Agreement Between EMA and HTA Organizations About Whether Alternative Treatments Exist and Associations with Relative Effectiveness Assessments

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02/12/2022

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Plain language summary

For a drug to be approved, the European Medicines Agency (EMA) studies its benefits and risks. If the drug has larger benefits than risks, it will be approved in the European Union. These studies are known as benefit-risk assessments. However, the drug will not be available immediately on the European markets. It will be up to the member states' national health authorities to decide whether they will pay for it. These national health authorities are also called health technology assessment agencies. To decide, they will study whether the drug is of additional benefit in comparison with alternative treatments available in the country. These comparisons are known as relative effectiveness assessments. It is unknown whether European and national health authorities agree when discussing what is an alternative treatment. It is also unclear if, for a given drug, there is a relation between the absence of alternative treatments and the determination of its relative effectiveness. This study tried to clarify this. Therefore, we searched for the files in which the relative effectiveness had been studied in six different national health agencies' websites: AEMPS (Spain), AIFA (Italy), HAS (France), IQWiG/G-BA (Germany), NICE (England and Wales), and ZIN (the Netherlands). We only included drugs that were approved by the EMA between 2019 and 2021, and we excluded vaccines and diagnostic tools. Afterward, we examined the agreement between EMA and national health authorities on the availability of alternative treatments and the relationship between the absence of alternative treatments and the study of a drug's additional benefit. Overall, for the 97 drugs that matched our criteria, there were 460 studies of relative effectiveness for the six national health agencies. There was a high agreement between the EMA and national health agencies on the presence of alternative treatments. Our study showed that when there was no alternative treatment for a drug, it was almost 2 times more likely to be considered of additional benefit by the national health authorities. In conclusion, there were differences in how the European and the national health agencies see alternative treatments and in the local availability of drugs. When there was no alternative, it was more likely for a drug to be considered of additional benefit. As one of the next steps in European collaboration between national health authorities will be the joint assessment of a

drug's relative effectiveness, the differences in the availability of treatments in the different European countries need to be considered.

Abstract

In Europe, the European Medicines Agency (EMA) and national and regional health technology assessment (HTA) organizations discuss alternative treatments when evaluating a drug. The EMA recommends about marketing authorization whereas HTA organizations recommend about reimbursement, and disagreement about available alternative treatments may lead to confusion on the road to patient access. The study aimed to investigate this (dis)agreement. For innovative drugs approved by EMA in 2019-2021 (excluding vaccines and diagnostic tools), HTA reports from AEMPS (Spain), AIFA (Italy), HAS (France), IQWiG/G-BA (Germany), NICE (England and Wales), and ZIN (the Netherlands) were identified. Agreement between EMA and HTA organizations about the availability of alternative treatments was assessed. Associations between the absence of alternative treatments and positive relative effectiveness assessments (REA) were estimated by calculating risk ratios (RRs) with Wald 95% confidence intervals (CI). We identified 97 drugs for which 460 REAs had been performed by HTA organizations until 1 June 2022. The aggregated agreement between EMA and HTA organizations on the availability of alternative treatments was 87%. The absence of alternative treatments was associated with a higher chance of positive REAs: RRs 1.9 (95% CI 1.5-2.4). In conclusion, there was a high agreement between EMA and HTA about the availability of alternative treatments. The absence of alternative treatment in each jurisdiction seemed to be associated with more positive REAs. Further collaboration in the EU, especially the joint assessments of drugs' effectiveness should consider the local availability of treatments.

Introduction

For a drug to be put on the market, it needs first to be granted marketing authorization.[1] There are two different procedures in Europe: centralized and decentralized.[1] In the centralized procedure, the drug is assessed at a European level, thereby resulting in a marketing authorization that is valid throughout the European Union (EU).[1] The European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) recommends whether or not the drug should be authorized, and the European Commission is responsible for providing the authorization.[1]

For that purpose, a benefit-risk balance will be performed, in which the absolute benefits and risks of a drug will be assessed.[2] Thereafter, national Health Technology Assessment (HTA) organizations provide a recommendation or decision – depending on their mandate – regarding reimbursement.[3] For that purpose, HTA organizations perform a relative effectiveness assessment (REA) in which they can split EMA's indications, assess the drug's effectiveness and safety compared to alternative treatments, and discuss UMN.[3] Some HTA organizations also perform cost-effectiveness assessment (CEA), budget impact analysis (BIA), and/or other evaluations.[4] Together with the REA, these will be weighed against each other and lead to a recommendation or decision on reimbursement.[4]

However, the EMA has several procedures for drugs that address an unmet medical need (UMN), in which also a relative assessment of benefits and risks is made.[5] These procedures are Accelerated Assessment (AA), Approval under Exceptional Circumstances (AEC), Conditional Marketing Authorization (CMA), and Orphan Designation (OD).[5] A drug that receives a CMA, unlike those which receive a Standard Marketing Authorization (SMA), needs less comprehensive clinical data.[6,7] CMA is used for drugs that target life-threatening diseases with an UMN not satisfied, and whose benefits outweigh the risks.[6] However, they are subject to Specific Obligations (SOB) to prove that the drug meets the expected standards.[5] On the other hand, AEC is granted for drugs for which comprehensive clinical data cannot be obtained.[5,7] The marketing authorization (MA) is valid for 5 years and is reassessed each year.[5,7] For a drug to be eligible for AA, it needs to be innovative, target an UMN, and be of major interest to public health.[8] Finally, OD is meant for drugs that target a disease

life-threatening with a prevalence lower than 5 in 10,000 and the drug must provide a significant benefit to patients.[9,10] A deeper insight into regulatory pathways can be found in Panel 1.

In general, there is an important difference between EMA and HTA decision-making, namely that decision-making about marketing authorization considers the absolute benefits and risks of a drug, while decision-making about reimbursement considers the relative effectiveness as compared to existing treatments - in principle the local standard of care.[2,3] Considerations about whether alternative treatments exist are thus likely to be different between EMA and HTA agencies, because of the different purposes of their assessment (for which alternative treatments may be relevant) and the different levels at which it is performed (European vs national/regional). Disagreements between the EMA and HTA organizations lead to confusion and sometimes unnecessarily obstruct patient access, one of the areas where disagreement is present is the comparator domain.[11] This study aims to clarify to what extent they disagree on the availability of alternative treatments.

The primary objective was to study whether there was an agreement on the availability of alternative treatments between EMA and HTA organizations. The secondary objective is to study whether there is an association between the absence of alternatives and the REA outcome. Subgroup analyses were performed for different regulatory pathways, and types of drugs.

Panel 1. Procedures for drugs that address an UNM

Accelerated Assessment (AA)

AA is a procedure that shortens the time limit for the European Medicines Agency (EMA) to issue an opinion from 210 to 150 days. A drug needs to be of major therapeutic interest for public health and therapeutic innovation to be eligible for this procedure. Committee for Medicinal Products for Human Use (CHMP) is responsible for assessing the Marketing Authorization (MA) application and accepting the request. The applicant will justify its application in its request: Unmet medical need (UMN), the extent to which the drug is expected to satisfy the UMN, and the strength of evidence. The EMA suggests applicants request a pre-submission meeting 6 to 7 months before applying for a MA to prepare the evaluation. Furthermore, the request should be sent 2-3 months before the submission of the MA application. At any moment throughout the assessment, the CHMP may withdraw the AA procedure if it deems the drug does not meet the criteria.[8]

Approved under Exceptional Circumstances (AEC)

AEC is a type of marketing authorization intended for drugs for which comprehensive clinical data on efficacy and safety cannot be provided. Comprehensive data on efficacy and safety may be lacking for diseases that are so rare that full collection of information is either not possible or unethical. The authorization is valid for 5 years and can be renewed. There are Specific Obligations (SOB) to conduct the required studies to guarantee the medicine meets the expected standards. Each year, the fulfillment of these SOB, as well as the impact of SOB on the benefit/risk balance, is reassessed. AEC does not normally lead to a Standard Marketing Authorization (SMA). The applicant is expected to seek scientific advice from the EMA about its marketing authorization application. Following that, and at least 6 months before submitting the marketing authorization application, the applicant must submit a statement justifying the procedure's appropriateness for their drug.[5,7]

Conditional Marketing Authorization (CMA)

CMA is a type of marketing authorization that is granted before comprehensive clinical data is available. It is intended for drugs with an UMN that target seriously debilitating or life-threatening diseases. The drug needs to have a favorable risk-benefit balance: with the benefits of immediate availability outweighing the risks associated with a lack of clinical evidence. However, the drug is subject to SOB to demonstrate compliance with the standards. The authorization is only valid for one year and can be renewed annually based on the fulfillment of the SOB. Unlike AEC, CMA is intended for drugs that are expected to have comprehensive clinical data in the near future. Once this data is provided, it can be converted into a SMA. Prior to submission, applicants are encouraged to seek early dialogue with EMA to discuss whether a drug is eligible for CMA. Applicants should notify the EMA of their intention to pursue a CMA at least 6 to 7 months before submitting the MA application.[5-7]

Orphan Designation

OD is intended for drugs that target a life-threatening disease with a prevalence of less than 5 in 10,000 or life-threatening, seriously debilitating, or serious and chronic conditions that are unlikely to be funded. There must be no comparable satisfactory drugs or, if such drugs exist, the evaluated drug must provide a significant benefit to patients. Sponsors can directly apply to EMA for their drug to receive OD. Sponsors are encouraged, however, to request a pre-submission meeting at least 2 months before their planned submission date. At this meeting, sponsors can explain the scope of their application, describe the active substance and its mode of action, and discuss its clinical data.[9,10]

Methods

Study design and cohort identification

The present retrospective cohort study included innovative drugs for human use that received an initial marketing authorization through the centralized procedure during the period 2019-2021. The European Commission's Union Register of medicinal products[1] was used to select these drugs. As exclusion criteria, all drugs that did not contain a new active substance were excluded, as well as vaccines and diagnostic tools. The reason behind it's that they have different product characteristics and are differently assessed by HTA bodies.

Six HTA organizations across Europe were analyzed: Agencia Española del Medicamento y Productos Sanitarios (AEMPS, Spain), Agenzia Italiana del Farmaco (AIFA, Italy), Haute Autorité de Santé (HAS, France), Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen and Gemeinsame Bundesausschuss (IQWiG and G-BA, Germany), National Institute for Health and Care Excellence (NICE, England and Wales), and Zorginstituut Nederland (ZIN, the Netherlands). The organizations were selected following the criteria used in previous studies: i) the agency needed to be circumscribed to a European jurisdiction during the study period, ii) the assessed reports needed to be publicly available, iii) the recommendations are relevant to the national HTA decision-making process, and iv) the agency studied needed to be the main body concerning decision-making in the country.[4,12]

Data collection

For the included drugs, basic information at the time of initial marketing authorization was extracted from the Union Register and European Public Assessment Reports (EPARs) on the EMA website[2]: EC decision date, ATC code and name, disease area, and information regarding the regulatory pathways (AA, AEC, CMA, OD), and type of drug (small molecule, biological, ATMP). Information

[1] European Commission's Union Register: https://ec.europa.eu/health/documents/community-register/html/

[2] European Medicines Agency: https://www.ema.europa.eu/en

about the initial indication, alternative treatments (presence, number of alternatives), and UMN was extracted from EPARs.

Subsequently, data for our cohort of drugs was extracted from the websites of the HTA organizations included in the study[3]: the indications, the alternative treatments (presence, number of alternatives), UMN (if present), and REA outcomes. We identified the first HTA report for each drug's initial EMA-approved indication(s) up to June 1, 2020. HTA recommendations without a REA were disregarded. If HTA organizations split the EMA-approved indication into different indications, these were included separately. The criteria for determining the number of indications in an HTA organization was the presence of a different REA (indication-REA combinations).

Data definitions and categorization

Several decisions were made concerning the definition of agreement, indication, alternative treatments, UMN and REA. Agreement on the specification of the indication was considered when both EMA and HTA organizations included the exact same indication. Reasons for disagreement were divided into two categories: split or reformulation. Agreement on the availability of alternative treatments was considered when both EMA and HTA organizations considered the assessed drug to (not) have an alternative. There were considered three different categories for alternative treatments: on-label, off-label, and non-pharmacological.[13] As further criteria, it was not considered supportive treatment as an alternative. Some drugs are intended to be used when all other therapies have failed, when there are resistances, or when no other alternatives are available. In these cases, unless the organization specifically stated otherwise, it was considered that the drug did not have an alternative. UMN was only considered if the organization (EMA as well as HTA organizations) explicitly mentioned it or noted that there is a need for more effective and/or safer therapies. As not all HTA organizations consistently included information about UMN, UMN was included as

[3] Agencia Española del Medicamento y Productos Sanitarios: https://www.aemps.gob.es/, Agenzia Italiana del Farmaco: https://www.aifa.gov.it/, Haute Autorité de Santé: https://www.has-sante.fr/jcms/, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen: https://www.iqwig.de/, Gemeinsame Bundesausschuss: https://www.g-ba.de/, National Institute for Health and Care Excellence: https://www.nice.org.uk/, Zorginstituut Nederland: https://www.zorginstituutnederland.nl/

described/assessed by EMA. REAs were classified as either positive (including positive with restrictions) or negative. Following the criteria of previous studies of our group, for a REA to be considered positive it needed to be of additional benefit in comparison with alternative treatments. All others (equal benefit, less benefit, and lack of benefit) were considered negative.[3]

Analyses

Agreement between EMA and HTA organizations was measured on an EMA indication level: Indication-REA combinations by HTA organizations were matched to drug-indication combinations by EMA. First, the agreement between EMA and the different HTA organizations on the specification of the indication and availability of alternative treatments was described, and the overall agreement between EMA and HTA organizations was calculated for all drugs in our cohort. Second, agreement on the availability of alternatives was described only for the drugs in which there was agreement on the specification of the indication. Then, the overall agreement between EMA and HTA organizations was calculated. Third, drugs in which there was disagreement were identified and categorized into two groups: i) drugs for which the EMA considered there were alternative treatments, but HTA organizations considered otherwise, and ii) drugs for which the EMA considered there were no alternative treatments, but HTA organizations considered otherwise. Fourth, it was compared and described the type of alternative treatments (pharmacological on-label, pharmacological off-label, and non-pharmacological) for the different organizations. Sixth, agreement on the availability of alternative treatments was described for the different subgroups (AA, type of marketing authorization, drug type, and OD).

Furthermore, it was assessed the potential associations between the availability of alternative treatments (yes/no) with the REA outcome (positive/negative) for the 6 included European HTA organizations both by visualizing proportions and by calculating risk ratios (RR) with Wald 95% confidence intervals (CI). This impact was also studied for the different subgroups (AA, type of marketing authorization, drug type, and OD) to determine if the presence of the subgroups affects the

potential association between the absence of alternative treatments and decision-making by national HTA organizations.

Results

Cohort characteristics

Between January 1, 2019, and December 31, 2021, 244 drugs were approved by the EMA. After the application of the exclusion criteria, 110 innovative drugs were eligible to be searched for at the different European HTA organizations' websites. Thirteen drugs were excluded from the final cohort since no HTA report was available for them by any agency. For the remaining 97 drugs and their 115 initial EMA-approved indication, 460 HTA recommendations (460 indication-REA combinations) were available until 1 June 2022. The inclusion flowchart is shown in Figure 1.

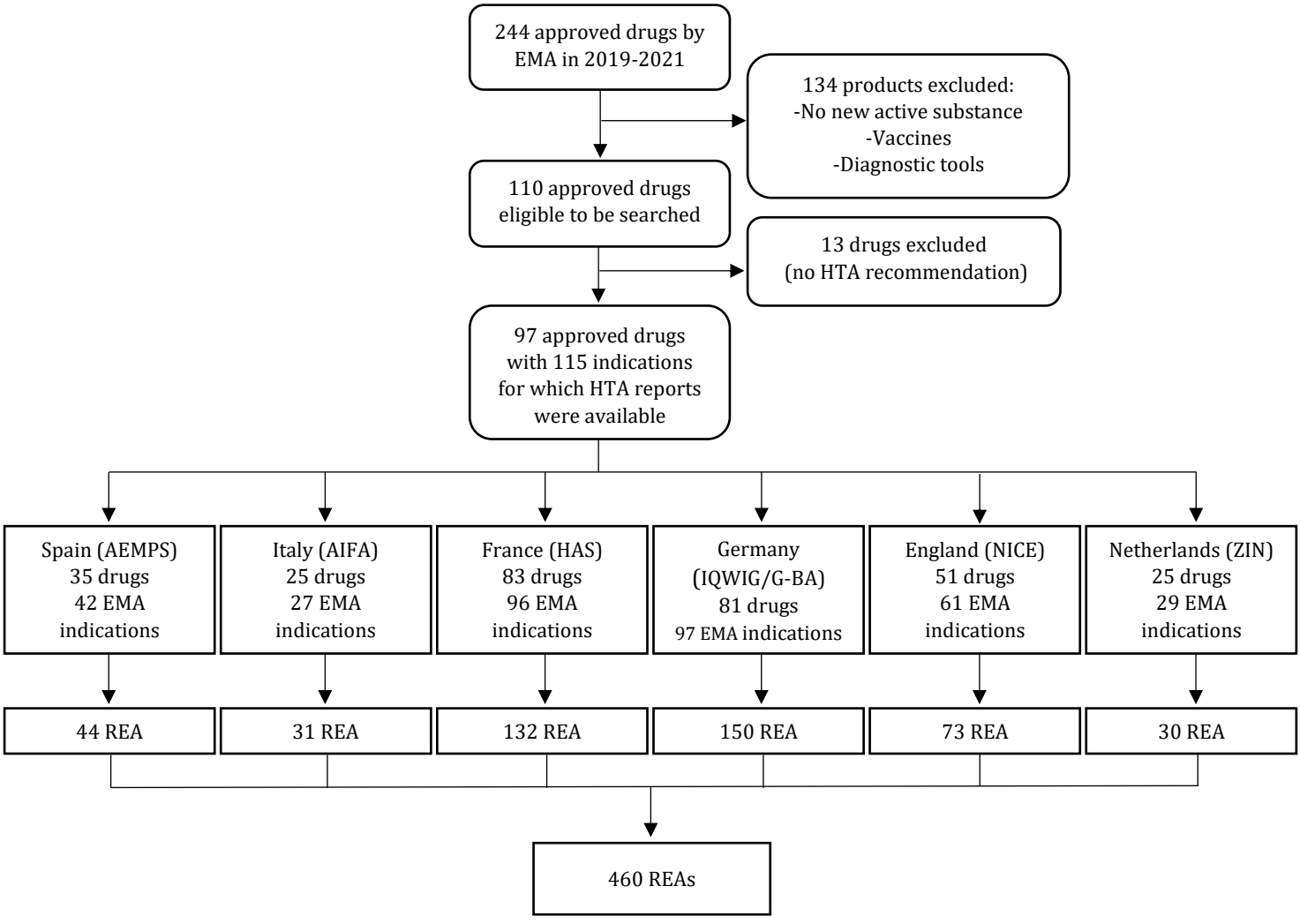

Figure 1. Flowchart of drugs included in the study cohort and drug-indication combinations for which relative effectiveness assessments (REA) were extracted. EMA, European Medicines Agency; AEMPS, Agencia Española del Medicamento y Productos Sanitarios; AIFA, Agenzia Italiana del Farmaco; G-BA, Gemeinsamer Bundesausschuss; HAS: Haute Autorité de Santé; HTA, health technology assessment; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; NICE, National Institute for Health and Care Excellence; REA, Relative Effectiveness Assessment; ZIN, Zorginstituut Nederland.

HAS assessed most drugs, 83; followed by IQWiG/G-BA, 81; NICE, 51; AEMPS, 35; and AIFA and ZIN, 25. If instead of drugs, we considered indication-REA combinations, IQWiG-G-BA included most, 150; followed by HAS, 132; NICE, 73; AEMPS, 44; AIFA, 31; and ZIN, 30. Table 1 shows the characteristics of the cohort of indication-REA combinations.

Table 1. Characteristics of the study cohort of indication-REA combinations.

Characteristic	**EMA**	**AEMPS**	**AIFA**	**HAS**	**IQWiG/ G-BA**	**NICE**	**ZIN**
Cohort							
N drugs	97	35	25	83	81	51	25
N indications (EMA)/ indication-REA combinations (HTA)	115	44	31	132	150	73	30
Drug type							
ATMP	7 (6%)	3 (7%)	5 (16%)	8 (6%)	8 (5%)	6 (8%)	3 (10%)
Biological	40 (35%)	11 (25%)	12 (39%)	49 (37%)	42 (28%)	22 (30%)	9 (30%)
Small molecule	68 (59%)	30 (68%)	14 (45%)	75 (57%)	100 (67%)	45 (62%)	18 (60%)
Disease area							
Antineoplastic agents	36 (31%)	17 (39%)	8 (26%)	42 (32%)	47 (31%)	22 (30%)	6 (20%)
Immunosuppressants	12 (10%)	4 (9%)	1 (3%)	18 (14%)	27 (18%)	18 (25%)	5 (17%)
Lipid modifying agents	10 (9%)	6 (14%)	1 (3%)	4 (3%)	8 (5%)	6 (8%)	3 (10%)
Antivirals for systemic use	7 (6%)	1 (2%)	1 (3%)	8 (6%)	11 (7%)	1 (1%)	1 (3%)
Antihemorrhagics	4 (3%)	3 (7%)	2 (6%)	3 (2%)	5 (3%)	3 (4%)	1 (3%)
Antibacterial for systemic use	3 (3%)	0 (0%)	1 (3%)	6 (5%)	1 (1%)	0 (0%)	0 (0%)
Another disease area	43 (37%)	13 (30%)	17 (55%)	51 (39%)	51 (34%)	23 (32%)	14 (47%)
Regulatory pathways							
Accelerated assessment	25 (22%)	10 (23%)	19 (61%)	35 (27%)	33 (22%)	14 (19%)	7 (23%)

Conditional marketing authorization + Authorization under exceptional circumstances	31 (27%)	14 (32%)	11 (35%)	39 (30%)	41 (27%)	22 (30%)	6 (20%)
Orphan designation	36 (31%)	11 (25%)	17 (55%)	47 (36%)	40 (27%)	15 (21%)	8 (27%)
Unmet medical need (EMA)	85 (74%)	30 (68%)	24 (77%)	89 (67%)	97 (65%)	46 (63%)	18 (60%)

Table 2. Alternative treatments characteristics

Characteristic	**EMA**	**AEMPS**	**AIFA**	**HAS**	**IQWIG/ G-BA**	**NICE**	**ZIN**
Alternative treatments							
N Alternative treatments	91 (79%)	39 (89%)	24 (77%)	111 (84%)	106 (89%)	58 (79%)	26 (87%)
Median + IQR	2 (2;6)	4 (2;5.5)	2 (1;3.3)	4 (2;7)	2 (1;5)	2 (2;5)	4,5 (2;8.5)
Type of alternative treatment							
Pharmacological on-label	75 (82%)	37 (95%)	15 (63%)	88 (79%)	104 (98%)	51 (88%)	25 (96%)
Pharmacological off-label	27 (30%)	7 (18%)	5 (21%)	36 (32%)	0 (0%)	7 (12%)	4 (15%)
Non-pharmacological	30 (33%)	10 (26%)	9 (38%)	40 (36%)	9 (8%)	10 (17%)	3 (12%)

Availability of alternative treatments and agreement between the EMA and HTA organizations

Of the indications assessed by each agency, EMA found 79% to have an alternative treatment, whereas most HTA organizations found a higher proportion of alternative treatments (table 2). The next step was to study the agreement between EMA and the different HTA organizations. This agreement was studied on an indication level (Supplementary materials Figure S1), and on an alternative treatment level (Supplementary materials Figure S2). The aggregated agreement on the specification of the indication between EMA and all HTA organizations aggregated was 66%. However, the agreement between EMA and single HTA organizations varied between HTA organizations, ranging from 57% to 90%. The aggregated agreement on the availability of alternative treatments between EMA and HTA organizations was 76%. Although here discrepancies between

countries existed as well, ranging from 72% to 93%. For 28 indications, IQWiG/G-BA did not study the alternative treatments, thereby not being included.

Agreement on the availability of alternative treatments for those drugs in which there was an agreement on an indication level was also studied (figure 2). The aggregated alternative treatment agreement between EMA and HTA organizations was 87%. However, there were differences between organizations on the agreement on the availability of alternative treatments, ranging from 79% to 96%. For 27 indications, IQWiG/G-BA did not study the alternative treatments, thereby not being included. The EMA and the HTA organizations disagreed because the EMA considered the presence of alternative treatments while the HTA organizations did not (n=13, including entrectinib, selpercatinib, givosiran, and atidarsagene autotemcel), and vice versa (n=13, including upadacitinib, fostamatinib, and larotrectinib). This disagreement happened more than once for upadacitinib (AEMPS, AIFA, and HAS disagreed with EMA), fostamatinib (AEMPS, IQWIG, and NICE), entrectinib (AIFA and NICE), selpercatinib (HAS, and NICE), and atidarsagene autotemcel (NICE disagreed with EMA for both indications).

For the drugs in which there was agreement on the specification of the indication, there were also differences between EMA and HTA organizations in the type of alternative treatment: pharmacological on-label and off-label, and non-pharmacological (Supplementary materials Figure S3). There were discrepancies between HTA organizations about for how many indication-REA combinations there were alternative pharmacological on-label treatments (ranging from 50% to 96%), and similarly for pharmacological off-label treatments (ranging from 0% to 28%), and non-pharmacological treatments (ranging from 13% to 50%). For the same indication-REA combinations, and in contrast to most HTA organizations, EMA identified a smaller proportion of pharmacological on-label treatments and a larger proportion of pharmacological off-label and non-pharmacological treatments.

Agreement on the availability of alternative treatments was also studied for the different subgroups (Supplementary materials Figure S4). In this case, there were no large differences in agreement,

although, for regulatory pathways that indicate an unmet medical need (AA, CMA+AEC, and Orphan Designation), agreement consistently seemed slightly higher.

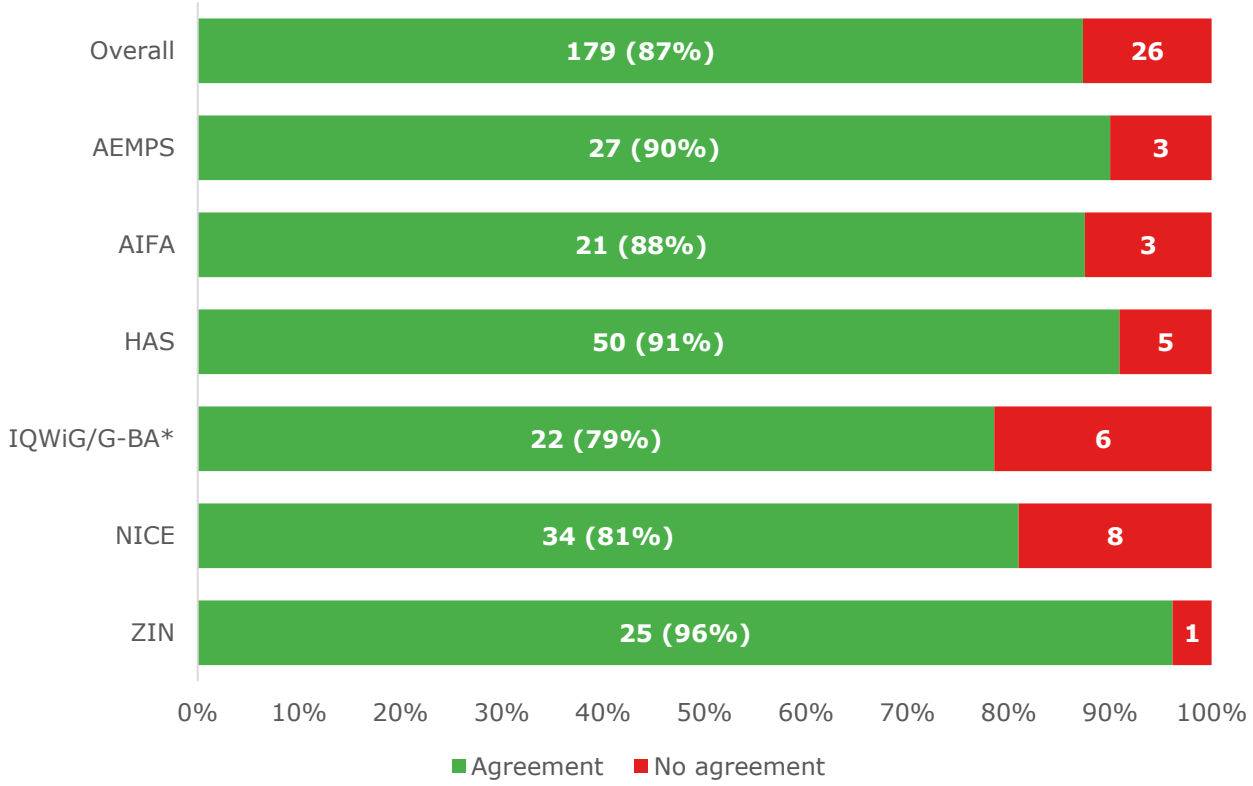

Figure 2. Alternative treatment-level agreement between the EMA and the HTA organizations after excluding those with disagreement on indication-level. 27 EMA's indications were excluded for IQWiG/G-BA since no assessment of the alternative treatments was present in their reports.

Association between the presence of alternative treatments and REA outcomes

When HTA organizations considered that no alternative treatments were available, all six organizations reported more positive REAs (Figure 3). The relative risk for receiving a positive REA was 1.9 (95% CI: 1.5–2.4) for drugs without an alternative treatment versus drugs with an alternative treatment (Figure 4). This association was studied as well for the different subgroups (Figure 5). As observed before, the absence of alternative treatments is associated with more positive REA for most subgroups. The relative risk for receiving a positive REA was above 1 for all the subgroups, although

there were major discrepancies between subgroups, ranging from 1.1 (95% CI: 0.8–1.6) to 2.4 (95% CI: 1.8–3.3) (Figure 5).

In proportion, AA and OD drugs received more positive REA outcomes than their counterparts, whether there were alternative treatments available. However, although CMA and AEC drugs had more positive REA outcomes than SMA drugs in the presence of alternative treatments, this effect was not observed when there were no alternative treatments available. In proportion, ATMPs were the type of drugs that received more positive REA outcomes, followed by biologicals, and small molecules. This was true both for the presence and the absence of alternative treatments.

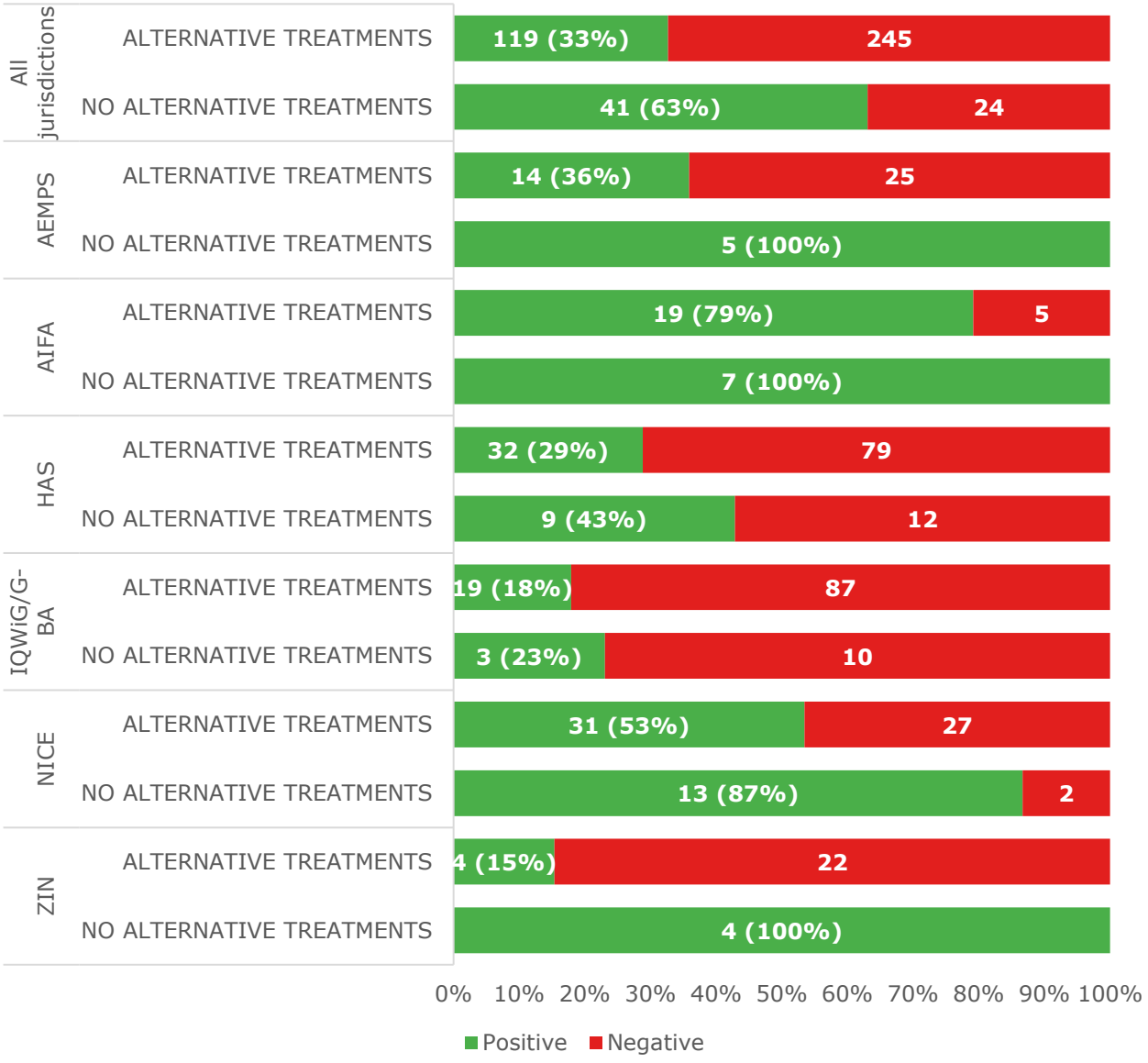

Figure 3. Association of the presence of alternative treatments in REA decision-making

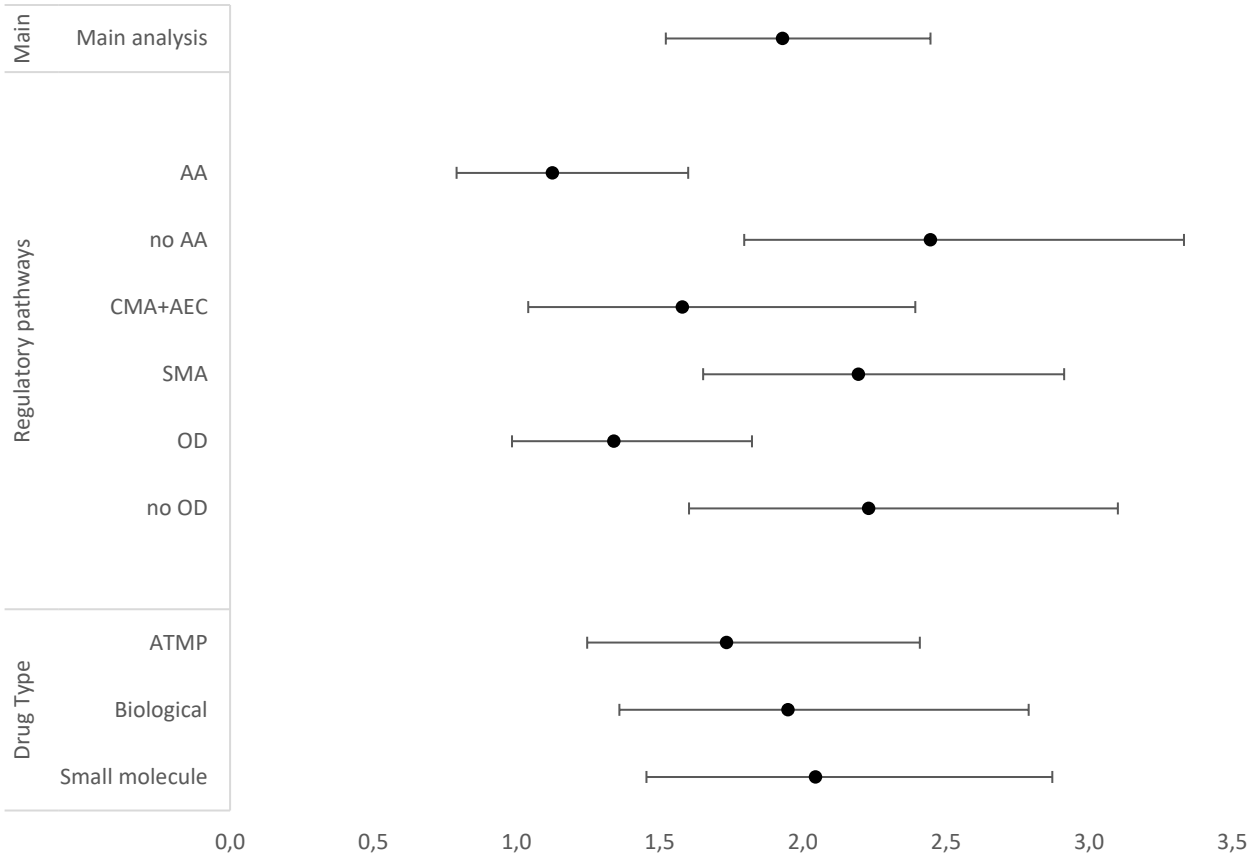

Figure 4. Forest plot with risk ratios for the main analysis, and the subgroups analyses

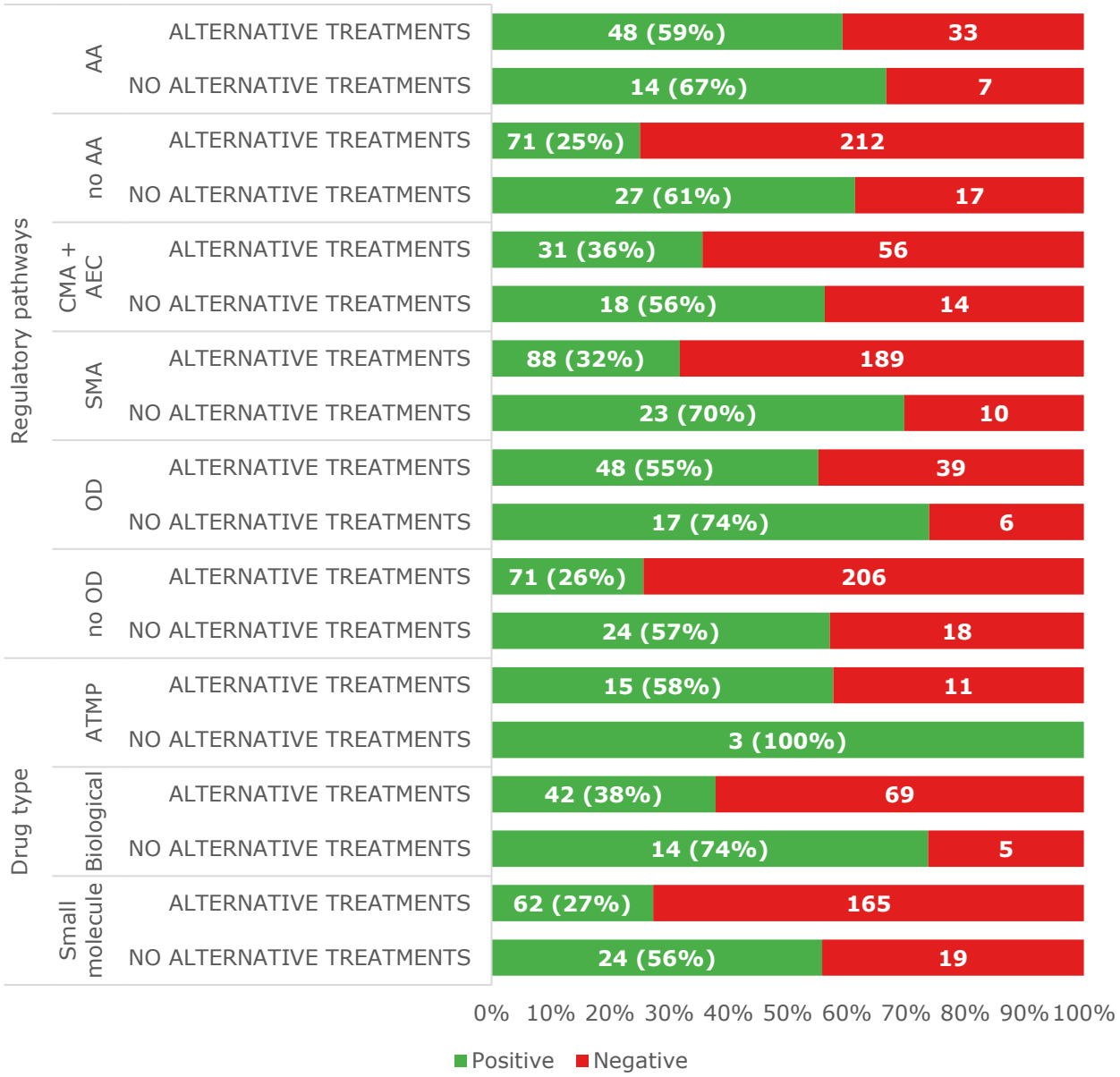

Figure 5. Association of the presence of alternative treatments in REA decision-making for the subgroups

Discussion

Summary of findings

The main objective of the present research project was to study the agreement on the availability of alternative treatments between EMA and HTA organizations. The aggregated agreement was 76%. After excluding indication-REA combinations for which EMA and HTA organizations did not

consider the exact same indication, the aggregated agreement increased to 87%, reflecting a high degree of agreement between EMA and HTA organizations. As a second objective, the potential association between the non-availability of alternative treatments and REA outcomes was studied. The absence of alternative treatments was associated with more positive REAs: RRs 1.9 (95% CI 1.5-2.4).

Agreement on the alternative treatment level

In 26 indication-REA combinations, EMA and HTA organizations did not agree on whether alternative treatments were available. Of these, in 13 cases EMA considered they were available while HTA organizations thought they were not, and in 13 cases was the other way around. For 4 drugs, more than one HTA organization did not agree with the EMA, i.e., upadacitinib, fostamatinib, selpercatinib, and entrectinib). There was disagreement about the availability of alternative treatments for upadacitinib between the EMA and 3 HTA organizations -AEMPS, AIFA, and HAS-. Upadacitinib is intended for patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). EMA considered the drug to be intended for patients who are intolerant to all available alternatives. However, HTA organizations considered there were alternatives for the subset of patients covered by the indication. In addition, there was disagreement between EMA and 3 HTA organizations -AEMPS, NICE, and IQWiG/G-BA- for fostamatinib. Similarly, fostamatinib is indicated for patients who are refractory to other treatments. EMA considered the indication to be intended for those patients in which all the other treatments have failed. However, the HTA organizations still considered alternative treatments in this line. According to EMA, there were off-label treatments, other than selpercatinib, for treating advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib. HAS did not consider other alternatives than sorafenib and lenvatinib, and NICE considered posterior lines of treatment as BSC. As for entrectinib, larotrectinib was approved by EMA for the exact same indication, thereby constituting an alternative. However, this product was not reimbursed in Italy and UK at the moment of the appraisal. EMA and ZIN only

disagreed on an alternative treatment level for one drug, givosiran. The reason behind this disagreement was that EMA considered hemin as a treatment, while ZIN considered hemin to be BSC. Atidarsagene autotemcel was one of the indications in which there was disagreement between EMA and NICE. EMA considered allogeneic hematopoietic stem cell transplantation (HSCT) as a treatment of metachromatic leukodystrophy, while NICE stated HSCT has not been used in the clinical setting for the past 10 years. As for larotrectinib, EMA considered the drug not to have alternative treatments due to the narrowness of the indication -the drug is only intended for those patients in which surgery is likely to result in morbidity and with no pharmacological options. However, IQWiG/G-BA still considered surgery as an option. Summarizing, there are three reasons for disagreement: what is a treatment (n=10; including selpercatinib, givosiran, larotrectinib), different interpretations of an indication (n=11; including upadacitinib, fostamatinib), and differences in the local availability (n=4; including entrectinib, atidarsagene autotemcel). Interestingly, for casirivimab/imdevimab (treatment of COVID-19 in patients who are at increased risk of progressing to severe disease) there were no alternatives according to EMA but HAS highlighted several approved drugs, some of them approved throughout the centralized procedure by the EMA. The presence of alternative treatments in HAS and not in EMA could be explained due to the time between assessments (11 November 2021, EMA; 18 May 2022, HAS). In this period, sotrovimab was granted MA (17 December 2021), being one of the drugs that appeared as an alternative treatment in HAS report for casirivimab/imdevimab.

Our study adds to the body of literature that described differences between how EMA and HTA organizations assess medicines. Previous studies observed differences in the target population, comparators, efficacy and surrogate endpoints, clinical relevance, and trial duration[14,15]. Our study suggests that there are differences as well about the definition and local availability of alternative treatments between organizations.

Association between the presence of alternative treatments and REA outcomes

Our results showed that there is a positive association between the absence of alternative treatments as assessed by HTA organizations and a positive REA outcome, thereby suggesting that the availability of alternative treatments would play a role in REA decision-making. This result is as expected, due to the nature of REA. As REA explores the effectiveness against comparators, if there are no alternative treatments the REA will be performed against a placebo. According to a study in which HTA was compared in France, Germany, and Italy, Italy was the country that was giving more importance to UMN and lack of alternative treatments.[16] This could explain why, according to our results, the absence of alternatives seemed more strongly associated with positive REAs in Italy.

Unsurprisingly, the non-availability of alternative treatments did not have an impact on REA for AA drugs, while it did for non-AA drugs. This could be explained by the presence, by definition, of an UMN in AA drugs, and by the absence of alternative treatments being one of the factors behind UMN, as was identified by *Vreman et al.*[17] Thereby, diluting the difference between the two categories (AA and non-AA drugs) when there is no an alternative treatment: both are targeting an UMN.

Concerning CMA and AEC, and SMA drugs, the absence of alternative treatments had an impact on REA decision-making. Given the confidence intervals, there is no difference between CMA-AEC and SMA drugs in terms of the effect of the absence of alternative treatments on REA. This is in disagreement with the literature, in which CMA drugs had a lower proportion of positive REA due to the presence of uncertainties.[12,18] Previous studies showed that uncertainties had a negative effect on the REA outcome[4]. Therefore, in case of a lack of alternative treatments, the clear UMN may to some extent outweigh uncertainties.

With respect to orphan drugs, the non-availability of alternative treatments likely had an impact on REA decision-making, however, this cannot be said categorially due to the lower CI interval. On the other hand, the absence of alternative treatments had an impact on REA for non-orphan drugs.

Given the confidence intervals, the effect of the absence of alternative treatments on REA could differ between orphan and non-orphan drugs. This would be consistent with a study that showed that more uncertainty was accepted for orphan-designated drugs.[19] This again suggests the impact that the absence of alternative treatments has on the definition of UMN.

Concerning the type of molecule that constitutes the active substance, the absence of alternative treatments had the same effect on REA for ATMPs, biologicals, and small molecules.

Policy implications

As emphasized by different articles, companies try to take into account both the opinion of regulators and HTA organizations. [20,21] Our study suggests that companies should also consider what is an alternative treatment for the different organizations, how differently the organizations understand the indications and the local availability of alternative treatments between jurisdictions.

Furthermore, joint assessment of drugs' effectiveness constitutes one of the next steps in European integration.[22] This joint assessment will materialize in the framework of EUnetHTA, a collaboration tool for European HTA organizations, for oncological drugs and ATMPs from 2025, and for orphan drugs from 2028.[23,24] Some studies have tried to characterize the differences between HTA organizations across the EU, showing that IQWiG/G-BA was including fewer comparators than other organizations.[25] In this way, joint assessment could potentially target and solve heterogeneities between EU countries. Although, as our study shows, joint assessment of drugs needs to consider the different availability of medicinal products and be aware of the differences in the definition of an alternative and how an indication is interpreted across EU countries.

Limitations

This study did not contemplate other factors, such as uncertainties, that affect HTA decision-making. Although our study showed that there was an association between alternative treatments and REA outcome, it was not possible to reach any conclusion about which of the two factors prevailed in REA decision-making. This study did not contemplate CEA or BIA, which also determines HTA decision-

making. Although our study it was compared EMA and HTA organizations, no comparison was performed between HTA organizations. Our results cannot be extrapolated to other European HTA organizations or non-European jurisdictions, since our data only reflect the reality of the organizations studied. Not all HTA organizations consistently included information about UMN (only HAS and NICE), so agreement on the definition of an UMN could not be assessed.

Conclusion

There is a high agreement between EMA and HTA organizations about the availability of alternative treatments, but there are some discrepancies due to differences in local availability and definition of alternative treatments, and how the indication is interpreted. The absence of alternative treatment in each jurisdiction seemed to be associated with more positive REAs by HTA organizations in Europe. Further collaboration in the EU, especially the joint assessments of drugs' effectiveness should consider the local availability of treatments.

Acknowledges

To Lourens T. Bloem and Rick A. Vreman for helping me to understand the topic. To Jan-Willem Versteeg for the data validation. And to the entire Division of Pharmacoepidemiology and Clinical Pharmacology for being so welcoming.

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Supplementary materials

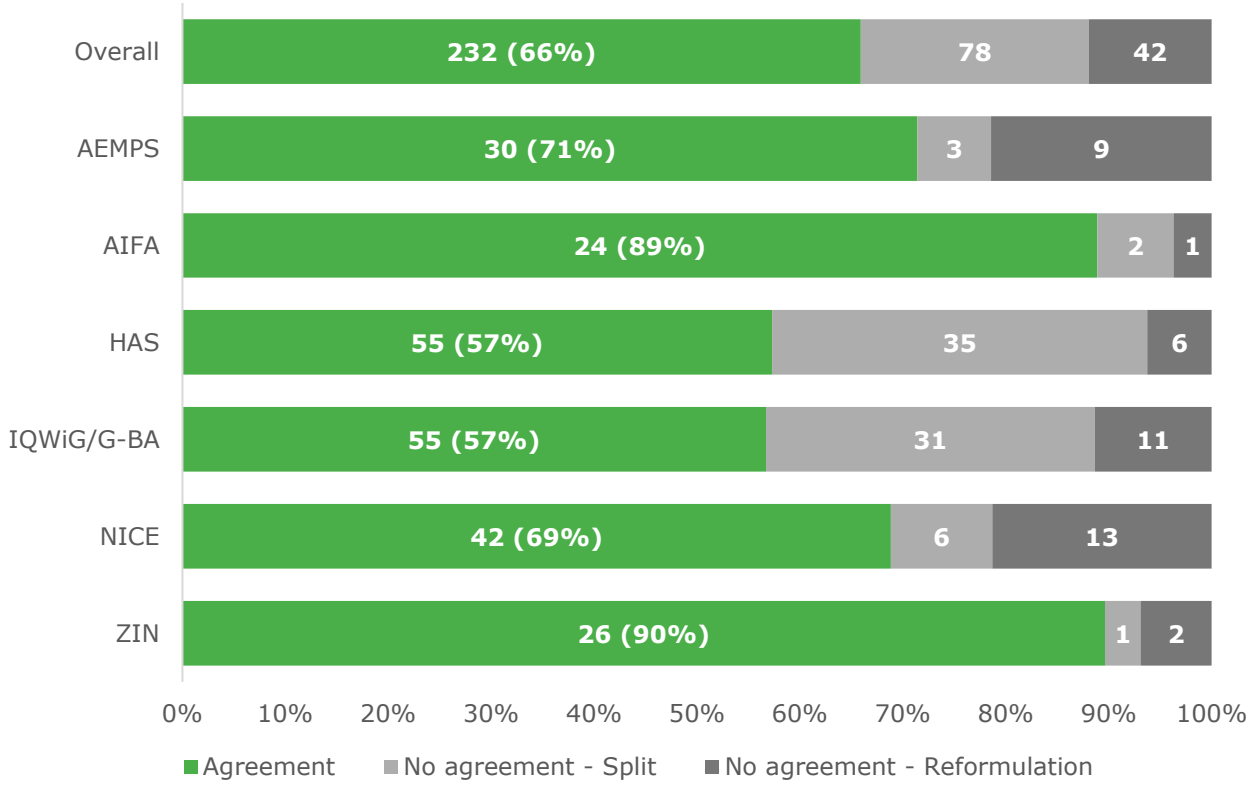

Figure S1. Indication-level agreement between the EMA and the HTA organizations

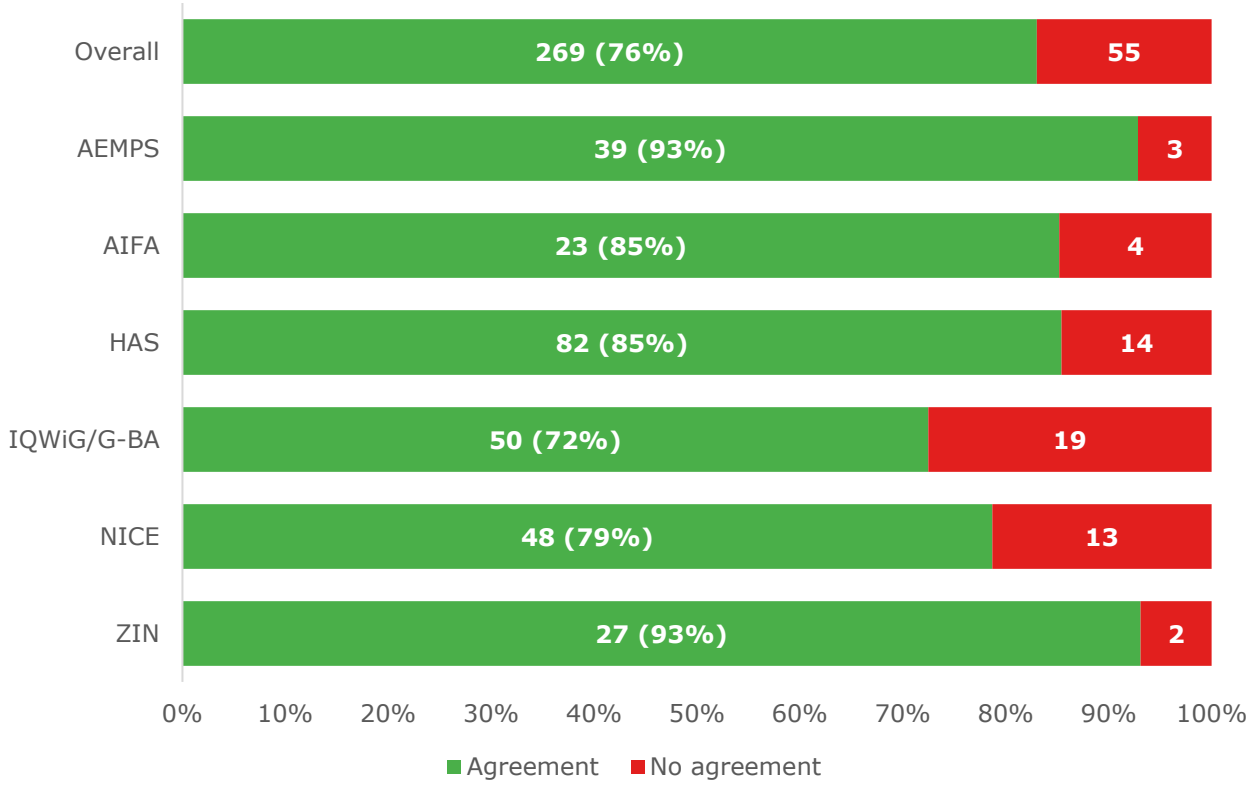

Figure S2. Alternative treatment-level agreement between the EMA and the HTA organizations.

* 28 EMA's indications were excluded for IQWiG/G-BA since no assessment of the alternative treatments was present in their reports.

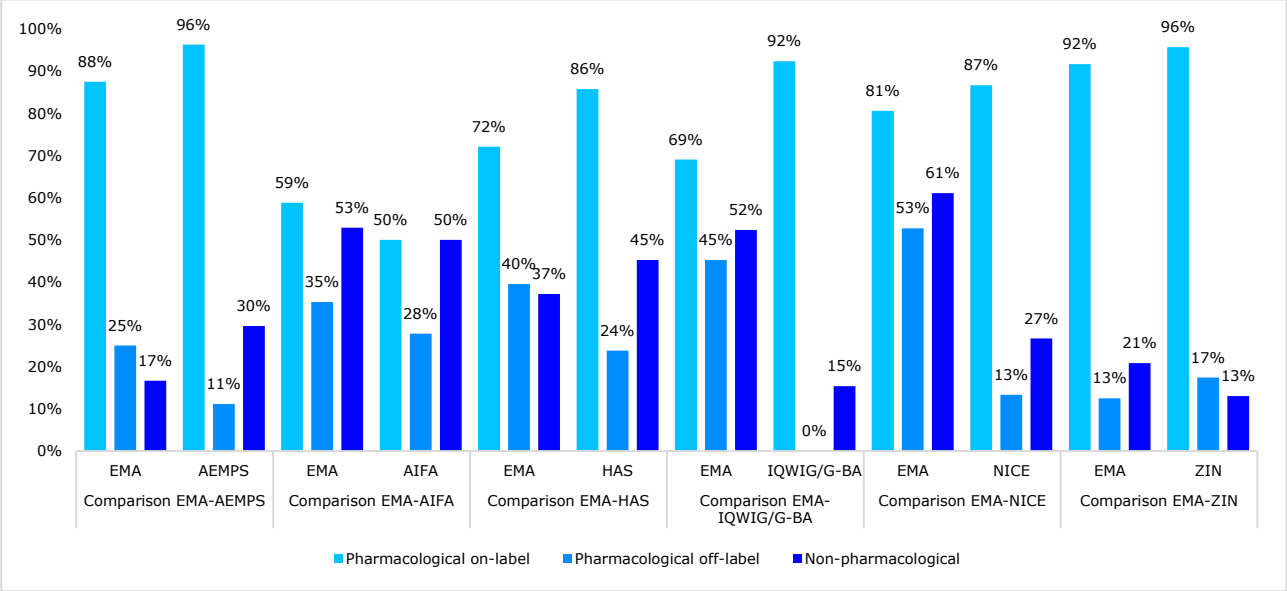

Figure S3. Type of alternative treatments per agency

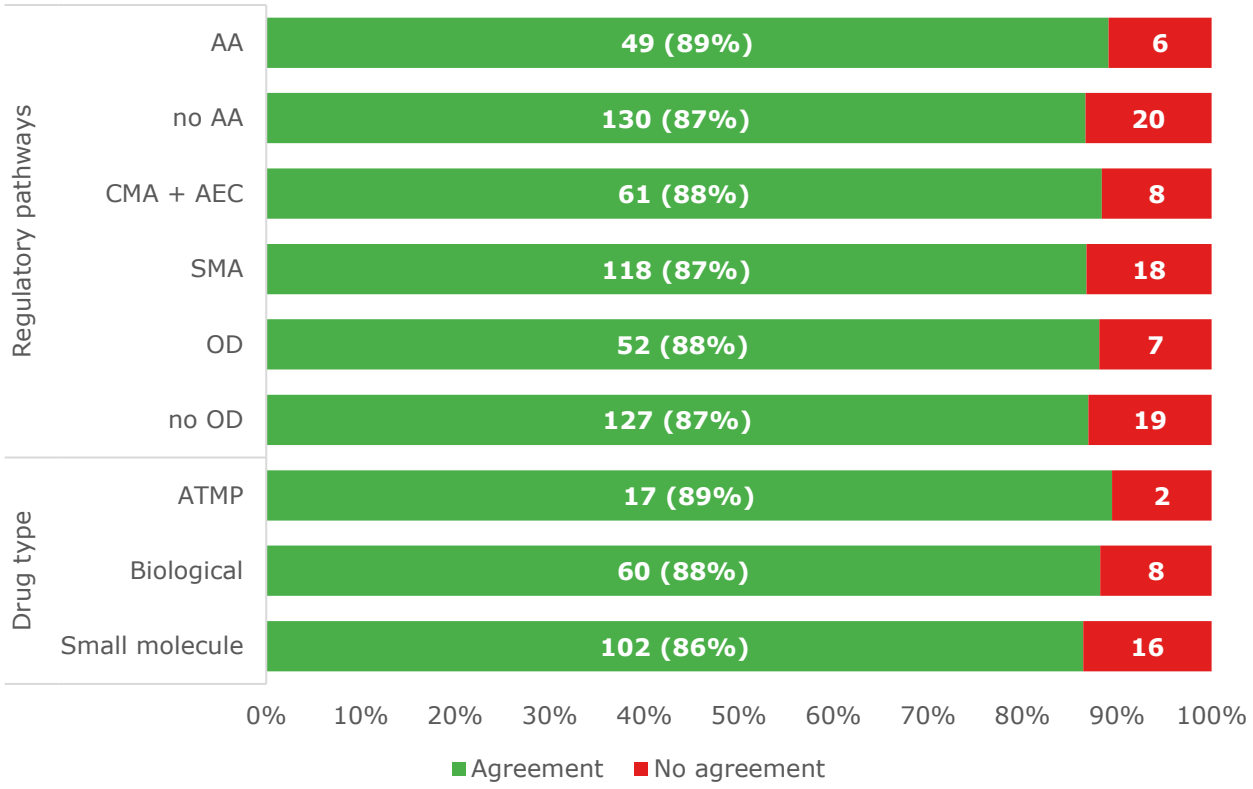

Figure S4. Alternative treatment-level agreement between the EMA and the HTA organizations combined. Data for the different groups after excluding those with disagreement on indication-level.