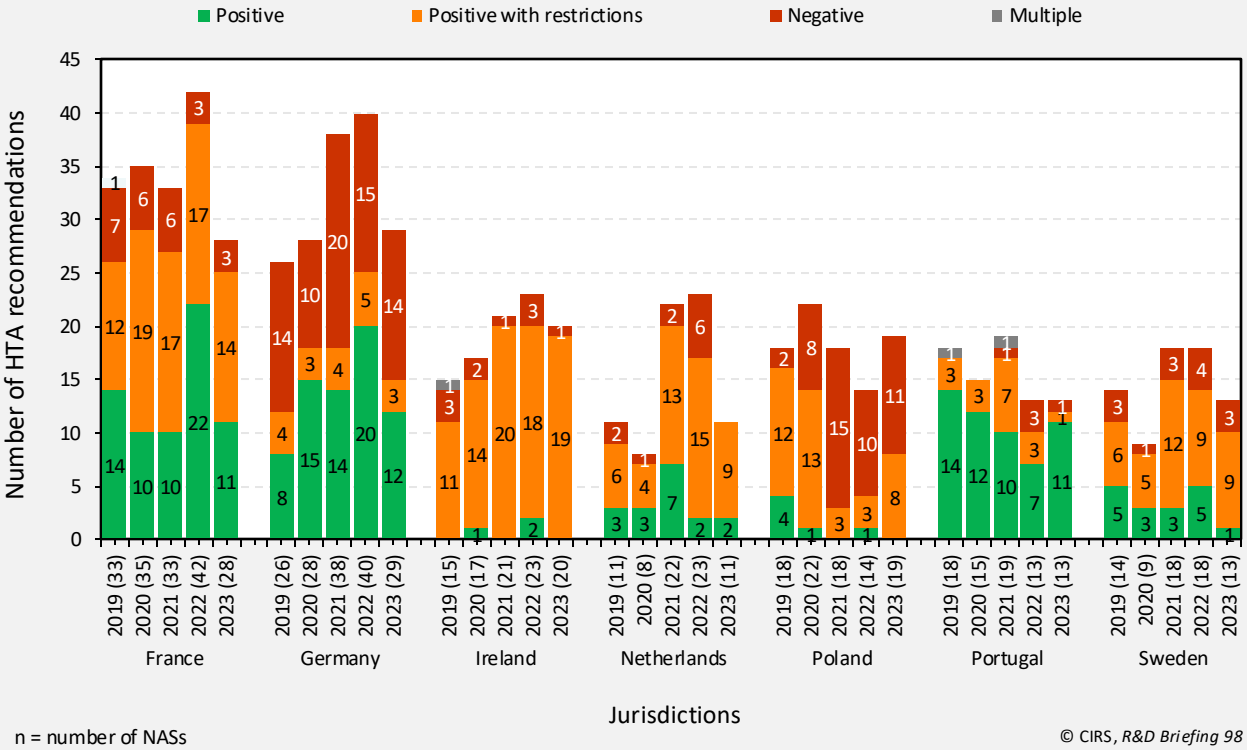
R&D BRIEFING 98

CIRS HTADock Project:

European HTA Trends: HTA Outcomes and Timelines Across Seven Markets (2019–2023)

Figure 1. First HTA recommendation of NASs assessed across key jurisdictions (1st HTA recommendation between 2019 and 2023)



n = number of NASs

The 2025 Centre for Innovation in Regulatory Science (CIRS) HTADock Briefing 98 centres on the primary performance metrics of seven health technology assessment (HTA) agencies in Europe, with a particular focus on the characteristics of 1st HTA recommendations and HTA timelines by products type.

EXPLORED IN THIS BRIEFING

- **Overview of new drug recommendations in Europe**
- **Common compounds assessed by HTA across all studied jurisdictions**
- **Oncology products and ATMPs – Their current HTA landscape**
- **HTA characteristics of NASs approved via EMA accelerated assessment**
- **HTA characteristics of EMA PRIME NASs**
- **Focus: HTA landscape in France and Ireland**

INTRODUCTION

In 2018, CIRS launched the HTADock project as part of its HTA programme. This project explores the synchronisation between the regulatory and HTA landscapes, aiming to increase transparency of the outcomes and timelines of HTA assessments. It also seeks to facilitate the enhancement of performance within HTA agencies.

This document is the third in a series of three briefings released in 2024 and early 2025. The HTADock R&D Briefing 95 is a broader exploration of the HTA landscapes in Australia, Canada, Europe, and the UK. The HTADock R&D Briefing 96, provides an in-depth analysis of Australia, Canada and the UK. Finally, this third briefing will focus on the HTA landscape of seven European jurisdictions.

CIRS has analysed publicly available data on new active substances (NASs) appraised between 2019 and 2023 by 7 European HTA agencies: (1) the French Haute Autorité de Santé (HAS), (2) the German Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), (3) the Irish National Centre for Pharmacoeconomics (NCPE), (4) Zorginstituut Nederland (ZIN), (5) the Polish Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT), (6) the Portuguese Autoridade Nacional do Medicamento e Produtos de Saude (INFARMED) and (7) the Swedish Tandvårds & läkemedelsförmånsverket (TLV).

Using a methodology outlined on page 3, the HTA recommendations in this report have been classified as positive, positive with restrictions or negative. The methodology page illustrates how specific recommendations by the HTA systems are captured within this trichotomous categorisation. In cases where more than one HTA dossier was submitted by a company for the same drug based on different sub-indications within an approved regulatory label, and the final HTA outcome for these individual sub-indications differed, the outcome was classified as multiple.

CONTENT

HTADock Methodology

The data on individual NASs appraised by HTA agencies between 2019 and 2023 were systematically collected from the respective agencies' official websites. Only the first HTA recommendation, derived from the initial assessment, was included in the analysis, unless specified. The figures below describe the research methodology, designed to enable robust benchmarking between agencies.

Regulatory and HTA process

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	Regulatory submission	Regulatory approval	HTA submission	HTA Recommendation
France	Submission to EMA	Approval issued by EU Commission	Date de validation administrative	Publication of Commission de la transparence review
Germany	Submission to EMA	Approval issued by EU Commission	Datum des Auftrags at IQWIG	Publication of Dossierbewertung
Ireland	Submission to EMA	Approval issued by EU Commission	Rapid Review commissioned	Rapid Review completed/ NCPE (full) assessment completed
Netherlands	Submission to EMA	Approval issued by EU Commission	Letter dated by Minister of health to ZIN	Date of Summary of recommendation by ZIN
Poland	Submission to EMA	Approval issued by EU Commission	Order of the Minister of Health publication	Publication of Rekomendacja Prezesa
Portugal	Submission to EMA	Approval issued by EU Commission	Not available from public domain	Data decisão
Sweden	Submission to EMA	Approval issued by EU Commission	Not available from public domain	Publication of the first released report by TLV

First HTA recommendations: Trichotomous categories

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	Positive	Positive with restrictions	*Implication for "positive" or "positive with restrictions"*	Negative
France HAS	Majeur/Important	Modéré ou faible, or mixed reviews for subpopulations	The NHI defines the reimbursement rate accordingly	Insufficient
Germany IQWiG	Considerable/Major added benefit	Minor/non-quantifiable added benefit	G-BA makes the binding resolution based on benefit assessment	Added benefit not proven/less benefit
Ireland NCPE	NAS is considered for reimbursement	NAS is considered for reimbursement with conditions	The HSE considers the NCPE recommendations and make decisions on reimbursement.	NAS not recommended for reimbursement
Netherlands Zorginstituut Nederland	To include	To include + restrictions	Recommendation for inclusion in the national health system	Not to include
Poland	Prezes Agencji rekomenduje	Prezes Agencji rekomenduje+restrictions	Agency's president's recommendation	Prezes Agencji nie rekomenduje
Portugal Infarmed	Deferido	Deferido + restrições	The MoH decides on reimbursement based on the Infarmed report	Indeferido
Sweden TLV	Ngå i läkemedelsförmånerna	Begränsningar	Include in pharmaceutical benefits scheme	Avslår

Note: The terminology used here is based on the individual agency's guidance on the official website. Green outline indicates that drug reimbursement is possible while red outline indicates that drug reimbursement is not possible.

KEY FINDINGS OF HTADOCK R&D 98

In 2023, Germany showed the highest number of 1st HTA recommendations across the studied jurisdictions (**Figure 1**). A decrease was observed in the number of HTA recommendations in 2023 compared to the average between 2019 and 2022 in France, Germany, Netherlands, Portugal and Sweden (**Figure 1**).

Germany presented the shortest median rollout time from regulatory approval to HTA recommendation in 2023, and maintained the highest consistency in rollout times from 2019 to 2023 (**Figure 2**).

The study highlighted differences in companies' submission strategies for NASs across European jurisdictions, with companies prioritising submission to France and Germany, and presenting later submissions to Ireland, the Netherlands, and Poland (**Figure 4**).

Between 2019 and 2023, ten NASs received HTA recommendations in all seven studied European jurisdictions. HTA outcomes and timings varied across countries, potentially leading to disparities in patient access to new treatments (**Table 2** and **Figure 5**).

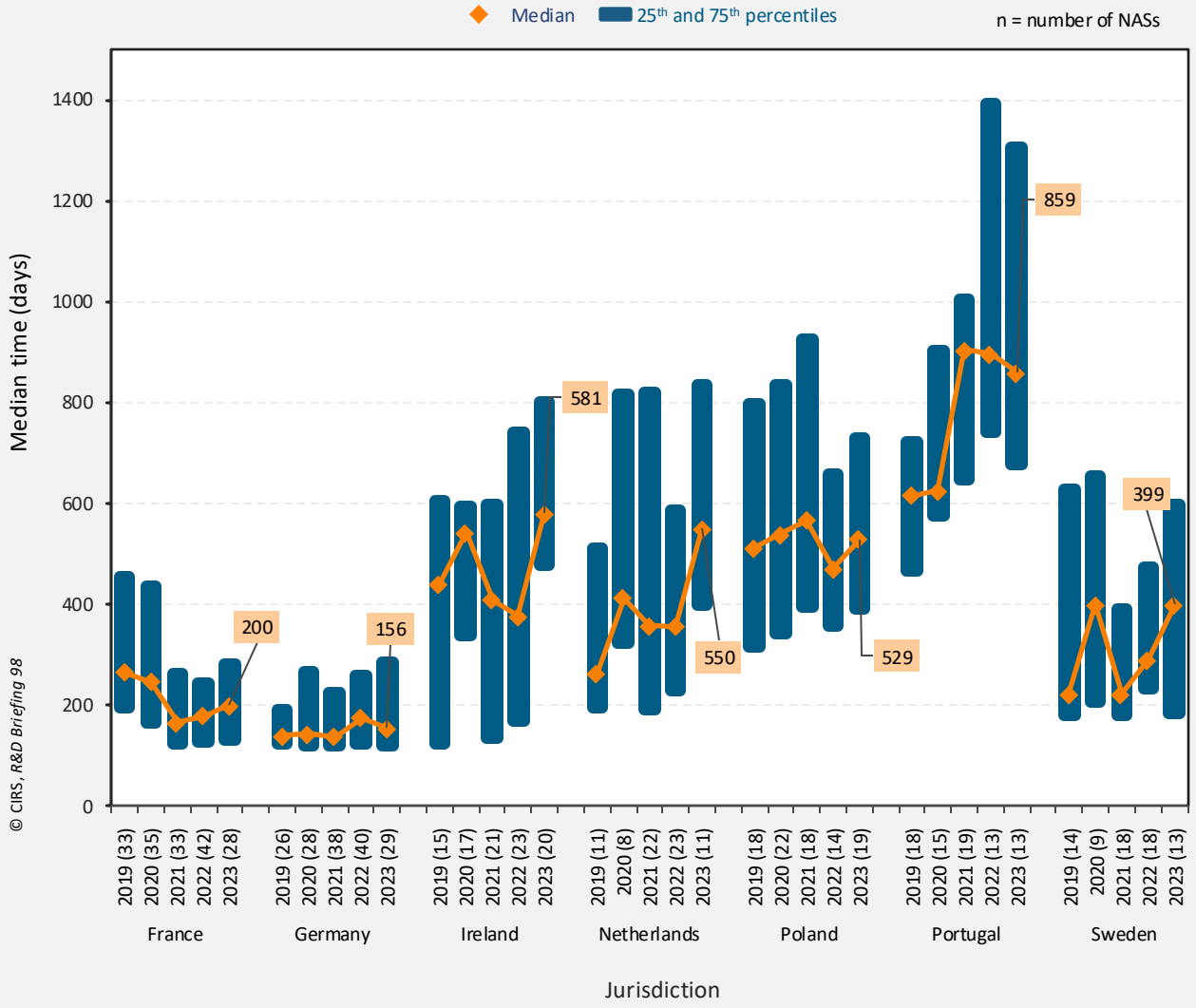
The upcoming EU HTA Regulation (HTAR), effective January 2025, will initially cover oncology products and ATMPs. Between 2021 and 2023, our analysis revealed variations in submission strategies, rollout times, and recommendation types across jurisdictions for these types of products (**Figure 7** and **Figure 8**).

The EMA's accelerated assessment generally reduced the time from regulatory submission to HTA recommendation compared to the standard pathway (**Figure 9**); however, products in the accelerated pathway often had longer HTA submission preparation times (**Figure 11**).

In 2023, 50% of NASs appraised by HAS were granted Early Access, with these products showing higher positive HTA recommendation rates compared to standard products, highlighting their unique therapeutic value (**Figure 14** and **Figure 15**).

Ireland introduced Rapid Reviews in 2009 to address the high demand for timely HTA reviews conducted by the NCPE. Overall, Rapid Reviews accelerated the time to HTA recommendations compared to full HTA appraisals (**Figure 21**).

Figure 2. Time from regulatory approval to 1st HTA recommendation (1st HTA recommendation between 2019 and 2023)



In 2023, Germany presented the highest number of 1st HTA recommendations across the studied European jurisdictions.

In 2023, Germany appraised the highest number of NASs (n=29), followed by France (n=28), Ireland (n=20), Poland (n=19), Portugal (n=13), Sweden (n=13) and the Netherlands (n=11) (**Figure 1**). The number of 1st HTA recommendations published by each agency can be influenced by the companies' submission strategy or agency remits, among other factors. The Netherlands presented the highest proportion of positive/positive with restrictions recommendations for NASs appraised by HTA agencies in 2023 (100%).

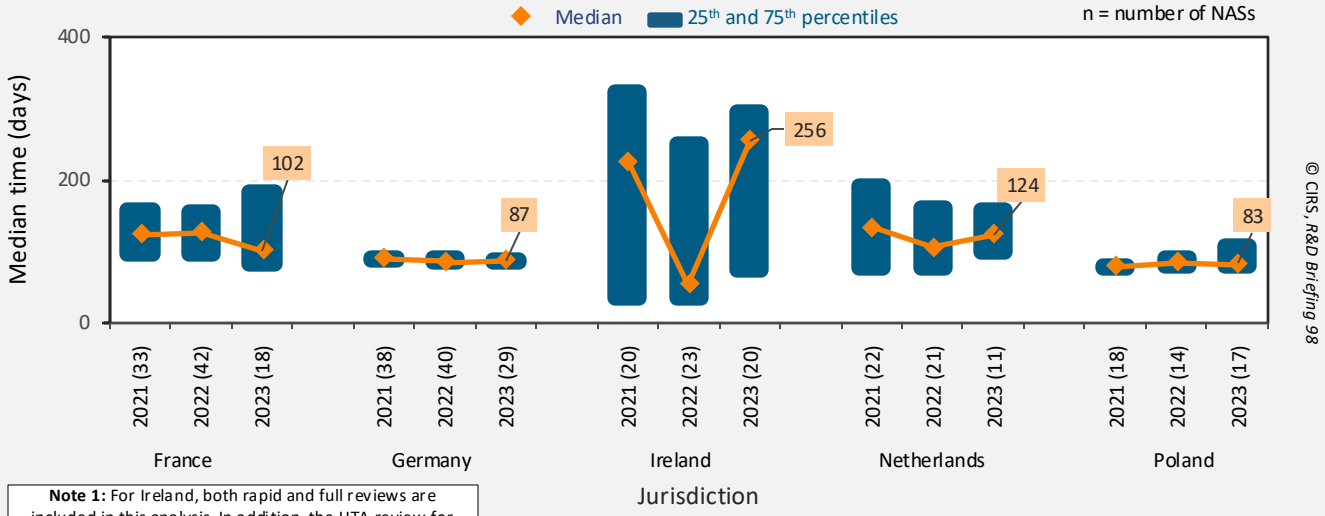
A decrease was observed in the number of 1st HTA recommendations in 2023 compared to the average between 2019 and 2022 for France, Germany, the Netherlands, Portugal and Sweden (**Figure 1**). The comparative numbers for 2019-2022 and 2023 in each jurisdiction were as follows: France: 36 vs 28, Germany: 33 vs 29, Ireland: 19 vs 20, Netherlands: 16 vs 11, Poland: 18 vs 19, Portugal: 16 vs 13, and Sweden: 15 vs 13, respectively. This could be influenced partly on a lower number of NASs approved by EMA in 2023 compared to previous years (see CIRS RD Briefing 93).

Germany had the shortest median rollout time from regulatory approval to 1st HTA recommendation in 2023, and maintained the highest consistency in rollout times from 2019 to 2023.

In 2023, Germany showed the shortest median rollout time from regulatory approval to first HTA recommendation, completing the process in 156 days (**Figure 2**). This was followed by France and Sweden, which required 200, and 399 days, respectively, to reach the first HTA recommendation. Germany showed the highest consistency in the median time from EMA approval to HTA recommendation over the years 2019-2023, with an interquartile range of 125 days. Interestingly, there has been a general increase in the timeto HTA recommendation in all jurisdictions, except for Germany and Portugal. Comparing 2022 to 2023, the time from EMA approval to recommendation are: France: 180 vs 200 days, Germany: 176 vs 156, Ireland: 377 vs 581, Netherlands: 357 vs 550, Poland: 472 vs 529, Portugal: 896 vs 859, and Sweden: 291 vs 399, respectively. It is important to note that these times include both the period that companies take to submit their data to the HTA body after EMA approval and the time required for the HTA body to complete its review. Further analysis of the HTA review times alone is provided in **Figure 3**.

OVERVIEW OF NEW DRUG RECOMMENDATIONS (CONT.)

Figure 3. Time taken from HTA submission to HTA recommendation (1st HTA recommendation between 2021 and 2023)



Note 1: For Ireland, both rapid and full reviews are included in this analysis. In addition, the HTA review for Ireland time is calculated as (Rapid Review completed - Rapid Review commissioned) + (NCPE assessment completed - Full submission received from applicant).

Note 2: Portugal and Sweden are excluded from this analysis due to the unavailability of their HTA submission dates in the public domain.

Note 3: The HTA review time can potentially include company time.

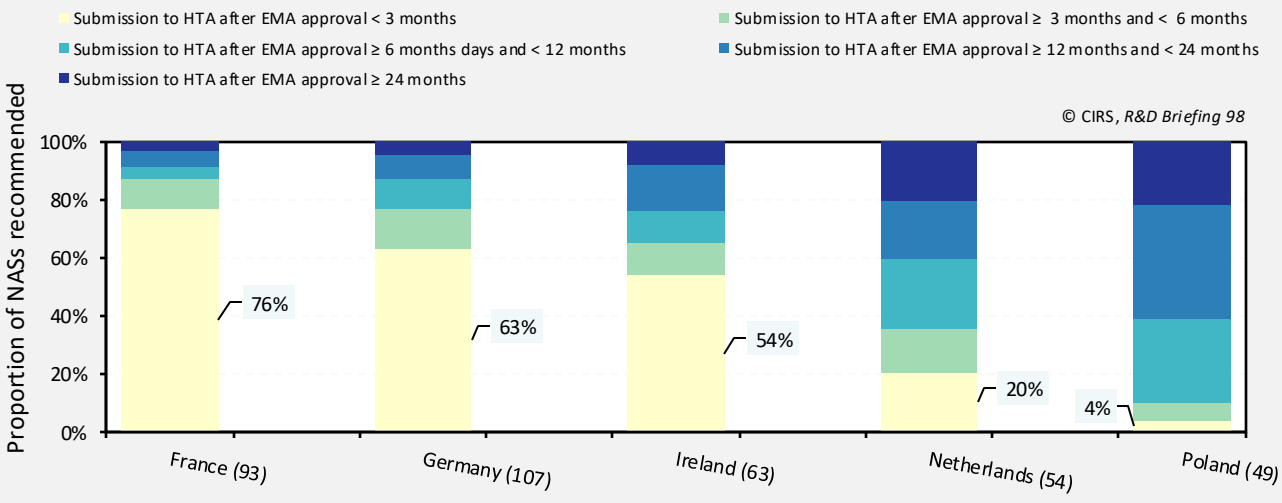
In 2023, Poland showed the fastest HTA review across the studied countries, while Germany presented the highest consistency in the HTA review time between 2021 and 2023, followed by Poland.

In 2023, Poland presented the shortest median time from HTA submission to HTA recommendation among the European jurisdictions in this study (83 days) (**Figure 3**), followed by Germany (87 days), France (102 days), the Netherlands (124 days), and Ireland (256 days). In line with the findings in **Figure 2**, Germany showed the highest consistency in the HTA review time over the years 2021-2023, with an overall interquartile range of 5 days (**Figure 3**). This consistency may be attributed to the German Act on the Reform of the Market for Medicinal Products (AMNOG), which establishes that IQWIG should complete the dossier assessment within three months of receiving the manufacturer's dossier.

Despite being the fastest HTA body to complete the review process in 2023, Poland also had one of the longest intervals from EMA approval to HTA recommendation. This suggests that the rollout time can be influenced not only by HTA review times, but also by the companies' submission strategy.

Figure 4 further explores the companies' submission strategies to the studied jurisdictions. Interestingly, data showed that 76% and 63% of the NASs that received an HTA recommendation in France and Germany, respectively, between 2021 and 2023 were submitted to HAS or IQWIG within three months of receiving EMA approval. In contrast, 54% of the NASs that received an HTA recommendation in Ireland during this time period were submitted after three months, followed by 20% in the Netherlands and only 4% in Poland. These results underscore notable divergences in submission approaches across European jurisdictions.

Figure 4. Submission strategy of NASs recommended in Europe (1st HTA recommendation between 2021 and 2023)



Note: Portugal and Sweden are excluded from this analysis due to the unavailability of their HTA submission dates in the public domain.

COMMON COMPOUNDS ACROSS ALL JURISDICTIONS

Table 1. Characteristics of common compounds rolled out to all 7 European jurisdictions (n=10) (1st HTA recommendation between 2019 and 2023)

Generic name	EMA approval year	Therapeutic area	EMA exceptional	EMA PRIME designation	EMA ATMP	EMA review type
Lanadelumab	2018	Blood and blood forming organs	No	No	No	Accelerated
Fremanezumab	2019	Nervous system	No	No	No	Standard
Darolutamide	2020	Antineoplastic and immunomodulating agents	No	No	No	Standard
Elexacaftor / Ivacaftor / Tezacaftor	2020	Respiratory system	No	No	No	Accelerated
Entrectinib	2020	Antineoplastic and immunomodulating agents	No	Yes	No	Standard
Ozanimod	2020	Antineoplastic and immunomodulating agents	No	No	No	Standard
Siponimod	2020	Antineoplastic and immunomodulating agents	No	No	No	Standard
Relugolix	2021	Systemic hormonal preparations, excluding sex hormones and insulin	No	No	No	Standard
Risdiplam	2021	Musculo-skeletal system	No	Yes	No	Accelerated
Finerenone	2022	Cardiovascular system	No	No	No	Standard

Between 2019 and 2023, ten common NASs received a 1st HTA recommendation in all seven studied European jurisdictions.

Our study identified ten NASs that received HTA recommendations in all seven jurisdictions studied between 2019 and 2023, which we refer to as "common compounds". **Table 1** lists these ten compounds along with their key regulatory characteristics. **Table 2** displays a traffic light system to compare the different HTA outcomes associated with these common products. This visualisation reflects the varied recommendations of these NASs across the compared agencies. The recommendation dates for each product were also compared across all seven agencies and the order of the first HTA recommendation was ranked from earliest recommendation (1) to last (7). 7 of the 10 common products were recommended first in Germany.

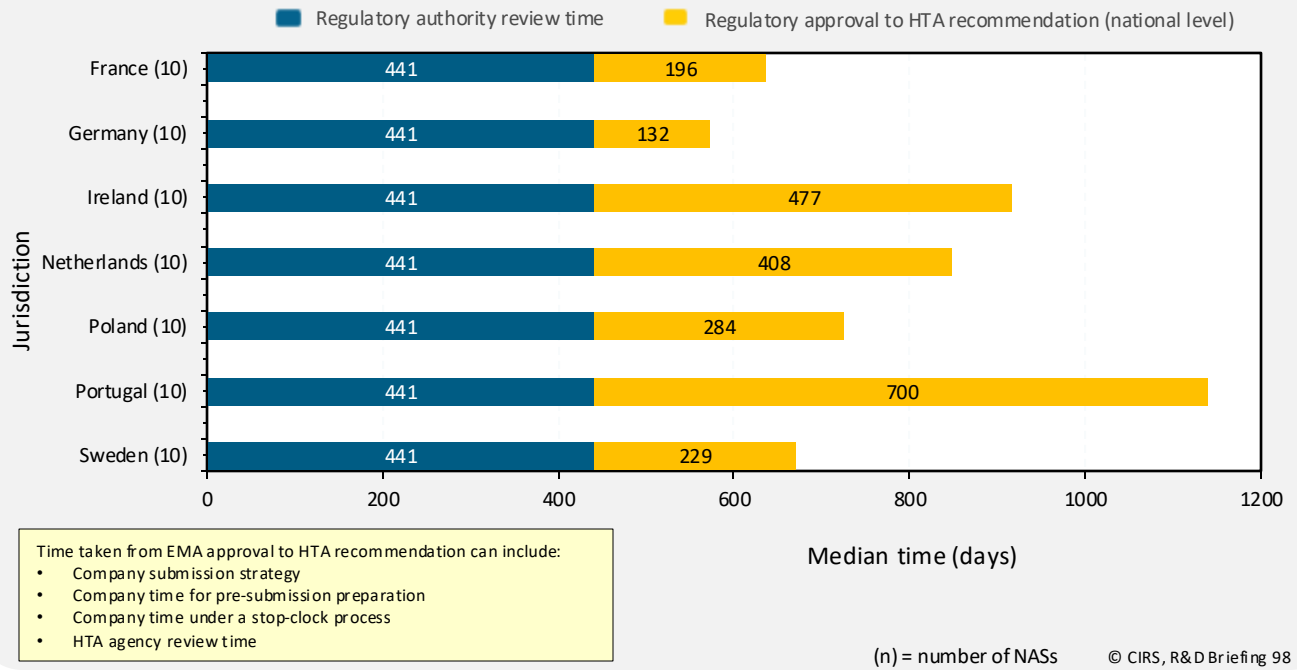
Table 2. First HTA recommendation comparison for common NASs reviewed by all seven agencies (1st HTA recommendation between 2019 and 2023)

Positive Restriction Negative

Generic name	France	Germany	Ireland	Netherlands	Poland	Portugal	Sweden
Darolutamide	2	1	5	7	3	6	4
Elexacaftor / Ivacaftor / Tezacaftor	1	2	7	4	5	6	3
Entrectinib	4	1	6	4	2	7	3
Finerenone	4	5	6	1	3	7	2
Fremanezumab	5	1	4	7	2	6	3
Lanadelumab	2	1	4	7	3	6	5
Ozanimod	4	1	3	2	5	7	6
Relugolix	4	2	3	5	6	7	1
Risdiplam	2	1	5	6	4	7	3
Siponimod	3	1	6	5	4	7	2

COMMON COMPOUNDS ACROSS ALL JURISDICTIONS (CONT.)

Figure 5. Breakdown of rollout time of common compounds rolled out to all seven European jurisdictions (n=10) (1st HTA recommendation between 2019 and 2023)



Time taken from EMA approval to HTA recommendation can include:
- Company submission strategy
- Company time for pre-submission preparation
- Company time under a stop-clock process
- HTA agency review time

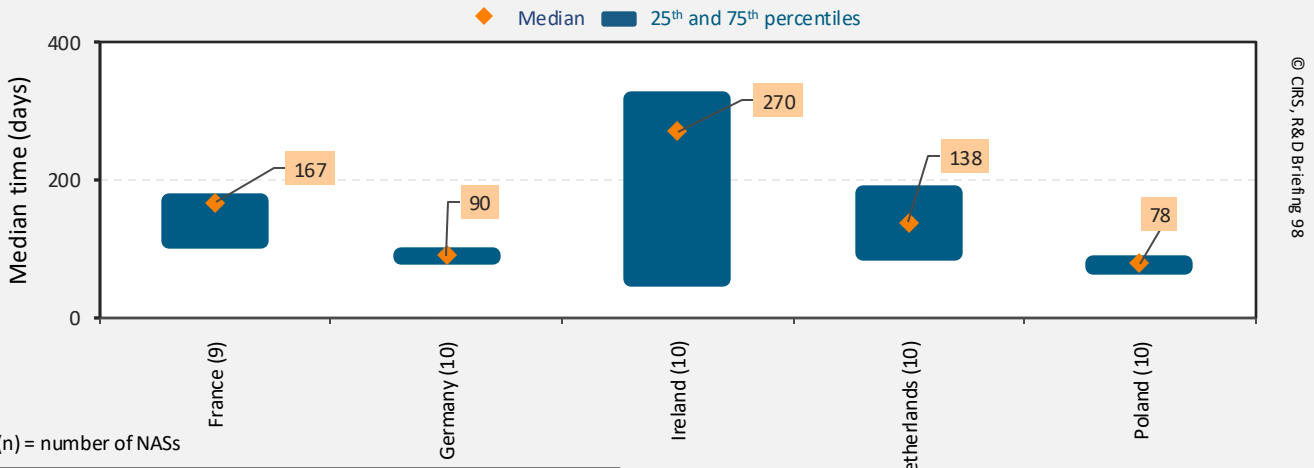
(n) = number of NASs

Between 2019 and 2023, common NASs showed varied timings in reaching HTA recommendations across seven jurisdictions, potentially leading to disparities in patient access to new treatments.

Figure 5 examines the rollout timeline for common compounds across seven jurisdictions, focusing on both regulatory review times and the duration from EMA approval to HTA recommendation. The data highlights that, despite centralised regulatory approval providing a unified timeline, the time to HTA recommendation varied among jurisdictions. This variation is influenced not only by national HTA review durations but also by differing submission strategies, as observed earlier in **Figure 4**.

Figure 6 specifically investigates the HTA review times for these common compounds. Poland demonstrated the fastest median HTA review time (78 days), followed by Germany (90 days), the Netherlands (138 days), France (167 days), and Ireland (270 days). The variation in HTA review time in Ireland for common NASs can be attributed to the fact that 3 NASs underwent only a rapid review, whereas 7 required both a rapid review followed by a full review. Consistent with prior findings, despite Poland's quick review time, it ranked fourth among the seven jurisdictions in time to HTA recommendation (**Figure 5**), underscoring the potential impact of companies' submission strategies on the timing of patient access to new treatments.

Figure 6. Time taken from HTA submission to HTA recommendation – common compounds (n=10) (1st HTA recommendation between 2019 and 2023)



(n) = number of NASs

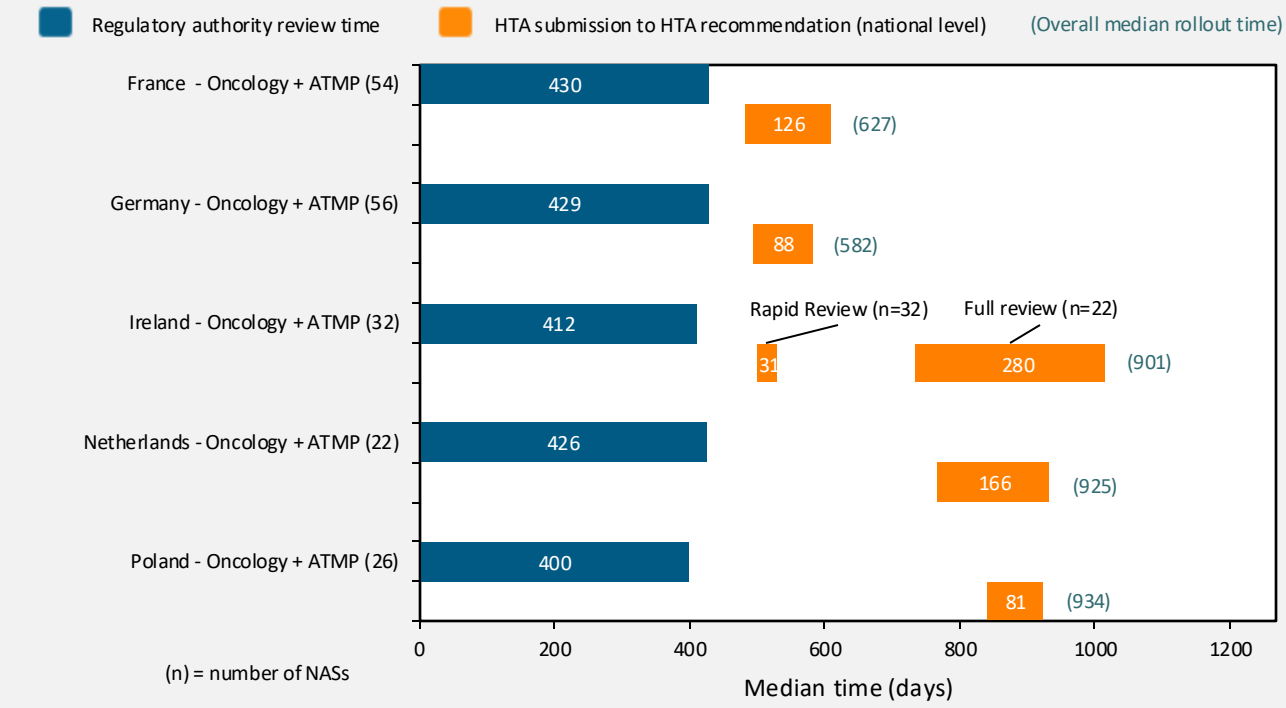
Note 1: For Ireland, both rapid and full reviews are included in this analysis. In addition, the HTA review for Ireland time is calculated as (Rapid Review completed - Rapid Review commissioned) + (NCPE assessment completed - Full submission received from applicant).

Note 2: The HTA review time can potentially include company time.

Note 3: There is one common product excluded from France because its HTA submission date is not available on the public domain.

CHARACTERISTICS: ONCOLOGY PRODUCTS AND ATMPS

Figure 7. Breakdown of rollout time of oncology + ATMP NASs (1st HTA recommendation between 2021 and 2023)



Note 1: For Ireland, all NASs were assessed in a Rapid Review, but only a portion of those were recommended for a full review.

Note 2: Portugal and Sweden are excluded from this analysis due to the unavailability of their HTA submission dates in the public domain.

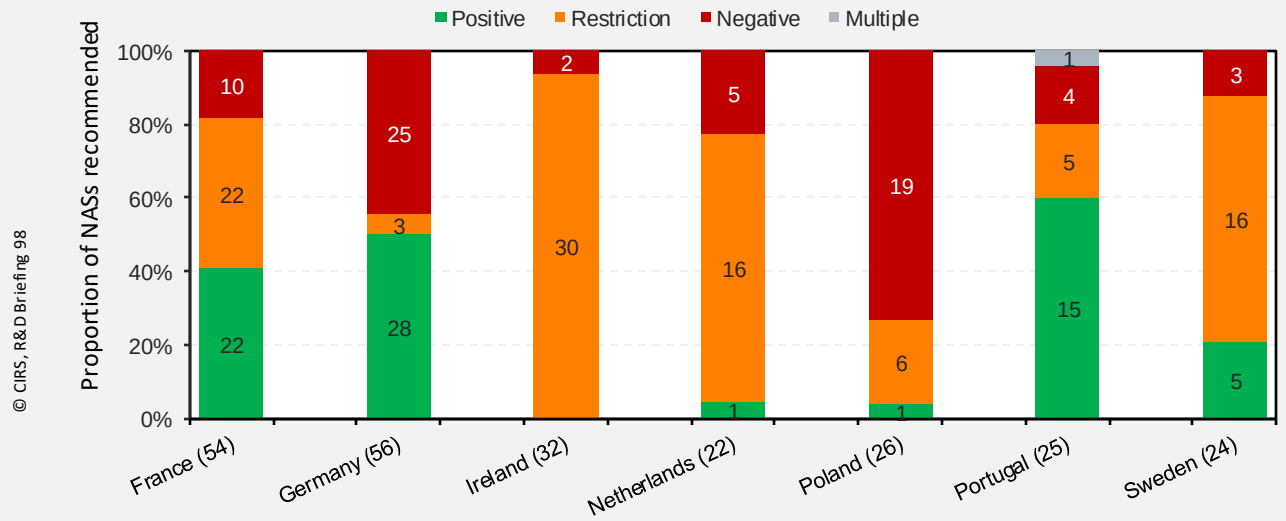
Note 3: The HTA review time can potentially include company time.

European jurisdictions exhibited variations in the time to 1st HTA recommendations and the outcomes of oncology products and ATMPs between 2021 and 2023.

The Regulation (EU) 2021/2282 on health technology assessment (HTAR) applies from 12 January 2025, initially covering oncology and advanced therapy medicinal products (ATMPs). **Figure 7** illustrates the current timeline for the rollout of oncology products and ATMPs that have been assessed by HTA agencies across selected jurisdictions from 2021 to 2023. While regulatory review times remain relatively consistent across countries, submission strategies and HTA review durations show notable variations. The latter led to varying overall median rollout times, Germany presenting the fastest rollout time (582 days), followed by France (627 days), Ireland (901 days), the Netherlands (925), and Poland (934 days).

Figure 8 explores the types of HTA recommendations for oncology products and ATMPs. The analysis displays variance in the recommendations to these products across jurisdictions.

Figure 8. Outcome of 1st HTA recommendation by oncology + ATMP (1st HTA recommendation between 2021 and 2023)



Characteristics: Oncology products and ATMPs (Cont.)

Table 3. ATMPs products assessed by HTA (n= 17) (1st HTA recommendation between 2019 and 2023)

Brand name	Regulatory approval year	France	Germany	Ireland	Netherlands	Poland	Portugal
Zalmoxis	2016		HTA recommendation in 2018*				
Spherox	2017						
Alofisel	2018		HTA recommendation in 2018*				
Luxturna	2018						HTA recommendation in 2024*
Yescarta	2018	HTA recommendation in 2018*					
Kymriah	2018	HTA recommendation in 2018*	HTA recommendation in 2018*		HTA recommendation in 2018*		
Zynteglo	2019				Application withdrawn		
Libmeldy	2020						
Tecartus	2020					HTA recommendation in 2024*	
Zolgensma	2020					HTA recommendation in 2024*	
Abecma	2021						
Carvykti	2022						
Upstaza	2022						
Roctavian	2022						
Breyanzi	2022				HTA recommendation in 2024*		
Ebvallo	2022						
Hemgenix	2023						

Positive Restriction Negative Multiple

* Out of the scope of this briefing

Note: Products highlighted in white indicate that there is currently no HTA recommendation for the product; however, alternative mechanisms for patient access may be available.

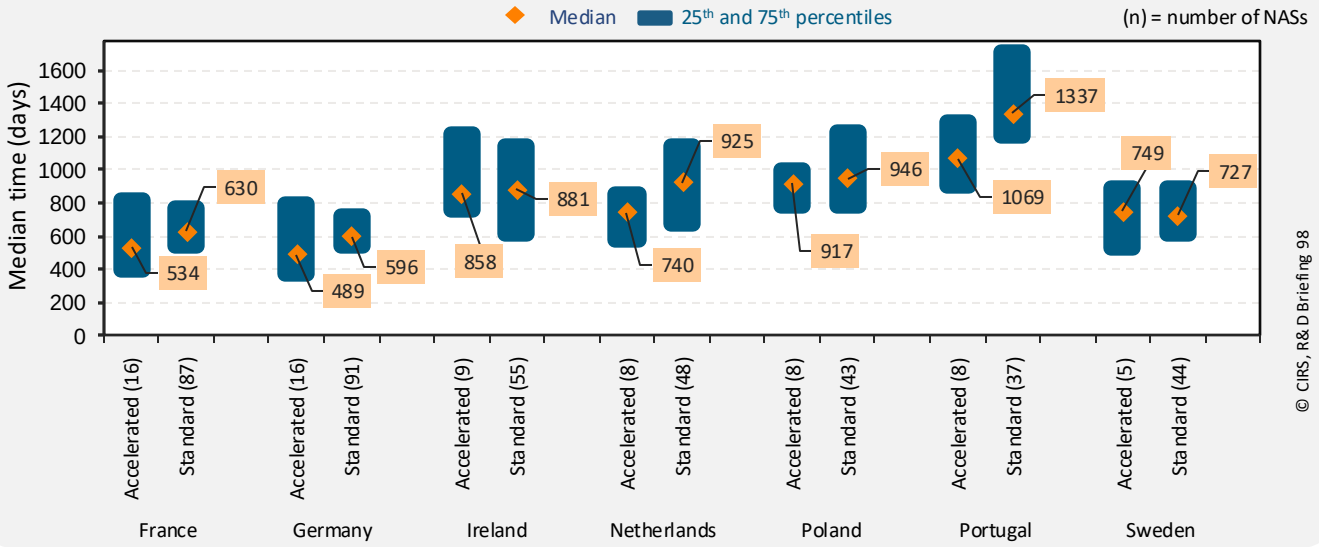
Between 2019 and 2023, 17 ATMPs received at least one HTA recommendation among the seven studied European jurisdictions.

The 1st ATMP product received regulatory approval by EMA in 2009 and since then 22 ATMPs have been granted regulatory approval. **Table 3** displays 17 ATMPs that have received HTA recommendations in at least one of the studied European jurisdictions between 2019 and 2023. The data displayed a low level of agreement on the type of HTA recommendation among jurisdictions. This divergency may be influenced by the high level of both clinical and economic uncertainty typically associated with these type of products.

In addition, while HAS and IQWiG presented HTA outcomes for most of the ATMPs in the table, other jurisdictions have provided fewer recommendations. This variation could be attributed to several factors, including the different rollout times of these therapies across jurisdictions and the distinct remits of the HTA bodies.

CHARACTERISTICS: EMA ACCELERATED PATHWAY

Figure 9. Time taken from EMA submission to 1st HTA recommendation by review type (2021 and 2023)



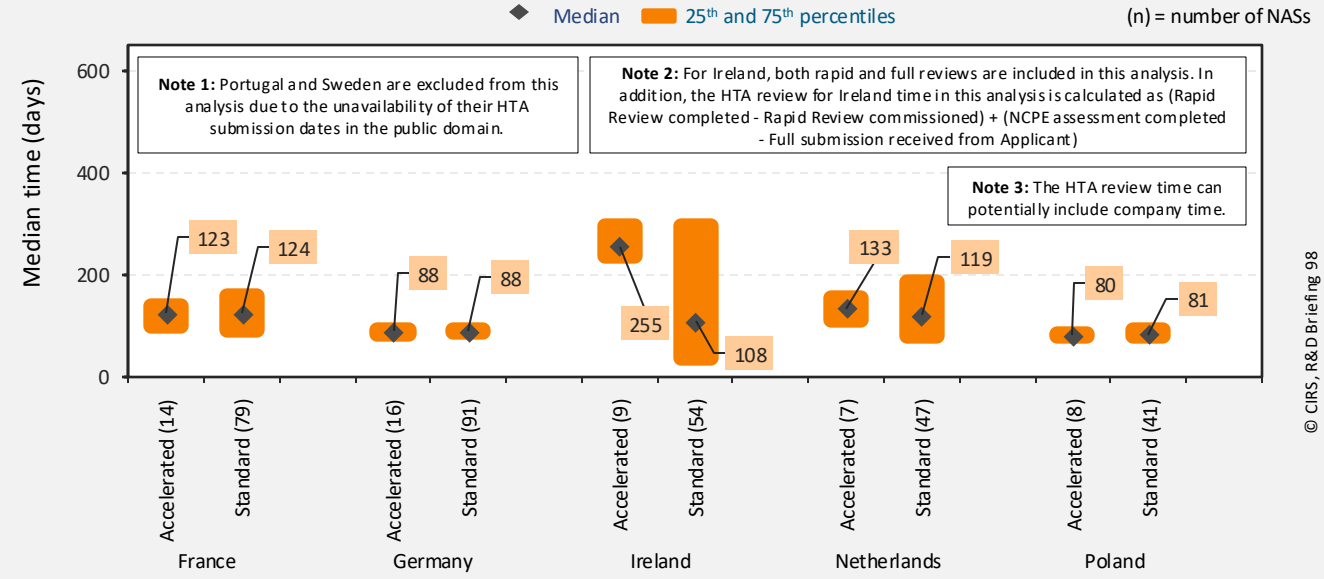
NASs assessed via EMA accelerated assessment present a faster rollout time from EMA submission to 1st HTA recommendation.

The EMA's accelerated assessment is aimed at products of major public health interest, reducing the review time for the Committee for Medicinal Products for Human Use (CHMP) to assess a marketing authorisation application. **Figure 9** shows the time from regulatory submission to HTA recommendation for NASs that received an HTA recommendation between 2021 and 2023. It compares products assessed through an accelerated pathway with those that followed the standard regulatory pathway. The results indicate that, generally - with the exception of Sweden - products undergoing an accelerated EMA assessment achieved a faster median rollout time: 534 vs 630 days in France, 489 vs 596 days in Germany, 858 vs 881 days in Ireland, 740 vs 925 days in Netherlands, 917 vs 946 days in Poland, 1069 vs 1337 days in Portugal and 749 vs 727 days in Sweden.

Figures 10 explores the time from HTA submission to HTA recommendation comparing the EMA accelerated vs standard route. The data suggest no difference between the median HTA review times of those products the underwent an accelerated regulatory path way and to those that followed a standard pathway (except for Ireland). This could be explained by the fact that both types of products (EMA accelerated and EMA standard products) followed the same HTA process, with generally no ad hoc HTA pathway existing for these types of products. The variation in HTA review time in Ireland for NASs approved via the standard regulatory pathway can be attributed to the fact that 28 NASs underwent only a rapid review, whereas 26 required both a rapid review and a full review. All nine accelerated regulatory approvals were assessed via a rapid review followed by a full review.

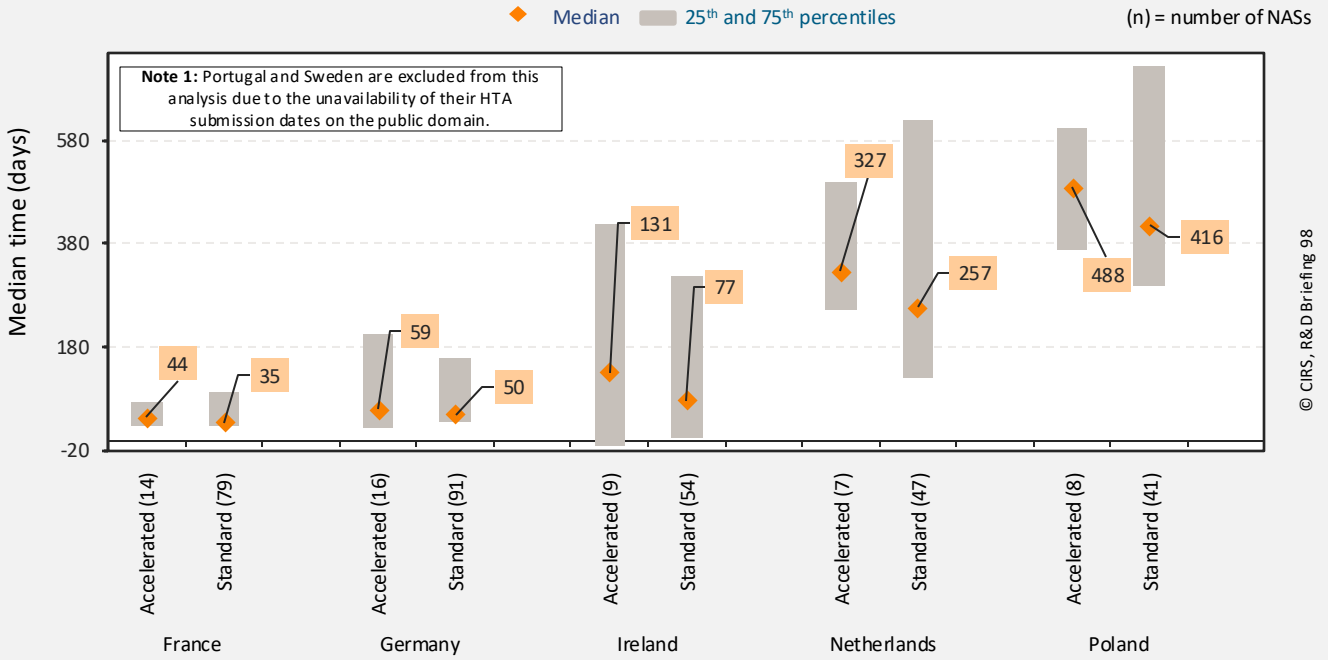
Finally, **Figure 11** explores the time from EMA approval to HTA submission. Interestingly, products that underwent an accelerated EMA pathway presented a longer median submission time to HTA, which may suggest a longer time needed by companies to prepare an HTA submission.

Figure 10. Time taken from HTA submission to 1st HTA recommendation by review type (2021 and 2023)



CHARACTERISTICS: EMA ACCELERATED PATHWAY (CONT.)

Figure 11. Time taken from EMA approval to HTA submission by review type (2021 and 2023)



Generally, EMA accelerated products received a similar or higher proportion of positive or positive with restrictions HTA recommendations compared to those assessed under the standard pathway.

The EMA's accelerated assessment process aims to prioritise critical medicines, ensuring faster access for patients. However, uncertainties surrounding the evidence supporting decisions on accelerated medicines may present challenges at the HTA stage. **Figure 12** examines the types of HTA recommendations for products that underwent EMA's accelerated assessment, comparing them with those assessed through the standard pathway. Generally, accelerated products received a similar or higher proportion of positive or positive-with-restrictions HTA recommendations compared to those assessed under the standard pathway, except in Sweden. However, the low sample size should be considered when interpreting these results. Interestingly, there was still a notable number of products approved through an accelerated EMA assessment that received negative recommendations from HTA bodies. This suggests that, while deemed of major public health interest, safe and effective, these products were not found to offer added value or improved cost-effectiveness for national health systems.

Figure 12. Outcome of 1st HTA recommendation by EMA accelerated vs. standard (1st HTA recommendation between 2021 and 2023)

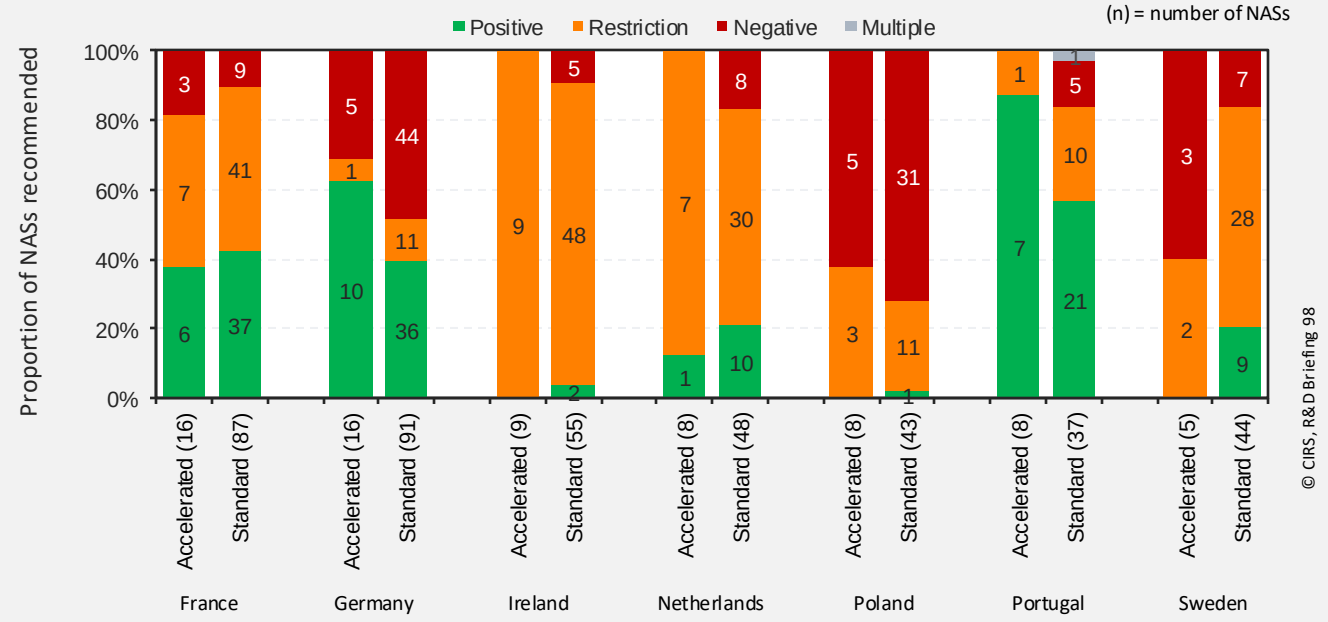


Table 4. PRIME products assessed by HTA (n= 27) (1st HTA recommendation between 2019 and 2023)

Generic name	EMA approval	France	Germany	Ireland	Netherlands	Poland	Portugal	Sweden
Axicabtagene ciloleucel	2018	HTA rec. in 2018*						HTA rec. in 2018*
Tisagenlecleucel	2018	HTA rec. in 2018*	HTA rec. in 2018*		HTA rec. in 2018*			
Betibeglogene autotemcel	2019				Application withdrawn			
Belantamab mafodotin	2020							
Brexucabtagene autoleucel	2020							
Bulevirtide	2020			HTA rec. in 2024*	HTA rec. in 2024*			
Entrectinib	2020							
Givosiran	2020							
Imlifidase	2020			HTA rec. in 2024*				
Lumasiran	2020							
Onasemnogene abeparvovec	2020							
Polatuzumab	2020							
Idecabtagene vicleucel	2021							
Odevixibat	2021							
Risdiplam	2021							
Setmelanotide	2021							
Avacopan	2022							
Ciltacabtagene autoleucel	2022							
Olipudase alfa	2022							
Nirsevimab	2022		HTA rec. in 2024*					
Teclistamab	2022			HTA rec. in 2024*	HTA rec. in 2024*	HTA rec. in 2024*		
Valoctocogene roxaparvovec	2022							
Voxelotor	2022							
Lisocabtagene maraleucel	2022				HTA rec. in 2024*			
Tabelecleucel	2022							
Etranacogene dezaparvovec	2023							
Talquetamab	2023	HTA rec. in 2024*						

Note: Products highlighted in white indicate that there is currently no HTA recommendation for the product; however, alternative mechanisms for patient access may be available.

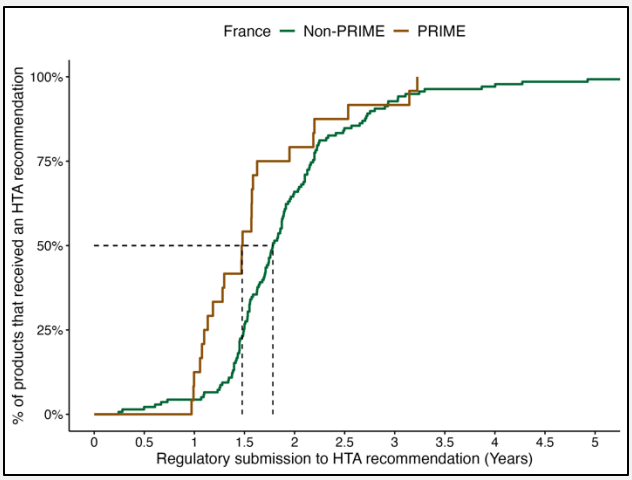
Positive Restriction Negative Multiple

* Out of the scope of this briefing

Among France, Germany, Ireland, the Netherlands, Poland, Portugal and Sweden, 27 PRIME products were assessed by HTA in at least one of these jurisdictions between 2019 and 2023.

PRIME is an initiative established by the EMA to strengthen support for the development of medicines that target unmet medical needs. **Table 4** contains the PRIME products that have been assessed by HTA in at least one of the European countries included in this study. Similar to the observations in **Table 3, Table 4** displays the heterogeneous recommendations of PRIME products across the agencies being compared. In addition, the cumulative analysis in **Figure 13** suggests the faster rollout of PRIME products in both France and Germany.

Figure 13. Time taken from EMA submission to HTA recommendation by PRIME designation in France and Germany (1st HTA recommendation between 2019 and 2023)



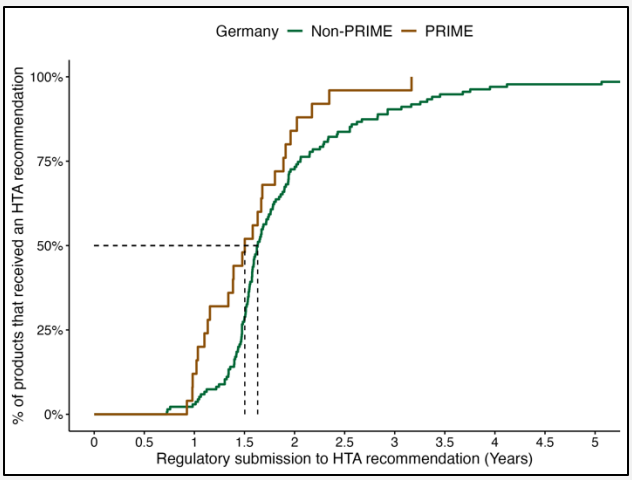
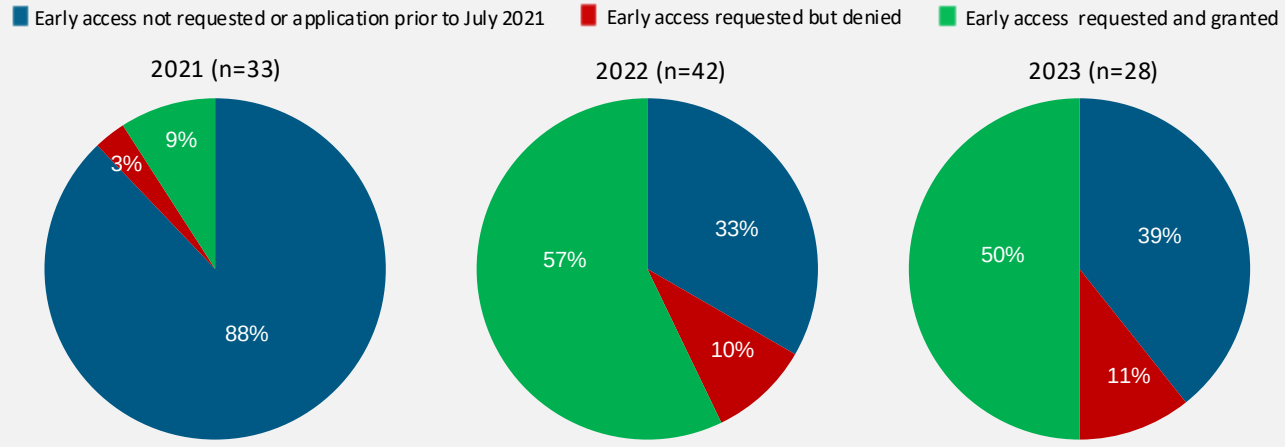


Figure 14. Proportion of NASs that received an HTA recommendation by type of Early Access application (2021-2023)



(n) = number of NASs

Note: The new Early Access is only available in France from 1st July 2021

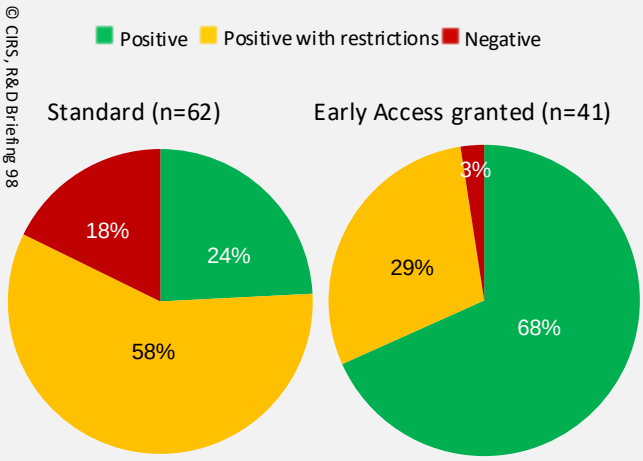
In France, there has been a growing utilisation of the Early Access mechanism since its implementation on the 1st July 2021.

Since 1st July 2021, HAS has evaluated and authorised medicines that are the subject of a request for coverage in the context of "Early Access". Overall, Early Access is a mechanism that allows patients to benefit exceptionally and temporarily from certain drugs not yet recommended for reimbursement yet in a specific therapeutic indication.

For an NAS to be considered eligible for Early Access, the following four conditions must be met: (i) the drug must be intended to treat serious, rare or disabling diseases, (ii) there is no appropriate treatment available, (iii) the implementation of the treatment cannot be postponed, (iv) the medicinal product is presumed to be innovative. Furthermore, Early Access can be requested for either a medicine already with a marketing authorisation or medicinal products that do not have a marketing authorisation, and these are referred to as post-approval Early Access and pre-approval Early Access, respectively.

Figure 14 illustrates that 50% of the NASs appraised by HAS in 2023 had received an Early Access designation, in line with the 57% of products granted with Early Access in 2022. In addition, **Figure 15** indicates that NASs that were granted Early Access between 2021 and 2023 presented a higher proportion of positive recommendations from HAS compared to standard NASs (68% vs 24%, respectively). The latter could be indicative of the unique therapeutic value of Early Access products. **Figure 16** further examines the HTA outcomes for products that received Early Access, comparing those granted Early Access before and after marketing authorisation. The results show that 89% of products granted Early Access pre-approval received a positive recommendation, while 63% of those granted Early Access post-approval received a positive recommendation.

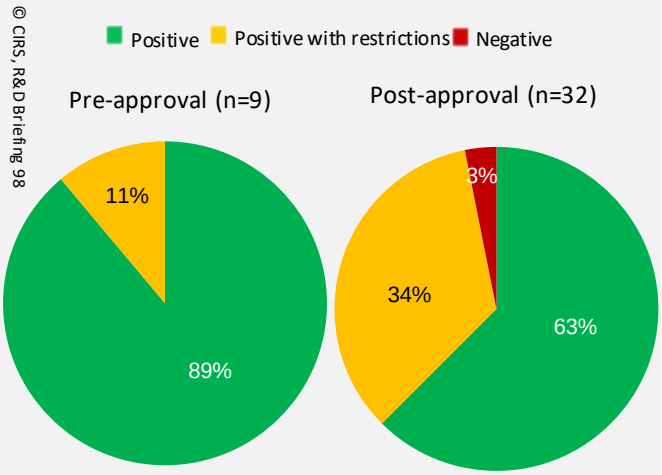
Figure 15. Proportion of HTA outcomes: Standard vs Early Access was granted (1st HTA recommendation between 2021 and 2023)



(n) = number of NASs

Note: The new Early Access is only available in France from 1st July 2021

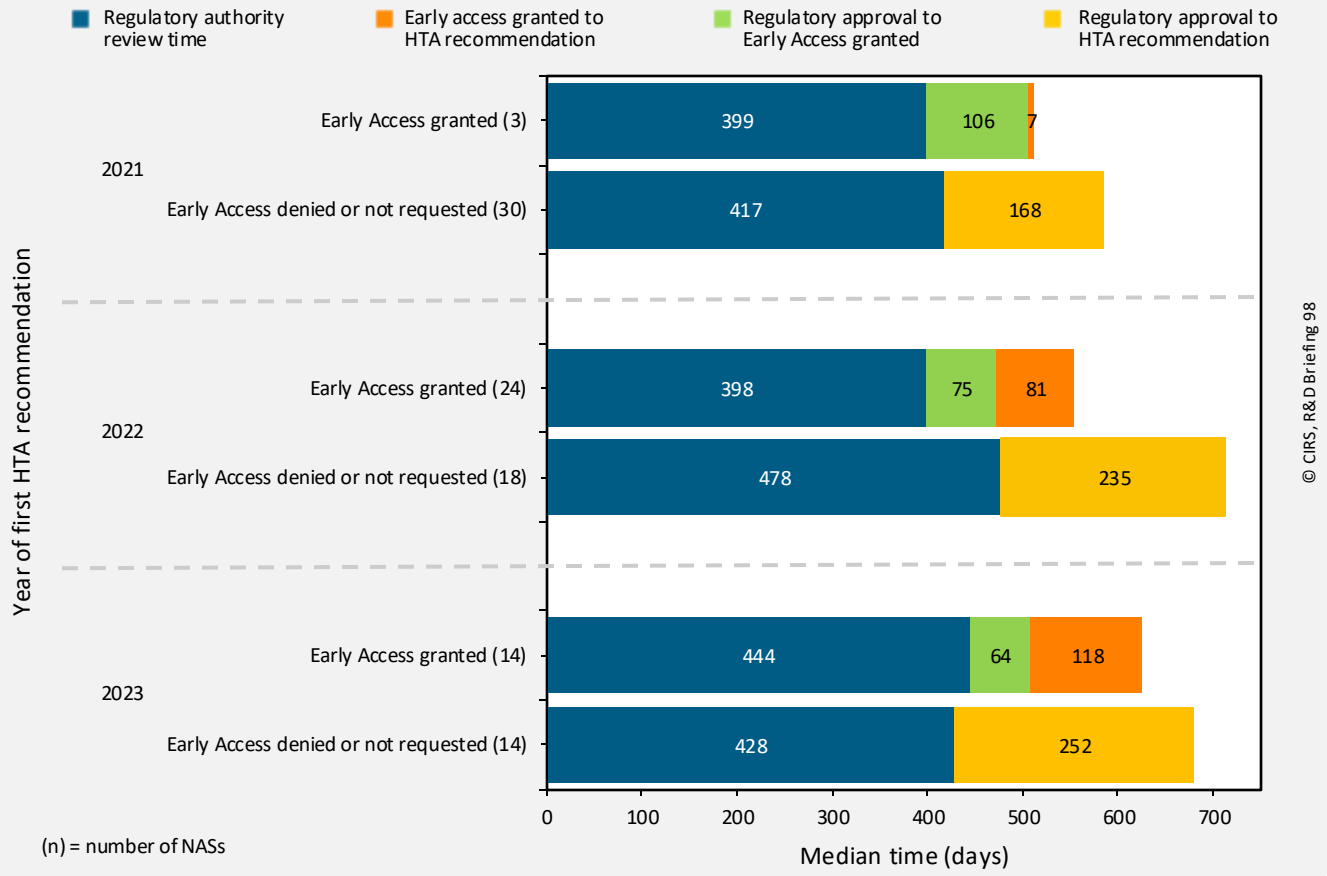
Figure 16. Proportion of HTA outcomes where Early Access was granted (n=41): pre-marketing authorisation vs. post-marketing authorisation early access (2021 and 2023)



(n) = number of NASs

Note: The new Early Access is only available in France from 1st July 2021

Figure 17. Rollout time of NASs in France (Early access granted vs. Standard)
(1st HTA recommendation between 2021 and 2023)



Products with an Early Access designation displayed a faster rollout time, potentially reflecting their underlying therapeutic urgency.

Figure 17 displays a faster rollout time for products that received an Early Access designation. This may reflect the underlying therapeutic urgency associated with these products. **Figure 18** provides a more granular analysis, suggesting that products granted pre-approval Early Access eventually received an HTA recommendation by HAS faster than those receiving post-approval early access.

Figure 18. Rollout time of NASs in France where Early Access was granted (Pre- vs. Post-approval)
(1st HTA recommendation between 2021 and 2023)

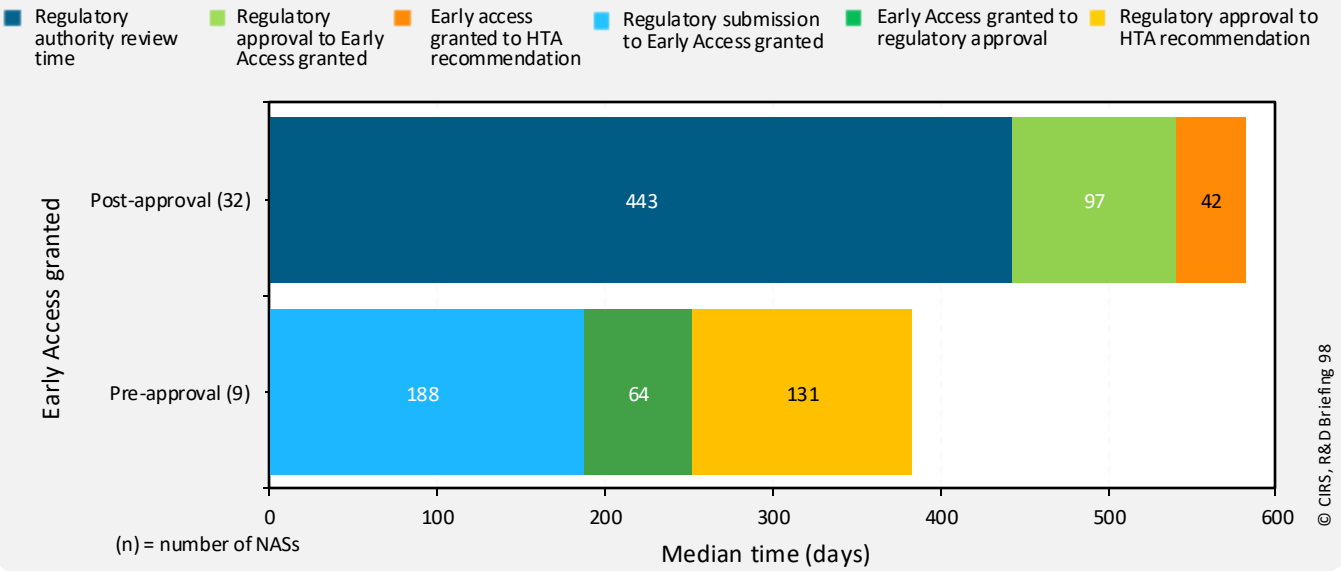
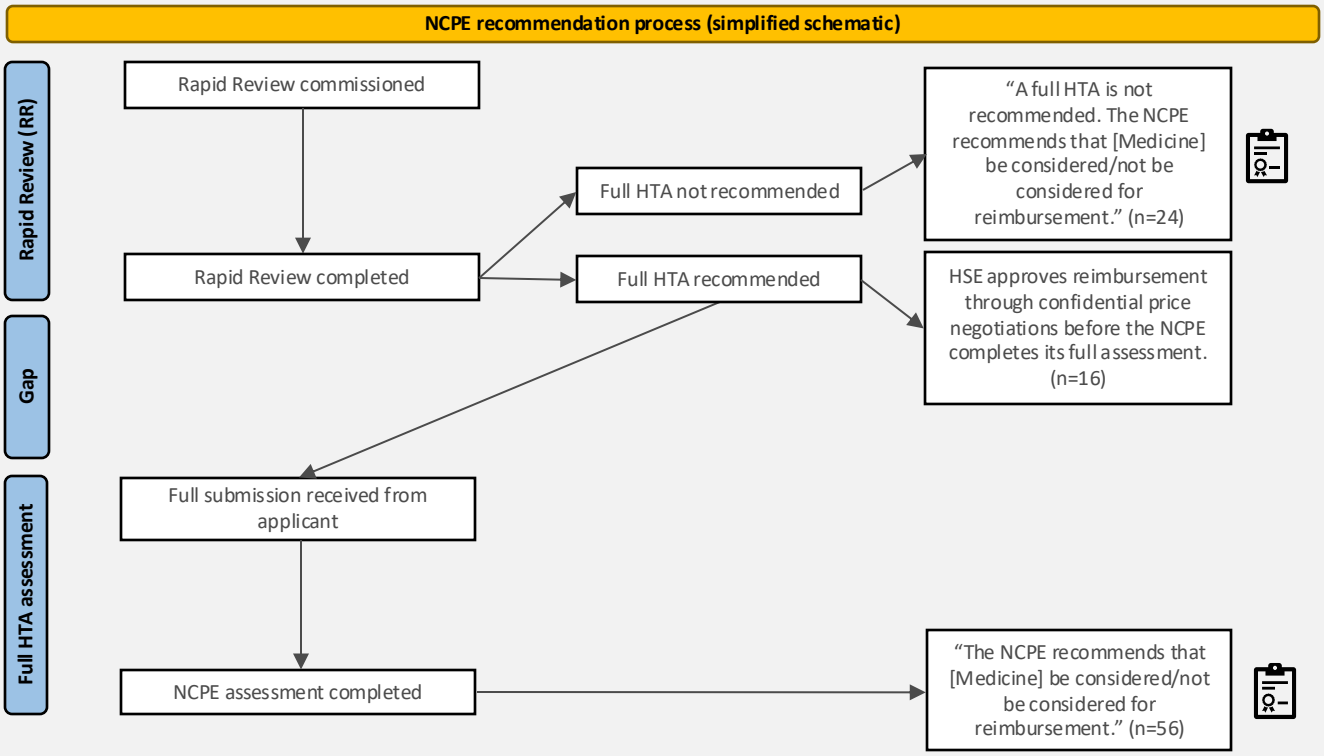


Figure 19. Simplified flow chart of the HTA recommendation system by NCPE



Rapid Reviews (RR) were introduced in Ireland in 2009 to meet the high volume and timeliness demands of HTA reviews by NCPE (**Figure 19**). The primary objective of a RR is to assess new medicines to determine if they require a more comprehensive evaluation through a full HTA. If a full HTA is not needed, the RR provides a recommendation on reimbursement. The NCPE aims to complete a RR within four weeks, and in order to do this, some aspects of the full review are not part of the RR, such as evidence synthesis analyses and formal cost-effectiveness analyses. Following the RR, a full HTA may subsequently be recommended for those drugs for which additional information and/or analysis is required to inform a reimbursement recommendation. In some case, a full health technology assessment may not be needed if the HSE can agree a suitable price reduction with the pharmaceutical company via confidential price negotiations.

Figure 20 illustrates the proportion of HTA recommendations published by NCPE that were reached either through an RR only or through an RR followed by a full HTA review between 2019 and 2023. The data indicate that a similar proportion of positive or positive with restrictions recommendations was observed for applications following an RR only and those undergoing an RR plus a full review, suggesting that the pathway type may not influence the HTA recommendation outcome.

Figure 20. Type of HTA recommendation in Ireland: rapid reviews vs full reviews (1st HTA recommendation between 2019 and 2023)

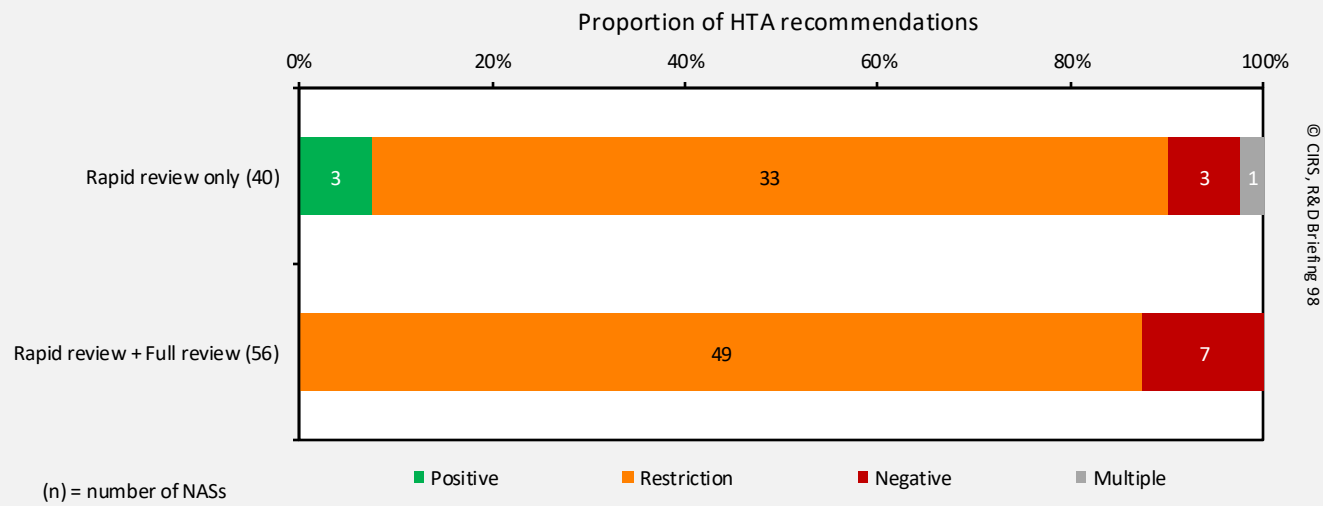
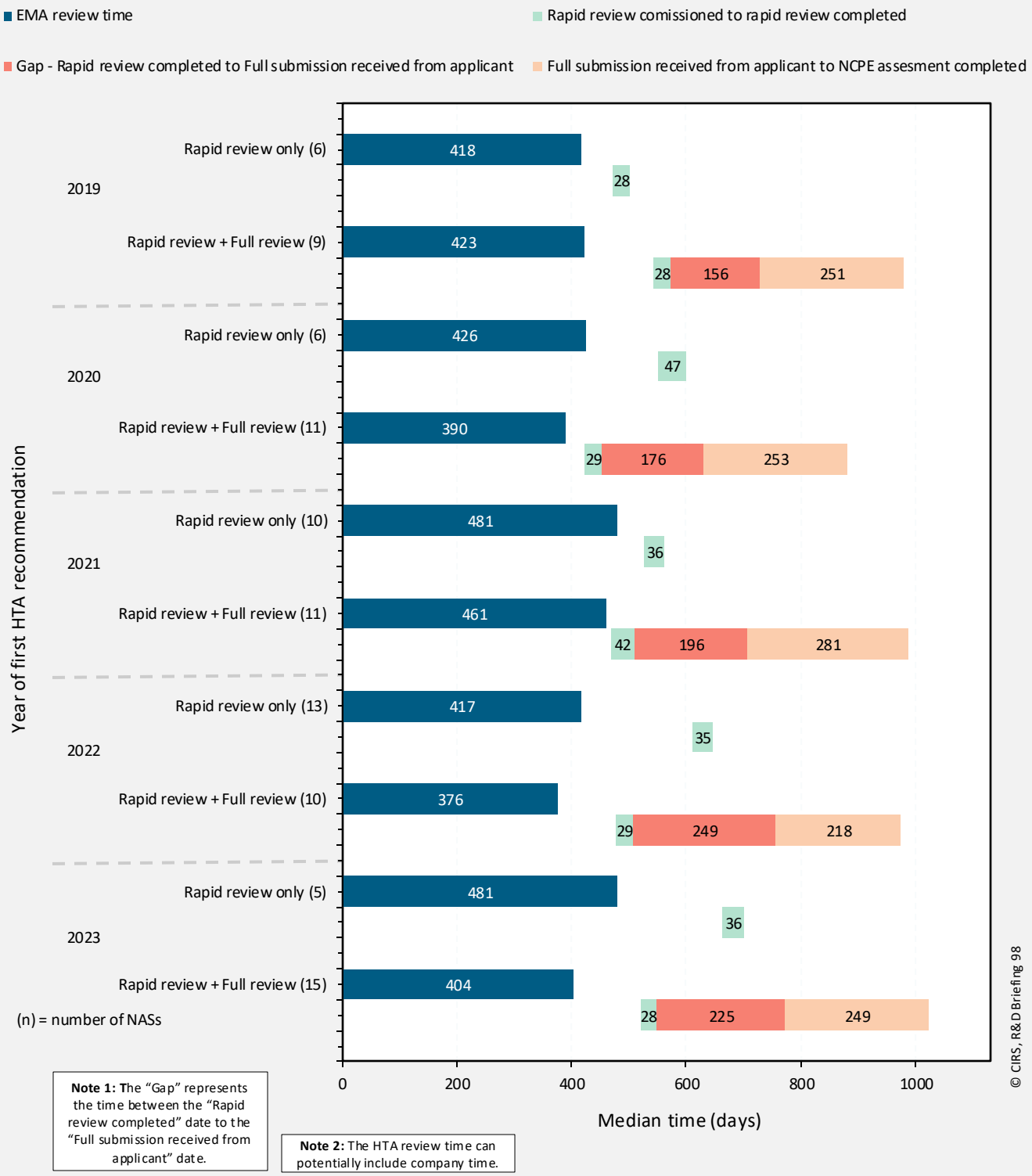


Figure 21. Breakdown of rollout time for NAS recommendations in Ireland (rapid vs full HTA reviews) (1st HTA recommendation between 2019 and 2023)



Note 1: The "Gap" represents the time between the "Rapid review completed" date to the "Full submission received from applicant" date.

Note 2: The HTA review time can potentially include company time.

Rapid Reviews reduced the time to 1st HTA recommendation by the NCPE in Ireland.

Figure 21 shows the breakdown of rollout time of NASs that received an HTA recommendation by NCPE between 2019 and 2023. The data indicated that the median time for the completion of RRs ranged from 28 to 47 days. For those applications that needed a subsequent full HTA review, the gap between rapid and full presented a median time between 156 and 249 days, and the full HTA review was completed in between 218 and 281 days. Overall, the analysis showcases that RR accelerates the time to HTA recommendation compared to RR + full reviews.

DEFINITIONS

Advanced therapy medicinal products (ATMPs)
Advanced therapy medicinal products (ATMPs) are medicines for human use that are based on genes, tissues or cells.

Anti-cancer (oncology) drug
In this briefing, anti-cancer drugs refers to anti-cancer and immunomodulators (ATC code L).

Exclusion criteria (HTADock study)
Applications that are excluded from the study:

- Vaccines
- Any other application, where new clinical data were submitted
- Generic applications
- Those applications where a completely new dossier was submitted from a new company for the same indications as already approved for another company
- Applications for a new or additional name, or a change of name, for an existing compound (i.e., a 'cloned' application)

EMA accelerated assessment
The European Medicine Agency (EMA) accelerated assessment reduces the timeframe for the EMA Committee for Medicinal Products for Human Use (CHMP) to review a marketing authorisation application; in this process, the Committee for Medicinal Products for Human Use (CHMP) opinion is shortened from 210 days to 150 days. Applications may be eligible for accelerated assessment if the CHMP decides the product is of major interest for public health and therapeutic innovation.

EMA PRIME: priority medicines
PRIME is a scheme run by EMA to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines to optimise development plans and speed up evaluation so these medicines can reach patients earlier.

First assessment report
The first assessment report is the earliest assessment available. Note that for some drugs; for example, those with the same international nonproprietary names (INN), strength and presentation, are listed more than one time. The reasons may be twofold – consideration of the drug in more than one indication or re-assessment of the drug by the agency.

Health technology assessment (HTA)
For the purpose of this project, HTA refers to the assessment and appraisal of pharmaceuticals prior to reimbursement. The HTA process includes clinical assessment, economic assessment and an appraisal that results in either a coverage recommendation or recommendation.

HTA review time
Time (calendar days) calculated from the date of submission to the date of recommendation by the HTA agency. Note: The HTA recommendation refers to the recommendation at the national level.

New active substance (NAS)
A chemical, biological, biotechnology or radiopharmaceutical substance that has not been previously available for therapeutic use in humans and is destined to be made available as a 'prescription-only medicine', to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in humans; the term NAS also includes:

- An isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously available as a medicinal product but differing in properties with regard to safety and efficacy from that substance previously available.
- A biological or biotech substance previously available as a medicinal product, but differing in molecular structure, nature of source material or manufacturing process and which will require clinical investigation.
- A radiopharmaceutical substance that is a radionuclide or a ligand not previously available as a medicinal product. Alternatively, the coupling mechanism linking the molecule and the radionuclide has not been previously available.

Regulatory submission gap
Date of submission at the first regulatory agency to the date of regulatory submission to the target agency.

Regulatory review time
Time (calendar days) calculated from the date of submission to the date of approval by the agency; this time includes agency and company time. Note: The EMA approval time includes the EU Commission time.

Rollout time
Date of submission at the regulatory agency to the date of HTA recommendation at the target jurisdiction (calendar days).

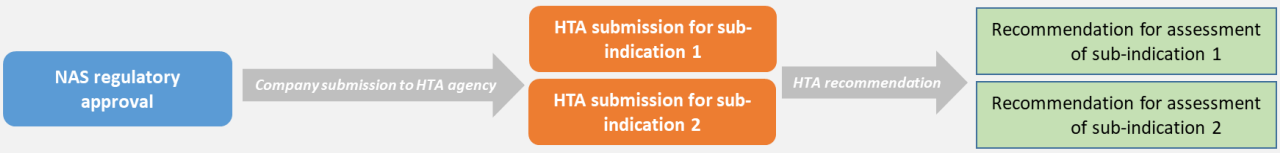
Sequential review
A regulatory review is conducted first to determine the benefit-risk profile of a new medicine, followed by the HTA review to assess the value of the medicine for a reimbursement decision. The regulatory-HTA sequence is seen at a national level in many countries, and also at a super-national level in Europe where a centralised regulatory decision made by EMA is followed by jurisdictional HTA recommendations by member states.

DEFINITIONS

Table 4: Scope of HTA agencies and assessments included in HTADock

Jurisdiction	Agency	Type of Medicinal Products Assessed	Scope HTADock – Type of product	Scope HTADock – Type of recommendation	Scope HTADock – Time frame
France	French National Authority for Health (Haute Autorité de santé or HAS)	Both outpatient and hospital use medicines	Only new active substances (NASs) are included. The NASs referenced in this briefing are medicines designated as NAS by the Committee for Medicinal Products for Human Use (CHMP). Major line extensions (MLEs) are excluded. For further details, please refer to the definition of NAS on the "Definitions" page	All types of recommendations are collected: positive, positive with restrictions, and negatives.	1st HTA recommendation for an NAS published between 2019 and 2023 – Resubmissions or re-assessment are excluded
Germany	Institute for Quality and Efficiency in Health Care (IQWiG)	Both outpatient and hospital use medicines. The added benefit is assumed to be proven for orphan drugs at the time of European approval.			
Ireland	National Centre for Pharmaco-economics (NCPE)	Both outpatient and hospital use medicines			
Netherlands	National Health Care Institute (ZIN)	Outpatient use medicines. The assessment of ATMPs by ZIN may occur if the therapy is for outpatient use in specialised clinics, but many ATMPs are used primarily in hospital settings. Recommendations for conditional inclusion are also collected.			
Poland	Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT)	Outpatient use medicines			
Portugal	National Authority of Medicines and Health Products (INFARMED)	Both outpatient and hospital use medicines			
Sweden	Dental and Pharmaceutical Benefits Agency (TLV)	Outpatient use medicines. The assessment of ATMPs by TLV may occur if the therapy is for outpatient use in specialised clinics, but many ATMPs are used primarily in hospital settings.			

Figure 22: Schematic of a multiple recommendation



In cases where more than one HTA dossier was submitted by a company for the same NAS based on different sub-indications within one approved regulatory label and the final HTA outcome for these individual sub-indications differed, the outcome was classified as multiple.

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About CIRS

The Centre for Innovation in Regulatory Science (CIRS) is a neutral, independent UK-based subsidiary of Clarivate plc. Its mission is to identify and apply scientific principles for the purpose of advancing regulatory and health technology assessment (HTA) policies and processes.

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