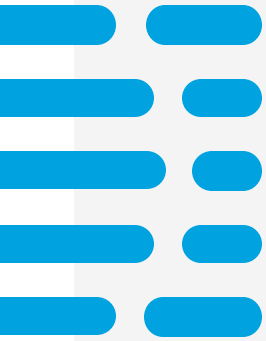




# 2024 Pipeline Review – Innovation for Unmet Need

*Final Report*

December 2024



# Table of Contents

- + **Global Disease Burden Overview**
- + R&D Pipeline Overview
- + Innovation Case Studies

# The global burden of disease is evolving, reflecting a balance of complex drivers

## Ageing population

The number of people over 65 is expected to double by 2050, driving complex comorbidities and increased susceptibility to infectious and non-communicable diseases

## Climate change

Climate change impacts air quality, water & food supplies, and affects the geographic distribution of infectious diseases

## Anti-microbial resistance

Use and misuse of antimicrobials in humans, animals, and plants is driving drug-resistant pathogens

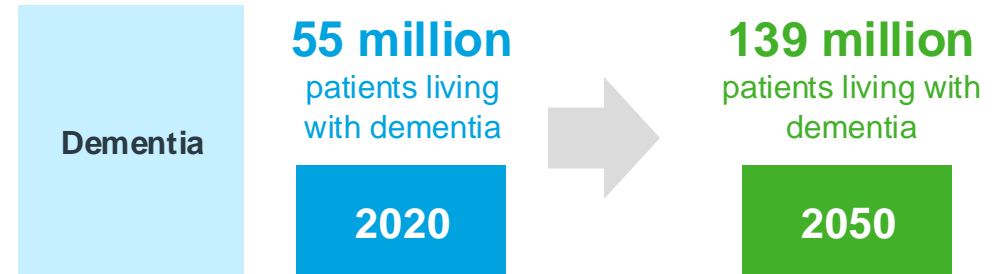
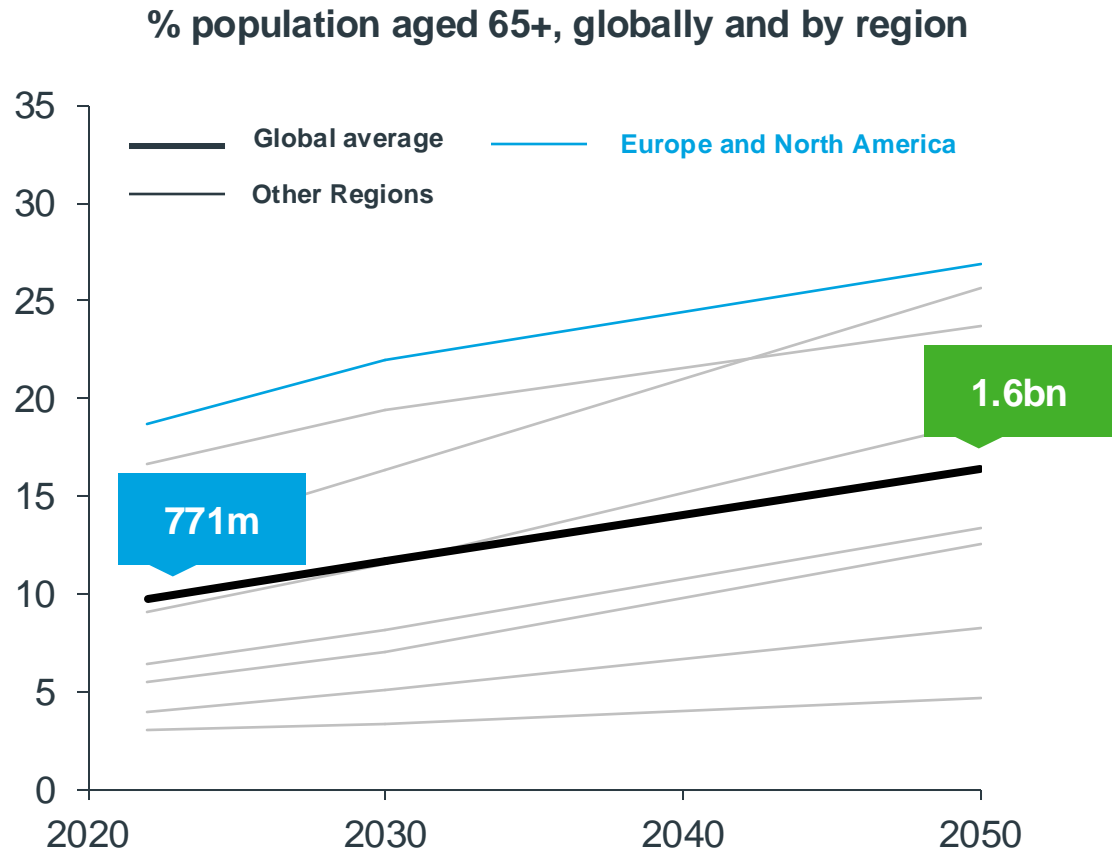
## Lifestyle choices

Evolving habits in smoking, alcohol, food, drug consumption, and global travel underpin many disease trends

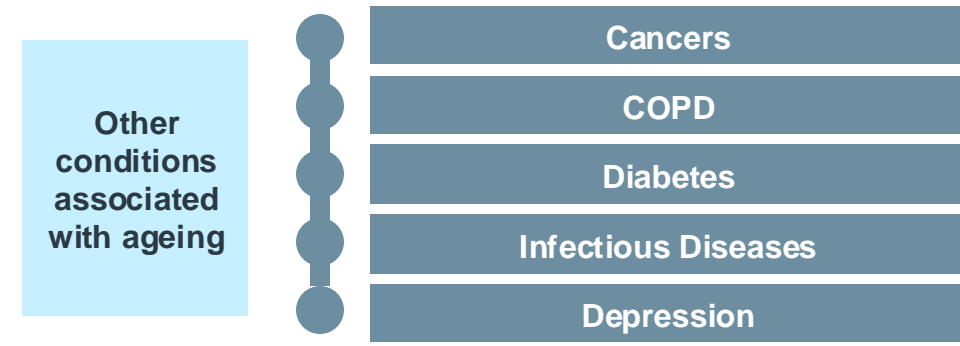
## Health system capacity

Many healthcare systems are facing capacity, workforce and skills constraints, impacting access to medicinal products for preventative and treatment purposes

# The number of people over 65 is expected to double by 2050, driving increases in dementia, diabetes, COPD, and depression and cancer



*Despite R&D efforts, few significantly disease-modifying treatments*



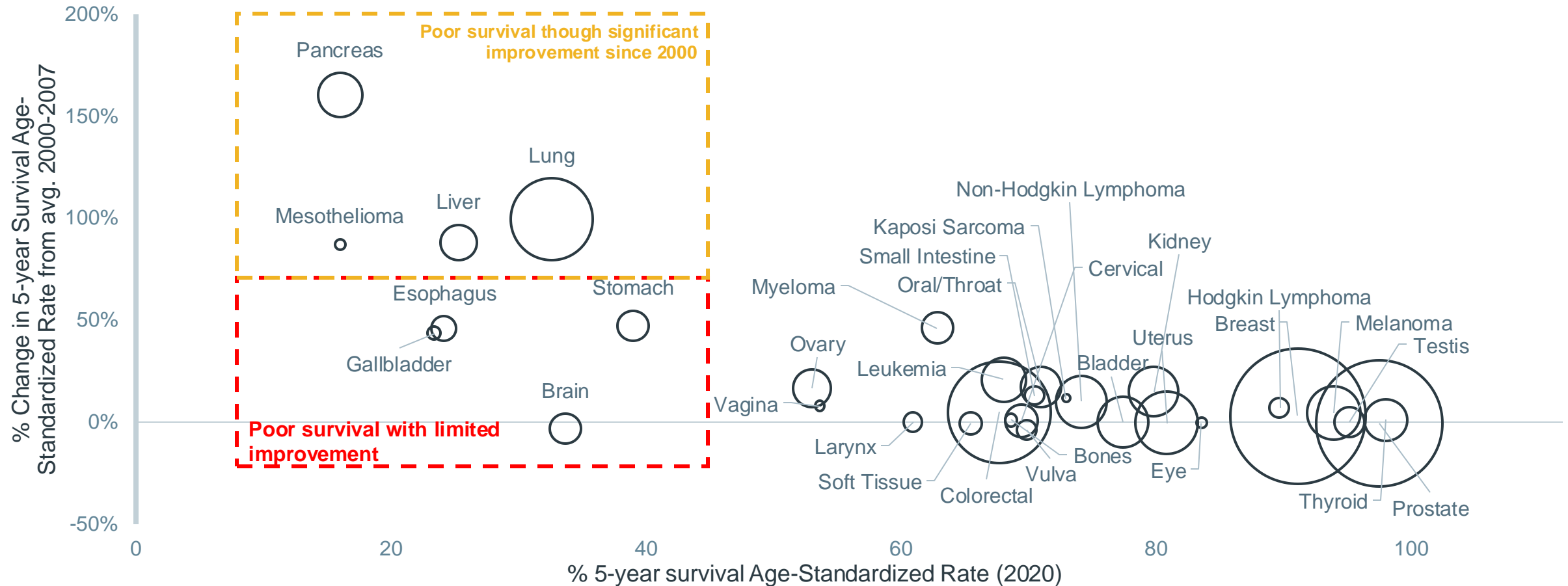
*Often developed as co-morbidities*

Age-related diseases are leading to significant increase in patient burden, alongside major healthcare and societal costs

Source: United Nations Department of Economic and Social Affairs, Population Division; Alzheimer's Disease International; WHO.  
COPD: Chronic Obstructive Pulmonary Disease  
2024 Pipeline Review – Innovation for Unmet Need

# Despite treatment improvements in the last ~20 years, many cancers continue to see low survival rates

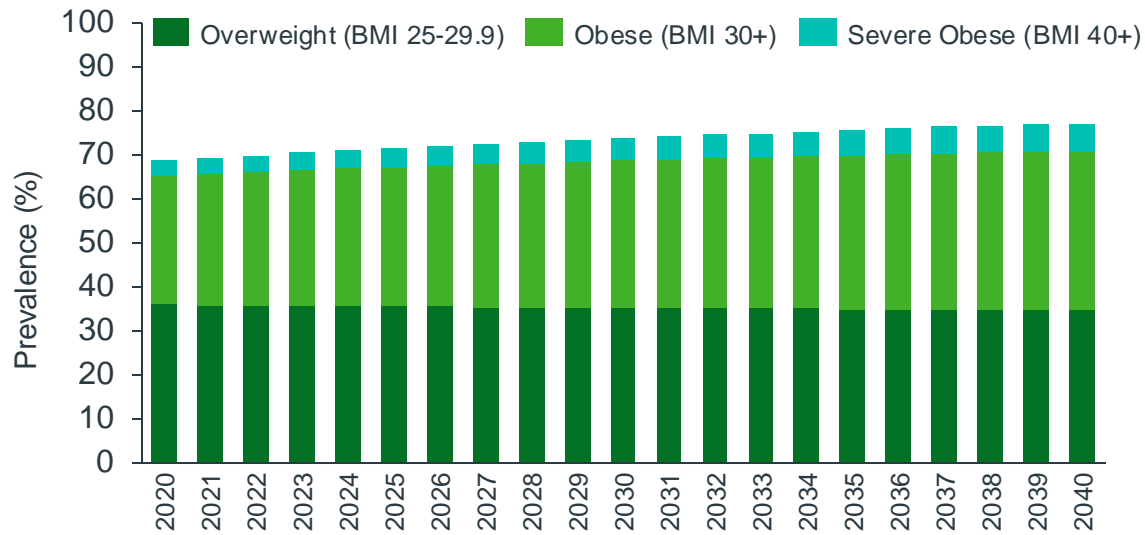
U.S. 5-year age-standardized survival in 2020 and % change from 2000-2007 average



In addition to poor overall survival, treatment tolerability and QoL are key to assessing overall burden

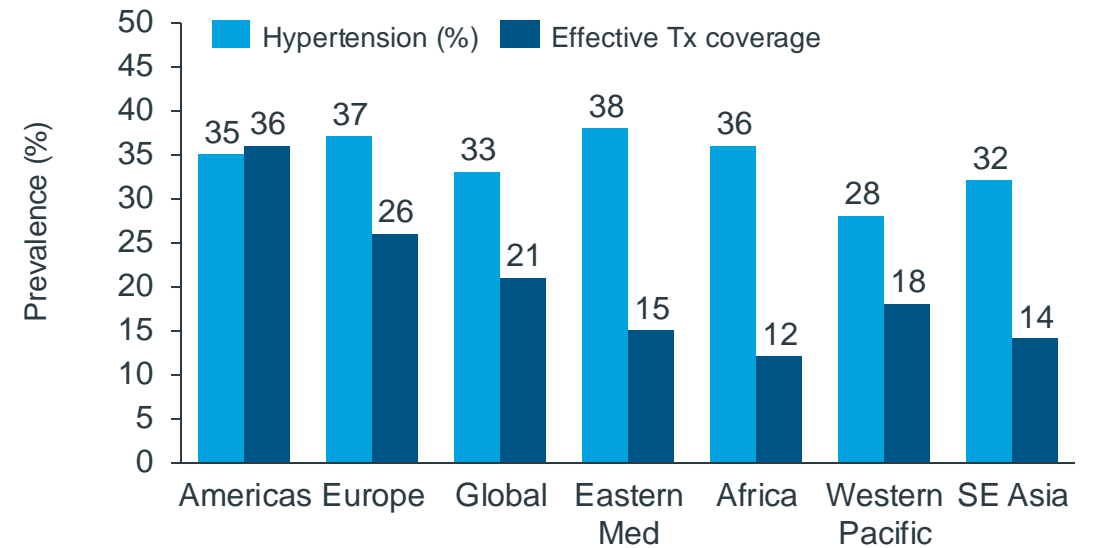
# In many countries, obesity is forecast to increase, and cardiovascular conditions (e.g. hypertension) are uncontrolled, with poor health outcomes

Overweight and obesity prevalence projections for adults (aged 16+) in the UK



- 21 million UK adults living with obesity by 2040, which equates to almost 4 in 10 of the UK adult population (36%)
- This risks major societal impact; the number of people who are living with obesity could overtake the number who are a healthy weight in the UK by 2040.

Hypertension prevalence and 'effective Tx coverage' by geographic region



- 1 in 3 adults have suspected hypertension in nearly all global regions, which is a major underlying driver of ill-health and mortality
- Effective treatment rates are particularly low in Eastern Mediterranean, Africa and SE Asia, however this is a global issue

New treatments – and policy levers - can help address the challenges of obesity and cardiovascular disease

# The burden of mental health issues across the European population is profound and multi-faceted

Approx. **1 in 6** people in the EU suffer from mental health issues. This translates to

**>84 million**  
people affected

## Patients

- Patients suffer from **social isolation, reduced ability to work** or study, and overall lower life satisfaction
- Mental health issues contribute to nearly **20% of all years lived with disability (YLDs)<sup>2</sup>**.
- Patients face barriers to accessing mental health care incl. **stigma, lack of awareness, financial constraints**

## Healthcare systems

- Mental health issues lead to a **high demand for healthcare services** including psychiatric care, counselling, and emergency services
- **Direct healthcare costs equate to €190 billion (1.3% of GDP)<sup>3</sup>**
- Shortages in mental health professionals can lead to long waiting times for patients and **increased workloads for existing staff**

## Society

- **Social security programs cost around €170 billion (1.2% of GDP)<sup>3</sup>**
- Poor mental health in the workplace leads to **absenteeism, reduced productivity, and increased turnover**
- **Indirect costs in the labour market are approx. €240 billion (1.6% of GDP)<sup>3</sup>**

New treatments for mental health are required to address this wide-ranging burden of disease

\*(and substance abuse disorders)

Source: 1. [Mental health in the EU \(europa.eu\)](#); 2. [Overview of mental health in Europe \(who.int\)](#); 3. [Health at a Glance: Europe 2018 - European Commission \(europa.eu\)](#);

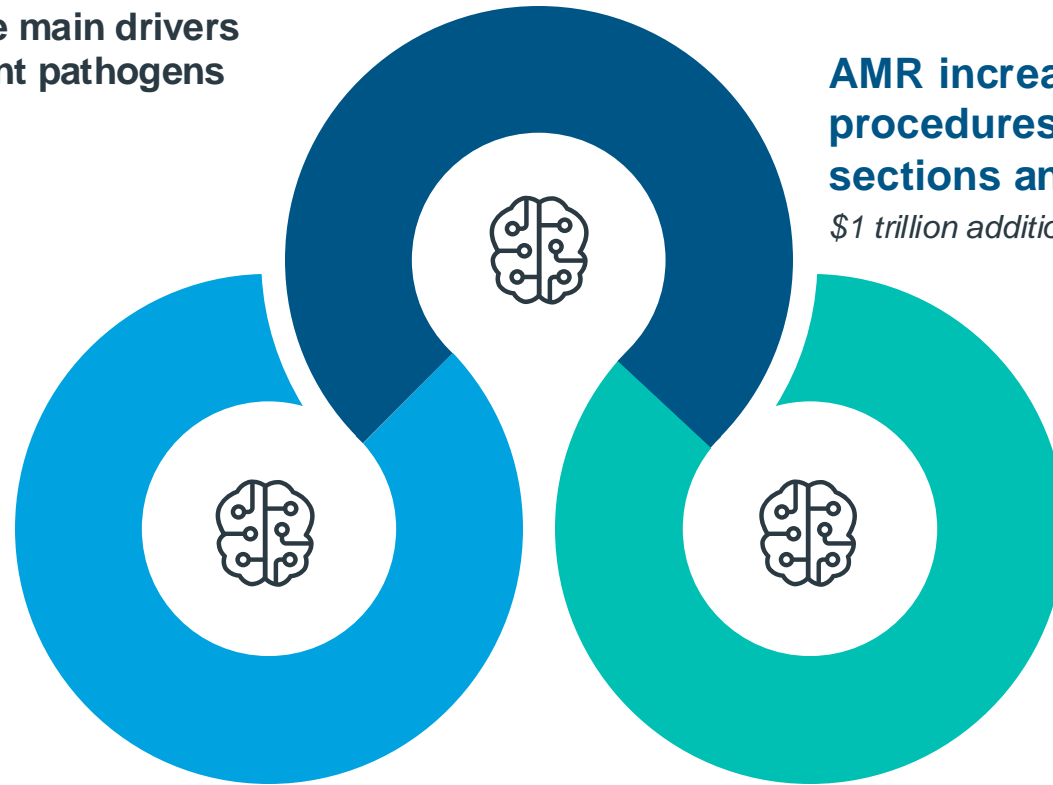
2024 Pipeline Review – Innovation for Unmet Need

# Tackling AMR requires careful antibiotic stewardship, leveraging immunisation and new medicinal products addressing antibiotic resistance

The misuse and overuse of antimicrobials in humans, animals, and plants are the main drivers in the development of drug-resistant pathogens

**AMR makes infections harder to treat**

*For urinary tract infections caused by E. coli, 1 in 5 cases exhibited reduced susceptibility to standard antibiotics*



**AMR increases risk of common medical procedures, such as surgery, caesarean sections and chemotherapy**

*\$1 trillion additional healthcare costs by 2050*

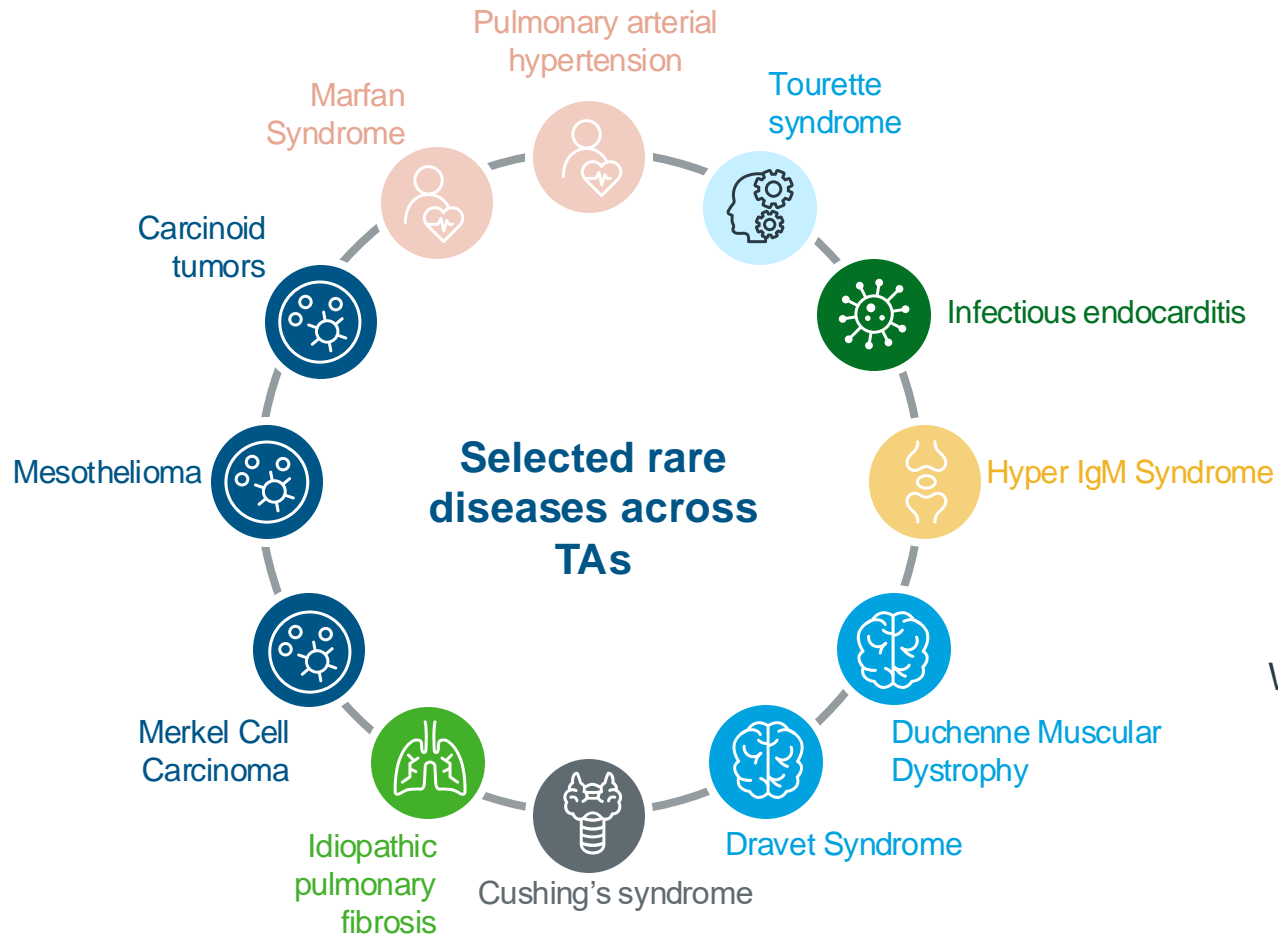
**AMR brings significant economic costs**

*Reduction in global GDP of US\$ 1-3.4 trillion per year by 2030*

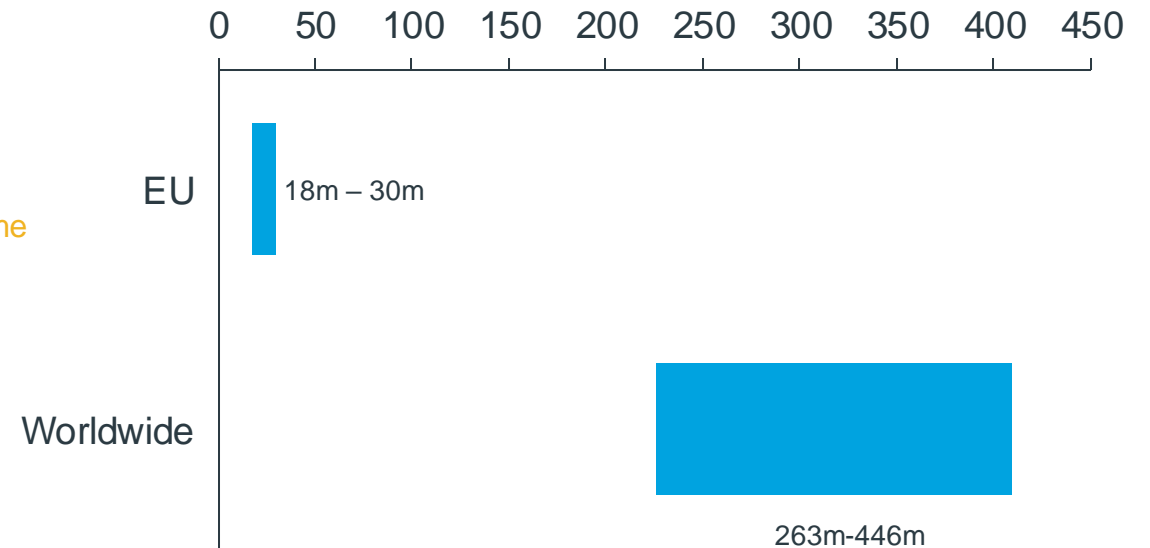
Managing AMR remains a critical challenge for policy makers and healthcare systems across the globe



# Rare diseases impact 20-30 million patients in Europe, many with limited treatment options

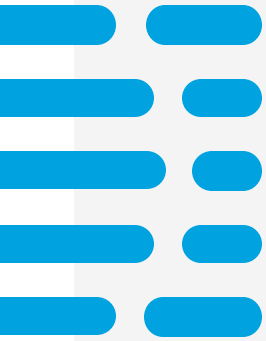


Estimated range of patients affected by a rare disease, EU and worldwide\* (millions, 2017 population)



Millions of patients are affected by rare diseases, representing a major burden on individuals and families

\*Forecast is based on the estimated minimum and maximum boundaries for global point prevalence of RDs  
 Source: [Nature](#), [MedScap](#)  
 2024 Pipeline Review – Innovation for Unmet Need

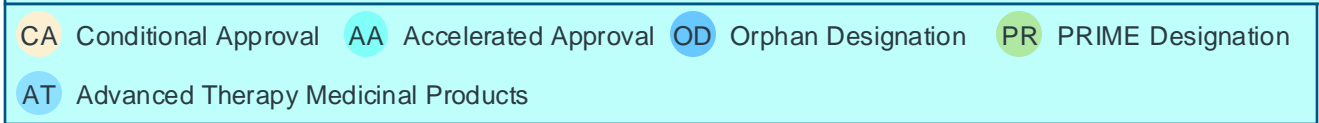
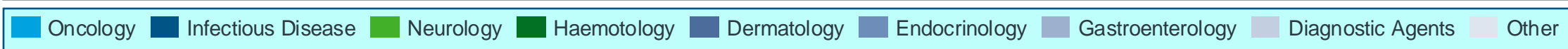


# Table of Contents

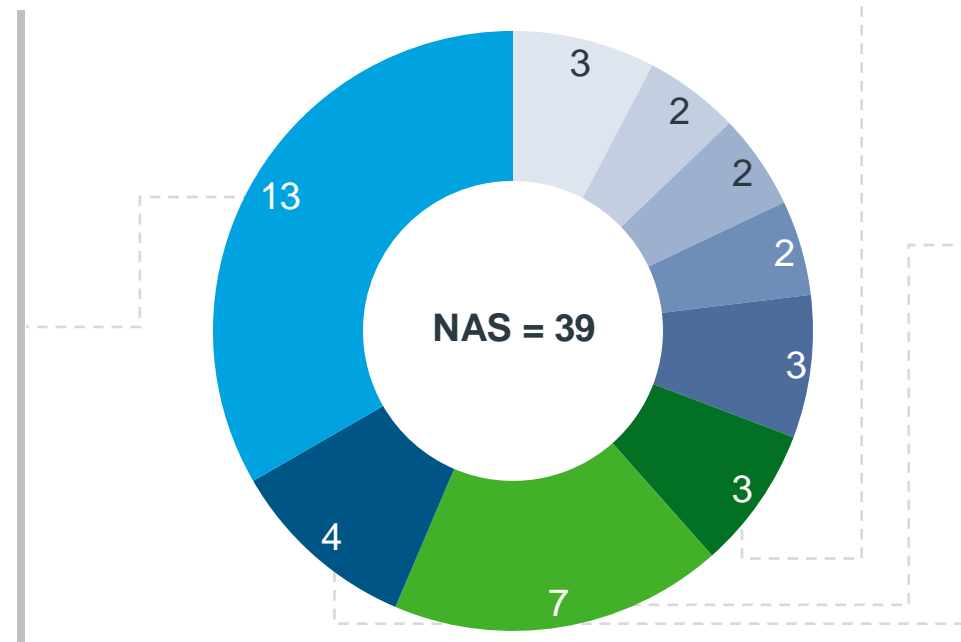
- + Global Disease Burden Overview
- + **R&D Pipeline Overview**
- + Innovation Case Studies

# In 2023, the EMA issued 77 market authorisations, 39 of which were new active substances (NAS)

## New Active Substance Approvals (2023)



- ### Oncology
- PR AA CA OD TALVEY (Multiple Myeloma)
  - CA OD COLUMVI (DLBCL)
  - CA OD TEPKINLY (DLBCL)
  - OD OMJJARA (Myelofibrosis)
  - OD TEVMIBRA (ESCC)
  - OD TIBSOVO (Myeloid Leukemia)
  - PR CA ELREXFIO (Multiple Myeloma)
  - CA JAYPIRCA (Mantle Cell Lymphoma)
  - CA KRAZATI (NSCLC)
  - CA LYTGOBI (Cholangiocarcinoma)
  - INAQOVI (Myeloid Leukemia)
  - ORSERDU (Breast Neoplasms)
  - VANFLYTA (Myeloid Leukemia)



### Hematology

- CASGEVY (Sickle Cell, BT) OD CA AT PR
- JESDUVROQ (CKD-induced Anemia)
- VAFSEO (CKD-induced Anemia)

### Neurology

- AGAMREE (DMD) OD
- RYSTIGGO (Myasthenia Gravis) OD
- SKYCLARYS (Friedrich's Ataxia) OD
- ZTALMY (CDKL5 Deficiency Disorder) OD
- AQUIPTA (Migraine)
- BRIUMVI (Multiple Sclerosis)
- ZILBRYSQ (Epileptic Syndromes)

### Infectious Disease

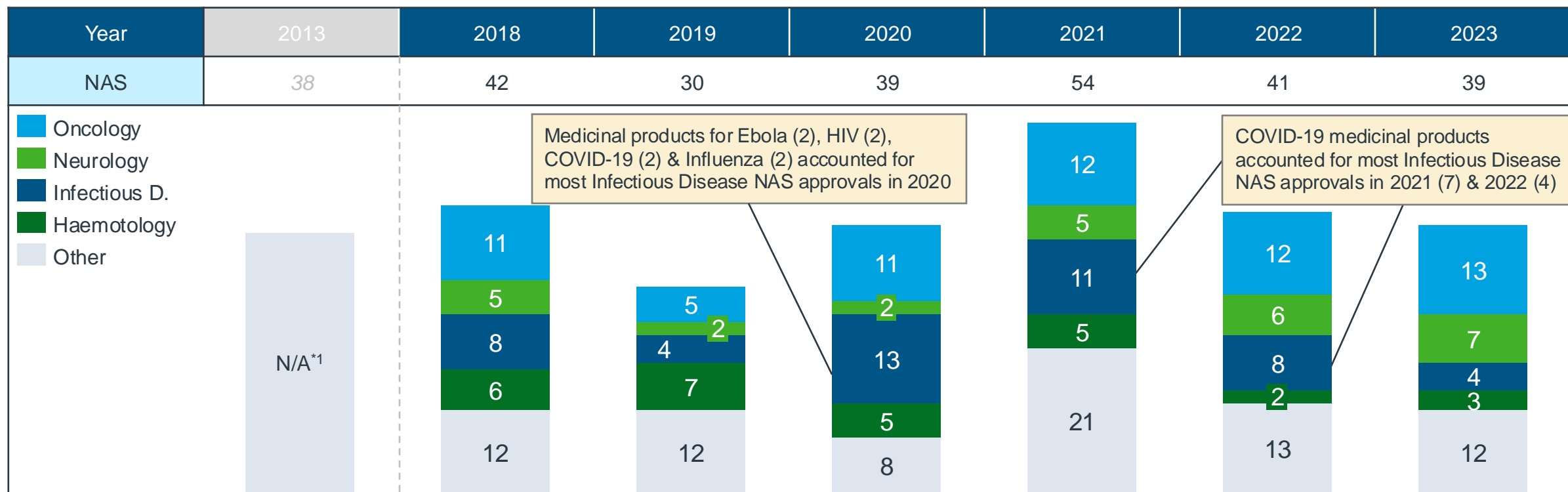
- ABRYSVO (RSV) AA
- AREXVY (RSV) AA
- BIMERVAX (COVID-19)
- REZZAYO (Invasive Candidiasis)

- **Oncology (13) & Neurology (7) TAs saw the highest number of NAS**, and together account for the majority of NAS approvals in 2023
- **Paediatric NAS (5)** included in the total NAS (39) - see appendix on page 76
- **Haematology TA saw the only ATMP approval with CASGEVY**, a CRISPR-based cell-therapy used in the treatment of Sickle Cell & Beta Thalassemia

Abbreviations: New Active Substance (NAS), Diffuse Large B-Cell Lymphoma (DLBCL), Oesophageal Squamous Cell Carcinoma (ESCC), Non-small Cell Lung Cancer (NSCLC), Beta Thalassemia (BT), Chronic Kidney Disease (CKD), Duchenne Muscular Dystrophy (DMD), Respiratory Syncytial Virus (RSV)  
 Source: EMA Human Medicine Highlights ([Link](#)). PRIME Designation: An EMA voluntary scheme for offering scientific advice & accelerated approval for medicines targeting an unmet medical need

# New active substance approvals have returned to pre-pandemic levels in 2023, partially driven by a fall in approvals for infectious disease indications

New Active Substance Approvals by Indication Trend (2013, 2018~2023)



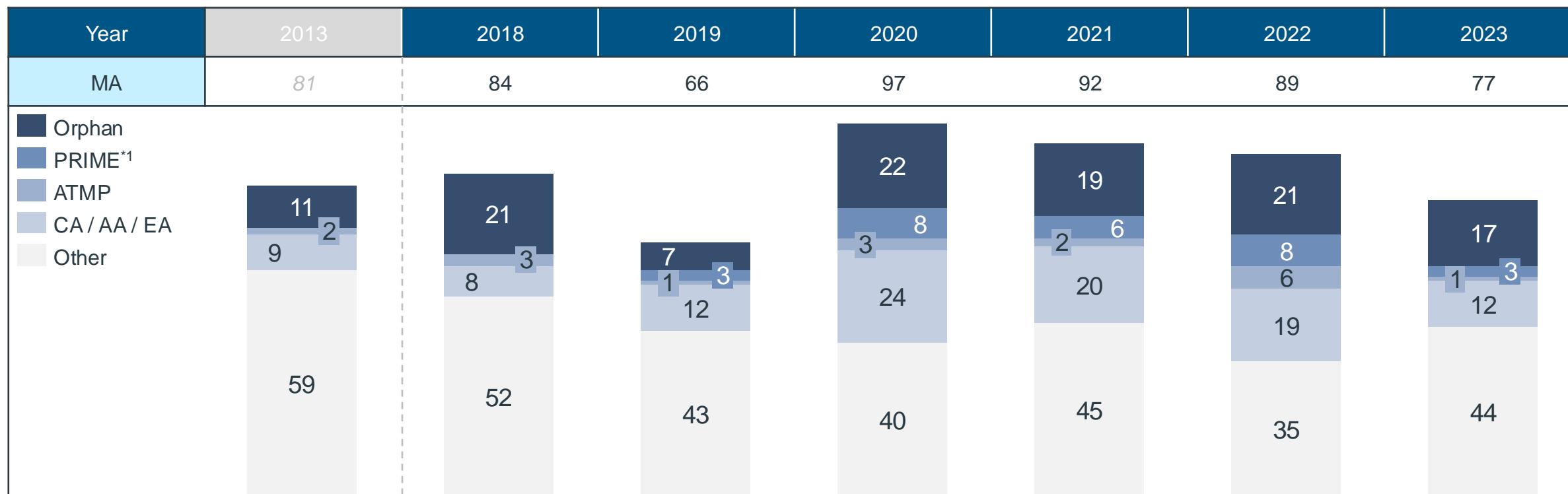
- Apart from 2019, the number of NAS approvals in Oncology have remained stable between 2018~2023
- NAS approvals in Neurology have increased from 2 to 7 between 2019~2023, driven by new treatments for rare neurological conditions
- NAS approvals in infectious disease have returned to pre-pandemic levels in 2023 as R&D focus has switched away from COVID-19

Abbreviations: NAS: New Active Substance, Infectious D.: Infectious Disease. \*1 Detailed breakdown of NAS approvals by TA is not available in 2013 EMA report

Source: EMA Human Medicine Highlights ([Link](#))

# Broader market authorisations returned to pre-pandemic levels, partially driven by a fall in exceptional approvals for COVID-19 medicinal products

Market Authorisation & Approvals by Type Trend (2013, 2018~2023)



- Medicinal products receiving orphan designation has increased from 11 to 21 between 2013~2018 and remained high between 2018~2023
- Medicinal products receiving conditional, accelerated & exceptional approval has fallen back to pre-pandemic levels in 2023
- A record number of ATMP approvals (6) were seen in 2022 and have fallen back to pre-pandemic levels in 2023

Abbreviations: CA: Conditional Approval, AA: Accelerated Approval, EA: Exceptional Approval, ATMP: Advanced Therapy Medicinal Product. \*1 PRIME Designation scheme was launched by EMA in 2016

Source: EMA Human Medicine Highlights ([Link](#))

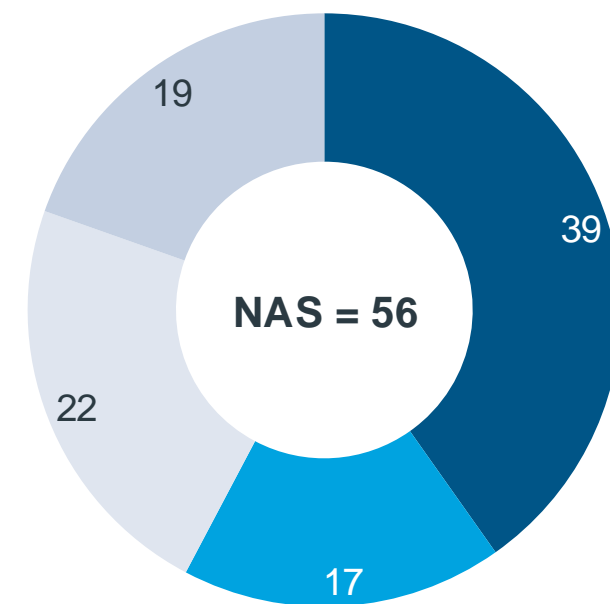
2024 Pipeline Review – Innovation for Unmet Need

# As of November 2024, the EMA had issued 97 market authorisations this year, 56 of which are new active substances

## Market Authorisations & NAS Approvals (As of November 2024)

■ NAS (non-orphan) ■ NAS (orphan) ■ Biosimilars ■ Generics

CATEGORY	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	
<b>NAS (non-orphan)</b>	2	3	3	4	6	5	5	0	2	5	4	
<b>NAS (orphan)</b>	0	4	2	1	2	2	2	0	3	1	0	
<b>Biosimilars</b>	0	1	3	2	1	1	6	0	2	2	4	
<b>Generics / Hybrids</b>	1	2	4	1	5	2	1	0	1	2	0	
<b>TOTAL MARKET AUTHORISATIONS</b>												<b>97</b>

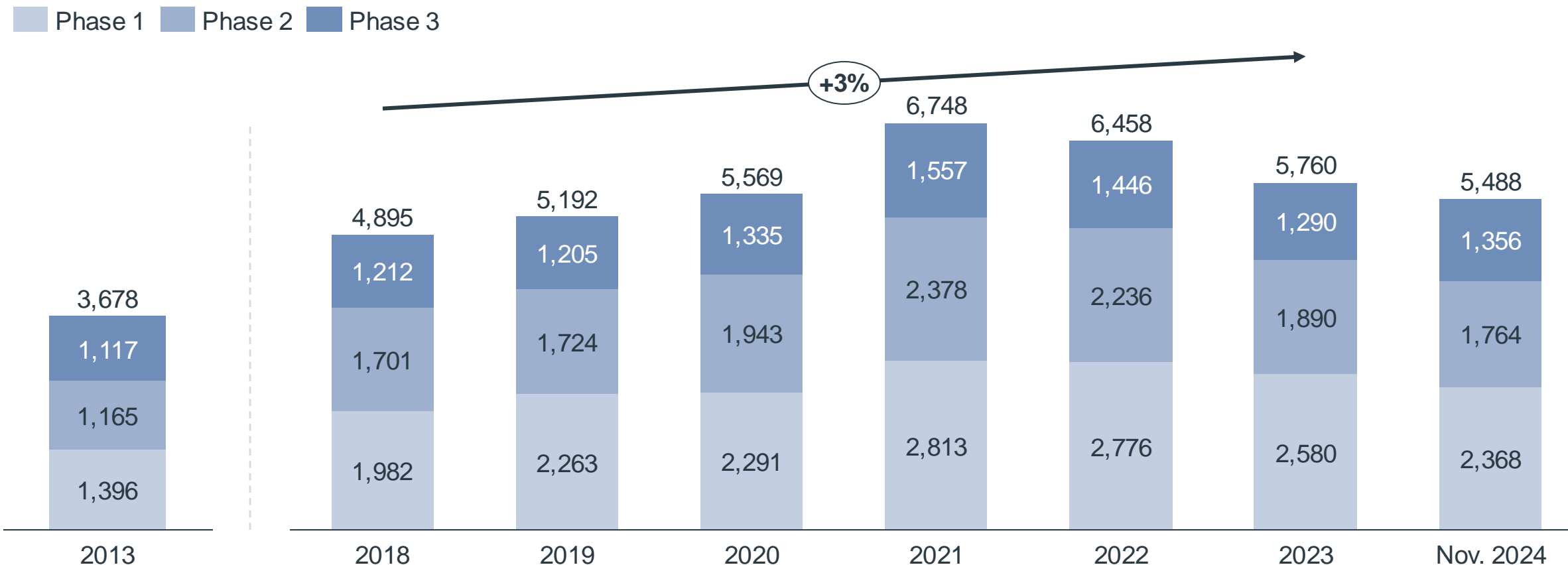


NAS: New Active Substance  
 Source: CHMP Monthly Meeting Highlights ([Link](#))  
 2024 Pipeline Review – Innovation for Unmet Need

No. MA (Nov. 2023): **97**, Full Year (2023): **77**

# The number of global industry-sponsored clinical trials has fallen back since the peak seen in 2021, but remains higher than pre-pandemic levels

No. Global Clinical Trials by Phase (2013, 2018~2024, Phase 1~3, Industry-sponsored Trials Only)\*1



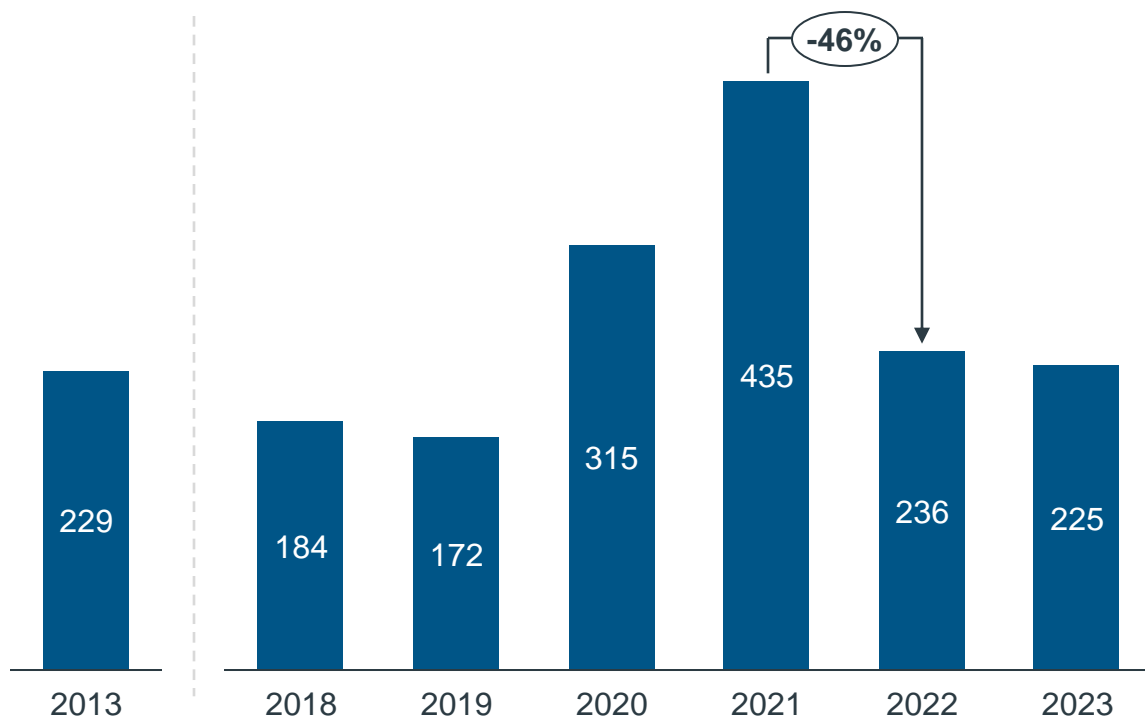
COVID-19 pandemic may have driven an increase in clinical trials between 2021~2022, but this impact has subsided in 2023

\*1 Phase 2 includes Phase 1/2, 2a & 2b trials. Non-industry sponsored trials, medical device trials & trials which were terminated or suspended are excluded from data

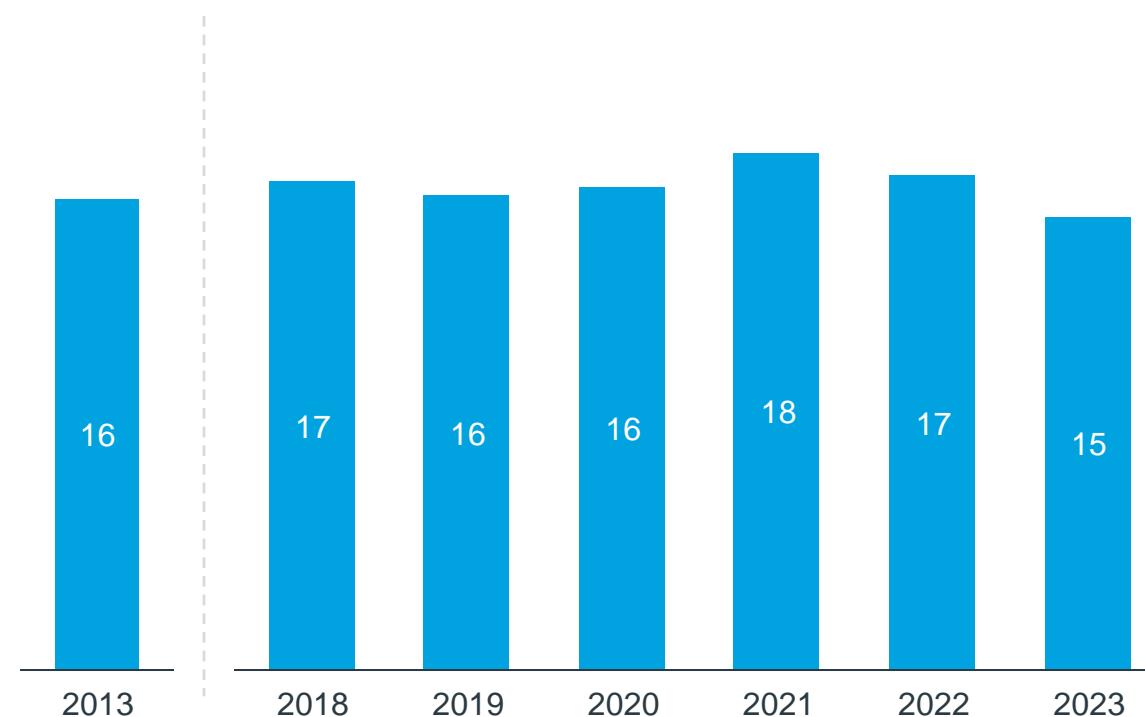
Source: Clinical Trial Repository (Access Date: November 25th 2024)

# After a surge driven by COVID-19, the number of patients per trial has mostly returned to pre-pandemic levels, whilst sites per trial has remained steady

Average No. Patients / Trial (2013, 2018~2023)\*<sup>1</sup>



Average No. Sites / Trial (2013, 2018~2023)\*<sup>1,2</sup>



**Number of patient / clinical trial increased in 2020~21, likely due to high enrolment in COVID-19 trials**

**This has largely returned to pre-pandemic levels in 2022~23 as the number of COVID-19 trials has fallen**

**Number of sites / clinical trial has remained broadly consistent between 2018~23, with only a small increase seen during the COVID-19 pandemic**

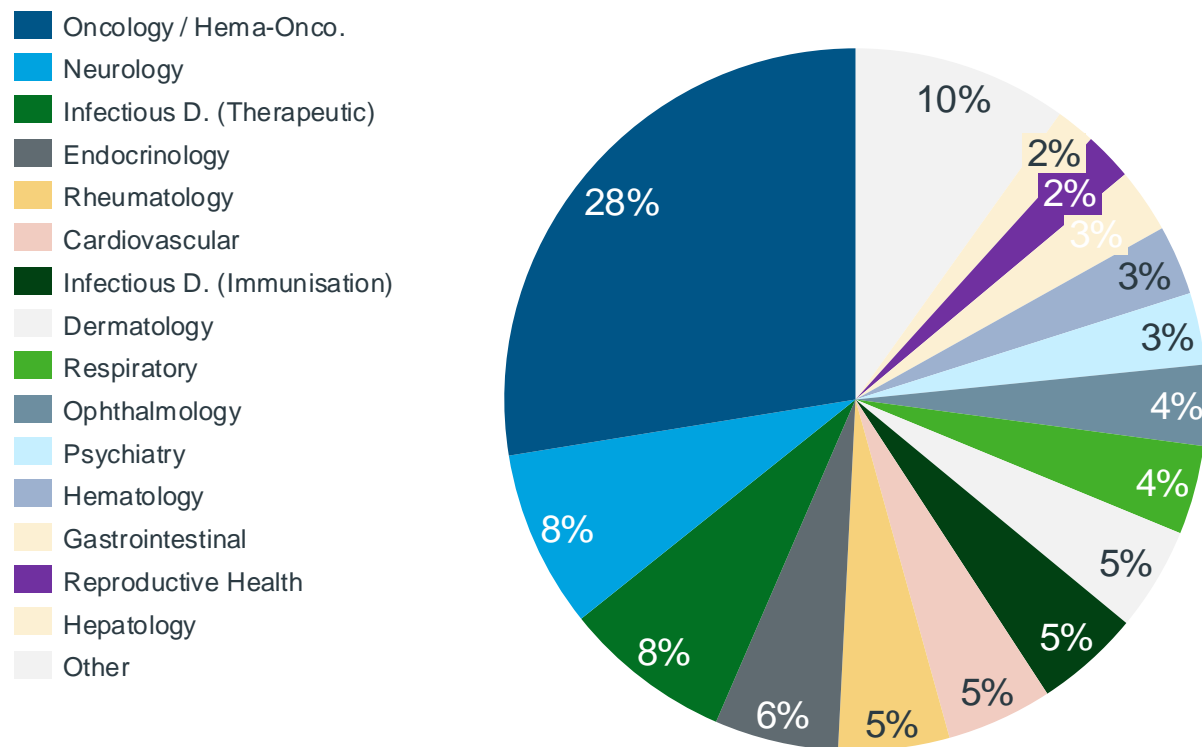
**2018~23 data is also consistent with 2013 historical data**

\*1 Includes phase 1~3 industry sponsored trials. Medical device trials & trials which were terminated or suspended are excluded from data. \*2 Data updates since 2022 report suggest the fall in years 2021/2022 were related to retrospective data updates, rather than representing a major fall in sites per trial  
Source: Clinical Trial Repository (Access Date: April 30th 2024)



# Oncology remains the largest TA for clinical trials, and accounts for 29% of trials initiated in 2023

**No. Clinical Trials by Therapy Area  
(Phase 1~3, Global, all trials conducted 2018~2023)\*1**



Infectious disease vaccines include prophylactic mAbs, Covid-19, respiratory syncytial virus, Influenza virus, Hepatitis B virus, and related vaccines. Hematology has fallen in TA ranking since last project iteration as the definition has been updated to no longer include hema-oncology trials

**No. Clinical Trials by Therapy Area Share Change**

Therapy Area	2018 % (TA Rank)	2023 % (TA Rank)
Oncology	27% (1)	29% (1)
Neurology	9% (2)	7% (2)
Infectious D. (Ther.)	5% (5)	6% (6)
Endocrinology	6% (4)	7% (3)
Rheumatology	5% (6)	6% (5)
<b>Cardiovascular</b>	5% (7)	6% (4)
<b>Infectious D. (Immun.)</b>	3% (13)	4% (8)
Dermatology	6% (3)	4% (7)
Respiratory	4% (10)	4% (9)
Ophthalmology	4% (8)	4% (10)
Psychiatry	4% (11)	3% (12)
Hematology	4% (9)	2% (15)
Gastrointestinal	4% (12)	3% (11)
<b>Reproductive Health</b>	2% (18)	3% (13)
Hepatology	1% (19)	2% (17)

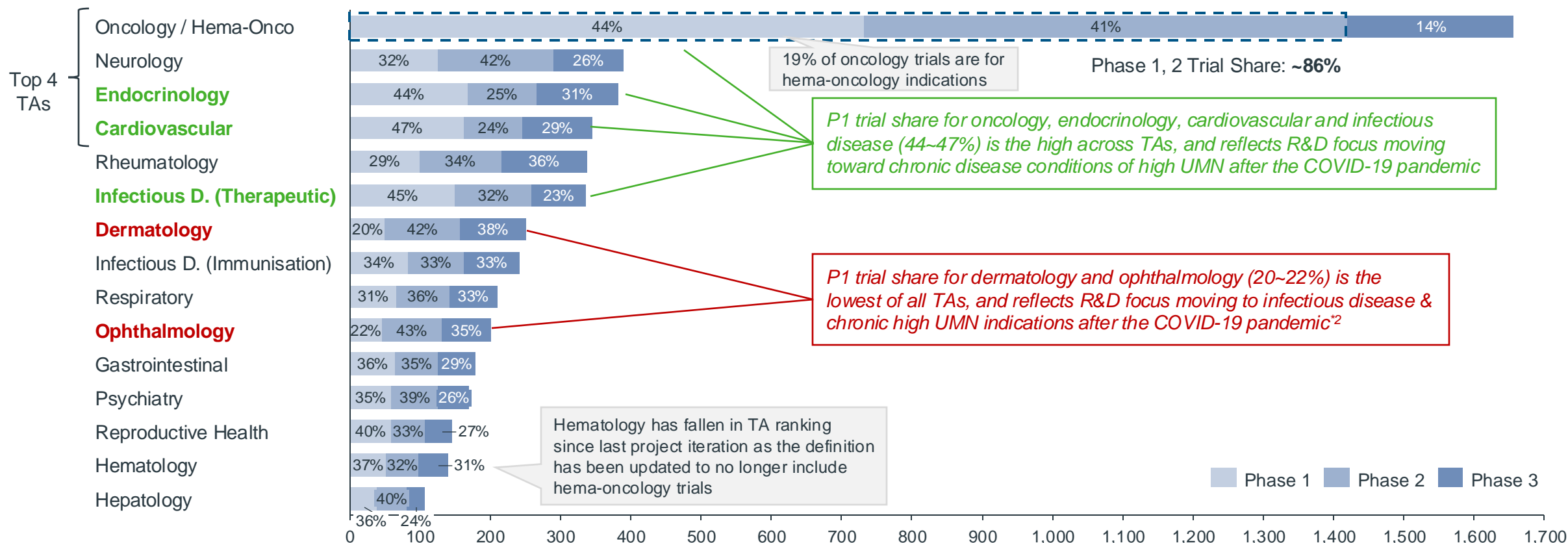
- **Oncology and neurology remain the top TAs in global clinical trials**, and together account for 36% of global clinical trials initiated between 2018~2023
- **Cardiovascular, infectious disease and reproductive health therapy areas have grown their respective share** of the clinical trial pipeline between 2018~2023

\*1 Phase 2 includes Phase 1/2, 2a & 2b trials. Non-industry sponsored trials, medical device trials & trials which were terminated or suspended are excluded from data.

Source: Clinical Trial Repository (Access Date: April 30th 2024)

# Oncology, endocrinology, CV and infectious diseases have the highest proportion of Phase 1 trials, suggesting this is a focus area of innovation

No. Global Clinical Trials by Therapy Area by Phase (2023, Phase 1~3, Industry-sponsored Trials Only)\*1

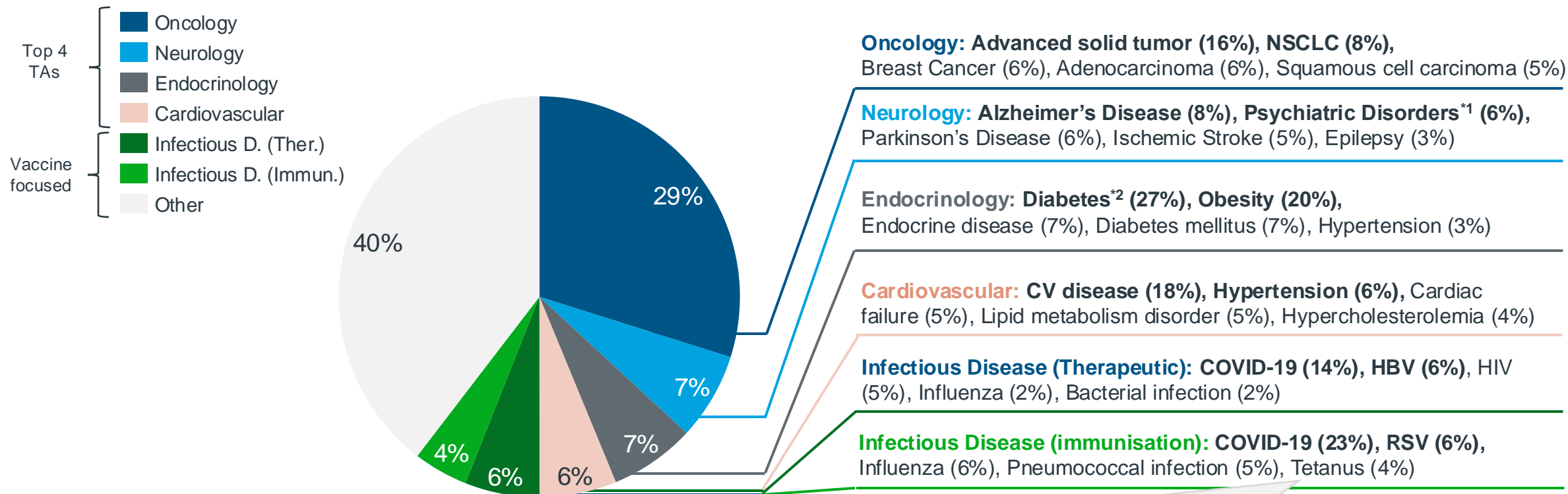


- **Oncology remains the focal point of R&D in the pharma industry** and will remain the top TA for NAS approvals, with ~86% of trials initiated in 2023 in P1 / P2
- **NAS approvals in Endocrinology & Cardiovascular TAs are expected to grow**, ranking 3<sup>rd</sup> and 4<sup>th</sup> in new trials between 2023~2024

\*1 Phase 2 includes Phase 1/2, 2a & 2b trials. Non-industry sponsored trials, medical device trials & trials which were terminated or suspended are excluded from data. Abbreviation: Cardiovascular (CV)  
 Source: Clinical Trial Repository (Access Date: April 30th 2024). IQVIA Internal Experts \*2 Dermatology CT Publications Decline due to COVID-19 (Link)

# Oncology trials initiated in 2023 prioritized advanced solid tumours, while diseases with high societal impact dominate other clinical activity

Top 6 Indications per Selected Therapy Area (2023, Phase 1~3, Industry-sponsored Trials Only)



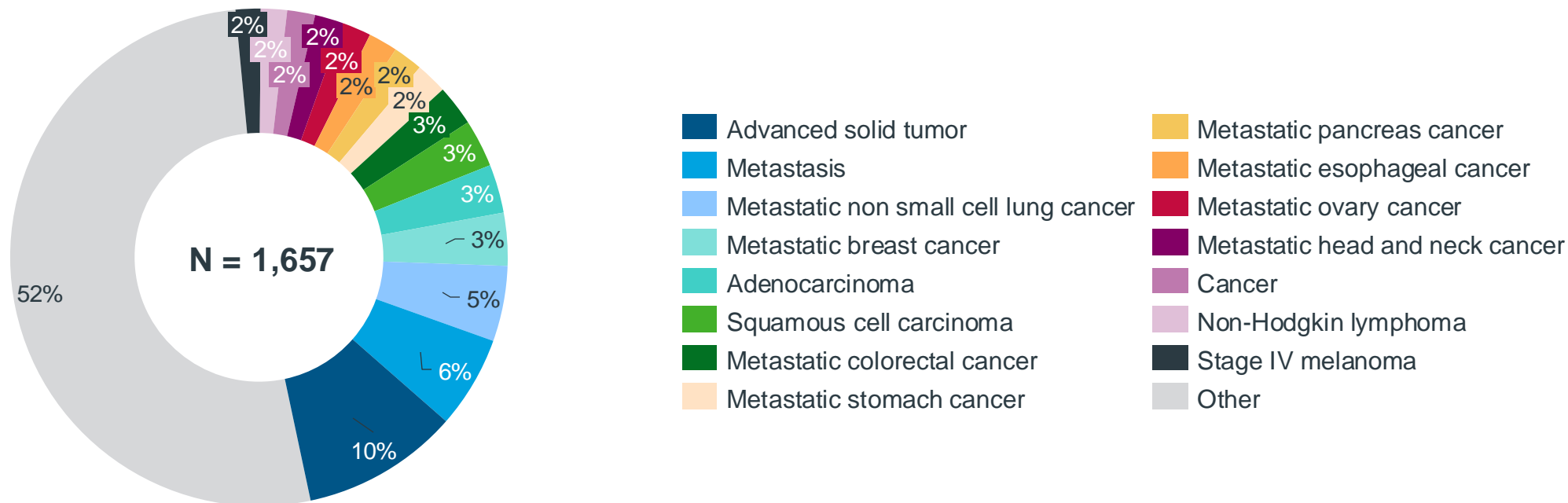
Tetanus trials are primarily adult booster/ paediatric combo trials conducted in Asia (e.g., China, Thailand, Vietnam)

- **Clinical trials for advanced solid tumours dominate the oncology pipeline**, representing 16% of all oncology trials initiated in 2023
- Across TA, **clinical trials for chronic age-related diseases (e.g., Alzheimer's disease, Obesity) dominate the pipelines of each TA**
- **COVID-19 is still dominant in the infectious disease pipeline**, accounting for ~23% of all immunisation trials and ~6% of therapeutic trials initiated in 2023

\*1 Psychiatric Disorders includes anxiety disorder, depression and other mental health disorders. \*2 The share of the diabetes pipeline for insulin-dependent diabetes is approximately 4%.  
 Abbreviation: Non-small cell lung cancer (NSCLC), Cardiovascular (CV), Hepatitis B virus (HBV), Human immunodeficiency virus (HIV), Respiratory syncytial virus (RSV). Source: Clinical Trial Repository (Access Date: April 30th 2024).  
 2024 Pipeline Review – Innovation for Unmet Need

# Oncology clinical activity is focused on metastatic and advanced solid tumours, with NSCLC (lung) and breast the most studied individual cancers

Oncology pipeline – Key indications (% of trials in 2023)



'Other' includes Cytotoxics, Hormonal therapy and Radiotherapeutics



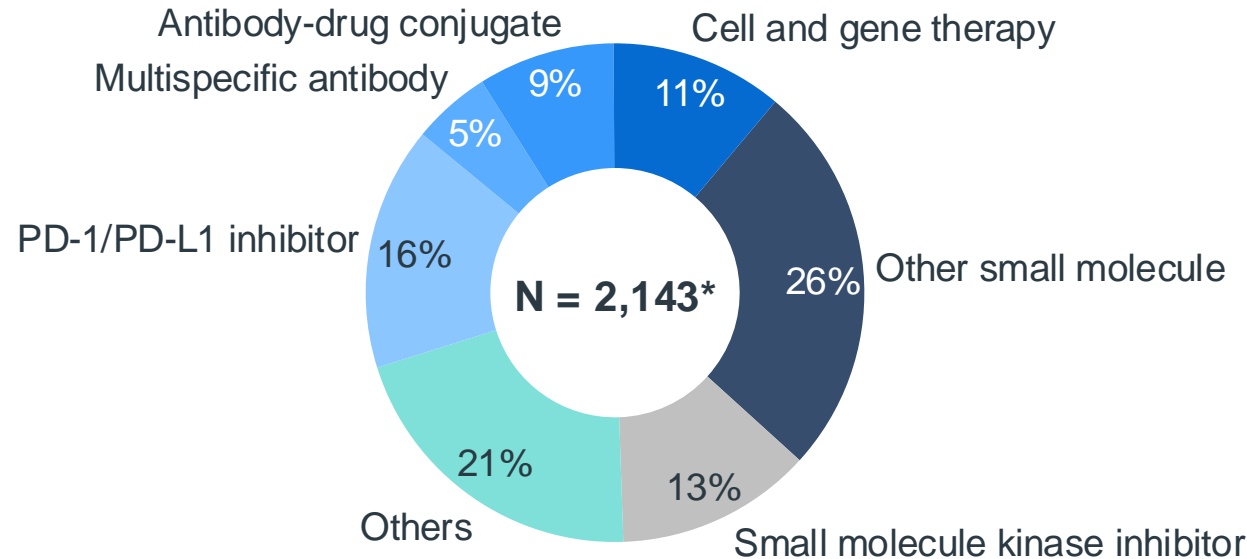
- Trials initiated in 2023 for oncology indications continue to **focus primarily on advanced or metastatic cancers, with high incidence cancers such as metastatic non-small cell lung cancer (NSCLC) & breast cancer particular focal points of clinical activity**
- Cancers with low survival rates such as **pancreas and colorectal cancer are also an active area** in clinical activity
- Research focused on early stages cancers may also be impacted by challenge of **enrolling patients at suitable time within disease progression**

\*1 Phase 2 includes Phase 1/2, 2a & 2b trials. Non-industry sponsored trials, medical device trials & trials which were terminated or suspended are excluded from data; Other includes Cytotoxins, Hormonal Therapy and Radiotherapeutics.

Source: Clinical Trial Repository (Access Date: April 30th 2024). NSCLC: Non-small cell lung cancer

# Considering oncology mechanisms of action: PD-L1, ADCs, Cell and Gene Therapy represent a significant proportion of clinical trial activity

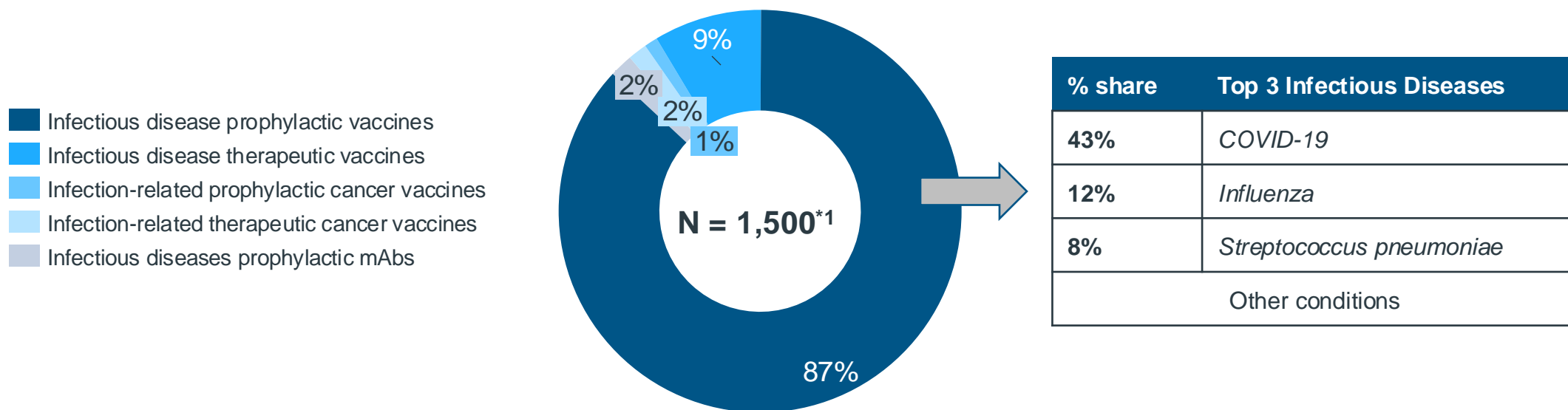
## Oncology Pipeline by MoA and Key Insights (Phase 1~3, 2023 Ongoing Trials)



- **Antibody-drug conjugates (ADCs) and immune checkpoint inhibitors (e.g., PD-1, PD-L1) continue to hold significant shares of overall pipeline**, indicating a continued focus on targeted therapies / immunotherapies in oncology R&D
- **Cell and Gene Therapies (CaGT) also hold a significant share of overall trials**, indicating strong investment in novel approaches to targeting cancer (e.g., CAR-T cell therapies)
- **Multispecific antibodies also hold a notable share**, indicating the interest in developing antibodies with enhanced targeting capabilities

# Within immunisation, prophylactic vaccines for infectious diseases are common, with therapeutic vaccines and monoclonal antibodies being trialled

## Vaccine Pipeline by Disease Target and Key Insights (Phase 1~3, 2018~2023)



- **Prophylactic vaccines targeting infectious diseases dominate the product class share**, representing 86% of all clinical trials. Key disease targets include COVID-19, Influenza and *Streptococcus pneumoniae*
- **Therapeutic vaccines are the second largest product class share**, representing 9% of all clinical trials
- **Therapeutic and prophylactic cancer vaccines represent a more limited proportion of the group**, representing 1~2% of trials

\*1 Clinical trials with multiple class labels (therapeutic vaccine, prophylactic vaccine, anticancer) were included in all relevant categories, once for each.  
 Abbreviation: Mechanism of Action (MoA). Source: Source: Clinical Trial Repository (Access Date: April 30th 2024).  
 2024 Pipeline Review – Innovation for Unmet Need

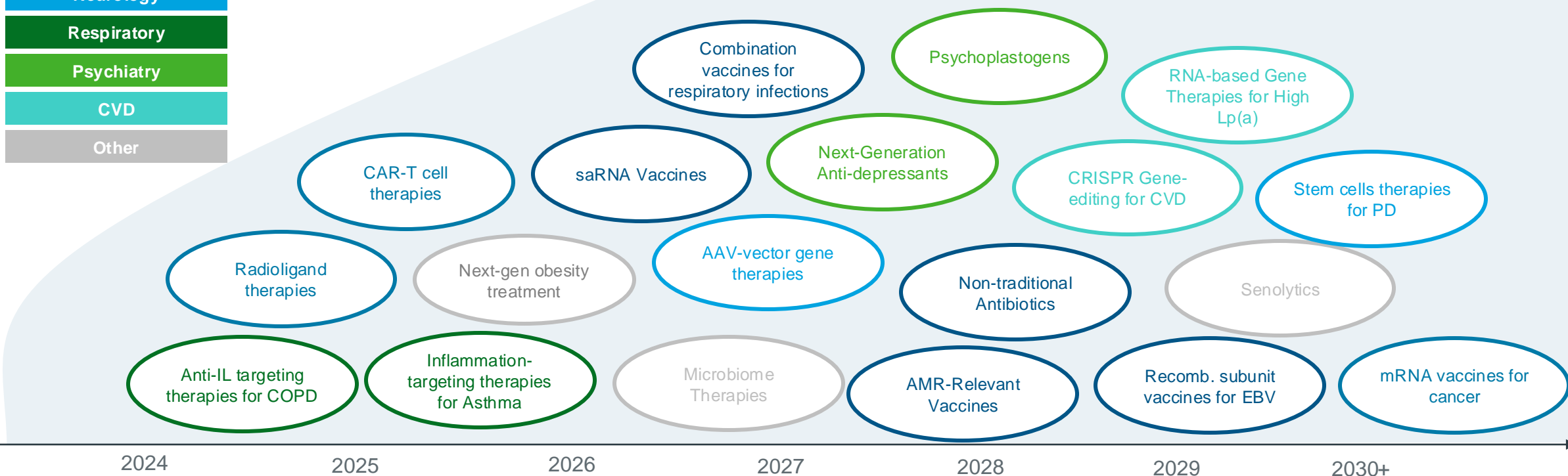
# Across the pipeline, many innovation areas are emerging that promise to alleviate a significant part of global disease burden

## OVERVIEW OF INNOVATION AREAS ON THE HORIZON

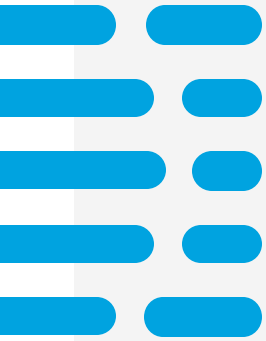
Key:

Infectious disease
Oncology
Neurology
Respiratory
Psychiatry
CVD
Other

Illustrative



Abbreviations: Antimicrobial resistance (AMR), Anti-interleukin (Anti-IL), Chimeric antigen receptor T cells (CAR-Ts), Chronic obstructive pulmonary disease (COPD), Cardiovascular disease (CVD), Epstein-Barr virus (EBV), Monoclonal antibodies (mAbs), Messenger RNA (mRNA), Respiratory syncytial virus (RSV), Self-amplifying RNA (saRNA), Therapies (Tx), Parkinson's Disease (PD)  
 2024 Pipeline Review – Innovation for Unmet Need



# Table of Contents

- + Global Disease Burden Overview
- + R&D Pipeline Overview
- + **Innovation Case Studies**



# This report showcases 10 specific areas of innovation, across the therapeutic and immunisation pipelines

Category	Examples of Innovation	Description
Tackling anti-microbial resistance	AMR-relevant vaccines	• Multiple synergistic pathways to reduce infections, combat drug resistance, lower selection pressures, and maintain continued effectiveness of antimicrobials
	Novel anti-bacterials	• New examples of traditional antibiotics, and brand-new Mechanisms of Action (MoAs), addressing a key unmet need in patients for whom existing antibiotics are ineffective
Novel applications of vaccines	Vaccines to protect against non-communicable diseases	• Vaccines against viruses (e.g. EBV), which are causally linked to development of non-communicable diseases e.g. certain cancers, autoimmune and neurodegenerative diseases
	mRNA vaccines <sup>1</sup> for cancers	• After establishing efficacy, safety, and success in COVID-19, mRNA vaccines herald a new era in personalized vaccines, particularly in cancer
Disease modifying treatments through advanced technologies	Gene therapy for DMD	• Gene therapies promise not just symptomatic relief, but to slow or stabilize disease progression within rare indications with poor prognosis and QoL, such as DMD
	RNA technology for high lipoprotein (a)	• New products specifically targeting high lipoprotein (a), an inherited risk-factor associated with CVD events e.g. stroke and heart attacks
	Stem cells for neurodegenerative disease	• Novel treatments for PD & other neurodegenerative diseases, which may reverse disease progression through regeneration of CNS cells
Incremental innovation for widespread conditions	Next-gen obesity management medications	• Building on recent GLP-1 launches, the new wave of GLP-1s and other MoAs can provide additional efficacy and improved side effect profiles
	Anti-IL treatments for COPD	• Redeployment of well-established anti-interleukin therapies into COPD, one of the major sources of global disease burden
Addressing mental health challenges	Novel therapies for major depressive disorder	• Novel MoAs to provide therapeutic options for increasing number of patients suffering with major depressive disorder

1. Terminology as described in registered RCTs; may not reflect GPL/EMA vaccine definition (e.g. restricted to infection-related diseases)

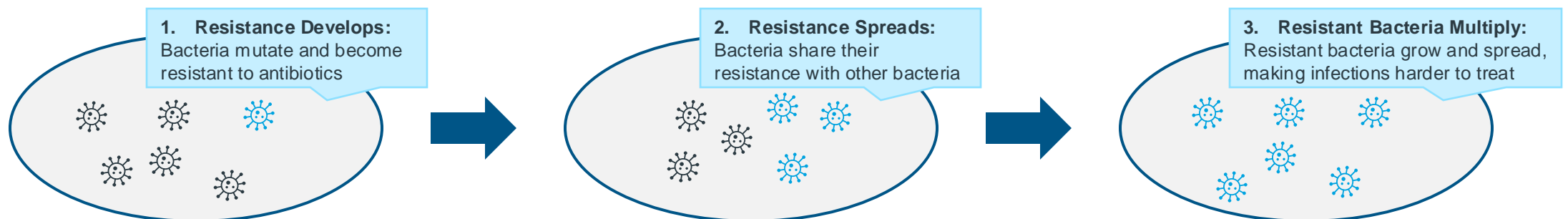
Abbreviations: Antimicrobial resistance (AMR), Anti-interleukin (Anti-IL), Chimeric antigen receptor T cells (CAR-Ts), Chronic obstructive pulmonary disease (COPD), Cardiovascular disease (CVD), Central nervous system (CNS), Duchenne Muscular Dystrophy (DMD), Epstein-Barr virus (EBV), Monoclonal antibodies (mAbs), Mechanism of action (MoA), Parkinson's disease (PD), Messenger RNA (mRNA), Respiratory syncytial virus (RSV), Self-amplifying RNA (saRNA), Therapies (Tx), Quality of life (QoL)

# Antimicrobial resistance (AMR) is one of the biggest health crises, contributing to 4.95m deaths globally

## INTRODUCTION TO ANTIMICROBIAL RESISTANCE (AMR)

- Antimicrobial resistance (AMR) occurs when **bacteria, viruses, fungi & parasites develop mechanisms to protect themselves from the effects of antimicrobial treatments** such as antibiotics
- **AMR is a natural evolutionary process** which occurs over time in pathogens, although **its emergence and spread is accelerated by human activity**, mainly through the misuse & overuse of antimicrobials to prevent / control infections in humans, animals and plants
  - **AMR is already impacting our ability to treat many common infections and contributed to 4.95m deaths globally in 2019**, with the global costs associated with AMR expected to reach €1.1 trillion by 2050<sup>\*1</sup>
  - **In Europe, there were 800k infections attributed to antibiotic-resistant bacteria, with 35k deaths in 2020<sup>\*2</sup>**
- **Antimicrobial treatments are the cornerstone of modern medicine, and AMR will impact countries of all income levels** through limiting the ability to treat common infections and perform life-saving procedures e.g., chemotherapy administration and childbirths
- ***Streptococcus pneumoniae* infections, and UTIs, represent two examples many unmet need areas where innovation could significantly impact the fight against AMR. The impact of innovation in these areas is detailed in the following case studies.**

### Mechanism for Antimicrobial Resistance<sup>\*3</sup>



Immunisation & novel antibiotics are two key innovations necessary to combat AMR

# *Streptococcus pneumoniae* is a major cause of pneumonia, meningitis, and septicaemia, with pneumococcal AMR a particular public health concern

## *Streptococcus Pneumoniae*

Class of highly invasive gram-positive bacteria, which causes infections ranging from mild (e.g., conjunctivitis) to severe (e.g., pneumonia). *Streptococcus pneumoniae* is the most common cause of community acquired pneumonia (CAP) in Europe\*<sup>1</sup>

### SOCIETAL BURDEN

#### WHO Public Health Priority\*<sup>10</sup>

macrolide-resistant *S. pneumoniae* listed as medium priority by WHO



#### High level of antibiotic resistance\*<sup>6</sup>

~9% of certain isolates resistant to penicillin and macrolide antibiotics

### PATIENT BURDEN

#### 38.1m DALYs\*<sup>2</sup>

Globally associated with *S. pneumoniae* infections in 2019



#### 600k Annual Deaths\*<sup>3</sup>

Globally associated with antibiotic resistant *S. pneumoniae* infections

Antimicrobial Resistance (AMR) Community acquired pneumonia (CAP), Disability-adjusted life year (DALY)  
Source: IQVIA Internal Expertise, Secondary Sources: (1), (2), (3), (4), (5), (6), (7), (8), (9), (10)  
2024 Pipeline Review – Innovation for Unmet Need

- *S. pneumoniae* causes a range of infections from mild to severe (e.g., pneumonia, sepsis)
- There are two principal vaccines (e.g., PPV & PCV) available in Europe today, although **immunisation coverage in adults over 65, a group at risk of severe disease, varies across Europe but averages 24%\*<sup>4</sup>**, with certain serotypes not covered by current vaccines\*<sup>5</sup>
- 1<sup>st</sup> line treatment for severe *S. pneumoniae* infection are antibiotics. In Europe, **up to 14.4% of isolates show resistance a single antibiotic** (penicillin non-wild type: 6.8%, macrolides: 6.5%), with **9.3% showing resistance to two types of antibiotics\*<sup>6</sup>**
  - *S. pneumoniae* is listed on the WHO bacterial priority pathogens list due to its growing antibiotic resistance\*<sup>7</sup>
- Globally, ***Streptococcus pneumoniae* is responsible for 38.1m DALYs\*<sup>2</sup>**, with estimated 1m children dying from infections caused by *Streptococcus pneumoniae* each year
  - Each year, **600k deaths from *S. pneumoniae* are directly attributable to AMR\*<sup>3</sup>**
- *S. pneumoniae* is the leading cause of CAP in Europe, with annual incidence estimated at 1 in 1,000 adults\*<sup>1</sup>
  - **1 in 3 infections caused by *S. pneumoniae* lead to invasive disease, which is associated with higher mortality**
  - **CAP is one of the most acute infections requiring hospitalisation\*<sup>9</sup>**
  - **CAP is associated with annual healthcare costs of €6.4bn in Europe**, with inpatient care costs estimated at €5.7bn; outpatient care costs at €0.5bn; and treatment costs €0.2bn annually\*<sup>8</sup>

# Vaccines are an indispensable tool in combatting AMR, acting through multiple pathways to prevent mechanisms which drive resistance

## INTRODUCTION TO VACCINES FOR ANTIMICROBIAL RESISTANCE

**Vaccines for Antimicrobial Resistance** – vaccines are an indispensable tool in combatting the public health crisis of antimicrobial resistance, acting through multiple synergistic pathways to reduce infection incidence and the selection pressures which drive pathogens to develop resistance to antimicrobials\*<sup>1</sup>

### Pathways Through Which Vaccines Combat Antimicrobial Resistance\*<sup>1</sup>



#### 1. Infection Prevention

- Vaccines protect individuals from primary and secondary infections, through direct protection

#### 2. Reduction of Disease Transmission

- Vaccines can reduce carriage and transmission of pathogens, thus limiting the spread of infections within a community (herd protection)

#### 3. Reducing Antibiotic Overuse and Misuse

- Reducing unnecessary or erroneous prescriptions of antibiotics

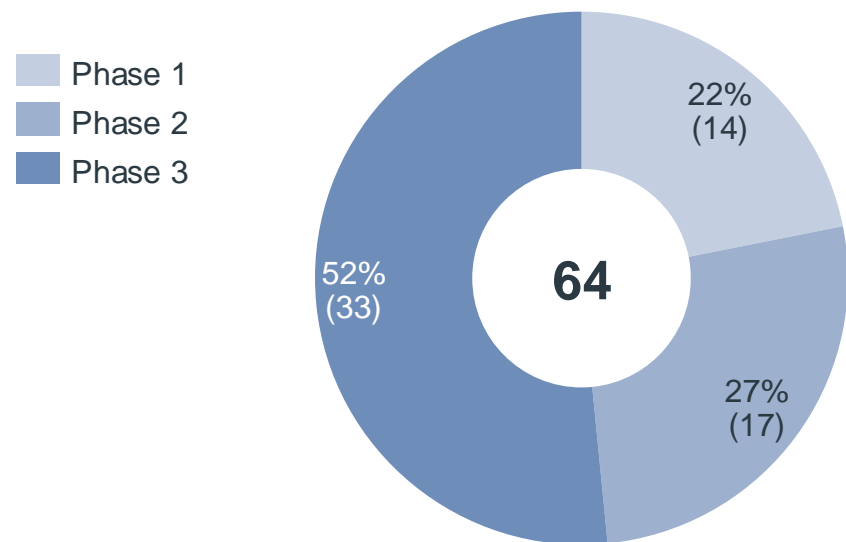
Reduction in overall antibiotic usage, which limits antibiotic-resistance evolution and may prolong the lifespan of novel antibiotics

Abbreviation: Antimicrobial resistance (AMR)  
Source: IQVIA Internal Expertise, Secondary Sources: (1)  
2024 Pipeline Review – Innovation for Unmet Need

# Vaccines against *Streptococcus pneumoniae* are a focal point of innovation, with 52 trials initiated since 2021

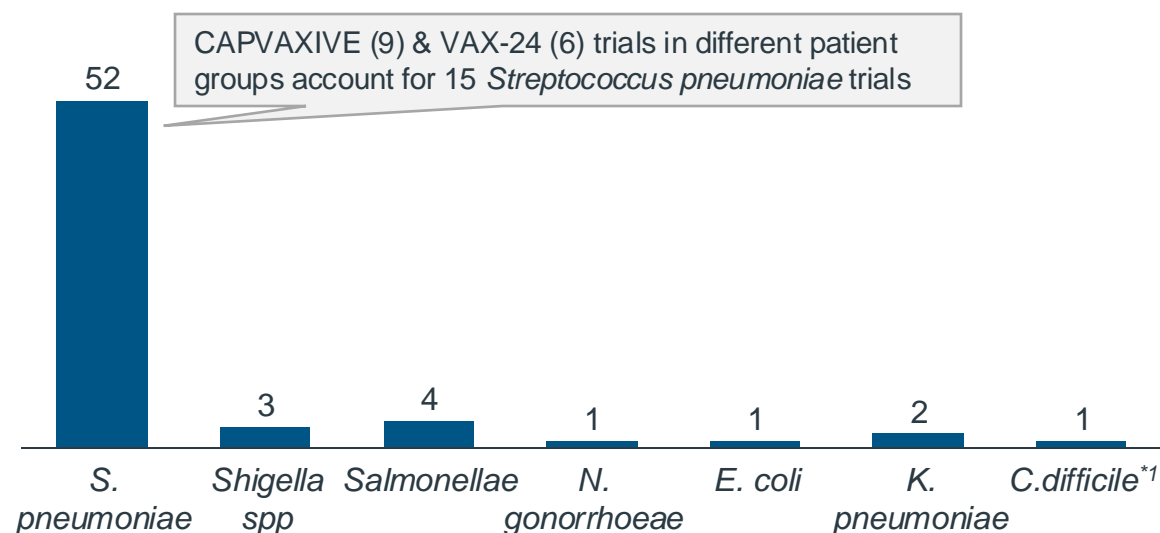
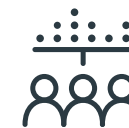
## INTRODUCTION TO PIPELINE OF AMR-RELEVANT VACCINES

### Number of Clinical Trials By Development Phase



**64 clinical trials for AMR-relevant vaccines have been initiated since 2021**, driven by vaccines for *S. pneumoniae* with increased valency vs. existing vaccines and vaccines targeting at risk populations\*<sup>1</sup>

### Number of Clinical Trials By Bacterial Target

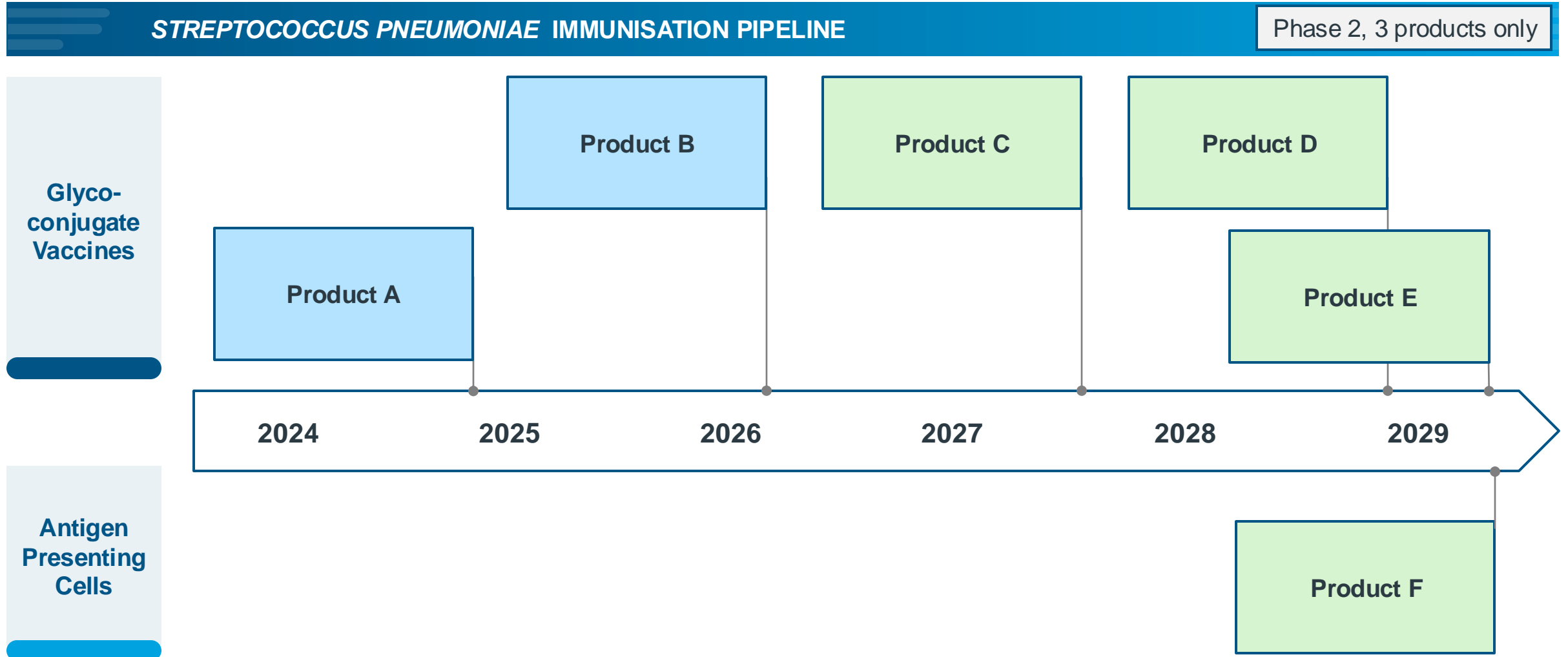


***Streptococcus pneumoniae* is the most active area of pipeline activity for AMR-relevant vaccines**, with 52 clinical trials initiated since 2021

Abbreviation: Antimicrobial resistance (AMR), *Escherichia coli* (*E. coli*), *Neisseria Gonorrhoeae* (*N. gonorrhoeae*), *Klebsiella pneumoniae* (*K. pneumoniae*), *Clostridioides difficile* (*C. difficile*)

\*<sup>1</sup> Trials for *c.difficile* vaccines are not available in public trial repositories but have been added based on company pipelines. Secondary Sources: (1). Source: Clinical Trial Repository (Access Date: April 30th 2024). Search Criteria: AMR Vaccines defined as vaccines for infectious diseases listed in Vaccines Europe report (Link), only industry-sponsored trials started since January 1<sup>st</sup> 2021 are included in the list.  
2024 Pipeline Review – Innovation for Unmet Need

# Several novel vaccines for *Streptococcus pneumoniae* are expected to be approved in the next five years






Approval Timeline Criteria: P3 Products: P3 primary completion date + 1 year, P2 Products: P2 primary completion date + 6 years. Vaccine technology is based on publicly available sources. Timeline includes phase 2 & 3 industry sponsored products with trial locations in US or EU. \*1 Product A was approved in the US in June 2024; Source: Clinical Trial Repository (Access Date: April 30th 2024), Company Websites  
 2024 Pipeline Review – Innovation for Unmet Need



# Novel vaccines for *Streptococcus pneumoniae* could lower infection-related mortalities, reduce antibiotic misuse and limit indirect HCS costs

## IMPACT OF NOVEL VACCINES FOR *STREPTOCOCCUS PNEUMONIAE* ON DISEASE BURDEN

IMPACT AREA	IMPACT
<p data-bbox="206 462 639 582"><b>SOCIETAL CONTRIBUTION TO AMR PREVENTION</b></p> 	<ul style="list-style-type: none"> <li data-bbox="802 439 2390 564">• <b>Opportunity to reduce the incidence and severity of <i>Streptococcus pneumoniae</i> infections</b>, through greater improved strain coverage, leading to <b>lesser disease burden</b> e.g. pneumonia and other related infections)                             <ul style="list-style-type: none"> <li data-bbox="896 586 2333 668">- Reduced <b>misuse of antibiotics will help combat AMR</b> by prioritizing antibiotics for patients with the greatest need and highest likelihood of response</li> <li data-bbox="896 691 2428 772">- This will <b>slow the rate at which resistance develops for current antibiotics</b>, and make <b>novel antibiotics effective for longer</b></li> </ul> </li> </ul>
<p data-bbox="226 805 619 882"><b>PATIENT FEWER MORTALITIES</b></p> 	<ul style="list-style-type: none"> <li data-bbox="802 819 2308 901">• Provide vaccines targeting <b>new strains of <i>S. pneumoniae</i></b>, and enabling immunisation programmes targeting at-risk patient groups (e.g., over-65s)                             <ul style="list-style-type: none"> <li data-bbox="896 923 2354 1005">- <b>Increased vaccine coverage could reduce the incidence of community acquired pneumonia (CAP)</b>, one of the leading causes of mortality in Europe</li> </ul> </li> </ul>
<p data-bbox="173 1059 672 1136"><b>HEALTHCARE SYSTEM REDUCTION IN HCS COSTS</b></p> 	<ul style="list-style-type: none"> <li data-bbox="802 1072 2372 1153">• <b>Managing disease incidence and severity of infections could reduce healthcare system costs associated with CAP</b>, which are estimated at €6.4bn annually in Europe                             <ul style="list-style-type: none"> <li data-bbox="896 1176 2418 1258">- Novel vaccines and immunisation programmes primarily could <b>reduce indirect inpatient costs associated with CAP-related hospitalisations</b></li> </ul> </li> </ul>

Sources: IQVIA Internal Expertise, Secondary Sources: (1), (2), (3), (4), (5), (6), (7), (8), (9). Abbreviations: Community acquired pneumonia (CAP), Healthcare System Costs (HCS)  
 2024 Pipeline Review – Innovation for Unmet Need

# Urinary tract infections are one of the most common hospital-acquired infections, and account for a significant portion of the AMR burden

## Urinary Tract Infections

Urinary tract infections (UTIs) are a common infection affecting all ages but more common in women. Primarily caused by *E. coli*, UTIs are characterized by frequent urination and pain. In severe cases, UTIs can lead to kidney infection and sepsis<sup>\*1,2</sup>

### PATIENT BURDEN

**400m UTI cases globally**

Annual incidence of UTIs

**520k global DALYs**

Associated with complex UTIs

**57%**

of UTIs resistant to at least one antibiotic



### SOCIETAL BURDEN

**~€400m societal costs in Europe**

due to UTIs<sup>9</sup>



- **Annual global incidence of UTIs is estimated at 401m**, affecting all age groups but with higher incidence in elderly patients and women<sup>\*2</sup>
- **UTIs are the most common hospital-acquired infection (HAI)**, accounting for 40% of all HAI, with 80% of these caused by an indwelling catheter<sup>\*3</sup>
  - **Hospital-acquired UTIs carry a higher risk of severe complications**, including sepsis, and can extend hospital stays by up to three days<sup>\*8</sup>
  - **Hospital-acquired UTIs are a key driver of antimicrobial resistance** due to the frequent use of antibiotics in patients with weakened immune systems<sup>\*4</sup>
- **Globally, UTIs are associated with 520k DALYs and 237k annual deaths**, primarily from complicated and healthcare-acquired UTIs<sup>\*2</sup>
  - **Deaths from UTIs have increased by 240% since 1990**, primarily driven by an aging population<sup>\*2</sup>
- **UTIs are usually treated with antibiotics**, although **due to growing antimicrobial resistance first-line antibiotics are less useful**, with 57% of UTIs are resistant to at least one antibiotic<sup>\*4</sup>
- **UTIs, and broader HAIs, are associated with significant healthcare burden** due to prolonged hospital stays; long-term disability and increased resource utilisation<sup>\*5</sup>
  - **Annual costs in Europe due to hospital-acquired infection are estimated to be more than €7bn**<sup>\*6,7</sup>

Abbreviation: Hospital Acquired Infection (HAI) Disability-adjusted life year (DALY), Escherichia coli (*E. coli*), Urinary tract infections (UTI), Antimicrobial resistance (AMR)  
Source: IQVIA Internal Expertise, Secondary Sources: (1), (2), (3), (4), (5), (6), (7), (8), (9)  
2024 Pipeline Review – Innovation for Unmet Need



# Although several novel antibiotic MoAs are in the early stages of development, the pipeline is fragile as many have yet to be validated in clinical trials

## INTRODUCTION TO NOVEL ANTIBACTERIALS

In addition to AMR-related vaccines, **novel anti-bacterials** may help combat the increasing global prevalence of drug-resistant bacterial infections<sup>\*1</sup>; however, many MoAs remain in the early stage of clinical development including pre-clinical research and development, and have not been validated in clinical trials where there is a high attrition rate of new therapies

### Traditional anti-bacterials

#### Antibiotics<sup>\*2</sup>

Includes new MoAs such as tethered macrocyclic peptides and combinations of existing antibiotics to selectively target cellular mechanisms unique to bacteria

#### Bacteriophage Enzymes<sup>\*3</sup>

Enzymes from bacteriophages (viruses which infect bacteria) are used to break down bacteria cell walls and induce cell death

### Non-traditional anti-bacterials

#### Antibacterial Antibodies<sup>\*4</sup>

Therapeutic antibodies and antibody-antibiotic conjugates (AACs) used to target specific bacterial pathogens and enhance the immune systems ability to fight infections

#### Antivirulence Agents<sup>\*5</sup>

Anti virulence factors do not destroy bacteria directly, but focus on specific bacterial components such as toxins which cause disease, making the bacteria less harmful to the host

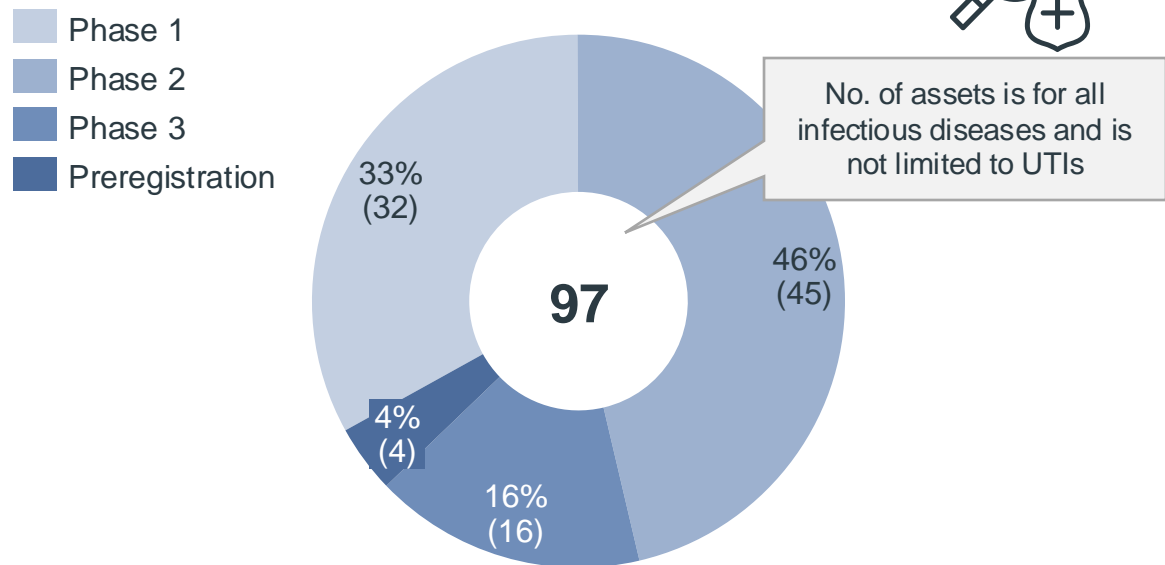
## PIPELINE CONSIDERATIONS

- The novel antibacterial pipeline is **subject to unique considerations**; the impact of **antibacterial stewardship means** that the traditional volume x price = commercial success does not apply. This is compounded by **low-cost pricing benchmarks**, the value not being the traditional “**superiority efficacy**”, and the **lower commercial lifespan** due to resistance development.
- **New payment models, value assessment approaches, and incentives are required to support sustainable investment in the novel antibacterial pipeline.**

# Additionally, there are 97 assets in development phase, but only 4 antibiotics would be considered as innovative and targeting a priority pathogen

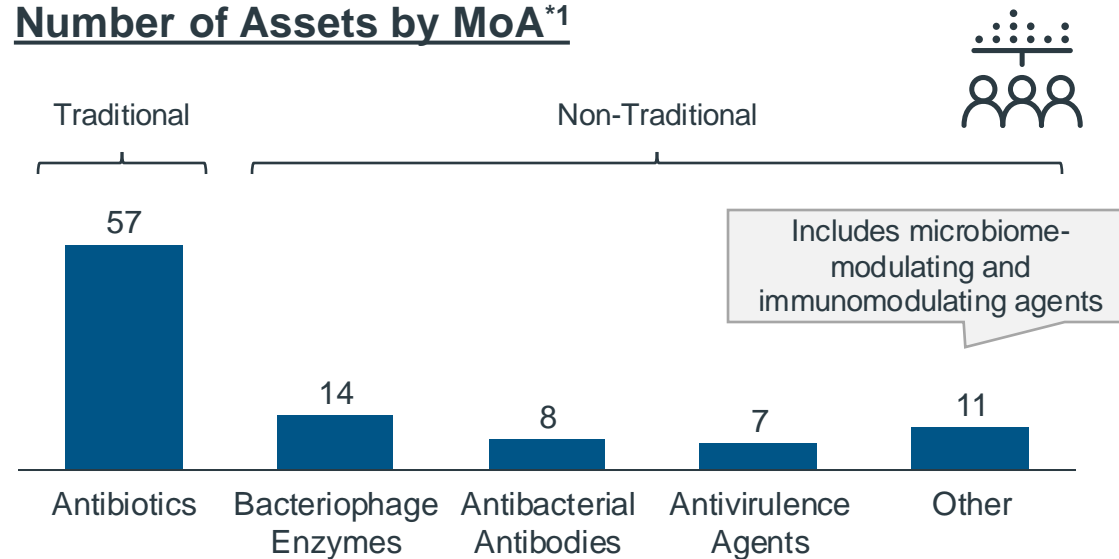
## NOVEL ANTIBACTERIAL PIPELINE

### Number of Assets by Development Phase\*1



**97 antibacterial products** (antibiotics and biologics) are currently in active clinical development, with 57 antibiotics and 40 non-traditional antibacterials, primary targeting priority pathogens

### Number of Assets by MoA\*1



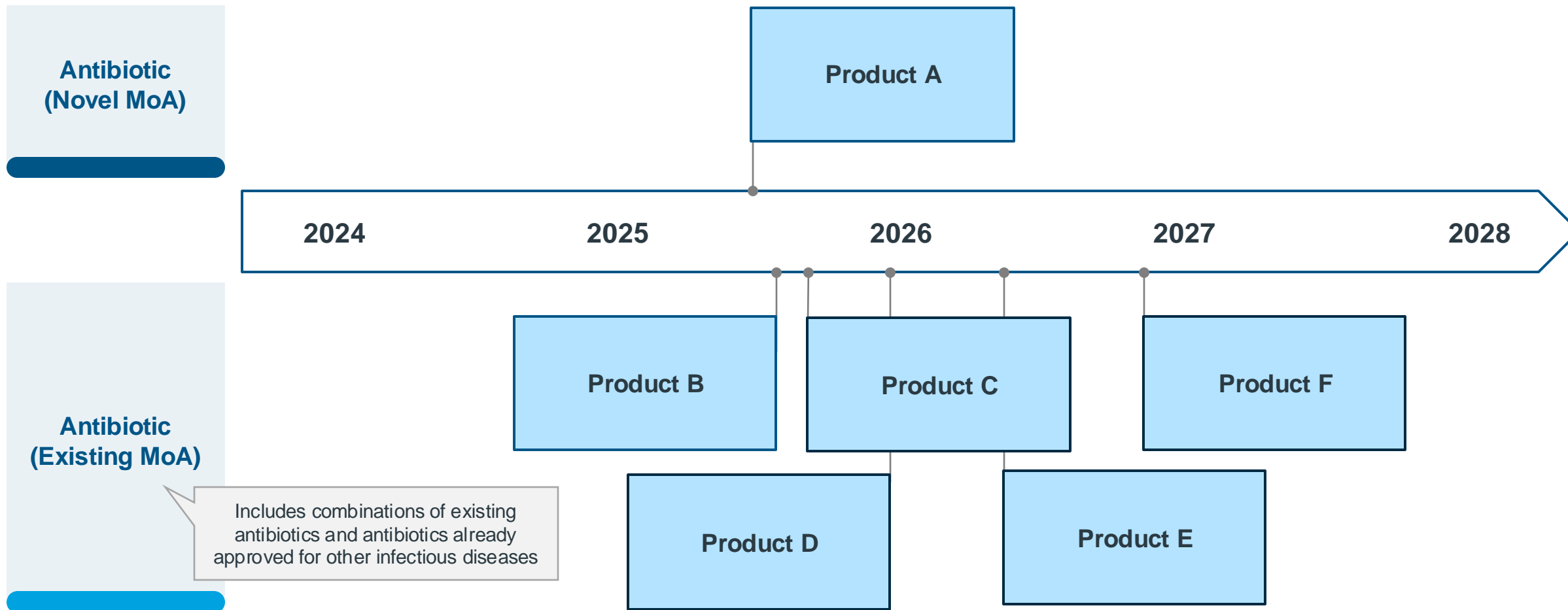
Despite the number of assets, WHO has highlighted limitations regarding the current scope of the antibacterial pipeline:

- Of the 57 antibiotics, **32 are intended against priority pathogens from the BPPL but only 12 can be considered innovative.**
- Furthermore, **only 4 of these 12 (innovative antibiotics) are active against at least 1 WHO 'critical' pathogen.**
- Overall, antibacterial agents in the clinical pipeline combined with those approved in the last six years **are still insufficient** to tackle the threat of drug-resistant infections.

\*1 Number of ongoing active trials as of December 2023. Abbreviation: Mechanism of Action (MoA); Bacterial Priority Pathogens List (BPPL)  
 Source: WHO Pipeline of Antibacterial Products ([Link](#))  
 2024 Pipeline Review – Innovation for Unmet Need

# Six antibiotics are in late-stage clinical trials for UTIs, although only one product has a novel mechanism of action

## ANTIBIOTIC PIPELINE FOR URINARY TRACT INFECTIONS Phase 3 products



Approval Timeline Criteria: P3 Products: P3 primary completion date + 1 year, P2 Products: P2 primary completion date + 6 years. Timeline includes phase 1, 2 & 3 industry sponsored products with trial locations in US or EU.

Source: WHO Pipeline of Antibacterial Products ([Link](#)), CT.gov, Company Websites.

2024 Pipeline Review – Innovation for Unmet Need

# New antibacterials promise to improve outcomes for individual patients, but also play a wider role in reducing the risk of societal-level antibiotic resistance

## IMPACT OF NOVEL ANTIBACTERIALS

### IMPACT AREA

### IMPACT

#### PATIENT IMPROVED OUTCOMES



- Enables **antibiotic resistant infections to be treated more quickly and effectively, including** UTIs, sexually-transmitted diseases, hospital-acquired infections
- Provides **alternative options for patients who may not tolerate, or respond to,** existing antibiotics

#### HEALTHCARE SYSTEM REDUCTION IN HOSPITALISATIONS



- **Promises to reduce hospitalisation stay time**
  - Hospital-acquired infection is associated with 10x increase in length of hospital stay<sup>1</sup>; new anti-bacterials could significantly impact hospital capacity if patients can be treated and discharged more quickly
- Reduces **clinical risks** associated with current **antibiotic stewardship protocols, which affects surgery, child-birth, chemotherapy,** amongst other areas

#### SOCIETY REDUCED RISK OF WIDESPREAD AMR



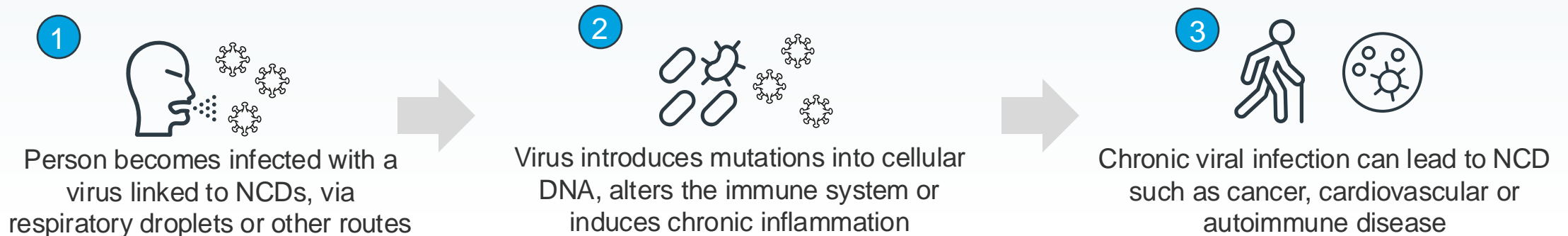
- **Reduces the societal and economic burden of infections,** which affect millions of patients annually, and often **requires additional caring responsibilities for elderly patients**
- Reduces the risk of widespread antibiotic resistance, which **risks economic impact in Europe of €100bn+**

# Chronic viral infections have demonstrated a causal role in the onset of severe non-communicable diseases

## INTRODUCTION TO VIRUS-INDUCED NON-COMMUNICABLE DISEASES

- **Non-communicable diseases (NCDs) are chronic health conditions that cannot be transmitted** from one person to another\*<sup>1</sup>
  - NCDs are responsible for 41m deaths globally each year, equivalent to 74% of all deaths globally\*<sup>1</sup>
- **Viruses have been found to have a causal role in the onset of various NCDs, such as cancer (cervical, liver) and cardiovascular disease (stroke, heart failure)**
  - It is estimated that **~10% of all cancers are caused by viruses**, with viruses also implicated in autoimmune and neurodegenerative conditions such as multiple sclerosis (MS)\*<sup>2,3</sup>
- **Not all viral infections will result in an NCD, however, the transmission mechanism is a key area of scientific study**

### Mechanism through which viruses can cause NCDs\*<sup>5,6</sup>



# Epstein-Barr virus (EBV) is one of the most common human viruses, and is implicated in the development of multiple sclerosis and certain cancers

## Epstein-Barr Virus

Epstein-Barr Virus (EBV) is one of the most common human viruses, with 95% of adults having dormant EBV in their B-cells. EBV causes glandular fever in infected persons, and has been implicated as having a **causal role in the onset of MS and several cancers**\*<sup>1,2</sup>

### PATIENT BURDEN

#### 95% of adult population

Have had a past infection with EBV

#### 5.8m global DALYs

From cancers caused by a historical EBV infection and MS, of which EBV is a leading cause



#### No approved vaccines

SoC focuses on symptom management

### HEALTHCARE SYSTEM BURDEN

#### €58k / patients

Annual healthcare system and social costs associated with severe MS in Europe



- Epstein-Barr Virus (EBV) infection is spread through saliva, is commonly acquired in children before the age of 5, and persists in B-cells throughout a person's life\*<sup>3</sup>
  - Glandular fever symptoms include fatigue & fever. Although most people recover within 2~4 weeks, immunocompromised individuals may suffer from complications such as meningitis or hepatitis\*<sup>7,8</sup>
- EBV is implicated in having a causal role in multiple cancers, such as Burkitt lymphoma, Hodgkin lymphoma & nasopharyngeal carcinoma\*<sup>3,4</sup>
  - Global DALYs for EBV-associated cancers is 4.6m\*<sup>3</sup>
- EBV is also implicated in multiple autoimmune conditions, and is now recognised as a cause of multiple sclerosis (MS)\*<sup>4</sup>
  - MS is a chronic autoimmune condition associated with 1.2m global DALYs\*<sup>5,6</sup>
- There is no vaccine for EBV, with the current SoC focused on symptom management, with hospital treatment required in severe cases. Management of EBV-associated NCDs is highly interventional, involving drug treatments, surgery and other support (e.g physiotherapy)
- The healthcare system & social costs for EBV-associated cancers & MS are high, with the annual cost of illness in severe MS patients estimated at €58k / patient\*<sup>10</sup>
  - MS also has a severe impact on productivity, with workforce participation for severe MS patients only 8%\*<sup>10</sup>

Abbreviation: Disability-adjusted life year (DALY), Multiple Sclerosis (MS), Non-communicable diseases (NCDs), Standard of Care (SoC)  
 Source: IQVIA Internal Expertise, Secondary Sources: (1), (2), (3), (4), (5), (6), (7), (8), (9), (10)  
 2024 Pipeline Review – Innovation for Unmet Need

# New vaccines against EBV and other viruses would be a crucial tool in preventing NCDs, by reducing the incidence and severity of viral infections

## INTRODUCTION TO VACCINES AGAINST EPSTEIN-BARR VIRUS

**Vaccines against Epstein-Barr virus (EBV)** – several prophylactic vaccines are in development for EBV and may reduce the incidence & severity of EBV infection, and the incidence of EBV-associated NCDs. The approval of a vaccine for EBV would be the first targeting a latent virus implicated in NCDs, and may pave the way for further innovation in this field

### Potential Technologies for Prophylactic EBV vaccines:

There are two types of vaccine technology which are currently being used to develop prophylactic vaccines for EBV:

- 1. Recombinant subunit vaccine** includes only the essential antigens involved in the immune response (e.g., surface protein, polysaccharides) and not the whole microbe




This technology is already widely deployed in vaccines for hepatitis B and herpes zoster\*<sup>2</sup>

- 2. mRNA vaccine** uses messenger RNA (mRNA) to instruct cells to produce a protein from the pathogen, triggering an immune response without using the pathogen itself

Recent advances in mRNA technology, enabled the first approval of an mRNA vaccine, against Covid-19\*<sup>3</sup>

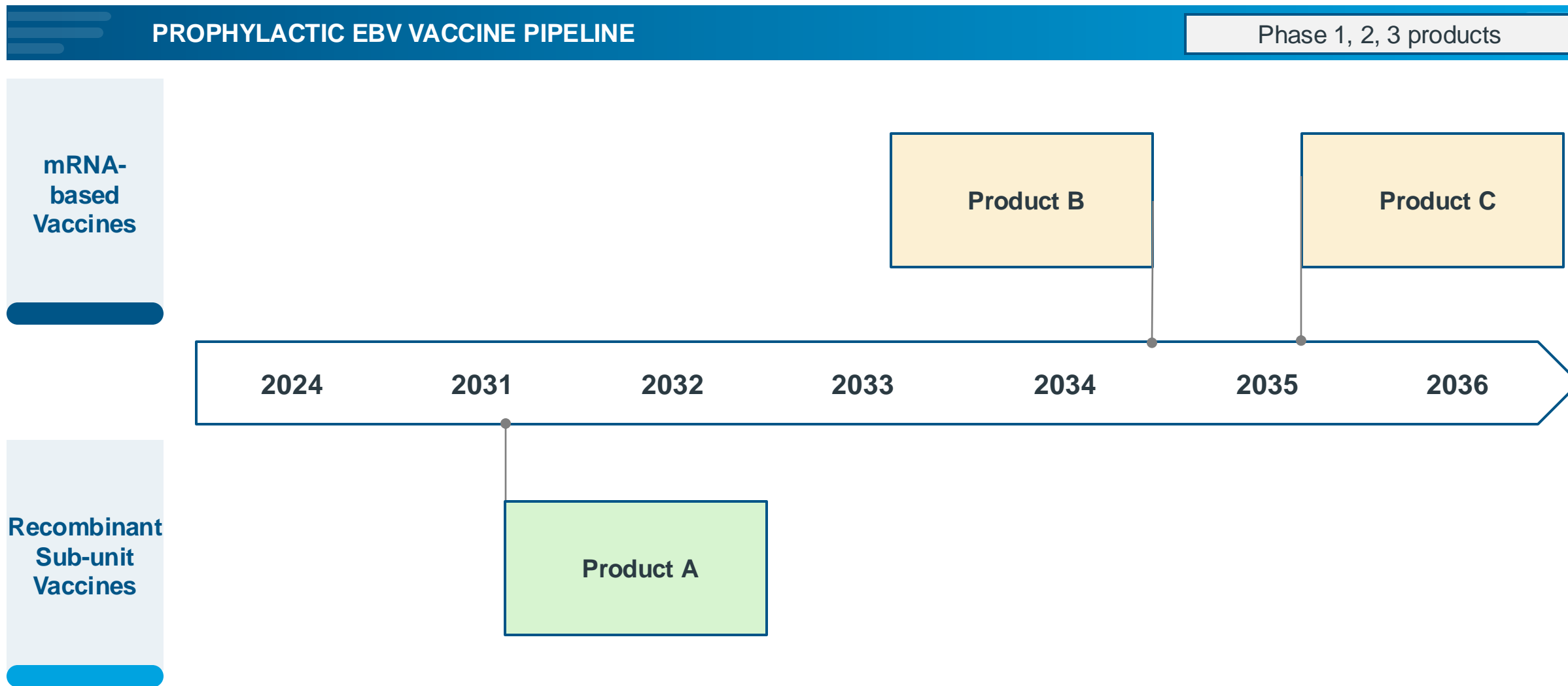
### Proposed Mechanism for the prevention of EBV-associated NCDs\*<sup>1</sup>

A novel vaccine for Epstein-Barr virus (EBV) may reduce the prevalence of associated NCDs through the following mechanism:

-  **1. Introduction of EBV vaccine into a childhood vaccination programme** may reduce the number of primary EBV infections
-  **2. A reduction in primary EBV infections will lead to a reduction in the level of latent EBV and chronic EBV infections** in the general population
-  **3. The reduction in latent EBV and chronic infections in the general population may then reduce the prevalence of associated NCDs**, such as certain cancers and multiple sclerosis



# There are three prophylactic vaccines currently in early-stage development for EBV, with the first approvals expected in the 2030's



Approval Timeline Criteria: P3 Products: P3 primary completion date + 1 year, P2 Products: P2 primary completion date + 6 years, P1 Products: P1 primary completion date + 9 years. Timeline includes phase 1, 2 & 3 industry sponsored products with trial locations in US or EU.

Abbreviation: Epstein-Barr virus (EBV). Source: Clinical Trial Repository (Access Date: April 30th 2024), ct.gov, Company Websites  
2024 Pipeline Review – Innovation for Unmet Need



# Prophylactic vaccines for EBV would bring major benefits for individuals, and significantly reduce downstream healthcare and societal costs

## IMPACT OF VACCINES AGAINST NCDs (e.g. EBV)

### IMPACT AREA

### IMPACT

#### PATIENT AVOIDED DISEASE BURDEN



- **Promise to reduce the incidence of Multiple Sclerosis** through a reduction in the incidence of chronic EBV infection
  - Would significantly reduce **health burden in patients who might otherwise develop MS**, given the **life-changing symptoms** (vision loss, mobility issues, chronic pain) associated with the disease
- Promise to reduce the incidence of EBV-associated cancers (**lymphomas, nasopharyngeal cancer**), which would **avoid negative impact on QoL and poor clinical outcomes**
- May also **reduce development of other autoimmune diseases**, such as rheumatoid arthritis, Sjögren’s syndrome, systemic lupus erythematosus

#### HEALTHCARE AND SOCIETY AVOIDED TREATMENT AND SOCIETAL COSTS



- Reduction in healthcare costs associated with MS and cancer treatment
  - Based on European incidence and treatment costs for MS, **EBV-vaccines could potentially avoid >€10bn in MS treatment costs**, particularly if able to reduce the development of severe MS

# Colorectal cancer is the second most common cancer in Europe, with growing incidence in younger patients making it a major public health concern

## Colorectal Cancer

Colorectal cancer (CRC) affects the colon (large intestine) or rectum. It is the second most common cancer type cause of cancer death in Europe, with 356k diagnoses in 2022<sup>\*6</sup>, with rising incidence, particularly in younger people, making it a major public health concern

### PATIENT BURDEN

#### Number of cases

1.9m cases globally, with rising incidence

#### Survival rates

5-year survival rates for colorectal cancer are ~65%, varying significantly by stage

#### 21.6m DALYs

Globally, associated with CRC

#### 900k Annual Deaths

Globally, associated with CRC

- **21.6m DALYs globally** associated with CRC, representing a major global health burden<sup>\*1</sup>
- **Primarily a disease affecting older patients** with average age of diagnosis between 63~69 years old<sup>\*2</sup>, although **early onset CRC incidence is increasing. The increase in incidence in younger patient incidence has been linked to:**<sup>\*8</sup>
  - Sedentary lifestyles and being overweight
  - Smoking, heavy alcohol use
  - Low-fibre, and high-fat diets, and diets high in processed meat
- **Early-stage CRC** is generally treated by **surgery to remove the tumour** and nearby lymph nodes; **adjuvant chemotherapy and radiation therapy may be required**<sup>\*3</sup>
- However, even when treated at early stage through surgery, **QoL for CRC patients can be significantly impacted; colostomy or ileostomy may be required**, which can bring physical and emotional challenges<sup>\*4</sup>
- **Advanced disease has poor survival rates**, and is treated through a combination of chemotherapy, surgery, targeted therapies (e.g., for patients with KRAS or BRAF mutations) and radiotherapy<sup>\*3</sup>
- **European health system costs for CRC are estimated at €5-10bn**, with **€9bn annual costs associated with premature death and productivity losses**<sup>\*8</sup>

Abbreviation: Colorectal Cancer (CRC), Disability-adjusted life year (DALY), Quality of life (QoL)  
Source: IQVIA Internal Expertise, Secondary Sources: (1), (2), (3), (4), (5), (6), (7), (8)  
2024 Pipeline Review – Innovation for Unmet Need

# mRNA therapeutic vaccines are a transformational new personalized cancer therapy, training the body's immune system to destroy cancerous cells

## INTRODUCTION TO mRNA THERAPEUTIC VACCINES

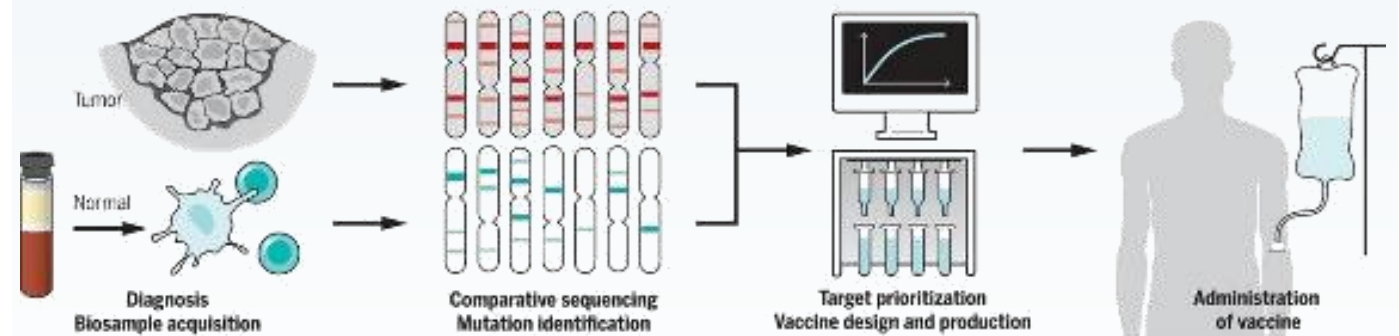
**mRNA Therapeutic Vaccines** – personalized therapy that trains the immune system to recognize and destroy cancerous cells

- **Work by introducing an mRNA sequence for a cancer-specific antigen into the body's cells.** The cells then produce this cancer-specific antigen, which triggers an immune response and trains the immune system to recognize and destroy cancer cells\*<sup>1</sup>.
- **Can be produced quickly to target an individual's unique cancer profile,** improving the efficacy of treatment while minimizing toxicity on healthy cells\*<sup>2</sup>
- The success of mRNA vaccines in combatting COVID-19 has led to **increased investment in mRNA therapeutic vaccines as a novel modality for treating cancer\*<sup>1</sup>**

**Key Mechanisms of Action\*<sup>1</sup>** - 3 main types of mRNA vaccine are used against cancer:

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

## Method of Administration\*<sup>3</sup>



A patient's **healthy and cancerous tissues are compared**, and **tumour-specific variations are identified**. These “mutant” variations are **assessed** for an **optimal vaccine target**, after which the **vaccine is produced and administered**.

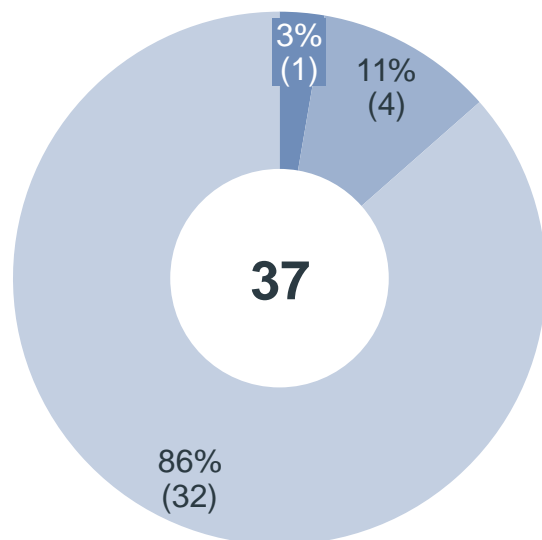
# mRNA therapeutic vaccines are an innovative modality in oncology, with 37 trials initiated since 2022, 86% of which are in Phase 1

## INTRODUCTION TO PIPELINE FOR mRNA THERAPEUTIC VACCINES IN ONCOLOGY

### Number of Clinical Trials By Development Phase

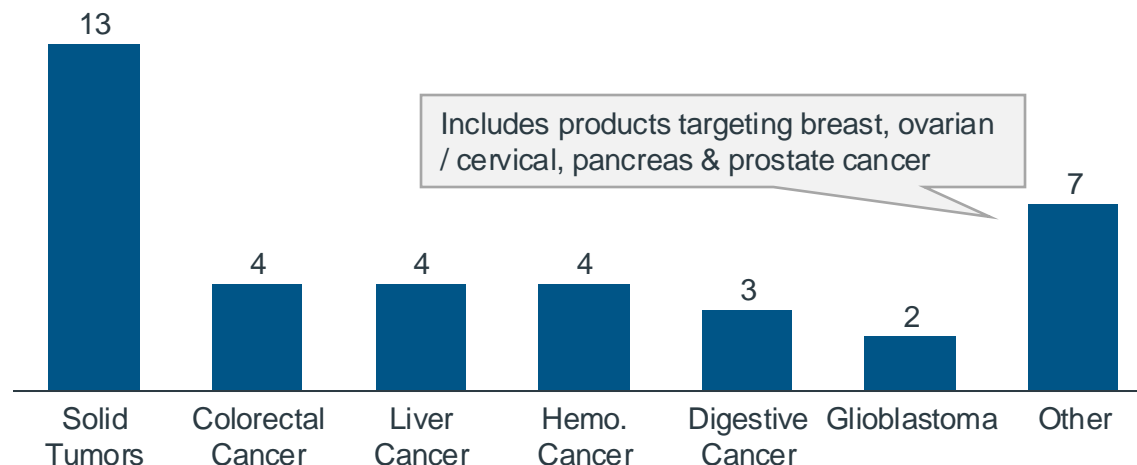
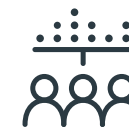


- Phase 1
- Phase 2
- Phase 3



**37 trials involving mRNA therapeutic vaccines in oncology have been initiated** since 2022, with most of them in early-stage clinical trials

### Number of Clinical Trials By Indication



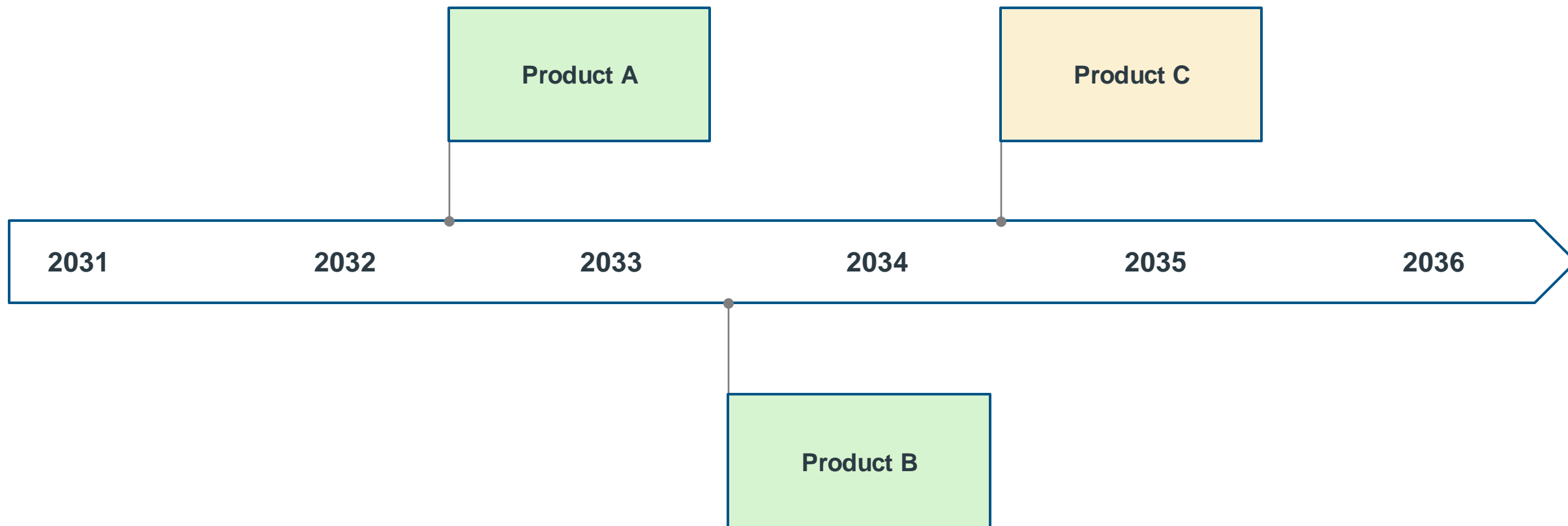
**Most trials are targeting a range of solid tumours, while there are specific trials against tumours such as colorectal and liver. Advanced (phase 3 clinical trials) for mRNA cancer vaccines are seen in melanoma\*<sup>1</sup>**

Search Criteria: Industry-sponsored P1~3 trials initiated since 2022. (Search terms: "Cancer", "mRNA Vaccine". Colorectal cancer trials identified in pipeline analysis have been added to the clinical trial list.  
 Source: ClinicalTrials.gov (Accessed on 18<sup>th</sup> July 2024). Secondary Sources: (1)  
 2024 Pipeline Review – Innovation for Unmet Need

# In colorectal cancer, there are three mRNA vaccines in P1/P2 clinical trials, with the first approval expected in the early 2030's

## mRNA THERAPEUTIC VACCINES IN COLORECTAL CANCER TREATMENT PIPELINE




Phase 1, 2, 3 products



Approval Timeline Criteria: P3 Products: P3 primary completion date + 1 year, P2 Products: P2 primary completion date + 6 years, P1 Products: P1 primary completion date + 9 years. Timeline includes phase 1, 2 & 3 industry sponsored products with trial locations in US or EU. Ph2 for Product C has not yet started, though remains in company pipeline. Approval time assumes Ph2 start in 2025. Source: Clinical Trial Repository (Access Date: April 30th 2024), ct.gov, Company Websites. 2024 Pipeline Review – Innovation for Unmet Need

# mRNA therapeutic vaccines for colorectal cancer promise improved survival rates, and minimising surgical procedures and associated complications

## IMPACT OF mRNA THERAPEUTIC VACCINES FOR CRC

IMPACT AREA	IMPACT
<p><b>PATIENT IMPROVED SURVIVAL RATES</b></p> 	<ul style="list-style-type: none"> <li>• Offer a <b>completely new treatment option for CRC patients</b></li> <li>• <b>Promise improved progression-free and overall survival rates for colorectal cancer patients</b>, through inducing long-term immune response and delayed tumor recurrence</li> </ul>
<p><b>PATIENT IMPROVED QOL</b></p> 	<ul style="list-style-type: none"> <li>• <b>Provide substantial improvements in treatment experience</b> due to superior side-effect profile/tolerability and non-invasive nature, when compared with the current SoC, which includes surgery, radiotherapy and chemotherapy</li> <li>• <b>Reduce the need for additional surgical procedures, such as colostomia</b>, which are associated with significant QoL impact through long-term side-effects and infection risks</li> </ul>
<p><b>SOCIETY ALLOWING PATIENTS TO REJOIN WORKFORCE</b></p> 	<ul style="list-style-type: none"> <li>• <b>Allow patients to return to the workforce</b> given the potential to improve survival rates with minimize long-term QoL effects                         <ul style="list-style-type: none"> <li>- <b>This could reduce the economic impact of CRC</b> (estimated at €9bn p/y in Europe), and is relevant given the increasing incidence of CRC in working age patients</li> </ul> </li> </ul>

*“Rising incidence of CRC, particularly amongst younger individuals, makes it a major public health concern. Survival rates remain low for patients diagnosed at advanced stages, highlighting the urgent need for new treatment options. One promising development is mRNA vaccines, which may enhance survival rates while preserving a good QoL for these patients”*

Digestive Cancers Europe

Abbreviation: Colorectal Cancer (CRC), Quality of life (QoL), Standard of care (SoC)  
 Source: IQVIA Internal Expertise, Secondary Sources: (1), (2), (3), (4), (5), (6), (7), (8)  
 2024 Pipeline Review – Innovation for Unmet Need



# DMD is an X-linked, rare genetic disorder characterized by progressive muscle wasting, with an average life expectancy of 30 years

## Duchenne Muscular Dystrophy

Severe genetic condition primarily affecting males characterized by progressive muscle wasting. DMD prevalence is around 1 in 5,000 people, with the average life expectancy in Europe being 30 years old<sup>\*1,2,3</sup>

### PATIENT BURDEN

**Affects 1 in 5,000 people<sup>\*3</sup>**

~26k patients estimated to be living with DMD in EU<sup>\*8</sup>



**30-year life expectancy<sup>6</sup>**

DMD patients also suffer from loss of ambulation at 12 years of age

**Severe side-effects with SoC<sup>\*4</sup>**

Life-long use of steroids is associated with severe side-effects

### HEALTHCARE SYSTEM BURDEN

**Annual Cost €165k / patient<sup>\*6</sup>**

For late-stage DMD patients in Europe



- **Duchenne Muscular Dystrophy (DMD) is a rare genetic disorder and the most severe form of muscular dystrophy<sup>\*1</sup>**. It is caused by genetic mutations in the dystrophin gene which leads to progressive muscle degeneration and premature death<sup>\*1</sup>
  - **DMD primarily affects males, with the incidence estimated at 1 in 3,500 male births<sup>\*3</sup>**
- **DMD is usually diagnosed soon after birth**, with disease progression broken down into four stages (early ambulatory, late ambulatory, early non-ambulatory, late non-ambulatory)<sup>\*1</sup>
  - Patients usually **lose ambulation by age 12**, and require **24-hour respiratory support by age 20<sup>\*2</sup>**
  - Life expectancy for DMD varies by country, but **the average life expectancy in Europe is approximately 30 years<sup>\*7</sup>**
- Current **SoC for DMD involves lifelong corticosteroids** (e.g., prednisone, deflazacort) to slow muscle degeneration, although this causes **severe side-effects such as weight gain, weak bones and behavioural changes<sup>\*4</sup>**
- Annual healthcare costs for DMD patients vary by country and disease stage, but are estimated at **€69k / patient in Germany for late non-ambulatory patients<sup>\*6</sup>**
- Annual non-medical and social costs for DMD also vary by country and disease stage, but are estimated at **€95k / patient in Germany for late non-ambulatory patients<sup>\*6</sup>**

Abbreviation: Duchenne Muscular Dystrophy (DMD), Disability-adjusted life year (DALY), Standard of Care (SoC), Disease Modifying Treatment (DMT)

Source: IQVIA Internal Expertise, Secondary Sources: (1), (2), (3), (4), (5), (6), (7), (8)  
2024 Pipeline Review – Innovation for Unmet Need

# Gene transfer therapy vectors such as Adeno-Associated Viruses can deliver a functioning dystrophin gene to patients with Duchenne Muscular Dystrophy

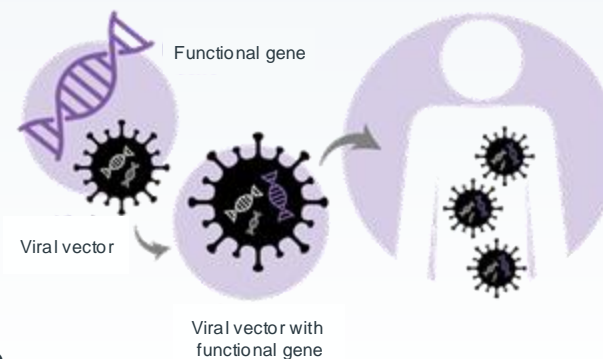
## INTRODUCTION TO AAV-BASED GENE THERAPIES

**AAV-based Gene Therapies** – gene therapies that use **adeno-associated viral vectors (AAV)** to deliver a functional version of a specific gene into cells to replace a defective or missing gene<sup>\*1,2</sup>

- Several types of viral vectors are used to deliver gene therapies, with **adeno-associated virus, adenovirus and lentivirus** the three main viral vectors in gene therapies<sup>\*7</sup>
  - Due to its superior safety profile and ability to establish long-term gene expression in human cells, **adeno-associated viral vectors are the most successful viral vector used in gene therapies**<sup>\*3</sup>

### Mechanism of Action in Duchenne Muscular Dystrophy<sup>\*4</sup>

- In DMD patients, **AAV vectors are used to deliver a functional version of the dystrophin gene (micro-dystrophin) directly into a patient's skeletal, respiratory and cardiac cells**, with specific promoters used to drive transgene expression
- Once the gene therapy has been administered, the **patient's own cells will produce micro-dystrophin**, which will protect the muscle cells and prevent them from degenerating
- **Gene therapies have been shown to increase muscle strength** in patients, and **may prolong the ambulatory phase in DMD patients**



### Method of Administration<sup>\*5</sup>

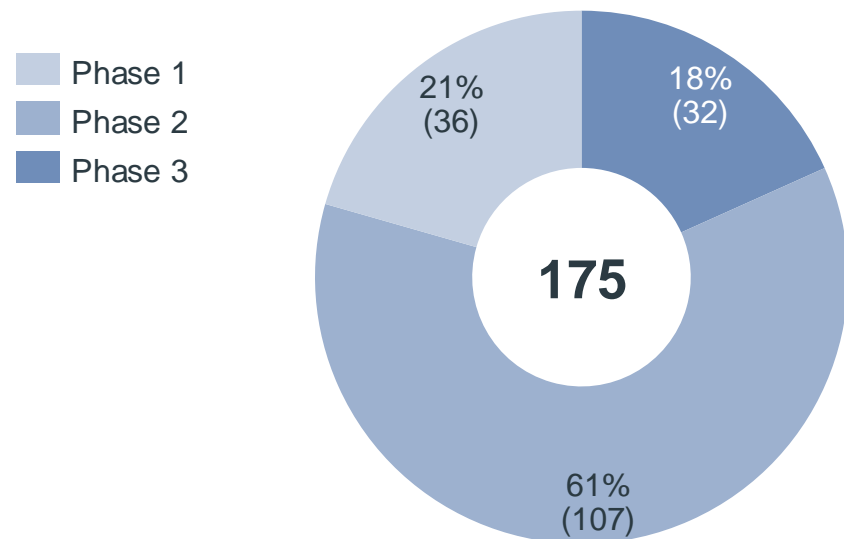
Gene therapies for DMD are delivered **intravenously**, with patients having to adhere to **strict corticosteroid regimens prior and post infusion to reduce the risk of an immune response**<sup>\*6</sup>



# 175 clinical trials involving AAV-based gene therapies initiated since 2022, with neurology and neuromuscular indications the focus of innovation

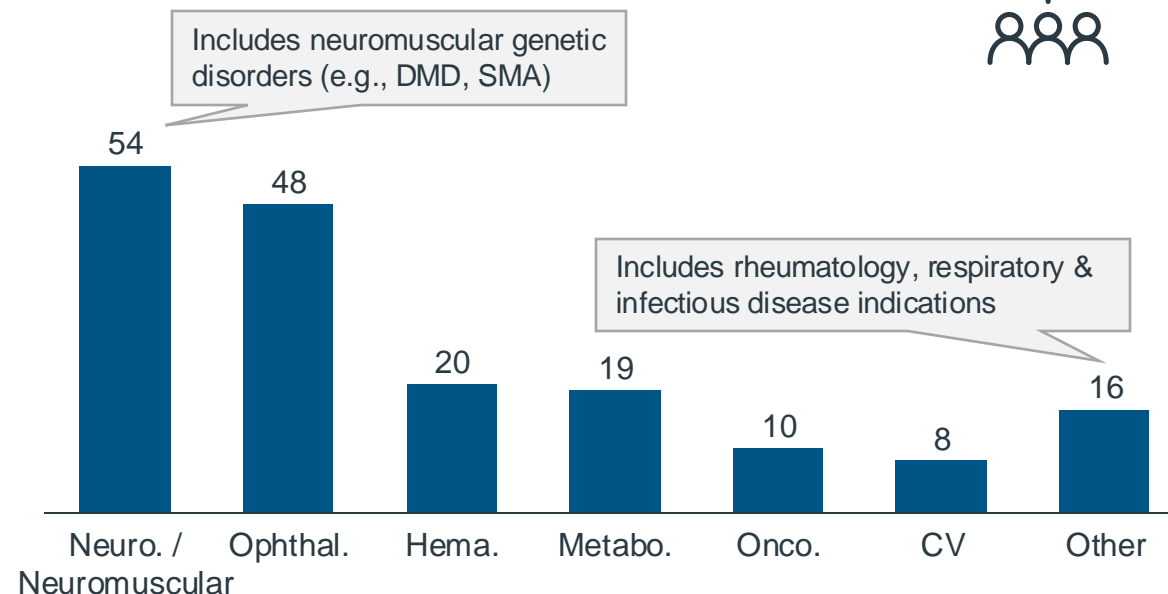
## INTRODUCTION TO PIPELINE FOR AAV-BASED GENE THERAPIES

### Number of Clinical Trials By Development Phase



175 clinical trials for AAV-based gene therapies have been initiated since 2022, with the 32 in phase 3 clinical trials indicating several approvals are likely in the next several years

### Number of Clinical Trials By Therapy Area



Neurology and neuromuscular indications are the primary focus for AAV-based gene therapy clinical development, with 54 trials initiated since 2022

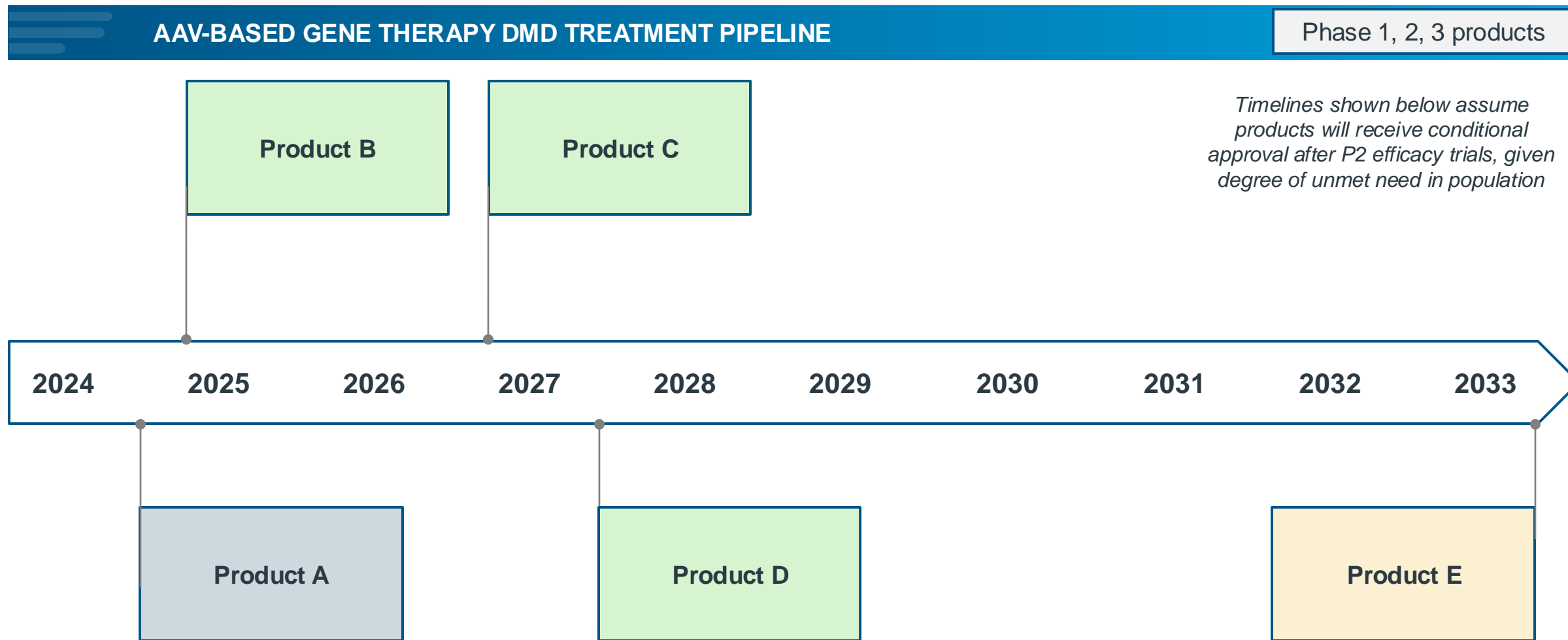
Search Criteria: Industry-sponsored P1~3 trials initiated since 2022. (Search terms: "AAV-based gene therapies". Trials have been grouped based in target indication therapy area)

Abbreviation: Adeno-associated viral vectors (AAV), Duchenne Muscular Dystrophy (DMD), Spinal Muscular Atrophy (SMA), Neurology (Neuro.), Ophthalmology (Ophthal.), Hematology (Hema.), Metabolism (Metabo.), Oncology (Onco.), Cardiovascular (CV)

Source: Clinical Trial Repository (Access Date: April 30th 2024)

2024 Pipeline Review – Innovation for Unmet Need



# Several AAV-based gene therapies are targeting approval in DMD in the next 5 years



Approval Timeline Criteria: For DMD, due to high UMN timeline assumes a conditional approval will be granted after P2 trials. P2 Products: P2 primary completion date + 1 year, P1 Products: P1 primary completion date + 6 years. Timeline includes phase 1, 2 & 3 industry sponsored products with trial locations in US or EU.  
 Source: Clinical Trial Repository (Access Date: April 30th 2024), ct.gov, Company Websites.  
 2024 Pipeline Review – Innovation for Unmet Need

# AAV-based gene therapies for DMD promise to slow disease progression, prolong ambulatory phase, and reduce frequency of hospital visits

## IMPACT OF AAV-BASED GENE THERAPIES ON DMD

IMPACT AREA	IMPACT
<p><b>PATIENT IMPROVED LIFE EXPECTANCY</b></p> 	<ul style="list-style-type: none"> <li>• <b>Promise to slow disease progression</b>, by introducing functional dystrophin genes, which will in turn <b>improve patient life expectancy</b> by slowing muscle degradation in muscles and the heart</li> </ul>
<p><b>PATIENT IMPROVED QOL</b></p> 	<ul style="list-style-type: none"> <li>• Offers to significantly <b>improve the lives of DMD patients</b>, by:                             <ul style="list-style-type: none"> <li>➢ <b>Reducing number of hospital visits and range of medical interventions required</b></li> <li>➢ <b>Reduce required dosage of corticosteroids, avoiding severe side-effects</b> such as weight gain, osteoporosis and behavioural changes</li> <li>➢ <b>Prolonging ambulatory phase</b>, giving patients greatly improved QoL</li> </ul> </li> </ul>
<p><b>HEALTHCARE AND SOCIETAL SYSTEM REDUCED COST BURDEN</b></p>	<ul style="list-style-type: none"> <li>• <b>Reduce the level of direct medical costs, particularly associated with late-stage DMD patients</b> (e.g., 24h ventilation equipment, formal care costs)</li> <li>• <b>Reduce the major burden on patients' families and informal carers</b></li> </ul>

*“We have long been optimistic that gene therapy could be a potential treatment for Duchenne”*

Parent Project Muscular Dystrophy (PPMD)

Abbreviation: Adeno-associated viral vectors (AAV), Duchenne Muscular Dystrophy (DMD), Quality of life (QoL). Sources: IQVIA Internal Expertise, Secondary Sources: (1), (2), (3), (4), (5), (6), (7), (8)  
 2024 Pipeline Review – Innovation for Unmet Need

# Elevated lipoprotein (a) levels are an independent risk factor for cardiovascular disease, determined largely by genetics

## Elevated Lipoprotein (a)

Lipoprotein (a) is a large lipoprotein produced by the liver to carry lipids around the body. Similar in structure to low density lipoprotein (LDL cholesterol), elevated lipoprotein (a) is strongly associated with cardiovascular disease and does not respond to conventional treatments\*<sup>1</sup>

### PATIENT BURDEN

**10-30% global population**  
with elevated lipoprotein (a)

**2x increase**

Risk of atherosclerotic cardiovascular disease

**No approved Tx specifically for high lipoprotein (a)**



### HEALTHCARE SYSTEM BURDEN

**Up to €282bn\*<sup>6</sup>**

Annual HCS costs in Europe due to overall CVD in 2021



- **Between 10~30% of the global population has elevated lkp (a)**, resulting in an approximate prevalence of **1.4 billion**<sup>2</sup>, with only a small proportion tested and formally diagnosed\*
  - **Lipoprotein (a) levels are determined by genetics and vary widely by population** with elevated lipoprotein (a) prevalence highest in African, and lowest in Asian populations\*<sup>3</sup>
- **Elevated lipoprotein (a) levels are an independent risk factor for multiple cardiovascular diseases**, such as heart attacks, strokes, atherosclerosis and heart valve disease\*<sup>4</sup>
  - Studies have shown that **elevated lipoprotein (a) levels can double the risk of atherosclerotic cardiovascular disease**\*<sup>4</sup>
- There are **no approved drug treatments specifically for elevated lipoprotein (a)**, and **traditional treatments for CVD (e.g., statins) are ineffective** at lowering lipoprotein (a)\*<sup>1</sup>
  - **PCSK9 inhibitors have been shown to partially reduce lipoprotein (a) levels** by 20-30%, but are not currently indicated for elevated lipoprotein (a)\*<sup>1</sup>
  - **Eating and exercise habits have limited impact** on lipoprotein (a)\*<sup>5</sup>
- **The main treatment option to reduce lipoprotein (a) is lipoprotein apheresis**, a **costly treatment only considered for patients with recurrent CVD** despite optimal control of other risk factors\*<sup>1</sup>
- Elevated lipoprotein (a) contributes to the wider **CVD healthcare costs** in Europe, estimated at **€280bn in 2021**\*<sup>6</sup>

Abbreviation: Cardiovascular disease (CVD), Healthcare System (HCS), Treatment (Tx)  
Source: IQVIA Internal Expertise, Secondary Sources: (1), (2), (3), (4), (5), (6)  
2024 Pipeline Review – Innovation for Unmet Need

# Several therapies based on RNA technology are in development, specifically targeting elevated lipoprotein (a) levels

## INTRODUCTION TO RNA-BASED THERAPIES FOR ELEVATED LIPOPROTEIN (a)

**RNA-based therapies for elevated lipoprotein (a)** – RNA (ribonucleic acid) is a molecule similar to DNA that serves as a template for ribosomes to synthesize proteins. **RNA-based gene therapies work by preventing or editing the expression of faulty proteins implicated in genetic disorders**<sup>\*1</sup>

- **RNA-based gene therapies are an established modality in several TAs**, ranging from rare disease (e.g., SMA) to ophthalmology<sup>\*2</sup>
  - **RNA-based gene therapies are also approved for genetic cardiovascular diseases** (e.g., LEQVIO for HeFH), and **work by selectively silencing genes which produce proteins implicated in CVD**, with many more in clinical development<sup>\*3</sup>

### Types of RNA-based Gene Therapy for CVD<sup>\*3</sup>

1. **Antisense Oligonucleotides (ASOs)** – ASO are **short, synthetic strands of nucleic acids which bind to mRNA, interfering with the production of proteins** by inciting protein degradation; blocking expression or editing gene splicing<sup>\*4</sup>
2. **Small Interfering RNA (siRNAs)** – siRNAs are **a class of short, non-coding double stranded RNA, which work by harnessing the cells natural RNA interference process** to prevent the expression of proteins<sup>\*5</sup>

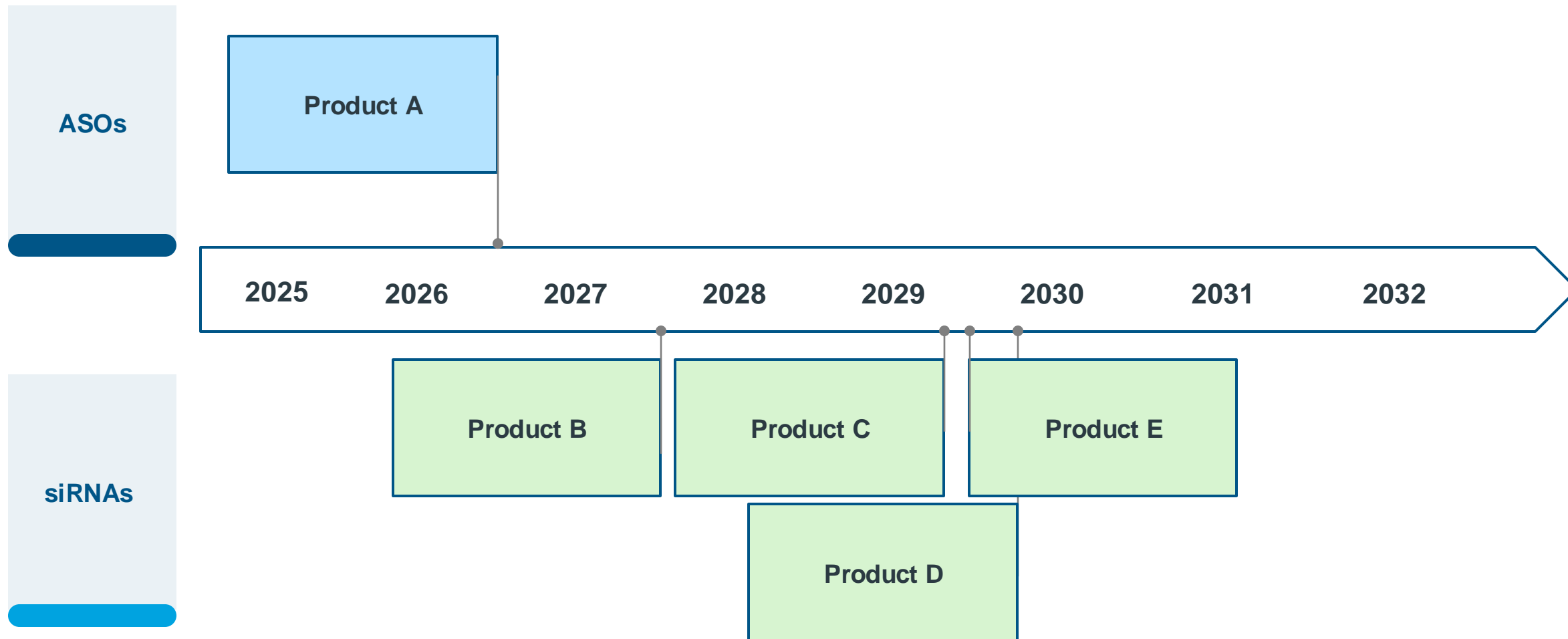
### Mechanism of Action in Elevated Lipoprotein (a)

- **RNA-based gene therapies have been shown in clinical studies to drastically reduce the amount of lipoprotein (a)** by between 50~90%<sup>\*6</sup>
- **These treatments work by silencing the expression of lipoprotein (a) through targeting of the LPA gene**, which is responsible for production of lipoprotein (a) from hepatocyte cells<sup>\*6</sup>
- **These ASO and siRNA gene therapies are administered subcutaneously each month to ensure long-term reduction of lipoprotein (a)**<sup>\*6</sup>

# A small number of Lipoprotein (a) targeting RNA gene therapies are expected to be approved in the next 5 to 10 years

## LIPOPROTEIN (A) TARGETING RNA-BASED GENE THERAPIES TREATMENT PIPELINE

Phase 2, 3 products






Approval Timeline Criteria: P3 Products: P3 primary completion date + 1 year, P2 Products: P2 primary completion date + 6 years. Timeline includes phase 2 & 3 products only with trial locations in US or EU.

Source: Clinical Trial Repository (Access Date: April 30th 2024), Company Websites  
2024 Pipeline Review – Innovation for Unmet Need

# Targeted therapies to reduce elevated lipoprotein (a) promise a new paradigm, which could reduce patient burden and avoid widespread societal costs

## IMPACT OF LIPOPROTEIN (A) TARGETING THERAPIES

IMPACT AREA	IMPACT
<p><b>PATIENT REDUCE CVD RISK</b></p> 	<ul style="list-style-type: none"> <li>• Offers to address a significant, under-addressed clinical risk factor, which can lead to major events such as <b>heart attacks and stroke</b></li> <li>• Reduces need for patients to utilize sub-optimal SoC, such as:                             <ul style="list-style-type: none"> <li>➢ <b>Statins</b>, which are known to be only partially effective, or</li> <li>➢ <b>Lipoprotein apheresis</b>, which is costly and burdensome on patients</li> </ul> </li> </ul>
<p><b>HEALTHCARE SYSTEM REDUCTION IN HOSPITALISATIONS</b></p> 	<ul style="list-style-type: none"> <li>• Promises to <b>avoid treatment and long-term management costs associated with heart attacks and stroke</b>, which could be avoided should lipoprotein (a) be better controlled                             <ul style="list-style-type: none"> <li>➢ While lipoprotein (a) is one of multiple stroke risk factors, <b>novel treatments could help to reduce the €155bn HCS costs</b></li> </ul> </li> </ul>
<p><b>SOCIETY AVOIDED ILL HEALTH</b></p> 	<ul style="list-style-type: none"> <li>• <b>Increase clinical awareness and testing for lipoprotein (a) and other inherited conditions</b></li> <li>• Provides opportunity to improve cardiovascular health at population level scale, which could <b>increase wider productivity and wellbeing</b></li> </ul>

Abbreviation: Cardiovascular disease (CVD), Healthcare system (HCS), Lipoprotein(a) (lp(a)), Treatment (Tx). Sources: IQVIA Internal Expertise, Secondary Sources: (1), (2), (3), (4), (5), (6)  
2024 Pipeline Review – Innovation for Unmet Need



# Parkinson's disease (PD) is a chronic neurodegenerative disease characterised by tremors, muscle stiffness and impaired co-ordination

## Parkinson's Disease

Parkinson's disease (PD) is a chronic, progressive and debilitating neurodegenerative disease characterised by a range of motor and non-motor symptoms, leading to significant disability, with a devastating impact on people with Parkinson's (PWP) and their families<sup>1</sup>

### PATIENT BURDEN

**10m PD patients worldwide\*<sup>7</sup>**

Fastest growing neurodegenerative disease, with patient numbers rising to 20m by 2050\*<sup>7</sup>



**10~20% early-onset PD**

10~20% PD patients diagnosed before age 50, with significant societal impact

**No approved DMTs\*<sup>6</sup>**

SoC focuses on symptom management

### HEALTHCARE SYSTEM BURDEN

**€13.9bn annual HCS costs\*<sup>8</sup>**

Associated with PD treatment, inpatient care and indirect medical costs from complications



- Parkinson's disease (PD) is associated with 5.8m DALYs globally, and is the fastest growing neurodegenerative disease\*<sup>7</sup>
- PD is typically diagnosed in patients aged 60-65, although 10~20% of patients have early-onset Parkinson's disease and are diagnosed before 50\*<sup>1,2</sup>
  - PD is characterized into five disease-stages\*<sup>3</sup>; 19% of PD patients fall into the most severe stage, characterised by loss of ambulation and non-motor symptoms\*<sup>4</sup>
  - Unlike other neurodegenerative disorders, there is no single biomarker used in PD diagnosis, making diagnosis of PD in its early stages challenging, although a recent novel diagnostic was shown to identify patients in over 85% of cases\*<sup>6,11</sup>
- There is no disease modifying treatment for PD, with the current SoC (carbidopa / levodopa) aimed at managing disease motor-related symptoms by increasing dopamine levels\*<sup>6</sup>
- Complications associated with PD have been shown to reduce life expectancy by up to 6.7 years in patients diagnosed at 65 years\*<sup>5</sup>
- PD is associated with significant healthcare system costs, with the average annual cost in Europe estimated at €11k / patient, amounting to €13.9bn overall\*<sup>8</sup>
- The societal impact of PD, particularly in early-onset PD, is also significant, with annual costs from early retirement, care and productivity losses in the US estimated at €24bn\*<sup>10</sup>

Note: (USD:EUR, 1:0.9). Abbreviation: Disability-adjusted life year (DALY), Disease modifying treatment (DMT), Healthcare system (HCS), Parkinson's disease (PD), Standard of Care (SoC)

Source: IQVIA Internal Expertise, Secondary Sources: (1), (2), (3), (4), (5), (6), (7), (8), (9), (10) (11)  
2024 Pipeline Review – Innovation for Unmet Need



# Stem cells are a novel treatment for PD & other neurodegenerative diseases, and may reverse disease progression through regeneration of CNS cells

## INTRODUCTION TO STEM CELL THERAPIES

**Stem Cell Therapy for Neurodegenerative Disease** – stem cells are defined as pre-cursor cells with the capacity to self-renew and differentiate into many different mature cell types (e.g., neurons, retinal cells) under appropriate conditions\*<sup>1</sup>

- **Neurodegenerative disorders are characterized by the death of neurons** (e.g., substantia nigra pars compacta in PD), which lead to CNS-related symptoms such as rigidity, bradykinesia, and memory loss\*<sup>2</sup>
- **Stem cell-derived neuronal transplants are potential brain repair treatments for neurodegenerative disease, by replacing dead or damaged neurons in patients**

### Stem Cell Classifications\*<sup>3</sup>

Stem cells therapies can be categorized into three main types:

#### Embryonic Stem Cells (ESCs)

Pluripotent stem cells derived from embryos with unlimited differentiation capacity

#### Induced Pluripotent Stem Cells (iPSCs)

Adult somatic cells reprogrammed into ESC-like state through forced gene expression

#### Neural Stem Cells (NSCs)

Immature neural precursors which can differentiate into CNS cell types

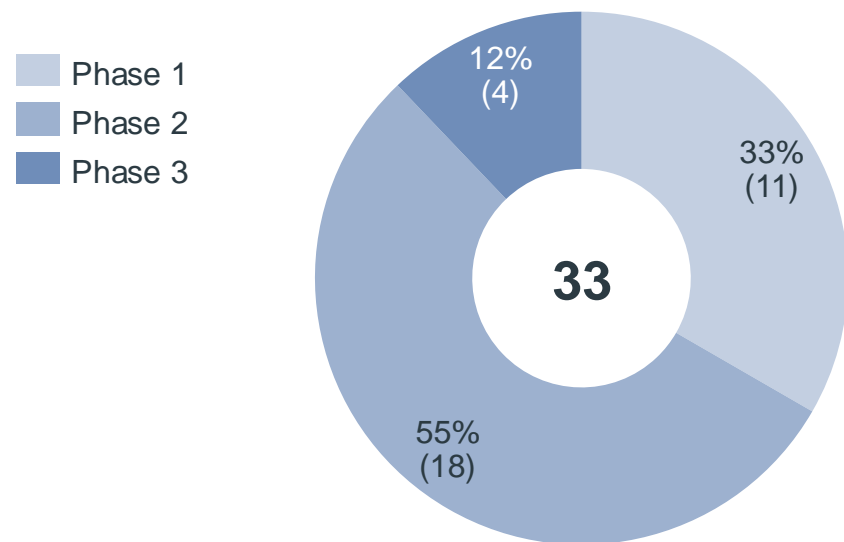
### Stem Cell MoA in PD\*<sup>5</sup>

- In PD, **stem cell derived neuronal cells are surgically inserted into a patient's brain**
- These **neuronal cells then multiply and re-innervate the patient brain**
  - Preliminary evidence suggests stem cells can repair the brain and significantly improve motor symptoms.
- **Ethical concerns around the harvesting and use of certain types of stem cell** (e.g., ESCs) in the treatment of PD exist and will need to be addressed before widespread adoption of this innovative technology\*<sup>4</sup>

# Stem cell therapies are in development for a broad range of CNS-related disorders, with PD an area of particularly high clinical activity

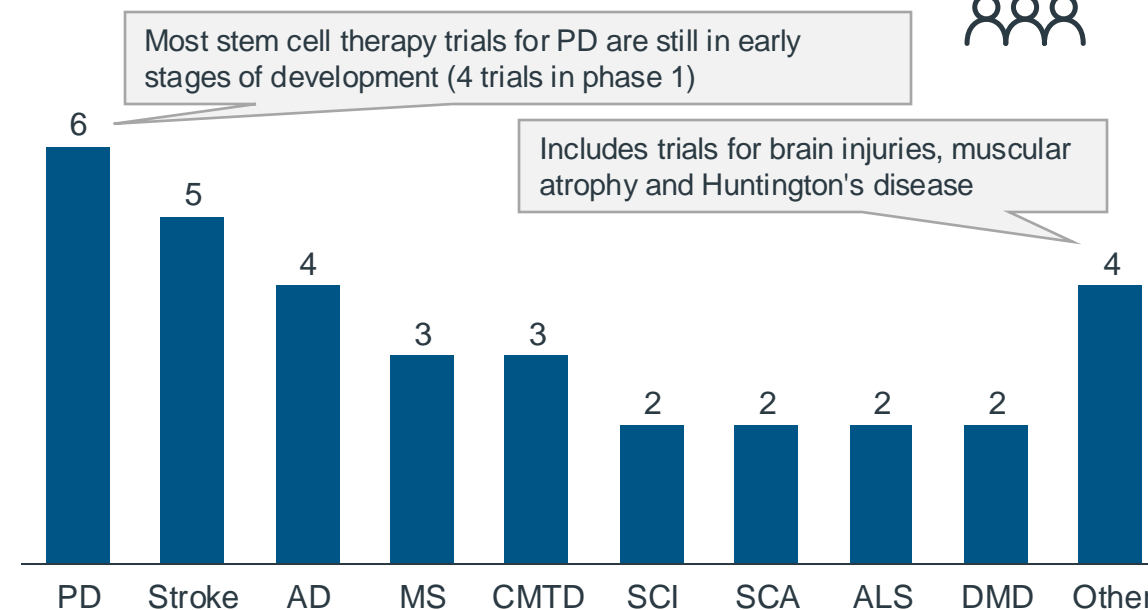
## INTRODUCTION TO PIPELINE FOR STEM CELL THERAPIES FOR CNS DISORDERS

### Number of Clinical Trials By Development Phase



**33 clinical trials for stem cell therapies targeting various CNS disorders** have been initiated since 2022, with most treatments in P2

### Number of Clinical Trials By Indication



**Stem cell therapies are in development for a diverse range of CNS-related disorders**, with Parkinson's disease, stroke and Alzheimer's disease areas of high clinical activity

Abbreviation: Parkinson's Disease (PD), Alzheimer's Disease (AD), Multiple Sclerosis (MS), Charcot-Marie Tooth Disease (CMTD), Spinal Cord Injury (SCI), Spinocerebellar Ataxia (SCA), Amyotrophic Lateral Sclerosis (ALS), Duchenne Muscular Dystrophy (DMD)  
 Search Criteria: Industry-sponsored P1-3 trials initiated since 2022. (Search terms: "Stem Cells"). Only trials for CNS conditions are included. Includes neuromuscular disorders (e.g., DMD, muscular atrophy) and genetic CNS disorders (i.e. DMD, CMTD)  
 Source: CT.gov (Accessed on 22<sup>nd</sup> July 2024). P1/P2 trials are counted as phase 2. P2/3 trials are counted as phase 3  
 2024 Pipeline Review – Innovation for Unmet Need

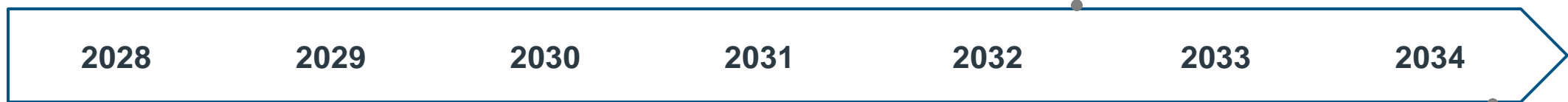
# In PD, stem cell therapies currently in early-stage clinical trials, with the first approval expected in the 2030s, though may be accelerated

## STEM CELL THERAPIES FOR PARKINSONS DISEASE TREATMENT PIPELINE

Phase 1, 2, 3 products

Human Embryonic Stem Cells (ESCs)

Product A



Induced Pluripotent Stem Cells (iPSC)

Product B

Approval Timeline Criteria: P3 Products: P3 primary completion date + 1 year, P2 Products: P2 primary completion date + 6 years, P1 Products: P1 primary completion date + 9 years. Timeline includes phase 1, 2 & 3 industry sponsored products with trial locations in US or EU.

Source: Clinical Trial Repository (Access Date: April 30th 2024), ct.gov, Company Websites  
2024 Pipeline Review – Innovation for Unmet Need

# Stem cell therapies for PD promise to improve patient symptoms and life expectancy, as well as reduce the HCS and societal cost burden

## IMPACT OF STEM CELL THERAPIES FOR PARKINSON'S DISEASE

### IMPACT AREA

### IMPACT

#### PATIENT

IMPROVED QoL & LIFE EXPECTANCY



- **Promises to reverse disease progression** through increased dopamine production, which will in turn improved motor symptoms and **ultimately, patient life expectancy**

#### HEALTHCARE SYSTEM

REDUCED INDIRECT COSTS



- Improved motor symptoms should lead to **fewer PD-related complication and falls**, which alongside individual patient burden, lead to health system management costs
  - Better management of PD symptoms and complications could reduce inpatient costs, which are currently estimated at €13.9bn in Europe

#### SOCIETY

IMPROVED PRODUCTIVITY



- **Promise to reduce the societal burden associated with the disease**, by reversing disease progression in early-onset PD patients, allowing them to remain in the workforce
  - Opportunity to reduce annual costs from early retirement, care and productivity losses, estimated at \$24bn for US

# Obesity is one of the greatest public health crises facing society, with an estimated 1 in 8 people around the world classified as living with obesity

## Obesity

Obesity is a chronic health condition defined by excessive fat deposits and a BMI greater than or equal to 30. Obesity affects all age groups but is more prevalent in adults. Obesity is a major risk factor for many chronic diseases, such as type 2 diabetes, CVD and cancer\*<sup>1</sup>

### PATIENT BURDEN

#### 1bn people globally

Classified as having obesity, with the number of adults affected by obesity doubling since 1990

#### 36m global DALYs

Associated with obesity

#### Significantly reduced QoL

Due to poor mental health, low self-esteem & co-morbidities

### HEALTHCARE SYSTEM BURDEN

#### €460bn Annual Costs\*<sup>9</sup>

Estimated obesity related economic impact in Europe



- **Obesity rates around the world have doubled in adults since 1990**, with an estimated 1 in 8 people around the world classified as living with obesity\*<sup>1</sup>
  - **Obesity rates are higher than average in Europe**, with 59% of adults and 28% of children defined as living with obesity\*<sup>2</sup>
  - The number of people with obesity in Europe and around the globe is **expected to increase in the future due to sedentary lifestyles and poor diet**\*<sup>8</sup>
- **Obesity is associated with 36m DALYs globally**, and can **shorten life expectancy by up to 14 years**\*<sup>3,4</sup>
  - **Obesity is also associated with severely reduced QoL** due to poor mental health, low self-esteem, co-morbidities and reduced ability to perform activities of daily living\*<sup>6</sup>
- **Since 2021, incretin-based therapies have been approved in Europe for the treatment of obesity**. As these treatments are not yet fully adopted or reimbursed, the **SoC for most patients remains diet & exercise therapy**\*<sup>5</sup>
  - **Adherence to diet and exercise therapy is a major challenge**, with **80% of patients regaining lost weight** within five years\*<sup>5</sup>
- **Obesity-related complications are a drain on HCS resources**, and are expected to account for 7~11% of healthcare expenditure in Germany, UK, Spain and Italy between 2020~2050\*<sup>7</sup>

Abbreviation: Disability-adjusted life year (DALY), Body mass index (BMI), Cardiovascular disease (CVD)

Quality of Life (QoL), Standard of Care (SoC)

Source: IQVIA Internal Expertise, Secondary Sources: (1), (2), (3), (4), (5), (6), (7), (8), (9). Cost of obesity in EU estimated from UK cost figure (£58bn, GBP:EUR 1:1.2)

2024 Pipeline Review – Innovation for Unmet Need

# Obesity plays a significant contributory role in the development of multiple NCDs, such as diabetes, CVD, MASH, Alzheimer's disease and cancer

## OBESITY ROLE IN THE ONSET OF NON-COMMUNICABLE DISEASES

**Obesity is a key risk factor in the onset of multiple NCDs, and plays a significant contributory role in their onset** via multiple mechanisms such as chronic inflammation, insulin-resistance and metabolic disruption<sup>\*1</sup>

### Type-2 Diabetes<sup>\*2</sup>

- Obesity causes chronic inflammation, disrupted fat metabolism and insulin-resistance, which can lead to type-2 diabetes

### Cardiovascular Disease<sup>\*3</sup>

- Obesity can increase blood pressure and cholesterol levels which can increase the risk of developing CVD

### MASH<sup>\*4</sup>

- Obesity can lead to MASH through inducing chronic inflammation, insulin-resistance and liver steatosis



### Obstructive Sleep Apnea<sup>\*5</sup>

- Obesity can lead to a build up of fat deposits in the neck, reduced lung volume and hormonal changes which may cause OSA

### Alzheimer's Disease<sup>\*6</sup>

- Obesity can lead to reduced blood flow to the brain, chronic inflammation and insulin-resistance which may cause Alzheimer's disease

### Cancer<sup>\*7</sup>

- Obesity can lead to chronic inflammation and increase the level of oxidative stress, leading to cellular damage which increases the risk of cancer

Abbreviation: Mechanism of action (MoA), Non-communicable Disease (NCD), Metabolic Dysfunction Associated Steatohepatitis (MASH), Obstructive Sleep Apnea (OSA) Cardiovascular Disease (CVD)  
Source: IQVIA Internal Expertise, Secondary Sources: (1), (2), (3), (4), (5), (6), (7)  
2024 Pipeline Review – Innovation for Unmet Need

# Building on recent incretin-based therapy approvals, a range of novel and incremental treatments are in clinical development

## INTRODUCTION TO NEXT GENERATION OBESITY MANAGEMENT MEDICATIONS (OMM)

**Next Generation Obesity Management Medications (OMMs)** – In addition to existing incretin-based therapies (e.g., semaglutide, tirzepatide), there are multiple OMMs under development, some of which target novel MoAs<sup>\*1</sup>

- **The next generation of treatments are based on novel or combinations of entero-pancreatic hormones**, which are produced by enteroendocrine cells in the pancreas or small intestine and regulate digestion; metabolism and feelings of hunger<sup>\*2</sup>
- These treatments **are aiming for greater weight loss than existing incretin-based therapies**. Oral OMMs are also in development which may improve adherence and convenience for patients<sup>\*1,7</sup>

### Obesity Management Medication Class Spotlight

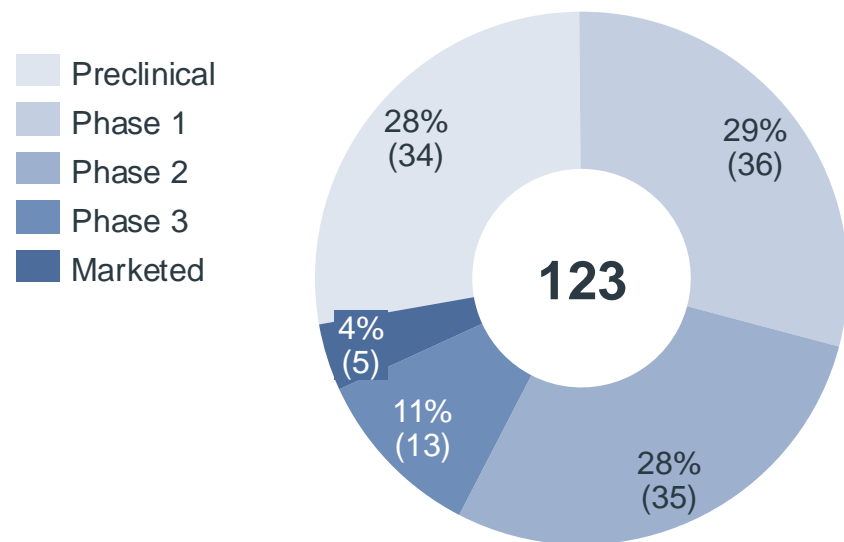
- **GLP-1 Receptor Agonists (GLP-1 RA)** – GLP-1 RA are the focus of clinical activity in the OMM space. Developed to treat type-2 diabetes, GLP-1 RA mimic the action of the hormone GLP-1, which is released after eating to stimulate insulin release; slow gastric emptying and increase feelings of fullness<sup>\*3</sup>
- **GIP Receptor Agonists (GIP RA)** – GIP RA is another focus of clinical activity in the OMM space. GIP is a hormone secreted by **K-cells in the small intestine** and works similarly to GLP-1 in stimulating insulin release and regulating fat metabolism<sup>\*5</sup>
- **Glucagon Agonists** – Glucagon is a hormone secreted from pancreatic cells, with its primary function to raise glucose levels and stimulate glucose production from the liver / fat cells. **Glucagon agonists are used in combination with GLP-1 RAs to increase weight loss** due to increased energy expenditure<sup>\*1,4</sup>
- **Amylin Agonists** – Amylin is secreted from  $\beta$ -cells in the pancreas and works by inhibiting glucagon; slow gastric emptying and increase feelings of fullness. Several amylin agonists and GLP-1 combinations are in development as potential OMMs<sup>\*1,6</sup>



# Activity in developing novel pharmacotherapies for obesity is high, with more than 120 products in pre-clinical and clinical development

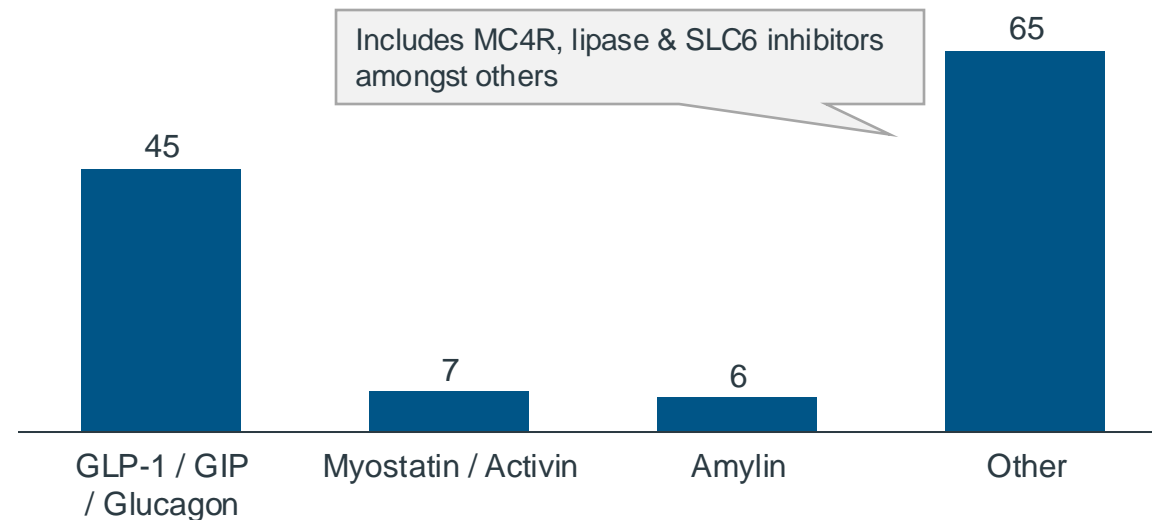
## INTRODUCTION TO PIPELINE FOR NEXT GENERATION OBESITY MANAGEMENT MEDICATIONS

### Number of Assets by Development Phase



**123 assets targeting obesity** are in development, including 48 in P2/P3 clinical trials, indicating that **more approvals can be expected in the near term**

### Number of Assets by MoA

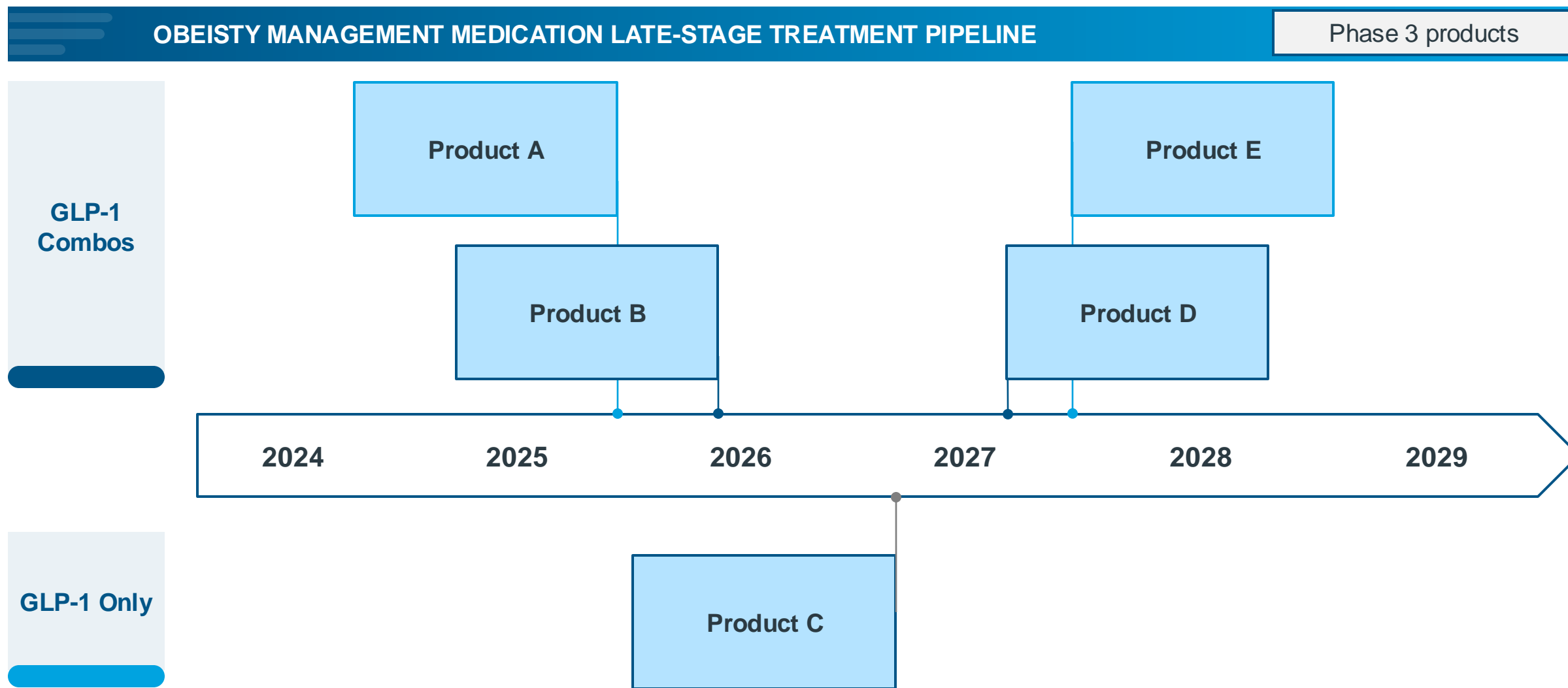


**GLP-1, GIP & glucagon agonists dominate the clinical pipeline**, with 45 assets in development with targeting this mechanism of action

Abbreviation: GIP Receptor Agonists (GIP), GLP-1 Receptor Agonists (GLP-1), Mechanism of action (MoA), Melanocortin-4 receptor (MC4R), Solute-carrier 6 (SLC6), Glucagon-like Receptor (GLP), Receptor Agonist (RA), Glucose-dependant Insulinotropic Polypeptide (GIP)  
 Source: IQVIA Obesity Report ([Link](#)), Number of assets currently in clinical development  
 2024 Pipeline Review – Innovation for Unmet Need






# For obesity, GLP-1 RAs and combination medications dominate the pipeline with several approvals expected in the next five years



Approval Timeline Criteria: P3 Products: P3 primary completion date + 1 year. Timeline includes phase 3 industry sponsored products with trial locations in US or EU.  
Source: Clinical Trial Repository (Access Date: April 30th 2024), ct.gov, Company Websites  
2024 Pipeline Review – Innovation for Unmet Need

# Next generation obesity management medications offer improved efficacy and side-effect profiles, which could increase usage and reduce obesity burden

## IMPACT OF NEXT GENERATION OBESITY MANAGEMENT MEDICATIONS (OMM)

IMPACT AREA	IMPACT
<p><b>PATIENT IMPROVED Tx EFFICACY &amp; ADHERENCE</b></p> 	<ul style="list-style-type: none"> <li>• <b>Promise improved efficacy vs. existing GLP-1 treatments</b>, and represent a drastic improvement over the historic SoC (diet control and management); with <b>average weight loss of up to 20% of body mass</b> seen in clinical trials*<sup>1</sup></li> <li>• <b>Oral products could improve adherence</b> by making treatments more convenient, cheaper, and less invasive than current injectables*<sup>3</sup></li> </ul>
<p><b>PATIENT REDUCTION IN CO-MORBIDITIES</b></p> 	<ul style="list-style-type: none"> <li>• <b>The reduction in obesity-related complications</b> such as diabetes, CVD &amp; cancer provide <b>major benefits to patients' quality of life and overall health</b></li> <li>• In addition to direct weight loss impact, OMMs such as GLP-1 treatments have also been shown to <b>reduce the risk of other non-communicable diseases such as CVD</b>*<sup>4</sup></li> </ul>
<p><b>HEALTHCARE SYSTEM REDUCTION IN INDIRECT HCS COSTS</b></p> 	<ul style="list-style-type: none"> <li>• <b>Indirect healthcare system costs associated with obesity can be greatly reduced</b> by the wider uptake next generation OMMs, as patients may avoid a range of complications and co-morbidities, requiring long term healthcare management</li> </ul>

Abbreviation: Cardiovascular disease (CVD), Routes of Administration (RoA), Standard of Care (SoC), Treatment (Tx), Obesity Management Medication (OMM)  
 Sources: IQVIA Internal Expertise, Secondary Sources. (1), (2), (3), (4)  
 2024 Pipeline Review – Innovation for Unmet Need

# Chronic obstructive pulmonary disease (COPD), is a common lung disease and the 3<sup>rd</sup> biggest cause of mortality globally, with 3.2m deaths in 2019

## COPD

COPD is the name for a group of lung conditions that includes emphysema and chronic bronchitis. COPD primarily affects middle-aged or older adults with a history of smoking, with symptom onset usually between the ages of 40 and 50<sup>\*1,2</sup>

### PATIENT BURDEN

**213m patients globally**

Living with COPD, projected to increase to 600m by 2050

**74m global DALYs**

Associated with COPD

**Significantly reduced QoL**

Associated with COPD due to poor mental health and ability to perform activities of daily living



### HEALTHCARE SYSTEM BURDEN

**€48bn Annual Costs**

Associated with COPD



- The global prevalence of COPD is estimated to be 213m, and is projected to increase to 600m by 2050 due to smoking, air pollution and aging populations<sup>\*1,3</sup>
  - In Europe, COPD prevalence is estimated at 37m, and is projected to increase to 49m by 2050<sup>\*4</sup>
- COPD is associated with 74m DALYs globally, and can reduce life expectancy by up to 6 years in patients with severe disease<sup>\*5,6</sup>
  - COPD also significantly impacts patient QoL, with many patients suffering from poor mental health and having reduced capacity to perform activities of daily living<sup>\*7</sup>
- Primary SoC for COPD involves smoking cessation, rehabilitation, inhaled therapies (LABA/LAMA) to improve lung function. Corticosteroids are also sometimes prescribed to reduce inflammation, with antibiotics used to treat lung infections<sup>\*8</sup>
  - Significant unmet need exists with the current SoC, particularly in the management of exacerbations, which are a primary driver of hospitalisations in COPD patients<sup>\*9</sup>
- COPD management is associated with significant healthcare system burden, with annual direct healthcare costs estimated at €10k / patient in Europe<sup>\*10</sup>
  - COPD is also associated with significant societal burden, with workplace productivity and early retirement costs estimated at €25k / patient in Germany<sup>\*10</sup>

**The overall healthcare and economic cost of COPD in Europe is estimated at €48bn<sup>\*10</sup>**

Abbreviation: Chronic obstructive pulmonary disease (COPD), Disability-adjusted life year (DALY), long-acting beta2 agonists (LABA), Long-acting muscarinic antagonists (LAMA) Quality of Life (QoL), Standard of Care (SoC)  
 Source: IQVIA Internal Expertise, Secondary Sources: (1), (2), (3), (4), (5), (6), (7), (8), (9), (10)  
 2024 Pipeline Review – Innovation for Unmet Need

# Anti-interleukin treatments are an established treatment in autoimmune diseases and asthma, and are now being widely tested in COPD

## INTRODUCTION TO ANTI-INTERLEUKIN TREATMENTS FOR COPD

**Anti-interleukin treatments (interleukin (IL) inhibitors)** – group of biologics which inhibit the action of interleukins –cytokines involved in immune system regulation and communication<sup>\*1,2</sup>

- To date, **many different types of interleukin (IL) have been identified** (e.g., IL-1, IL-2), with **many implicated in the onset of chronic inflammation and autoimmune diseases**<sup>\*3</sup>
- **Anti-interleukin treatments are widely used in the treatment of autoimmune diseases**, such as rheumatoid arthritis (tocilizumab) and psoriasis (e.g., (secukinumab), and asthma (e.g., mepolizumab, benralizumab)

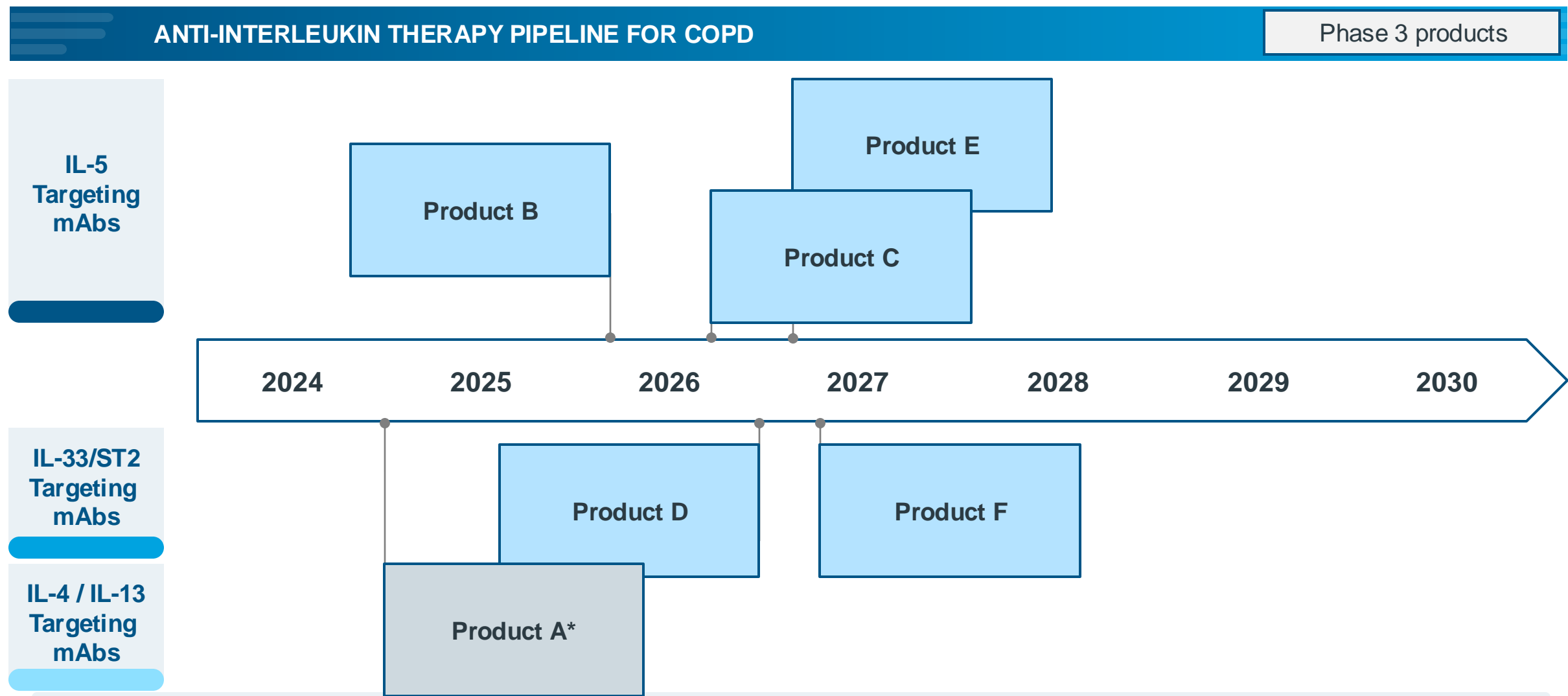
### Key Targets for Anti-interleukin Treatments in COPD

- **IL-4: plays a role in chronic inflammation** by promoting activation of macrophages and allergic responses<sup>\*4</sup>
- **IL-5: a key mediator in the onset of asthma**, through promotion of inflammation and hyper-responsiveness<sup>\*5</sup>
- **IL-13: induces inflammation and fibrosis** by promoting fibroblasts and collagen production<sup>\*4</sup>
- **IL-33/ST2: promotes fibrosis and inflammation** as well as allergic responses by promoting the production of IL-5 and IL-13<sup>\*6</sup>

### Mechanism of Action in COPD

- **Anti-ILs are being tested other chronic disorders such as COPD**, where inflammation management is required
- **Several anti-interleukin treatments are in late-stage clinical trials for COPD**, and have been shown to:
  - **Reduce the frequency of exacerbations** experienced by patients by up to 30%<sup>\*7</sup>
  - **Improve overall lung function** by reducing inflammation in cells such as eosinophilic cells<sup>\*8</sup>

# Several established products are being tested in COPD, with several in Phase 3 and close to potential approval



Approval Timeline Criteria: P3 Products: P3 primary completion date + 1 year, P2 Products: P2 primary completion date + 6 years. Timeline includes phase 3 industry sponsored products with trial locations in US or EU. \*Product A is approved by EMA in July 2024 as the first targeted therapy for COPD.

Source: Clinical Trial Repository (Access Date: April 30th 2024), ct.gov, Company Websites. Chronic Obstructive Pulmonary Disease (COPD)  
2024 Pipeline Review – Innovation for Unmet Need

# Anti-interleukin treatments for COPD promise to reduce the frequency of exacerbations, and provide greater autonomy in patients lives

## IMPACT OF ANTI-INTERLEUKIN TREATMENTS FOR COPD

### IMPACT AREA

### IMPACT

**PATIENT**  
IMPROVED QUALITY OF LIFE



**HEALTHCARE AND SOCIETY**  
REDUCTION IN HCS COSTS AND  
LOST ECONOMIC VALUE



- The translation of existing MoAs into COPD promises to improve QoL by reducing the frequency of exacerbations, which are a source of great distress to patients, by **up to 30% vs. current SoC<sup>\*1</sup>**
- **Allow COPD patients to have greater autonomy in their lives and overall activity levels** by reducing chronic inflammation, which will in turn improve overall lung function vs. current SoC<sup>\*1</sup>
- **Reduce the number of hospitalisations associated with COPD** by reducing the frequency of exacerbations<sup>2</sup>
  - New treatments offer potential to **reduce €10k / patient direct healthcare costs** in Europe
- **Reduce the overall care costs for COPD by improving the lung function of COPD patients**, which will allow them greater autonomy in conducting activities of daily living and less reliant on carers
  - New treatments offer potential to **increase workplace productivity and avoid early retirement costs**, associated with **€25k / patient costs** in Europe

*As often happens, no one thought it was COPD, until shortness of breath meant she wasn't even able to walk to the mailbox*

-Patient advocate

Abbreviation: Chronic obstructive pulmonary disease (COPD), Quality of life (QoL), Standard of Care (SoC)  
Sources: IQVIA Internal Expertise, Secondary Sources. (1), (2)  
2024 Pipeline Review – Innovation for Unmet Need

# Major depressive disorder (MDD) is a common mental disorder affecting ~5% of adults and has a severe impact on quality of life

## Major depressive disorder

Major depressive disorder (MDD) is a debilitating disease affecting ~5% of the population, characterized by persistent low mood, despondency, disturbed sleep and appetite. Depression affects all age groups but is more prevalent in females and younger people<sup>\*1,2</sup>

### PATIENT BURDEN

**280m patients globally**

Living with MDD, with 32m in Europe

**37m global DALYs**

Associated with MDD

**Significantly reduced QoL**

Associated with MDD due to impact on emotional / mental & physical health, relationships and productivity



- **Global prevalence of MDD is estimated at 280m, and has increased significantly in recent years due to the COVID-19 pandemic<sup>\*1,3</sup>**
  - Depressive disorders are expected to become the leading cause of disability by 2030<sup>\*4</sup>
  - In Europe, MDD prevalence is estimated at ~32m<sup>\*5</sup>
- **MDD is associated with 37m DALYs globally, with more than 700k people dying each year from suicide<sup>\*1,6</sup>**
  - **MDD strongly impacts patient QoL by worsening patients physical and mental health;** as well as impacting personal relationships and workplace productivity<sup>\*7</sup>
- Currently, **treatment options for management of depression** can be broadly be divided into antidepressants, electroconvulsive therapy and psychosocial interventions, yet are often correlated with poor treatment compliance<sup>\*8</sup>
  - **Treatment resistant depression (TRD),** the failure to respond to  $\geq$  two treatments, manifests in ~20% of patients with MDD<sup>\*9</sup>
- The **healthcare system burden for MDD is extremely high, with annual costs in Europe estimated at €42bn<sup>\*10</sup>**
- **Societal costs for MDD are also extremely high, with annual costs in Europe estimated at €76bn,** driven by early mortality and lower workplace productivity<sup>\*11</sup>

### HEALTHCARE AND SOCIETAL BURDEN

**€118bn Annual Costs**

HCS and societal costs associated with MDD in Europe



Abbreviation: Disability-adjusted life year (DALY), Major depressive disorder (MDD)

Treatment Resistant Depression (TRD), Quality of Life (QoL)

Source: IQVIA Internal Expertise, Secondary Sources: (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11)

2024 Pipeline Review – Innovation for Unmet Need



# Several novel treatments for MDD are currently in development, with many focusing on improving neuroplasticity

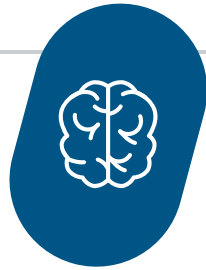
## INTRODUCTION TO NOVEL TREATMENTS FOR MDD

Several novel mechanisms for antidepressants are currently in development for major depressive disorder, with most aiming to promote neuroplasticity within the brain to relieve depression symptoms



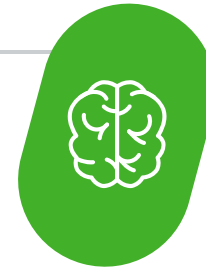
### Psychoplastogens\*<sup>1</sup>

Psychoplastogens (e.g., psilocybin) work by enhancing neuroplasticity by promoting neuron growth / connectivity. However, as many are classed by authorities as recreational drugs, there are challenges to widespread adoption



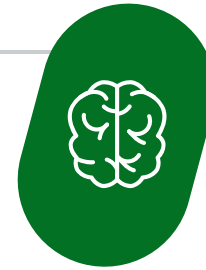
### KOR Antagonists\*<sup>2,3</sup>

Target opioid receptors, which play a central role in modulating mood and well-being. Products may be particularly useful in addressing symptoms often resistant to conventional treatments (e.g., anhedonia (inability to feel pleasure))



### NMDA Antagonists\*<sup>4</sup>

Products target NMDA receptors involved in synaptic plasticity and neurotransmission. NMDA antagonists can facilitate new memory formation, fear extinction and the restructuring of traumatic memories, improving MDD symptoms\*<sup>4</sup>



### Neuroactive Steroids\*<sup>5,6</sup>

Target the GABAergic system, which plays a crucial role in mood regulation. Neuroactive steroids work through modulation of GABA-A receptors, restoring the balance between excitatory and inhibitory neurotransmission, which is often disrupted in MDD



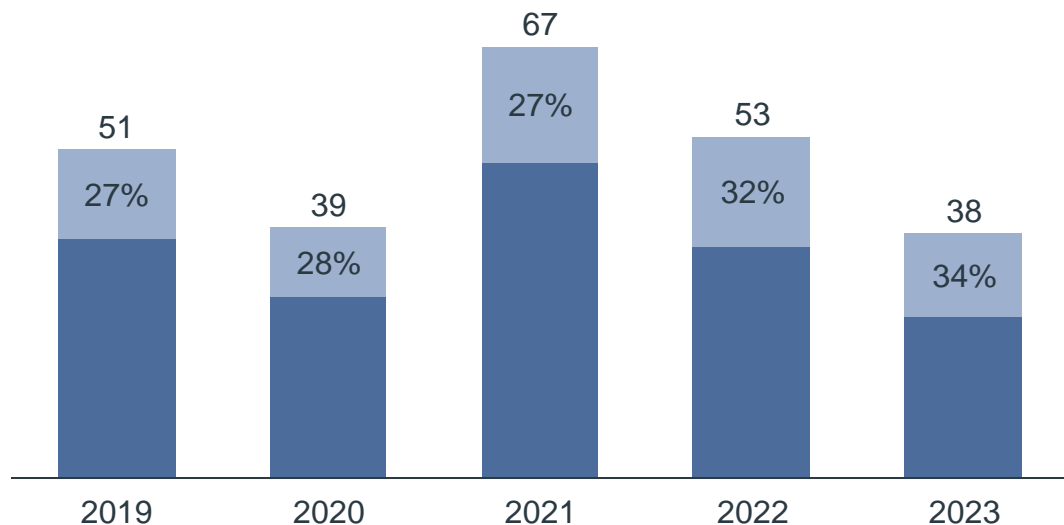
# Clinical trial activity in the MDD space is high, with 248 trials initiated since 2019

## INTRODUCTION TO PIPELINE FOR NOVEL THERAPIES FOR MDD

### Number of Depression Trials Initiated (Ph1-3)

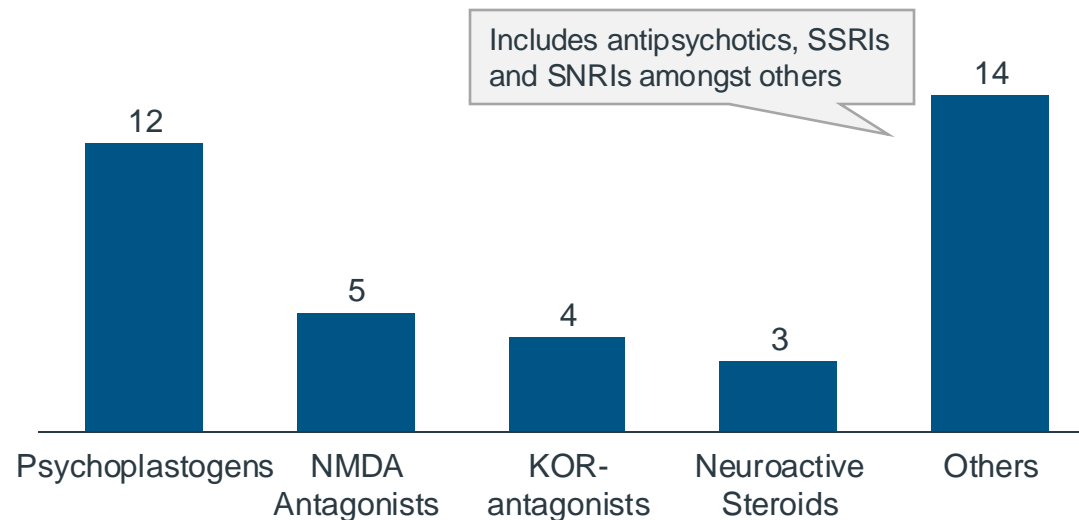
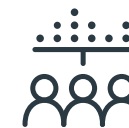


■ Treatment Resistant Depression



**38 assets targeting MDD** are in development in 2023, while the ratio of treatment-resistant depression research has increased by 7% over the past five years

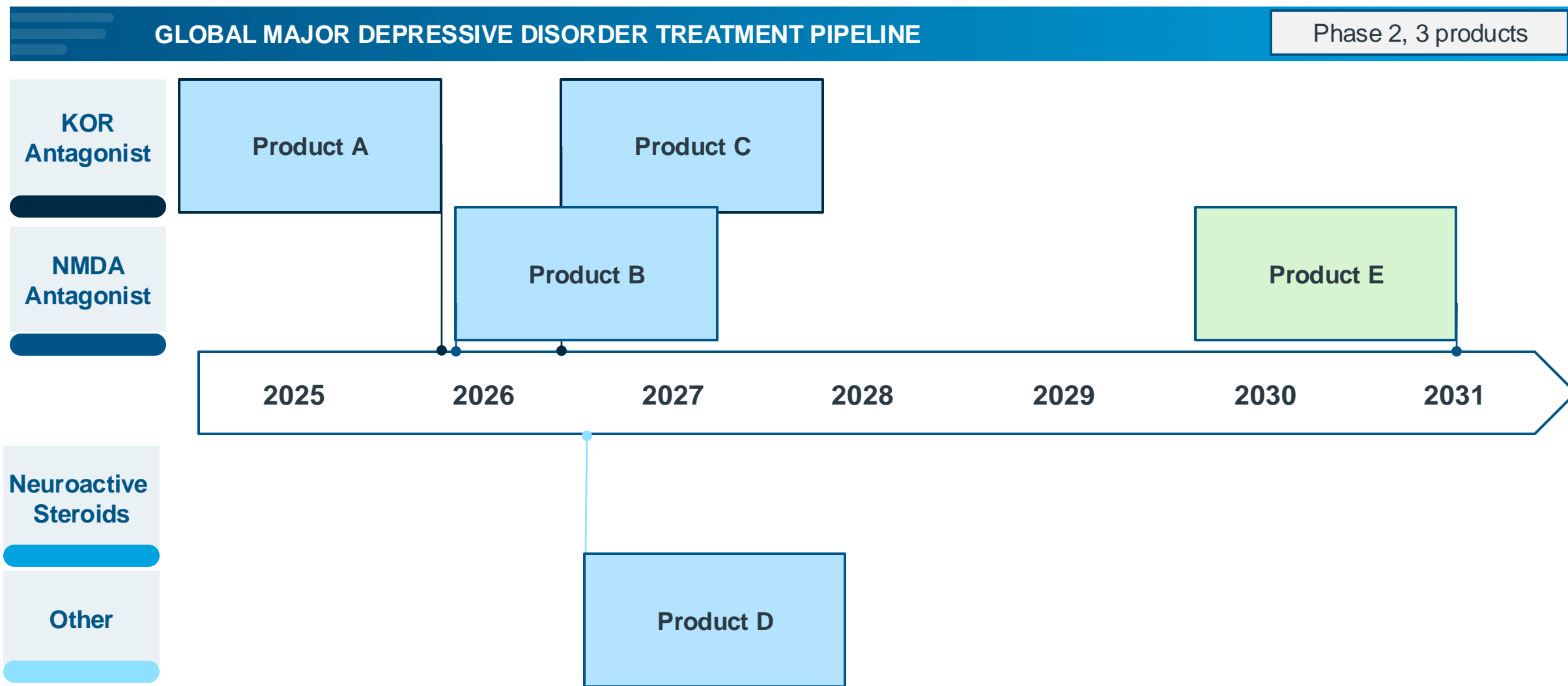
### Number of Depression Trials by MoA (2023)



**Psychoplastogens were a primary focal point of clinical activity for MDD trials in 2023**, with 12 new P1~3 trials initiated

Abbreviation: Major depressive disorder (MDD), Mechanism of Action (MoA), Serotonin and norepinephrine reuptake inhibitors (SNRI), Selective serotonin reuptake inhibitors (SSRI), Mechanism of Action (MoA), Kappa-opioid Receptor (KOR), N-methyl-D-aspartate (NMDA)  
 Source: IQVIA Global Trend in R&D 2024 Report ([Link](#)). Number of P1~3 trials initiated in 2023  
 2024 Pipeline Review – Innovation for Unmet Need

# There are at least four assets currently in late-stage development for MDD across these novel MoAs






Approval Timeline Criteria: P3 Products: P3 primary completion date + 1 year, P2 Products: P2 primary completion date + 6 years. Timeline includes phase 2 & 3 industry sponsored products with trial locations in US or EU.

Source: Clinical Trial Repository (Access Date: April 30th 2024), ct.gov, Company Websites  
2024 Pipeline Review – Innovation for Unmet Need

# New treatments for MDD would provide a breakthrough to patients, and reduce the costs associated with lost economic and social contribution

## IMPACT OF NOVEL TREATMENTS FOR MDD

IMPACT AREA	IMPACT
<p><b>PATIENT IMPROVED QOL</b></p> 	<ul style="list-style-type: none"> <li>• Opportunity to improve quality of life for patients for MDD patients, <b>particularly those with treatment resistant depression (TRD)</b> <ul style="list-style-type: none"> <li>➢ New treatments promise <b>improved physical and mental well-being, personal relationships and workforce participation</b></li> </ul> </li> <li>• <b>Ultimately may reduce suicides, which is one of the greatest causes of death in young adults</b></li> </ul>
<p><b>HEALTHCARE SYSTEM REDUCTION IN HOSPITALISATIONS</b></p> 	<ul style="list-style-type: none"> <li>• <b>Offer to reduce healthcare system costs by decreasing MDD-related hospitalisations and co-morbidities</b> <ul style="list-style-type: none"> <li>➢ Direct and indirect HCS costs in Europe associated with MDD estimated at €42bn, given significant inpatient management costs</li> </ul> </li> </ul>
<p><b>SOCIETY IMPROVED PRODUCTIVITY</b></p> 	<ul style="list-style-type: none"> <li>• <b>Improve productivity and workforce engagement in patients grappling with chronic depression, who are often absent from the job market for an extended period</b> <ul style="list-style-type: none"> <li>➢ Opportunity to reduce high societal costs, with annual costs in Europe estimated at €76bn, driven by <b>early mortality and lower workplace productivity</b></li> </ul> </li> </ul>

Abbreviation: Healthcare system (HCS), Major depressive disorder (MDD), Quality of Life (QoL), Treatment resistant depression (TRD)  
 Sources: IQVIA Internal Expertise, Secondary Sources: (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11)  
 2024 Pipeline Review – Innovation for Unmet Need

# *Appendix*



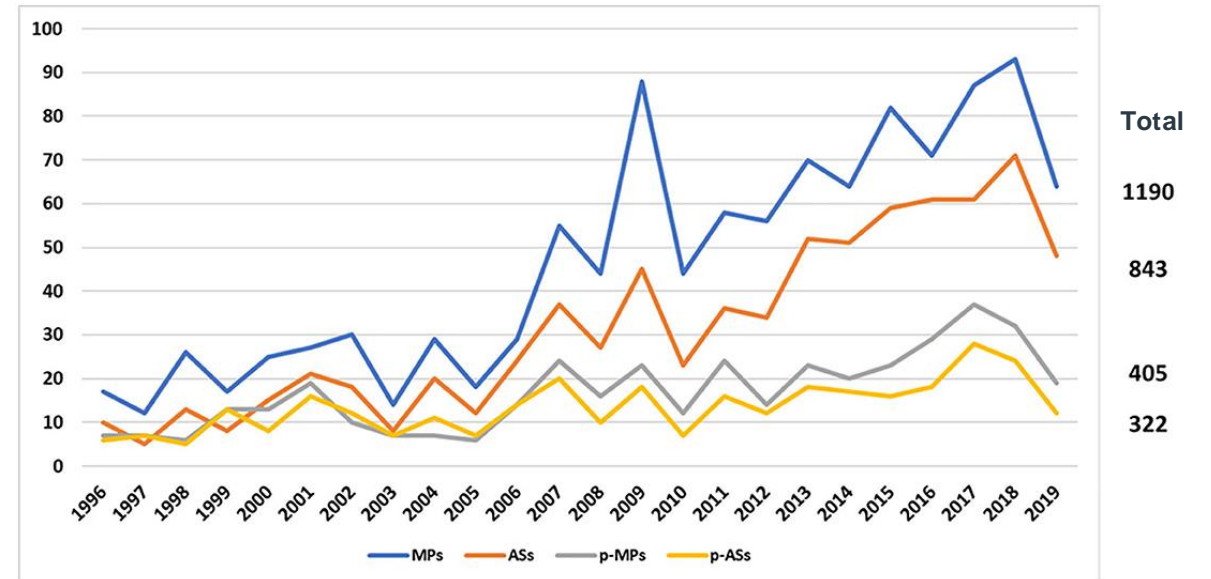
# EMA approval trends: Total and paediatric medicines

**Near term trends: NAS and MA, total and paediatric (2013, 2018-2023)**

Year	2013	2018	2019	2020	2021	2022	2023
NAS	38	42	30	39	54	41	39
MA	81	84	66	97	92	89	77
Paediatric NAS (excl. Covid-19)	n/a	5	3	7 (6)	5 (2)	9 (5)	5
Paediatric extension	n/a	n/a	n/a	n/a	35	38	38

NAS: New active substances; MA: Market authorisation  
 Source: *Analysis of annual EMA reports*

**Longer term trends: MPs, ASs, total and paediatric (2013, 2018-2023)**



MPs: Medicinal products; ASs: Active substances p-: paediatric  
 Source: [Toma et al. 2021](#)

# Clinical Trial Repository Databases

Database	Region / Country
CT.gov	Global
EudraCT	EU
UMIN, JAPIC, JMAC	Japan
ISRCTN	Global
ANZCTR	Australia, New Zealand
IRCT	Iran
NTR	Netherlands
HKCT	Hong Kong
DRKS	Germany
ChiCTR	China
CTRI	India

Database	Region / Country
CRiS	Korea
NMRR	Malaysia
HAS CTR	Singapore
ReBec	Brazil
PHRR	Philippines
TCTR	Thailand
SRM CTR	Russia
Mexico CTR	Mexico
SLCTR	Sri Lanka
PACTR	Africa
RPCEC	Cuba