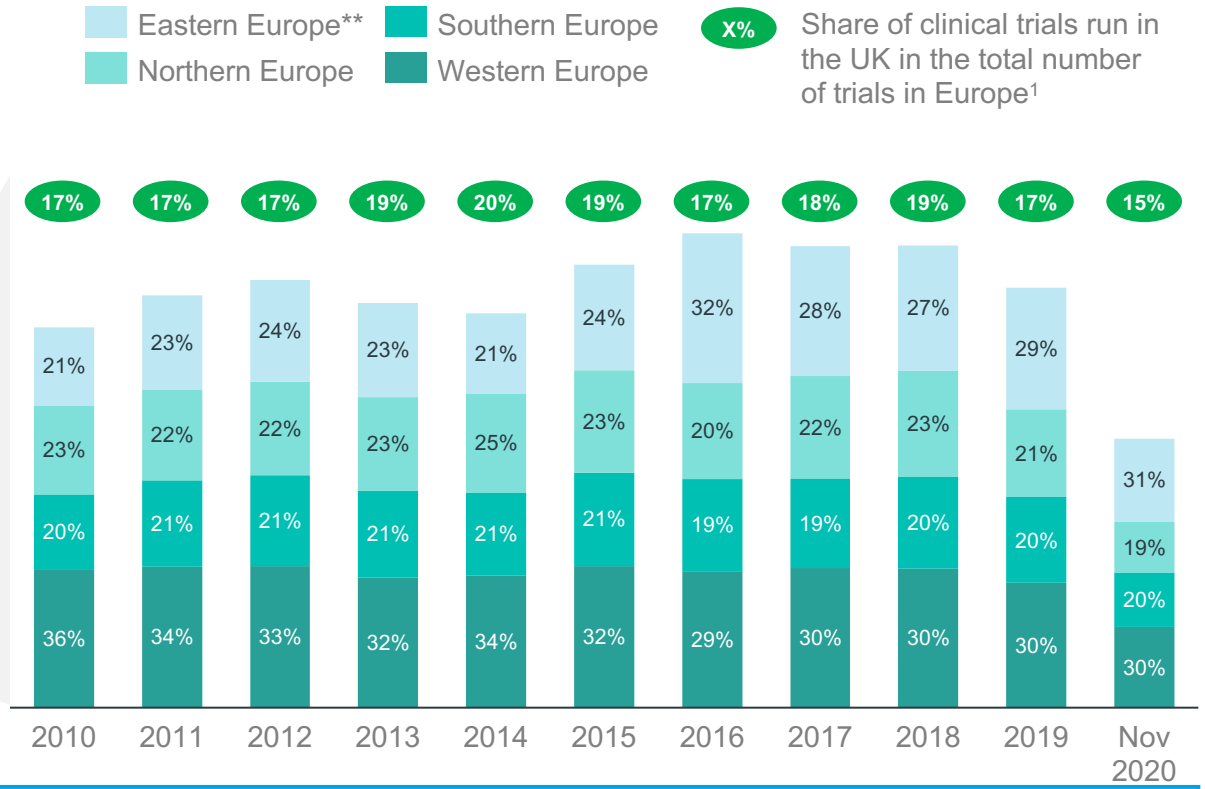
Source: Clarivate Analytics Cortellis, **Nov 2020**; Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. Terminated trials were excluded from the analysis. Trials not industry sponsored and device trials were excluded; (1) Total number of trials started in 2020 to be defined – final number will be available in the beginning of 2021

The impact of COVID-19 on trials geographic split is not visible to date; increasing share of Asia in clinical development is observed

Full pipeline – trials started in 2010-2020 per region[1]



European pipeline – trails started in 2010-2020 per sub-region[1]

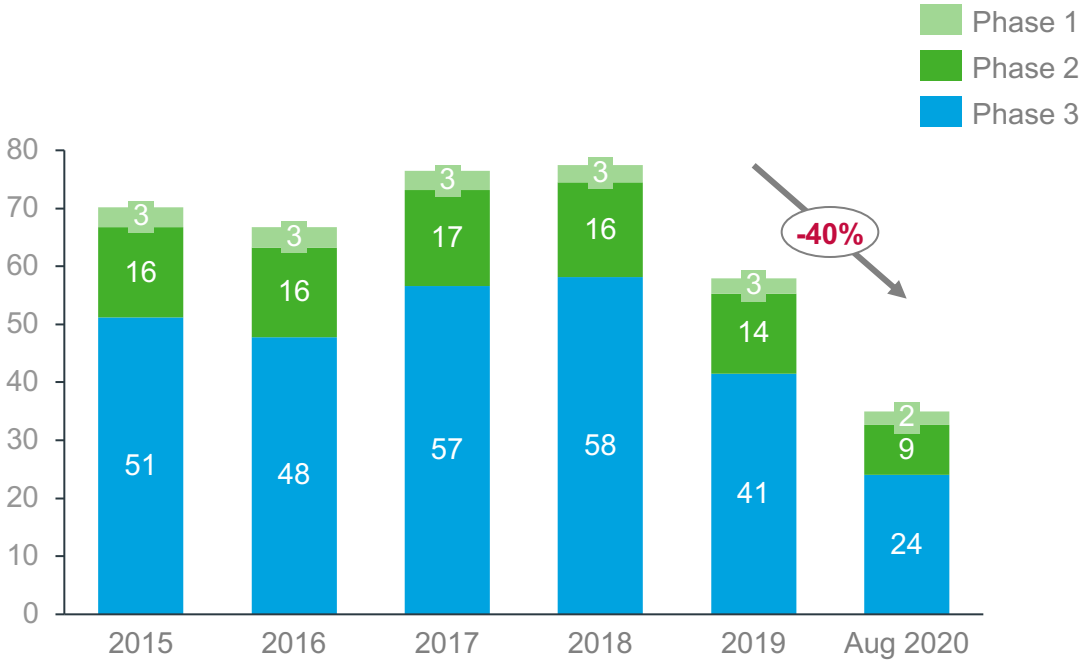


The geographic distribution of clinical trial location has not changed significantly compared to previous year, which indicates that the COVID-19 pandemic has not forced pharmaceutical companies to move their development activities. The long-term trend observed is the increasing share of clinical trials conducted in Asia (mainly China, South Korea), which grew from 14% in the years 2011-2013 to 24% in 2020.

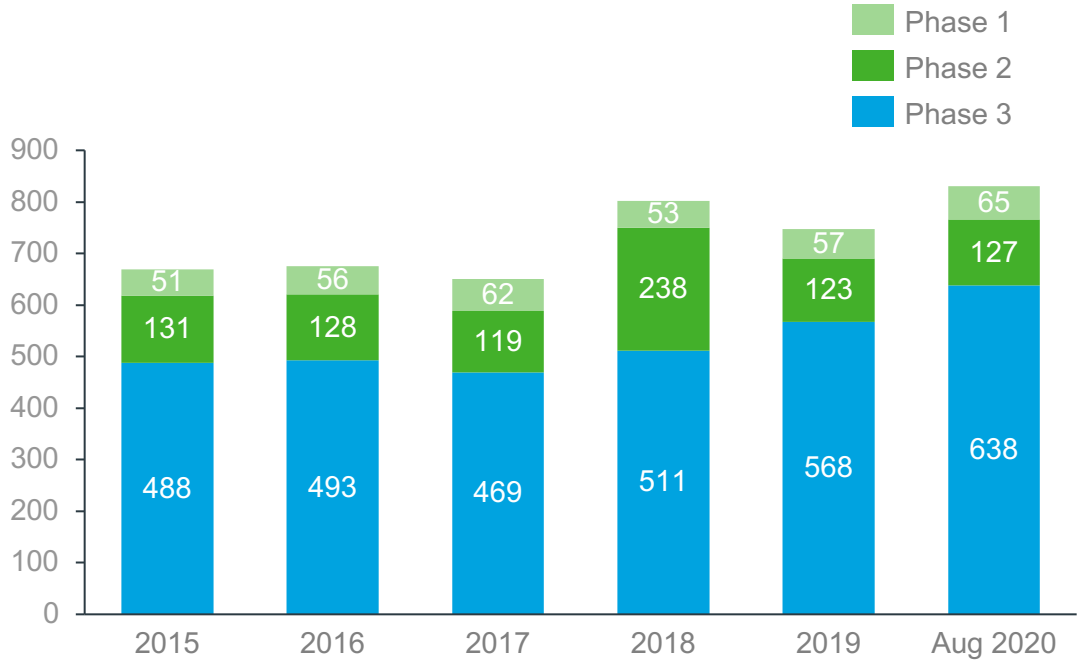
Source: Clarivate Analytics Cortellis, **Nov 2020**; Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. Terminated trials were excluded from the analysis. Trials were industry sponsored and device trials were excluded; (*) Including Caribbean; (**) Including Georgia; (1) Please note that 1 trial may be run in several locations – resulting in differences in total number of trials versus number of trials in geographic split

However, looking into the average number of sites engaged in clinical trials, a decrease was observed across the globe in 2020

Average no. of sites per trial – trials started in 2015-2020



Average no. of subjects per trial – trails started in 2015-2020

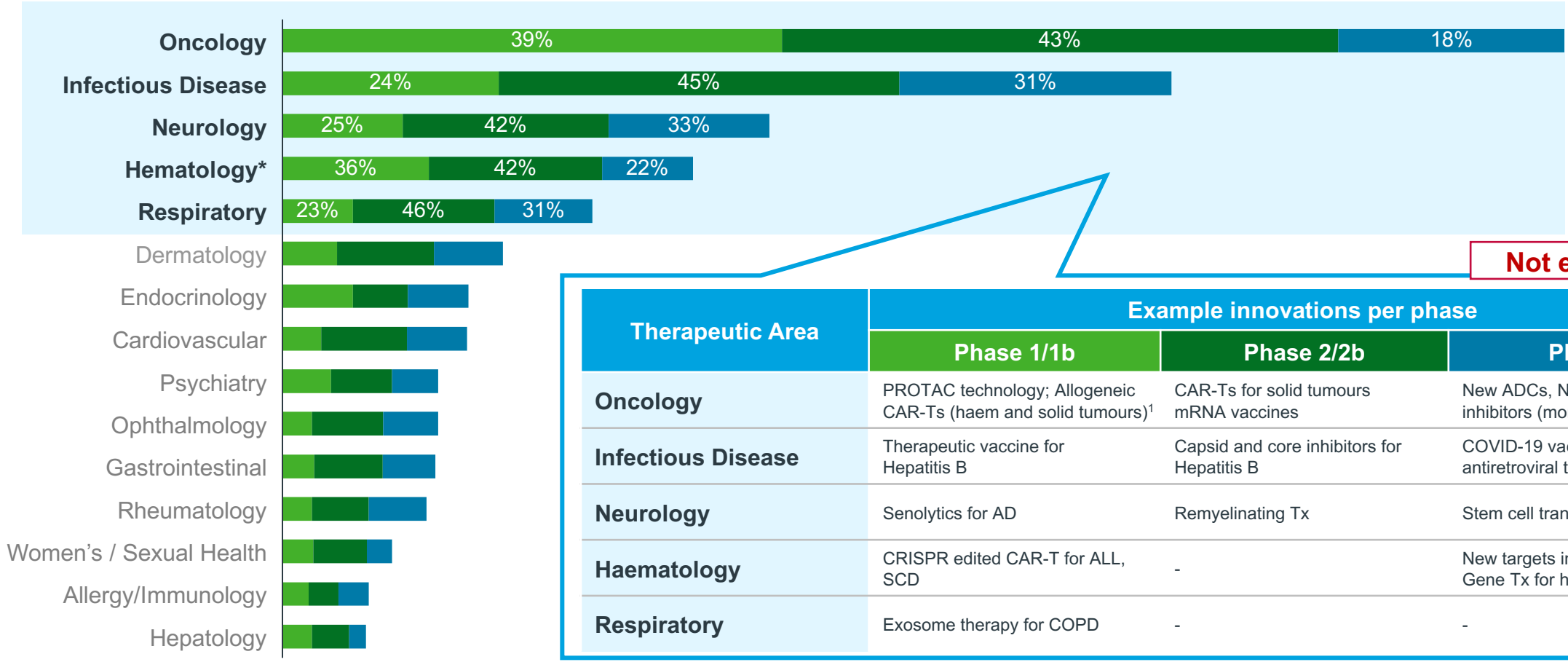


Detailed analysis of clinical trial characteristics shows that the COVID-19 pandemic might have impacted the number of sites engaged in a clinical trial – we observed a 40% decrease in the average number of sites per clinical trial in 2020 versus 2019. Potential reasons behind this change may include the increased use of digital tools and virtualisation of trials[1]. It is to be observed if whether this trend will continue in 2021. No other significant changes to clinical development activity were revealed (e.g. average number of subjects per trial remained the same).

Source: Clarivate Analytics Cortellis, **Aug 2020**; Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. Terminated trials were excluded from the analysis. Trials were industry sponsored and device trials were excluded; (1) Nature.com

With ~40% of the oncology pipeline in Phase 1, this therapy area is expected to witness significant changes over the next 3-5 years

Full pipeline – split per clinical trial phase [share in the no. of trials]



(*) Incl. onco-haematology

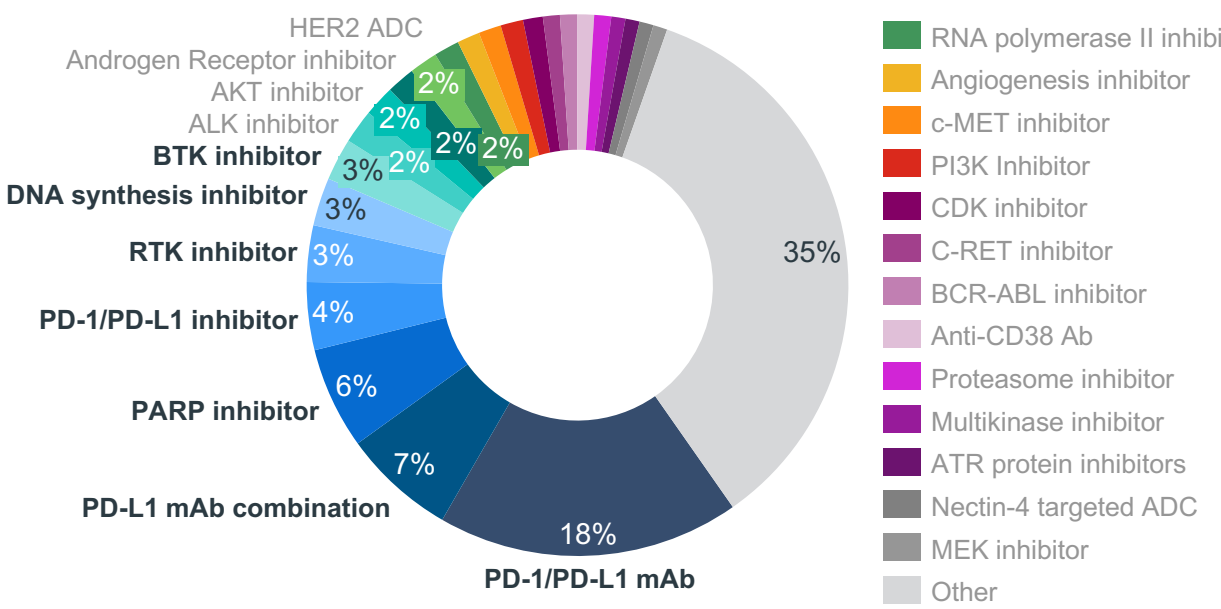
Not exhaustive

Therapeutic Area	Example innovations per phase		
	Phase 1/1b	Phase 2/2b	Phase 3
Oncology	PROTAC technology; Allogeneic CAR-Ts (haem and solid tumours)[1]	CAR-Ts for solid tumours mRNA vaccines	New ADCs, New checkpoint inhibitors (mono and combo Tx)
Infectious Disease	Therapeutic vaccine for Hepatitis B	Capsid and core inhibitors for Hepatitis B	COVID-19 vaccine; Long-acting antiretroviral therapies for HIV
Neurology	Senolytics for AD	Remyelinating Tx	Stem cell transplantation in MS
Haematology	CRISPR edited CAR-T for ALL, SCD	-	New targets in CAR-T therapies Gene Tx for haemophilia
Respiratory	Exosome therapy for COPD	-	-

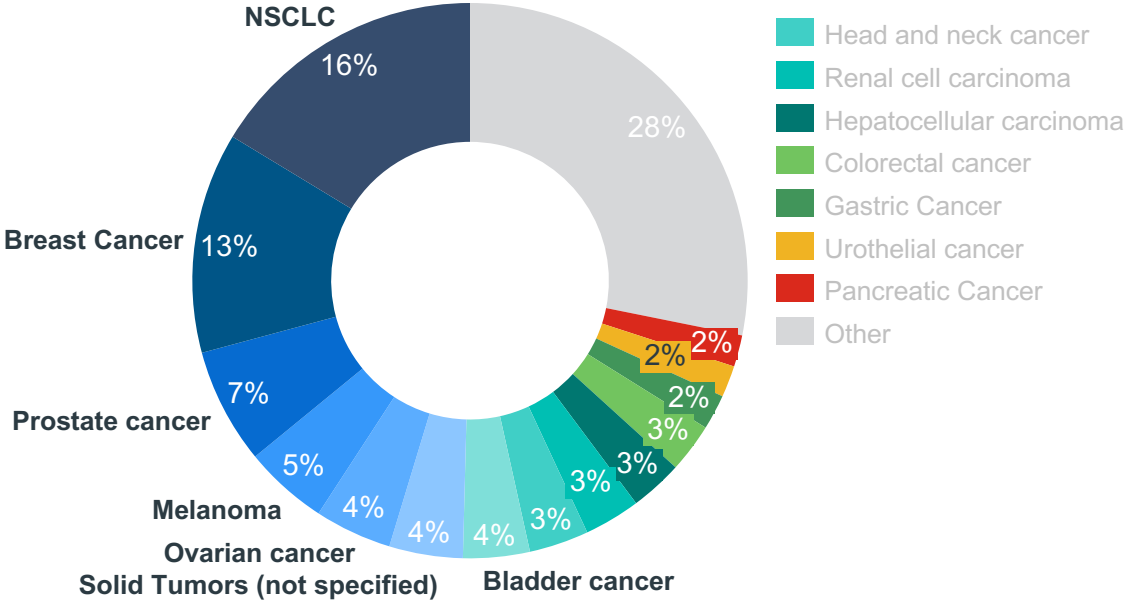
Abbreviations: Proteolysis Targeting Chimeras (PROTAC), Chimeric antigen receptor T cells (CAR-Ts), antibody drug conjugate (ADC), Alzheimer's disease (AD), acute lymphocytic leukaemia (ALL), sick cell disease (SCD), Chronic obstructive pulmonary disease (COPD) - link to glossary Source: Clarivate Analytics Cortellis**, Aug 2020**; Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. Terminated trials were excluded from the analysis. Trials were industry sponsored and device trials were excluded; (1) Nature.com

Established PD-1/PD-L1 mono and combo therapies constitute ~30% of the oncology pipeline; key focus on NSCLC, breast cancer

Oncology pipeline – key technologies [share in the no. of trials]



Oncology pipeline (solid tumour)* - key indications [share in trials]



Next to well-established, high-presence technologies, the oncology pipeline includes a large number of highly specific, low incidence treatments(1), constituting a significant part of the „Other" category

High prevalence indications – such as lung cancer, breast, prostate cancer – remain the focus areas for clinical development in oncology, accounting for 36% of trials

Source: IQVIA Launch Pipeline Database, active trials phase 2-3 for 56 pharmaceutical companies
(1) E.g. LAG-3 inhibitors, WEE1 inhibitors, Mesothelin-targeting ADCs, Anti-TM1 antibodies

(*) Blood cancers/ haematological cancers included under Haematology on the next slide

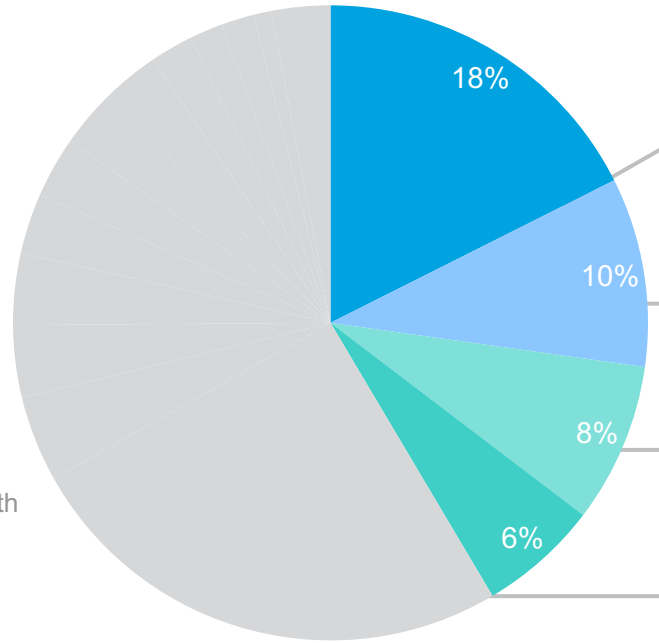
Abbreviations: Non small cell lung carcinoma (NSCLC) - link to glossary

Outside oncology, trials in diseases with high societal impact (e.g. COVID-19, Alzheimer's Disease, Asthma) dominate the pipeline

Full pipeline – key therapeutic areas [no. of active trials, share]

Top 3 indications for selected TAs [share in the no. of trials]

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



Infectious diseases: COVID-19, HIV, Influenza, Pneumonia (VAP, HAP)

Neurology: Alzheimer's Disease, Multiple Sclerosis, Neuropathic pain

Haematology/Onco-haematology: Multiple Myeloma, DLBCL, AML, NHL

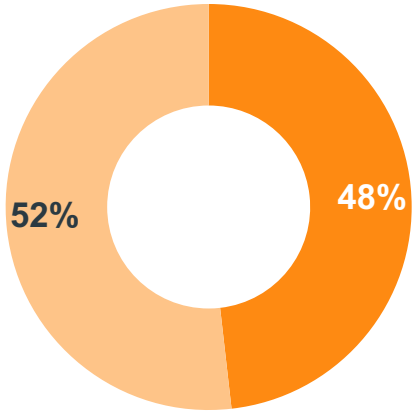
Respiratory: Asthma, COPD, Cystic Fibrosis

Indications in bold are of high importance for European (and global) society due to high incidence rates and the burden they place on healthcare systems. They are also key focus areas in the current clinical development.
More details on the pipeline of each selected TA available in the appendix.

Source: IQVIA Launch Pipeline Database, active trials phase 2-3 for 56 pharmaceutical companies, **Aug 2020; Abbreviations:** Human immunodeficiency virus (HIV), ventilator associated pneumonia (VAP), hospital-acquired pneumonia (HAP); acute myeloid leukaemia (AML); non-Hodgkin lymphoma (NHL), chronic obstructive pulmonary disease (COPD) - link to glossary

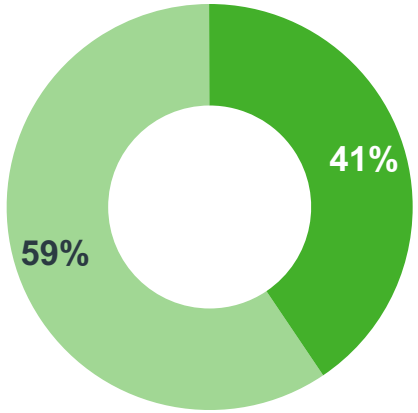
The pipeline is highly innovative, with half being new substances and cell and gene therapies gradually gaining importance

Indication expansions vs new products



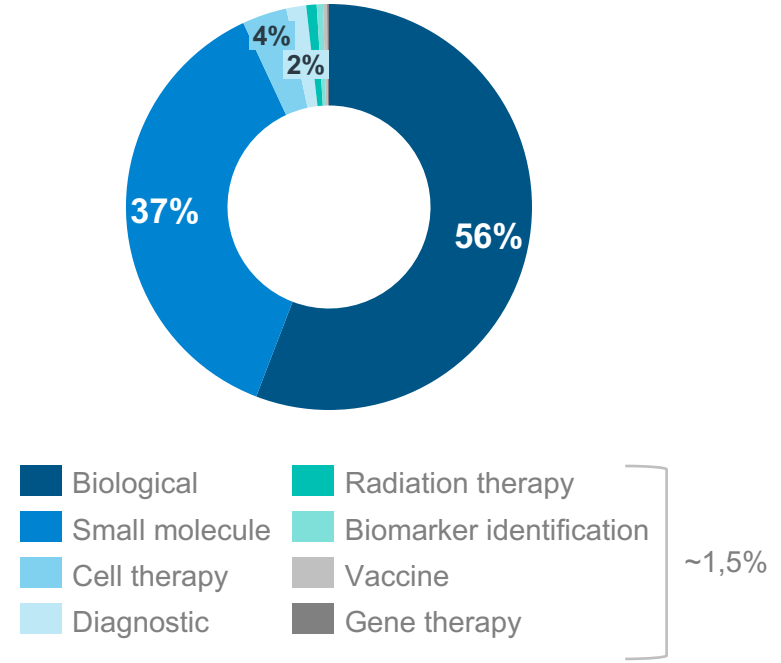
Source: IQVIA Launch Pipeline Database **June 2020**, active trials phase 2-3 for 56 pharmaceutical companies

Orphan vs non-orphan drugs



Source: IQVIA Launch Pipeline Database **June 2020**, active trials phase 2-3 for 56 pharmaceutical companies

Key categories



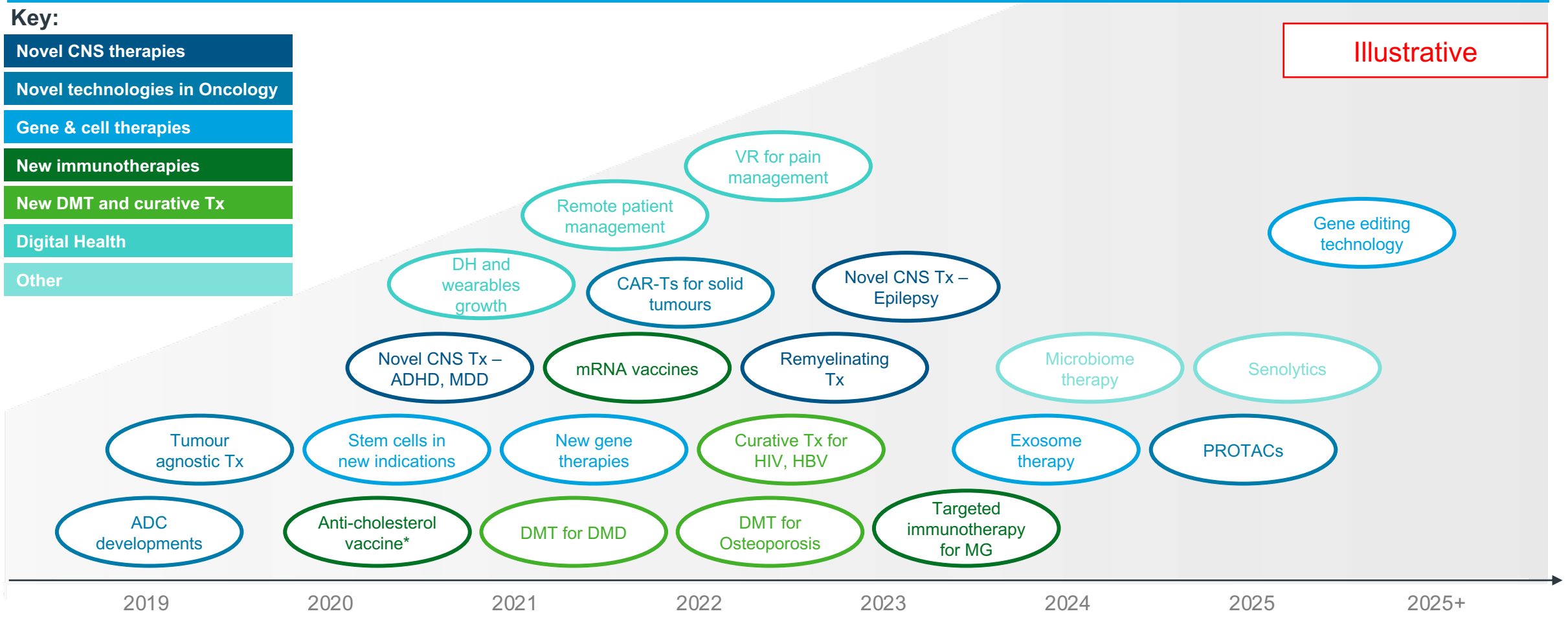
Source: Clarivate Analytics Cortellis, **Aug 2020**

Almost 50% of therapies in development are **new products**, among which lower incidence, **previously omitted diseases** are gaining interest (and investment), with 40% of the pipeline being orphan drugs. More than 90% of products in the pipeline are **biologics and small molecules**. However, the share of Next-Generation Biotherapeutics (NGB), such as **cell, gene, and nucleotide therapies** in clinical development continues to increase. In years 2014-2019 the **number of NGB products has more than tripled**, as they have high potential especially in previously intractable diseases[1].

(1) 2019 R&D Achievements, IQVIA Institute, Mar 2020

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

High-level overview of new innovation areas coming to the market in the 5-year perspective



Abbreviations: Disease modifying therapies (DMTs), therapies (Tx), Digital health (DH), virtual reality (VR), central nervous system (CNS), attention deficit hyperactivity disorder (ADHD), major depressive disorder (MDD), 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) - link to glossary Source: IQVIA analysis

Some of these therapies are expected to reach the market in short- to mid-term (1/2)…

Novel CNS therapies

Remyelinating therapies

Other CNS treatments (attention deficit hyperactivity disorder, major depressive disorder, schizophrenia)

Novel technologies in Oncology

Tumour agnostic Tx

CAR-Ts for solid tumours

Anti-body drug conjugate developments

New immunotherapies

mRNA vaccines

Cholesterol lowering vaccine

Novel immunotherapies

New DMT and curative therapies

Curative therapies for infectious disease

Disease modifying therapies (DMTs)

Gene & cell therapies

New gene therapies

Stem cells in new indications

Digital Health

Digital health and wearables growth

Remote patient management

Virtual reality for pain management

Short- to mid-term = up to 3-5 years **Abbreviations**: - link to glossary Source: IQVIA analysis

Innovations included in original shortlist – more details available in the appendix

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

Other CNS treatments
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 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)

ADCs developments
Extensive research focuses on identifying new targets and improvements for ADCs, as well as potential combinations

Gene & cell therapies

New gene therapies
Multiple clinical trials evaluating AAV vector gene therapy are currently ongoing, targeting, among others, haemophilia, ophthalmological disorders, rare diseases

Stem cells in new indications
High regenerative potential of stem cell Tx is further explored in

New immunotherapies

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

Cholesterol lowering vaccine
provides an alternative to available Tx (statins, mAbs)

Novel immunotherapies
e.g. targeted IO for Myasthenia gravis

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 for DMD was granted an accelerated approval by FDA and 9 DMTs are in development for osteoporosis

Digital Health

DH and wearables growth
Telehealthcare and wearable medical devices driving growth of this market

Remote patient management
It is one of the biggest Digital Health Trends, with a focus on CV patients

VR for pain management

Short- to mid-term = up to 3-5 years **Abbreviations**: - link to glossary Source: IQVIA analysis

Innovations included in original shortlist – more details available in the appendix

…whereas other interesting technologies are further on the horizon, worth keeping an eye on in the coming years

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 than inhibitors, at the same time causing less undesired toxicities and side effects. [1]

Gene editing technology

CRISPR/Cas9 is a gene editing technology that is applicable across disease areas - cancer, infection, muscular dystrophy, etc. Works by injecting a DNA construct, which **targets a defective gene, replacing it with a functional gene**[2].

CRISPR-Cas9 system has a potential to be faster, cheaper, more accurate and efficient than other genome editing methods[3].

Exosome therapy

Exosomes are nano-vesicles released by nearly every cell in the body, which may be used as a diagnostic/therapeutic agents. Pre-clinical research has shown that exosomes reduced scar tissues caused by a heart attack[4].

Exosomes may be a next step in stem cell therapies, offering an improved safety profile[5].

Senolytics

New class of drugs that are able to induce **death of senescent cells responsible for aging** and age-related diseases[6].

Targeting aging itself might be a novel strategy to prevent a number of conditions that elderly patients struggle with.

First-in-human trial of senolytic drugs are preliminary, but encouraging.

Microbiome therapy

Microbiome therapy aims to restore healthy gut microbiota to control a variety of local and distant pathologies[7].

This field continues to garner interest from the pharmaceutical industry with extensive research, funding and multiple collaborations.

With **new advances in machine learning and diagnostic techniques**, microbiome research will likely keep growing and becoming more data science-driven and precise.

(1) ScienceDirect; (2) Nature.com (3) Genetics Home Reference (4) NCBI (5) Exopharm (6) NCBI (7) EFPIA **Abbreviations**: - link to glossary

Innovations included in original shortlist – more details available in the appendix

Contents

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Innovation area	Decription and pipeline	Impact assessment
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Alzheimer's Therapies	Link	Link
Gene Therapies	Link	Link
Cell Therapies including CAR-T	Link	Link
NASH (PPAR/FXR agonists)	Link	Link
Remyelinating CNS Therapies	Link	Link
mRNA Vaccines	Link	Link
Curative Tx – Hepatitis B and HIV	Link	Link

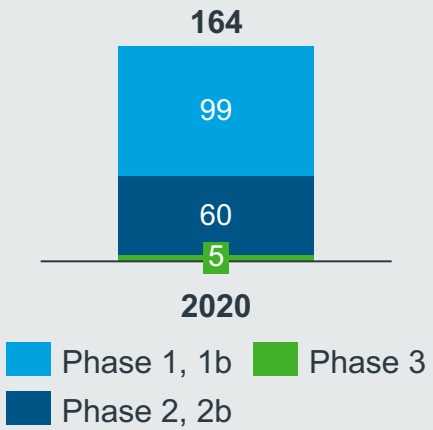
Checkpoint Inhibitor Combinations

Link - back to innovations contents page

Checkpoint inhibitor combinations have become frontline treatment options for NSCLC with high levels of ongoing research

2020 updates vs. the 2019 report

CLINICAL DEVELOPMENT



+11
trial progressions

+5
new trials

-2
trials withdrawn*

ADDITIONAL CANCERS STUDIED IN TRIALS

Renal cell carcinoma

Recurrent ovarian carcinoma

Melanoma

IMPACT AND OTHER UPDATES

1. *Immunotherapy combinations have shifted from investigational regimens to **novel frontline treatment options in NSCLC***
2. *Combination regimens could **extend the lives of patients** and offer **potential for a cure** in patients where prognosis is very poor*
3. *Combination regimens will **see more patients survive-long term** allowing them to return to work, where an **estimated €717 mn. could be generated in GDP each year***

Note: (*) Includes withdrawn, terminated, and suspended trials
Source: clinicaltrials.gov, IQVIA analysis; **abbreviations**: non small cell lung carcinoma (NSCLC) - link to glossary

Combination regimens targeting PD-L1 have delivered life saving therapies for cancer patients

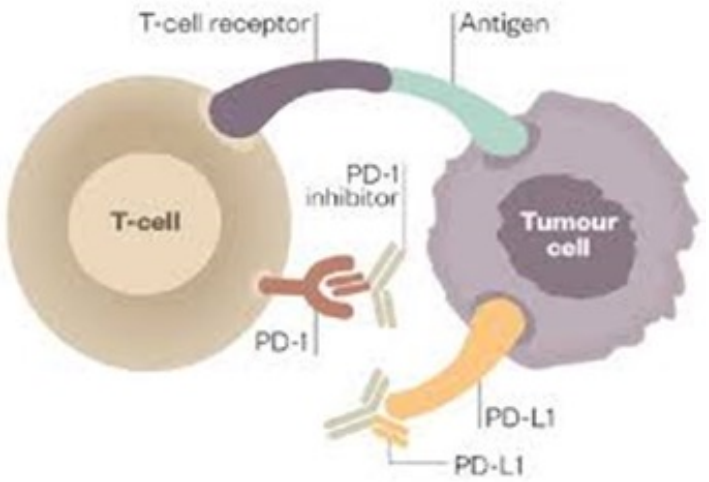
Checkpoint Inhibitor Combos

- Unlike traditional regimens, formed by adding a novel agent to an established chemotherapy regimen, manufacturers are forming new combinations with two targeted agents
- Both novel and established agents are under consideration for combination regimens:
  - **Immunotherapies**: Restarts the patient's immune response to tumour cells
  - **Targeted/Epigenetic Therapies**: Directly destroy and/or inhibit the proliferation of tumour cells
- Combination regimens promise to deliver superior outcomes vs. monotherapies by manipulating different mechanisms of action or multiple pathways across the tumour response cycle

Mechanism of Action[1,2]

- Some tumour cells present PD-L1 antigens that interact with the PD-1 protein on immune cells (T-cells) preventing them from identifying the tumour cell
- Anti-PD-1/PD-L1 therapies blocks the interaction allowing immune cells to destroy the cancer
- Combinations with other anti-cancer agents are designed to restart the immune cell response to tumour cells or exploit alternative pathways to improve the ability of immune cells to identify the tumour cells

PD-1/PD-L1 Pathway[1]



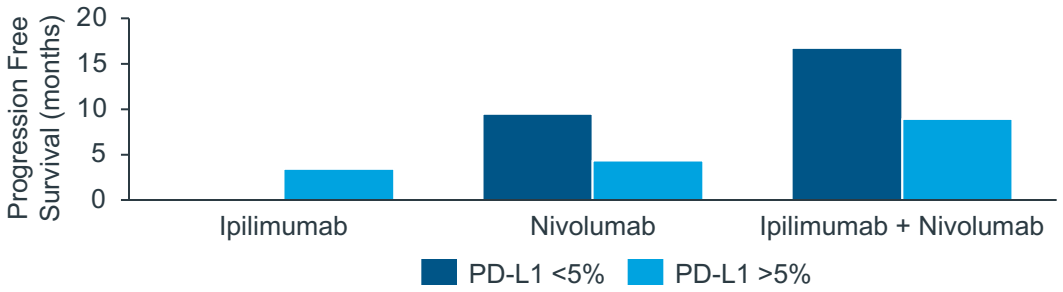
Source: (1) ASCO, (2) ASCO; **abbreviations**: non small cell lung carcinoma (NSCLC) - link to glossary

By targeting multiple pathways combination regimens promise to increase the number of patients that benefit from treatment

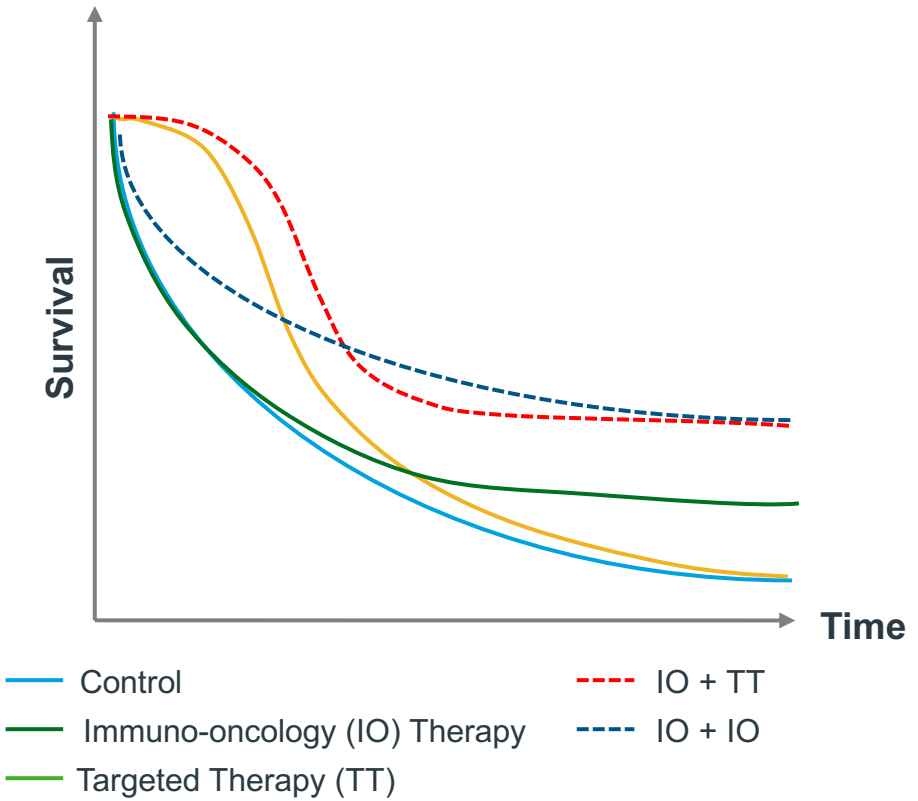
The Promise

- Currently, only a subset of patients benefit from receiving immuno-oncology (IO) therapy as monotherapy
- However, those that do, may experience long-term survival
- Conversely, patients that receive targeted therapy may initially benefit but often the tumour will develop treatment resistance mutations rendering the therapy ineffective
- Combining IOs and/or targeted therapies promises to increase the number of patients experience a long term benefit from treatment
  - *Proof-of-concept demonstrated by nivolumab/ipilimumab (IO+IO) in melanoma (see below)*

Monotherapy vs. combination efficacy split by PD-L1 expression (CheckMATE-067)



Hypothesised Survival Rates of Oncology Combination Regimens*



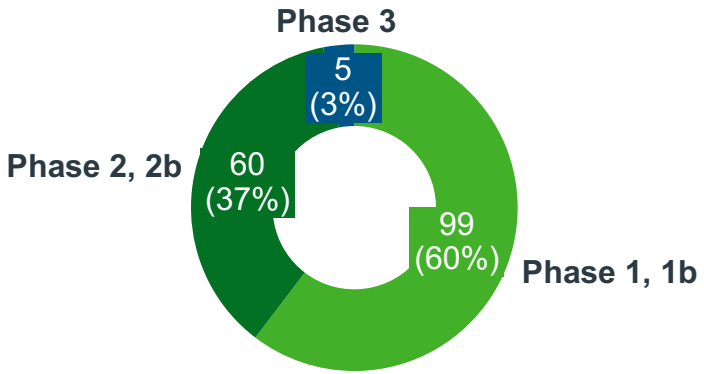
We will now assess the implications of combination regimens in NSCLC…

Source: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/04/WC500204597.pdf; **abbreviations**: non small cell lung carcinoma (NSCLC) - link to glossary

Significant activity in checkpoint inhibitor combination continues, with this potential expanding beyond NSCLC into other tumours

Novel checkpoint inhibitor combination therapies (active trials)

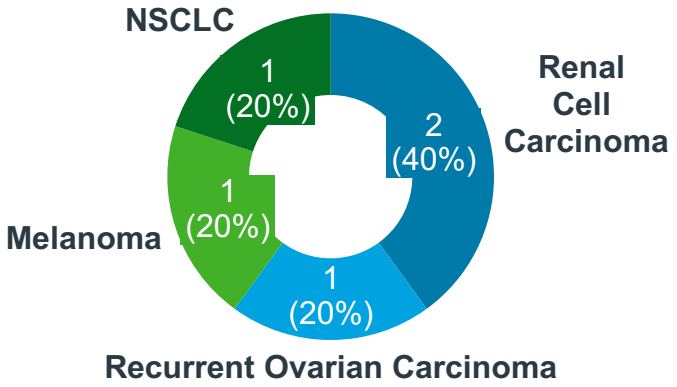
N=164



- There are currently **over 150+ ongoing trials** studying checkpoint inhibitor combinations
- The majority of these trials (99) are new, and are in **early development phases**
- There are 5 products in Phase 3 – all of which are being **studied for cancers**

Indications studied in trials (Phase 3 only)

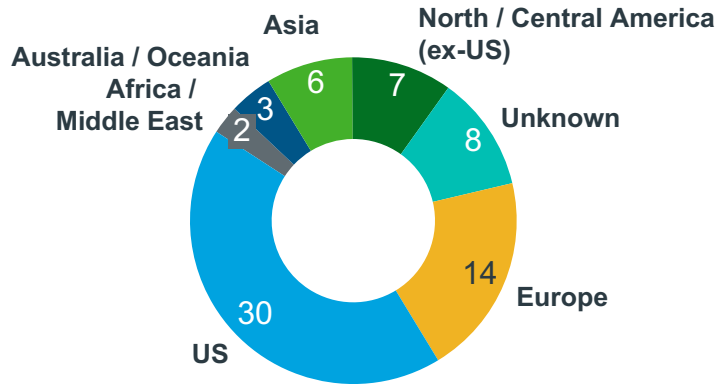
N=4



- In addition to the 2019 update, where much activity was seen for NSCLC, we also now see **additional tumour types also part of the picture**

Active studies by geographic location

N=70*



- Trials studying checkpoint inhibitor combinations are happening globally, across **all continents**
- The majority of trials are happening in the **US and Europe**

Note: (*) one trial may be happening in multiple countries
Source: clinicaltrials.gov; **abbreviations**: non small cell lung carcinoma (NSCLC) - link to glossary

Non small cell lung cancer (NSCLC) is the 2nd most common form of cancer, with low survival beyond five years

Non small cell lung carcinoma (NSCLC)

Lung cancer is the second most common cancer and the leading cause of cancer death for men and women, where NSCLC is the most common type

~490.000[1]
Patients diagnosed in EU
(71 per 100,000 population)

Patient type [2]
Mainly affects smokers, and people aged 65 years or older with an average diagnosis age at 70 years

Quality of Life[2]
Lowered physical ability, as well as psychological health – incurred by the disease and side effects of treatment

6,630[3]
Annual HC cost / patient
and further social and economic costs

High Mortality[2]
99% of advanced NSCLC patients die within 5 years, only ~11% of patients are expected to live beyond 5 years after diagnosis

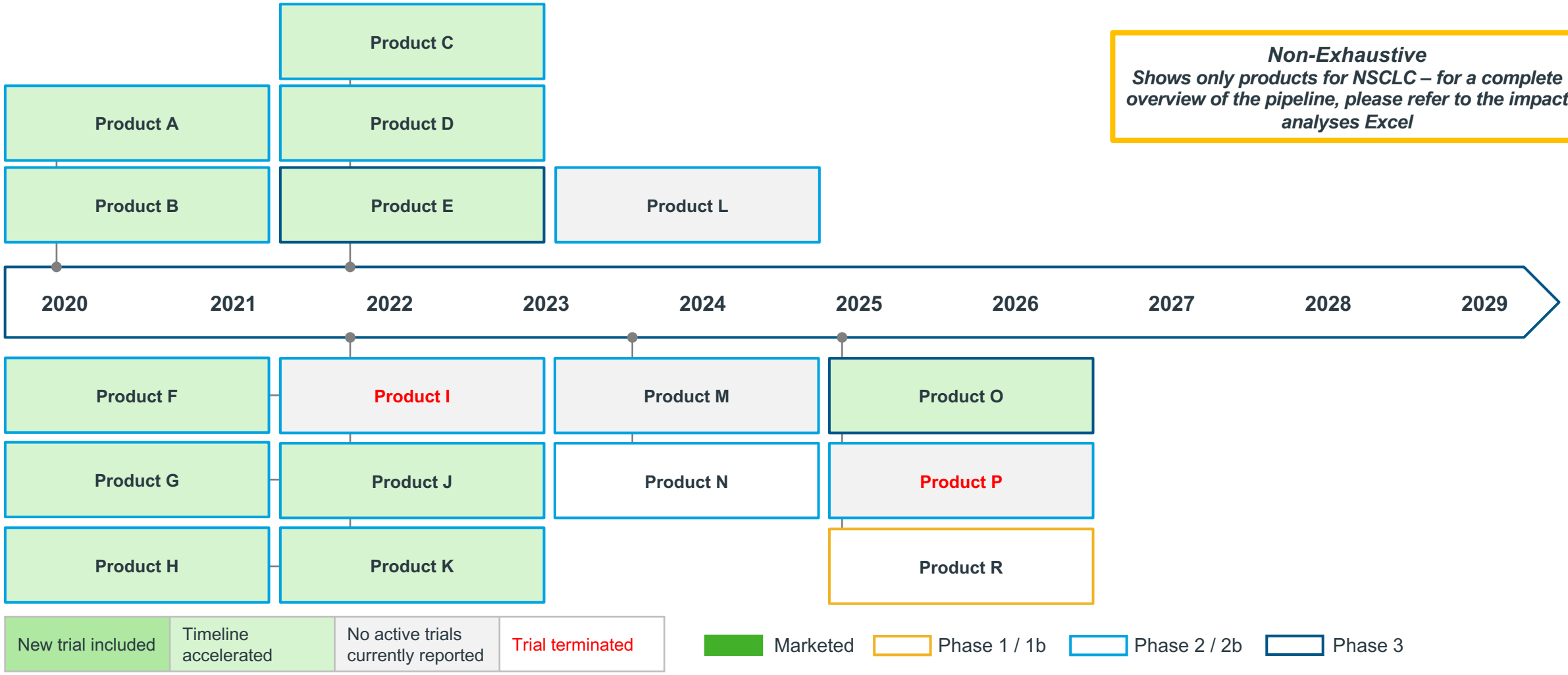
- **~80-85%** of lung cancers are NSCLC, the main subtypes being:
  - **Adenocarcinoma**: most common form, and more prevalent in women and more likely to occur in younger people than other types of lung cancer
  - **Squamous cell carcinoma**: linked to a history of smoking and tend to be found in the central part of the lungs, near a main airway (bronchus)
  - **Large cell carcinoma**: tends to grow and spread quickly, which can make it harder to treat

- Treatment for NSCLC varies with chemotherapy remaining the standard of care for the majority
- **Stage 0-2**: surgery could be sufficient, however, adjuvant chemotherapy after surgery can lower the risk that cancer will return – followed by additional chemotherapy, or surgery if needed
- **Stage 3**: a combination of radiation therapy, chemotherapy, surgery, and/or immunotherapy (e.g. pembrolizumab)
- **Stage 4**: for NSCLC that has spread widely, the tumour will first be tested for certain gene mutations (e.g. EGFR, ALK), where a targeted therapy can be chosen
  - For patients where a targeted therapy has not worked, a **combination therapy of immunotherapy products** can also be used (e.g. nivolumab + ipilimumab)

Source: (1) Cancer Research UK, (2) cancer.net, (3) IQVIA Impact Analysis, (4) what is NSCLC, (5) treating NSCLC; **abbreviations**: non small cell lung carcinoma (NSCLC) - link to glossary

Multiple checkpoint inhibitor combination therapies are set to launch for NSCLC in the next 7 years

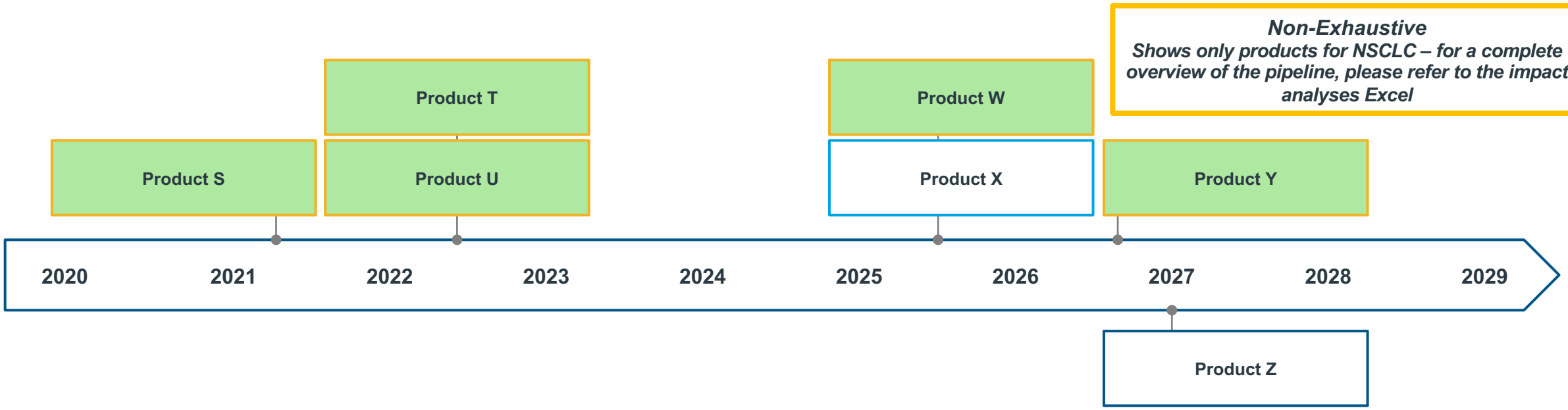
2021: NSCLC checkpoint inhibitor combinations: Estimated trial completion dates



Source: clinicaltrials.gov; October 2020, active clinical trials (Not yet Recruiting, Recruiting, Enrolling by invitation, Active not recruiting), Excluded trials without specified phase, Device trials

We have also identified additional pipeline products which were not captured in the 2019 report

2021: NSCLC checkpoint inhibitor combinations: Estimated trial completion dates



New trial included	Timeline accelerated	No active trials currently reported	Trial terminated

Marketed | Phase 1 / 1b | Phase 2 / 2b | Phase 3

Source: clinicaltrials.gov; October 2020, active clinical trials (Not yet Recruiting, Recruiting, Enrolling by invitation, Active not recruiting), Excluded trials without specified phase, Device trials

Combination regimens offer multiple benefits for patients, their families, caregivers, healthcare systems and society

Checkpoint Inhibitor Combination Regimens - NSCLC

1 **Patients, families and caregivers**

- Combination regimens could extend the lives of patients and offer potential for a cure in patients where prognosis is very poor – allowing them to lead a normal life
- Longer term survival could also mean a reduction in emotional distress for patients and families as a result of reduced exposure to toxic chemotherapy

2 **Healthcare systems and healthcare professionals**

- Combination regimens could reduce hospital based healthcare burden by reducing the need for palliative care from oncologists
- This frees up resources that can be used to diagnose and treat more patients faster and more effectively

3 **Society**

- Combination regimens will see more patients survive-long term allowing them to return to work. This will reduce the care burden on families and friends, who will also need to take less time off from their work or other responsibilities

Source: Impact analysis, IQVIA internal expertise

Checkpoint inhibitor combinations are already shifting the SoC in NSCLC, with future research focused on further optimization

Shift in care

Combination immunotherapy as frontline Tx

- Immunotherapy combinations have shifted from investigational regimens to **novel frontline treatment options in NSCLC**
- For the majority of patients with advanced NSCLC, **most will need combination therapy** in order to achieve maximum benefit from immune checkpoint inhibitor therapy[1]
- With such great benefits seen, **triple combinations** are also now being studied[3]

"*A few years ago, there were a slew of immunotherapy trials, but I think we're starting to see now that* ***immunotherapy has now been established as a frontline treatment option*** *for most NSCLC patients*."
- Michael Shafique, MD[2]

What the future holds

Optimized therapy

- With so many combinations now being studied in the pipeline, **ongoing research efforts will continue to optimize** these therapies – this means:
  - Understanding and addressing **patient resistance** to immunotherapy[2]
  - Investigating and **adding flexibility** to optimize the dose, schedule, and configuration of each agent[3]
  - Revising *typical* endpoints used in clinical studies, as the use of **PFS survival may be misleading** given the delayed kinetics of response that can occur with some agents and regimens (may be better to consider immune-related response criteria or durable response rate)[3]

Abbreviations: standard of care (SoC), progression-free survival (PFS) - link to glossary

Source: (1) supported by trial data for pembrolizumab, atezolizumab, and nivolumab as well as the CTLA-4 inhibitor, ipilimumab, (2) OncLive, (3) BMC, (4)

Combination regimens offer patients longer term survival, reduced emotional distress and may allow a return to work

Checkpoint Inhibitor Combination Regimens in NSCLC

1

Patients, families and caregivers		
	Current Therapy	**Future = Combination Therapy**
Quality of Life	• Historical therapeutic options are known to significantly impact QoL given toxicities • Patients and their families often experience depression upon diagnosis	• Combination therapies have potential to improve patient quality of life vs. chemotherapy alone *(please refer next slide)* • Potential for increased number of patients experiencing long term survival could see a reduction in emotional distress for patients and families and fewer patients relying on toxic chemotherapy
Life Expectancy	• The benefit current therapies provide patients is dependent on patient eligibility for recent targeted (ALK, EGFR) and immunotherapies (PD-L1); chemotherapy remains 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** • *Keytruda + pemetrexed + carboplatin has demonstrated 12 month OS of 70% vs. 50% in chemotherapy arm; median PFS was 9 vs. 5 months* • *New combinations like ipilimumab + pembrolizumab demonstrated OS of 21,2 months vs. 14,0 months in the chemotherapy arm[1]* • *5-year overall survival rate in all types of lung cancer is ~18% as per SEER cancer database*
Financial Pressure	• Stress due to pressures associated with income decline and travel costs increases (to/from hospital)	• Potentially curative effect of certain combination regimens could see **patients returning to work and cutting back on treatment-related expenditure**

Abbreviations: - link to glossary; Source: Impact analysis, (1) Nivolumab + ipilimumab;

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

Checkpoint Inhibitor Combination Regimens in NSCLC

2

Healthcare systems and healthcare professionals

	Current Therapy	Future = Combination Therapy
Hospital Utilisation: *Palliative Care*	• **Advanced tumours have low survival rates;** this places a large burden on health care resources due to the need for palliative care/overnight stays	• Increased number of patients experiencing long term survival would see **fewer patients requiring palliative care or over night stays;** reducing waiting times for hospital beds and increasing the availability of healthcare practitioners - *Nivolumab (Opdivo) has shown **significant benefit in overall survival** (~9 months) compared to conventional chemo like docetaxel (~6 months) for NSCLC patients* - *Pembrolizumab (Keytruda) has shown **significant benefit in overall survival** (10-12 months) compared to conventional chemo like docetaxel (~8 months) for NSCLC patients* - *120.000 patients with NSCLC could be saved using the novel combination treatment approach in the metastatic stage of the disease[1,2]*

Note: (1) Based on previous KOL estimate of potential OS achievable within NSCLC with combination therapy, (2) Revised up from 30,000 patients, to include all patients, rather than just working age patients
Abbreviations - link to glossary Source: Impact analysis

By providing a long-term treatment option for the disease, combos could allow more patients to contribute to society

Checkpoint Inhibitor Combination Regimens in NSCLC

3

Society		
	Current Therapy	**Future = Combination Therapy**
Productivity Loss	• Poor long term survival and high risk of progression means that many patients do not return to work following a diagnosis	• More patients could survive-long term **allowing patients to return to work, pay taxes and actively contribute towards society** • *E.g. for NSCLC patients diagnosed in 2020; an **estimated €717 mn. 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

Abbreviations - link to glossary; Source: Impact analysis

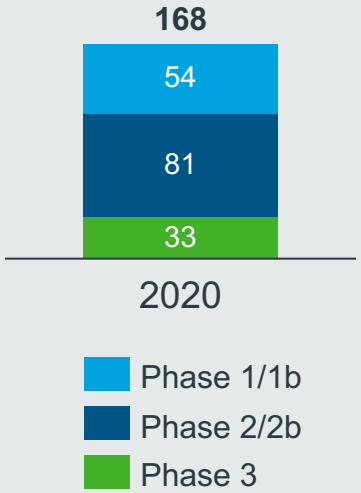
Alzheimer’s Therapies

Link - back to innovations contents page

Despite an extensive pipeline, their remains a need for accurate diagnosis and effective therapies for Alzheimer's Disease

2020 updates vs. the 2019 report (covers updates from July 2019 – October 2020)

CLINICAL DEVELOPMENT



+4 phase 2 and 3 trials expected to enter the market by 2023

3 therapies with timelines accelerated vs last year

-3 trials withdrawn

SELECTED TECHNOLOGIES

β-amyloid mAbs

remain the focus area with the biggest body of evidence

Anti-tau mAbs and stem cell therapies

are investigated in the number of trials, raising hopes for effective AD treatment – high-level analysis included

KEY UPDATES

At the moment, aducanumab is the β-amyloid therapy closest to receiving market authorisation; ***final decision from FDA is expected by March 2021[1,2]***

Without an effective therapy, the unmet need related to AD will continue to escalate; the ***number of patients will nearly double by 2050***

The ***healthcare cost per AD patient is also increasing*** *- updated based on recent data for the UK (increase by 28% vs previous update)*

The total disease cost for Europe is forecasted to increase by about 43% between 2008 and 2030 to over ***EUR 250 billion[3]***

Note: (*) Includes withdrawn, terminated, and suspended trials

Abbreviations - link to glossary; Source: (1) Science Magazine; (2) EMA filing for aducanumab was also accepted for review at end of October 2020; (3) Alzheimer Europe; clinicaltrials.gov, IQVIA analysis

Alzheimer's is one of Europe's largest public health crises with the greatest impact upon quality of life of patients and family

Alzheimer's disease

A progressive, irreversible neurological disease that impairs cognition, orientation and functional capacity

15,9 million
AD patients in Europe by 2050 (+90% since 2019)

149 million at risk
Increase in the number of 65+ inhabitants in the EU by 50% by 2050 (from 101 million in 2018) (1)

Highly impacted QoL
Moderate and severe patients requiring support in daily activities; high risk of co-morbidities and decreased life expectancy

€110 billion+
Total healthcare and social care costs
Not including informal care costs

Disease burden
Lack of effective treatment, despite high investment

- Alzheimer's is one of Europe's largest public health crises and the most common cause of dementia (60-80% of all dementia patients); today >**8,3 million patients**[1] suffer from Alzheimer Disease across Europe
- Due to the anticipated rapid growth of the over-65 segment of the population, this number is expected to **nearly double over the next 35 years**, reaching **15,9** million in Europe by 2050[2]
- While dementia caused by Alzheimer's does shorten life, its **greatest impact is upon quality of life**, both for patients and for their family, friends and carers
  - Dementia leads to gradual loss of memory/intellect and a change in their mental stability (e.g. aggression, hallucinations, psychosis)
  - Overtime patients are unable to care for themselves or recognise family/friends
- Direct medical and indirect costs associated with Alzheimer's are high as healthcare systems and families are forced to provide home care and/or pay for assisted living; **direct medical costs constitute only ~20% of total cost of AD**[3]
- Current treatments only address the worsening of symptoms and are only effective in some individuals for a limited time frame; there is a significant **unmet need for a treatment to prevent, cure or slow the progression** of Alzheimer's disease
- Since 1998, **146** Alzheimer's drugs have been rejected[4]; in that time, only 4 new medicines were approved to treat symptoms of AD – **"failed" projects outnumber approved medicines 36 to 1**

(1) Based on updated prevalence rate of dementia in Europe (Alzheimer Europe Yearbook 2019) and estimated AD share in dementia cases (Alzheimer's Association, 2020); (2) Alzheimer Europe Yearbook 2019; (3) Information from Biogen; (4) Bright Focus Foundation, 2020; **abbreviations** - link to glossary

Disease modifying therapy such as those targeting the β-Amyloid pathway may delay the onset of this highly debilitating disease

Introduction to Disease Modifying Therapy in Alzheimer's

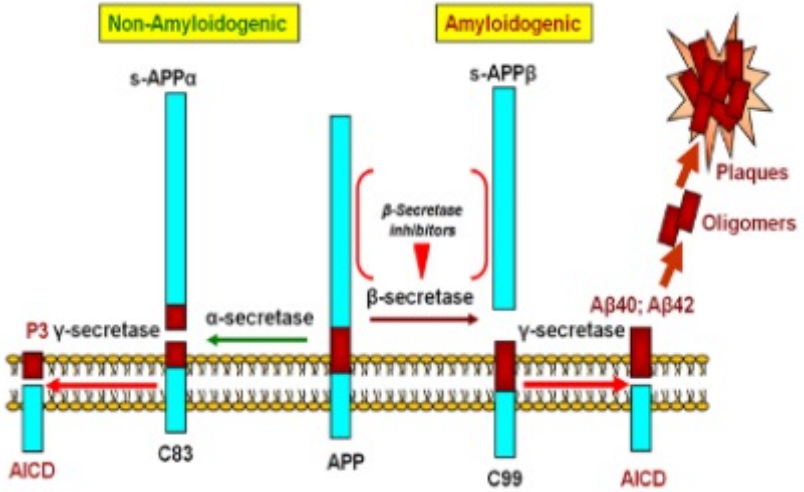
- The exact disease pathology is unknown; one hypothesis attributes damage to formation of β-Amyloid and/or tau protein plaques in the brain
- Disease modifying therapies in Alzheimer's seek to breakdown or inhibit the formation of these plaques via alternative pathways
- Therapies are in development for pre-dementia and mild Alzheimer's dementia and **could delay the onset and/or progression of a highly debilitating disease** for which only symptomatic treatment is currently available

β-Amyloid Pathway: Therapeutic Approaches

Although other agents are in development, those targeting the β-Amyloid pathway have the largest body of clinical evidence:

- **β-Amyloid Immunotherapies (antibodies):** disrupt established plaques, and encourage plaques to move out of the brain
  - **Active (aka vaccination):** introduction of synthetic full-length or a fragment of the β-Amyloid protein to stimulate immune cells to produce antibodies that neutralise the plaque-causing β-Amyloid peptides and clear the plaques
  - **Passive:** direct introduction of antibodies (mAbs) targeted against β-Amyloid
- **BACE Inhibitors:** prevent production of β-secretase, enzyme responsible for formation of amyloid plaques

β-Amyloid Pathway: BACE Inhibition

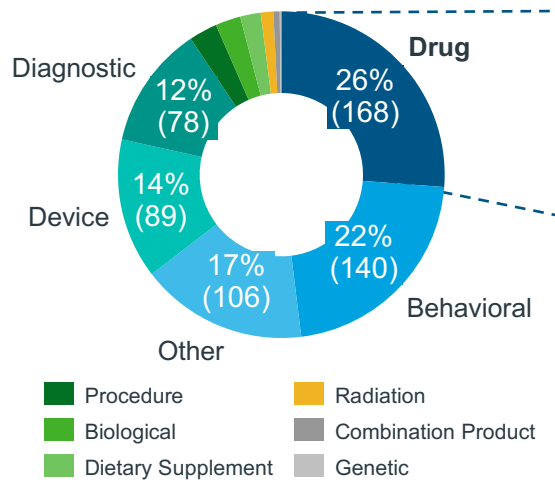


Note: pre-dementia = pre-clinical, prodromal and mild; **abbreviations** - link to glossary

Previous failures have not discouraged the industry from this therapy area; a number of new technologies are on the horizon

Number of active trials for Alzheimer's Disease

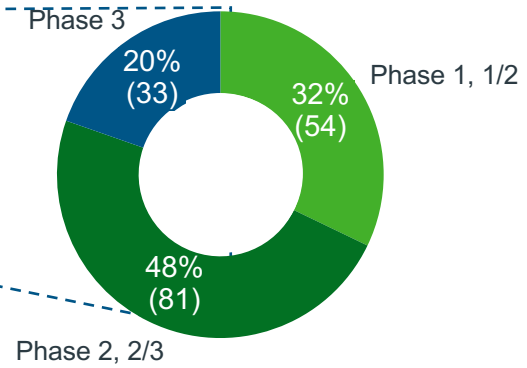
N=641



- 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 one fourth of the pipeline, with behavioural therapies, devices and diagnostic agents also high on the agenda

Clinical trials for Alzheimer's drugs by development phase

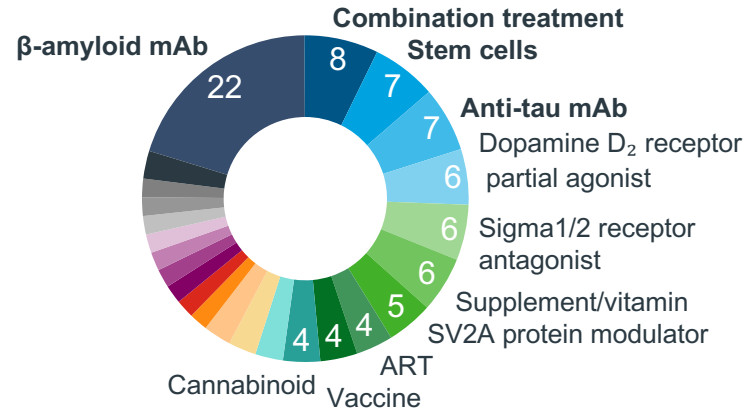
N=168



- Many investigative therapies for Alzheimer's Disease are still **in early development stages**, with 80% of active clinical trials in phase 1 or 2
- Phase 3 studies raise hopes for new drug entering the market in the next 3-5 years

Clinical trials for Alzheimer's drugs - key technologies

N=109*



- **β-Amyloid targeting therapies** remain the focus area in AD clinical trials; however, several other technologies are gaining interest

(*) Shown technologies with at least 2 clinical trials ongoing; Source: clinicaltrials.gov, IQVIA analysis; **abbreviations** - link to glossary;

Several approaches are being investigated as disease modifying therapies; β-Amyloids have the largest body of evidence to date

Select approaches to curative treatment for Alzheimer's Disease

β-amyloid monoclonal antibodies and anti-tau monoclonal antibodies

β-Amyloid peptide and pathological forms of the tau protein are known to "cooperate" in causing AD genotypes. Better understanding of this link will support development of effective therapeutics for AD[0]. Build up of both β-Amyloid peptides and tau proteins in the brain in AD is thought to lead to nerve cell damage and death. **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**[2]. Tau protein is not only directly toxic to cells but is also a mediator of β-amyloid toxicity. **However, latest trial of tau-blocking drug has brought disappointing results**[3].

Stem cell therapy

The investigated stem cell therapies, e.g., involving Mesenchymal Stem Cells, **aim to replace the brain cells damaged by AD with healthy cells**, potentially resulting in the improvement of functional memory, neurons regeneration and the overall functional recovery improvement[4]. Despite many challenges, stem cell therapy remains a prospective method for AD treatment[5].

β-Amyloid clearance through plasma exchange with albumin replacement

Recent results from GRIFOLS[6] show positive outcomes of the AMBAR protocol* on the reduction of disease progression in mild-to-moderate AD. Based on the hypothesis that most the β-Amyloid protein is bound to albumin and circulates in the plasma; the protocol involves regular plasma replacement aimed at flushing the β-Amyloid peptides from the brain into the plasma – reducing the build up before is causes neuronal damage

Combination treatments

As Alzheimer's Disease is characterised by multiple complex pathways, and a number of possible targets within these pathways, researchers are paying more and more attention to potential combination therapies[7]. Combinations are able **to target multiple disease pathways to achieve clinically meaningful benefits**, while investigated monotherapies have had modest effects to date.

Vaccines

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].

(*) AMBAR - Alzheimer Management by Albumin Replacement; **abbreviations** - link to glossary

References 0-10 available in speaker notes

Key: Largest body of evidence | **More information in the Appendix**

Initiation of β-amyloid immunotherapies during the pre-dementia is expected to offer the greatest clinical benefit

β-amyloid monoclonal antibodies deep dive

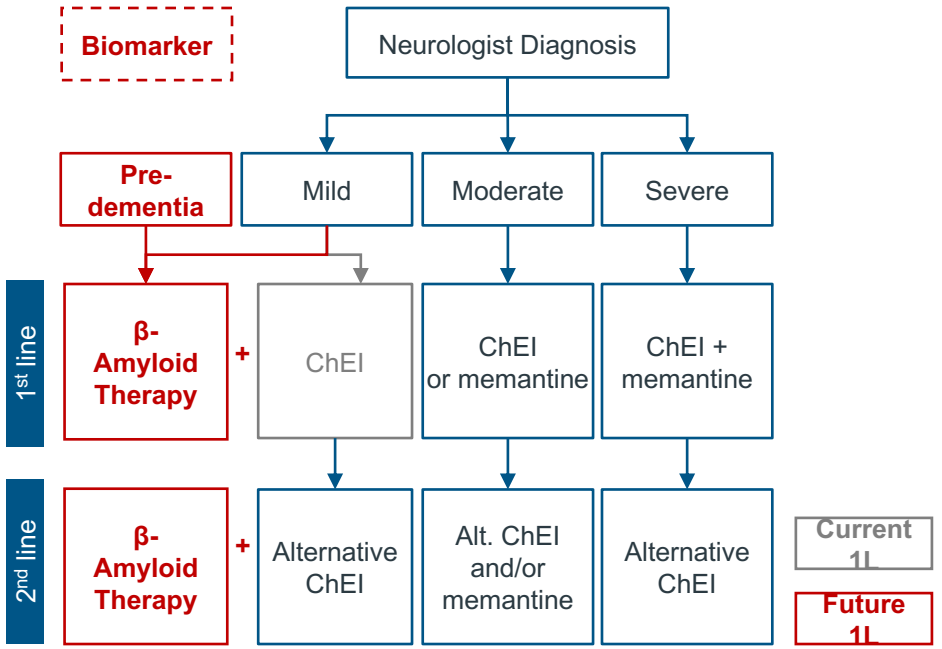
The promise

- Currently available AD treatments provide **only symptomatic relief**, temporarily improving brain function in patients with mild to moderate disease; these symptomatic treatments include cholinesterase inhibitors (donepezil, rivastigmine) and NMDA-receptor antagonist (memantine)
- **β-Amyloid therapy is expected to slow the progression or delay onset of the debilitating symptoms** and it is hypothesised that the benefit will be greatest if treatment is initiated in pre-dementia (pre-clinical, prodromal, and mild dementia)
- However, diagnosis and treatment of patients in pre-dementia (pre-clinical and prodromal) and mild dementia will require development and utilisation of **effective biomarkers**

β-Amyloid Pathway: Efficacy

- Preliminary impact on scales designed to measure cognitive decline (e.g. MMSE, CDR-SB and ADSC-ADL) suggest
  β-Amyloid plaque manipulation could slow the rate of progression of the disease allowing patients to spend more time in earlier disease stages
- Magnitude of efficacy of 1st wave products is not yet confirmed in the clinical setting; however even a short delay in onset/progression is expected to have a large impact

Current and 'future' treatment paradigm



ChEI (Cholinesterase inhibitor); *Note:* **pre-dementia** = pre-clinical, prodromal and mild

Abbreviations - link to glossary

Final FDA's decision on aducanumab is expected by March 2021; another β-amyloid mAb - BAN-2401 - is in Phase 3

β-amyloid monoclonal antibodies - selected therapies

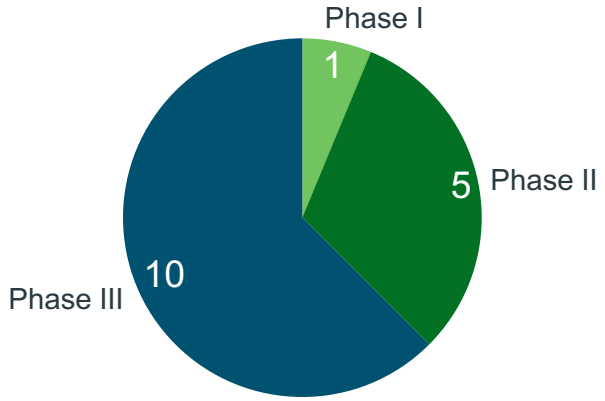
BAN-2401 (BioArctic, Biogen, Eisai)

- BAN-2401 is thought to have a highly-selective binding profile which allows the antibody to bind to toxic forms of amyloid beta cells and eliminate them – as confirmed by **positive results from phase 2b studies**[1]
- In May 2019 Eisai started a **phase 3 study (Clarity AD)** in patients with mild cognitive impairment due to AD or mild AD with confirmed brain amyloid pathologies[1]; the primary endpoint is **change in the patients' cognition and function**, and results are expected in 2022
- In parallel, a phase **3 AHEAD 3-45** study investigates BAN-2401 ability to delay memory decline in patients **even before they develop the AD symptoms**[2]

Aducanumab (Biogen, Eisai)

- Aducanumab **has the potential to meaningfully limit the AD's impact on patients' cognitive and functional decline**[3]
- In August 2020 FDA accepted Biogen's application for aducanumab's Priority Review for patients with Alzheimer's Disease[3]
- FDA's **final decision on Biogen and Eisai's drug is expected by March 7 next year**[4]
- At the end of October 2020, EMA accepted aducanumab's Marketing Authorisation application

Pipeline activity – no. of active trials



Other β-amyloid mAbs in development:

Phase	Therapy (Originator)
Pre-clinical	No information
Phase I, I/II	LY3372993 (Eli Lilly)
Phase II	Crenezumab (Roche) Donanemab (Eli Lilly)
Phase III	Gantenerumab (Roche) Solanezumab (Eli Lilly)

Not exhaustive

(1) BioArctic; (2) Eisai; (3) Investors Biogen; (4) Medscape;

Abbreviations - link to glossary

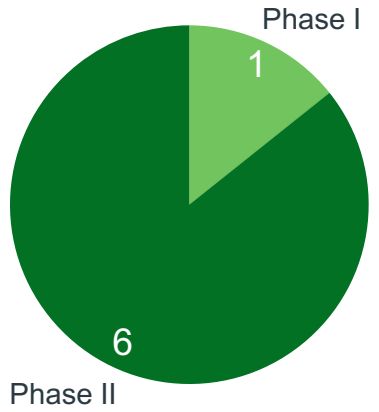
Reason behind the lack of success of anti-tau treatments is still to be confirmed; improved agents or hypothesis revision required

Anti-tau monoclonal antibodies - selected therapies

ABBV-8E12 (AbbVie)

- ABBV-8E12 is a humanised IgG4 antibody being developed by C2N Diagnostics and AbbVie to treat tauopathies[1]
- In December 2016, AbbVie launched a phase 2 study comparing the efficacy of ABBV-8E12 to placebo in **progressive supranuclear palsy** (rare progressive disease caused by brain cells damage); however, trial was terminated in July 2019 due to unsatisfactory results
- At the same time, AbbVie continues the ABBV-8E12 phase 2 trial in patients **with early Alzheimer's Disease**, with primary completion date set to July 2021; no interim results in AD were published to date

Pipeline activity – no. of active trials



Semorinemab (Roche, AC Immune)

- As of September 2020, phase II Tauriel trial of semorinemab in patients with prodromal to mild Alzheimer's Disease **did not meet its primary and secondary endpoints** - the drug showed no benefit over placebo in changing the clinical dementia (based on rating-sum of boxes score)[2]
- More data are expected in CTAD meeting in November 2020; the analysis of tau biomarker data may help assess **whether the trial failed due to semorinemab's low efficacy in clearing tau, or perhaps the overall tau hypothesis should be revised**
- Meanwhile, the second phase 2 LAURIET trial in patients with moderate AD is ongoing (3)

Other anti-tau mAbs in development:

Phase	Therapy (Originator)
Pre-clinical	No information
Phase I, I/II	Lu AF87908 (H. Lundbeck)
Phase II	BIIB092 (Biogen) LY3303560 (Eli Lilly)
Phase III	-

Not exhaustive

(1) ALZ Forum; (2) Nature.com

Abbreviations - link to glossary

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

Currently available biomarker tests - lumbar puncture (CSF) and neuroimaging (amyloid PET scan) are not widely used in clinical practice due to barriers related to reimbursement (CSF specifically), as well as high price and limited scalability of PET scans.

Identifying molecular therapeutic targets, addressing right patient populations/ detecting disease in early stages are key success factors for effective Alzheimer's therapy

- Multiple molecular therapeutic targets are currently under scrutiny
  - ➢ At the moment, **tau and β-amyloid proteins** are recognized as **major hallmarks of neurodegeneration** and used as key therapeutic targets[2]
- There is an increasing realisation that the **stage of disease is key to stopping AD's progression**; patients with mild cognitive impairment and dementia are most likely to benefit from DMTs[1]

Beta-amyloid pathway

Doubts regrading 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 are expected to 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, hypothesis remains unconfirmed, as a number of anti-tau therapies have failed in clinical trials[5].

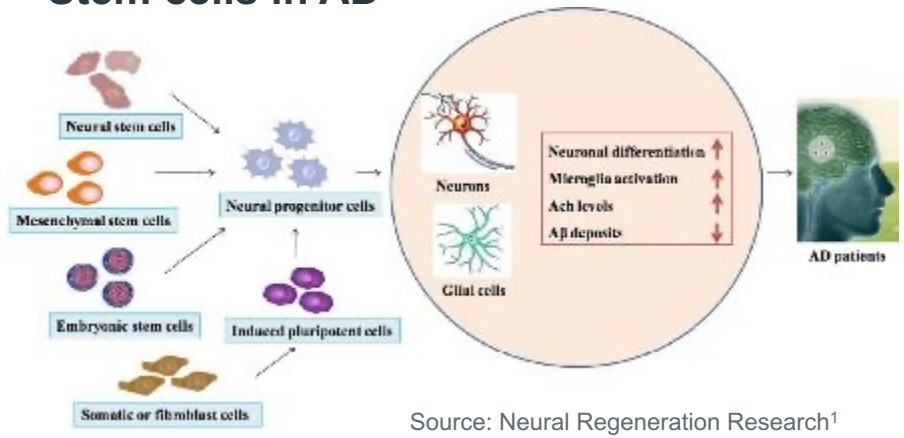
The key step in preparing the healthcare systems for DMTs in Alzheimer's is development of a reliable and accessible biomarker to identify the right patient population for the treatment. **Diagnostic solutions in development**, e.g., blood tests for beta-amyloid plaques[6] and for tau abnormalities[7], offer great hope for earlier detection of AD and for targeting right patients with effective treatment.

Aβ - beta-amyloid; AE- Adverse events; Sources: (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; (6) AJMC; (7) Alzheimer's Association; **abbreviations** - link to glossary

The expanding research and emerging technologies in stem cells area raise hopes for effective cell therapy for Alzheimer's

Stem cells - selected therapies

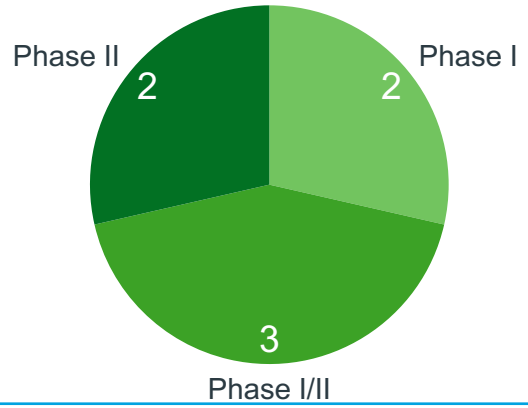
Stem cells in AD



Source: Neural Regeneration Research[1]

Different stem cells types (neural, mesenchymal, embryonic, induced pluripotent) have the potential to generate neural progenitor cells, resulting in the **generation of new neurons or the replacement of damaged neurons**, offering unique regenerative properties.

Pipeline activity – no. of active trials



HB-adMSCs (Hope Biosciences)

- Autologous adipose-derived mesenchymal stem cell therapy by Hope Biosciences is currently being tested in phase 2 clinical trial for **COVID-19**, but also in **phase 1/2 trial in patients with Alzheimer's Disease**[2]
- Hope Bioscience's proprietary technology is believed **to address the challenges of traditional cell therapies**, such as difficulty in producing enough cells to make a significant impact and also reduces risk of donor rejection[3]
- Stem cell therapy offers the potential **to reduce the disease effects in Alzheimer's patients and grant patients more time with better cognitive functions**[4]
- Trial's primary completion date is set to February 2021

Other stem cell therapies in development:

Phase	Therapy (Originator)
Pre-clinical	No information
Phase I, I/II	NEUROSTEM-AD (Medipost) CB-AC-02 (CHABiotech)
Phase II	AstroStem (Nature Cell Co.) aMBMC (Stemedica)
Phase III	-

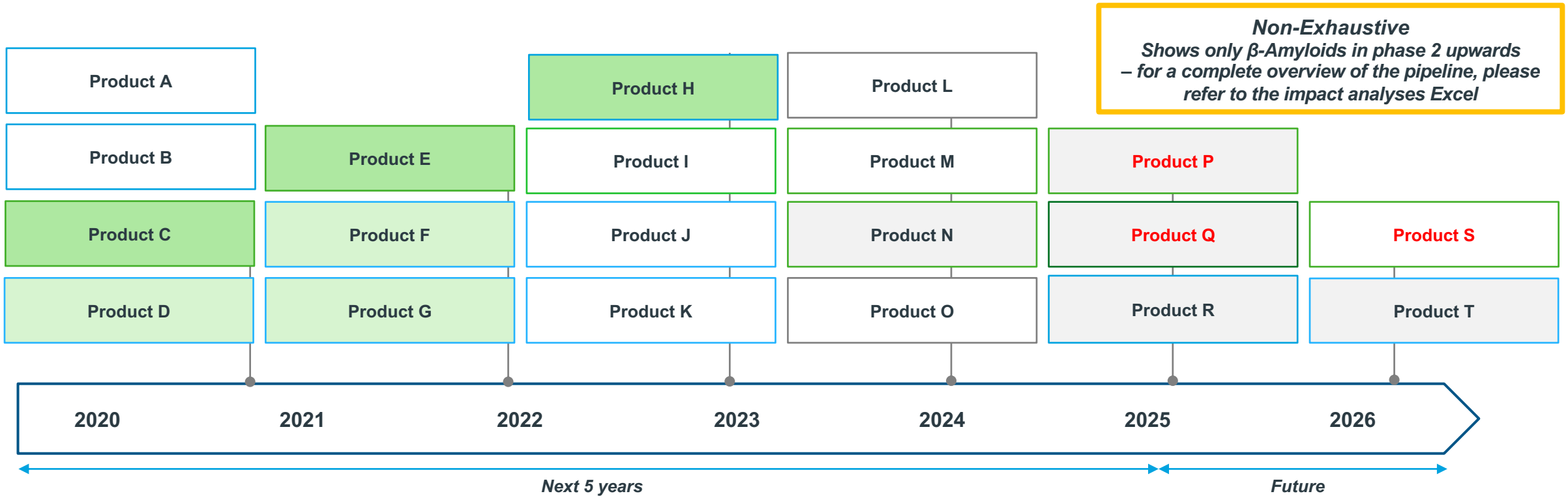
Not exhaustive

(1) Neural Regeneration Research; (2) clinicaltrials.gov; (3) Trial Site News; (4) NCBI

Abbreviations - link to glossary

Several trial progressions for β-amyloid therapies increased the number of potential product launches by 2023 from 3 to 10

2021: β-Amyloid Therapy Pipeline: Estimated trial completion dates



Source: clinicaltrials.gov; October 2020, active clinical trials (Not yet Recruiting, Recruiting, Enrolling by invitation, Active not recruiting), Excluded trials without specified phase, Device trials
(*) Planned Phase 3 trial to launch in early 2021 (data not available yet) (1)

Disease modifying t offer a great hope to reduce the high burden of Alzheimer's Disease on all affected

Disease modifying therapies for Alzheimer's Disease

1 **Patients, families and caregivers**

- Disease modifying therapies offer to delay the onset or progression of Alzheimer's Disease, allowing patients to retain higher function and have more time to live a normal life with their friends and family
- Disease modifying therapy could reduce the Alzheimer's impact on patients, families and caregivers allowing them to experience a better quality of life

2 **Healthcare systems and healthcare professionals**

- Healthcare systems would benefit as disease modifying therapies would delay the need for high levels of healthcare resource utilization associated with the severe disease state

3 **Society**

- Disease modifying therapy could reduce the burden Alzheimer's places on society: families will take less time off work to care for loved ones and it will reduce the amount of money spent on social care services

Abbreviations - Disease Modifying Therapy (DMT) - link to glossary

Delaying disease progression will allow patients to extend the time with friends and family before severe disease onset…

Disease modifying therapies for Alzheimer's Disease

1

Patients, families and caregivers

	Current state	Future = Disease Modifying Therapies
Economic independence	• With the age of retirement >65 in many countries, Alzheimer's Disease significantly impacts patients' ability to continue their professional careers and limits their economic independence	• Delaying disease progression will allow patients to continue working and remain fully engaged in social and professional lives and maintain financial autonomy
Emotional Wellbeing	• Distressing loss of intellect, memory and sleep • Behavioural 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 • Allows for the quality of the relationships with friends/family to be maintained for longer • Provides time to 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, allowing co-morbidity diagnosis and treatment

… and will make a positive impact on the lives of their caregivers, alleviating the pressure and emotional distress

Disease modifying therapies for Alzheimer's Disease

1

Patients, families and caregivers

	Current state	Future = Disease Modifying Therapies
Social Care/ Detention	• Moderate-to-severe patients require care within residential/nursing homes • Aggression due to behavioural conditions can see patients detained against their will under EU mental health legislation	• 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

Healthcare systems will benefit from new therapies delaying the need for high care levels associated with severe disease

Disease modifying therapies for Alzheimer's Disease

2

Healthcare systems and healthcare professionals

By delaying the onset of Alzheimer's; prevalence and expenditure on severe cases is expected to decline due to patient mortality from other diseases

	Current state	Future = Disease Modifying Therapies
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**[1] per year; this amounts to **~€26,6 billion** across the EU[2]	• Reduced pressure on hospital services; increased bed space and shorter waiting times for healthcare consultations
Drug Expenditure	• As severity increases patients require additional symptomatic regimens (AChEi + memantine) and treatment of co-morbidities	• Potential for reduced expenditure on symptomatic therapy and medication for co-morbidities (e.g. urinary tract disorders, epilepsy, depression etc.)
Caregiver Healthcare Costs	• Caregivers report higher rates of morbidity (e.g. depression) and mortality placing further pressure on healthcare systems	• Potential for reduced dependency of patients on caregivers leading to better overall health and wellbeing

Although care costs may decline, this may be offset by extra costs due to increased longevity; however, extra cost will equate to improved patient QoL

References for (1-2) in speaker notes

Society will benefit as patients and families would otherwise have to take time off work or use savings to provide care

Disease modifying therapies for Alzheimer's Disease

3

Society

	Current state	Future = Disease Modifying Therapies
Social Care Costs	• The greatest direct cost of Alzheimer's is the cost of social care • **Social care is estimated to cost €6.800 per patient every year, (€9.000 in severe cases)[1]** • However, two thirds of this cost is borne by patients and their families	• Delays disease progression and therefore payment for social care; the delay also provides more time to prepare for the costs associated with the disease • The total cost of social care in severe cases across the EU is estimated at **~€32bn[1]**; even incremental savings would be substantial
Opportunity Cost	• 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 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 caregiver quality of life could see lower absenteeism and better overall health of carers, reducing healthcare resource utilization • Delaying the onset of the disease could see patients working longer and retiring later

References for points (1-2) available in speaker notes

Gene Therapies

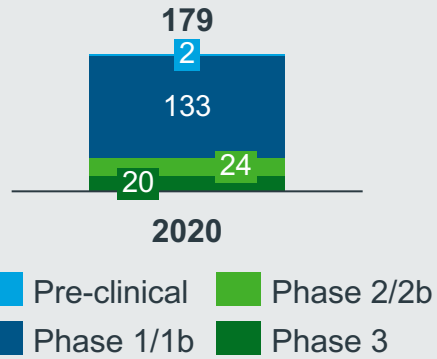
Link - back to innovations contents page

Gene therapy in seeing increased clinical activity, specifically in Haemophilia A, as well as other rare diseases

2020 updates vs. the 2019 report

CLINICAL DEVELOPMENT

All Gene Therapies



Haemophilia A & B only

+1 trial progression

+3 new trials

-1 trial withdrawn*

ADDITIONAL INDICATIONS STUDIED IN TRIALS

Beta-thalassemia

Sickle cell disease

Muscular and other dystrophies

Ophthalmological disorders

IMPACT AND OTHER UPDATES

1. *There are almost **179 active trials** currently for gene therapy, with highest activity in rare diseases, specifically, **Haemophilia A&B and ophthalmological disorders***
2. *Although Haemophilia B was the focus of last year's deep dive research, **investigation into Haemophilia A has increased** – with 3 products in late-stage development*
3. *For Haemophilia A, gene therapy could **minimize hospital visits and allow a return to work**, where an estimated **€67 million could be generated in GDP** each year*

Note: (*) Includes withdrawn, terminated, and suspended trials

Source: clinicaltrials.gov, IQVIA analysis; **abbreviations** - link to glossary

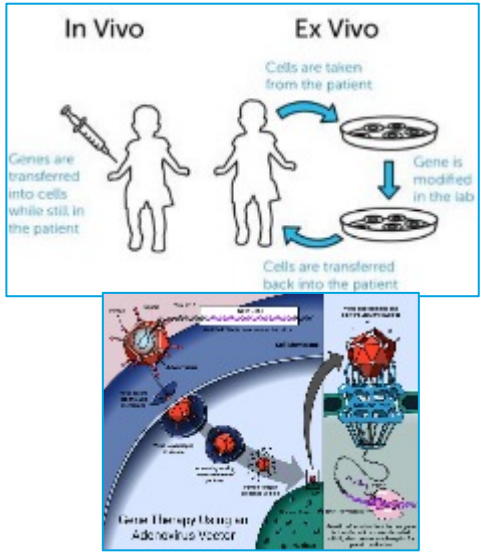
Gene therapy is being applied to various orphan diseases to restore the missing functions of damaged genes

- **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 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** or to make a **beneficial protein**
- If a mutated gene causes a necessary protein to be faulty or missing, a **normal copy of the gene is introduced to restore** the 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

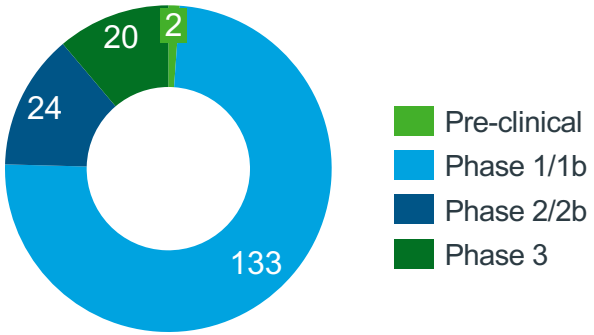
Notes: HSCT - hematopoietic stem cell transplantation

Abbreviations - link to glossary; Source: (1) FDA, (2) Cancer Research UK, (3) Medlineplus, (4) Center for Molecule Medicine

There are ~179 trials ongoing for gene therapies; most extensive pipelines are in Haemophilia A and ophthalmological disorders

Gene therapies (active trials)

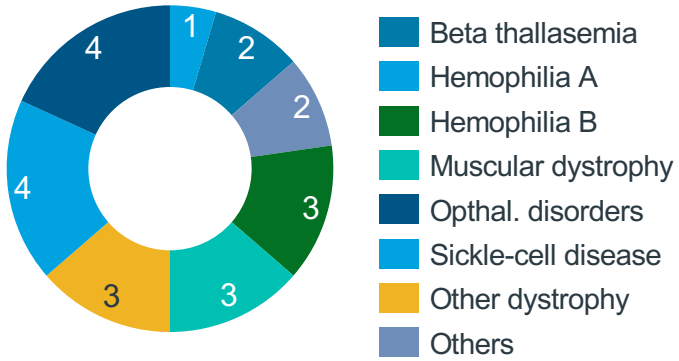
N=179



- There are currently **~179 ongoing trials** studying gene therapies
- As with other innovative areas, the majority of these trials are in **early development phases**

Indications studied in trials (Phase 2b & 3 only)

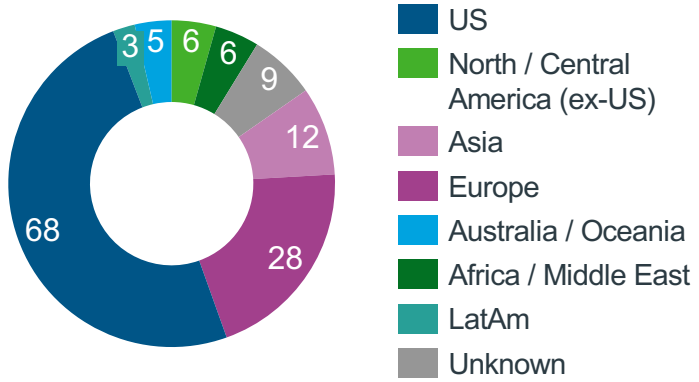
N=23



- Most of the Phase 2b and Phase 3 trials are being studied in Haemophilia
- **As opposed to** the 2019 update, where Haemophilia B was the key focus area, **Haemophilia A has also seen increased activity,** with 4 trials ongoing in 3 different therapies

Active studies by geographic location

N=137*



- The majority of trials are happening in the **US and Europe**
- Gene therapy trials are also happening globally, across all continents

Note: (*) one trial may be happening in multiple countries
Source: clinicaltrials.gov, IQVIA analysis; **abbreviations** - link to glossary

With multiple gene therapies being investigated in clinical trials, we also see a rise in approvals – Zolgensma being the latest

Marketing authorizations in gene therapy

Product *Indication* (Lead Developer)	Date of authorization	Product overview
Luxturna *Defects in RPE65* (Novartis/ Spark Therapeutics)	**Nov 22, 2018**	• **Approved in the EU in November 2018**, and is used to treat adults and children with loss of vision due to **inherited retinal dystrophy**, a rare genetic disorder of the retina • Was granted an **orphan drug designation** for **retinitis pigmentosa** (July 2015) and **Leber's congenital amaurosis** (April 2012)
Zynteglo *Beta-Thalassemia* (bluebird bio)	**May 29, 2019**	• Used to treat **beta-thalassemia** (blood disorder) in patients 12 years and older who require regular blood transfusions • Like the other approved gene therapies, **Zynteglo was granted an orphan drug designation** for beta thalassaemia following its **EU marketing authorization in May 2019**
Zolgensma *Spinal muscular atrophy* (Novartis)	**May 18, 2020**	• Approved in the EU on **conditional marketing authorization in May 2020**, and received an **orphan drug designation later in June** – with the EMA awaiting additional data from studies in **patients under 6 months** (Type 1), and **under 6 weeks who do have symptoms** • Indicated for patients with **inherited mutations affecting SMN1 genes**, who have either been diagnosed with SMA type 1 (the most severe type) or have up to 3 copies of the SMN2 gene

Source: (1) EMA, (2) EMA, (3) GWQ website; **abbreviations** - link to glossary

There are ~69.000 patients with Haemophilia A in Europe, who are mainly undergoing prophylactic therapy, causing great burden

Haemophilia A[1]

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

69.000[2]
Patients diagnosed in EU
(10 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

€200.000[3]
Annual HCS 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

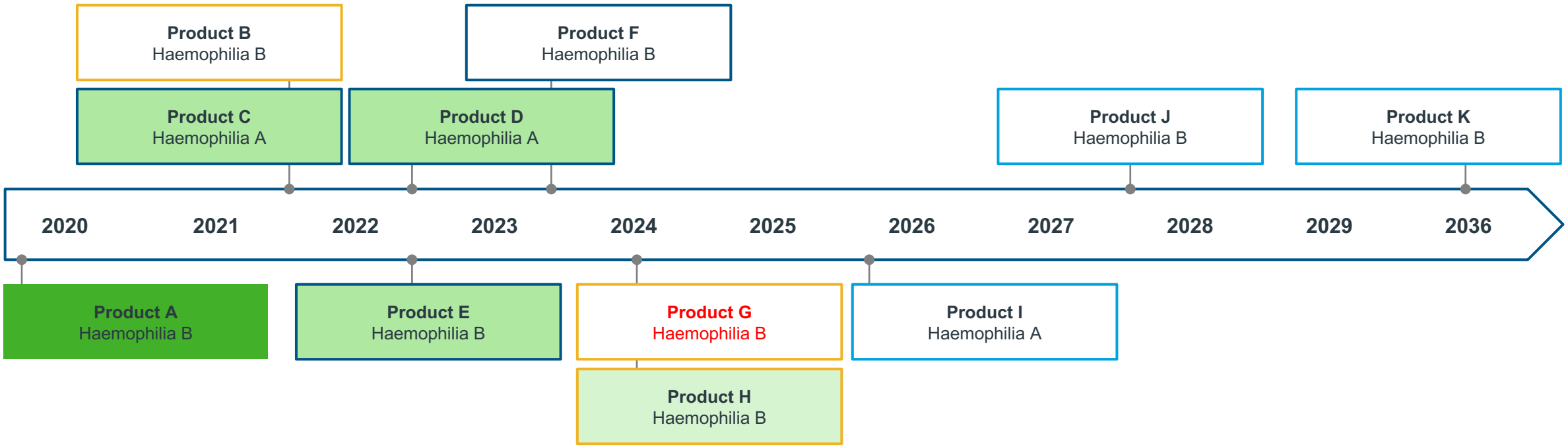
- Caused by a faulty gene that is unable to produce a **key protein needed for blood clotting** (factor VIII), with more than half of A patients suffering from a **severe form**
  - **Severe** (factor levels less than 1%) represent approximately 60% of cases
  - **Moderate** (factor levels of 1-5%) represent 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
- Medication to treat Haemophilia A is a **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) EUHANET, (3) Chess Study; **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

2021: Gene therapies for Haemophilia: Estimated trial completion dates

Non-Exhaustive
Shows only products for Haemophilia A and B – for a complete overview of the pipeline, please refer to the impact analyses Excel



New trial included	Timeline accelerated	No active trials currently reported	Trial terminated

Marketed | Phase 1 / 1b | Phase 2 / 2b | Phase 3

Source: clinicaltrials.gov; October 2020, active clinical trials (Not yet Recruiting, Recruiting, Enrolling by invitation, Active not recruiting), Excluded trials without specified phase, Device trials

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

*Gene therapies for Haemophilia A and B**

1 **Patients, families and caregivers**	• Gene therapy may improve patient quality of life for patients with Haemophilia A (and B*) by reducing disease management burden, the stress of spontaneous haemorrhages and the long term disabilities, specifically arthritis, that they cause
2 **Healthcare systems and healthcare 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 haemorrhages
3 **Society**	• Gene therapy offers a potential life change for patients with Haemophilia A and their families, thereby reducing absenteeism and increasing economic productivity

Note: (*) Please refer to the 2019 impact analysis
Source: Impact analysis, IQVIA internal expertise, JMPC; **abbreviations** - link to glossary

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

Gene therapies for Haemophilia A

1

Patients, families and caregivers

	Current Therapy	Future = Gene Therapy
Treatment Burden	• Moderate-to-severe cases 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
Lifestyle	• 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

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

Gene therapies for Haemophilia A

2

Healthcare systems and healthcare professionals

	Current Therapy	Future = Gene Therapy
Hospital Utilisation: ***Disease Management***	• Care provided at specialised clinics by multi-disciplinary teams including haematologists, physiotherapists, dentists and orthopaedists	• Decline in consultation expenditure (due to decline in use of prophylactic therapy + treatment of internal haemorrhages) • Decline in clinic overhead costs (e.g. imaging, laboratory tests, hospital beds) • Improved access to specialist care
Hospital Utilisation: Severe *Haemorrhages*	• Severe intracranial haemorrhages require hospitalisation	• 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/year)	Drug Cost (per patient/year)	Total Cost (per patient/year)	Total EU Annual Cost
Current Therapy	€8.600	€113.000	€122.000	€1,80 bn

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

Gene therapies for Haemophilia A

3

Society

	Current Therapy	Future = Gene Therapy
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 Loss	• 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

Treatment	Days of work lost (per patient/year)	Estimated Impact on Nominal GDP (per patient/year)	Total loss of Nominal GDP (per year)
Current Therapy	~35 days	€2.400	€89,0 million
Gene Therapy		€630	€21,8 million

Cell Therapies including CAR-T

Link - back to innovations contents page

In cell therapy, patient or donor cells are introduced in patient's body to replace unhealthy cells and allow proper cell functioning

Cell therapy

What is it?[1]

- Cell therapy is the **administration of viable, often purified cells** into a patient's body to **for the treatment of a disease**
- Two common types include (1) **stem cell transplants (SCT)** and (2) **Chimeric antigen receptor cell type** (CAR-T) therapy

How does it work?[1,2]

- The cells used in this therapy may originate from **the patient (autologous cells)** or a **donor (allogeneic cells)**
- Once administered into the body, these new cells ***replace*** **unhealthy cells** or damaged tissue and allow proper functioning

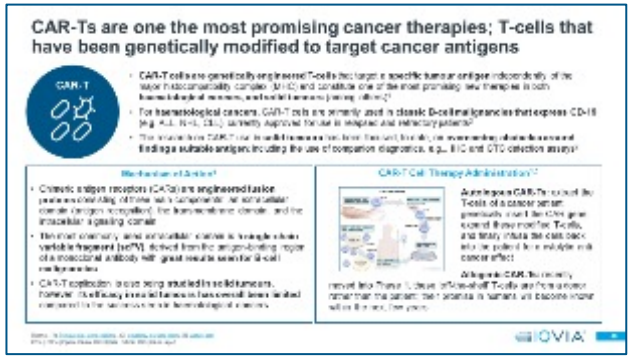
Common cell therapy types

Stem cell therapy (SCT)[3,4,5]

- SCT involves **harvesting stem cells from the bone marrow** or **blood of a patient or donor**, and then **transfusing them into the patient** after their unhealthy bone marrow has been destroyed
- Stem cells can also be harvested from **adipose** (fat tissue), **umbilical cord tissue**, **placental tissue**, or **umbilical cord blood**
- Multipotent stem cell therapy can be **deployed intravenously** or **injected locally** to target specific sites, depending on patient needs

Chimeric antigen receptor cell type (CAR-T)

- CAR T-cell is a form of cell therapy that involves **modifying a patient's T-cells** to recognize and **attack cancer cells** (please see section on CAR-Ts)

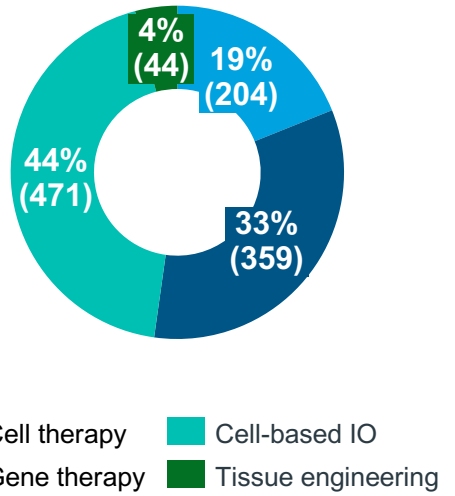


Source: (1) AABB, (2) ASGCT, (3) Alliancerm, (4) U Chicago Medicine, (5) Medicine Net; **abbreviations** - link to glossary

The pipeline for cell therapies is going strong despite COVID-19, mostly in phase 1 and 2 of development with a focus on oncology

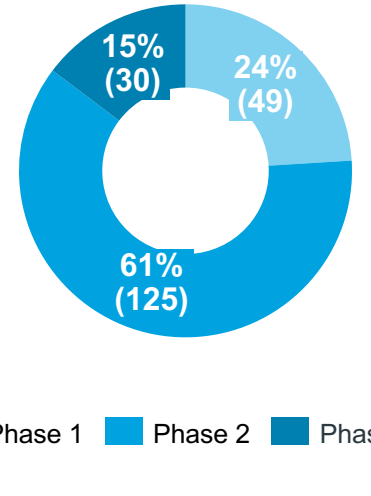
1.078 clinical trials are ongoing worldwide in advanced therapies*

Trails for advanced therapies by technology



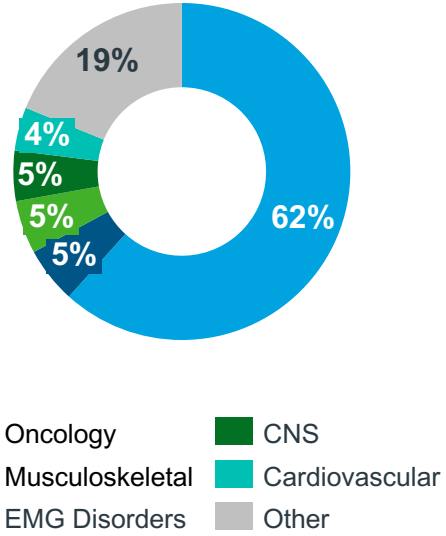
204 out of these trials are for cell therapies

Trials for cell therapy by phase



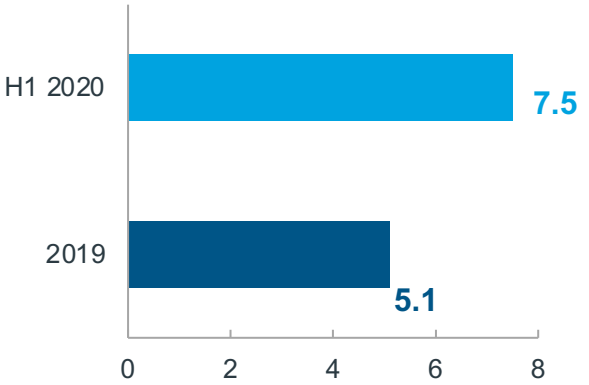
>50% of trials for advanced therapies* are in oncology

Trials for advanced therapies by indication



More financing for cell therapy raised in H1 2020 than in all of 2019

Financing for cell therapy in bn USD



"In spite of the economic challenges of COVID-19, 2020 is on track to be a record-breaking year for regenerative medicine and advanced therapy financings (including cell therapies)"

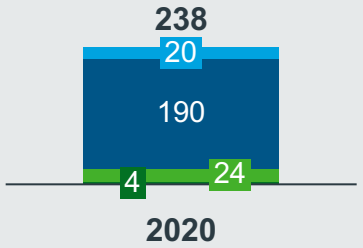
Note: Advanced therapies – gene therapies, cell-based IO, cell therapy, tissue engineering; bn (billion); CNS (Central Nervous System); EMG (Endocrine, Metabolic & Genetic Disorders)
Source: ARM Global Regenerative Medicine & Advanced Therapy Sector Report H1 2020; ARM Global Regenerative Medicine & Advanced Therapy Sector Report 2019 ; **abbreviations** - link to glossary

CAR-Ts have shown to be life saving – with research progressing outside of haem. cancers into solid tumours and CRISPR

2020 updates vs. the 2019 report

CLINICAL DEVELOPMENT

***All* CAR-T Trials**



+17
completed trials

+98
new trials

-43
trials withdrawn*

ADDITIONAL CANCERS STUDIED IN TRIALS

Solid tumours

Neoplasms and pancreatic cancer

APPROVALS AND OTHER NEWS

1. *Compared to the SoC, CAR-T has **already shown to be a life saving therapy for patients**, improving response rates and QoL in haematological cancers*
2. *There has been increased research into use of **CAR-T for solid tumours**, however, many **challenges will first need to be addressed***
3. *New research has kicked-off with 4 new trials studying the application of **CRISPR to edit genetic material of T-cells** which also has the potential to expand CAR-T possibilities*

Note: (*) Includes withdrawn, terminated, and suspended trials
Source: clinicaltrials.gov, IQVIA analysis; **abbreviations** - link to glossary

Haematological cancers have a high unmet need for innovation; treatment is aggressive and severely impacts patient QoL

Haematological Cancer

Cancer that affects the blood, bone marrow or lymphatic system, usually sub-grouped into leukaemia, myelomas and lymphomas

18.650
Incidence in the EU*
(2.7 per 100,000 population)

50%
Of all childhood cancers

Low Quality of Life
Lowered physical ability, as well as psychological health – incurred by the disease and side effects of treatment

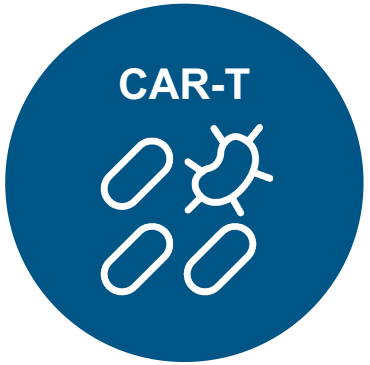
€88.000
Annual HC cost / patient
and further social and economic costs

High Burden Disease
Mainly a paediatric patient population, lack of an effective treatment, inability to identify high risk patients early on

- Haematological cancers most often begin in the bone marrow when uncontrolled growth of **abnormal blood cells** overtakes the development of normal blood cells and interferes with the regular functions of these cells – these cancers fall into three categories: leukaemia, lymphoma, and myeloma[2]
- **Leukaemia is cancer of the blood cell** and is commonly seen in children under the age of 15, and particularly in adults over 55 years[2] (e.g., AML)
- **Lymphoma occurs when lymphocytes develop abnormally** and eventually aggregating in lymph nodes and other tissues – it ranks as the 10th most frequently occurring cancer, yet contributes 6th most years of life lost (YLL) of all cancers[1,2] (e.g., non-Hodgkin's lymphoma, DLBCL, FL)
- **Myeloma** occurs when **abnormal plasma cells develop**, interfering with antibody production[1,2] (e.g., MM)
- Approximately **50% of children younger than 15** who suffer from cancer have **leukaemia** or **lymphoma**[1]
- **Toxic, and aggressive chemotherapy regimens remain SoC** across a number of indications (e.g., AML) with QoL during and after treatment severely impacted (e.g., patients undergoing allogenic stem cell transplantation often suffer from graft-vs.-host disease) with ~50% of these patients relapsing following treatment

Note: (*) based on an average incidence of FL, DLBCL, and ALL (sources in speaker notes)
Source: (1) The Lancet: Global Burden of Disease Study 2013, (2) ACCC Cancer, **abbreviations** - link to glossary

CAR-Ts are a promising therapy for haematological cancers – modifying T-cells to target cancer antigens

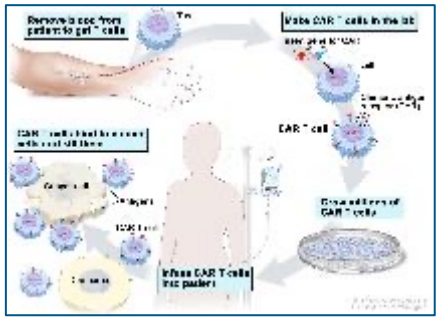


- **CAR-T cells are genetically engineered T-cells** that target a **specific tumour antigen** independently of the major histocompatibility complex (MHC) and constitute one of the most promising new therapies in both **haematological cancers, as well as in solid tumours**[1]
- For **haematological cancers**, CAR-T cells are primarily used in **classic B-cell malignancies that express CD-19** (e.g. ALL, NHL, CLL), currently approved for use in relapsed and refractory patients[2]
- The research on CAR-T use in **solid tumours** has been focused, to date, on **overcoming obstacles around finding a suitable antigen**: including the use of companion diagnostics, e.g.,. IHC and CTC detection assays[2]

Mechanism of Action[1]

- Chimeric antigen receptors (CARs) are **engineered fusion proteins** consisting of three main components: an extracellular domain (antigen recognition), the transmembrane domain, and the intracellular signalling domain
- The most commonly used extracellular domain is a **single-chain variable fragment (scFV)**, derived from the antigen-binding region of a monoclonal antibody with **great results seen for B-cell malignancies**
- CAR-T application is also being **studied in solid tumours**, however, its **efficacy in solid tumours has overall been limited** compared to the success seen in haematological cancers

CAR-T Cell Therapy Types[1,3]



Autologous CAR-Ts (majority of current CAR-T therapies): extract the T-cells of a patient, insert the CAR gene, expand these modified T-cells, and infuse back into the patient

Allogenic CAR-Ts: recently moved into Phase 1, these 'off-the-shelf' T--cells are from a donor rather than the patient; their promise in humans will become known within the next few years

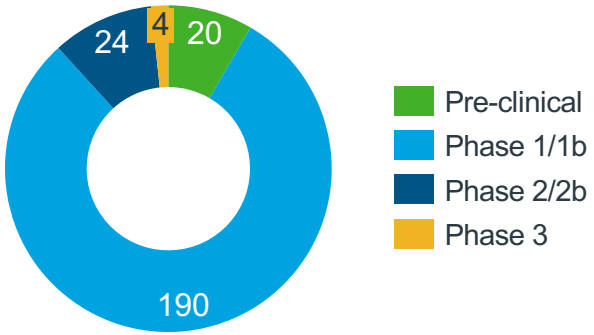
Allogeneic CAR-T cells **may have many advantages** over autologous approaches, such as **better efficacy** (more targeted), however **there are also some drawbacks**, including a more difficult administration and higher risk of cell rejection/elimination

Source: (1) Therapeutic gene editing , (2) oncology nursing news (3) cancer.gov; **abbreviations** - link to glossary

Over 200 CAR-Ts are being studied, with the 28 in Phase 2-3 trials focusing on haematological cancers

CAR-T therapies (all active trials)

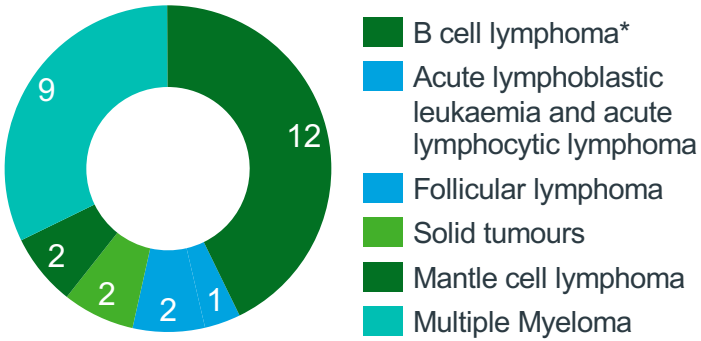
N=238



- There are multiple CAR-Ts currently in clinical development – with the majority in Phase 1 / 1b
- Many of these studies include research into the **novel applications of CAR-T's** e.g. for treatment of solid tumours, or in combination with CRISPR/CaS9

Indications studied in trials (Phase 2, 2b and 3 only)

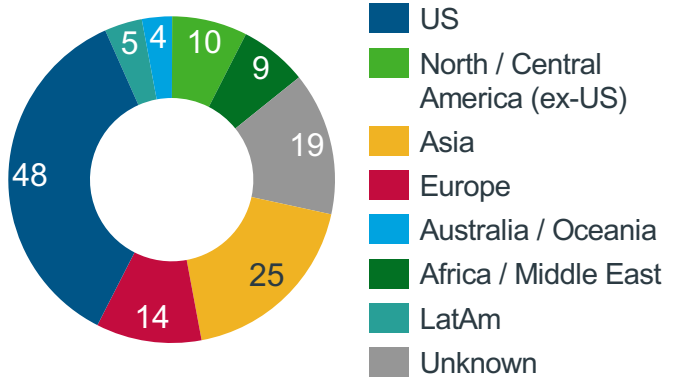
N=28



- Most CAR-Ts in the late development stage are being studied to treat **haematological cancers**, namely multiple myeloma, and acute lymphoblastic leukaemia
- There are also a few late stage trials for **solid tumours**

Active studies by geographic location

N=134

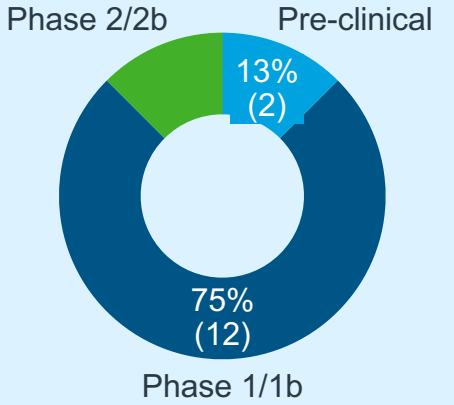


- CAR-T trials are happening globally, across **all continents,** however, the majority of trials are happening in the **US and Europe**

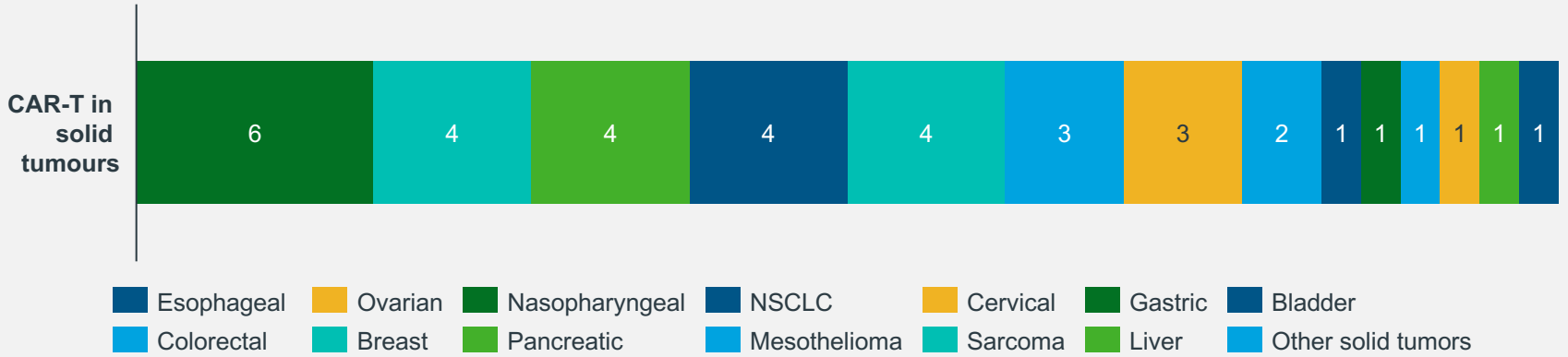
Note: (*) includes Hodgkin's and non-Hodgkin's lymphomas, diffuse large b-cell lymphoma (DLBCL); ALL (Acute lymphoblastic leukaemia), MM (multiple myeloma)
Source: Impact analysis, clinicaltrials.gov; **abbreviations** - link to glossary

Recently research into CAR-T for solid tumours has increased, however, many challenges will first need to be addressed

Number of CAR-Ts in Solid Tumours by Development Phase[1]



Indications Studied: CAR-Ts in Solid Tumours[1]*



Overview

- With the success of CAR-T in haematological cancers, research has been ongoing into its potential **application for treatment of solid tumours** – **positive results have already been seen** in reductions of tumour size[2,3]
- However, the **success of CAR-T in solid tumours have overall been limited** – with experts perceiving that its **application in the future will likely be in combination with existing therapies**, e.g. PD-1 inhibitors[4,5]

Challenges[6]

- The **challenges posed by CAR-T** for solid tumours can be described in three steps: **finding, entering, and surviving in the tumour** – where research to address them is currently ongoing:
  - Dual CAR designs that **recognize multiple antigens at once** and **local administration of CAR-T cells** to address issues in finding the tumour
  - **CARs with checkpoint blockade** or **depletion of other suppressive factors** in the tumour to mitigate T-cell exhaustion

Note: in some clinical trials, more than 1 indication is studied; **abbreviations** - link to glossary
Source: (1) clinicaltrials.gov (2) Targeted Onc , (3) Immuno-oncology news (4) Advancing CAR-T therapy (5) Adoptive T-Cell therapies, (6) CAR-T for solid tumours

CAR-T possibilities are also being expanded, with advancing research for combination with CRISPR to edit genetic material

+4 new trials

CRISPR/Cas9 and CAR-T therapy combo

- Just days after Emmanuelle Charpentier and Jennifer A. Doudna shared the Nobel prize for their work on CRISPR/Cas9, **CRISPR Therapeutics ($CRSP) is showing off early success** for an **off-the-shelf CAR-T approach** to CD-19 B-cell malignancies[1]
- Results have shown a **complete response in 50%** of a cohort of patients, however, with 1 death reported, it is clear that research will need to continue[1]
- There are 3 other ongoing studies using the combination and the **CRISPR/Cas9** gene editing approach that represent a promising opportunity to optimize T-cells due to its **simplicity, high efficiency, and multiplexing in precise genome editing**[3]

What the future holds

Next-generation CAR-T therapy

- CRISPR/Cas9 genomic editing technology holds promising explorations and applications to create next-generation CAR-T cell products, including:
  - **More targeted CAR-T cells** by disrupting endogenous TCR or HLA
  - **More potent CAR-T cells** by ablating of inhibitory modulators
  - **More controllable CAR-T cells** by adding inducible safe switches or suicide genes

Indications currently studied:

B-cell malignancies

Multiple myeloma

Renal cell carcinoma

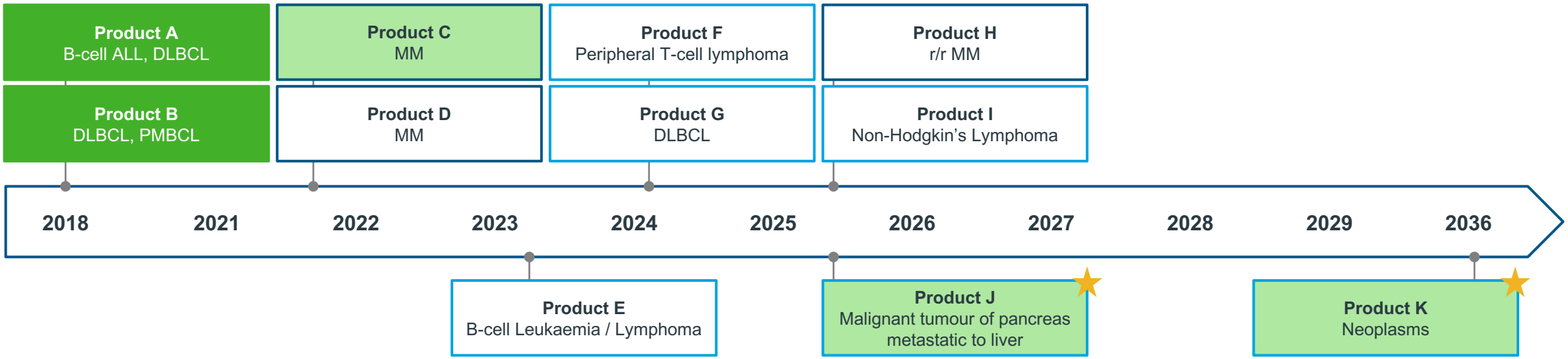
T-cell lymphoma

Source: (1) Endpoint News, (2) Nature Research article, (3) Explorations in CRISPR/CAR-T, (4) clinicaltrials.gov; **abbreviations** - link to glossary

The late stage CAR-T pipeline includes multiple promising products that are set to launch in the next 5 years

CAR-Ts: Estimated trial completion dates

Non-Exhaustive
Shows only products in Phase 2 / 2b and 3 – for a complete overview of the pipeline, please refer to the impact analyses Excel



New trial included	Timeline accelerated	No active trials currently reported	Trial terminated

Marketed | Phase 1 / 1b | Phase 2 / 2b | Phase 3 | Solid tumours

Abbreviations: ALL (Acute lymphoblastic leukaemia), PMBCL (primary mediastinal large B-cell lymphoma), DLBCL (Diffuse large B-cell lymphoma) - link to glossary
Source: clinicaltrials.gov; October 2020, active clinical trials (Not yet Recruiting, Recruiting, Enrolling by invitation, Active not recruiting), Excluded trials without specified phase, Device trials

CAR-Ts offer a step-change in treatment and benefits for haem-cancer patients, families, healthcare systems and society

1. **Patients, families and caregivers**
   - CAR-Ts have potential to continue **to be a life saving therapy certain groups of patients**, allowing them to **live longer**, **healthier lives** and sparing families the agony of losing loved ones early
2. **Healthcare systems and healthcare professionals**
   - **Hospitalisation costs could decline**, assuming relapse rates fall, as patients will no longer require lengthy stays in hospital, clinician attendances or stem cell transplants
   - **Future generation CAR-Ts (including CRISPR combination and allogenic CAR-Ts) could further enhance these benefits** for more patients across more disease areas – although these benefits **remain a long way behind** due to the numerous barriers that would first need to be overcome, *e.g.* for non-haematological malignancies
3. **Society**
   - The curative potential of CAR-Ts 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**

Source: Impact analysis, IQVIA internal expertise, NCBI paper; **abbreviations** - link to glossary

Compared to the SoC, CAR-T has already shown to be a life saving therapy for patients, improving response rates and QoL

Has CAR-T lived up to its promise?

1

Patients, families and caregivers

CAR-T vs. standard of care (chemotherapy) in haematological cancers

54% vs. 8%

Complete response

54% of haematological cancer patients experienced a complete response after CD-19 CAR-T therapy

6 months vs. 1

Paediatric ALL patients

2/3 of all patients are still in the remission after 6 months following CAR-T

41%

Better health and quality of life (QoL)

41% of patients reported a better QoL after three months of CD-19 CAR-T with fatigue, pain, physical function being the key domains

Note: Based on results from CD-19 CAR-T cell therapy studies
Source: CINJ, Science Direct, NHS; **abbreviations** - link to glossary

Lower relapse rates and better treatment tolerability has the potential to reduce costs through fewer/shorter hospitalisations

CAR-Ts for haematological cancers

2

Healthcare systems and healthcare professionals

Healthcare System Benefits

- CAR-Ts are beginning to **realise their potential to eliminate long term costs** associated with current healthcare provision
- **Current expenditure on targeted therapy could decline by ~55-100%** following displacement of high-cost salvage and maintenance treatment paradigms in the relapsed/refractory setting
- **Expenditure on SCTs could also decline significantly**, especially if CAR-Ts offer a complete cure
- This **impact could be greatest in DLBCL**, where autologous SCTs are used in approx. 35% of patients at a cost of ~€78.000*; SCT displacement by CAR-TS will offer significant cost savings
- **Hospitalisation costs may decline** as a patient survives longer; depending on required setting for long term follow ups (outpatient/ambulatory setting vs. inpatient setting)

Best-case health system benefits from CAR-T therapy

High-Cost Items	NHL (FL)	NHL (DLBCL)	ALL Ph+	ALL Ph-
Current expenditure avoided per patient	€ 68.300	€ 91.700	€ 35.500	€ 29.000
% Change in targeted therapy expenditure	-90%	-90%	-70%	-55%
% Change in SCT costs	-7%	-86%	-87%	-93%
% Change in days spent in hospital	-3.7%	-31%	-49%	-34%

Note: (*) includes total healthcare costs, FL (follicular lymphoma), DLBCL (diffuse large B-cell lymphoma), ALL (Acute lymphoblastic leukaemia)
Source: Impact analysis; **abbreviations** - link to glossary

Finally, the curative potential of CAR-Ts can allow people to live longer, healthier, more productive lives

CAR-Ts for haematological cancers

3

Society

Impact on Society

- CAR-Ts have the potential to cure haematological cancers allowing more people to actively contribute to economic productivity
- In ALL this would result in an additional annual contribution of ~€5.0 billion to nominal GDP[1] across the EU for all patients diagnosed in 2020 *(EU GDP in 2013 was €13,07 trillion)*
- CAR-Ts 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

Best-case societal impact from CAR-T therapy

High-Cost Items	NHL (FL)	NHL (DLBCL)	ALL Positive	ALL Negative
Total Life Years gained (across EU)	62.300	15.800	81.400	106.600
Increase in EU nominal GDP (for 2020)			€ 5.0 billion	

Abbreviations: FL (follicular lymphoma), DLBCL (diffuse large B-cell lymphoma), ALL (Acute lymphoblastic leukaemia) - link to glossary
Source: Impact analysis;

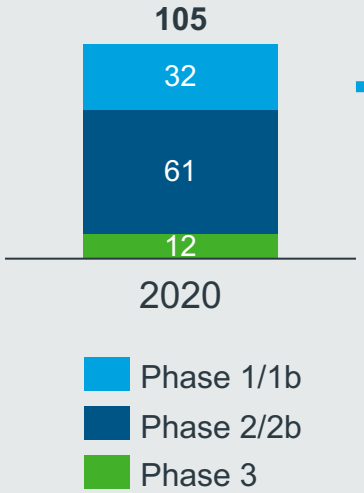
NASH (PPAR/FXR agonists)

Link - back to innovations contents page

Several NASH therapies are in late development stages, with potential to reach market soon and address growing unmet need

2020 updates vs. the 2019 report (covers updates from July 2019 – October 2020)

CLINICAL DEVELOPMENT



+11 phase 2 and 3 trials expected to enter the market by 2022

4 therapies with timelines accelerated vs last year

-4 trials withdrawn

SELECTED TECHNOLOGIES

PPARs and FXRs

remain the drug classes with the most extensive pipeline and highest potential to reach market in the next years

GLP-1/GR dual agonists

Treat obesity as the cornerstone of NASH management and also have potential as effective therapies – high level analysis included

KEY UPDATES

*The **prevalence rate** of NASH in European countries is **expected to increase by more than 40% by 2030**[1]*

*This **epidemiological challenge emphasizes the need for efficient therapy**, as well as increased disease awareness and education*

*NASH is also becoming the leading cause for **liver transplant**[2]*

Failed phase III trial of elafibanor** brought disappointment; however, other promising PPARs (as well as FXRs) are in **late development stages

Note: (1) Projections for the UK and Germany, EMA; (2) NCBI
Source: clinicaltrials.gov, IQVIA analysis; **abbreviations** - link to glossary

NASH has high prevalence and leads to costly complications, yet there are no therapies currently indicated for NASH treatment

NASH

NASH is the unnatural build up of fat in the liver as part of non-alcoholic fatty liver disease (NAFLD), causing inflammation and leading to fibrosis and cirrhosis of the liver

10 million
Prevalence in the EU[1]
(18% of general population)

Patient type
Young to middle-aged patients with obesity high blood pressure, high cholesterol, type 2 diabetes, smoking as key risk factors

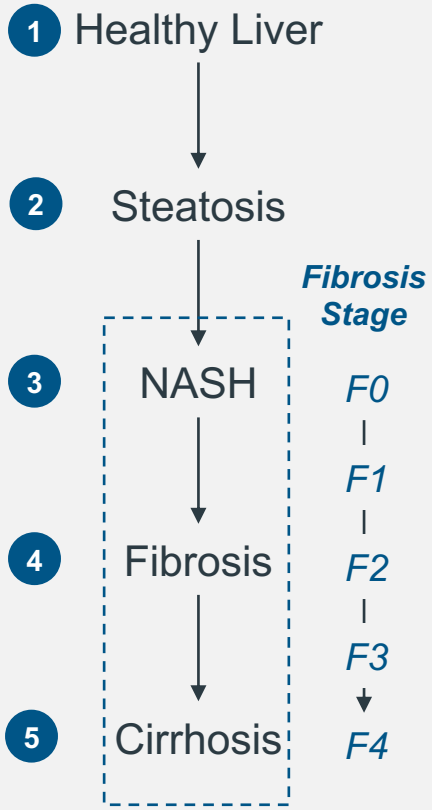
Quality of Life
Majority of patients remains asymptomatic (F1-F3); negatively impacted QoL and risk of liver failure in severe patients (F4)

€4.000 – €13.000
Cost of complications
in advanced NASH patients (without considering liver transplant costs)

20%
of F4 patients reach liver decompensation requiring liver transplant; 50% do not qualify for transplant (age, co-morbidities)

- **European prevalence of NAFLD is 27,6%;** of NAFLD patients, more than **64%** of patients suffer from NASH (for biopsy-proven patients)[1]
- Patients typically do not feel pain even during advanced cirrhosis and **QoL is not significantly affected**; instead, NASH is diagnosed through abnormal liver function tests, conducted to monitor other co-morbidities
- NASH co-morbidities include obesity, heart disease, insulin resistance, metabolic syndrome and type 2 diabetes
- After years of inflammation and fibrosis, **NASH will develop into full cirrhosis of the liver;** severe NASH accounts for 4-10% of liver transplants and transplant prevalence is rising significantly
- Costs are also **driven by complications** associated with advanced NASH / NAFLD (e.g. ascites, variceal bleeding, hepatic cellular carcinoma)
- Procedures associated with treating these complications can cost **from €4.000 to even €13.000** (for HCC treatment) per patient[2]
- There are currently **no therapies indicated for treatment or prevention of NASH**; patients are advised to modify diet and activity level in an effort to lead to weight loss

Non-alcoholic fatty liver disease (NAFLD) progression



References for points (1-2) available in speaker notes; **abbreviations** - link to glossary

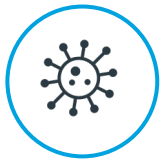
NASH is becoming the leading indication for liver transplant; at the same time NASH patients are less likely to receive the transplant

***Increasing prevalence** of NASH, paralleling the growing prevalence of MS, diabetes and obesity*

More and more NAFLD/NASH patients need liver transplant due to …

Absence of valid non-invasive **diagnostic tools** for early diagnosis of the disease

Absence of effective therapies to prevent disease progression



Decreasing number of **HCV-related transplants**, as the disease can be now cured with new direct-acting antivirals

At the same time they are less likely to undergo the transplant than patients with other diseases …

NASH patients are often older due to **late disease diagnosis** (50 years on average)

They tend to have **higher prevalence of obesity, type 2 diabetes** and other metabolic co-morbidities – being contraindications for transplant

Their waiting list period is longer because of a **slower disease progression rate**

1 year probability of receiving LT is significantly lower in NAFLD (40.5%) than in HCV or Alcoholic Liver Disease (47% for both)

Source: NCBI; **abbreviations** - link to glossary

The introduction of first NASH therapies should be supported with educational programmes; disease awareness is very low to date

Increasing awareness around NASH among patients and healthcare professionals regarding the preventative measures and disease management is critical to decrease the burden of this liver condition. NASH is a silent disease (until advanced stages) that is often diagnosed incidentally. In the absence of lifestyle change and treatment, it can lead **to life-threatening hepatic and cardiovascular co-morbidities** (1)

Patient education

Based on the survey on NAFLD & NASH patients and/or people at risk of NAFLD and NASH in the UK (Health Unlocked, 2018):

72% patients heard about NAFLD/NASH **for the first time during a medical consultation**

70% patients were not aware that **unhealthy diets and lifestyles** could induce a fat deposit accumulation in their livers

51% feel **poorly informed** about NAFLD/NASH consequences and clinical management and how to improve liver condition to avoid disease progression

HCPs education

Based on the pilot survey on French specialists, in partnership with the JIM (The Nash Education Program, 2017):

90% hepatogastroeneterologists expressed their need for education on emerging therapies and NASH patient management strategies

47% hepatogastroeneterologists stated that most of their NAFLD/NASH patients are identified during routine screening on potential signals

70% diabetologists, endocrinologists and cardiologists believe that their Patients are at higher risk of developing NAFLD/NASH

Abbreviations - link to glossary

A number of different novel classes are being developed to treat NASH with PPARs and FXRs having the largest body of evidence

Select approaches to curative treatment for NASH

Peroxisome proliferator-activated receptors (PPARs)

PPARs* modulate the expression of genes involved in lipid metabolism, energy homeostasis and inflammation.
When activated, PPAR subunits (α/β/δ) suppress **fat metabolism**, reduce **lipid production** and suppress **inflammation**[1].

Farnesoid X receptors (FXRs)

FXR activation suppresses carbohydrate and lipid metabolism, and **activates liver growth and regeneration** following liver injury.
FXR can also reduce level of fibrosis, and may play a **protective role** against hepatic cellular carcinoma[2].

GLP-1/glucagon receptor dual agonists

The dual-acting GLP-1/glucagon agonists activate both the GLP-1 and glucagon receptors, two key gut hormone receptors, and **may offer better outcomes in controlling blood glucose level and weight loss** than currently available single-agonist treatments[3].

Thyroid hormone receptor-β agonists

Thyroid hormone receptor-β agonists affect metabolic processes by lowering serum lipids such as low-density lipoprotein (LDL) cholesterol, serum triglycerides, and other metabolic factors. These changes may **lower the level of liver fat and reduce the fat toxicity** in patients with non-alcoholic fatty liver disease (NAFLD)[4].

Ketohexokinase (KHK) inhibitors

Ketohexokinase (KHK) is intended to modulate the effect of fructose in a patient's metabolism. By inhibiting KHK, less sugar is metabolized into fat and less fat is stored in liver cells. This may **lower the risk of patient's progression from NAFLD to NASH** and ameliorate the NASH symptoms[5].

Other

Some other approaches investigated to bring cure for NASH disease include **CCR2/CCR5 receptors inhibitor** (Cenicriviroc), **antisense therapy** (AZD2693), **RNAi therapeutics** (AZD4076, BMS-986263) and multiple others.

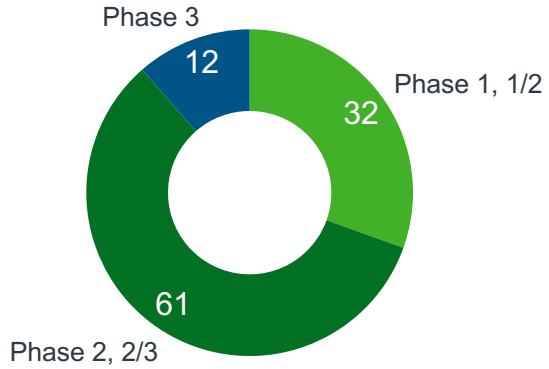
Abbreviations: PPAR = Peroxisome proliferator-activated receptor - link to glossary
References for points (1-5) available in speaker notes

Key: Largest body of evidence | More information in the Appendix

PPARs and FXRs have the most extensive pipelines representing over 20% of the trials targeting NASH

Number of novel therapies for NASH in development (active trials)

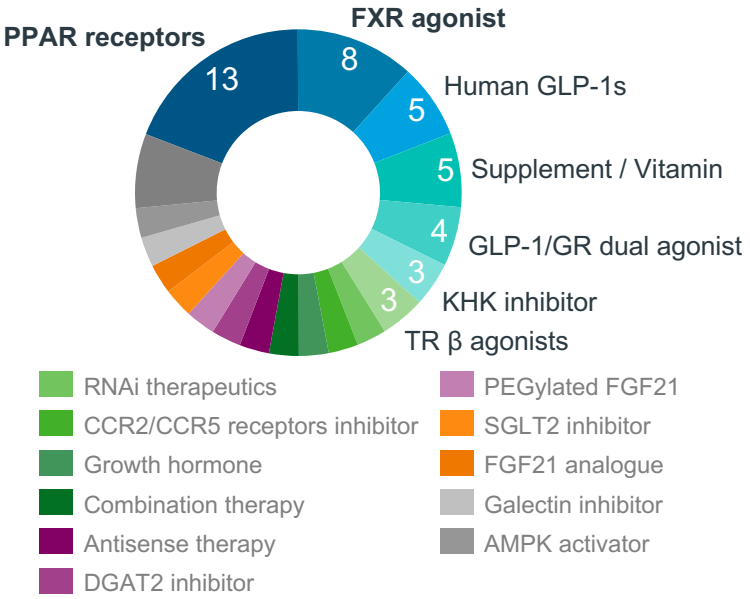
N=105



- First products, currently in Phase III trials, **are expected to enter the market in 2021**
- More than 70 trials in phases 2 and 3 shows that NASH **is in the spotlight of a number pharmaceutical companies**, given it is in an area with high unmet need and a potential to help a significant number of patients

Technologies studied in trials (selected*)

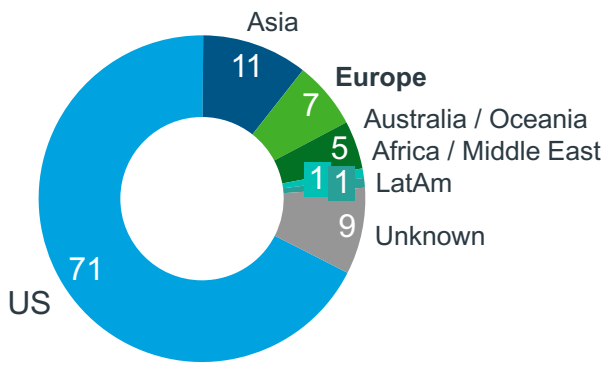
N=68*



- **PPAR and FXR still have the highest potential** to become first NASH therapies
- **GLP-1/GR dual agonists, ketohexokinase (KHK) inhibitors and thyroid hormone receptor-β agonists** are other product classes under investigation

Active studies by geographic location

N=105



- Almost 70% of clinical trials investigating NASH therapies are taking place in the United States, followed by Asia (mainly China, South Korea, India and Japan) – 10% and **Europe - 7%**

(*) Technologies with at least 2 clinical trials ongoing; **abbreviations** - link to glossary

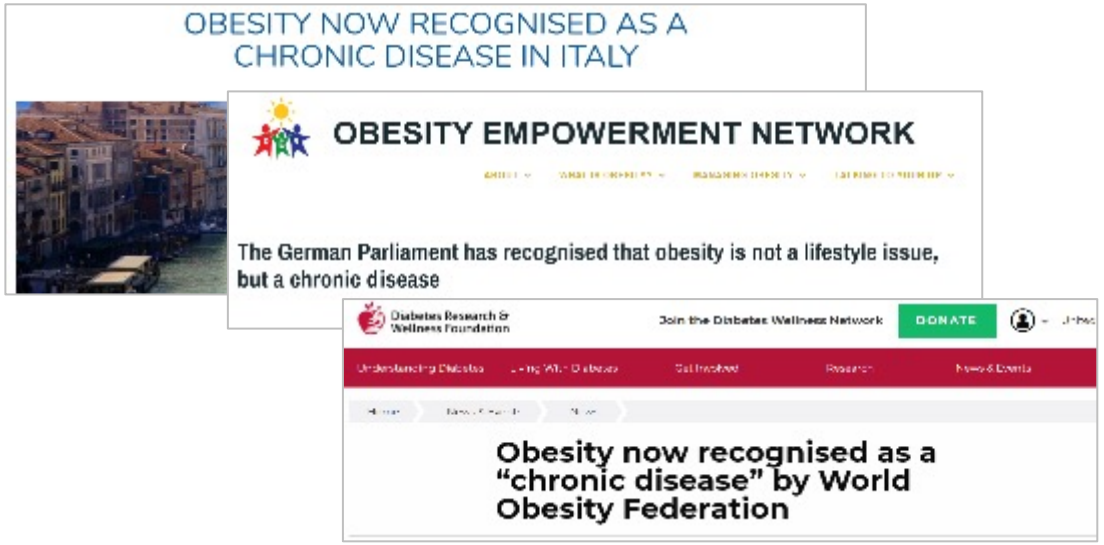
Source: clinicaltrials.gov, IQVIA analysis;

For this innovation area to be successful, the awareness of obesity as a chronic disease (and NASH cause) needs to be raised

Obesity is increasingly recognised as a chronic disease (as opposed to a lifestyle disease) by an increasing number of Health Authorities across Europe. This is an important step in increasing the access to effective obesity prevention and treatment. Taking similar approach to NASH would help increase disease awareness and support development of effective therapies.

Health authorities around the world start recognizing obesity as a chronic disease resulting from multiple environmental and genetic factors

Examples: Italy (Nov 2020)[1], Germany (Jul 2020)[2], World's Obesity Federation (2017)[3]



In some countries, however, this change is in progress and still a lot needs to be done to address obesity as one of the key health crises today

In the UK, the Royal College of Physicians is calling for obesity to urgently be recognised as a disease by government and broader health sector, warning that until this happens its prevalence is unlikely to be reduced[4]

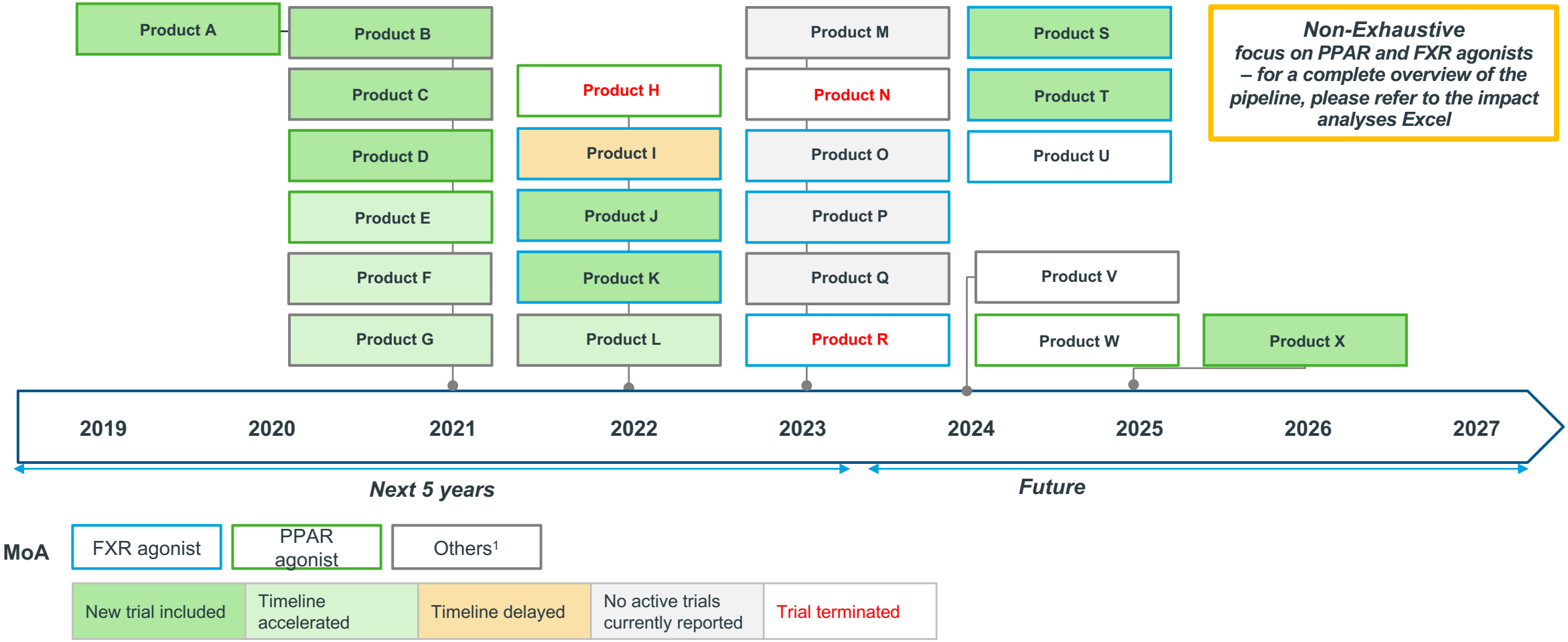
> [Obesity] is not a lifestyle choice caused by individual greed but a disease caused by health inequalities, genetic influences and social factors.
>
> – Professor Andrew Goddard, RCP president

According to a survey conducted by EU Observer in 2016, **only 19 EU member countries confirmed they had obesity strategies in place**[5]

(1) The European Association for the Study of Obesity; (2) Obesity Empowerment Network; (3) Diabetes Research & Wellness foundation; (4) Royal College of Physicians; (5) The European Association for the Study of Obesity, key messages; **abbreviations** - link to glossary

Based on estimated primary completion dates, more than 10 products are expected to launch in the next two years

2021: NASH Therapies in Development: Estimated trial completion dates



Source: clinicaltrials.gov; October 2020, active clinical trials (Not yet Recruiting, Recruiting, Enrolling by invitation, Active not recruiting), Excluded trials without specified phase, Device trials

1) Others MoAs are caspase inhibitor, CCR2 chemokine antagonist, Galectin-3 inhibitor, Gut mediated immuno-modulator; IBAT (ileal bile acid transporter) inhibitor, pan caspase protease inhibitor, ACC inhibitor

PPAR and FXR hold the promise to create new treatment paradigm and help reduce the number of severe NASH patients

1 **Patients, families and caregivers**	• The PPAR and FXR agonists represent **the first ever products to treat the cause of NASH** and promise a **significant improvement inpatient prognosis** and the reduction in the need to undergo a liver transplant
2 **Healthcare systems and healthcare professionals**	• The ability to reverse disease progression would see **fewer patients requiring costly liver transplants** and **treatment associated with severe liver failure complications**
3 **Society**	• The significant reduction in debilitating complications and time spent receiving care will **reduce patients' absenteeism, improving economic productivity**

The prevalence rate of NASH in European countries is expected to increase by more than 40% by 2030 (projections for the UK and Germany)[1]. This epidemiological challenge emphasizes the need for efficient therapy, as well as increased disease awareness and education.

Source: Impact analysis, IQVIA internal expertise, NCBI paper; (1) EMA Workshop on Liver Diseases; **abbreviations** - link to glossary

These new drugs will provide novel treatment options in NASH, enabling disease reversal and reduction in transplants

PPARα/β/δ and FXR Agonists for NASH

1

Patients, families and caregivers

	Current Therapy	Future = PPAR and FXR agonists
Provide a new treatment option	• No pharmacotherapy is currently available for NASH patients • Patients that reach final stages of NASH have poorer prognosis (1 year survival of decompensated liver disease is <50%)	• New therapies may reverse liver fibrosis, thereby reversing disease progression, lowering associated risks with late stage disease (e.g. ascites, variceal bleeding, hepatic cellular carcinoma), and improving overall patient prognosis
Lower likelihood of transplant	• Patients that reach decompensated liver disease are likely to require liver transplant, if eligible • Being placed on a liver transplant list will increase the worry and fear patients and families will experience, especially driven by long transplant wait times	• Up to 15% of patients[1] may be able to avoid liver transplant, as new therapies can reverse disease pathology; this translates to **~13.500**[2] fewer transplants in Europe in the current patient population • Fewer patients and families will be subjected to the worry and fear of transplantation

References for points (1-2) available in speaker notes; **abbreviations** - link to glossary

Reducing the need for liver transplants will lower the risk of surgery-related complications and life-long drug-burden

PPARα/β/δ and FXR Agonists for NASH

1

Patients, families and caregivers

	Current Therapy	Future = PPAR and FXR agonists
Reduce risk of complications	• Liver transplants in NASH are associated with higher risk of complications due to other co-morbidities (obesity, CVD, etc.)	• Reducing the number of transplants will in turn reduce the number of surgery-related complications patients suffer • In turn, patients will spend less time in hospital, and can return home to their families faster, improving their QoL
Reduce immuno-suppression burden	• Following transplants, patients must take life-long immunosuppression therapy • Drug-burden can be high, at the minimum taking monotherapy twice-daily (e.g. tacrolimus), but may be increased to double or triple therapy as needed	• Fewer patients will be required to take life-long immunosuppression
Reduce risk of liver cancer	• Hepatic cellular carcinoma (HCC) occurs in **~8%**[1] of late-stage NASH patients • Treatment will involve intensive chemotherapy, multiple hospital visits and will be associated with greater emotional burden	• With new therapies, NASH patients will have a lower risk of HCC development • Fewer patients must endure the reduced QoL associated with cancer

Reference for point (1) available in speaker notes; **abbreviations** - link to glossary

Lowering the number of patients in late stage disease will in turn reduce the need for expensive healthcare

PPARα/β/δ and FXR Agonists for NASH

2

Healthcare systems and healthcare professionals

	Current Therapy	Future = PPAR and FXR agonists
Lower burden on transplant waiting list	• The number of liver transplants due to NASH has grown in region of 500% in the last 10 years, driven in part by the obesity epidemic • There are not enough livers available to provide a transplant for every patient on the waiting list	• New product classes will reduce the number of required transplants, lowering the demand on transplant waiting lists • In turn, this will enable a greater proportion of patients to receive transplants in a timely manner

Lower healthcare resource use	• Late stage NASH patients are by far the highest burden on the HCS, from monitoring, complications (e.g. ascites, variceal bleeding), transplant and HCC
	  • **Complications** such as ascites and variceal bleeding require ~5 days hospitalization and can cost ~€4.000 per stay
	  • Late stage liver patients cost EU43 HC system **~€9,4bn** per year[1], with majority of spend driven by transplants
		• Entry of PPAR and FXR agonists could reduce the number of late stage NASH patients by more than **134.000** in Europe per year[2]
		• The number of complications and transplants will in turn be lowered, which could lead to cost savings for the HC system of **~€1,4bn** for current patient population[3]:
		  • Transplants cost >€80.000 per patient
		  • Complications cost ~€4.000 per patient
		  • HCC treatment cost ~€13.000 per patient

References for points (1-3) available in speaker notes; **abbreviations** - link to glossary

New therapies are expected to have a limited impact on GDP, as days lost to the disease are relatively low

PPARα/β/δ and FXR Agonists for NASH

3

Society

	Current Therapy	Future = PPAR and FXR agonists

Improve productivity and GDP	• Patients undergoing liver transplant and chemo for HCC will lose on average 40 and 50 days from work per year, respectively
	  • This translates to a total loss of nominal GDP of **~€700m** per year[1]
		• Future therapies are expected to reduce the number of days lost by ~15%
		  • GDP lost will fall to approximately **€600m** / year

Reference for point (1) available in speaker notes; **abbreviations** - link to glossary

Remyelinating CNS Therapies

Link - back to innovations contents page

Multiple Sclerosis afflicts 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. This results in a number of symptoms such as 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 is 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]

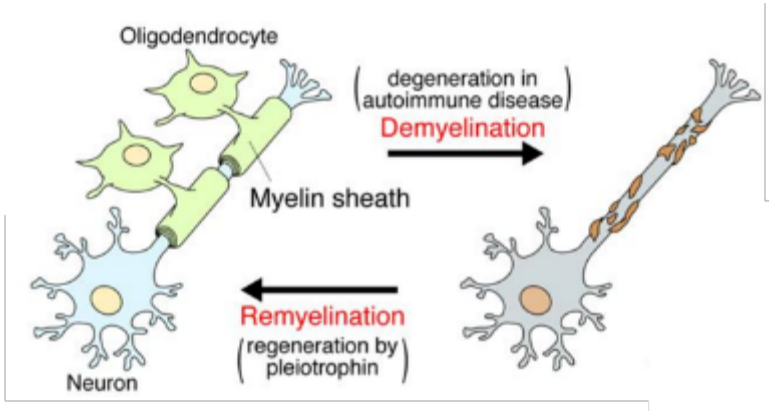
References for points (1-6) available in speaker notes;
(*) HRQoL – Health Related Quality of Life; (**) At least two clinically significant relapses within the last 2 years; **abbreviations** - link to glossary

Remyelinating therapies have 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 sheaths 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 and **hold the 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

Abbreviations: MS – Multiple Sclerosis; ALS – Amyotrophic lateral sclerosis; PD – Parkinson's Disease - link to glossary

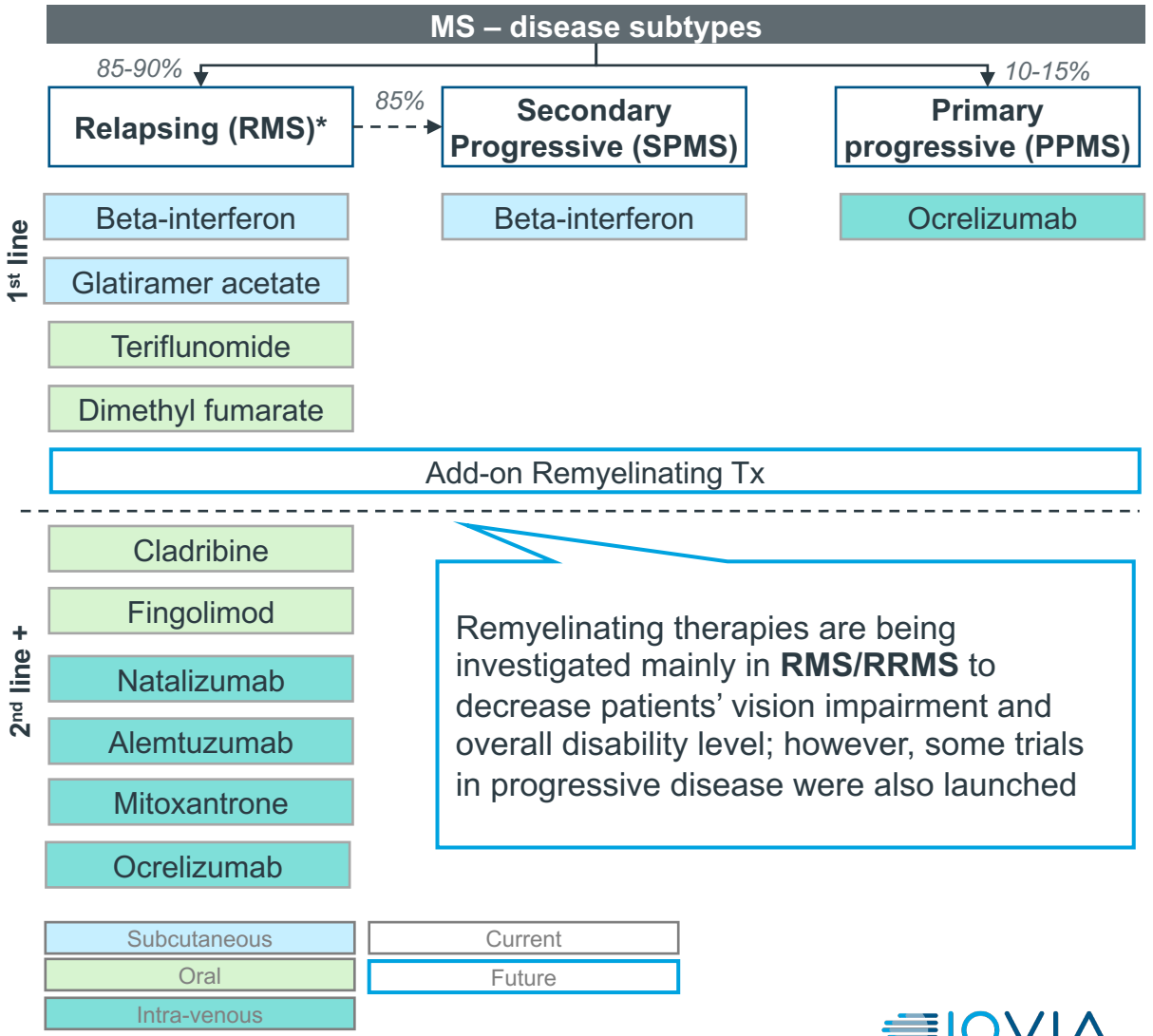
References for points (1-3) available in speaker notes

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) are able to 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 sheaths 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 - link to glossary

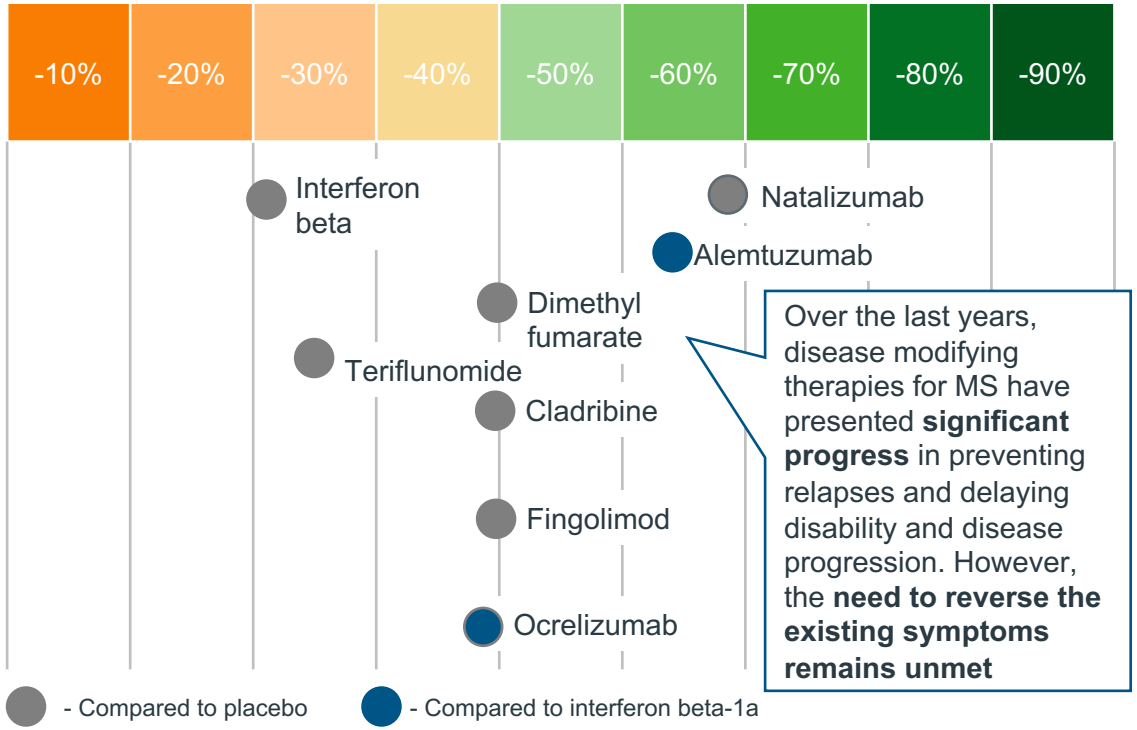
References for points (1-2) available in speaker notes

While disease-modifying therapies focus on delaying progression, remyelination promises to restore mobility, cognition, 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 II 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 II VISIONARY-MS trial for CNM-Au

Overall disability improvement

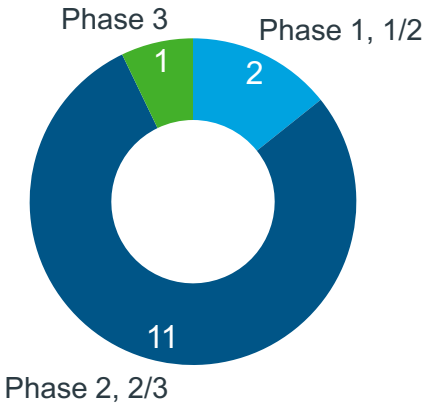
- Measured with Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk, Nine-Hole Peg Test and the three-second Paced Auditory Serial Addition Test
- Based on phase II SYNERGY trial for opicinumab (results not conclusive) and AFFINITY trial results

Abbreviations: DMT – Disease Modifying Therapies - link to glossary; Source: EMA, FDA (2018)

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

Active studies on remyelination by trial phase

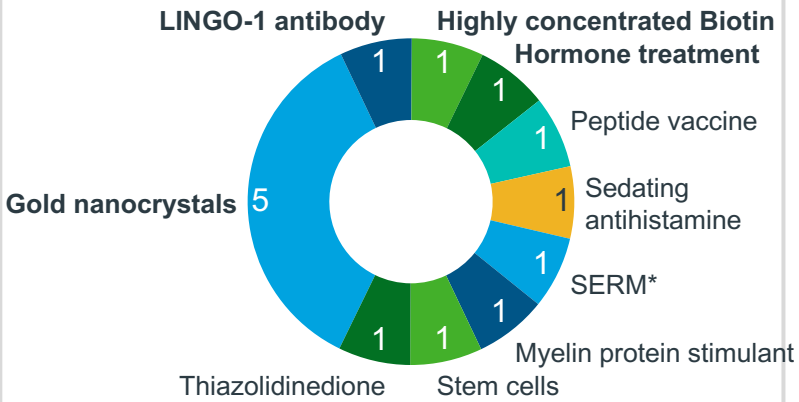
N=14



- More than 85% of active clinical trials investigating remyelinating agents are currently in **phase 2 and 3**
- In addition to these agents in-human trials, there are a number of additional candidates being investigated in **pre-clinical studies**

Active studies by technology

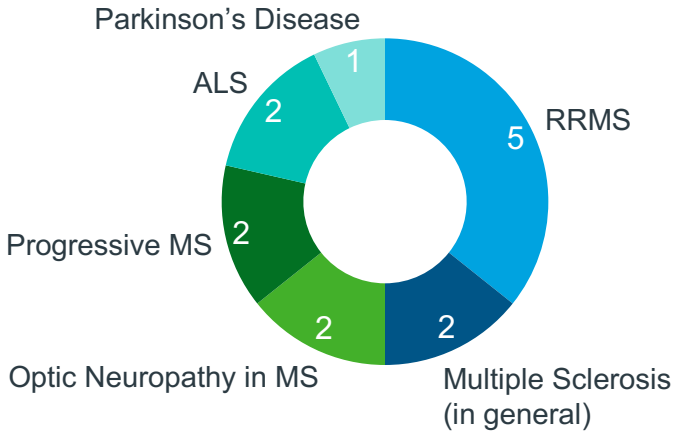
N=14



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

Indications studied in active trials

N=14



- 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: clinicaltrials.gov (data accessed Sept 28, 2020), IQVIA analysis; (*) SERM - Selective estrogen receptor modulator; **abbreviations** - link to glossary

Different remyelination strategies are being investigated to repair myelin sheaths 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[1] 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[2]

Selected mechanisms of action investigated

Gold nanocrystal suspension	Lingo-1 antibody	Myelin protein stimulant	Highly concentrated biotins
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]	Lingo-1 is a protein in the human brain which prevents OPCs developing into functioning oligodendrocytes. Blocking Lingo-1 with an antibody allows OPCs to mature, therefore encouraging natural myelin repair processes and potentially reducing MS symptoms[4]	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]	The therapy has the potential to increase the production of myelin through activation of cellular processes in oligodendrocytes. Biotins also activates the Krebs cycle, supporting the energy demands of demyelinated nerve fibers[6]
CNM-Au8 (Clene Nanomedicine)	**Opicinumab** (Biogen)	**BIIB061** (Biogen)	**MD1003** (MedDay Pharmaceuticals)

Abbreviations: OPC – oligodendrocyte precursor cells; CNS – central nervous system; MS – Multiple Sclerosis - link to glossary

References for points (1-6) available in speaker notes

Key: **More information in the next slides**

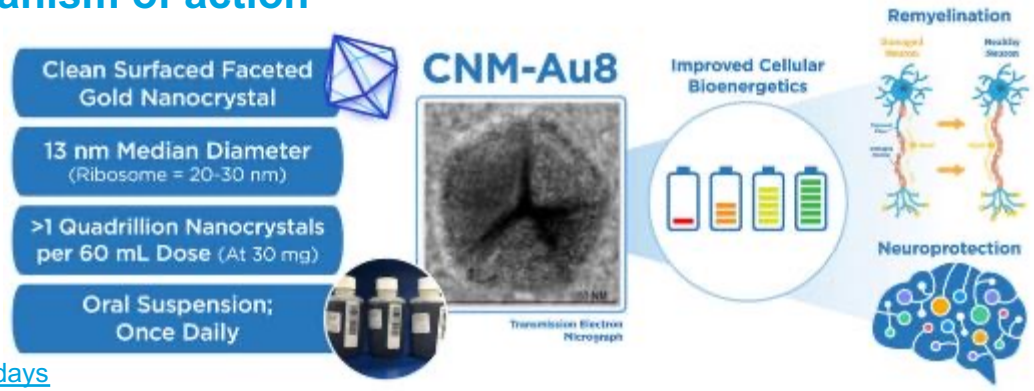
CNM-Au8 is being investigated across different CNS disorders, with first promising outcomes confirmed in a phase 2 MS study

Gold nanocrystal suspensions – selected therapies

CNM-Au8 (Clene Nanomedicine)

- CNM-Au8 is a bioenergetic nanocatalyst under investigation for neuro-reparative and remyelination capabilities[1]
- Interim results from the VISIONARY-MS Phase 2 study in stable RMS patients with visual impairment (chronic optic neuropathy) **demonstrated clinically relevant, median improvements** across the overall patient population in accepted MS functional scales, including **low-contrast vision**[1]
- **Over 90% of patients receiving approved DMTs as background standard of care**
- The full unblinded results from the study are anticipated mid-2021[2]

Mechanism of action



Source: BioTuesdays

VSIONARY-MS – Interim blinded results, September 2020 (5)

For the first 44 enrolled participants notable median improvements were seen in:

- **Low-contrast letter acuity** (vision),
- **Symbol Digit Modalities Test** (cognition),
- **9-Hole Peg Test** (upper extremity function),
- **and Timed 25-foot Walk** (gait)

Other indications for CNM-Au8 under investigation

Apart from being investigated in MS trials (VISIONARY-MS and REPAIR-MS), **the neuro-reparative potential** of CNM-Au8 is investigated in Phase 2 studies for Amyotrophic Lateral Sclerosis (REPAIR-ALS and RESCUE-ALS) and for Parkinson's Disease (REPAIR-PD)[3]

References for points (1-3) available in speaker notes; **abbreviations** - link to glossary

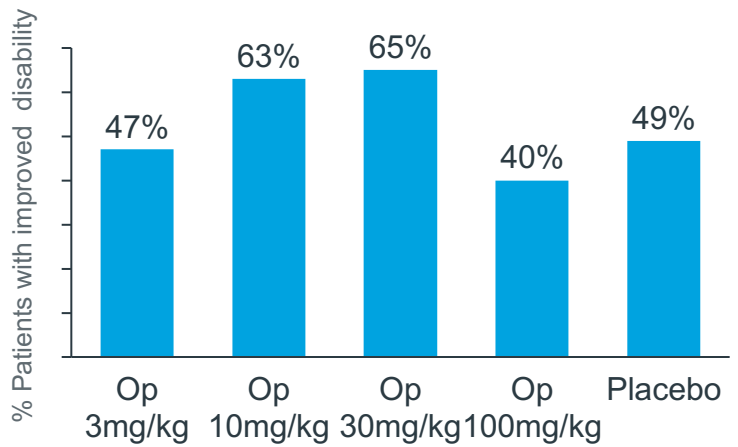
For now, the development of anti-LINGO-1, opicinumab, was discontinued based on unsatisfactory phase 2 data

Anti-LINGO-1s – selected therapies

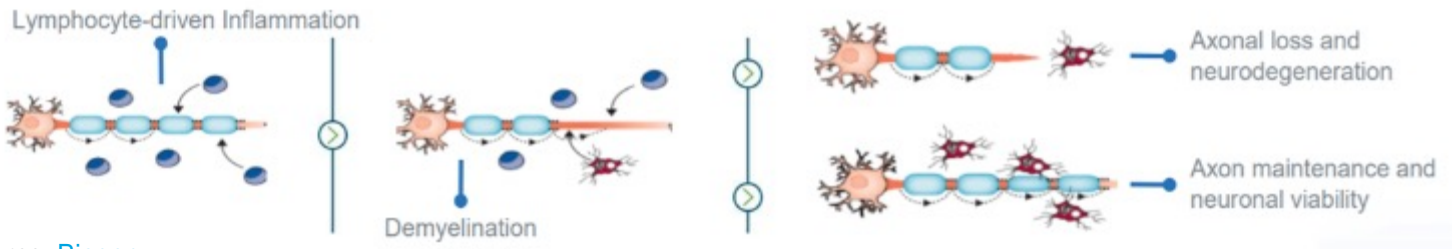
Opicinumab (Biogen)

- Opicinumab is the first remyelinating agent investigated by Biogen
- It is an anti-LINGO-1 monoclonal antibody that was supposed to promote remyelination in MS patients. Results from the previous Phase 2 SYNERGY trial were promising (see chart on the right)
- However, In October 2020 Biogen halted the development of opicinumab, as in the Phase 2 AFFINITY trial, the trial drug did not promote significant functional improvements or delay disability progression, when compared with placebo[1]

Opicinumab (Op) versus placebo – Phase II SYNERGY trial results[1]



Mechanism of action

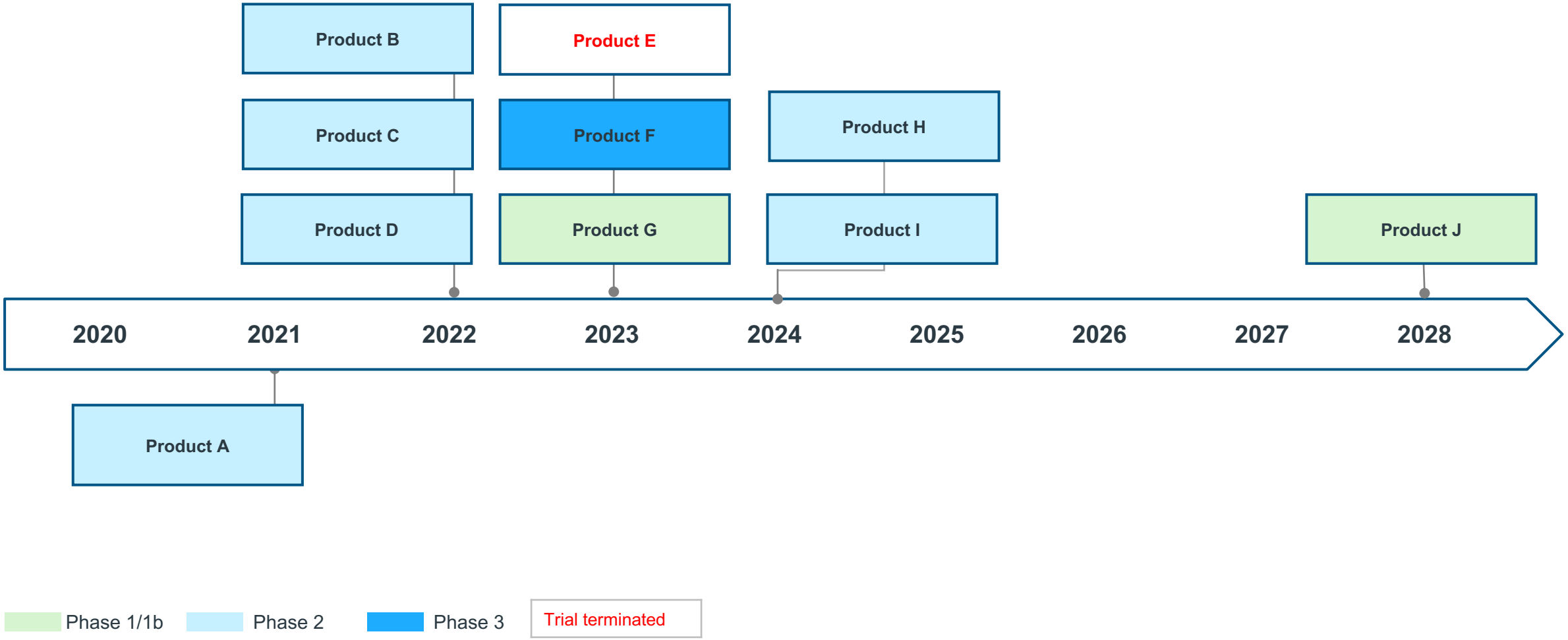


Source: Biogen

(1) Source: Multiple Sclerosis News Today; Fierce Biotech; **abbreviations** - link to glossary

By 2026, 6 remyelinating products are anticipated to complete clinical trials for Multiple Sclerosis indication

2021: Remyelinating Therapies in Development for MS: Estimated Trial Completion Dates



Source: clinicaltrials.gov; October 2020, active clinical trials (Not yet Recruiting, Recruiting, Enrolling by invitation, Active not recruiting), Excluded trials without specified phase, Device trials
MS - Multiple sclerosis; RRMS - Relapsing-remitting multiple sclerosis

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

Remyelinating therapies for MS

1 **Patients, families and caregivers**

- Remyelinating therapies have the potential to increase the quality of life of MS patients **by reducing or improving their level of disability (improving mobility, cognition and vision),** and positively impact their psychological health and allow for a broader range of daily and work activities
- This would also **bring a positive change to the lives of MS patients' families and caregivers** by reducing the burden of the disease

2 **Healthcare systems and healthcare 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**

- Through decreasing or improving patients' disability, remyelinating therapies may decrease social costs related to providing MS patients with such services as home care, transportation, etc.
- By improving patients' functional abilities, remyelinating therapies may also **increase the workforce participation rate** among MS population and their families and caregivers; this will affect positively **GDP generation, as well as patients' psychological health**

Remyelination may improve physical and cognitive functions of MS patients, positively affecting also their psychological health

Remyelinating therapies for MS

1

Patients, families and caregivers

	Current state	Future = Remyelinating therapies
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 improving their quality of life
Positively impact psychological 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**

Through reduced disability level and increased independence patients require less support from their families and caregivers

Remyelinating therapies for MS

1

Patients, families and caregivers

	Current state	Future = Remyelinating therapies
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

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

Remyelinating therapies for MS

2

Healthcare systems and healthcare professionals

	Current state	Future = Remyelinating therapies

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

(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

On the other hand, they will limit the costs of social services, which increase with disease progression

Remyelinating therapies for MS

3

Society

	Current state	Future = Remyelinating therapies
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	• 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

(1) Calculation based on the previous assumptions: impacting 15% of eligible patients, decreasing disability by 25% - see Impact Analysis file

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

Remyelinating therapies for MS

3

Society

Social services costs related to MS

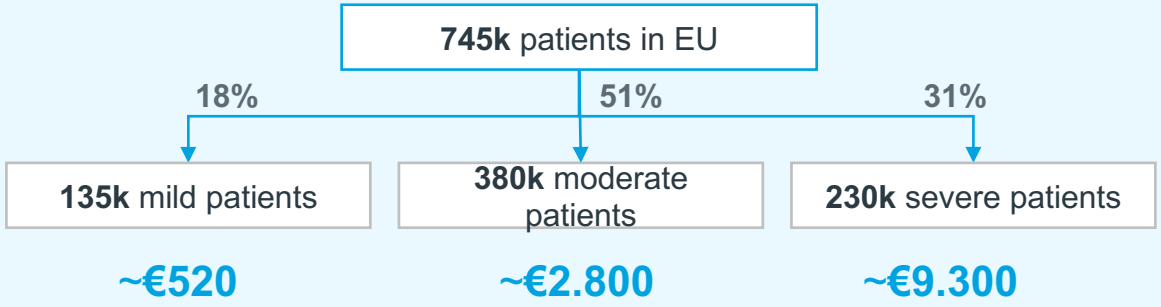
€3,3bilion — **total cost** of social services provided to MS Patients across Europe

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

Reduction of patients' disability will increase work participation of them and their families, positively impacting GDP level

Remyelinating therapies for MS

3

Society

	Current state	Future = Remyelinating therapies
Increase work participation of patients and their families	• 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** • Also patients' family members are often require to skip work to provide them with daily support – **spending more than 90 hours per month on informal care**	• Remyelinating therapies may reverse or improve disability caused by Multiple Sclerosis, having twofold impact – **enabling more patients to keep their jobs and also reducing the time off work for their family members**, bringing overall positive impact on GDP generation across Europe of **~800 million per year**[1]

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**

(1) Calculation based on the previous assumptions: impacting 15% of eligible patients, decreasing disability by 25% - see Impact Analysis file

mRNA Vaccines

Link - back to innovations contents page

Vaccines train the body to fight a real antigen, where an engineered one has been produced via a specific mRNA code

mRNA Vaccines

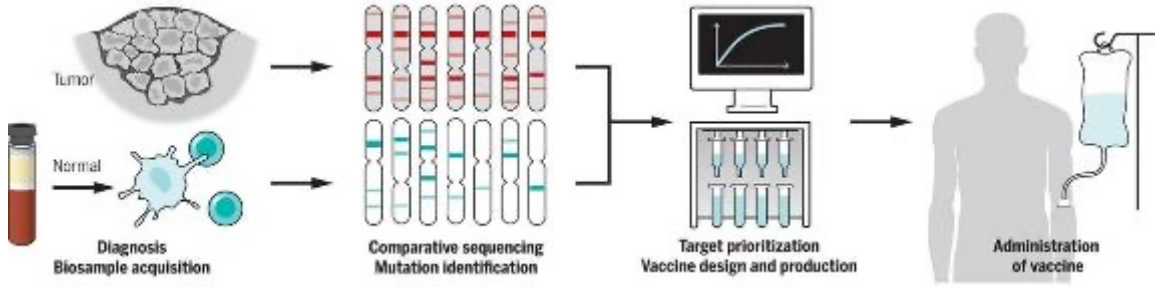
- mRNA vaccines for **both prevention *and* therapy** work by **introducing an mRNA sequence** (messenger RNA, the molecule which tells cells what to build) which is **coded for a disease specific antigen**, once produced within the body, the **antigen is recognised** by the immune system, **preparing it to fight the disease**[1]
- mRNA vaccines are manufactured using **DNA templates which are complex to create**; however, once this step is complete, they are **faster* and cheaper to produce** than traditional vaccines, and an mRNA-based vaccine is also **safer for the patient**, as they are not produced using infectious elements[1, 2]
- **Pfizer/BioNTech** demonstrated an **mRNA vaccine against SARS-CoV-2 (COVID-19)** achieved success in first interim analysis (Phase 3), showing the promise of this innovation to combat infectious diseases[4]

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

Customizing a patient-specific cancer vaccine[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

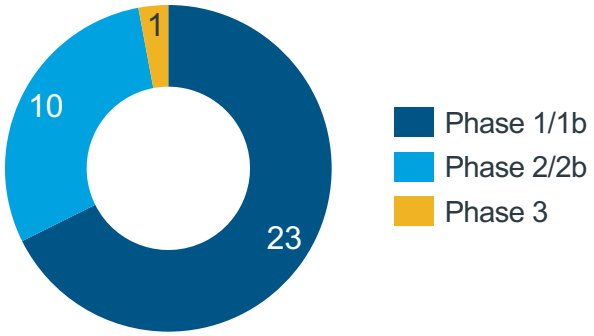
Source: (1) PHG foundation, (2) https://www.path.org/articles/mrna-and-future-vaccine-manufacturing/ (3) ScienceMag, (4) Pfizer press release; **abbreviations** - link to glossary

*This incredible difference in speed is owed to the fact that viral vaccines rely on animal cell biology while RNA manufacturing is a cell-free, biochemical process performed with synthetic enzymes

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

mRNA vaccines (active trials)

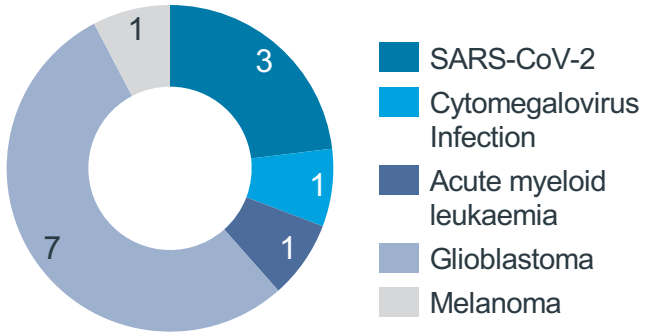
N=34



- There are currently **~34 trials** studying the possible use of mRNA vaccines
- As it is a **highly innovative and new** area, the **majority of these trials are in Phase 1 and 1b**, with 1 trial (SARS-CoV-2*) in Phase 3 development

Indications studied in trials (Phase 2, 2b & 3 only)

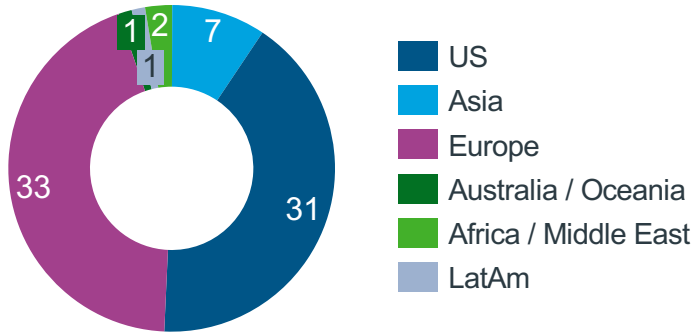
N=11



- Most of the mRNA vaccines in Phase 2, 2b and Phase 3 trials are being developed for viral infections and cancer
- **SARS-CoV-2 (COVID-19) and glioblastoma** are the two areas with the highest activity

Active studies by geographic location

N=75*



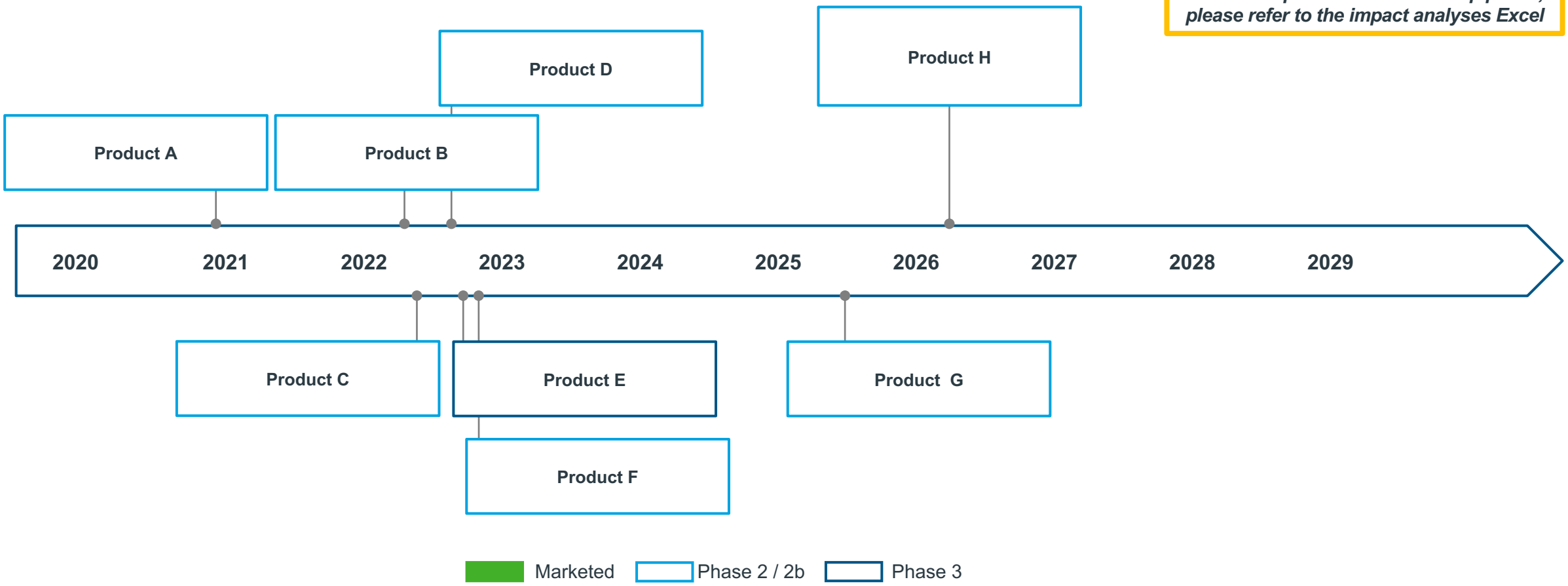
- Trials for mRNA vaccines are also **happening globally**, across all continents, with the majority of trials happening ***especially in*** **Europe**

Note: Phase 3 product being studied for SARS-CoV-2 funded by "other" entity, (*) one trial may be studied in multiple countries
Source: clinicaltrials.gov, IQVIA analysis; **abbreviations** - link to glossary

mRNA vaccines are predominantly being studied in glioblastoma as well as SARS-CoV-2 due to the pandemic

2021: mRNA vaccines: Estimated trial completion dates

Non-Exhaustive
Shows only products in Phase 2 / 2b and 3 – for a complete overview of the pipeline, please refer to the impact analyses Excel



Note: DC (dendritic cell); (1) Another Phase 2 study is currently ongoing, estimated completion 08/2021

Source: clinicaltrials.gov; October 2020, active clinical trials (Not yet Recruiting, Recruiting, Enrolling by invitation, Active not recruiting), Excluded trials without specified phase, Device trials

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

Glioblastoma[1,2]

An aggressive type of cancer that can occurs mainly in the brain, but can also appear in the brain stem, cerebellum, and spinal cord

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

16% Of all primary brain and central nervous system neoplasms[3]

Low Quality of Life[4]
Lowered physical ability, as well as psychological health resulting from seizures, fatigue, insomnia, and treatment

€43.000[5]
Annual HC cost / patient
and further social and economic costs

High Mortality
Following diagnosis, 25% of patients survive more than 1 year and only 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, making them very difficult to 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 tumor location)

Treatment

- 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 tumor as possible
- **Radiation and chemotherapy** are used for tumors that cannot be removed with surgery (for diffuse cases) and to slow down the growth of residual tumor after surgery
- **Tumor Treating Fields** (TTFields) may be also be offered in combination with chemotherapy
- Treatment for newly depends on a variety of factors, including molecular biomarkers (MGMT status & IDH mutation) and age while recurrent treatment is based on the patient's response to initial treatments and assessment of disease progression

Note: (*) based on an EU population of 690,712,271: **Abbreviations**: IDH (Isocitrate dehydrogenase) - link to glossary
Source: (1) The Brain Tumour Charity, (2) ABTA, (3) Europe PMC, (4) HRQoL in glioma patients, (5) Impact analysis

An mRNA vaccine for glioblastoma would offer patients longer term survival, and in turn increase the societal productivity

mRNA vaccines – Glioblastoma

1 **Patients, families and caregivers**

- mRNA vaccines could be a life saving therapy for certain groups of patients, allowing them to live longer, healthier lives and sparing families the agony of losing loved ones early
- Longer term survival could also mean a reduction in emotional distress for patients and families as a result of reduced exposure to toxic chemotherapy

2 **Healthcare systems and healthcare professionals**

- mRNA vaccines for glioblastoma could reduce hospital based healthcare burden by reducing the need for palliative and surgical care from oncologists
- This frees up resources that can be used to diagnose and treat more patients faster and more effectively

3 **Society**

- mRNA vaccines will see more patients survive long term allowing them to return to work
- This can reduce the care burden on families and friends, who will also need to take less time off from their work or other responsibilities

Source: Impact analysis, IQVIA internal expertise; **abbreviations** - link to glossary

mRNA vaccines offer patients longer term survival, reduced emotional distress and may allow a return to work

mRNA vaccines – Glioblastoma

1

Patients, families and caregivers		
	Current Therapy	**Future = mRNA vaccines**
Life Expectancy	• Glioblastoma patients have **low survival rates** – following diagnosis, 25% of patients survive more than 1 year and only 5% of patients survive more than 5 years • **Surgery, radiation therapy, and chemotherapy with temozolomide** (median OS of 10-20 months) 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)
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	• Stress due to pressures **associated affordability of care and travel cost increases** (to/from hospital)	• Potentially curative effect / prevention of progression of certain mRNA vaccines could see **patients returning to work and cutting back on treatment-related expenditure**

Source: Impact analysis, The brain tumour charity, Mayo Clinic, Nature Article, Long Term Survival in Glioblastoma; **abbreviations** - link to glossary

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

mRNA vaccines – Glioblastoma

2

Healthcare systems and healthcare professionals

	Current Therapy	Future = Combination Therapy
Hospital Utilisation: *Surgical and Palliative Care*	• 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** due to the need for surgical and palliative care, as well as overnight stays	• 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** - *Following a temozolomide chemotherapy + 3 doses of an mRNA vaccine (pp64-DC), a median **PFS of 25.3 months**, and **OS of 41.1 months** were reached* - *In another study investigating a PEP-3-KLH mRNA vaccine, a median **PFS of 15.2 months**, and **OS of 23.6 months** were reached – **without autoimmune adverse events***

Source: Impact analysis, The brain tumour charity, Mofitt Cancer Center, Long Term Survival in Glioblastoma, Vaccination in the immunotherapy of GBM; **abbreviations** - link to glossary

By providing a long-term treatment option for the disease, mRNA vaccines could allow more patients to contribute to society

mRNA vaccines – Glioblastoma

3

Society

	Current Therapy	Future = Combination Therapy
Productivity Loss	• **Poor long term survival** and **high risk of progression** means that many patients do not return to work following a diagnosis*	• 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 2020; 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
Source: Impact analysis; **abbreviations** - link to glossary

Curative Therapies for HBV and HIV

Link - back to innovations contents page

Curative therapies for HIV and chronic hepatitis B eradicate virus from patients' organisms, saving them from life-long treatments

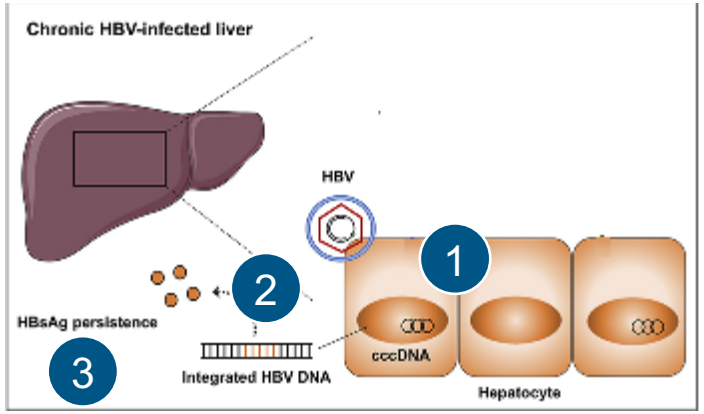
Introduction to curative therapies for hepatitis B and HIV infections

- **Curative therapies eliminate viruses from infected cells and therefore prevent virus replication and transmission**
- For HIV, two key approaches to curative therapy development are being investigated - **eradication (or sterilisation) therapies** are aimed at removing the **viral reservoir** from patient's organism, whereas the goal of **functional therapies** is to maintain a sustainable infection level in the absence of medical intervention (ART)[1]
- As in the case of HIV, two approaches to cure HBV infection are being investigated. First approach is to develop a sterilising cure, leading to **complete elimination of HBV cccDNA** (covalently closed circular DNA - so far indestructible „mini-chromosome" of HBV responsible for virus persistence even in treated patients) and integrated DNA from liver cells. The second approach is to achieve a functional cure, defined as **undetectable hepatitis B surface antigen** (HBsAg) or HBV DNA in blood after discontinuation of antiviral treatment[2]
- The currently available treatment options (mainly antiretroviral therapies) are **efficient in suppressing the disease symptoms and lowering the risk of transmission** by stopping the virus replicating in the body[3]; however, they do not remove the virus from patients' organisms and **any treatment interruption or failure may resume viral replication** to levels comparable to those that existed before treatment[4]

Sterilising versus functional cure

Based on HBV example, **sterilising cure** removes virus DNA - cccDNA (1) and integrated DNA (2) - completely from patients' organisms

Functional cure results in undetectable HBsAg in patients' blood, successfully preventing virus from further spreading



Source: Frontiers in Immunology (5)

(1) Contagion Live; (2) InfoHep; (3) NHS; (4) NCBI; **abbreviations** - link to glossary

Even though HIV became a manageable chronic condition, life-long stigmatisation affects the lives of millions of infected patients

HIV infections

The human immunodeficiency virus (HIV) targets the immune system of infected person and causes immunodeficiency. This results in increased vulnerability to a wide range of infections, cancers and other diseases[1]

2,3 million
Patients diagnosed in EU
(330 per 100,000 population)

Patient type
Average age at diagnosis is 36, with 3 times more infected men than women

Quality of Life
Physical symptoms managed effectively, however – still significant psychological and societal impact

€9.000
Annual HC cost / patient
for ART and co-morbidities treatment

High Burden Disease
Lifetime treatment required, additional societal costs related to HIV patients' discrimination

- HIV remains one of the a major public health issues globally, with more than 2 million people infected in Europe only
- With improving access to preventative and diagnostic solutions, treatment and care, HIV infection has become a **manageable chronic health condition**, allowing HIV patients to lead long and relatively healthy lives[2]
- However, with no curative therapy currently available, HIV patients require **life-long treatment with ART to avoid the rebound and further spreading of the virus[3]**
- Additionally, recent studies have shown that people living with HIV are at higher risk of developing non-HIV related co-morbidities, particularly at older ages, as compared to their peers not infected with HIV; **this results in additional costs incurred by healthcare systems, apart from the cost of HIV treatment[4]**
- Further, an European survey from October 2017 found that **people with HIV still experience a lower quality of life than their HIV-negative peers**, with the fear of transmitting the virus to others and the barrier to having children naturally as the key drivers[5]; according to **HIV Stigma Index[6]**, a significant proportion of HIV patients experiences stigma and discrimination related to HIV infection e.g. from families, peers, employers and healthcare providers

Abbreviations: ART – Antiretroviral therapy - link to glossary; (1) HIV.gov; (2) WHO; (3) Science Daily; (4) NCBI; (5) AIDS map; (6) AVERT

Curative therapy would eradicate the HIV virus, reducing need for life-long anti-retroviral therapy and limiting risk of co-morbidities

Current Treatment Paradigm

As HIV easily develops resistance to a single drug, patients are required to take a combination of different antiretroviral therapies (ARTs) (with standard of care being three ARTs)[1]

HIV ART treatment guidelines based on British HIV Association[3]

Therapy element	Preferred	Alternative
NRTI backbone	Tenofovir-DF and emtricitabine Tenofovir-AF and emtricitabine	Abacavir and lamivudinea
Third agent (alphabetical order)	Atazanavir/r Darunavir/r Dolutegravir Elvitegravir/c Raltegravir Rilpivirined	Efavirenz

ART versus novel HIV therapies

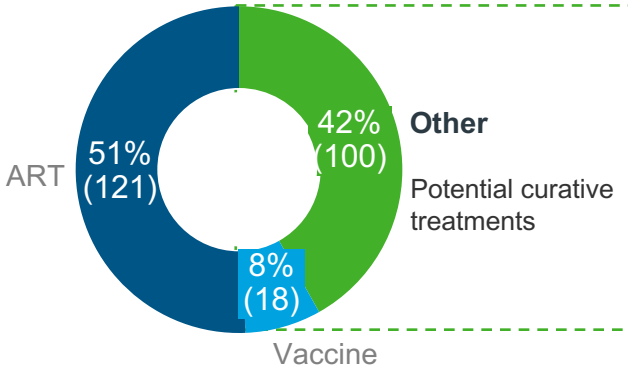
- Current combination antiretroviral therapies (CAR-T) offer **85-90% viral suppression** in compliant, treatment-naive patients[2]
- New classes/drugs are still needed to treat **resistant patients** without treatment options
- Also, even though cAR-T offer high efficacy in suppressing HIV replication, they fail to eliminate latently infected cells from the patient's organism and patients are required **to remain on the antiretroviral therapies throughout their lives**
- **Curative therapies have potential to bring benefits related to:**
  - **Efficacy:** virus eradication from the patient, preventing HIV remission even in the absence of ART
  - **Convenience**: avoiding life-long treatment regimens
  - **Safety and tolerability**: limiting effects of ARTs' long term toxicity and development of HIV co-morbidities
  - **Reducing risk of virus transmission**: patients' incompliance with current ART regimens is a significant cause for disease spread; curative therapies mitigate this risk

(1) NHS Inform; (2) NCBI; (3) British HIV Association; **abbreviations** - link to glossary

Antiretrovirals and preventative vaccines remain important; with 40% of trials investigating new, potentially curative therapies

Key approaches in development for HIV (active trials)

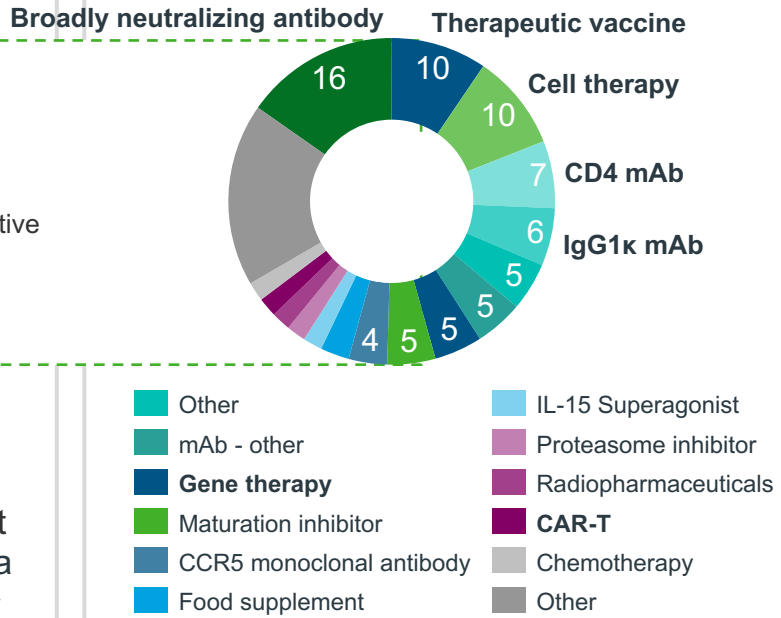
N=239



- **Antiretroviral therapies** – providing current standard of care in HIV treatment – remain a target for development activity and currently constitute 50% of the pipeline
- **Preventative HIV vaccines** account for 8% of active clinical trials
- **The remaining 42%** of drugs in development cover diverse technologies, including the **first curative HIV therapy**

Key technologies in development for curative HIV treatment (active trials)

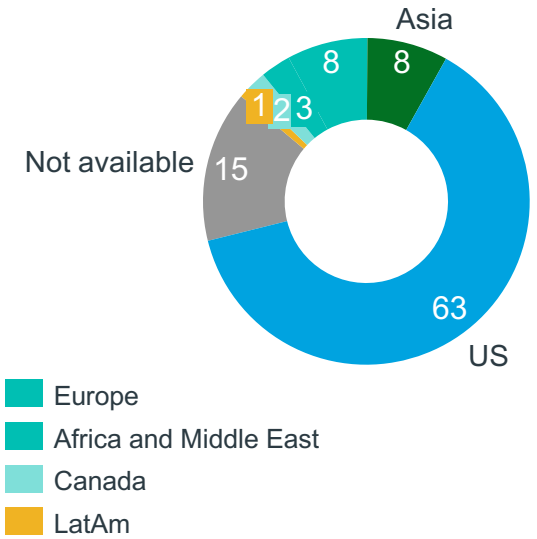
N=100



- Broadly neutralizing antibodies, cell therapies therapeutic vaccines and mAbs are **novel HIV therapies with the highest volume of clinical trials ongoing**
- **CAR-Ts and gene Tx** are less popular, though interesting approaches investigated

Active studies by geographic location (excluding ARTs and vaccines)

N=100



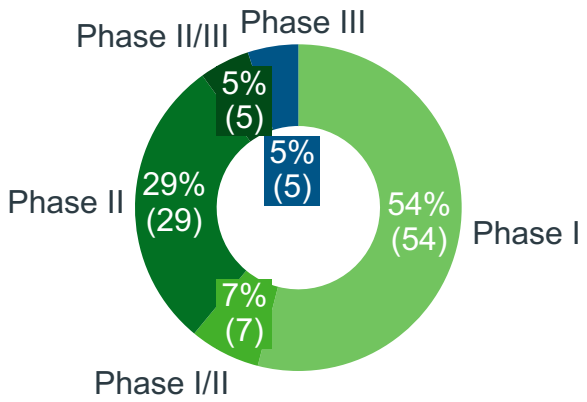
- Almost 65% of clinical trials for novel HIV therapies are located in the United States, with further **8% taking place in Europe** and 7% in Asia

Source: clinicaltrials.gov (data accessed Sept 28, 2020), IQVIA analysis; **abbreviations** - link to glossary

Novel approaches to HIV treatment are relatively early on in the clinical development, as compared to established antiretrovirals

Curative therapies pipeline
active studies by trial phase

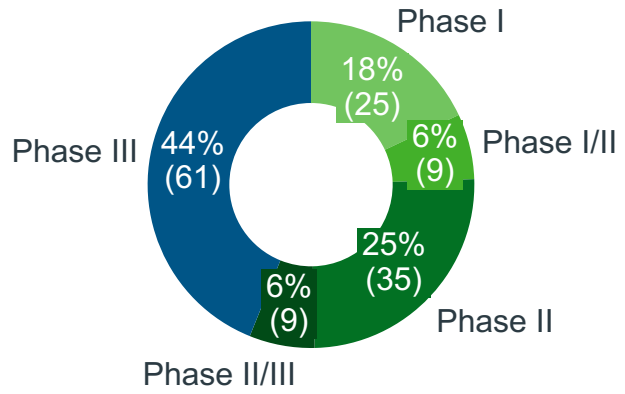
N=100



- Other technologies investigated for HIV treatment (e.g. mentioned in the previous slide broadly neutralising antibodies, cell and gene therapies, curative vaccines) are **earlier in the clinical development, with ~60% of active trials still in phase I or I/II**
- However, some **mAb therapies** have started entering phase II/III and III trials

ARTs and preventative vaccines
active studies by trial phase

N=139



- New antiretroviral drugs and combination therapies are being investigated in late development stages (75% in phase II onwards), holding promise for **even better efficacy and safety in suppressing the HIV** to stop disease progression and onward transmission
- However, as the mechanism of action remains the same, ARTs **are not able to fully dispose of the virus** from the infected organism

Source: clinicaltrials.gov (data accessed Sept 28, 2020), IQVIA analysis; **abbreviations** - link to glossary

However, interim trials results have confirmed the therapies' potential to suppress HIV after discontinuation of antiretrovirals

Select approaches to curative treatment for HIV

Broadly neutralising antibodies (bnAbs)

Multiple studies are testing the ability of HIV broadly neutralising antibodies (bnAbs) to **promote the immune control of HIV** in infected patients and potentially to **eliminate HIV-infected cells**[1].
Recent studies have shown that combination therapy of potent **bnAbs with latency-reversing agents (LRAs)** could also target latent reservoirs of HIV and remove them by recruiting effector cells, such as natural killer cells[2].
BnAbs may also progress development of first HIV **therapeutic vaccine**.

DNA-based therapeutic vaccines

By introducing a small amount of HIV DNA directly into cells, **therapeutic vaccines trigger a virus-specific immune response**. This improved anti-HIV immune response may help the organism fight the remaining HIV and reduce the viral reservoir[3] to prevent viral replication in the absence of ART[4].
Some positive interim results were reported for Inovio's investigative vaccines: VGX-3100 (decrease in no. of precancerous lesions) and PENNVAX-GP (90% subjects demonstrated specific antibody response).

Gene and cell therapies

In August 2020 FDA-approved the launch of phase 1 trial for AGT103-T, an **autologous, genetically modified T-cell therapy** for the treatment of HIV[5]. AGT103-T is made from blood cells using an 11-day process that increases the HIV-fighting T-cells and applies a gene therapy to help these cells survive in the body[6]. It may be able to **prevent HIV remission**.
SB-728-T by Sangamo Therapeutics and VRX-496 by VIRxSYS are other investigational gene Tx created by changing a gene in CD 4 immune cells.

Monoclonal antibodies

Monoclonal antibodies targeting CD4 (UB-421, TMB-365) and CCR5 receptors (PRO-140) are also being investigated for the **long term viral suppression** after discontinuation of antiretroviral therapy (1).
Interim phase 2 trial results for UB-421 have confirmed that the drug was able to maintain virologic suppression in all participants during antiretroviral treatment interruption (**94.5% of subjects, for up to 16 weeks**)[7]. Further studies will investigate mAb's longer term efficacy and safety.

(1) Science Translational Medicine; (2) NCBI; (3) Canadian HIV Trials Network; (4) PubMed; (5) Healio; (6) Globe Newswire; (7) Practice Update; **abbreviations** - link to glossary

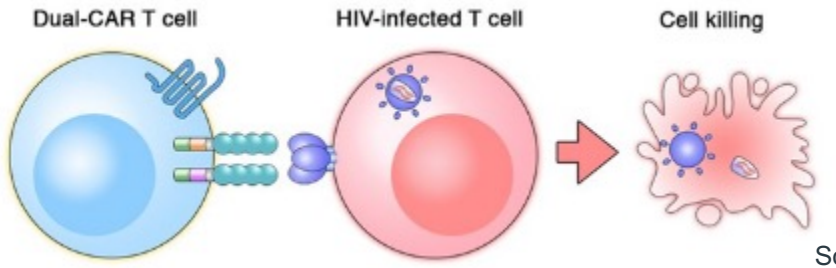
Dual CAR-Ts and gene editing technology are further on the horizon as potent curative therapies for HIV infections

Curative treatment for HIV **further on the horizon**

Dual CAR-Ts

To leverage the CAR-T technology in HIV treatment, researchers (Harvard Medical School) had to develop a T-cell able to (a) target and remove HIV-infected cells, (b) survive and reproduce in the body and (c) **resist HIV infection**[1]. That is how the **Dual CAR-T cell** was made – through engineering two CARs into a single T-cell. Each CAR has a CD4 protein that allows it to target HIV-infected cells, as well as a costimulatory domain, which stimulates the cell to increase its immune functions.
While the **first CAR stimulates cell proliferation, the second one increases its ability to kill HIV-infected cells**[2].
Finally, an added C34-CXCR4 protein **prevents HIV from attaching to the cell and infecting it.**

CAR-Ts for HIV treatment are currently in **pre-clinical development**, with first products entering **phase 1 trials**.

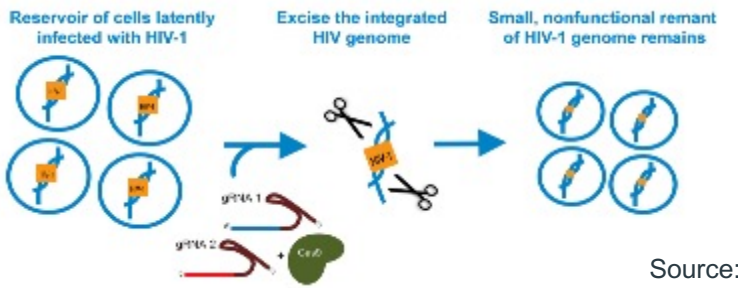


Source: Ragon Institute

CRISPR/Cas9 Gene editing

Currently available drugs are not able to fully remove HIV from the infected person's organism, **because the virus integrates into the cells' genomes** and remains there hidden, beyond the reach of ART.
Some of the recent pre-clinical trials have demonstrated that CRISPR-based gene editing tools **can remove HIV DNA from cell genomes**.
CRISPR uses sequence-specific guide RNAs to direct a scissors-like bacterial enzyme (Cas9) to cut out or replace disease-causing DNA sequences, such as HIV DNA[3].
As the CRISPR alone was able to eliminate 60-80% of HIV DNA from the organism, researchers used it **in combination with a highly potent ART.**

The biggest challenges to address in further development of gene editing Tx in HIV are related to **off-target effects**, effective delivery to infected cells (due to relatively large size) and additional safety concerns[4].



Source: AddGene's Blog

(1) Science Daily; (2) Medical Express; (3) DrugAbuse.gov; (4) NCBI; **abbreviations** - link to glossary

Chronic hepatitis B infections pose a challenge to healthcare systems, being one of the leading causes of liver cancer

Hepatitis B

Hepatitis B is a liver inflammation caused by a virus (HBV) that spreads through blood and body fluids. The infection is usually transmitted from infected pregnant women to their children, from child-to-child contact, as well as through sexual activity or drug injection[1]

4,7 million
Patients diagnosed in EU
(700 per 100,000 population)

Patient type
Highest incidence of acute disease among 35-44 olds and chronic disease among 25-34 olds; female-to-male ratio 1,5:1

Quality of Life
25% of chronic HBV patients develop cirrhosis and/or liver cancer, significantly impacting life expectations and quality

€28 billion
Total cost for HC
and further social and economic costs

High Burden Disease
Lifetime ART treatment required
Oncological treatment for patients with HCC*

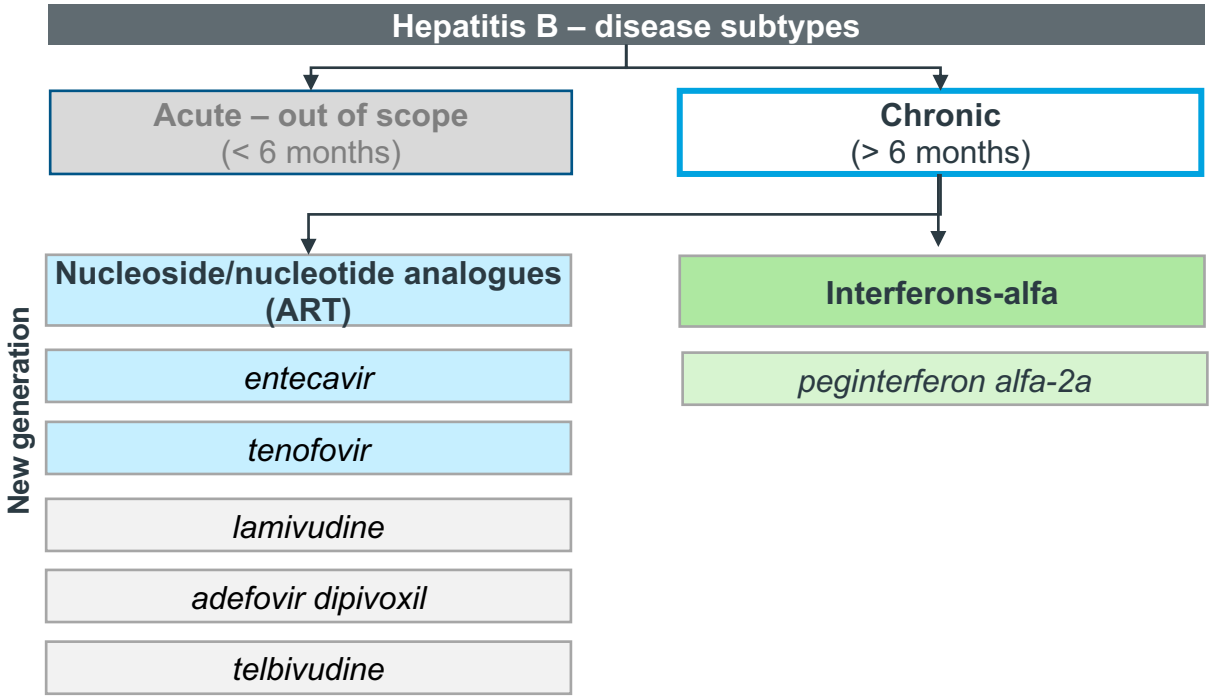
- While hepatitis C tends to get more attention and research funding (with curative combination treatments already available), hepatitis B is even **more common and causes more liver-related cancer and death** worldwide than hepatitis C[2]
- The highest incidence rate is observed for **25–34-year-olds**, with higher infection rates among men than among women, by 1.5:1 ratio[3]
- The rate of acute cases continues to decline over the last few years, likely as a result of **national vaccination programmes**[3]
- **More than half of patients** infected with hepatitis B are diagnosed with **chronic infection** (lasting for more than 6 months)[3], out of which **~25% develop serious liver disease**, such as liver scarring (cirrhosis) and cancer (hepatocellular carcinoma)
- Even though the cost of peginterferon alfa 2a and ART, being the standard of care in HBV treatment, is relatively low (generics available for tenofovir and entecavir), **treatment needs to be continued throughout patient's life**, which places a burden on the healthcare systems
- Additionally, the **healthcare costs related to oncological treatment** of patients developing liver cancer need to be taken into account

Due to alarming prevalence, high disease burden and unmet need, the latter parts of this section focuses on chronic Hepatitis B impact

References for points (1-3) in speaker notes
Abbreviations - link to glossary

Current therapies effectively suppress hepatitis B virus, but need to be continued over the patient's lifetime

Current Treatment Paradigm[1]



ARTs efficiently suppress viral replication and may inhibit formation of new cccDNA molecules, but they have little effect on established pools of cccDNA or formation of cccDNA in newly infected cells

Usually administered as a pegylated molecule to improve bioavailability and durability of antiviral action. In addition to immunomodulation, peginterferons act to inhibit viral DNA replication.

Promise of novel hepatitis B therapies

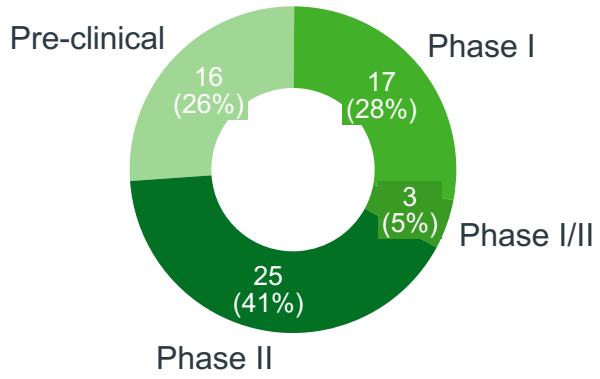
- **Current drug treatments** for chronic hepatitis B infection are able to suppress viral replication in majority of patients[2], slow the progression of liver fibrosis and related diseases, as well as reduce infectivity
- New generation antiviral agents available, such as tenofovir and entecavir, cause minimal risk of resistance and **provide viral suppression of over 99%**, at a high tolerability rate
- However, ART **can rarely clear the viral cccDNA responsible for HBV persistence (only in ~10% of patients**[2] and therefore patients require life-long treatment
- **Complete eradication of the virus is the ultimate goal of HBV therapy and will probably require combination therapy**[1]
- **New therapies in development hold the promise for either functional or complete cure for Hepatitis B**; a functional cure eliminates all antigens (e.g. HBsAg, surface antigens of the hepatitis B virus) and prevents viral replication after treatment is stopped; complete cure involves elimination of all viral elements from an infected patient, including cccDNA[1]

(1) NCBI; (2) PubMed; **abbreviations** - link to glossary

With 61 ongoing trials and the majority of pipeline activity still in the early stages, this area is likely to continue bringing innovation

Number of novel therapies for chronic HBV in development* (active trials)

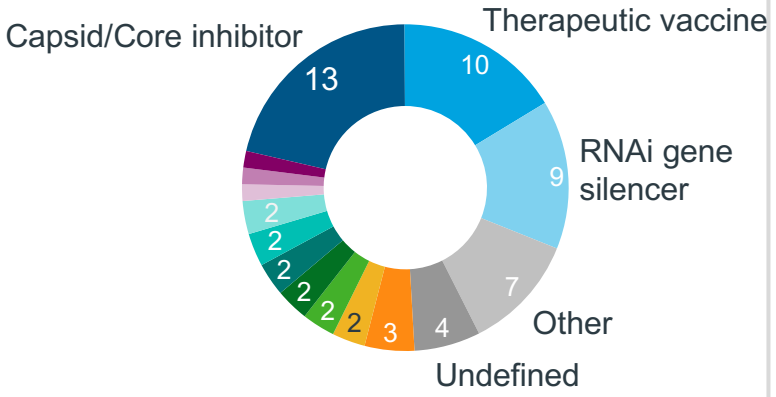
N=61



- First products, currently in Phase II trials, **expected to enter the market in 2021**
- **Extensive clinical activity in pre-clinical and early clinical stages** shows the industry's interest in this areas, as well as potential for further development in the coming years

Technologies studied in trials

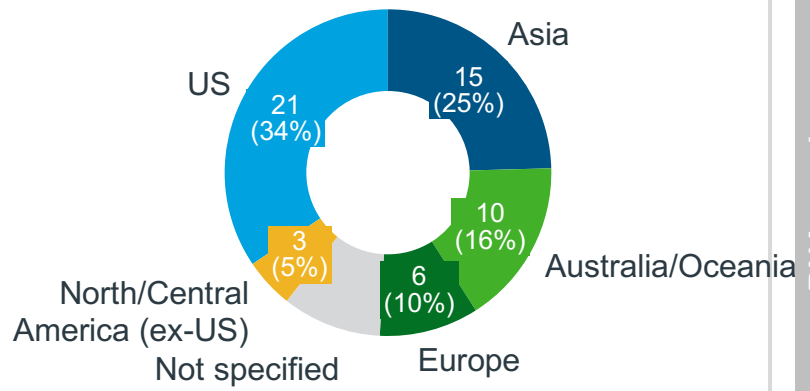
N=61



- The **latest technologies** are investigated as potential curative Tx for chronic HBV infection (e.g. gene editing or siRNAs)

Active studies by geographic location

N=61



- **In total, 60% of trials are ongoing in the US and in Asia** (mainly China) – 34% and 25% respectively.
- However, significant development activity is also reported in Australia/Oceania (16% of active trials) and in Europe (10%).

(*) Excluded antivirals, peginterferon therapies and preventative vaccines, representing current standard of care, and not curative treatments (N=19)

Source: clinicaltrials.gov (data accessed Sept 28, 2020); IQVIA analysis; **abbreviations** - link to glossary

Several approaches are being investigated to cure Hepatitis B, with siRNA drugs and therapeutic vaccine holding best promise

Select approaches to curative treatment for hepatitis B

Small interfering RNA (siRNA) drugs

siRNA molecules seem to be the **most promising therapeutic option for HBV infection** with their possible effect on synthesis of viral antigens and indirect immunomodulatory effects[1]. This therapeutic strategy is based on **viral gene silencing,** leveraging the RNA interference pathway, and **may effectively suppress HBV replication**. Potentially, they may even lead to disabling the viral cccDNA[2].

Therapeutic vaccine

Therapeutic vaccination in chronic HBV infected patients can cause **anti-HBV immune responses able to remove and/or cure infected hepatocytes** without damaging host cells through stimulating B-cell and T-cell responses[3]. In particular, the efficacy of therapeutic vaccine may be further improved by applying them in combination therapies.

Core/Capsid inhibitors

Core/capsid inhibitors (core protein allosteric modulators, CpAMs) are a novel drug class that **targets the hepatitis B core protein shield and may have a potential application as a functional cure**. Functional cure can be defined as sustained hepatitis B surface antigen (HBsAg) seroclearance and is rarely achievable with current treatments[4].

CRISPR/Cas9 gene editing therapies

Applying CRISPR gene editing technology to **mutate cccDNA** may provided the means to **inactivate HBV gene expression permanently** [5]. However, gene editing therapy is still in its early stages of exploration and there are many challenges to be addressed before clinical application is viable, especially related to off-target effects[6].

TLR-7 and TLR8 Agonists

Toll-Like Receptor Agonists under investigation may offer a direct anti-HBV effect[7], as well as increase immune activation and promote an antiviral response[8]. They may be used as adjuvants to enhance response to Hepatitis B therapeutic vaccines in development and maximise the immunity[9].

Other

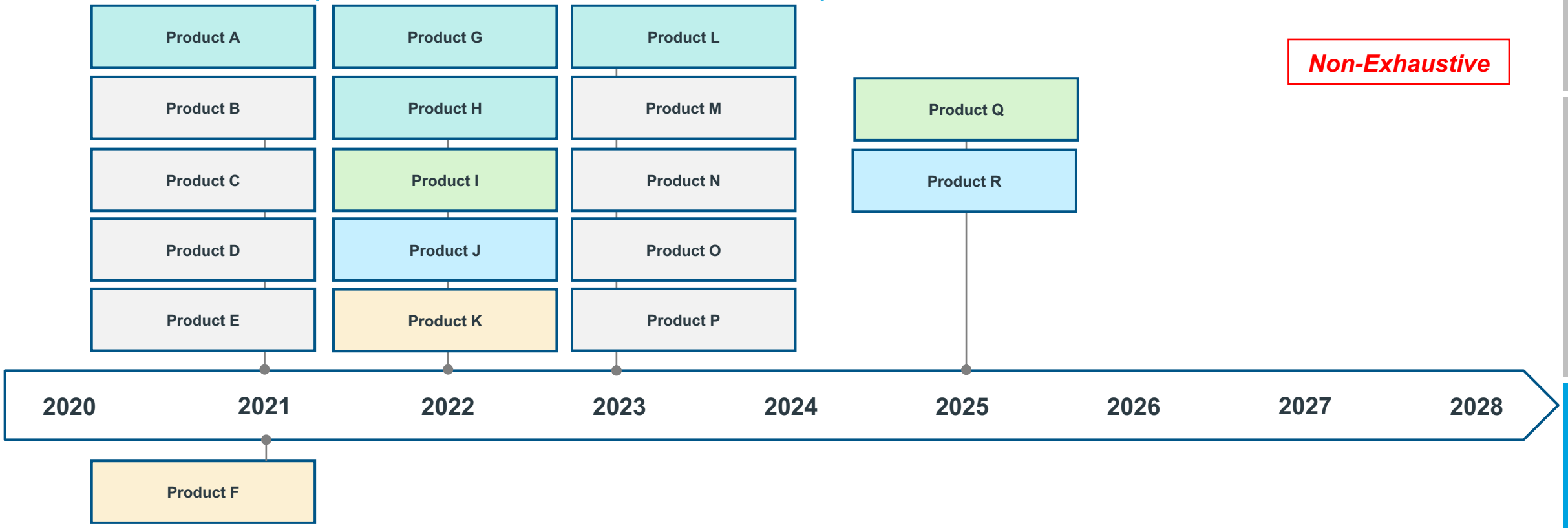
Several additional technologies in clinical development that may provide the cure for chronic hepatitis B infection include: viral protein inhibitors, sAg inhibitors, monoclonal antibodies, T-cell immunotherapy, oral microbiotic[10].

*Adeno-associated viral vectors

References for points (1-10) available in speaker notes; **abbreviations** - link to glossary

By 2025, approx. 6 products are anticipated to receive marketing authorization as curative therapies for Hepatitis B

2021: Curative therapies for HBV: Estimated trial completion dates



RNAi silencers	Capsid/Core inhibitors	Therapeutic vaccine	TLR-7/8 agonist	Other

Other mechanisms of action: (1) EGFR modulator; (2), (10) PD-1/PD-L1 antibody; (3) Combination treatment; (4) FXR agonist; (5) Undefined; (6) Immunoglobulin; (7) Viral protein inhibitor; (8) Apoptosis Inducer

Source: clinicaltrials.gov; October 2020, active clinical trials (Not yet Recruiting, Recruiting, Enrolling by invitation, Active not recruiting), Excluded trials without specified phase, Device trials

Curative therapies for HIV and chronic HBV will improve patients' quality of life, bring savings to HCS and to society as a whole

Hepatitis B and HIV curative therapy

1 **Patients, families and caregivers**	• Curative therapies can **eradicate viruses completely** from patients' bodies, **minimising the risk of co-morbidities** and **further disease spreading** and positively impacting the psychological health of infected people
2 **Healthcare systems and healthcare professionals**	• HCS would benefit from both elimination of **life-long treatment with ARTs** and the cost of treatment of co-morbidities, including **liver cancer**
3 **Society**	• Result in a **society free from chronic hepatitis B and HIV infections** and enable full inclusion of previously infected patients into social and professional lives

First cures will improve lives of HIV and chronic HBV patients, sparing them life-long treatments and limiting co-morbidities

Hepatitis B and HIV curative therapy

1

Patients, families and caregivers

	Current state	Future = Curative therapies
Removes need to life-long treatment	• Both HBV and HIV are **diagnosed at relatively young age** (30-36 years) and patients are required to receive **antiretroviral treatment for the rest of their lives** in order to suppress the disease progression • Toxicity resulting from **long term ART use** causes higher risk of developing bone disease, renal and metabolic disorders, CNS disorders, cardiovascular and liver disease[1]	• Curative therapy will eradicate the virus from patient's organism (being it chronic HBV infection or HIV), allowing them to **have their normal lives back**, without having to follow strict, often daily, treatment regimens • This way, patients will also **avoid the adverse effects** related to long term use of antiretroviral drugs
Reduces the risk of severe co-morbidities	• Cirrhosis (scarring of the liver) and hepatocellular carcinoma developed by ~25% of chronic HBV patients cause a **large disease burden;** HBV is one of the three key indications for liver transplant • People living with HIV are at high risk of developing non-HIV related co-morbidities, particularly at older ages, such as CV **disease, COPD, liver disease and cancers**	• Curative therapies will improve the quality of live of HIV and chronic HBV patients through **mitigating the risk of co-morbidities,** allowing them to live longer, healthier lives

(1) NCBI; **abbreviations** - link to glossary

They will also address the challenge of stigmatisation and discrimination of infected patients

Hepatitis B and HIV curative therapy

1

Patients, families and caregivers

	Current state	Future = Curative therapies

Prevents life-long stigmatisation of infected patients	• HBV and HIV significantly impact the psychological health of infected patients due to:
	  • **Fear of infecting others** that may result in self-isolation and decision to no start their own families
	  • **Stigmatisation and discrimination** in social and professional lives that is still present, especially for HIV patients
		• Curing the disease will allow the patients to **fully return to their social and professional lives**, without fear of being stigmatized

Current treatment costs for chronic HBV patients are driven by antiretrovirals, costs of liver cancer treatment, liver transplants

Hepatitis B and HIV curative therapy

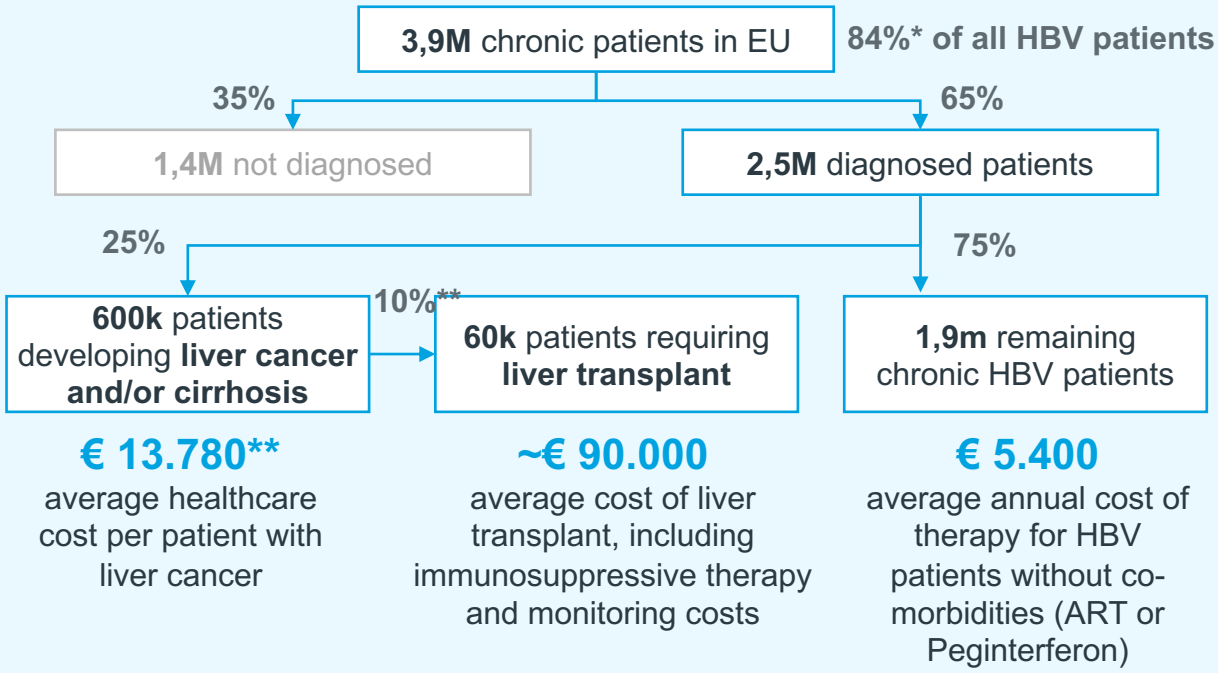
2

Healthcare systems and healthcare professionals

Chronic hepatitis B and liver disease

- **10%** of liver transplants globally are due to hepatitis B
- **60%** of liver cancers result from chronic hepatitis B
- **43%** of liver cancer deaths are patients with chronic hepatitis B
- **15 – 25%** of children infected with hepatitis B at birth will die prematurely from cirrhosis, liver failure, or liver cancer, if the infection is not diagnosed and treated early enough[1]

Cost of chronic HBV treatment for HCS in EU



(1) Hepatitis B Foundation (*) Excluded with disease status unknown/ not possible to classify – ECDC; (**) Based on NASH: 20% of patients with advanced cirrhosis will require transplant, 50% will be eligible; (***) Based on sorafenib, TACE, TARE treatments; **abbreviations** - link to glossary

Similarly, HIV treatment costs include antiretrovirals, but also costs related to treatment of co-morbidities in the aging patients

Hepatitis B and HIV curative therapy

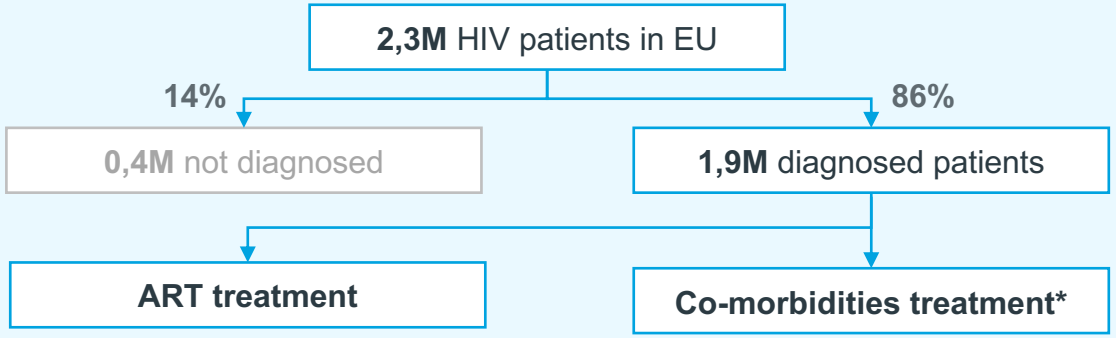
2

Healthcare systems and healthcare professionals

HIV and age-related co-morbidities

- Since the approval of first antiretroviral therapy in 1987, the effectiveness of ART has improved significantly and the focus of HIV treatment has shifted from preventing disease progression to **managing HIV as a life-long condition in an aging population with various co-morbidities**[1]
- It is estimated that total healthcare costs per HIV-infected patient is **on average €4.500 higher* than for non-infected patients, excluding ART costs**[2]
- Some of the **co-morbidities frequently associated with HIV** infections include cardiovascular disease, COPD, liver disease, non-AIDS cancers, any many others[1]

Cost of HIV treatment for HCS in EU



€ 4.509
Is average additional healthcare cost per HIV patient per year (as compared to non-HIV patient)

€ 4.500
Is average annual cost of therapy for HIV patients excluding co-morbidities (ART)

~€ 18 billion total HCS cost

(1) HIV.eu; (2) NCBI; (*) Medication excluding ART, outpatient and inpatient care – NCBI; **abbreviations** - link to glossary

Curative therapies will reduce cost of antiretrovirals and co-morbidity treatment, bringing benefits to healthcare systems

Hepatitis B and HIV curative therapy

2

Healthcare systems and healthcare professionals

	Current state	Future = Curative therapies
Limits the cost of life-long antiretroviral therapy	• Despite ARTs are relatively non-expensive, they need to be maintained throughout the patients' lives which results in average lifetime therapy cost per patient of **~€260.000** for HBV and **~€200.000** for HIV* • In total, only ARTs for these two diseases generate a cost of more than **€22 billion** for European healthcare	• Potential curative therapies for HBV (specifically therapeutic vaccine) hold **the promise for curing ~95% of all chronic HBV patients in Europe**, removing the need for ARTs and related costs almost completely • It is still to be confirmed whether the target for the HIV therapies under investigation will be the same
Reduces the cost of co-morbidities treatment	• HBV is the leading cause of liver cancer and one of the key indications for liver transplant, resulting in further costs of **€8,5 billion and €5,7 billion** respectively • On average, annual healthcare costs for treating HIV-infected patient is by **€4.500** higher than for non-HIV patient (excluding HIV therapy), which results in total additional cost of **€8,8 billion** across Europe	• If a significant proportion of co-morbidities are avoided in cured patients, **curative therapies would bring savings in the billions** for European healthcare systems (up to €22 billion in total)

(*) Higher cost for HBV driven by peginterferon alfa 2-a (part of the SoC), at least 2 times more expensive than antiretroviral drugs (often generics); **abbreviations** - link to glossary

Finally, cured patients will be able to fully participate in labour market, leading to increased GDP generation

Hepatitis B and HIV curative therapy

3

Society

	Current state	Future = Curative therapies
Limits the productivity loss from discrimination (HIV) and absenteeism (HBV)	• HIV patients in Europe are **14%** less likely to find a job than their non-infected peers, which results in a high unused potential in the labour market • HBV patients developing liver cancer or undergoing a liver transplant lose on average **40-50 working days** as a result of the disease • These result in a total nominal loss of GDP of >**€12 billion** across European countries	• Introduction of curative therapies will lead to full integration of HIV patients into the labour market and the avoidance of work absenteeism of HBV patients with liver complications, bringing savings of up to **€11,9 billion***

(*) Based on the assumption that from 95% patients are cured, and ~100% of those will avoid co-morbidities (see impact analysis); **abbreviations** - link to glossary

Contents

Providing access to previous innovations is driving the next innovation wave, bringing cures to previously untreatable diseases

Each innovation wave moves us towards new cures

Not exhaustive

Increasing innovation

		Before 2000	2000-2020	2022 onwards
Therapy type	**Technology**	**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, discrete	Traditional, biomarkers, discrete	Traditional, biomarkers, genomics, digital, PCEs, longitudinal
	Data ownership	Pharma	Pharma	Pharma + Payer + Provider + Patient
	Probability of success	Low to moderate	Moderate	Moderate to high
Rate of change	**Innovation rate**	Slow, many me-toos	More new classes, fewer me-toos	Man 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 miximisation	Price-volume optimisation	Outcome-based / personalised

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

Introducing antiretrovirals allowed us to take control of the HIV epidemic back in 1990s; curative Tx is the next step in this battle

Further investment is required to completely eliminate HIV health crisis

Before 2000

Case study: Curative therapies for HIV as a next step after introducing antiretrovirals

Before antiretrovirals, HIV was a deadly infection with a mortality rate of more than 90% and average time from infection to death of 8-10 years[1].

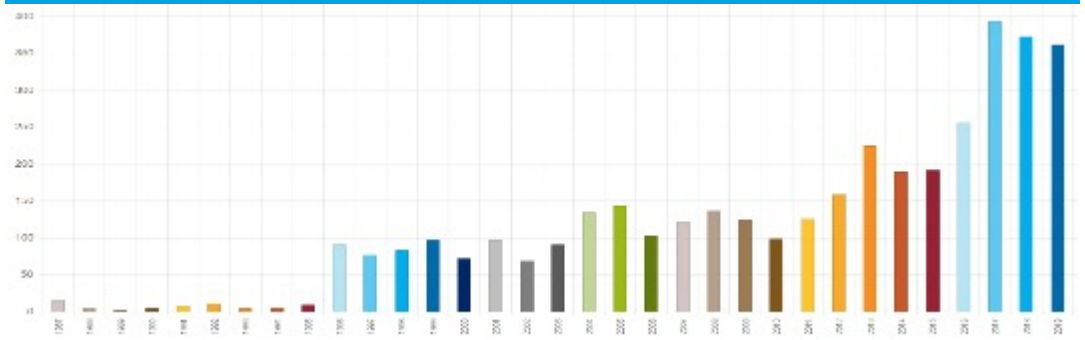
In March 1987, AZT (zidovudine) became the **first drug to gain FDA's approval for treating AIDS**. These NRTIs (nucleoside analog reverse-transcriptase inhibitors), used alone, decreased deaths and opportunistic infections, albeit with serious adverse effects[2].

In the early 1990s, additional NRTI drugs gained FDA approval. The development of AZT and other NRTIs showed that treating HIV was possible, and **these drugs cleared the way for discovery and development of new generations of antiretroviral drugs[2],** combination treatments, and further breakthroughs, e.g. single pill regimens and PrEPs (pre-exposure prophylaxis).

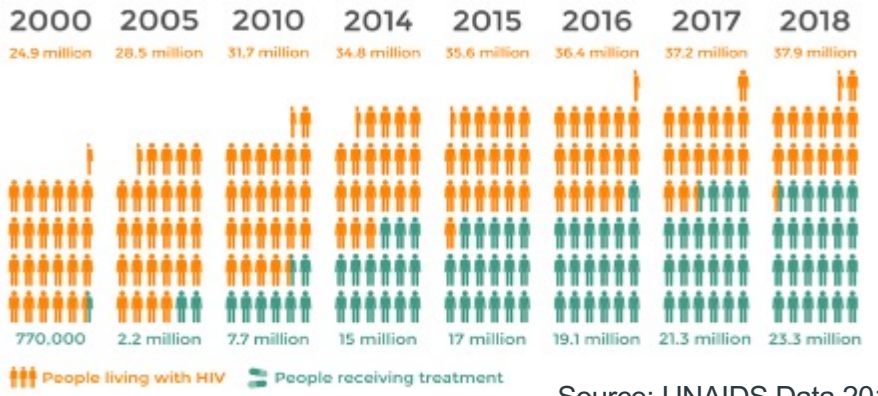
Today people with HIV can live long, relatively healthy lives, however they are required to continue lifetime treatments.

Curative therapies will be the **next wave of innovation** in this areas, holding the promise to **eliminate HIV and finalise this battle.**

Increasing availability of HIV treatments[3] …



…resulted in increase in patients receiving treatment from 3% in 2000 to 62% in 2018[4]



Source: UNAIDS Data 2019

(1) Medscape; (2) National Institute of Allergy and Infectious Diseases; (3) IQVIA Analytics Link, # of launches of antiviral products specifically used to treat HIV in 1987-2019; (4) Avert.org;

Though expensive in the short-term, curative therapies bring substantial benefits in the long-term, as HCV therapies have shown

Lessons learnt from HCV treatments can be applied to curative Tx

2000-2020

Case study

In 2013, when Gilead's Sovaldi was approved as a breakthrough therapy for Hepatitis C (FDA), it **caused an international outcry due to its high price**, - at $1,000 a pill and $84,000 total for a typical patient.[1,2]

In the US, the unexpected budget impact was seen as the main economic issues**, resulting from superior efficacy, tolerability and convenience.**[3]

In Europe**,** payers put **pressure put on the high price** (with discounts of up to 50% negotiated) with heavy **restrictions** on eligible patients leading to **severe delays**[7] – causing **patient protests** in Spain and Portugal[8] and leading patients to seek treatment in other countries[9]

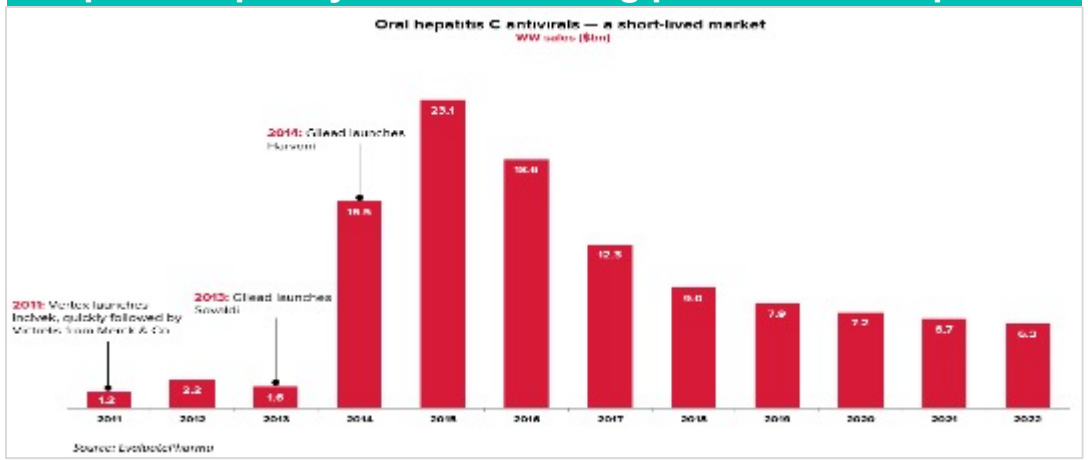
Sovaldi eventually paved the way to market approvals for **other novel antiretroviral HCV** therapies, and increased the no. of drugs available.

After 2015, the **total market value of HCV therapies decreased sharply,** due to entry of these new options, generics, as well as increasing number of cured patients no longer requiring treatment.[4,5]

Through **achieving cure rates above 95%,** new treatments helped limit HCV prevalence across Europe*, and **WHO target is to reduce new infections by 80% until 2030**[6].

Initial shock caused by cost of novel HCV therapies…

…passed quickly with decreasing prevalence and prices



(1) New York Times, Aug 2020; (2) FT; (3) Financial Times, Jan 2014; (4) Evaluate, Feb 2018; (5) Market Watch; (6) World Hepatitis Alliance; (7) UK, (8) ES, (9) Sweden
(*) By 2021, the number of individuals cured of HCV would supersede the number of actively infected individuals in France, Germany, Spain and the UK (BMJ Open)

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

Effective assessment, funding, and delivery are closely linked and face a number of challenging complexities...

…and access to the right data and effective stakeholder education will be integral to addressing these challenges

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 propose ideas for stakeholders to consider to allow for provision of early and effective access to innovation (1/2)

Updating regulatory guidance & procedures	1	Regulatory guidance is needed to ensure that manufacturers are able to generate the necessary information for HTA/EMA stakeholders to make informed decisions minimising access delays
RWE to address payer clinical uncertainty	2	RWE generation through temporary access schemes or post launch data collection should continue to be utilised to mitigate the benefit uncertainty at launch given limited data
Valuing and rewarding innovation	3	Continual adaptation of HTA/value assessment processes in order to fairly assess and reward the long-term clinical, economic and societal value of innovation; given possibility of limited evidence at launch or large patient populations
Adapting financing models for upfront investment	4	Innovative finance models such as annuities should be considered given the long-term, system-wide benefits; these will help overcome limits posed by annual as well as siloed budgets

We propose ideas for stakeholders to consider to allow for provision of early and effective access to innovation (2/2)

Developing infrastructure to support care delivery	5	Optimisation of approaches to managing patients is needed to ensure that innovation is effectively incorporated into patients journeys; this will be key for optimising patient outcomes and reducing the risk of adverse events
Optimising patient/ treatment strategies	6	Healthcare systems and manufacturers need to work together to optimise approaches to managing patients; collaboration is key to optimise patient outcomes and reduce the risk of adverse events
Enabling data science and technology partnerships	7	Regulations and infrastructure to support increasing use of health data and more sophisticated data science will be vital to enable better care pathways, more informed innovative agreements, and optimal patient outcomes
Horizon scanning and stakeholder dialogue	8	Collaboration from early stages of innovation development ensures pan-stakeholder stake in its success and helps to ensure that innovation potential is fully realised

The incremental future implications of the innovations discussed will also be summarised

These proposed ideas are relevant across all prioritised innovation areas

	Proposed Ideas	1 Combos in Oncology	2 Alzheimer's Disease	3 CAR-Ts	4 Gene Therapy	5 PPAR & FXR for NASH	6 Remyelinating therapies	7 mRNA vaccines	8 Curative Tx for HBV and HIV
1	Updating regulatory guidance & procedures	✓	✓	✓	✓	✗	✓	✓	✓
2	RWE to address payer clinical uncertainty	✓	✓	✓	✓	✗	✓	✓	✓
3	Valuing and rewarding innovation	✓	✓	✓	✓	✗	✓	✓	✓
4	Adapting financing models	✓	✗	✓	✓	✗	✓	✗	✓
5	Developing infrastructure to support care delivery	✗	✗	✓	✓	✓	✗	✓	✗
6	Optimising patient management/ treatment strategies	✓	✓	✓	✓	✓	✓	✓	✓
7	Enabling data science and technology partnerships	✓	✓	✓	✓	✓	✓	✓	✓
8	Horizon scanning and stakeholder dialogue	✓	✓	✓	✓	✓	✓	✓	✓

Content Navigation

Link - back to detailed navigation page

Updating regulatory guidance & procedures

Link - back to from innovation to access contents page

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 **-** therefore regulatory procedures **need to consider how to address clinical uncertainty:***

Early and ongoing consultation

- **Trial design:** pro-active engagement with EMA through working groups with multiple manufacturers to receive guidance on broader methodological or policy /regulatory issues, or manufacturers can interact directly with EMA for specific guidance and scientific advice to establish reliable and relevant endpoints
- **Manufacturing processes:** pro-active development of standards is key given ongoing technological advancements, especially within the fields of cell/ gene therapy
  - Standards would settle uncertainty associated with the manufacturing process during assessment *e.g.* process control, material quality and contamination

Adaptive pathways and living labels

- **Broader use of adaptive pathways,** through adapting the definition of unmet need to include the societal perspective, *(i.e., for innovation targeting indications that do not fall under the currently stringent criteria of "high unmet need")* could see conditional access provided for important new treatments that are not able to demonstrate their full value at launch
- **A greater emphasis on inclusion of RWE to enable a 'living label'** will allow the label to evolve in terms of indication, patient sub-groups etc, especially as products come to market sooner with more limited data

Consideration of novel evidence generation in submissions

- Expanding the type of evidence accepted for regulatory approval **beyond the traditional "randomised controlled trial"** (e.g.,. basket trials, RWD/RWE, synthetic comparator arms, data collected through digital platforms) will allow manufacturers to generate evidence that demonstrates the benefit/risk profile of a product in a more efficient and pragmatic manner (i.e., more reflective of efficacy and safety in real world clinical practice)

While the first EMA approved gene therapy, Glybera, was withdrawn, new gene therapies may benefit from past learnings and PRIME scheme

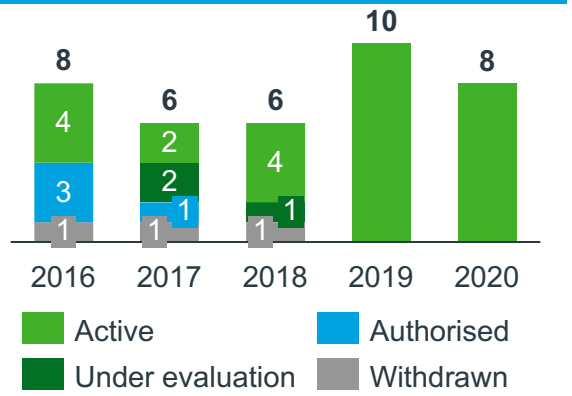
UPDATED CASE STUDY: Learnings from past ATMPs

- Marketing authorisation of first EMA-approved gene therapy - Glybera (Alipogene tiparvovec) - was not renewed in October 2017 due to insufficient uptake[1]
- With a very limited target population and a price of one million euros, **it was the most expensive therapy back in 2012**, making it difficult to convince payers to finance it[2]
- Learnings from previous ATMPs should be applied to improve the access to new gene therapies, e.g. **Luxturna** for inherited retinal dystrophy approved in Nov 2018 and **Zynteglo** for beta thalassaemia, which received conditional approval in Jun 2019
- As both treatments target rare diseases (prevalence of inherited retinal dystrophy in Europe is ~3,7 in 10.000, even smaller population has RPE65 gene mutations targeted by Luxturna; and of beta thalassaemia ~1 in 10.000 in the EU), **they may face similar challenge to reach the level of uptake that will secure commercial targets if a different approach is not applied**

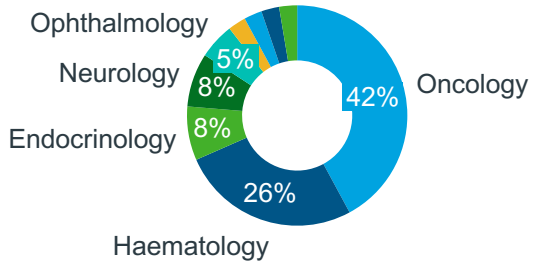
UPDATED CASE STUDY: EMA Priority Medicines (PRIME)*

- 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.
- Out of 83 therapies covered by the PRIME scheme between 2016-2020, almost 50% were ATMPs (38 therapies), including cell and gene therapies; only **in 2019-2020 18 ATMPs received PRIME** eligibility, mainly in oncology (42%) and haematology (26%)[3]
- One recent product is **AT-GTX-501**, a gene therapy for children living with CLN6 Batten disease, often associated with childhood deaths[4]

# of ATMPs granted PRIME eligibility



ATMPs granted PRIME per TA



(1) BioNews; (2) Labiotech; (3) EMA, 20.11.2020; (4) GlobeNewswire;
(*) PRIority MEdicines

The FDA aims to support development of novel gene therapies by releasing new guidelines, e.g. on orphan designation and exclusivity

CASE STUDY: FDA guidelines on gene Tx in orphan diseases

- In February 2020 FDA finalised six **new guidelines to support development of novel gene therapy products** plus released a new draft guidance in this area
- It is a response to more than 900 investigational new drug applications ongoing for gene and cell therapy clinical studies, and FDA's struggles to tackle the related challenges with current resources
- The new draft guideline focuses **on how FDA will decide if orphan exclusivity will be awarded** if two gene therapy products are intended for the same use or indication[1]
- It also specifies whether products under review should receive seven-year market exclusivity[2]
- The FDA stresses that it does not want to discourage the development of multiple gene therapy products to treat the same disease or condition. Rather, **their policy should lead to a competitive marketplace with more choices for patients**[2]

Guidance for gene therapies released by FDA[3]
Human gene therapy for Haemophilia
Human gene therapy for Retinal Disorders
Human gene therapy for Rare Diseases
CMC information for human gene therapy investigational NDS***
Long-term follow-up after administration of human gene Tx products
Testing of retroviral vector-based human gene therapy products […]
DRAFT: Interpreting Sameness of Gene Tx Products Under Orphan Drug Reg.

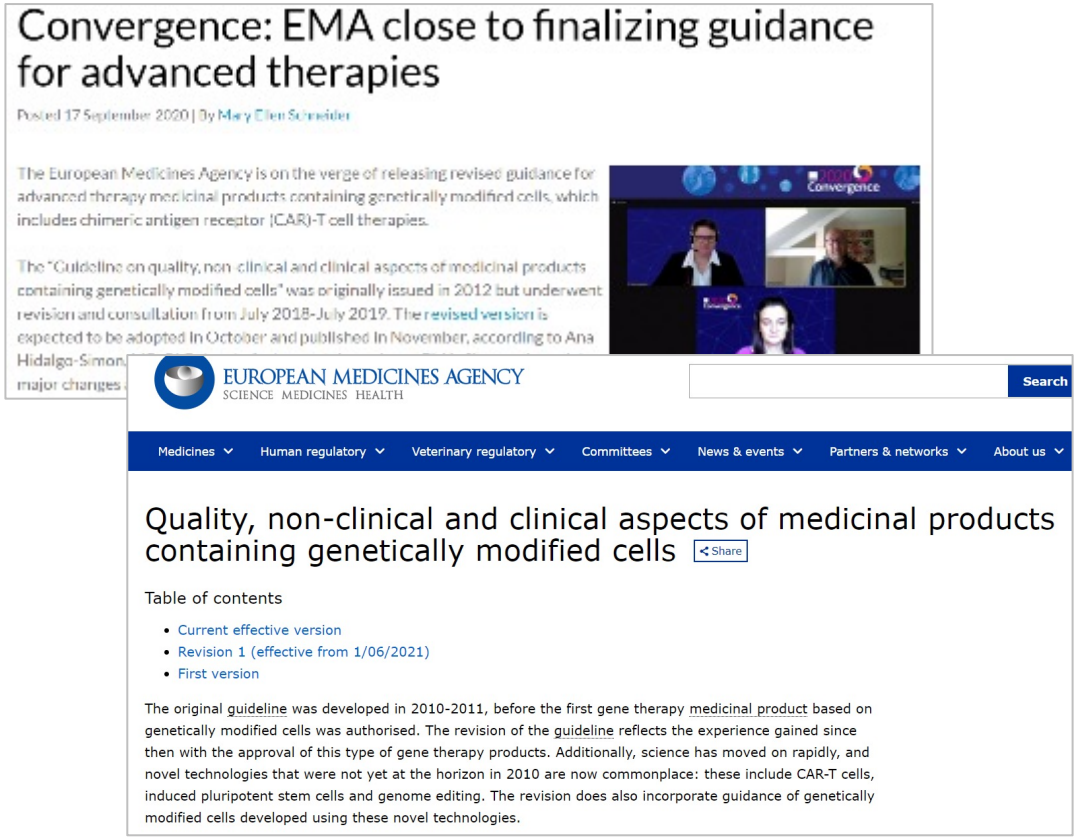
Guidance expected to enable multiple gene therapy products for an orphan disease/ condition

(1) Regulatory Affairs Professionals Society; (2) BioNews; (3) Global Regulatory Partners;
(*) CMC - Chemistry, manufacturing and control; (**) NDA - New drug applications

In parallel, EMA has now revised the guidance on gene modified cell therapies to reflect their increasing importance

CASE STUDY: EMA guidance for ATMPs containing genetically modified cells[1]

- In Nov 2020 EMA finalised **revised guidance for advanced therapy medicinal products containing genetically modified cells**, including chimeric antigen receptor (CAR)-T-cell therapies
  - ➢ *Updates will be effective from June 2021*
- 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 authorisation



(*) Cells reprogrammed back into an embryonic-like state, enabling development of any type of human cell needed (1) Regulatory Affairs Professionals Society; https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-clinical-aspects-medicinal-products-containing-genetically-modified_en-0.pdf

Evidence requirements from regulators are evolving to account for new data collection capabilities, as seen with new case studies

US: Introduction of 21st Century Cures Act

- The 21st Century Cures Act, signed into law on 13th Dec 2016, is designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently
- The Act enhances the FDA's ability to modernize clinical trials and requires FDA to draft a framework for the use of RWE
  - The framework addresses acceptable sources of RWE for various purposes
- Section 3022 of the act calls for use of RWE for
  - Indication expansions
  - Post approval safety studies
  - Historical comparator studies (natural history comparators and *synthetic control arms")

EU: Increasing Use of Adaptive Pathways

- Avelumab (Bavencio) received **conditional marketing authorisation** (MA) in June 2017
  - It was submitted for MA with an open label, single arm trial with a total of 88 patients enrolled
  - On top of this trial, supporting data from an observational study was submitted to assess efficacy of comparator chemotherapies; data from the observational study was considered as supportive due to issues with the quality of the data collected by registries
  - To achieve full authorisation, the manufacturer is required to submit further RWE to validate the benefit/risk profile

Example:
- In 2019 there were 17 cell and gene therapy products approved by FDA
- Now, the momentum to bring innovative therapies to market is further increasing - FDA anticipates approval of 10 to 20 cell and gene therapy products a year over the next five years

These recent case studies demonstrate a growing willingness of regulators to engage on RWE; *however it will be important for the updated guidance to be accompanied by submissions with robust RWE generation proposals*

(1) Map BioPharma; (2) PharmaPhorum, Aug 2020;

An indication expansion was approved by FDA based predominately on RWE and EMA initiatives encourage effective use of registry data

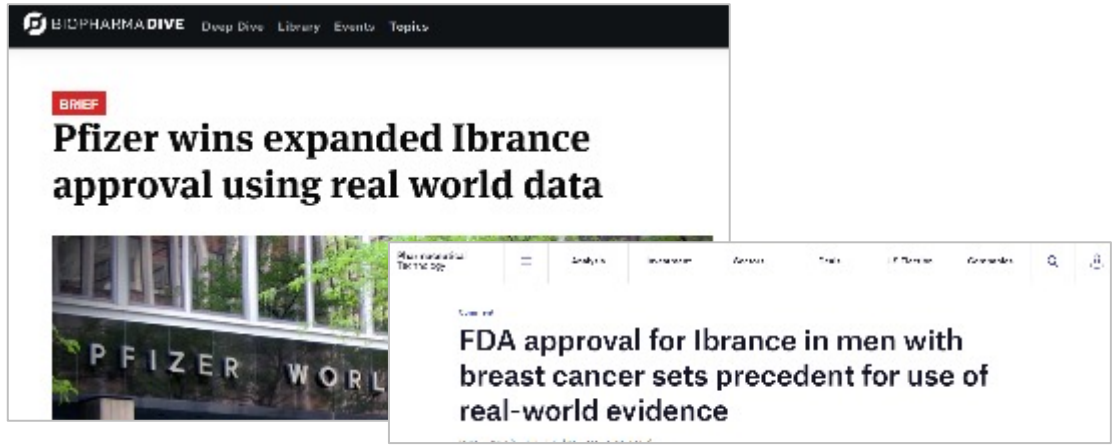
Regulatory agencies are adapting to the ongoing industry changes

CASE STUDY: Expanded Ibrance approval based on RWD mainly

- In April 2019, the FDA approved the indication expansion for Pfizer's Ibrance (palbociclib) in combination with endocrine therapy for hormone HR-positive, HER2-negative* advanced or metastatic breast cancer in men[1]
- This approval was unique as the **process was largely based on an analysis of real world evidence**, specifically from electronic health records and post marketing reports from male patients treated with Ibrance sourced from databases including Flatiron Health's, IQVIA's and Pfizer[2]
- RWE has been increasingly used by FDA (and other regulatory bodies) to inform reimbursement decisions and to support clinical decision making, **but its use in expanding a drug indication is still rare**
- **The approval demonstrates the increasing strategic importance and utility of RWE for pharmaceutical industry, also in new use cases[1]**

…And ongoing changes by EMA[3]

- 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 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]



(*) Hormone receptor-positive, human epidermal growth factor receptor 2-negative
(1) Pharmaceutical Technology; (2) Biopharma Dive;

Healthcare systems across Europe need to adapt quickly to face the unprecedented challenge of the COVID-19 pandemic

COVID-19 may be a change catalyst for future innovative treatments

CASE STUDY: Regulatory innovation in the fight against COVID-19

- COVID-19 pandemic requires **taking strong actions and adapting to an unprecedented challenge** – which applies to both governments, public health institutions and healthcare regulators
- So far, European **regulatory system has been showing resilience against dynamic changes** and the industry had to work mainly within the existing legislation to leverage the opportunities offered by science to alleviate this healthcare crisis
- Still, some steps were taken to **optimise clinical development and streamline regulatory process**, such as:
  - **Publishing safety monitoring plan** for COVID-19 vaccines (EMA)[2]
  - **Highlighting that all COVID-19 vaccines should go through the centralized procedure** for marketing authorization, regardless of their production process (EMA)[3]

COVID-19 as change catalyst

- Further steps are recommended to European regulators to address this pandemic challenge
- **If implemented, these actions can facilitate patients' access not only to COVID-19 vaccine or medications, but also improve access to innovation in post-pandemic reality**

Steps recommended to European Regulators by EFPIA[1]

Support Innovative Trial Designs (ITDs)	Support the appropriate use and acceptability of ITDs (e.g. through master protocols, adaptive studies, decentralised trials) to continue clinical development
Increase RWE/RWD use	Develop and adopt cross-industry guidance on RWD/RWE use, including clear principles on data quality, access, analysis and regulatory acceptance
Provide dynamic regulatory pathways	Design guidelines for a flexible regulatory pathway for more rapid approval of novel treatments, including approach to data collection and analysis
Adjust regulatory pathway for drug-device comb.	Adopting streamlined, EU-integrated pathway for the assessment of diagnostics and drug-device combos (currently evaluated by different authorities)

(1) EFPIA, Regulatory Road To Innovation In the Fight Against Covid-19; (2) EMA; (3) EMA

Coordination between EMA and HTA agencies was historically facilitated by SEED but now through Parallel Consultation

Example of Previous Action Taken:

Scientific Advice

- Shaping European Early Dialogues for health technologies (SEED) was an international project financed by the EC between 2013-2015 and consisted of 14 European HTA agencies
- SEED conducted pilots on early dialogues between member HTA agencies and manufacturers of products currently in the development stage
- Early dialogues allowed manufacturers to meet with European HTA agencies in order to present their development plan for the product in question, and to ask specific questions relative to their plan
- In doing so, SEED was able to reduce the risk of production of data that would have been inadequate to support the company's future reimbursement request
- Learnings from SEED have been taken forward and integrated into the guidance for Parallel Consultation (*see next case study*)

Example of Current Action Taken:

EMA Guidance for Parallel Consultation

- In June 2017, Parallel Consultation (PC) replaced the earlier procedure of parallel "Scientific Advice", to provide coordination and communication between EU HTA agencies and EMA
  - PC provides a single gateway for requests for parallel discussions before the start of pivotal clinical trials
  - Aims to ensure that clinical trials are designed to meet requirements for both regulatory and HTA approval
- PC is facilitated by the European Network for Health Technology Assessment (EUnetHTA), which facilitates the recruitment of HTA bodies to the process
- EUnetHTA provides the early dialogue through either consolidated PC (through the "Early Dialogue Working Party" with multiple HTA bodies) or individual PC (HTA bodies participate on voluntary basis)
- EUnetHTA will cease to exist as of May 2021, and the European Commission has launched a tender notification for provision of joint HTA work supporting the continuation of EU cooperation on HTA which will focus as well on Joint Scientific Consultations

RWE to address payer uncertainty

Link - back to from innovation to access contents page

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

Real world evidence (RWE) generation through temporary access schemes

- 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 schemes

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 II/III 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

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

Impact of RWE "at launch" and "post launch" on price and market access

- In Europe, evidence available at launch tends to shape price and access achievable and evidence available post launch has less leverage and tends to only 'course correct' (e.g. net price erosion)
- ***Updates to (and standardisation around) how RWE influences price and access could improve speed of patient access by allowing preliminary Pricing and Market Access to be updated after RWE is generated***

At launch – "unbranded RWE"

- Today, RWE may be taken into consideration if available. However, it currently has **limited benefit in shaping the price and access of a drug** on top of evidence from conventional RCTs, given the strict criteria on types of evidence being applied in national assessments

Current applications of RWE

LOW – limited benefit; used to "support" RCT data

Post launch – "branded RWE"

- There are more applications for RWE generated post launch, yet the **impact varies significantly across and within markets**, e.g.,:
  - In France, every 5 years there is a re-evaluation, that can impact the price-volume agreement or net price. RWE could be utilised as a powerful tool to confirm value, and avoid net price erosion
  - In Spain, RWE acceptance is low as payers often do not trust the data

Current applications of RWE

MODERATE - "course correct" in certain markets only

CASE STUDY: ICER - US health system operates differently and, as such, the US could be the one market where RWE at launch may influence the price and access of a newly launched product. In April 2018, ICER (US' Institute for Clinical and Economic Review) in collaboration with the Office of Health Economics (OHE) **published guidance on improving the development and use of RWE for drug coverage and formulary decisions**.

Real world evidence will help to mitigate potential uncertainties with efficacy at launch

Given early development stage of innovation, several issues are anticipated at launch

1. **Controlled trial data:** Benefits only shown in carefully-selected patient groups in controlled trial settings due to small patient population indications and ethics surrounding placebo or double-arm studies *e.g. CTL019 (tisagenlecleucel (Kymriah)) was studied in 78 patients in a single arm, open label Phase II study*

2. **Short trial durations:** Endpoints will be short-term and surrogate; some innovation will be unable to prove that effect is curative/persists for duration of a patient's life as long-term monitoring is required; investment is required to validate these endpoints

3. **Small patient populations:** Breakthroughs occurring in gene therapy often have very small patient populations leading to poor statistical significance, and trouble identifying which sub-populations could benefit most

4. **Qualitative-based clinical endpoints:** In many neurological conditions, endpoints are often based on qualitative scoring systems e.g. pain, cognition etc. The actual benefit of a specific % increase in these scores is uncertain when applied to the real world *e.g. Alzheimer trials rely on qualitative measures of cognitive function/decline; migraine relies on subjective measures of pain relief*

5. **Unknown Technology:** No standards currently exist for many new products due to the novel technologies they are based on, raising uncertainty over long-term safety *(e.g. CAR-Ts, microbiome therapy, gene therapy);* recent launch of CAR-Ts in US will help pave the way for collection of RWE and enable safety monitoring

Generation of reliable RWE data requires a joint effort between stakeholders (including payers, manufacturers, academic institutions, etc.)

Imatinib (Glivec), as the first tyrosine kinase inhibitor launched with limited data, and has shown very positive long-term data

Case Study:

- Imatinib (Glivec), the first **tyrosine kinase inhibitor,** launched in 2001 for **treatment of Ph+ CML**
  - Now authorised for use in six indications which has triggered concerns about costs associated with expansion into orphan indications
- Prior to imatinib, 5 yr 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 on the basis of results from three single arm studies (Phase I and 2 Phase II)
  - Increased healthcare systems budget impact of CML by 120% in the UK and 73% in Germany
- Yet most EU markets recognised value and, despite incidences of delayed/restricted entry, patients were granted access
- Despite uncertainties at launch the investment in imatinib was rewarded
  - Longer-term data has shown: At 8 years: ~81% of patients were event free, ~92% were free of progression

TKI – tyrosine kinase inhibitor; Ph+ CML – Philadelphia chromosome–positive chronic myeloid leukaemia; IFN – interferon; SCT – stem cell transplant

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

Example:

- EMA has accepted real world data "where available evidence of efficacy required contextualization" or where uncertainties existed around "long-term safety and efficacy"
- RWE has helped in different ways as below:
  - **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 III trial and a specific set of matching parameters
  - **Was used to confirm a response rate in a single-arm trial**
    - For Yescarta, RWE was used for a retrospective patient-level pooled analysis of two Phase III randomized control trials (RTCs), 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 are: Biogen Inc.'s antisense oligonucleotide Spinraza (nusinersen) and Orchard Therapeutics Ltd.'s stem cell gene therapy Strimvelis

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

Case studies: G-BA and NICE to include RWE in their guidelines

Case Study: Germany increasing acceptance of RWE for HTA – starting with registry-based studies for orphan and other drugs assessment

- A new bill enacted by the German legislative process (*GSAV*)* in 2019, 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]

Case Study: 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
  - 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]

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

Valuing and rewarding innovation

Link - back to from innovation to access contents page

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

Key challenges for assessing value

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
- Challenges for HTAs arise from:
  - Use of inflexible criteria, e.g., are not able to adequately consider surrogate endpoints
  - Difficultly considering the longer-term benefits of a high cost therapy
  - Inability to adequately assess and incorporate value to broader society
  - Difficultly rewarding patient centred innovation from value added medicines (i.e., improvements in administration)

Case Study

Durvalumab + ibrutinib

Ipilimumab + nivolumab

Pembrolizumab + ipilimumab

- A key challenge is demonstrating the value of free dose combination therapies to secure an appropriate price
  - This challenge will be particularly pronounced in oncology, where list prices are anticipated to be significantly higher than their monotherapy components

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 innovation

- 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

MCDA: Multi-criteria decision analysis

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

New elements of HTAs have been introduced…

Case Study: Economic Impact HTA

- In 2013, the Commission d' Evaluation Economique et de Sante Publique (CEESP) – (a HAS sub-committee) 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

Case Study: MCDA HTA

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

- 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

E.g., NICE has adjusted the ICER threshold to enable access to higher cost drugs; PBS have updated the life saving drugs program

Updates to access conditions for select medicines include …

NICE National Institute for Health and Care Excellence

Case Study: NICE Cost-Effectiveness Thresholds

NICE has recently introduced a new ICER threshold for specific therapy types

- On 1st April 2017, NICE and NHS England introduced a new 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/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

PBS

Case Study: PBS Life Saving Drugs Program

Updates to Life Saving Drugs Program (LSDP)

- The Life Saving Drugs Program aims to provide subsidised access for eligible patients to expensive and life saving drugs for serious and rare medical conditions in Australia
- In January 2018, the LSDP was updated, with stricter but more transparent drug assessment criteria, excluding treatment for diseases with >1:50,000 prevalence

NICE is currently reviewing their health technology evaluation methods to account for more innovative products reaching market

Recent updates to access conditions for select medicines

NICE National Institute for Health and Care Excellence

Case Study: NICE revises evaluation methods of novel health technologies[1,2]

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

Expected implementation launch: October 2021

(1) NICE, July 2019; (2) NICE, Review timeline

NICE is undertaking this review at a time of unprecedented change in the healthcare system, where developments such as personalised medicine, digitalisation of health, and use of cell and gene therapy, mean products are becoming ever more challenging to evaluate.

Sir Andrew Dillon, NICE chief executive

… whereas IQWiG changed their approach to PRO data assessment; potentially driving change across Europe

Changing approach to evaluating QoL data

IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

Case Study: IQWiG adjusted their assessment method relating to PRO data evaluation[1]

The German HTA agency has specified new requirements regarding the PRO data being submitted for analysis, with regards to:

- **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)
- **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
- **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 so far limited trust in QoL data and increase their relevance in the future HTA evaluations in Germany**

…and potential next steps across Europe

As the discussions at the EU-level about **centralizing the clinical evaluation across countries are getting traction**, it will be interesting to see how the evaluation of QoL data will be taken into account

The EU is working towards a harmonised **Joint Clinical Assessment (JCA)** process to enable a consistent, comparative clinical assessment across members states; estimated timeline is ~2025

Additionally, Spain has announced its plans for a **consolidation of their therapeutic positioning reports** as part of a **revised HTA process**[2]

PRO: Patient-reported outcome; MID: Minimal important difference; ITT: Intention-to-treat; AE: adverse events; 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 patient 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

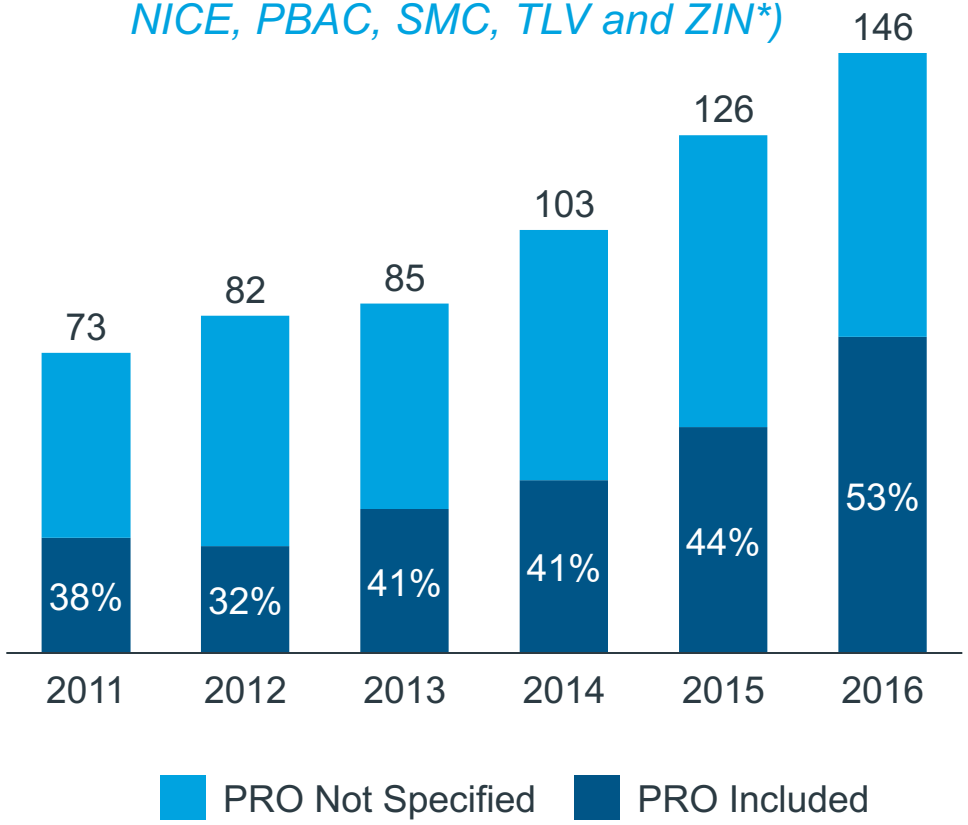
The actual **influence** of PRO data on HTA bodies varies, but use is generally **increasing** over time

- In **Germany, England, Scotland**, **70-80%** of HTA submissions include PRO data
- In **France**, PRO data is included in **<60%** of HTA submissions and only has a **very minor impact** on ASMR[1] rating

Consistent evaluation of PROs by HTA bodies, alongside pro-active planning of PRO endpoint development by manufacturers, will be important for acceptance of future innovations where the patient perspective is key

- ***E.g., PROs will be key for CGRP inhibitors for migraine or remyelinating therapies for Multiple Sclerosis given their lack of mortality endpoints***

Increasing use of PROs in oncology HTA submissions *(CADTH, G-BA, HAS, NICE, PBAC, SMC, TLV and ZIN*)*



ASMR: Amélioration du Service Médical Rendu (Actual Medical Benefit). French authorities assess drugs on an ASMR scale of 1-5; ASMR 1 is highest medical benefit; ASMR 5 is lowest

*CADTH (Canadian Agency for Drugs and Technologies in Health), G-BA (Gemeinsame Bundesausschuss), HAS (Haute Autorité de Santé), NICE (National Institute for Health and Care Excellence), PBAC (Pharmaceutical Benefits Advisory Committee), SMC (Scottish Medicines Consortium), TLV (Tandvårds- och läkemedelsförmånsverket), ZIN (Zorginstituut Nederland).

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

PRO acceptance seen in EU and US

Case Study: Move towards PRO acceptance

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

Case Study: Recent use of PROs in assessments

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 measure 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

OS: Overall Survival PFS: Progression Free Survival

In order to pay for innovation, several innovative models could be employed

Potential solutions: Innovative models to facilitate fair valuation

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 IRP inactive** in order to maintain a tiered pricing system

Pricing by Indication- and Combination

- In pricing by indication, evaluating a product for each indication would allow for a **more transparent pricing process, leading to a price that better reflects the value** the product delivers in clinical practise; this would also prevent the dis-incentivisation of innovation due to price penalties suffered at indication expansion
- **Pricing by combination indication** addresses the challenge that the value of products used in combination **is not simply the added value of the medicines used separately**; allows resolution of the complexities in assigning value and negotiating prices when different MA holders of drugs used in combination

Pricing by Performance (Outcomes-based Agreements)

- List price can be modulated based on collected real world evidence; this can enable **price** to **be increased over time**, if stronger efficacy is demonstrated compared to clinical trial data *(or decreased if the data indicates lower efficacy)*
- However, pricing by performance (PbP) will be difficult to achieve in the short-term; **a stepping stone towards PbP is paying for performance**
- **Paying for performance** involves modulating net price, **based on individual patient outcomes;** rebates or discounts will be 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 studies: ***Innovative payment models are starting to be implemented…***

Sofosbuvir (Sovaldi) and ADA gene therapy* (Strimvelis) have required 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

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

Examples of outcomes-based agreements

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

Voretigene neparvovec (Luxturna)	Case studies provided on slides 54
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. microbiome therapies, tracking readmission and recurrence)

Examples exist but Europe is lagging behind the US in terms of willingness to adopt these new models

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

Novel gene and cell therapies require new approaches; Zolgensma's entry into Germany was facilitated by an outcome-based pricing model

Case study: risk-sharing scheme for high-priced gene therapy

$2 mn.

ZOLGENSMA (Novartis) – SPINAL MUSCULAR ATROPHY

Following recent approval in Germany, Novartis is set to launch **Zolgensma**, a **gene therapy** for spinal muscular atrophy, in July 2020 priced at €1.945 mn.

Individual country discussions on gene therapy pricing (Zolgensma) and pricing model

- Following the US approval, the price of **Zolgensma raised concern in several EU countries**
- This concern highlights the **importance of having innovative payment models** in place and provides and example of how such schemes addresses cost concerns – such as seen in Germany
- Novartis Gene Therapy has signed **an innovative payment model for Zolgensma** with the GWQ in Germany – where Novartis Gene Therapy assumes the risk of repaying 100% of costs should the medicine not work, with a **similar scheme planned for the UK**

Note: GWQ (Gesellschaft für Wirtschaftlichkeit und Qualität bei Krankenkassen, Society for Efficiency and Quality in Health Insurance)
Source: Arrival of a ground-breaking gene therapy (2019)

… similarly, Luxturna and Kymriah adopted outcomes-based pricing models to reflect the step change in treatment paradigm

Case study: outcome-based pricing for CAR-Ts

Case Study: Luxturna pricing model[1]

LUXTURNA voretigene neparvovec-rzyl

- **Luxturna, a gene therapy,** is the first approved treatment for patients with **Inherited Retinal Disease** and has a current price tag of **$425k per eye**
- **Spark Therapeutics** enhances patient access in the US to **reduce risk and financial burden with a 3-step plan**:
  - Firstly, an **outcome-based rebate based on effectiveness at different points in time** (30 & 90 days, then 30 months) is offered
  - Secondly, **contracts are formed directly with commercial payers**, leaving it to them to negotiate appropriate payment with the treatment centres
  - Thirdly, Spark is working on a plan with the CMS* for **allowing payers to reimburse the treatment in instalments** spread over multiple years

Case Study: Kymriah pricing model[2]

KYMRIAH® (tisagenlecleucel) Suspension for IV infusion

- **Kymriah**, a treatment for **certain types of blood cancer,** was the first gene therapy approved by the FDA at a **price of $485k**
- **Novartis** has established **alternative payment models in multiple countries**, both in the US and Europe:
  - **In the US**, an outcome-based model was agreed with the CMS* for **full payment only if patients respond by the end of the first month** after treatment
  - Similarly**, in Italy**, an outcome-based payment scheme was established with AIFA**, **spreading payment over multiple instalments based on results at different time points only if the therapy is shown to be effective**
  - **In Germany**, a deal has been reached with a group of health insurance providers that requires **Novartis to partially reimburse the treatment if the patient dies of their illness within a set period of time**

(*) CMS = Center for Medicare & Medicaid Services; (**) AIFA = Agenzia Italiana del Farmaco
Source: (1) FiercePharma; Reuters; Spark Therapeutics (2) FiercePharma; MAP BioPharma; LinkedIn

Adapting financing models

Link - back to from innovation to access contents page

Current HC budgets are constrained to "silos" and are unable to adapt to finance new high cost / high-budget impact innovations

Challenges with current healthcare budgets

New Innovations

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

Challenges		Potential Solutions
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	**National Funding Schemes**
Funding Delays	**Patient outcomes suffer as a result of delaying patient access in countries where treatments are covered by 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 realised long-term**	**Annuity-Based Agreements, Subscription models**
Risk Exposure	**Current finance models provide upfront reimbursement, exposing healthcare budgets to risk** with little evidence of lasting benefit	

Spreading the cost of therapy and sharing the risk of treatment failure is crucial if healthcare systems are to be able to successfully provide access while rewarding innovation

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

Potential solutions: ***National funding models***

National Funding Schemes | Annuity-Based Agreements | Subscription payments

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 models

New UK Cancer Drugs Fund (CDF) – from 29th July 2016

- Enables rapid access to funds for innovative oncology products
- Managed Entry Agreements including a Data Collection and a Commercial Agreement will be negotiated; the Commercial Agreement will determine the level of reimbursement, and must ensure cost-effectiveness
- If the annual CDF budget is exceeded, all CDF-funded manufacturers must rebate the CDF, pro-rated based on CDF-spend

National Loan to Regions, Hepatitis C, Spain

- To enable the Spanish regions to pay for the new Hepatitis C medications, a “Hep C national strategic plan” was developed
- This constitutes a loan of €727M which is distributed to regions over a period of 3 years, to be paid back interest free over ten years

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

Annuity-based agreements can be used to stagger payments; combining both annuity and national budgets will be vital

Potential solutions: ***Annuity-based agreements***

National Funding Schemes | **Annuity-Based Agreements** | Subscription payments

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

- Payments made to the manufacturer over the **expected duration of a treatment's therapeutic effect**, with payments ending when treatment is no longer effective
- Allows the **risk of failure to be shared** with manufacturers and upfront payments to be reduced
- **Insurance** can be bought to counter the risk such models pose to fund, especially if upfront costs remain somewhat high or if the long-term outcomes remain uncertain

Examples

- GSK's Strimvelis for severe combined immunodeficiency - under agreement with Italian Medicines Agency (2016), payments are staggered over a set timeline for each patient; if drug does not demonstrate a sufficient curative benefit, GSK returns a part of the reimbursement[1]
- Bluebird's Zynteglo for beta-thalassemia – company offers (2019) to spread total cost over 5 years, and if the treatment is unsuccessful only first instalment is charged for administration cost[2]

Over-time payments can apply particularly to novel cell therapies (e.g. CAR-Ts) and gene therapies, characterised by high upfront cost (related to one-off treatment) and high clinical uncertainty

(1) Cell & Gene; (2) PharmaPhorum

*"We need a system where we pay annually so the insurance companies can pay over time and share the risk" – **DE KK Payer***

Subscription payments are another innovative payment model that could be applied for curative HBV and HIV therapies, among others

Potential solutions update: ***Subscription payments***

National Funding Schemes | Annuity-Based Agreements | **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[5]
- May help payers predict the budget impact associated with treating patients in a given disease area and **ensure its sustainability in the long run[1]**
- Model differs from lump-sum payments, where a fixed amount is paid for a given volume

Examples

- NHS England offered Vertex Pharmaceuticals a subscription payment model comprising a **guaranteed sum** for **unlimited access to their existing and future cystic fibrosis therapies over a defined time period**; although the exact terms and conditions are confidential, Vertex has since entered into portfolio-based agreements in the UK and Denmark[2;3;4]
- Previously model has been successfully used in the US - Washington is leveraging subscription- based deals to on their way to eliminate HCV prevalence in the state by 2023

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

(1) EFPIA, Novel Pricing and Payment Models: New solutions to improve patient access; (2) ISPOR; (3) Pharmaceutical Technology; (4) NHS signs agreement with Vertex; (5) Decision Resources Group

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

Potential solutions update: ***Subscription payments***

National Funding Schemes | Annuity-Based Agreements | **Subscription payments**

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]


PharmaTimes online

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

Share

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

10m deaths by 2050

Costing £66 trillion

Print Friendly

(1) Pfizer; (2) Pharma Times; (3) BMJ;

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-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]

(1) USC Schaeffer;

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

Developing infrastructure to support care delivery

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

Logistical considerations will be important

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

Infrastructure Required for Delivery

	Manufacturing Plants	Logistics	Specialist Centres

Cell / gene therapies	• 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, 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))

AD**	• *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; ** Alzheimer' s Disease

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

Alzheimer's Disease – The need for early disease diagnosis

- The burden of Alzheimer's disease 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 AD diagnosing; therefore HCS should focus on increasing the access to diagnostic tests before the DMTs become available**

(1) Alzheimer Europe Yearbook 2019; (2) NCBI; (3) EFPIA - Alzheimer's Disease Health System Readiness – The Time to Act is Now
(*) MCI – Mild cognitive impairment

For other innovations, restructuring care pathways will be required to accommodate the influx of patients that were sub-optimally treated

Redesigning care pathways and care hubs will be key

Certain innovations (e.g. in migraine, NASH, HBV and HIV infections) will enable treatment of a large number of patients who have otherwise not had access to therapy

Restructuring Care Pathways

	Specialist Centres	New Care Pathways
Migraine	• Currently, up to 50% of migraine sufferers do not seek medical support, partly driven by being refractory to treatment • A new mechanism of action and higher efficacy will likely access a new cohort of patients • HCS may need to develop specialist hubs, where new therapies are prescribed, to improve pathway efficiency	• Specialist centres should be incorporated into a modified patient pathway – The pathway should enable better communication between GPs and secondary care specialists to enable smooth patient transition between settings
NASH	• Due to high potential patient numbers, prescribing is likely to be in specialist centres, to manage prescribing and ensure relevant expertise is available	• New NASH therapies will increase patient care pathway throughput, due to awareness, greater treatment and more follow-ups • Clinics may need to re-visit pathway design to cope with increased numbers
Curative Tx for HBV/HIV	• For curative therapies to be successful (i.e., to eliminate the diseases completely) large number of patients needs to be tested and treated • Dedicated centers to treat chronic HBV and HIV infections would allow to effectively manage diagnosis and prescribing process	• The focus of adapting the care pathways for HBV and HIV once curative Tx are available should be on identifying the eligible patients – the share of undiagnosed patients in these indications is still considerable; engagement of specialists in ensuring compliance

*'I would suspect that the current set up is not going to be tenable in the long-term, and prescribing of CGRP inhibitors will be centralised in hubs. I expect that only certain specialists will be able to prescribe the drugs – **UK Neurologist***

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

Potential solution: Joint Investment in Centres of Care

Joint Public-Private Investment

Centres of Care Excellence

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

Manufacturing

- In order to limit logistical difficulties, manufacturing facilities of CAR-Ts and cell therapies could occur at centres 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 centre of excellence

Logistics

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

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***

Some centres of excellence have already been set up to increase expertise and efficiency in delivering innovative care

Centres of Excellence include

Centres 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 160 onsite specialists across the cell and gene therapy life cycle, to help companies to perfect their manufacturing processes and scale up quickly
- Cell and Gene Catapult has been backed by more than £60m in government funding
- It is already working with four biotechs – Autolus and Cell Medica (CAR-Ts), AdaptImmune (T-cell therapy) and Freeline (gene therapy for haemophilia) – to conduct research and pivotal trials

Centres of Excellence: Alzheimer's Disease Early Detection

Karolinska Hospital, Sweden

- At the Karolinska Hospital, a new Highly Specialised Cognitive Reception (HSCR) is in process of being 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 decision to set up the HSCR was taken by the Stockholm Health Board in 2017, with plans to open at the Karolinska hospital by mid 2018
- 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

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 setting

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]**

(1) CAR-T Treatment dynamics and funding, IQVIA November 2019; (2) EMA; (3) AJMC; (4) Cancer Therapy Advisor; (5) Med City News; (6) Healio
(*) Joint Accreditation Committee ISCT-Europe & EBMT; (**) Intensive Care Unit

Optimising patient management/ treatment strategies

Link - back to from innovation to access contents page

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

Providing care through ongoing clinical trials is becoming more important; stakeholder awareness will be vital to deliver success

HIV is one area where clinical trials have been used to deliver care

Clinical Trials to Provide Care

- Using clinical trials to deliver care for innovative technologies will become increasingly important in the future
- This change in the paradigm will be driven by three key factors:
  - Technologies will require increased medical expertise to administer care: trial investigators can offer this expertise
  - Care pathways will become more complex; clinical trials will help to simplify these pathways
  - Capacity (especially in UK, Nordics) will become more constrained
- To ensure this shift is successful, it will be necessary to effectively communicate ongoing clinical trials to the relevant stakeholders and update clinical guidelines to include trial options

Case Study: HIV

Emtricitabine/ tenofovir disoproxil fumarate (Truvada)

EMA awarded approval for emtricitabine/tenofovir disoproxil fumarate (Truvada) indication expansion from HIV treatment to include HIV PrEP in July 2016*

- At present, emtricitabine/tenofovir disoproxil fumarate for PrEP is not routinely commissioned in UK due to concerns over budget and NHS England demand for CCGs to provide commissioning
- A High Court ruling in November 2016 meant NHSE is obliged to give consideration to PrEP, but does not guarantee PrEP funding
  - NHSE will provide £10m over three years to fund a clinical trial (n=10,000), to resolve implementation concerns
- The trial will serve to provide temporary access to emtricitabine/tenofovir disoproxil fumarate in England, for those patients eligible for the trial

*PrEP – Pre-exposure prophylaxis

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 AD

- 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

- The number of oncology combinations is growing at a very fast rate
- Guidelines will not be able to keep up with the pace of combination 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

Treatment Strategy

PPAR/FXR agonists for NASH

- PPAR/FXR agonists represent a new treatment option for NASH patients, where previously no treatment was available
- With these new therapies, a fundamental shift in how NASH patients are screened, triaged and treated will be required
- Guidelines will need to be updated to enable physicians to incorporate good clinical practice into their treatment
- Physicians will also have to change the way they approach treatment of severe NASH patients
- Patient education programs are also required to increase awareness of NASH as a valid disease

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	Guideline Revision	Treatment Strategy
Remyelinating therapies for MS	**mRNA vaccines**	**Curative therapies for HBV and HIV**
• 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	• 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 first (1) maximise patients access to anti-SARS-CoV-2 vaccines and secondly (2) to facilitate the development and authorisation of mRNA vaccines in other TAs after the pandemic	• Curative therapies for chronic HBV and HIV infections have potential to completely eliminate these conditions • To achieve this, significant number of patients need to be tested and treated once the cure is available • Therefore, the associated short-term cost for treating HBV and HIV may be high (when both newly diagnosed patients and currently treated patients are included) • However, previous learnings from introducing antiretrovirals and from HCV therapies show that incurring this cost in a short-term may translate into even higher benefits in the long run • Novel payment models can also be investigated (e.g. subscription-based) to make budget planning more predictable

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]

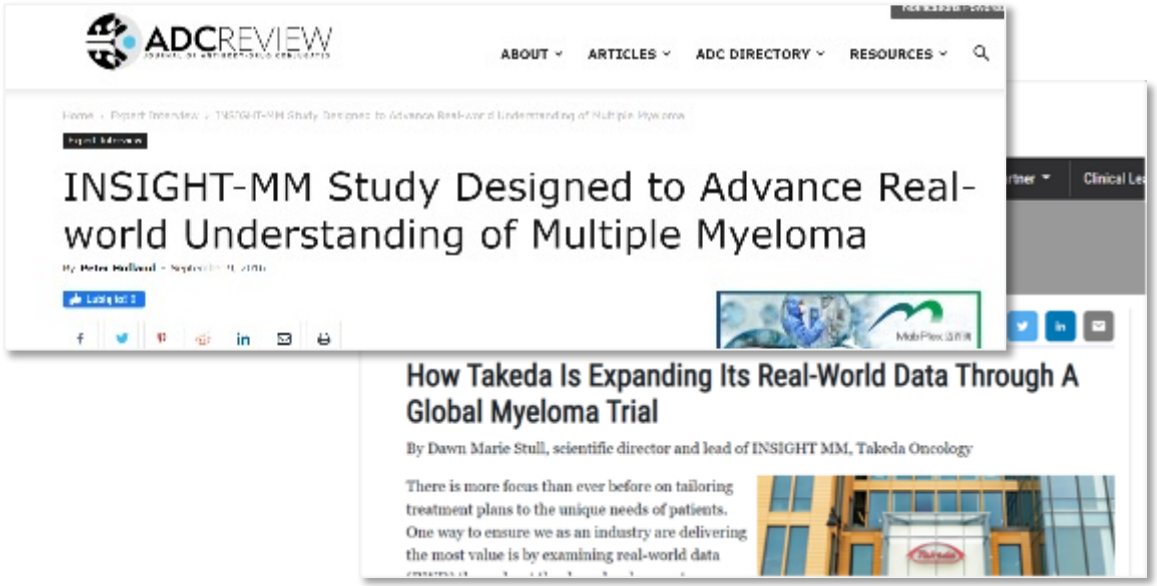
- Rare diseases, such as multiple melanoma (MM), **often lack large data sets due to the scarcity of patients**
- Hence, HCP decision making is **based on limited evidence**, compromising the quality of care for rare disease patients
- **INSIGHT-MM** is the largest, pharmaceutical-company-sponsored global 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

Use in regulatory activities: FDA[3]

Following a recommendation from American Association for Cancer Research**, FDA should use real world evidence from studies such as INSIGHT-MM** and others to refine information on efficacy and tolerability of MM therapies on patient sub- populations under-represented in clinical trials[3].

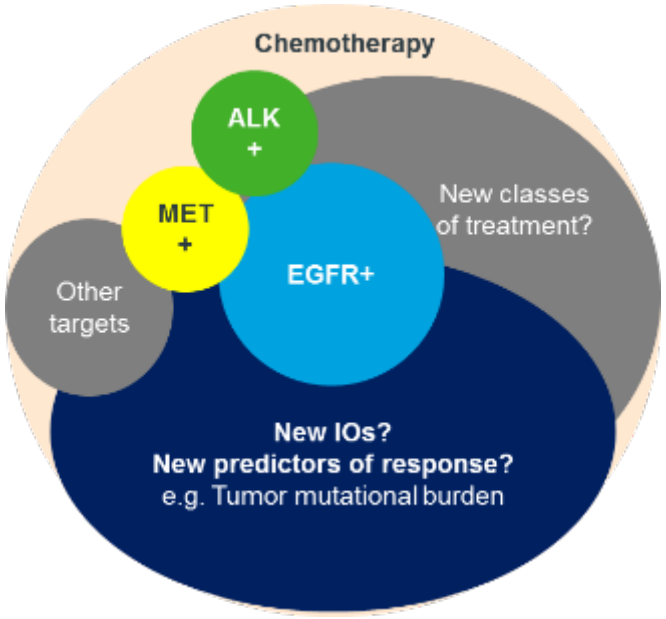


Source: (1) Takeda, (2) ClinicalTrials.gov; (3) AACR

At least in oncology, treatment is becoming increasingly complicated; paradigms may need to shift to being more holistic

Evolution of treatments will mean greater collaboration is required to properly integrate into care

Potential Future Treatment Paradigm in 2L NSCLC



- In context of oncology, the treatment pathway is becoming less defined
- There is becoming less focus on site-specific mutations / biomarkers, and more focused on 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

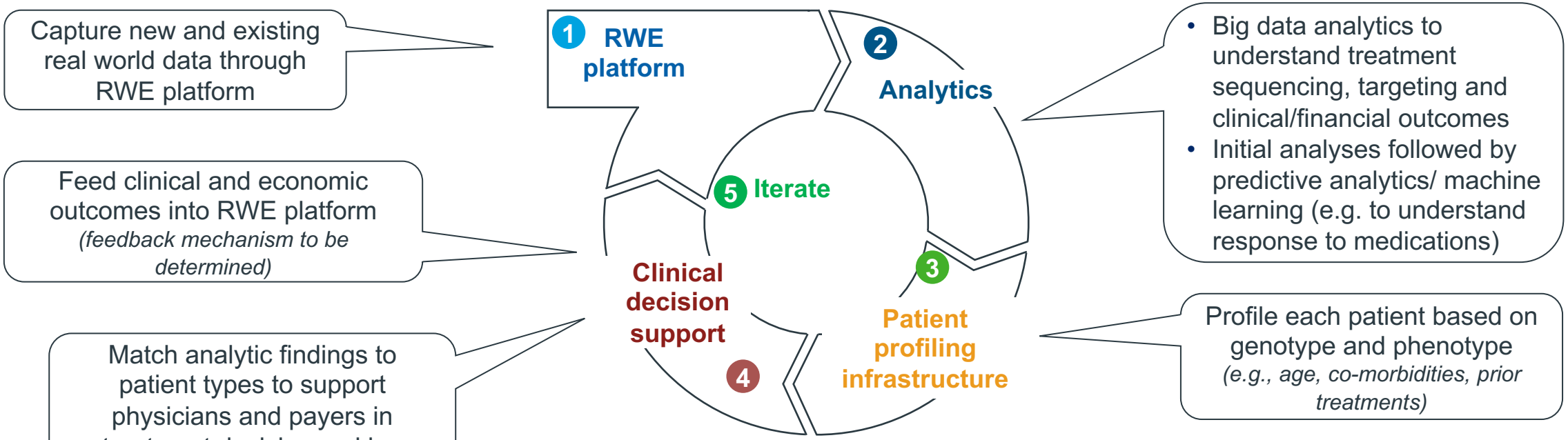
A tumour is not made up of all cells with the same types of mutations. A single tumour can have cells with several different types of mutations
MSI-H = Microsatellite instability-high; **dMMR** = deficient DNA mismatch repair

Enabling data science and technology partnerships

Link - back to from innovation to access contents page

Data generation driven by stakeholder collaboration can be used to improve HC, from patient profiling to clinical decision support

Data generation supports increasing use and generation of Health Data



Collaborative Effort

Providers	***Payers***	***Tech/data***	***Manufacturers***
EMR data, expertise, infrastructure	Claims data, funding	Data, analytics, technology	Data, expertise, funding

Increasing data availability is driving change across stakeholders, leading to many new possibilities, with some yet to be imagined

Payers

CVS Health IBM Watson Health

IBM Watson

CVS Health & IBM Watson predicting declining health risk

Tech companies

Memorial Sloan Kettering Cancer Center

IBM Watson

Memorial Sloan Kettering training IBM Watson to develop a tool that can help medical professionals choose the best treatment plans for individual cancer patients

Providers

Genomic Health LIFE. CHANGING.

OncotypeDx predicts response to chemo for breast cancer patients based on DNA analysis

Manu-facturer

Roche + flatiron

Pfizer Healthcare Hub Igniting Innovation

Pharma companies improving discovery and R&D productivity

New Products and Services

Crowdsourced Drug Development
New biomarkers and therapeutic candidates, or recycling of existing drugs through analysis of large genotype & phenotype datasets

Custom Treatment Solutions
Third-parties identify gaps in treatment and develop new algorithms and patient-management solutions independent from pharma and current providers

Tailored Pricing and Coverage
Personal insurance plans that best match their needs and risk profile in premium, benefit type, OOP max, term lengths, provider organization, with varied payment schemes

Improved Outcomes
Wearables and digital tests (via phone apps) allow 3rd party innovation in monitoring treatment and symptoms at the patient-level

Microbiome therapies have opened gateways to new research and partnerships- Takeda, Pfizer, and Bristol-Myers Squibb have signed generous partnerships with microbiome companies. With new advances in machine learning and diagnostic techniques, microbiome research will keep growing and becoming more precise

- Example: Novartis plans to use data science to drive more of their decisions and programs—including medicines—which would be digitalized (NVS commercial team is working with Pear Therapeutics to develop apps for multiple sclerosis and dissociative disorders and to commercialize an app for substance abuse disorder)

However, in Europe, regulations, guidelines, payer awareness and physician acceptance are currently limited

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

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

Key Hurdles

Payer 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

Physician Acceptance

- Physicians are generally **not** aware of specific technologies to help them in their specialism
- Where they are aware, physicians are unwilling to accept them, as outputs may be generated without clear rationale, and physicians may not be willing to relinquish responsibility

These hurdles are limiting further incorporation into the clinical setting

Standardising national and international policy will be needed to set clearer targets and guidelines for all stakeholders

Four policy elements will be vital for success (1/2)

National and international policy is needed to ensure quality data can be readily generated and accessed for analysis

Standardised Definitions

- *Current regulation and policy at national and international level on these new data technologies is generally limited or unclear*
- Better defining data types and analysis platforms will help to improve transparency and enable stronger regulation
  - The FDA recently published draft guidance (Dec 2017) 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

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

Improving data generation and access policy will improve overall data quality, allowing insights to be more accurate and relevant

Four policy elements will be vital for success (2/2)

Data Generation and 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

Improvement in quality of data and better access to health data will improve strength of analyses and accelerate clinical developments in this space

GDPR = **General Data Protection Regulation**; new EU legislation to replace the existing data protection directive and establish one single set of rules across Europe; one implication will be that a legitimate purpose will be required to capture data

Collaboration is key to ensure the development of data capture systems given the numerous challenges they present

Physicians

- *Physicians need to be open to using 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

"The average oncologist already spends a lot of time with bureaucracy; inputting data, filling out prescriptions etc. only a few of us keep detailed records" – ***Italian Oncologist***

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 real world data (RWD)

"[We need to start] looking at patient-level data in more detail, it is currently not available and therefore we are not using it [during decision making]" – ***UK CCG Commissioner***

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*
  - *Introduction of GDPR in May 2018 will further increase importance of relevant data collection*
- The systems required to capture RWD vary depending upon the setting in which they are offered and the variables under observation

GDPR = **General Data Protection Regulation**; new EU legislation to replace the existing data protection directive and establish one single set of rules across Europe; one implication will be that a legitimate purpose will be required to capture data

Increased payer engagement, manufacturer investment and academic involvement will be vital for use of new data technologies

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

Greater collaboration between stakeholders is required to overcome development and implementation hurdles; overcoming these will enable HCS to better cope with innovative, impactful therapies

EFPIA is promoting the standardisation of data collection and health outcome measures to build relevance and utility for the future

The Issue

- Currently, the ability of healthcare systems to scrutinise the effectiveness of different healthcare interventions and understand best practice is limited
  - These limitations prevent systems making effective decisions
- To be able to better make these decisions, 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

- Improvements in data collection, through systemic improvement in data availability, capture and storage, will provide a platform for better use of an outcomes-based decision approach
- However, a standardised set of health outcomes measures for all diseases and conditions will need to be defined
- This should be done in collaboration with patients as well as with data collectors (such as Healthcare Professionals), and will allow for systematic measurement and comparisons across providers and countries

The Cause

- There are two overarching reasons for HC systems currently not using an outcomes-based approach:
  1) Data collection systems and infrastructure are not yet sufficiently advanced to collect the correct data
  2) Outcomes are not yet well defined; outcomes measured for a disease can vary between countries, and even within countries

The Outcome

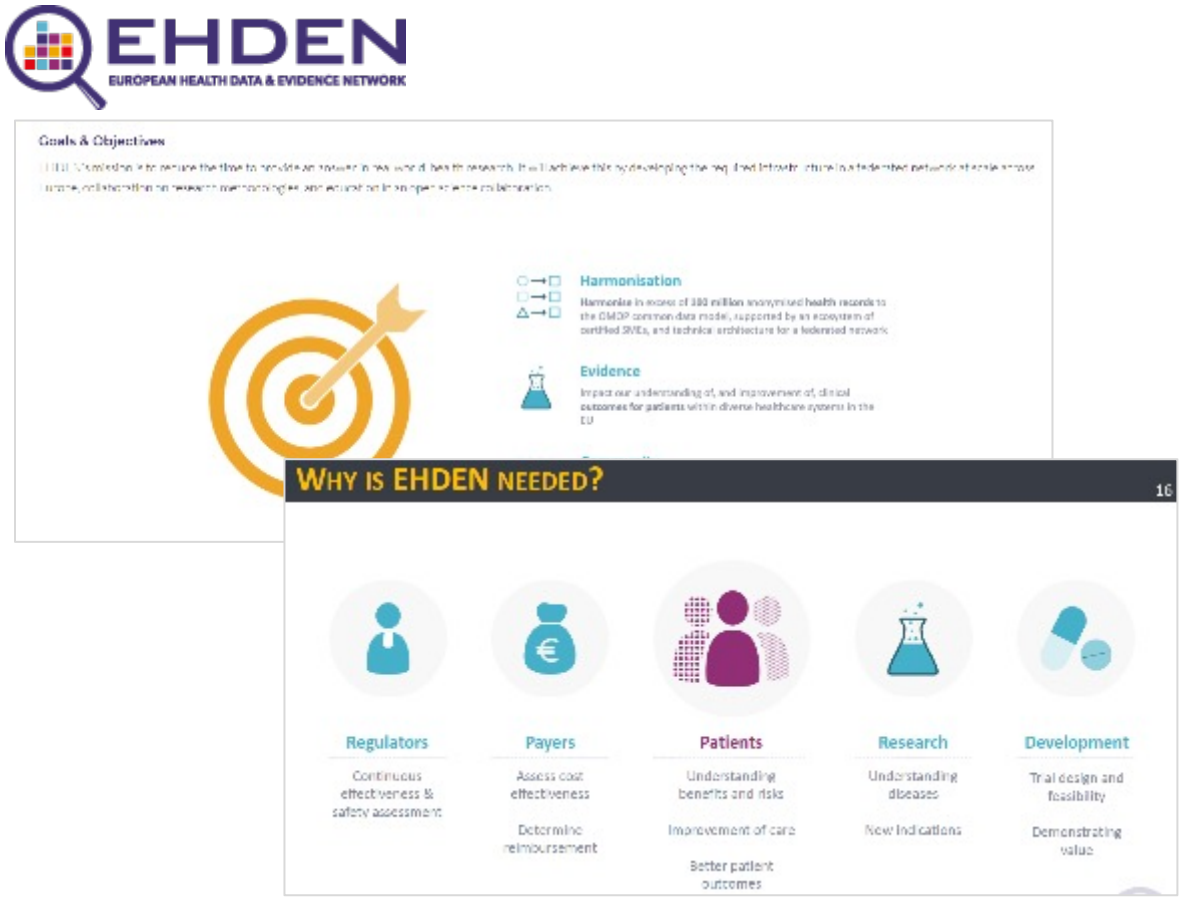
- With more information about how different interventions actually compare in terms of health outcomes for patients, healthcare managers and policymakers will be able to make more informed decisions on implementing clinical practice and resource allocation
- This will create better patient outcomes and improve the value for money healthcare systems receive

Cross-industry actions are needed to ensure this data is used in optimal, efficient way

EHDEN: facilitating cooperation from European HI through data exchange and analysis*

CASE STUDY: EHDEN (European Health Data and Evidence Network)[1,2,3]

- The current challenge related to RWD is now no longer about data availability – it is about defining a unified, optimal approach to utilising and generating insights from large amounts of real world data coming from diverse sources and study types
- EHDEN is a cross-industry initiative of 22 partners who will work together until 2024 to **create a large-scale, standardized network of data sources** to harmonise around **100 million 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



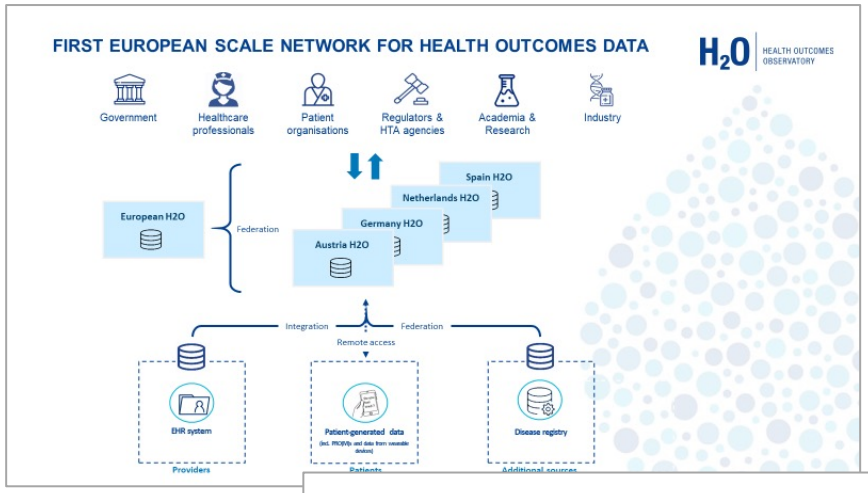
(1) From EMIF to EHDEN: scaling up the big data ecosystem across Europe, 2020; (2) EFPIA Guest Blog; (3) EFPIA; (4) EHDEN
(*) HI – Health Institutions
https://www.ehden.eu/

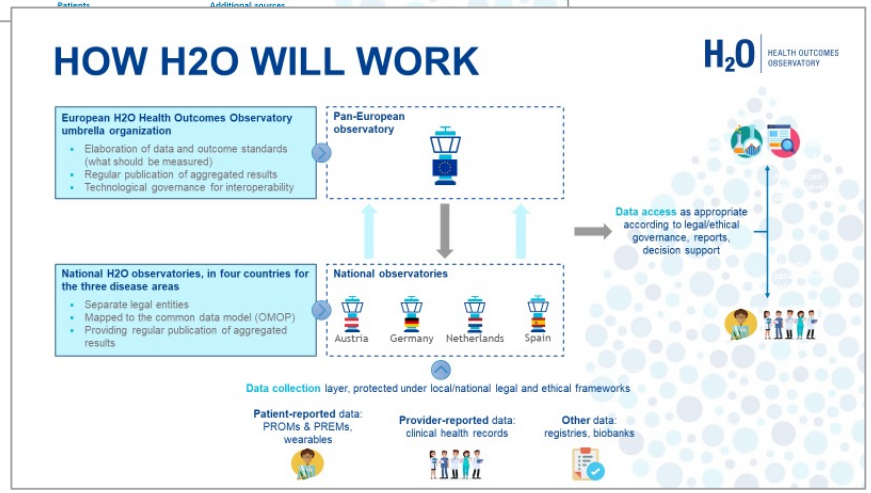
The IMI H2O project sets up "outcomes observatories" in EU countries to collect standardised patient reported outcomes

H2O: collecting patient reported outcomes in selected disease areas

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** both in their own healthcare and in healthcare systems more broadly
- The observatories will work by **providing patients with digital tools**, including an app, to report their health outcomes
- The **data will then be anonymised and tracked** so that individual patients and their clinicians can compare their progress with other patients with similar health issues.
- The project will focus on setting up observatories in **4 countries** (Germany, Spain, the Netherlands, and Austria) covering: **diabetes, inflammatory bowel disease, and cancer**. In the longer term, the project hopes that more observatories, covering a wider range of disease areas, will open up across Europe.





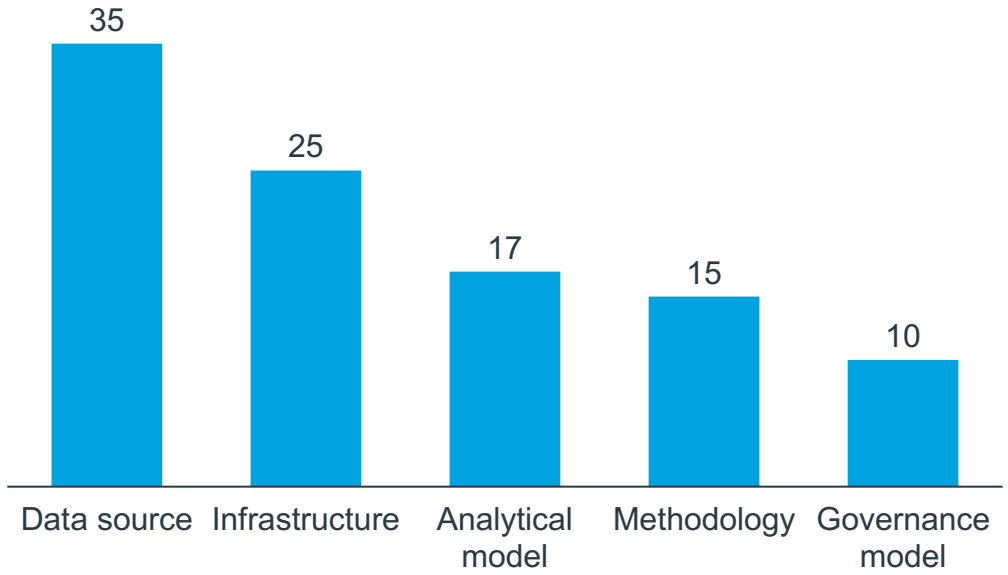
(1) https://www.imi.europa.eu/projects-results/project-factsheets/h2o

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), among others
- Of these initiatives, **5 key topic areas were identified**:
  - **Data source**: database linkage, unique 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, code of conduct
- 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

Source: BMJ article

The AIFA and DAWN patient registries collect patient, to allow tracking of prescriptions, test scores, appointments and outcomes

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
- The system is able to deliver RWD in a robust and timely manner; in November 2015 AIFA was aware that the terms of the agreement with a manufacturer concerning two drugs for Hepatitis C had been breached within five days

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 CCGs have already procured 4s DAWN, to aid in anti-TNF and multiple sclerosis patient monitoring

EUResist and the Rare Diseases Registries Programme collect patient disease data to increase access for research and treatment

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]

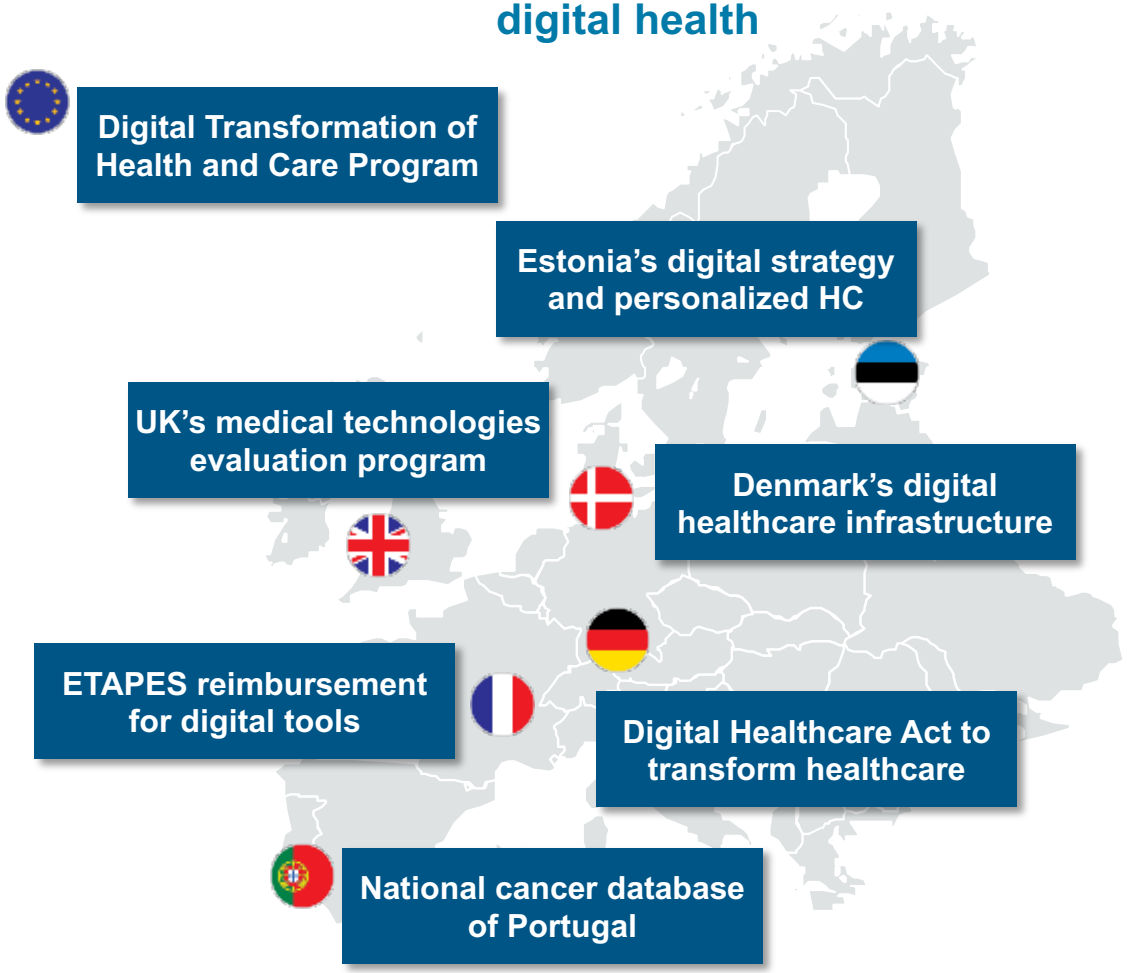
Digital Health area	Blockchain initiatives for clinical discovery	Innovations in clinical development	Patient monitoring solutions	Leveraging Big Data	Other
Examples	**Melloddy** – using predictive Machine Learning models on decentralised data of 10 PharmaCos to increase efficiencies in drug discovery[2] **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

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

Horizon scanning and stakeholder dialogue

Link - back to from innovation to access contents page

Horizon scanning will be vital for payers and providers to ensure awareness is high and that new innovations are planned for

Horizon scanning is becoming increasingly important

Problem

- Hepatitis C drugs (such as sofosbuvir) and immunotherapies (such as pembrolizumab) took some healthcare systems by surprise
- Prices were not adjusted to cover their impact, and has resulted in short-term concerns over affordability
- In the future, disruptive innovations have the potential to impact healthcare systems in similar ways, both in terms of step changes for patients, health system organisation and budget impact

Solution

- Horizon scanning will enable better prediction of the impact of new or pipeline drugs on the healthcare system
- Understanding the potential impact will enable HC systems to appropriately plan for innovation entry

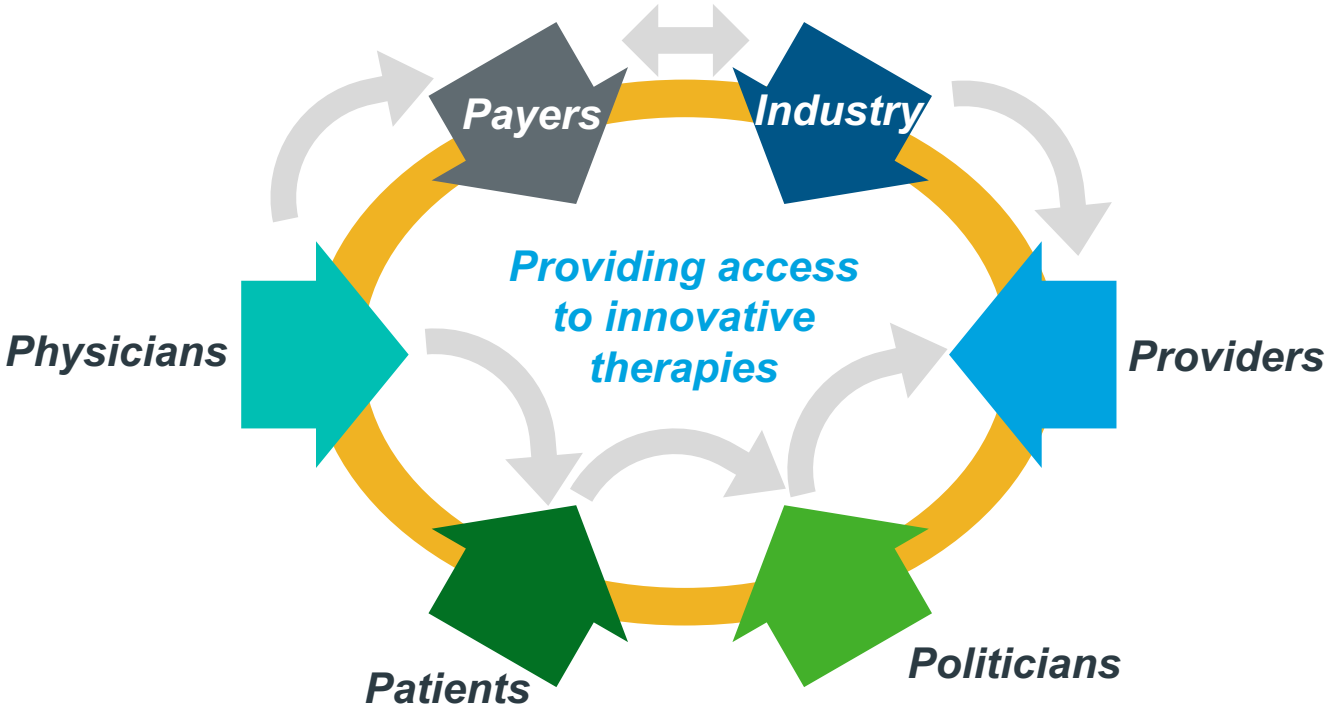
For example:

UK PharmaScan

- In the UK, PharmaScan was set up as a secure horizon scanning database populated with information on new medicines in development for launch in UK
  - It considers medicines up to three years before their launch, or start of phase III clinical development, whichever is the earlier
- Run by NICE, >120 registered manufacturers provide information on all new medicines, indications, formulations and in-licensed medicines
- This mechanism allows the NHS to effectively plan budgets and services according to customers' needs
  - NICE, NHS England, SMC, AWMSG, and NI Health and Social Care Board all use this information

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)*

Thank you!