Orphan Drug Pipeline Final Report

Prepared for LIF

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LIF has asked IQVIA to validate TLVs estimation of the orphan drug pipeline

This report provides LIF with an assessment of the orphan drug pipeline, in order to prepare for further dialogue around TLVs principles and methods to let patient numbers and sales volumes to a higher extent influence what cost can be accepted for innovative drugs

RESEARCH OBJECTIVE

Estimate the number of orphan drugs that may enter the Swedish market in the next 10 years – divided into the four categories defined by TLV –
to validate TLVs estimations in appendix 6 of TLVs suggested methods published December 2024*

Faktor		Typ-läkemedel 1 "ovanlig cancer"	Typ-läkemedel 2 "genterapi"	Typ-läkemedel 3 "långvarig kontinuerlig behandling."	Typ-läkemedel 4 "långvarig kontinuerlig behandling."
Antal lanserade läkemedel per år	Slump	Likformig:	Likformig:	Likformig:	Likformig:
		Bas: 0–3	Bas: 0–3	Bas: 0–5	Bas: 0–3
		Hög: 0–6	Hög: 0–4	Hög: 0–7	Hög: 0–5
		Låg: 0–1	Låg: 0–2	Låg: 0–3	Låg: 0–1

*Source: *Praktiska förutsättningar för stärkt tillgång till läkemedel vid sällsynta hälsotillstånd:* www.tlv.se/download/slutrapport.pdf

METHODOLOGY

- IQVIA Pipeline Link collects information on new active substances that are under development and may be launched over the next 10 years.
- IQVIA Nordics has analyzed the products in the Pipeline Link, added desk research to assess prevalence, and applied fact-based assumptions
- **Outcome: 216 orphan drugs are estimated to seek reimbursement in Sweden over the next 10 years**

End 2024, TLV published how it will work on accepting a higher ICER to improve access to orphan drugs in some situations

Rare condition

Patient population

- Combined measure of patients based on prevalence and factored incidence
- Appendix 3 explains calculation & reasoning
- Appendix 6 calculates impact based on treated patients

Severity

Very high, High, Medium, Low

- Health-related QoL
- Duration of condition
- Impact frequency
- Impact on lifespan

Only conditions with “very high” overall severity qualify for higher acceptable ICER

Clinical benefit

Evaluation of evidence

- Clear evidence that the treatment improves the patient's quality of life or survival,
- compared to existing treatments
- Mode of Action

Not: size of clinical benefit

Uncertainty (Appx 4)

- Situations with high uncertainty entail higher risk that actual ICER exceeds acceptable ICER → TLV will set a lower acceptable ICER.
- For ultra rare, TLV is considering to allow simplified assessments

Accepting higher ICER

Patient population	Acceptable ICER (mSEK)
1-5	4
5-15	3
16-30	2.5
31-50	2
51-100	1.5
101+	1

Let patient numbers and sales value to a higher degree influence acceptable drug cost

Reasoning and intentions

TLV explains reasoning and will start to implement new ways of working, while learning and improving methods

Estimated impact

TLV calculates the impact of implementing the changes for both retail and hospital orphan drugs in terms of increased access and increased cost

Out of scope

In addition, TLV deems a different system for pricing, negotiations, and reimbursement is needed to further improve access to orphan drugs

TLV has defined four typical drugs for rare disease and assessed the impact of the new procedures on access & cost

TLV definitions, assumptions and outcomes

Appendix 6

TLV definitions, assumptions, simulations

TLV definitions and impact	Scenario	Type 1 – Orphan oncology	Type 2 – Gene therapy	Type 3 – Ultra Rare	Type 4 – Rare	TLV Total
Definition by TLV		Short treatment duration, rare cancer	Single administration gene therapy, rare condition	Long-term treatment 1 – 30 pts per year	Long-term treatment 31 – 100 pts per year	
Nr of launched products in 10 years (multiplying TLV estimations per year with 10)	High	30	20	35	25	**110**
	Base	15	15	25	15	**70**
	Low	5	10	15	5	**35**
Prevalence intervals		1 - 50	5 - 25	1 - 30	31 - 100	
QALY gain intervals		0,1 - 2	1 - 8	1 - 4	1 - 4	

TLV outcomes

Cost increase over 10 years, in billion SEK	Base	1,07	2,14	1,27	1,83	**6,31 billion SEK**
Access (i.e. reimbursement) **increase 10 years in % points**	Same across scenarios	25 (from 71 % to 96 %)	39 (from 46 % to 85 %)	38 (from 26 % to 64 %)	27 (from 73% to 100%)	**”between 29-39”** *according to §6.1.1*

In 2023 access improvement was estimated at 35, from 55% to 90% (TLV 02039/2022)

Source: *Praktiska förutsättningar för stärkt tillgång till läkemedel vid sällsynta hälsotillstånd – Appendix 6:* www.tlv.se/download/slutrapport.pdf

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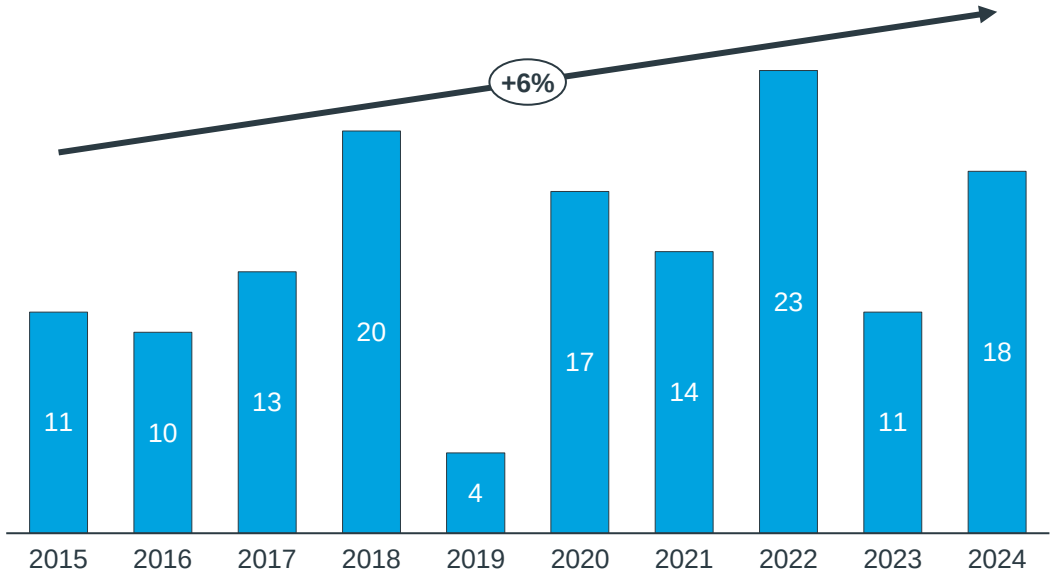
EMA orphan drug approvals have grown at a 6% CAGR over the past decade and are expected to keep rising

Orphan drugs approved and in development

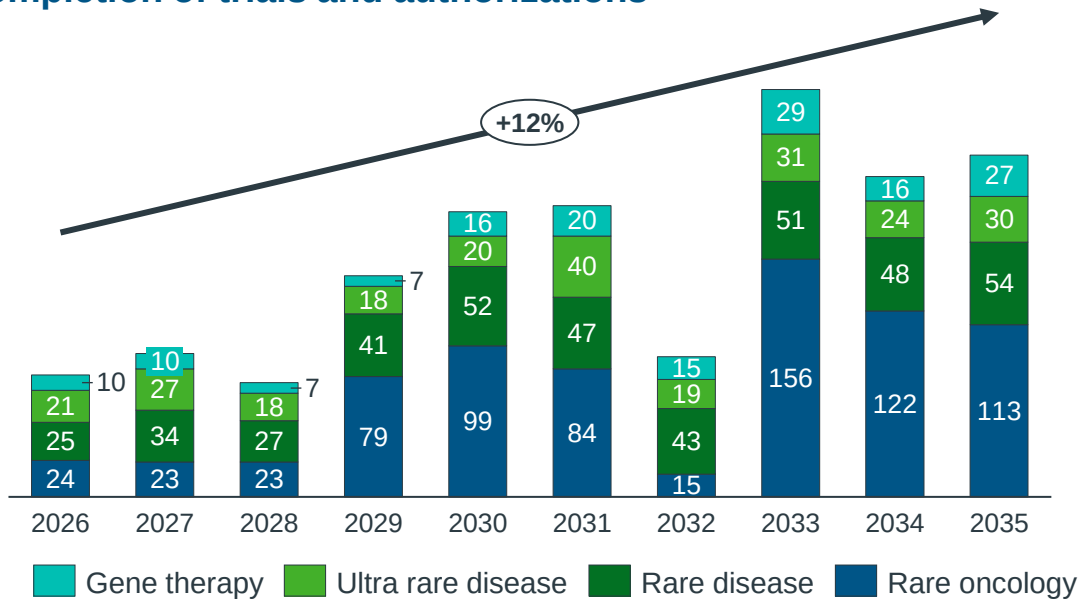
141 EMA approved orphan drugs* (NAS) in the past 10 years



EMA has approved on average 14 New Active Substances (NAS) with orphan designation per year in the past decade.
Activity was lower in general in 2019 due to the move of EMA to Amsterdam

Source: EMA orphan NAS drug authorizations 2015-2024 – database accessed April 2025. Annual Report 2019
*141 out of 537 (26%) total approved NAS were orphan drugs

1565 NAS for rare diseases* are under development and expected across the EU per expected launch year, assuming completion of trials and authorizations

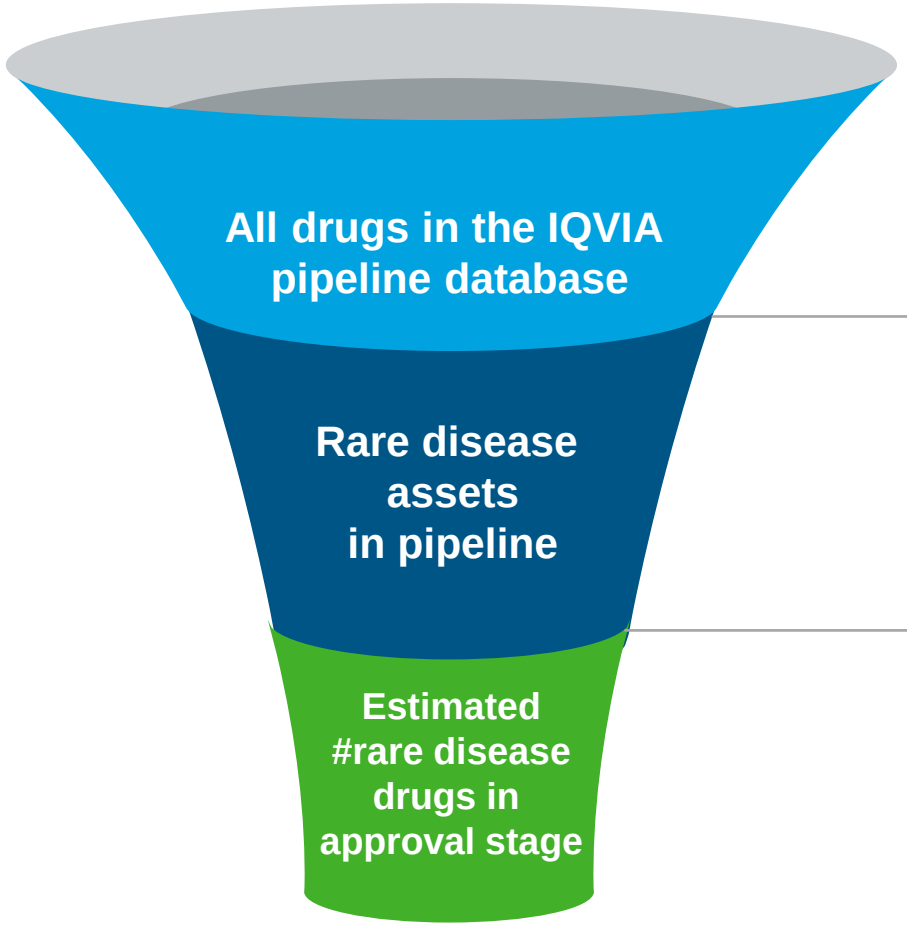


IQVIA Pipeline Link includes new active substances under development and their expected launch year based on current research phase. Since it does not consider the probability of trial success, the number of launched products will be much smaller. IQVIA Nordics has categorized the assets based on the expected indication.

Source: IQVIA Pipeline Link
*1565 out of 6872 (23%) drugs under development are for rare diseases

Analysis and categorization of the Pipeline Link resulted in an estimation of orphan drugs to apply in Sweden the next 10 years

Methodology



IQVIA pipeline drugs

- Includes all New Active Substances under development in the IQVIA pipeline data estimated to seek approval over the next 10 years in Sweden, assuming 100% success in trial and market authorization

Categorization of rare & manual exclusion of non-rare

- Gene therapies were flagged to stay included
- Orphan drug designations by EMA and FDA were considered, desk research conducted and pipeline assets with a non-rare or non-oncology indication excluded
- For oncology assets, a share of orphan (29%[1]) was applied based on EMA approvals for the latest 5 years

Final estimated number of rare disease drugs seeking for approval

- To estimate the number of assets for rare diseases in the 10-year pipeline that will potentially apply for approval and reimbursement in Sweden, the average success rates per stage in the drug development process were applied

Sources: 1) EMA authorizations 2020-2025

IQVIA classified the assets for rare diseases in the Pipeline Link data into four categories to align with TLVs typical drug types

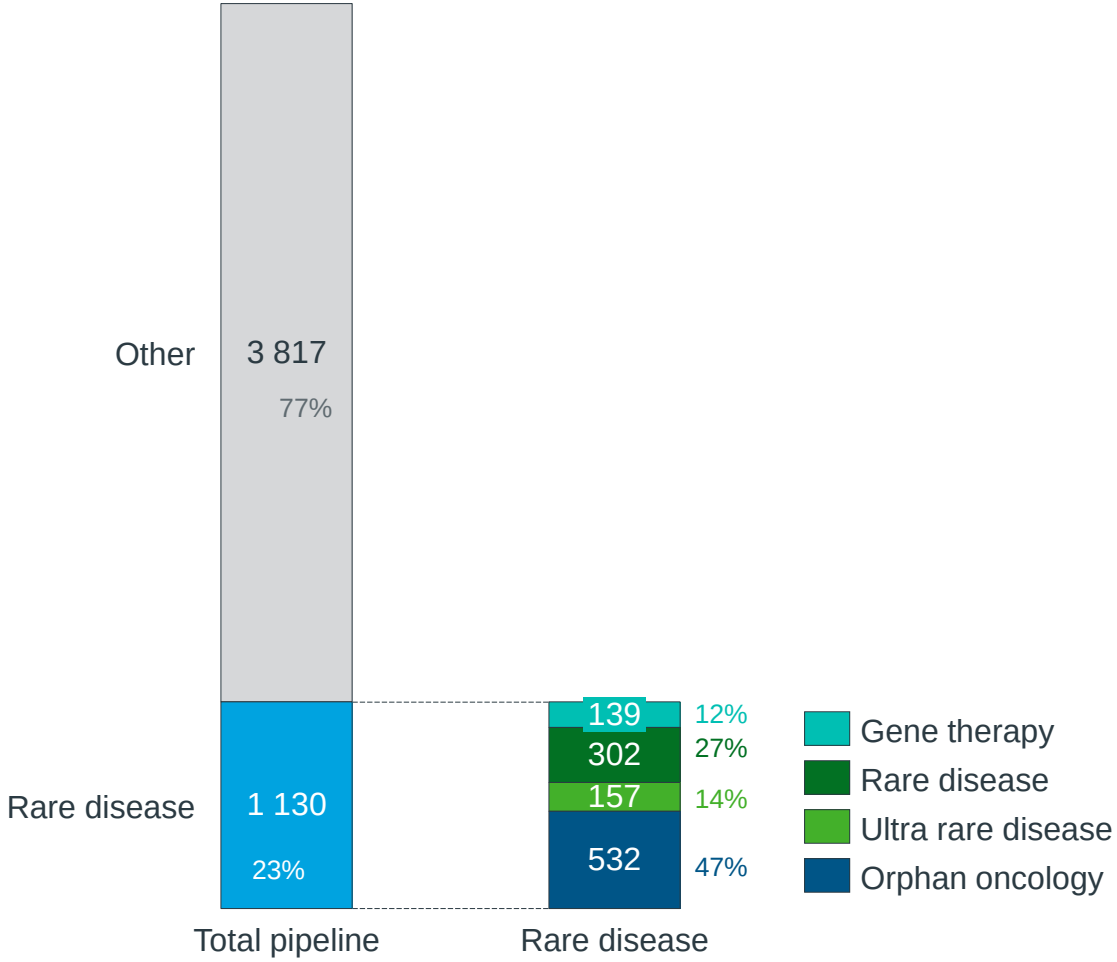
IQVIA rare disease categories and research caveats

Drug category*	IQVIA definition	Research caveats	Source
Orphan oncology	IQVIA assumes that 29% of total oncology drugs in the IQVIA Pipeline Link data are orphan oncology. This assumption is based on EMA approvals for new active substances in oncology over the last 5 years (2020-2025), out of which the share of orphan oncology was calculated, equalling 29%.	It is estimated that the oncology drugs in the 10-year pipeline will have the same share of orphan oncology as the historical data. This assumption was applied due to the complexity of assessing whether oncology assets could get orphan designations	EMA approvals 2020-2025
Rare disease (EMA definition)	Assets targeting a rare condition with prevalence of maximum 5 in 10,000** (reflecting ~5300 patients in Sweden), and at least 100 patients in Sweden	The desk research on prevelance of rare diseases is not always specific to Sweden in which case prevalence has been calculated by using any available prevalence rate applied to the Swedish population.	Desk research on prevalence rates of the expected indications of the assets in the Pipeline Link
Ultra-rare disease (type 3 & 4 TLV)	Assets targeting a rare condition with a prevalence of fewer than 100 patients in Sweden (reflecting ~1 in 1M in Sweden), to accommodate TLVs drug types.	As above for rare disease Note references to ultra-rare being defined as 200 patients in Sweden[1], or 1 in 50,000 in Europe	Desk research on prevalence rates of the expected indications of the assets in the Pipeline Link
Gene therapy	Assets in development classified in the Pipeline Link as gene therapies.	No caveats	IQVIA Pipeline Link

*categories are mutually exclusive, each pipeline product has been classified into one category only
**according to EMAs orphan drug designation. Source: 1 iSL analysis of TLVs model

Pipeline assets in IQVIA Pipeline Link were analyzed and classified based on indication to identify those for rare diseases

Total versus rare disease pipeline in Sweden



4 947 drugs in Pipeline Link

- Based on IQVIA Pipeline Link, there are in total 4 947 assets (NAS) under development in the 10-year pipeline for Sweden

1 130 rare disease drugs in pipeline

- The inclusion and exclusion criteria were applied on the total pipeline drugs to include only assets for rare diseases
- 1 130 assets for rare diseases were identified

The rare diseases drugs in pipeline were further classified according to their indication into:

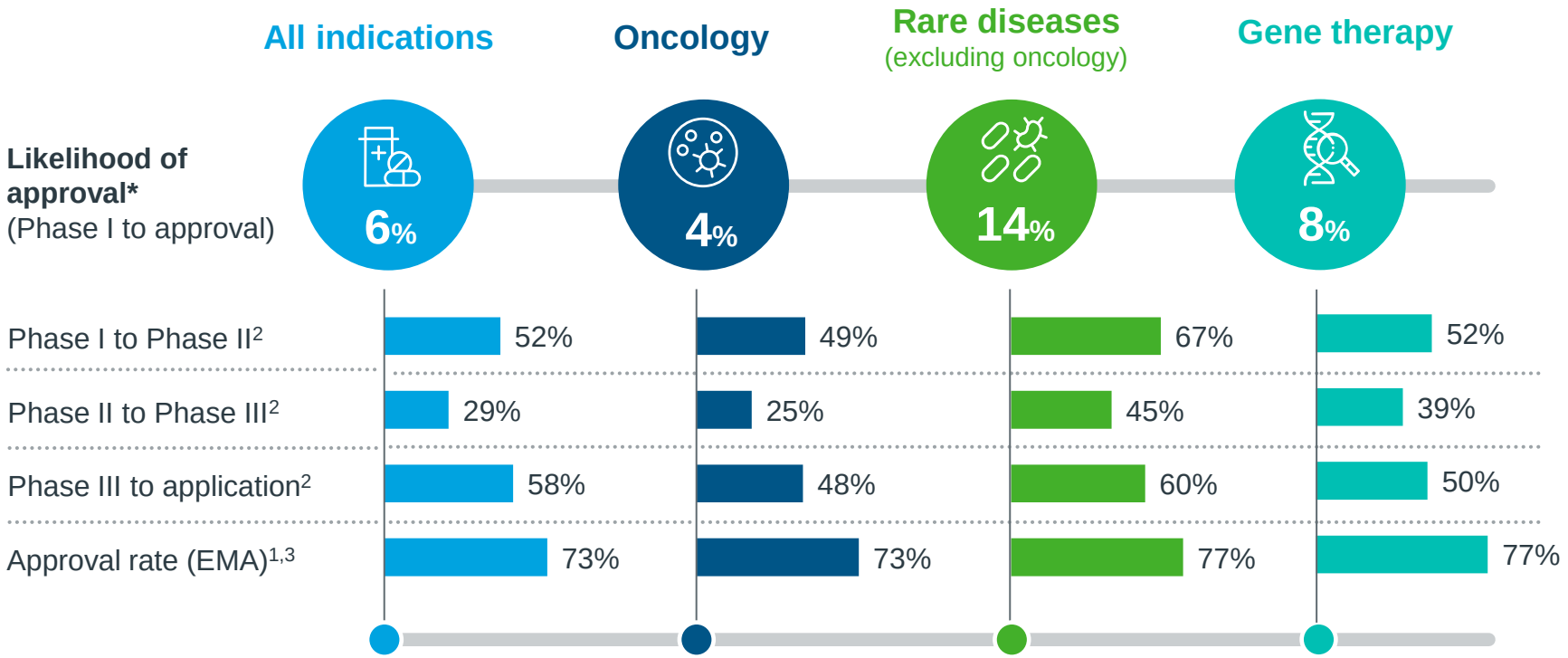
- 139 Gene therapy drugs
- 302 Rare disease drugs (>100 patients in Sweden)
- 157 Ultra rare disease drugs (<100 patients in Sweden)
- 532 Orphan oncology drugs (the 29%[1] share of orphan oncology within total oncology drugs was applied)

Sources: IQVIA Pipeline Link; 1) EMA authorizations 2020-2025

Research shows rare disease assets have a higher phase I to approval success rate than drugs overall

Phase II to phase III has the lowest success rate across all disease categories

Average success rate for each phase of drug development:



The differences in success rates can have multiple causes. Rare diseases frequently have a targeted, well-defined patient population. In contrast, higher prevalence diseases, where large heterogeneous patient populations will be treated, likely entail more trial complexity.

The scientific complexity and more competitive dynamics for oncology products can have adverse impact on the success rates for oncology therapies.

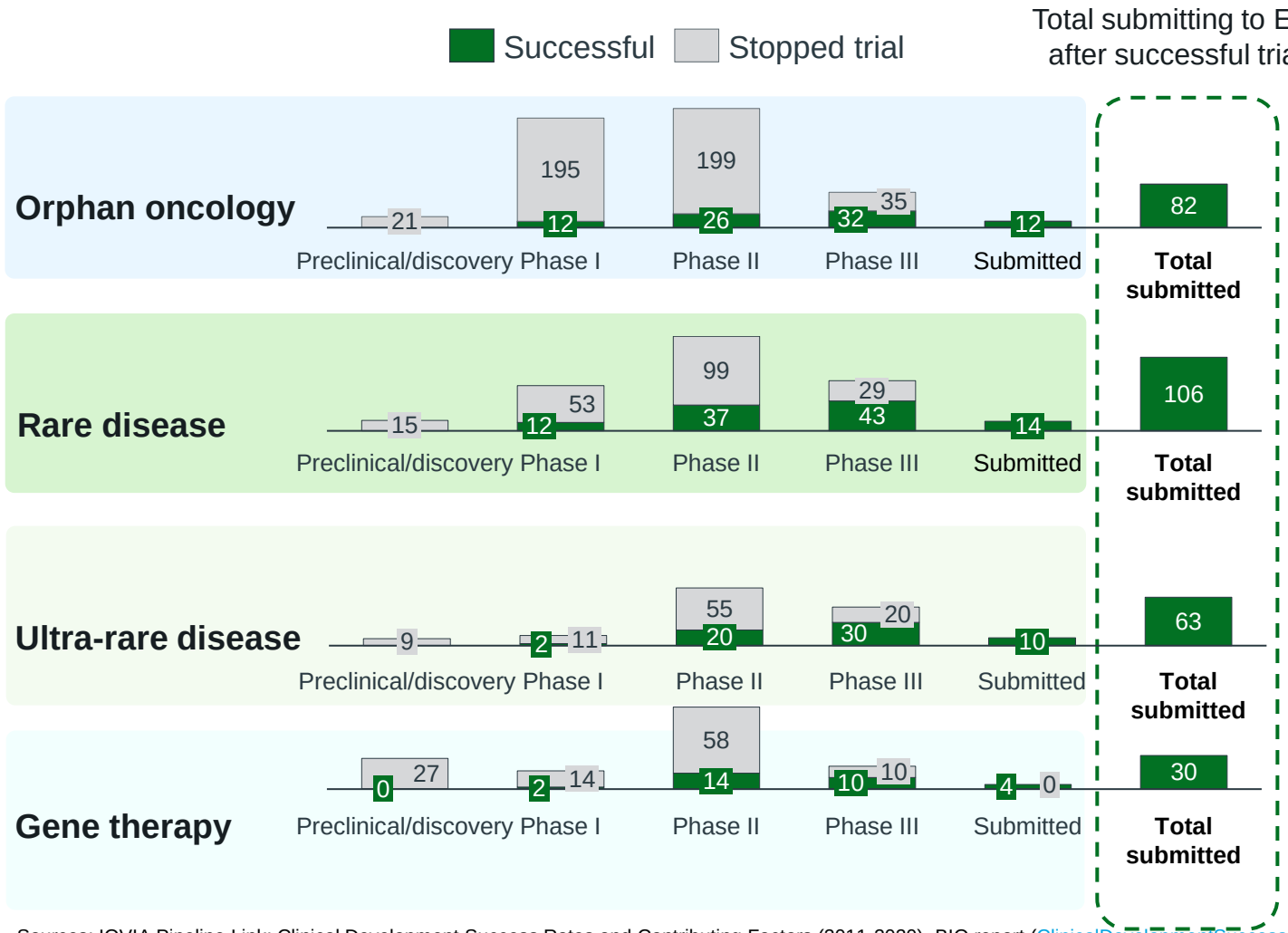
Avg. success rate from discovery to approval **~0,01%**

Sources: 1) EMA authorizations 2020-2025;
2) Clinical Development Success Rates and Contributing Factors (2011-2020), BIO report (ClinicalDevelopmentSuccessRates2011_2020.pdf);
3) Assessing Availability of New Drugs in Europe, Japan, and the U.S., Dec. 2024, IQVIA Institute (iqvia-institute-availability-of-new-drugs-11-24-forweb.pdf)

*Likelihood of approval is the product of the success rate of the stages of drug development

Applying trial success rates, 281 orphan drugs are estimated to seek approval at EMA in the next 10 years

Orphan drugs by research phase, to which average success rates are applied



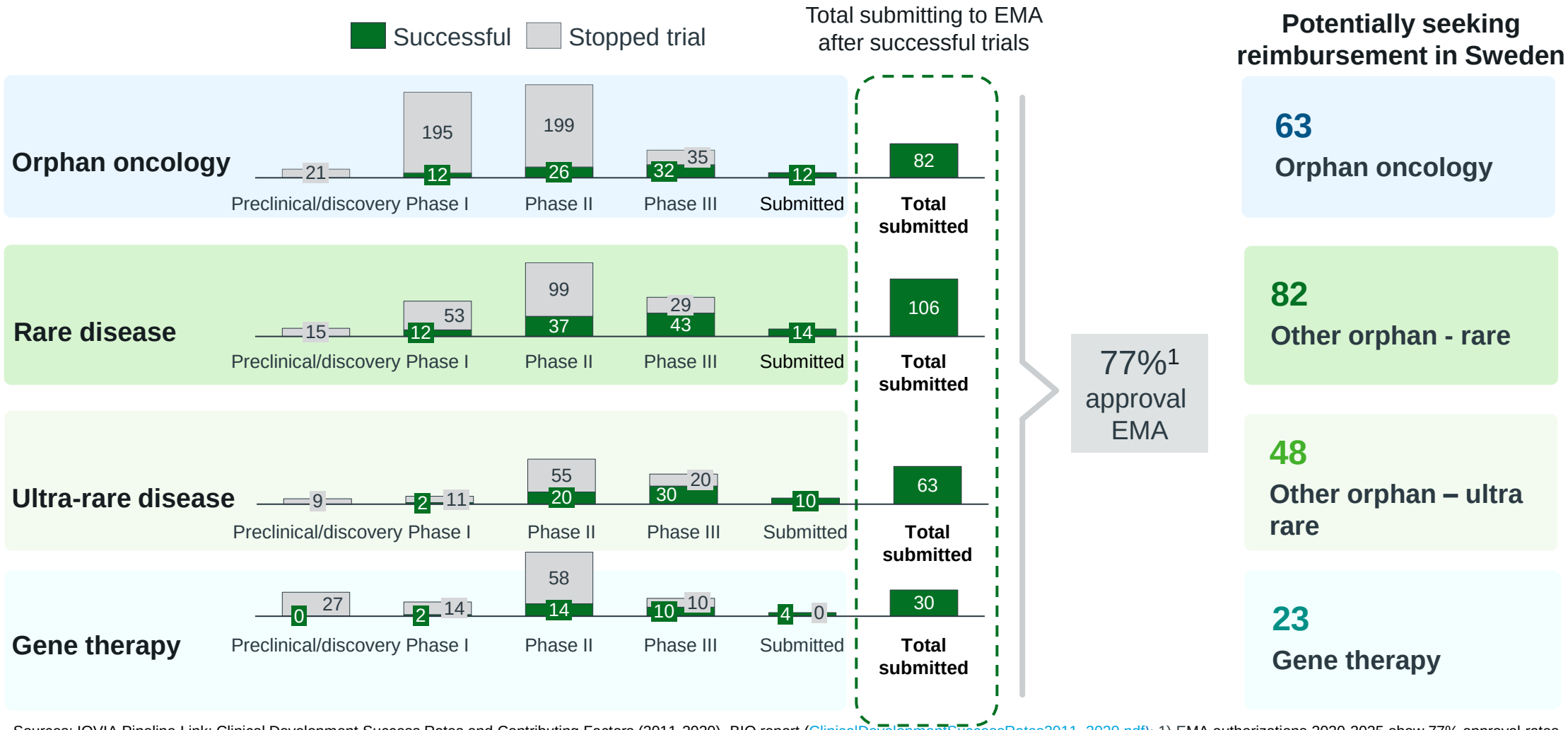
281 assets are expected to seek approval at EMA after successful trials

77%[1] of orphan and oncology drugs have gained EMA authorization 2020-2025

Sources: IQVIA Pipeline Link; Clinical Development Success Rates and Contributing Factors (2011-2020), BIO report (ClinicalDevelopmentSuccessRates2011_2020.pdf); 1) EMA authorizations 2020-2025

At an approval rate of 77%, in total 216 orphan drugs are expected to apply for reimbursement in Sweden

Orphan drugs by research phase, and adding success rates to EMA approval



Sources: IQVIA Pipeline Link; Clinical Development Success Rates and Contributing Factors (2011-2020), BIO report (ClinicalDevelopmentSuccessRates2011_2020.pdf); 1) EMA authorizations 2020-2025 show 77% approval rates

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TLV scenarios are quite aligned with IQVIA estimates for the types in scope, while 82 orphan drugs are not eligible for higher ICER

IQVIA orphan oncology class includes a wider range than TLV rare cancer class

Estimated number of launches potentially seeking for reimbursement in Sweden over the next 10 years:

TLV Scenarios*	**TLV** Type 1 drugs	**IQVIA** Orphan oncology	**TLV** Type 2 drugs	**IQVIA** Gene therapy	**TLV** Type 3 + 4 drugs	**IQVIA** Ultra-rare	**TLV total**	**IQVIA total**	**IQVIA** Rare disease
High	30		20		60		**110**		
Base case	**15**	**63**	**15**	**23**	**40**	**48**	**70**	**134**	**82**
Low	5		10		20		**35**		

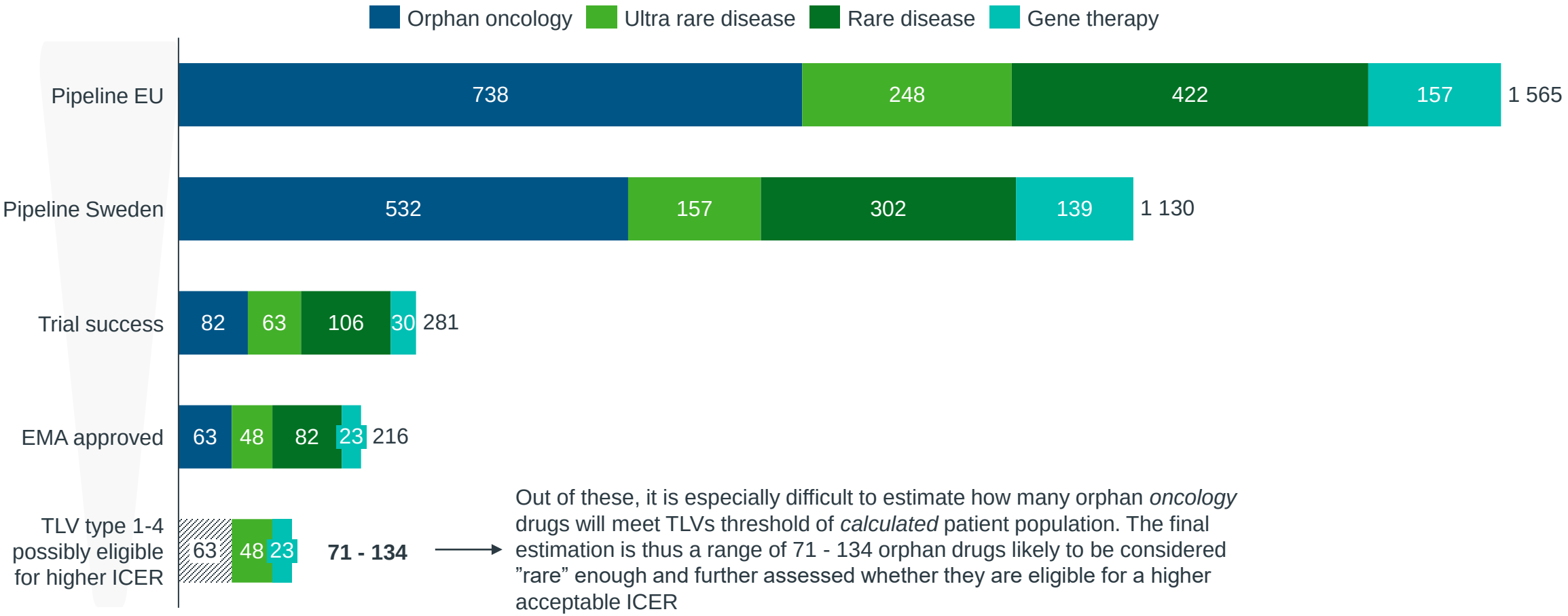
TLV distributes drugs into four types, which can be compared to IQVIA's categories. Note however differences in classification methodologies as described below.

- **TLV type 1** is defined to treat a rare cancer that is given for a short period of time. TLV historically sees 1-50 patients in Sweden. The **IQVIA orphan oncology** category includes assets labelled according to the EMA classification for orphan oncology, hence **IQVIAs higher estimated number of launches than TLV.**
- **TLV type 2** is defined as a gene therapy for a rare health condition that is given on one occasion, independent of patient numbers treated. It is equivalent to **IQVIA gene therapy** category. **The pipeline suggests that TLVs high case scenario is most appropriate.**
- **TLV type 3** is defined as a long-term, continuous treatment for a rare health condition *affecting* up to 30 patients in Sweden. **TLV type 4** is defined to *affect* 31–100 patients with a rare condition in Sweden. TLVs type 3 + 4 estimations can be compared to **IQVIA ultra-rare disease therapy** class, which includes drugs for indications with a *prevalence* of fewer than 100 patients in Sweden. Note that affected patients and prevalence can deviate and **TLVs base case scenario may be appropriate.**
- IQVIA includes **rare disease drugs** as an additional category, with a prevalence of 100 to ~5300 patients in Sweden, based on the EMA orphan drug designation. TLV would NOT grant these drugs a higher ICER, unless **their calculated population could result in fewer than 100 patients.** It is unclear from the report if TLV could consider drugs with an *affected* population of less than 100 in cases where prevalence of the condition is more than 100.

*Values for the TLV scenarios are based on the estimated mean of TLV's uniform distribution for each scenario and each drug class, per year. The average number of yearly launches are multiplied by 10 to obtain the 10-year estimation.

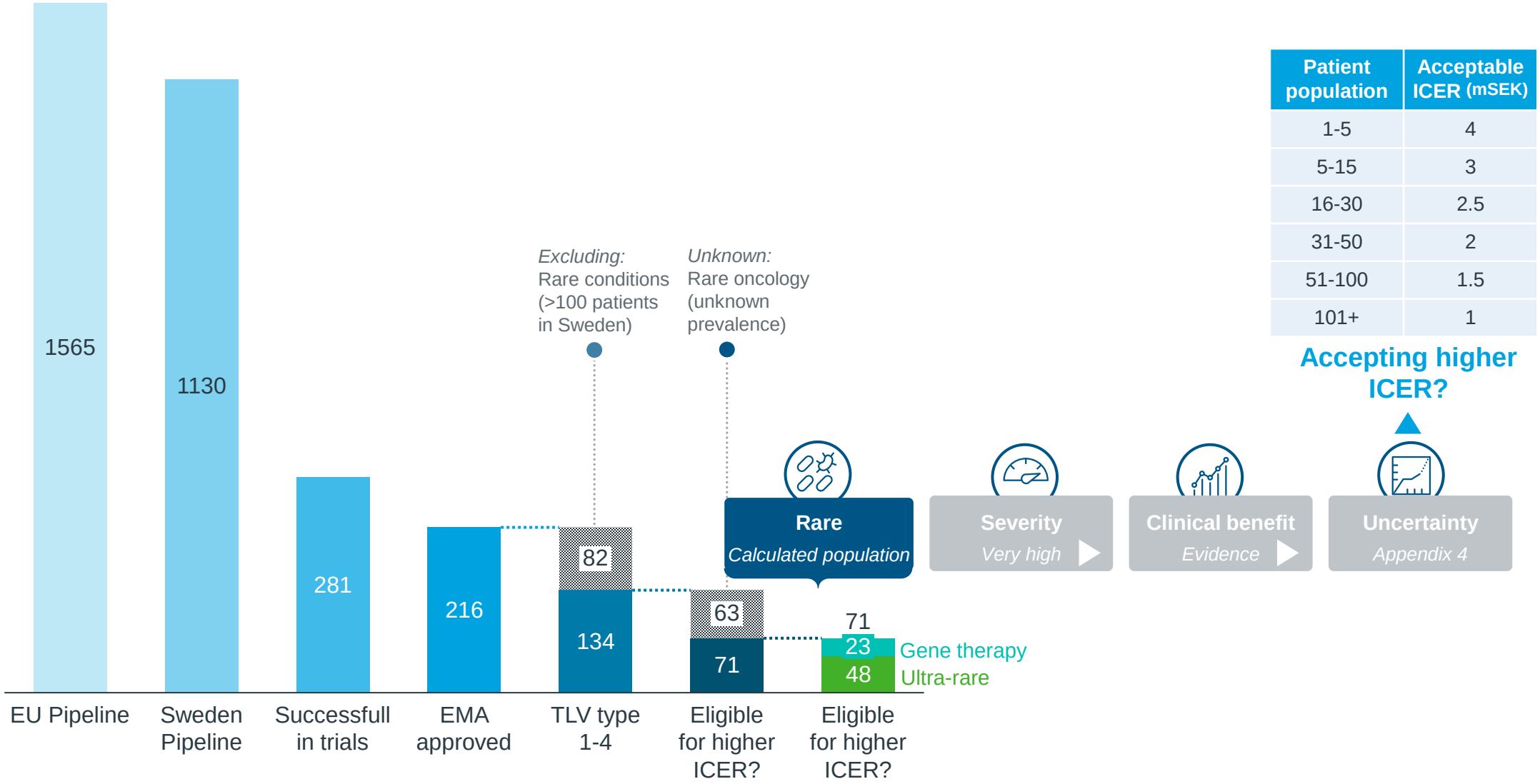
Sources: *Praktiska förutsättningar för stärkt tillgång till läkemedel vid sällsynta hälsotillstånd*, TLV (2024); IQVIA Pipeline Link; Clinical Development Success Rates and Contributing Factors (2011-2020), BIO report; EMA authorizations (2020-2025)

In the next 10 years, 216 orphan drugs may apply for funding in Sweden, of which 71 to 134 may meet TLVs population size criteria



Out of these, it is especially difficult to estimate how many orphan *oncology* drugs will meet TLVs threshold of *calculated* patient population. The final estimation is thus a range of 71 - 134 orphan drugs likely to be considered ”rare” enough and further assessed whether they are eligible for a higher acceptable ICER

Once these 71 to 134 orphan drugs are considered, they still need to meet the other criteria to be allowed a higher ICER



Patient population	Acceptable ICER (mSEK)
1-5	4
5-15	3
16-30	2.5
31-50	2
51-100	1.5
101+	1

Knowledge of prevalence, incidence and SoC are needed to forecast if a drug is eligible for higher acceptable ICER

IQVIA reflections

TLVs definition of typical drug types deviates from international definitions in two ways, which makes it complicated to forecast which drugs and how many will be eligible for a higher acceptable ICER.

1. TLV does not use the EMA definition of rare disease (maximum 5 in 10,000* (reflecting ~5300 patients in Sweden).
2. TLV does not use the common definition of ultra-rare disease (maximum 1 in 50,000 – reflecting ~200 patients in Sweden)
3. TLV considers **a calculation of** patient numbers in their definition, combining prevalence and incidence, and setting limits at 30 and 100 patients defining payment of the drug in scope – both are lower than the above definitions.
4. TLV explains the reasoning for this calculation in appendix 3, referring to objectives around revenue and aggregated health benefits.
5. There is room for interpretation of the payment defining population which may in reality be dependent on the expected indication of the drug, the standard of care at that point in time, and likely the division of adult versus pediatric population – where drugs may first research in and apply for adult populations.
6. For orphan ***oncology*** drugs, it will be even more complicated to calculate patient population, predict requirements on biomarkers and tumor expressions, predict relevant standard of care at assessment, and with that the relevant line of treatment and patient population in scope.

The most recent NT-council decision for a gene therapy did not mention the new methods

IQVIA reflections

While TLVs gene therapy classification is most straight-forward, it is interesting to note that the NT-council published a negative recommendation for Hemgenix in April 2025, based on the TLV health economic assessment. There was no reference to considering or not considering a higher acceptable ICER based on the new methods.

- The population with condition was expected to be around 100 patients, while the **treatable population was considered fewer** than 100 adults eligible for treatment.
- The (moderate to severe) condition was considered serious, however well-treated, and thus the level of severity for decision-making was concluded at **moderate severity.**
- The cost of the single treatment is 29 mSEK (list price). Negotiations were held around discount and pay-for-performance was considered, but not resulting in an acceptable ICER.
- The uncertainty of the clinical benefit was high, and the **uncertainty of the health economic evaluation is very high**, both related to lack of long-term data, but in the latter also related to uncertainties in the development of the prices of current standard treatemnt with factor IX, with high confidential rebates and price competition.

Sources: Press release - Samverkanläkemedel; Decision; Decision NT-council

Appendix

Appendix 1 – Terms and definitions

Term	Definition	Source
NAS	New Active Substance – note that IQVIAs Pipeline data and analysis ONLY take into account NAS and their first indication. TLV also considers unique drugs. Chapter 3 describes that TLV will follow-up on usage and actual patients treated. In case the number of patients is larger than expected, or increases due to additional indications, TLV will reassess reimbursement and the acceptable ICER. This IQVIA analysis and TLV report both include retail and hospital drugs in their scope – TLV assuming that the NT council will adopt the same way of reasoning and lowering the acceptable ICER in certain situations.	-
Orphan drug (EMA definition)	The EU offers incentives to encourage companies to research and develop medicines for rare diseases that otherwise would not be developed. To access these incentives, companies can apply for orphan designation for their medicine, provided certain criteria are met. Orphan-designated medicines that eventually make it to the market are granted 10 years of market exclusivity, provided it can be demonstrated that the criteria for their designation still apply. There are over 260 orphan medicines authorised in the EU, and over 3000 medicines with orphan designation To qualify for orphan designation by EMA, a medicine must meet several criteria: - Intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating; - Prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development; → *in Sweden in 2025: ~5300 patients* - No satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorized, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.	EMA
Orphan drug (FDA definition)	Orphan drug is defined as a drug intended for the treatment, prevention or diagnosis of a rare disease or condition, which is one that affects fewer than 200,000 persons in the US (~6 in 10,000)	FDA
Orphan drug (TLV definition)	TLVs general definition of ”Sällsynt hälsotillstånd”: Rare health conditions usually have lasting consequences on the conditions of life and bring special problems caused by the rarity of the condition. They require special expertise and often coordinated efforts from the health care system and the rest of society. As a guide, prevalence in less than 5 per 10 000 inhabitants can be considered as low prevalence. This is *NOT* the definition used in the staircase model. For the staircase model, TLV does not consider any orphan drug designation, and TLV calculates relevant population based on a formula of prevalence and incidence.	

Appendix 2 – Description of assumptions made by IQVIA

Description	Assumption	Source
IQVIA Pipeline Link	IQVIA Pipeline Link collects information on new active substances that are under development and may be launched over the next 10 years. Pipeline Link data only considers the first launch of a NAS, i.e. it does not cover indication extentions. Pipeline Link doesn't consider the probability of trial success, hence the data includes all products under development. IQVIAs analysis started with all products that the Pipeline Link expects relevant for Sweden. These products were categorised into orphan oncology, rare disease drugs, ultra-rare disease drugs and gene therapy. The number of products that are expected to launch were then estimated per category and stage of development. Therefore, the results in this report are showing much fewer drugs than reports covering the full Pipeline Link data.	IQVIA
Success rate (%)	The success rate at each phase of drug development is calculated by the share of drug candidates that advances to the next phase versus the ones that were suspended by the sponsor. The success rates were based on average success rates from 2011 to 2020. It is estimated that the drugs in the 10-year pipeline will be subject to the same success rates as the historical data.	Clinical Development Success Rates and Contributing Factors (2011-2020), BIO report (ClinicalDevelopmentSuccessRates2011_2020.pdf)
Likelihood of approval calculation	To calculate the likelihood of approval for a phase I drug, success rates for "phase I – phase II", "phase II – phase III", "phase III – submission" and "submission – approval" are cumulatively applied. To calculate the likelihood of approval for a phase II drug, success rates "phase II – phase III", "phase III – submission" and "submission – approval" are cumulatively applied. To calculate the likelihood of approval for a phase III drug, success rates for "phase III – submission" and "submission – approval" are cumulatively applied. To calculate the likelihood of approval for a submitted drug, the success rate for "submission – approval" is used. *Note that the analysis does not assume any drugs to apply for approval earlier than finishing phase III*	IQVIA calculations based on Clinical Development Success Rates and Contributing Factors (2011-2020), BIO report (ClinicalDevelopmentSuccessRates2011_2020.pdf)
EMA approval rate	The approval rates for oncology and orphan drugs were calculated from EMA approvals for new active substances from 2020-2025 (77% approval rate for both oncology and orphan drugs). It is assumed that the drugs in the 10-year pipeline will be subject to the same approval rates as the historical data.	EMA approvals 2020-2025

Appendix 3 – List of rare indications in the Pipeline Link

Indications have been shortened by grouping all subtypes together

Achondroplasia
Thrombotic Thrombocytopenic Purpura
Acromegaly
Adult growth hormone deficiency
Aggressive Fibromatosis
Alport Syndrome
Amyotrophic lateral sclerosis
ANCA associated vasculitis
Anemia-associated Myelodysplastic Syndrome
Anemia-associated Myelofibrosis
Angelman Syndrome
Aphthous Ulcers of Behcet's Disease
Atopic keratoconjunctivitis
ATTR amyloidosis
ATTR-CM
Autosomal Dominant Hypocalcemia Type 1
Becker Muscular Dystrophy
Bronchopulmonary dysplasia
Buerger's Disease
Cerebral Cavernous Malformations
Cerebral Palsy
Charcot-Marie-Tooth disease
Charcot-Marie-Tooth Type 1A
Charcot-Marie-Tooth Type 2

Chronic Fibrosing Interstitial Lung Diseases
Chronic hypoparathyroidism
Demyelinating Polyneuropathy
Chronic pulmonary sarcoidosis
Cold agglutinin disease
Postcapillary and Precapillary Pulmonary Hypertension
Congenital adrenal hyperplasia
Connective Tissue Disease-ILD
Cutaneous Lupus Erythematosus
Cystic fibrosis
Dermatomyositis
Dravet Syndrome
Eosinophilic Esophagitis
Facioscapulohumeral Muscular Dystrophy
Familial Adenomatous Polyposis
Fragile X syndrome
Growth Hormone Deficiency
Hemophilia
Hereditary Angioedema
High Risk Essential Thrombocythaemia
HTLV-1 associated myelopathy
Huntington's Disease
Hyperphosphatemia
Hypoparathyroidism

Idiopathic Hypersomnia
Idiopathic Pulmonary Fibrosis
IgA nephropathy
Immune Thrombocytopenia
Lennox-Gastaut Syndrome
Lupus nephritis
Myasthenia gravis
Myelodysplastic syndrome
Narcolepsy Type 1
OPA1 Mutation-Associated Autosomal Dominant Optic Atrophy
Prader-Willi Syndrome
Systemic lupus erythematosus with nephritis
Vaso-Occlusive Episodes in Sickle Cell Disease

Appendix 4 – List of ultra rare indications in the Pipeline Link

Indications have been shortened by grouping all subtypes together

AChR-negative Myasthenia Gravis
Acquired fibrinogen deficiency
Acute Radiation Syndrome
Adrenoleukodystrophy
Alexander Disease
Ataxia Telangiectasia
ATTRv-PN
Autoimmune Pulmonary Alveolar Proteinosis
Barth syndrome
Bronchiolitis Obliterans Syndrome (BOS)
C3 Glomerulopathy
C9orf72 gene mutated ALS
Choroideremia
Congenital Hyperinsulinism
Congenital Muscular Dystrophy
Cushing's Disease
Dravet Syndrome
Duchenne muscular dystrophy
Eosinophilic granulomatosis with polyangiitis
Fabry disease
Familial chylomicronemia syndrome (FCS)
Farber disease
Fibrodysplasia Ossificans Progressiva
Focal segmental glomerulosclerosis

Friedreich Ataxia
Glycogen Storage Disease
GNE Myopathy
Gorlin Syndrome
Graft versus host disease
IDH1-mutated Higher-risk Myelodysplastic Syndromes
Idiopathic Multicentric Castleman's Disease
Immunoglobulin Light Chain Amyloidosis
Lafora Disease
Limb-girdle muscular dystrophy type 2I/R9
Long-chain fatty acid oxidation disorders
Maple syrup urine disease
Menkes Disease
Methyl CpG Binding Protein 2 Duplication Syndrome
Methylmalonic acidemia
Microvillus Inclusion Disease
Mitochondrial Encephalomyopathy
MPS II, Hunter syndrome
MPS IIIA (Sanfilippo Syndrome)
MPS type I (Hurler syndrome)
Mucopolysaccharidosis type IIIB (sanfilippo B)
Netherton syndrome
Neuromyelitis optica spectrum disorder
Paroxysmal nocturnal hemoglobinuria

Paroxysmal nocturnal hemoglobinuria
Phelan-McDermid syndrome
Phosphoinositide 3-Kinase Delta Syndrome
Primary Focal Segmental Glomerulosclerosis
Menkes Disease
Primary Hyperoxaluria Type 1, 2 and 3
Prion disease
Progressive Multifocal Leukoencephalopathy
Pseudoxanthoma elasticum
Rett Syndrome
ROSAH syndrome
Secondary Hemophagocytic Lymphohistiocytosis
Spinocerebellar Ataxia Type 2
Thymidine kinase 2 deficiency
Vascular Ehlers-Danlos Syndrome
Von Willebrand Disease Type 1
Wilson's Disease
X-linked adrenoleukodystrophy
X-linked Hypophosphatemia
X-Linked Protoporphyria

Appendix 5 – List of gene therapy indications in the Pipeline Link

Indications have been shortened by grouping all subtypes together

Achromatopsia
Advanced Gynecological Tumors
Amyotrophic lateral sclerosis
Autosomal Dominant Optic Atrophy
Best vitelliform macular dystrophy
Bietti Crystalline Corneoretinal Dystrophy
Blue Cone Monochromacy
Breast Cancer
Canavan Disease
Chronic Hepatitis B
Crigler-Najjar Syndrome
Critical Limb Ischemia
Cystic fibrosis
Danon Disease
Diabetic Retinopathy
Dry Age-Related Macular Degeneration
Duchenne Muscular Dystrophy
Fabry Disease
Facet Syndrome
Fanconi Anemia Subtype A
Friedreich’s Ataxia Cardiomyopathy
FTD-GRN
Fukutin-related protein (FKRP) limb-girdle muscular dystrophy type 2I/R9
Gaucher Disease

Geographic Atrophy
Glycogen Storage Disease Type 1a
GUCY2D-associated Leber congenital amaurosis
Hemophilia A
Hemophilia B
Hereditary Spastic Paraplegia Type 50
High-grade Bacillus Calmette-Guerin Therapy
Hunter syndrome (MPS II)
Huntington's Disease
Infantile Batten Disease (CLN1)
Leber's Congenital Amaurosis
Limb girdle muscular dystrophy
Lysosomal storage disorders
Mucopolysaccharidosis Type I
Mucopolysaccharidosis type IIIA
Neovascular (wet) Age related Macular Degeneration
Neurogenic Detrusor Overactivity
Neuronal Ceroid Lipofuscinosis Type 2
Neuropathic Pain From Lumbosacral Radiculopathy
Neurotrophic Keratopathy
Non-congenital Myotonic Dystrophy Type 1
Non-ischemic cardiomyopathy
Ornithine transcarbamylase (OTC) deficiency
Parkinson's Disease
Phelan-McDermid Syndrome

Phenylketonuria
PKP2 Variant-Mediated Arrhythmogenic Cardiomyopathy
Pompe disease
Primary Hepatocellular Carcinoma
Primary Hyperoxaluria Type 1
Recessive Dystrophic Epidermolysis Bullosa (RDEB)
Recurrent glioblastoma multiforme
Retinitis Pigmentosa
Retinol dehydrogenase 12
Rett syndrome
Severe AADC Deficiency
Severe Combined Immunodeficiencies
Sickle Cell Disease
Solid tumors
Spinal Muscular Atrophy
STARGARDT DISEASE
TGM1-deficient autosomal recessive congenital ichthyosis
Unilateral Refractory Mesial Temporal Lobe Epilepsy
Vestibular Schwannoma
Wilson Disease
Wiskott Aldrich Syndrome
Xerostomia caused by radiation therapy
X-linked myotubular myopathy
X-Linked Retinoschisis (XLRS)

IQVIA Pipeline Link collects information on clinical trials, company websites and financial statements to define a 10-year pipeline

Company A & Q reports, Company websites

1 Harvest

Unstructured Global Pipeline Data

- Harvest raw pipeline data from latest company-reported sources (AR, QR, website)

2 Taxonomize

Structured Global Pipeline Data

- Rigorously map harvested pipeline data to systematic dimensional taxonomies for drugs, diseases, companies, targets, ATC3, route of admin

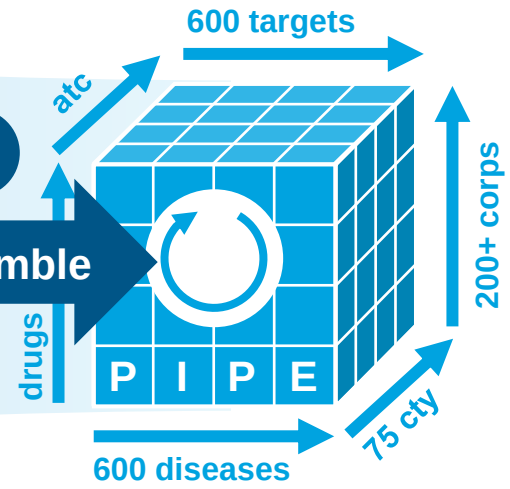
3 Country-adjustment

Country-specific Pipeline Data

- 'Mesh' the structured *global* pipeline data with *country-specific* information derived from country-specific clinical trial databases
- Each pipeline project now unambiguously defined at country-level

4 Assemble

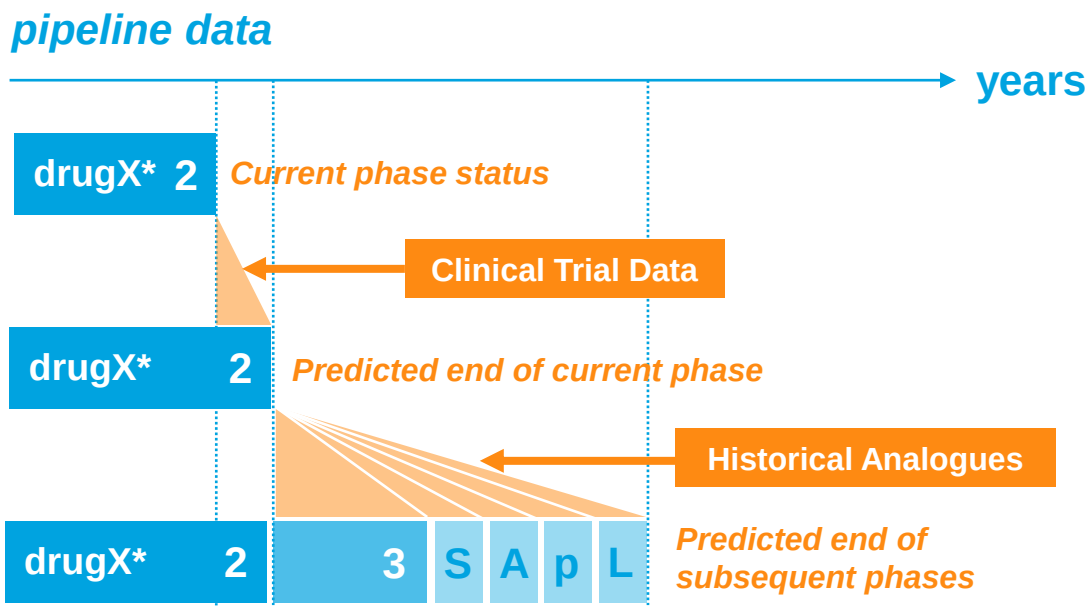
Pipeline Link datacube



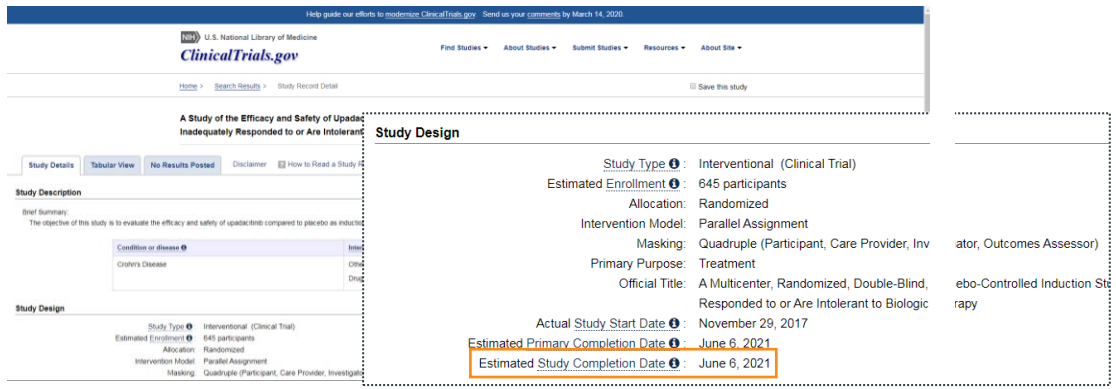
- Assemble building blocks to create Pipeline Link master data cube
- Pipeline data becomes cross-comparable and super-segmentable
- View pipelines by drug, disease, company, target, route of admin etc

Timing of the pipeline is based on research phase progression - modelled based on country- and disease-specific analogues

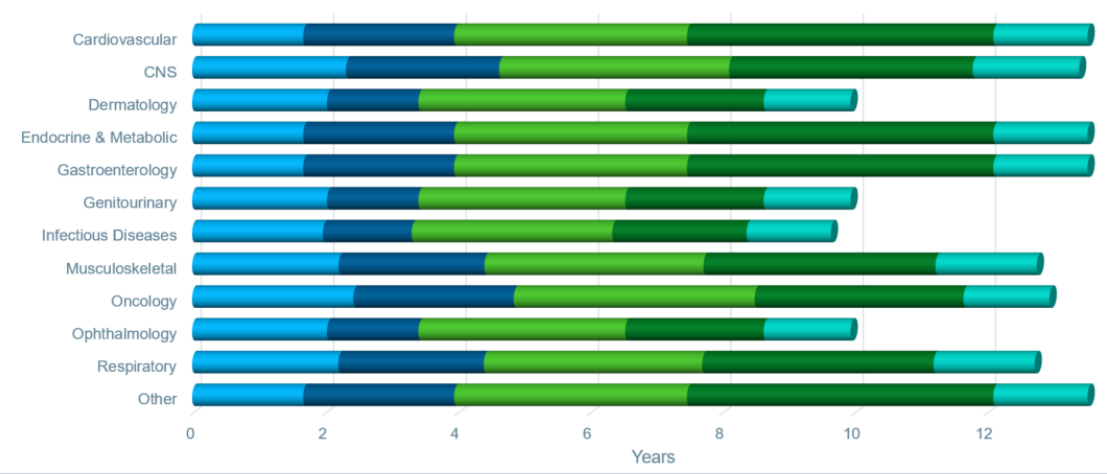
- Clinical trials are selected and reviewed by Pipeline Link's team of analysts to predict when the current stage of development will be completed, and the product will move into the next stage
- Completion dates for subsequent phases are based on analogues of the average duration products spend in each phase, varying by disease area



Progression Timeline for *current phase* based on clinical trial data



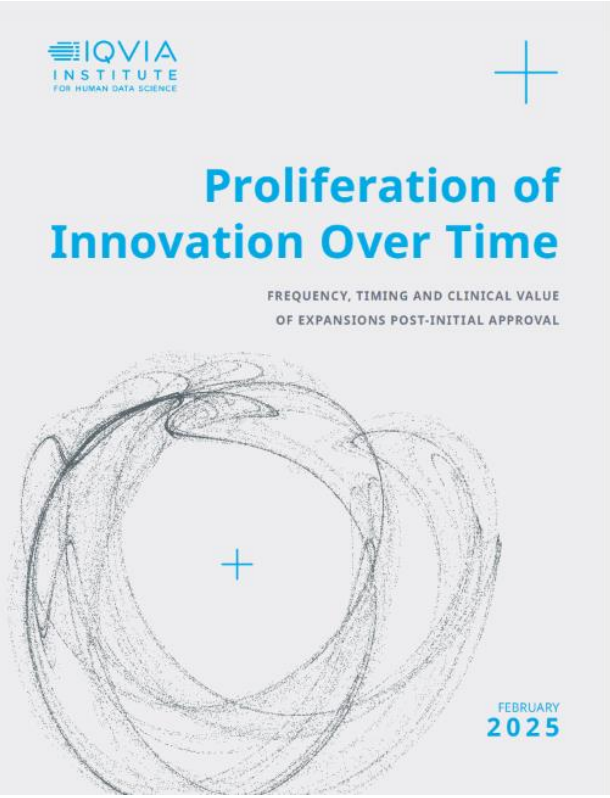
Progression Timeline for *subsequent phases* based on disease area-specific analogues of phase duration



Additional reading – IQVIA White papers

Initial NAS approvals are often followed by additional indications – also in the case of orphan drugs

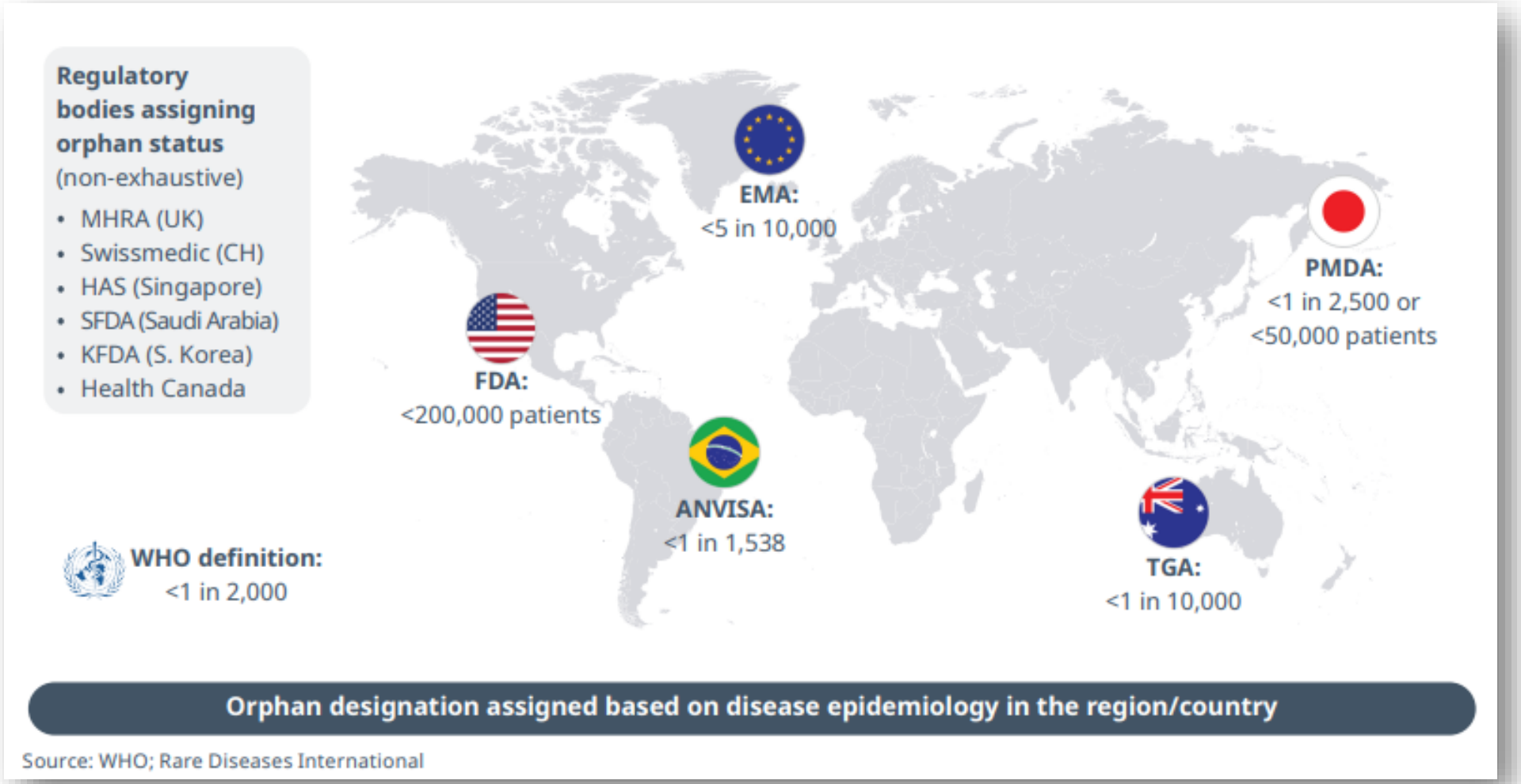
Note that TLV will reassess the acceptable ICER in case of higher use or additional indications



- Drugs are generally not finished with their innovation cycle with respect to therapeutic value at time of initial approval. More than half of NASs approved between 2000 and 2023 received at least one expansion post-initial approval.
- Overall, 75% of these post-initial approval expansions of a drug are focused on new patient populations and indications.
- Of the 1458 expansions received by the 446 NAS in scope, 29% were expansions for orphan drug populations.
- Drugs can receive approvals for expansions several years after their first approval. Biologics on the market for 13 years and longer achieved only 31% of their lifetime approvals within the first year of approval.

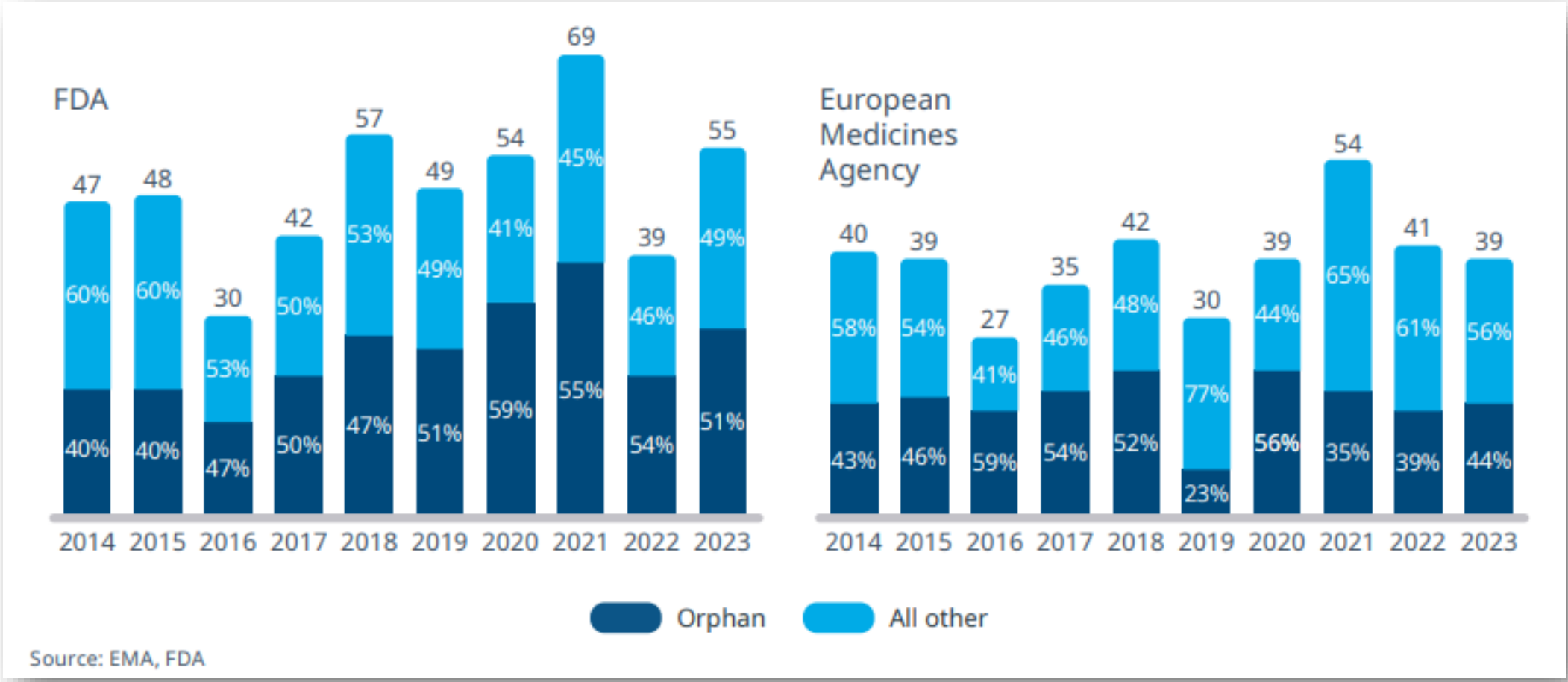
Proliferation of Innovation Over Time - IQVIA

Orphan drug designations differ



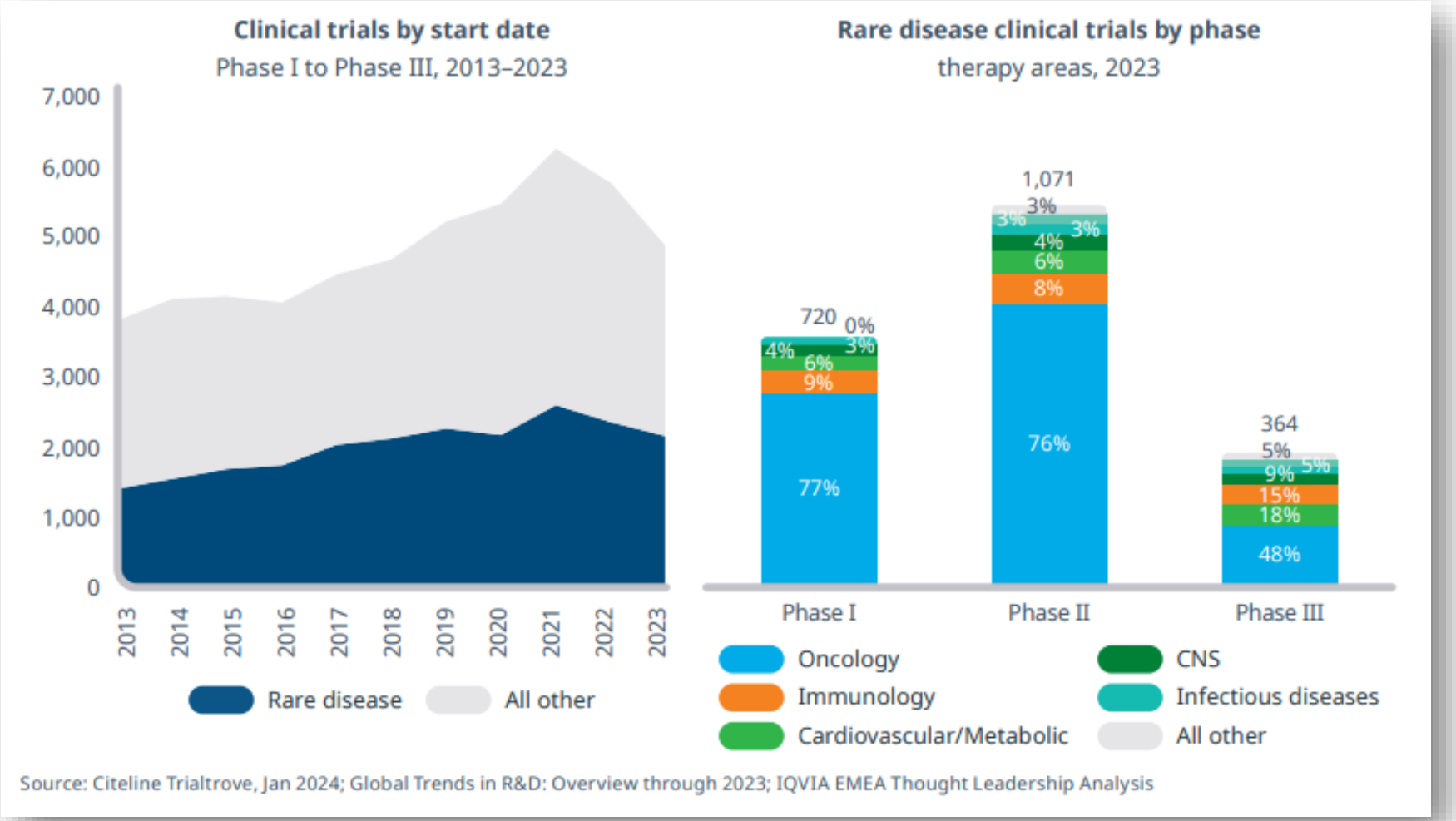
Source: [From Orphan to Opportunity: Mastering Rare Disease Launch Excellence - IQVIA]

Orphan drug approvals as share of total approvals – FDA & EMA



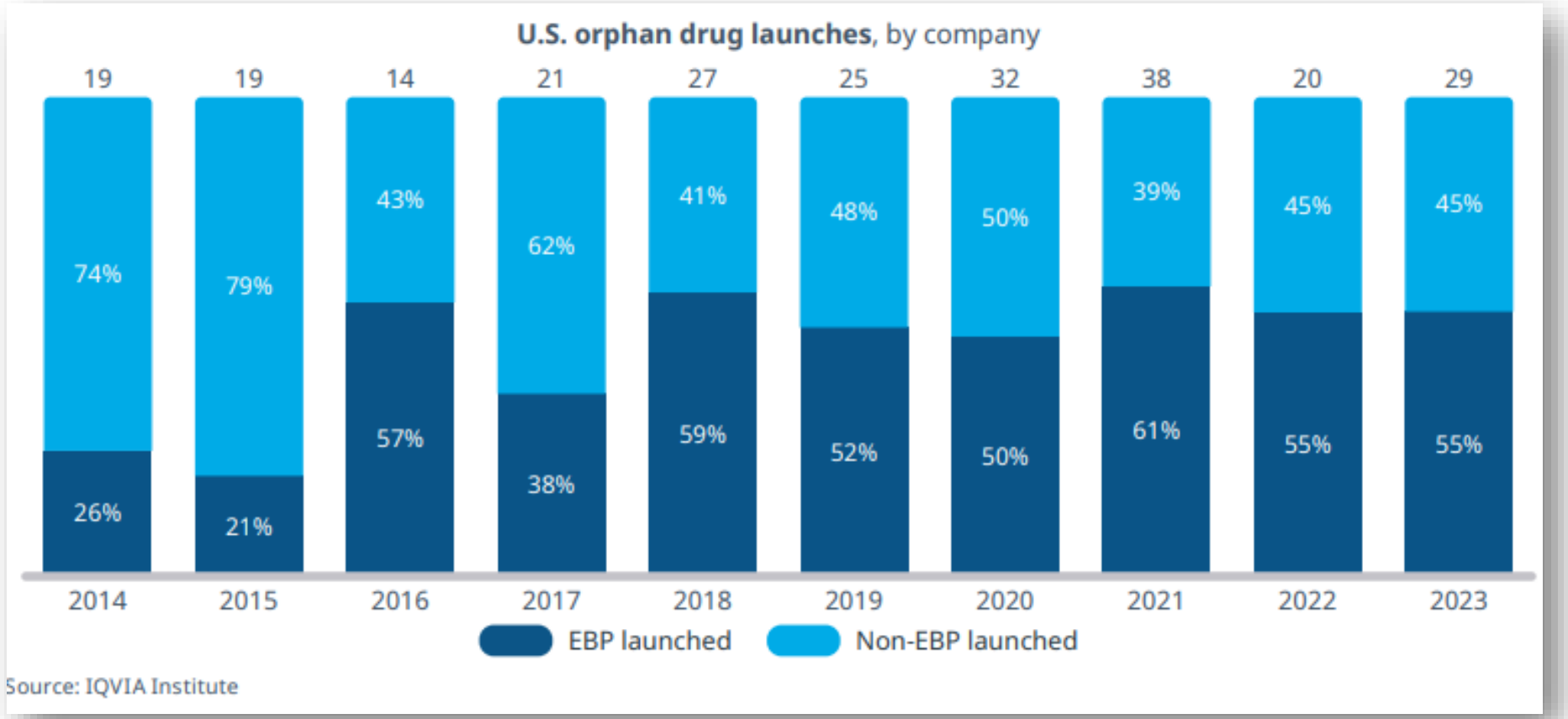
Source: [From Orphan to Opportunity: Mastering Rare Disease Launch Excellence - IQVIA]

Rare disease clinical trial activity



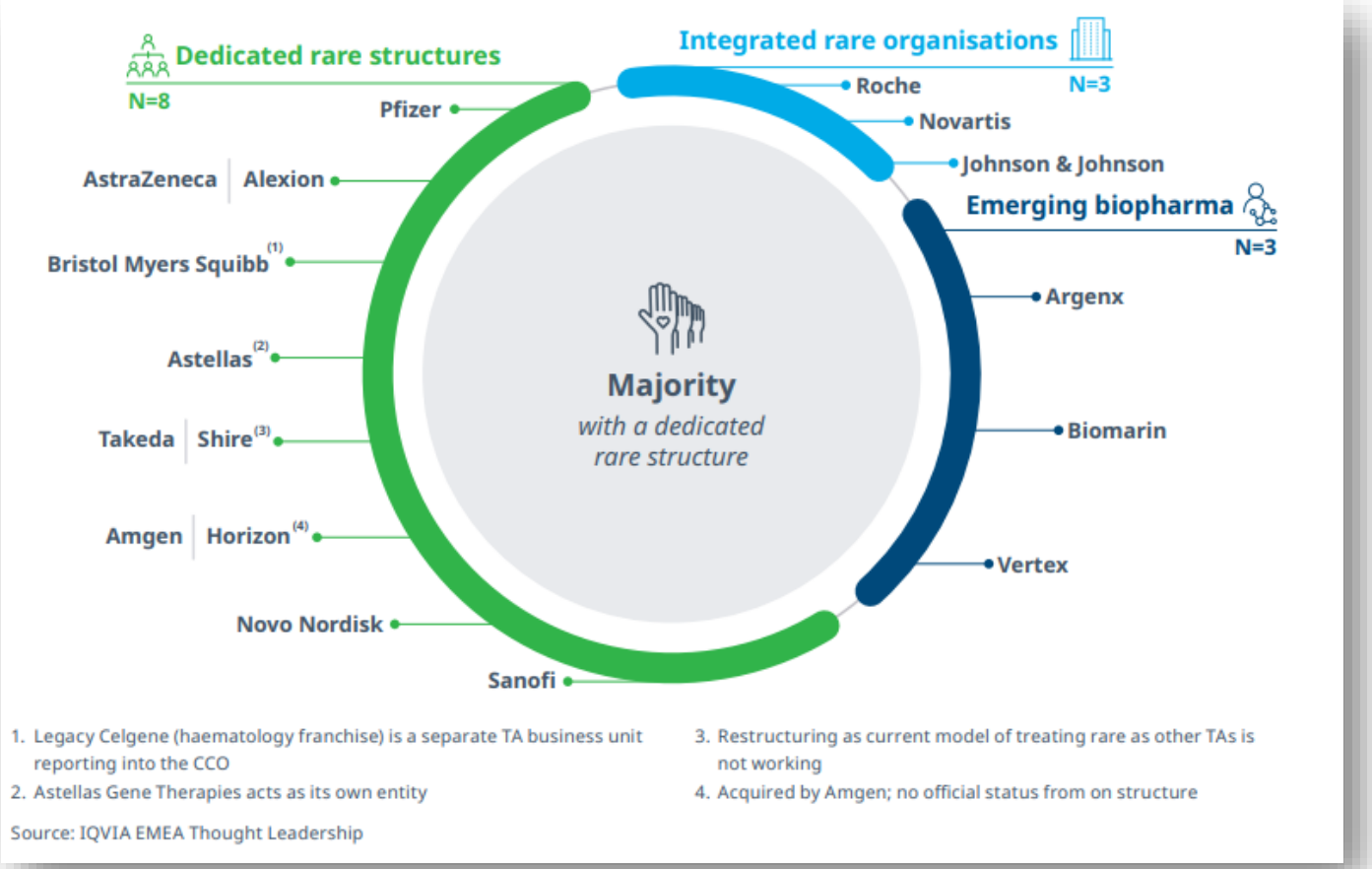
Source: From Orphan to Opportunity: Mastering Rare Disease Launch Excellence - IQVIA

Around half of US orphan drugs are launched by Emerging Biopharma rather than larger pharma



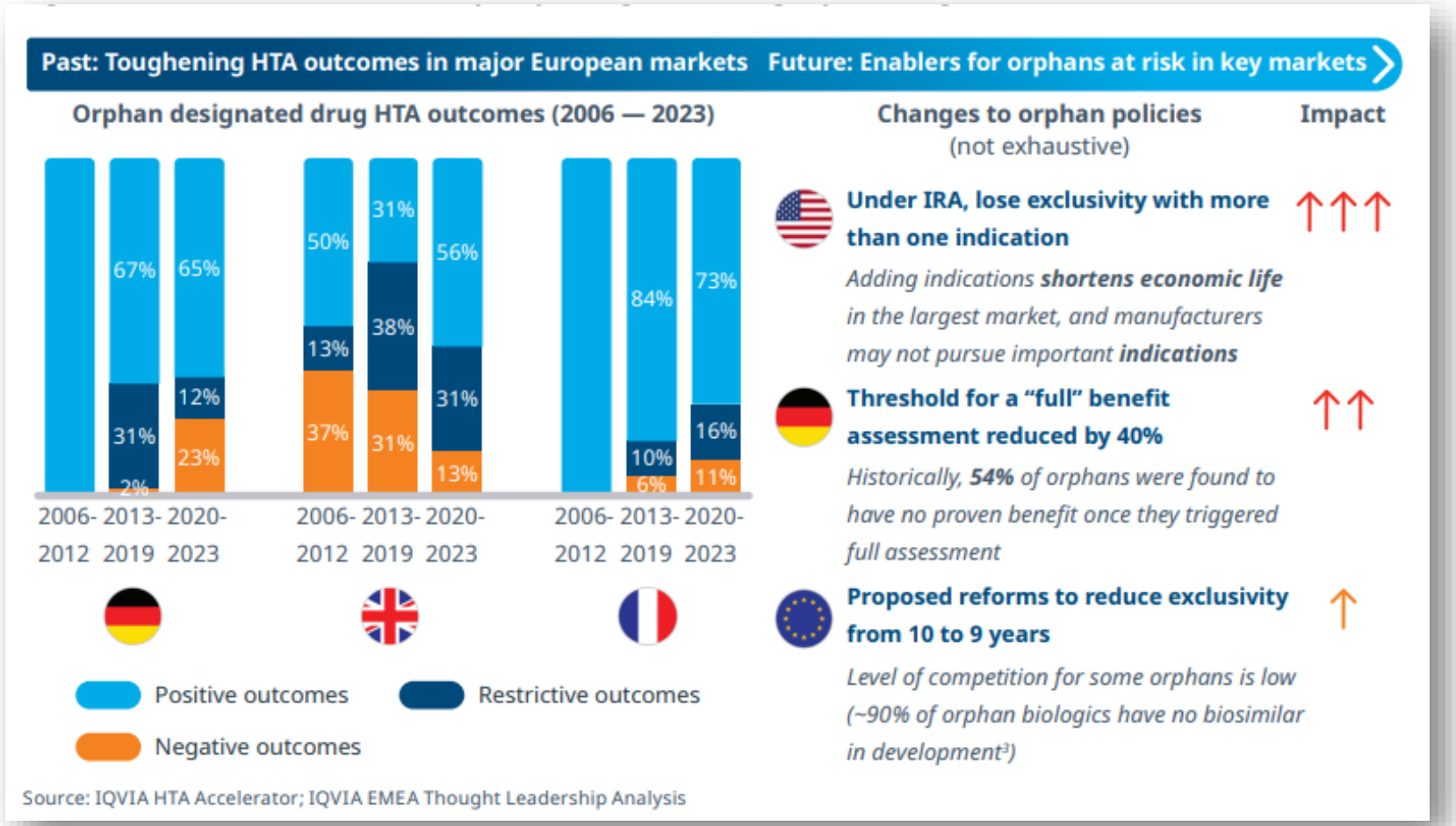
Source: From Orphan to Opportunity: Mastering Rare Disease Launch Excellence - IQVIA

Pharma companies may have dedicated rare structures



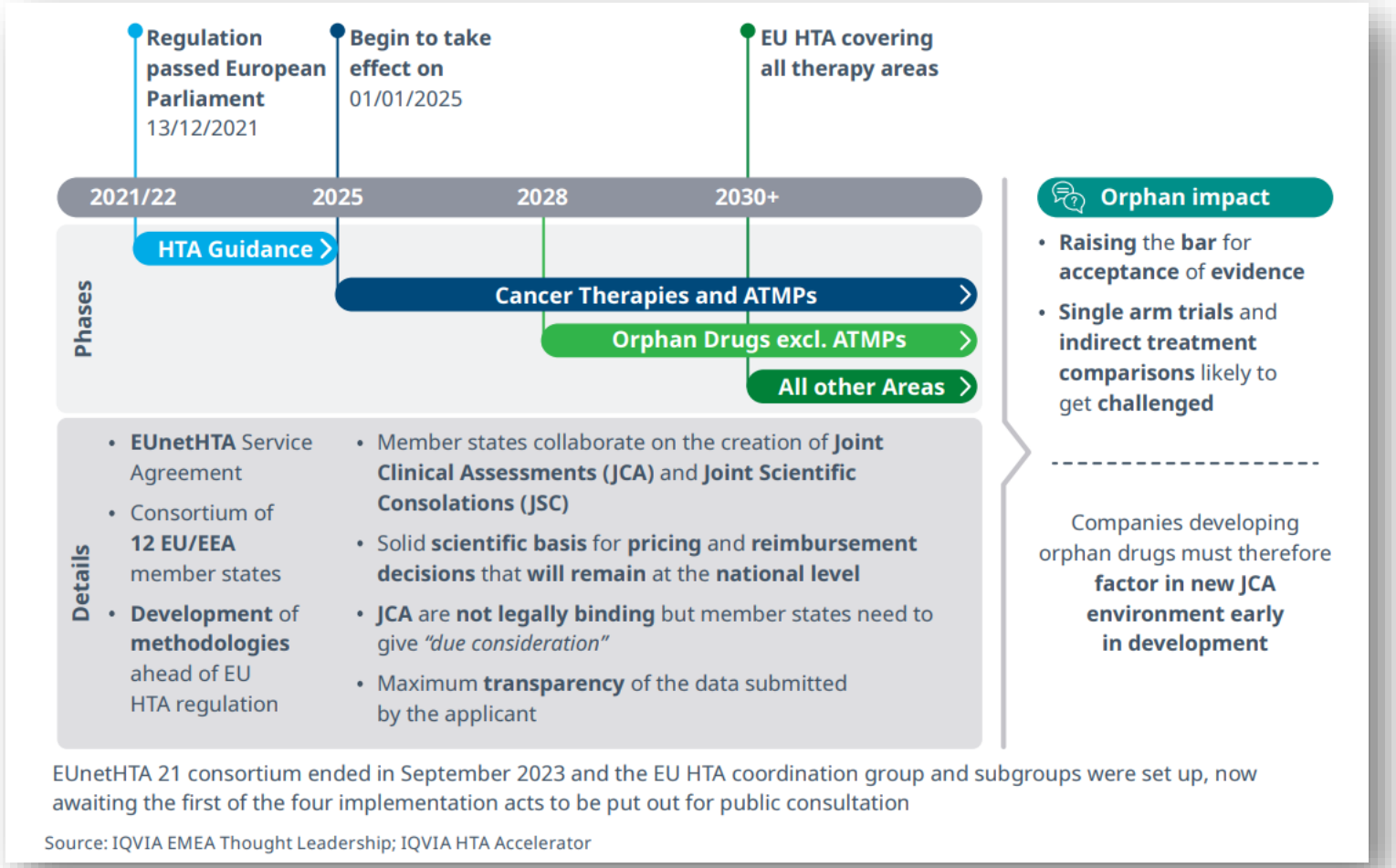
Source: From Orphan to Opportunity: Mastering Rare Disease Launch Excellence - IQVIA

HTA outcomes the last 20 years and future policy changes affecting orphan drugs



Source: [From Orphan to Opportunity: Mastering Rare Disease Launch Excellence - IQVIA]

EU HTA and its impact on orphan drugs



Source: From Orphan to Opportunity: Mastering Rare Disease Launch Excellence - IQVIA

TLV is using the calculated population as the benchmark to allow a higher acceptable ICER, rather than traditional HTA or label

Start with the end in mind to maximise the treated population

Label population

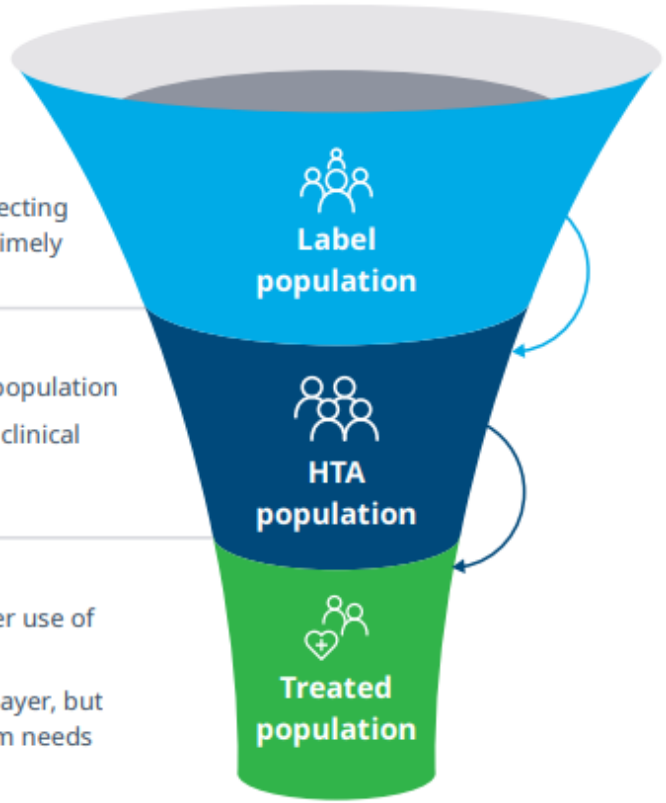
- Clinical development effectiveness, and label
- Getting an optimal label approved, reflecting the clinical potential of a product, in a timely and efficient fashion

HTA population

- Minimise the gap to ensure large HTA population
- Early stakeholder engagement around clinical trial design

Treated population

- Integrated evidence strategy with better use of health system data
- Focus on satisfying the regulator and payer, but also patient, HCP and healthcare system needs



Source: IQVIA EMEA Thought Leadership

Source: From Orphan to Opportunity: Mastering Rare Disease Launch Excellence - IQVIA

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