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ACCESS TO INNOVATIVE NEUROLOGICAL DRUGS IN EUROPE: ALIGNMENT OF HEALTH TECHNOLOGY ASSESSMENTS AMONG EUROPEAN COUNTRIES

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Summary

1. Introduction

According to recent data, neurology represents one of the therapeutic areas with the greatest number of development projects, perhaps reflecting scientific advances in the understanding of the basis of these diseases useful for potential novel intervention (1). Neurological conditions historically have been among the most difficult for which to develop effective and safe new therapies, due to the complexity in physiopathology and clinical presentation, and curative treatments for important diseases, such as neurodegenerative diseases, are still lacking (2).

Actually, this is one of the most challenging therapeutic fields in terms of likelihood of drug approval, with the longest time for review and recommendation (3-6).

In 2020, the European Medicines Agency (EMA) issued 78 positive opinions for new active substances (NASs), including eight medicines recommended for approval in the therapeutic area of neurology (10%)(7).

Among medicines recently approved by the EMA, which represent potential innovative treatment for neurological diseases, we can find gene therapies for rare genetic unmet medical needs.

Gene therapies may provide significant health benefits generally with a single administration, allowing to act on the primary cause of a disease with the possibility of complete recovery and improvement of patient outcome potentially over the long term.

For example, in 2020 EMA recommended the conditional approval of the first gene therapy Zolgensma® (onasemnogene abeparvovec) for spinal muscular atrophy (SMA), a group of

genetic disorders which affect the spinal motor neuron and represent the leading cause of infant mortality due to genetic disease.

It is usually diagnosed in the first year of life and most patients with the severe form do not survive early childhood. Patients affected do not produce sufficient amounts of the protein *survival motor neuron* (SMN), which is essential for the normal functioning and survival of motor neurons. Loss of motor neurons leads to progressive loss of muscle control, strength and function, swallowing, breathing and, ultimately, death.

The SMN protein is produced by the *SMN1* and *SMN2* gene. The *SMN1* gene produces a full-length transcript that encode the SMN protein, whereas the *SMN2* gene produces a truncated, not functional protein and only a small percentage (10%-15%) of the full-length, functional SMN.

Patients with SMA lack the *SMN1* gene and are dependent from the *SMN2* gene: individuals with ≤ 3 copies of *SMN2* have a high probability of developing a severe phenotype which will result in significant motor function limitations (inability to walk, respiratory complications requiring ventilatory support, high risk for orthopedic complications such as painful contractures and scoliosis) and reduced life expectancy.

Until recently, no causal treatment was available, and patients were treated only with supportive care, including orthopedic and spinal management, gastrointestinal management, pulmonary management, acute care, and palliative care.

The antisense oligonucleotide (ASO) nusinersen (Spinraza®) is the first drug approved for SMA. It modulates the splicing of the *SMN2* gene increasing the production of the SMN protein, allowing to compensate for the underlying genetic defect. However, despite Spinraza® approval, an unmet medical need for alternative treatment options of SMA remained.

Zolgensma® is a one-shot intravenous treatment which supply a fully functioning copy of the human *SMN1* gene enabling the production of enough functional protein, improving the muscle function, movement, and survival of children with the disease.

Moreover, several disease-modifying therapies have been approved for multiple sclerosis (MS), one of the leading causes of neurological disability in particular in young adults, resulting in the need for lifetime support and remarkable socioeconomic impacts (8). It is a chronic demyelinating autoimmune condition of the central nervous system (CNS) characterized by inflammation and neuro-axonal degeneration, leading to disease relapses and disability progression (9-11). The clinical course of the disease is variable and unpredictable in terms of both the severity and the evolution of symptoms. Most patients develop the relapsing–remitting form (RRMS), with or without permanent neurological deficits and disability (secondary progressive MS, SPMS)(9). Moreover, a progressive disease from the onset characterizes the primary progressive form (PPMS) in some patients.

A total of 2.8 million people are estimated to be affected by MS worldwide (12), with increasing prevalence in the last years.

The mechanisms behind the CNS damage in MS are still incompletely clarified (13). As an immune- mediated disease, inflammation characterizes white matter lesions, and T and B cells infiltrate the zones of demyelination, axonopathy, microglial activation, and astrogliosis (14). Inflammatory reaction can resolve despite inadequate tissue repair, resulting in astroglial scars, or become organized, fostering chronic tissue damage and remodeling (15, 16). In patients with MS, axon and neuron injuries are closely related to inflammation but also to oxidative stress and mitochondrial dysfunction(17-19).

The treatment landscape of MS has expanded very rapidly in recent years, and several therapeutic options are available for RRMS. In contrast, therapeutic alternatives for SPMS and PPMS are still limited (11, 20).

Disease-modifying therapies (DMTs) available for the treatment of RRMS in the EU include drugs with different mechanisms of action, routes and frequencies of administration, effectiveness, and safety that are demonstrated to effectively reduce the inflammatory activity and relapse rate(21).

Nevertheless, the efficacy of immunomodulating or immunosuppressive agents on disability progression is limited. The lack of efficacy in stopping disability progression in patients with progressive MS is due to the different underlying pathological mechanisms beyond inflammation, including CNS-intrinsic immune and degenerative processes not sufficiently targeted by the available immunomodulatory compounds (21).

From EU approval to patient access

A new drug (and/or an old drug for new indications) requires the authorization from a regulatory authority to be marketed(22-26). Moreover, price and reimbursement procedures need to be performed by competent authorities to find an agreement between companies and payers for market access(27).

Today, in accordance with regulation 726/2004, in order to be marketed in the EU, the great majority of new, innovative medicines pass through a centralized procedure, which is compulsory for human medicines containing a new active substance to treat a lot of diseases,

including neurodegenerative and rare diseases, for advanced-therapy medicinal products (ATMPs), and medicines derived from biotechnology processes in general(28, 29).

According to this procedure, the company submits a single marketing authorization (MA) dossier to EMA, and a MA for all the European Economic Area will be granted if the drug's benefit–risk profile is positive according to the quality, non-clinical and clinical data on safety and efficacy submitted by the applicant.

The aim of the centralized procedure is to enable rapid, EU- wide authorization of medicinal products (30, 31). EMA has produced an efficient marketing authorisation system for human medicines, ensuring appropriate control and monitoring of medicinal products and adequate protection of patients.

However, marketing authorization obtained through the regulatory approval is necessary for drug launch but is not sufficient to guarantee patient access.

Indeed, despite the successful unification of the European procedures for drug approval, each country is responsible for national market access and pricing and reimbursement agreements, in line with national health needs and resources. This can result in access inequalities among European countries, due to differences not only in terms of the willingness to pay but also in the recognition of drug therapeutic value (32-35). Moreover, in recent years, MA requests are submitted at earlier stages of development, especially for high-unmet medical need and/or rare diseases, through accelerated assessment or conditional marketing approval (CMA), before conclusive data are available, thus potentially leading to reduced quality of evidence and to uncertainty in terms of therapeutic value (34, 36-38).

Acceleration of drug approval might therefore not always translate into positive and rapid patients access due to the uncertainties about the clinical benefits and the expected high impact on healthcare system, hindering patient access in some countries (32, 35).

The big challenge for policy makers is ensuring equitable access to medicines, balancing a timely patient access with the health system sustainability, in the era of precision medicines and advanced high-cost therapies (39). The selection of medicines to be reimbursed is usually made by national Health Technology Assessment (HTA) bodies, and, in some countries, by regional and hospital organisms too, based on cost-effectiveness, added value, and therapeutic need in the context of local standard of care (22, 24, 40).

HTA is a multidisciplinary process whose purpose is to systematically evaluate new healthcare interventions based on clinical (efficacy and safety), economic, ethical, and organizational aspects in support of policy decision making about reimbursement and price negotiation (39, 41).

General criteria for HTA recommendations include unmet medical needs, relative effectiveness and safety of the new drug compared to the current standard of care if any, budget impact and cost-effectiveness. However, this step may produce disparities among European patients in terms of access, due to the heterogeneity of HTA recommendations, thereafter, reflected in national reimbursement decisions and pricing agreements (e.g. coverage or not, innovative medicine designation, treatment restrictions as regard to patients' eligibility, Managed Entry Agreements application).

The heterogeneity of HTA recommendations is related to differences in assessment methodologies and health care systems organization but also to the available evidence and, above all, willingness to accept uncertainty(37).

2. Aim of the study

This study aims to provide a review of the current evidence about innovative drugs for neurological diseases approved by EMA in recent years and to perform a comparative analysis of HTA recommendations issued by EU countries for national pricing and reimbursement decisions.

3. Methods

The project has been divided into the following sub-studies:

- Sub-study 1: Access to innovative drugs with neurological indications in Europe;
- Sub-study 2: Access to innovative drugs for Multiple Sclerosis in Europe.

For the *sub-study 1*, all new therapies with neurological indications approved in Europe between January 2011 and July 2021 have been identified on the registry published on the official EMA website (42); medicines of interest have been selected based on the Anatomical Therapeutic Chemical Classification (ATC) code N (*Nervous System*, excluding drugs with exclusive psychiatric indication—ICD-10-CM Codes F01- F99) and M09 (*Other Drugs For Disorders Of The Musculo-Skeletal System*, to include drugs for neuromuscular disorders); generics and biosimilars were excluded, as well as those not representing a potential disease- modifying therapy (e.g., me-too drugs, namely, drugs structurally related to a first-in-class compound, belonging to the same therapeutic class, and used for the same therapeutic purposes).

For the *sub-study 2*, all new therapies approved for MS in Europe in the reference period have been identified on the same EMA registry (42), excluding generics and biosimilars.
Medicines centrally approved by EMA have been identified by consulting the agency's official documents and classified by type (e.g., gene therapy, small molecule, monoclonal antibody), according to the orphan drug designation, and by type of authorization issued by the EMA (full, conditional, and for exceptional circumstances). For each medicine, pivotal clinical trials were reviewed, analyzing the study design, the number of patients enrolled, the primary and secondary outcomes, and the main study results.

Then, in both sub-studies, the HTA assessments of selected drugs performed by the national authorities of EU countries (France, Germany, and Italy) have been collected from the official website.
The selection of the countries was based on the availability of the assessments for public consultation and on the clear definition of therapeutic values through comparable rating scales. Available HTA reports and official administrative act of the three EU countries have been analyzed to compare the assessments.

The level of clinical benefit (*Service Médical Rendu*—SMR) and the added therapeutic value compared to the available therapeutic alternatives (*Amélioration du Service Médical Rendu*—ASMR) was extracted from the official HTA documentation resulting from the assessment of the Transparency Committee (TC) of the French National Authority (*Haute Autorité de santé*—HAS)(43, 44). The SMR is used to decide the reimbursement status, whereas the ASMR is used, among other parameters, to negotiate drug price.
As regards Germany, we consulted the reports of the competent national bodies (*Federal Joint Committee or Gemeinsamer Bundesausschuss*, G-BA, and *Institute for Quality and Efficiency*

in Health Care, IQWIG) containing a complete HTA on the additional therapeutic benefit of the product compared to recognized standard therapies (45).

Finally, we identified the therapeutic need, the added therapeutic value, and the quality of the evidence from the Innovation Assessment Reports published by the *Italian Medicines Agency* (AIFA)(46).

A direct comparison among national opinions was possible in terms of "*added therapeutic value*," a measure included in all the available assessments (Figure 1, Figure 2).

Descriptive analyses of the sample of each sub-study were conducted, using frequency for quantitative data.

The final analysis was conducted putting together data of the 2 sub-studies, and by grouping the ratings into "*higher added value*" (H) and "*lower or no added value*" (L) as previously reported (Figure 3) (47). Since the G-BA's "*non-quantifiable*" rating is not clearly classifiable, it was not considered in the analysis. Moreover, in case of multiple and conflicting ratings, these assessments were excluded from the analysis to minimize possible biases. To investigate concordance between HTA evaluations, Cohen k-values were used (48, 49) (Figure 4).

4. Results

Sub-study 1

In the reference period, we identified 11 innovative medicines authorized in Europe (three gene therapies, two small molecules, three monoclonal antibodies, two antisense oligonucleotides, and one small interfering ribonucleic acid) for five for neurological diseases (cerebral adrenoleukodystrophy, spinal muscular atrophy, metachromatic leukodystrophy, migraine, and polyneuropathy in patients with hereditary transthyretin amyloidosis; Table 1 and Table 2):

- elivaldogene autotemcel for cerebral adrenoleukodystrophy;
- risdiplam, nusinersen, and onasemnogene abeparvovec for spinal muscular atrophy (SMA):
- atidarsagene autotemcel for Metachromatic Leukodystrophy (MLD);
- fremanezumab, galcanezumab, and erenumab, monoclonal antibodies for the prophylaxis of migraine;
- patisiran, inotersen, and tafamidis for transthyretin amyloidosis.

Eight out of 11 medicines received orphan designation, all for genetic rare diseases. Only ATMP Zolgensma® received a conditional approval, whereas Vindaqel® was the only one approved under exceptional circumstances (Table 2).

In general, for all drugs (excluding Evrysdi® and Libmeldy®), data from phase II/III trials are available, almost half randomized, double blind, placebo controlled (Table 3). The median number of patients enrolled in these studies was 118 (range 6–1,949), followed for a median of 14 months (range 0.8–96).

Except for the latest approved by the EMA (Skysona® and Libmeldy®), all drugs are reimbursed in the three EU countries.

Data analysis showed that for 10/11 medicines, at least one public HTA evaluation from at least one of the three selected countries is available, and for six of these products, HTA reports have been published by all the three countries (Table 4). At the time of the analysis, no opinion has been published for Skysona®, the last medicine approved by the EMA. The highest score (important/considerable or major/maximum added value) has been recognized only by Italy (3/11, 27%; Zolgensma®, Onpattro®, and Spinraza®) and Germany (5/11, 45%; antibody for migraine, Onpattro® and Spinraza®).

No agreements among the three EU states' assessments were identified. German assessment was in accordance with the Italian one for Onpattro® and Spinraza®, with the French one for Tegsedi®, and at least in part for Zolgesma® and the three monoclonal antibodies for migraine.

Sub-study 2

In the reference period, we identified 11 DMTs authorized in Europe (including three monoclonal antibodies) for the relapsing form of MS (RMS, n=4), for RRMS (n=6), for SPMS (n=1), and for PPMS (n = 1; Table 5):

- ponesimod;
- ofatumumab;
- ozanimod hydrochloride;
- siponimod fumaric acid;
- ocrelizumab;
- cladribine;

- peginterferon beta-1a;
- dimethyl fumarate;
- alemtuzumab;
- teriflunomide;
- fingolimod hydrochloride.

No drugs received a conditional approval, an approval under exceptional circumstances, or an orphan designation.

Data analysis showed that for all medicines, at least one public HTA evaluation from at least one of the three selected countries was available, and for 3/11 drugs, HTA reports have been published by all three countries (Table 6). The low number of reports published by Italy is related to the fact that the assessment of innovativeness is made exclusively at the request of the pharmaceutical company.

The highest score ("*important/considerable added value*") has been recognized only for one product by Italy (fingolimod for pediatric patients aged 10years and older with highly active RRMS disease despite a full and adequate course of treatment with at least one DMT or with rapidly evolving severe RRMS) and Germany (ponesimod in adults with active RMS disease). Overall, 19/32 [59,3%; 10/14 (71,4%) France; 9/15 (60%) Germany] evaluations resulted in the lowest score ("*additional benefit not proven/no clinical improvement*"), and two Italian assessments out of three (66%) reported a "*low additional benefit*".

In general, no agreements among the three EU States assessments were identified. However, the German assessment was completely in accordance with the French assessment for cladribine, dimethyl fumarate, and teriflunomide ("*additional benefit not proven/no clinical improvement*").

Concordance between HTA evaluations

A low level of inter-agency agreement was found analyzing the concordance of the decisions made by the three agencies (Table 7). Comparing the AIFA and HAS assessments of the added value, an agreement rate of 41.7% was found, with Cohen k-value equal to -0.23, corresponding to '*no agreement*' (Table 8). A similar level of agreement was found for G-BA compared with AIFA (agreement rate of 45.5%, with Cohen k-value equal to -0.06, '*no agreement*') and HAS (agreement rate of 58.3%, with Cohen k-value equal to 0, '*no agreement*').

5. Discussion

In accordance with European regulations, medicines containing new active substances to treat neurodegenerative diseases as well as autoimmune and other immune dysfunctions must be approved by the centralized procedure before they can be marketed in Europe. After EMA approval, each national HTA body is involved in decisions about market access, following the assessment of the risk–benefit profile and the comparative therapeutic value.

The therapeutic added value of new drugs versus available treatments is one of the main points of the HTA process. In line with previous observation, we found heterogeneity of the HTA opinion issued by Member States, while relying on the evaluation of the same clinical data (24, 27). This heterogeneity does not necessarily translate into different reimbursement decisions but can determine different eligibility criteria among countries resulting in variable patient access.

In this study, we selected medicines recently approved by EMA, which represent potential innovative treatment for neurological diseases, including gene therapies for rare genetic unmet medical needs.

Advanced therapies may provide significant health benefits generally with a single administration, allowing to act on the primary cause of a disease with the possibility of complete recovery and improvement of patient outcome potentially over the long term (27).

Sub-study 1

Our results showed a lack of agreement on the therapeutic value (in particular the "*added value*") of drugs recently approved for neurological indications in Europe. Despite the differences in terms of assessment, the access has been guaranteed in the three countries even if with various type of limitations.

Overall, the assessments issued by the German authorities were particularly positive, since the added therapeutic value has been classified as "*major*" or "*considerable*" in five cases out of 11 (45%), corresponding to five over nine drugs for which the evaluation has been made public (55%). Similarly, the AIFA granted the therapeutic value "*important*" for three drugs (3/11, 27%; 3/6 drugs for which the assessment has been made public to date, 50%), in particular in the case of treatments for spinal muscular atrophy (SMA) (Zolgensma® and Spinraza®) and of one treatment for hereditary transthyretin- mediated amyloidosis (hATTR) (Onpattro®). The Italian and German assessments were in accordance only for Spinraza® and Onpattro®. No drugs were judged to have a "*major*" or "*important*" added value according to HAS.

The quality of evidence supporting drug approval is undoubtedly a key point of the HTA process. Even if almost half of the studies are well-designed randomized, double-blind, placebo-controlled trials, it is noteworthy that no direct comparisons among the selected drugs

with the same indication are available. This is one of the major issues for the HTA process management, especially with medicines approved earlier and earlier, since the lack of clear and robust evidence determines uncertainty about their therapeutic value and place in therapy.

In general, a direct comparison among drugs has been considered necessary for an adequate assessment of the additional benefit in Germany. For example, the G-BA considered the additional benefit of the ATMP Zolgensma® not proven, due to the lack of direct comparison with the available alternative nusinersen, and due to the limited clinical data available so far. Therefore, the German G-BA for the first time recommended to collect real-world evidence about Zolgensma® and Spinraza® through a registry study to close this evidence gap (50). Moreover, even for the third molecule approved for SMA, risdiplam, the G-BA concluded that no meaningful results are currently available, due to the lack of direct comparation versus existing appropriate therapeutic alternatives and recommended to collect data within the routine practice in order to improve the evidence for the benefit assessment.

Similarly, the French institutions considered that the lack of a direct comparison in clinical trials did not allow to clearly define the place in therapy of medicines for SMA (51). However, in the absence of comparative data, in type 1 SMA and in pre-symptomatic patients with up to three copies of the *SMN2* gene, HAS considers Spinraza® and Zolgensma® as first-line treatments; Evrysdi® can be used as first line in symptomatic patients with type 1 SMA, but has no place in pre-symptomatic setting. The choice among these alternatives must be performed according to age, clinical status, comorbidities, different route of administration, and family choice. For example, the daily oral administration of risdiplam may be an attractive option compared to the other available modalities of administration but may not be suitable for the youngest children due to treatment compliance. In type 2 SMA, Spinraza® and Evrysdi® are the treatment to be preferred, while in type 3, they represent the only therapeutic option.

On the contrary, the Italian agency explicitly accepted the possibility of having low-quality evidence in the case of rare and ultra-rare diseases (46), including the lack of a direct comparison with available alternatives. Indeed, in the case of Zolgensma®, the experts of the Italian Commission considered "*important*" the added value compared to the antisense oligonucleotide nusinersen (52), even with the limitations of the indirect comparison. Nevertheless, its use has been limited to a restricted population, specifically only in patients weighing up to 13.5 kg with clinical diagnosis of type 1 SMA and onset of symptoms during the first 6 months of life or with genetic diagnosis of SMA type 1 and up to two copies of the *SMN2* gene. Indeed, this subpopulation has been identified as the one with the greatest benefit and eligible to be reimbursed.

As regards to the monoclonal antibodies approved for migraine, the regulatory authorities of the three countries were in accordance with a low or no clinical added value in the management of the disease. In addition, the German institution delivered an opinion of "*hint for a considerable additional benefit*" of monoclonal antibodies compared to best supportive care (BSC), such as psychotherapy or relaxation techniques, only in adults who have at least four migraine days/month and for whom other substances used for prophylaxis (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, valproic acid, or Clostridium botulinum toxin type A) have failed or have not been an option and BSC is the only alternative.

Thus, limitations for the prescription of these drugs have been introduced, different among countries despite the overall agreement about the lack of added value.

A favorable opinion for reimbursement has been issued in France only in adults with severe migraine who have at least eight migraine days per month, after failure of at least two prophylactic treatments and without cardiovascular disease.

In Italy, the prescription can be performed according to the criteria of the AIFA Registry, in particular for adults with at least 8 days of disabling migraine per month in the last 3 months and with insufficient response after at least 6 weeks of treatment or being intolerant or having clear contraindications to at least three classes of prophylaxis migraine drugs.

According to the decision of the German GBA, a prescription is possible in patients with episodic migraine if at least 5 substances from the available pharmacological groups (beta-blockers, flunarizine, topiramate, valproic acid or amitriptyline) were not effective, not tolerated, or contraindicated(53).

The variability in terms of regulatory decisions determining different patients access is probably related to the uncertainties about clinical value, the lack of long-term data and the demonstration of the superiority only versus placebo, as well as other non-clinical variables such as treatment cost.

Sub-study 2

In the sub-study 2, we selected medicines recently approved by EMA which represent potential innovative treatment for MS. Our results showed a lack of agreement among EU national authorities about the therapeutic value of drugs recently approved for different forms of MS. Overall, the opinions issued by national authorities were negative because the added therapeutic value has been classified as "*not proven*" in 19 out of 32 (59.3%) assessments, in particular in France (10/14; 71.4%), underlining that the unmet medical need for MS, especially for some forms and clinical settings, is still high, and new molecules with better efficacy and safety profile are expected.

In line with this demand, several clinical trials are ongoing, as detected on *clinicaltrials.gov* (Table 9, update February 2023). In general, progressive forms of MS represent a high unmet

need because therapies that convincingly affect progression in these patients have yet to be identified (54), due to poor characterization of the pathological processes behind progression, the lack of good animal models, and absence of validated surrogate endpoints.

Inflammation is certainly part of the process but the anti-inflammatory DMTs available for RMS can control at most only the relapse-related disability progression (55). Drugs targeting the other pathological features of progression, such as demyelination, axonal loss, mitochondrial dysfunction, and neurodegeneration, are still not available.
Neurodegeneration may be related to loss of myelin-protective functions, abnormalities of blood–brain barrier (BBB), and also to dysregulation of function of glial cells, including microglia (56). Neuroprotection can be achieved by different mechanisms of action, including the regulation of axonal function, glial function, BBB integrity, and myelin- protective function.

In this context, we found ongoing studies with Bruton's tyrosine kinase inhibitors (BTKi), which act on key pathways regulating activation, proliferation, survival, and differentiation of B cells and other immune cells and also microglia (57). The modulation of microglial activity by BTKi can be useful in MS suppressing inflammation and in supporting remyelination (58, 59). Tolebrutinib and fenebrutinib reached relevant concentration in the CNS and currently are under evaluation in phase III clinical trials (PERSEUS-NCT04458051 in PPMS, HERCULES-NCT04411641 in SPMS comparing tolebrutinib versus placebo, and FENtrepid-NCT04544449 in PPMS comparing fenobrutinib versus ocrelizumab) (56, 60, 61).

A critical point in the comparative analysis typical of the HTA process is the choice of an appropriate comparator.

A comparator in a relative effectiveness assessment (REA) is a technology or an intervention with which compare the new technology in order to establish its added therapeutic value (62,

63). In general, the appropriate comparator should be used in the routine clinical practice in the individual healthcare system according to updated European or international guidelines and be approved by regulatory authorities for the appropriate indication. However, there is no consensus across European countries on the definition of routine clinical practice; moreover, sometimes the choice of comparator is controlled by law and can take into account the cost of treatment. The definition of standard of care is facilitated only for rare diseases, in particular for the lack of therapeutic options. Our previous study about the alignment of HTA assessments for advanced therapeutic medicinal products (ATMPs), mostly developed for rare diseases, showed a low rate of agreement on the therapeutic value of ATMPs approved in Europe (27). In this case, the choice of comparator was not a critical variable due to the lack of alternatives in most of the indications or the availability of one single comparator.

In contrast, in the current study, we found some critical issues in this area. For example, France identified rituximab, an anti-CD20 that demonstrated effectiveness and safety in patients with PPMS, as appropriate comparator to evaluate the value of ocrelizumab (21, 64). In the lack of direct comparison, the role of ocrelizumab remains unknown, and France recommended performing randomized clinical trials versus rituximab to clarify the value of the drug in this population. Meanwhile, Italy and Germany did not include rituximab in the analysis and considered the therapeutic need in this setting as "*maximum*," due to the lack of approved treatment options, even if many off-label immunosuppressants are used in routine clinical practice. It is noteworthy that a non-inferiority phase III study (the DanNORMS trial-NCT04688788, promoted by a Danish hospital) directly comparing ocrelizumab and rituximab in active MS, including progressive MS, is currently ongoing, with an estimated completion date in 2028.

The lack of direct comparisons, in particular versus other second-line DMTs, probably affected also the assessment of fingolimod in the pediatric population.

The French authority recognized ponesimod as a first-line treatment option in active forms of RRMS. The drug demonstrated superiority versus teriflunomide in terms of reduction of the annual rate of relapses, without demonstration of superiority over reduction of the progression of disability (65, 66). However, because robust comparative data against other medicines are not available, according to HAS the choice among the different treatments in RRMS must be made based on to the safety profile, the modes of administration, and the preferences of the patients. Moreover, because the OPTIMUM trial included patients with SPMS with superimposed relapses (65), this population was also considered in the HTA process. However, in the absence of robust evidence, ponesimod has no place in the management of forms of SPMS in France (67).

The SMR is "*important*" only in the treatment of adults with active forms of RRMS defined by clinical or imaging parameters and "*insufficient*" in other forms of MS (67). The TC considered that ponesimod does not improve the medical service provided (ASMR V), in the same way as ozanimod, in the management of active forms of RRMS (67). In contrast, Germany made a distinction according to the disease severity defined by the expanded disability status scale (EDSS) score and recognized that ponesimod offered a "*hint of considerable added benefit*" for adults with active RMS (without prior DMT or with prior DMT whose disease is not highly active) and an EDSS ≤3.5 (39, 40).

The HTA assessments were in line for cladribine, a therapeutic option approved in patients with highly active RMS. Its efficacy has been established versus placebo in patients with predominantly not very active RRMS in terms of relapse rate and imaging criteria (68, 69). A comparison versus other available options has been made by analyzing observational data from

the CLARITY trial and an Italian multicenter database, including more than 3,000 patients who started a DMT (IFN β-1a and β-1b, glatiramer acetate, fingolimod, natalizumab, dimethyl fumarate, and teriflunomide) (70). The study showed a lower relapse rate in patients with RRMS treated with cladribine compared with matched patients treated with IFN, glatiramer acetate, or dimethyl fumarate. The effect was higher in patients with high disease activity except versus fingolimod and natalizumab (70). The data in highly active RRMS are based on post hoc analyses, and no data for highly active forms of SPMS are available. In the absence of direct comparison with current treatments for highly active RMS (natalizumab, fingolimod, alemtuzumab, and ocrelizumab) and due to still limited knowledge related to the safety profile, HAS considered the clinical benefit of cladribine as "*low*" with "*no clinical added value*" (V) in the management of patients with highly active RMS and recommended the use of the drug after failure of alternatives or for ineligible patients (71).

For the same reason, namely, the lack of relevant data provided for the benefit assessment, the German authority granted the lowest score to cladribine ("*an additional benefit is not proven*") both for patients who have not yet received DMTs or those with highly active disease despite treatment (72).

Dimethyl fumarate has not been tested in a superiority study versus an active treatment (73-75), even though a network meta-analysis showed a reduction in the relapse rate compared to interferon beta, glatiramer acetate, and teriflunomide. The HAS considered the indirect comparison not sufficient to draw any conclusions concerning the superior efficacy of dimethyl fumarate compared to these treatments for RRMS as well as the G-BA (76, 77).

As regard to DMTs specifically approved to treat progressive forms of the disease, the efficacy and safety of siponimod were investigated in a phase III study (EXPAND trial) (78), in

participants with SPMS, of whom over 50% showed an EDSS ≥6 at study entry. Siponimod slowed the disability progression and cognitive impairment more than placebo, with an advantage in terms of relapse rate, MRI lesion activity and brain volume loss, and a safety profile comparable to that of the other drugs of the same class. Nevertheless, according to HAS, the drug has no role in the therapeutic strategy for active SPMS, taking into account the available evidence and therapeutic alternatives (79). Therefore, TC considered the clinical benefit of siponimod insufficient and issued an unfavorable opinion for reimbursement.

For G-BA, the additional benefit is "*not proven*" for both patients with SPMS with active disease with relapses compared to interferon-beta 1a or interferon-beta 1b or ocrelizumab and patients with SPMS with active disease without relapses compared to best supportive care (80).

As regard to DMTs approved for PPMS, ocrelizumab is recognized as a first-line treatment for patients with early-stage PPMS in terms of duration of disease and degree of disability associated with a demonstration of inflammatory activity (81-83).

In contrast, the efficacy and safety in the severe forms of PPMS have not been established, and the use should not be considered in patients with advanced disabilities (84, 85).

Based on randomized clinical trials, the clinical benefit of ocrelizumab has been considered "*moderate*" by HAS in early- stage PPMS in terms of disease duration and degree of disability but with "*no clinical added value*" even in the early-stage PPMS (64). France included as rituximab as an appropriate comparator, another anti-CD20 used in PPMS even if off-label. Thus, in the lack of comparative studies versus rituximab, the role of ocrelizumab is considered unknown, and the TC recommended performing well- designed clinical trials to clarify the role of the drug in the therapeutic strategy of PPMS compared to a well-known drug, such as rituximab, that has proven to be effective and safe in this population (21, 64).

AIFA assigned an additional benefit of "*low*" (IV) for adults with PPMS at an early stage in terms of duration of illness and level of disability, with typical radiological characteristics of inflammatory activity (86). Unlike France, Italy considered the therapeutic need "*maximum*" due to the lack of approved treatment options. Indeed, even if the agency recognized that many off-label immunosuppressive drugs are used in clinical practice by physicians, including rituximab, no drugs are effectively approved. Then, although the magnitude of the effect on the primary outcome, the confirmed disability progression (CDP) for 12 weeks, is limited to a modest reduction compared to placebo (HR 0.76 [95% CI: 0.59, 0.98], p = 0.0321) (84), the drug induced statistically significant effects in a population without authorized therapeutic alternative, but the added therapeutic benefit is considered small. Thus, AIFA restricted the use of ocrelizumab for patients according to the main inclusion criteria of the ORATORIO pivotal trial(84, 87):

- 18–55 years;
- EDSS at screening from 3 to 6.5 points;
- Disease duration from onset of MS symptoms less than 15 years if EDSS greater than 5 and less than 10 years if EDSS greater than or equal to 5;
- T1 lesions G+ and/or active T2 lesions, new or expanding.

Finally, the G-BA identified best supportive care as appropriate comparative therapy and gave indication of a low additional benefit (88).

Lastly, we found disagreement about the added therapeutic value of fingolimod in pediatric patients.

Pediatric multiple sclerosis has become relatively frequent and is characterized by a high relapse rate, rapid accumulation of CNS damage, and negative long-term outcome, with a high level of physical and cognitive disability at a young age (89).

The standard first-line DMTs for pediatric MS are interferons beta-1a/1b and glatiramer acetate, based on data collected from single- or multicenter open-label observational studies that showed their effect on clinical and MRI parameters of inflammation (90-92). However, a high rate of treatment failure in response to first-line therapies has been reported, ranging from 25% to 64% (93), resulting in the need to switch to more aggressive DMTs.

In Italy, in adolescents aged between 12 and 18 years with rapid-changing RRMS (defined by two or more disabling relapses in 1 year and with one or more gadolinium-enhancing MRI lesions or a significant increase in the load of T2-lesions compared to a recent MRI), natalizumab may be used according to Law 648/96 as second-line treatment (94). Other possible alternatives (methotrexate, azathioprine, cyclophosphamide, rituximab, alemtuzumab, and ocrelizumab) are all used off- label, and the efficacy and safety profile were not specifically studied in children and adolescents through randomized controlled clinical trials (95). In this scenario, AIFA considered the therapeutic need of the pediatric population to be important.

The effectiveness and safety of fingolimod in pediatric MS were evaluated in the PARADIGM study versus IFN beta-1a, but no direct comparison has been performed versus other DMTs currently used as second-line therapies.

The drug demonstrated a significant reduction in the annualized rate of relapse compared to IFN beta-1a (RR 0.181; 95% CI 0.108–0.303; $p < 0.001$) and in other secondary endpoints (96), including an improvement of the quality of life. Thus, in the presence of data obtained through randomized controlled clinical trials, the lack of other approved options, and the advantage of once-a-day oral administration, AIFA considered the added therapeutic value "*important*".

According to HAS, the choice of first-line treatment for pediatric patients with MS should be made according to the safety profile, the route of administration, and the patient preference (97). In the case of highly active disease despite therapy, a more active treatment is recommended.

Fingolimod is the first product to obtain a marketing authorization in this setting for a pediatric population and to be recognized as first-line or second-line treatment for highly active forms of RRMS in pediatric patients over the age of 10 years.

Given the absence of data on the disability progression, the quality of life, and the uncertainties about the medium- and long- term tolerance, in particular related to the cardiovascular toxicity, the TC considers that fingolimod brings "minor improvement" of the medical service rendered (ASMR IV) for highly active forms MS in pediatric patients aged 10–18 years.

G-BA distinguished several situations among the general pediatric approved indication (98):

1. Children and adolescents ≥10 and <18 years with highly active RRMS despite treatment with at least one DMT for whom escalation of therapy is indicated;

2. Children and adolescents ≥10 and <18 years with highly active RRMS despite treatment with at least one DMT, for whom a change within the basic therapeutics is indicated;

3. Children and adolescents ≥10 and <18years with rapidly evolving severe RRMS defined by two or more disabling relapses in 1year and with one or more gadolinium- enhancing lesions on MRI or a significant increase in T2 lesion load as compared to a recent exam who have not yet received DMTs;

4. Children and adolescents ≥10 and <18 years with rapidly evolving severe RRMS defined by two or more disabling relapses in 1year and with one or more gadolinium- enhancing lesions on MRI or a significant increase in T2 lesion load as compared to a recent exam despite DMT.

The German authority issued an opinion for each clinical situations; in particular, "*an additional benefit not proven*" for 1 and 4 and "*hint for a non-quantifiable additional benefit*" for 2 and 3.

6. Conclusions

The HTA process is a critical point for the assessment of drug value and patient access. Universally recognized clinical criteria for HTA recommendations include unmet medical needs, relative effectiveness, and safety of the new product compared to the available standard of care(22). The therapeutic added value versus available treatments should be one of the key determinants of patients access to innovative medicines.

Given the importance of new medicines especially for rare and severe unmet needs, it is crucial to understand and act on the causes of inconsistency among the HTA assessments, to ensure rapid and uniform access to innovation for patients who can benefit.

In this context, the proposal for a Regulation of the European Parliament and of the Council on health technology assessment amending the Directive 2011/24/EU drafted in 2018 and modified in 2021 aims to ensure a permanent cooperation on HTA at the EU level, sharing joint clinical assessments, joint scientific consultations, horizon scanning, and voluntary cooperation in non-clinical areas. The adoption of this Regulation on HTA would be useful to harmonize HTA methodologies, hopefully leading to reduced disparities of medicine assessment among European countries.

It is hoped that the adoption of the new regulation on HTA with the aim to harmonize HTA methodologies in Europe will reduce disparities of assessment of medicines among European countries(41).

Unfortunately, the joint clinical assessment reports do not include the overall benefit, nor the added clinical value, and Member States are still solely responsible for national HTA processes for the definition of the therapeutic added value. Moreover, the Regulation does not guarantee

overcoming this critical issue as regard to the selection of comparator in order to align the HTA approaches (99).

Therefore, the Regulation will probably represent a missed opportunity to unify the HTA in EU and ensure rapid and uniform access to innovation for patients who can benefit.

Figure 1. Grading of added therapeutic value according to national opinions. A direct comparison among national opinions was possible in terms of "added therapeutic value," a measure included in all the available assessments. For Germany is possible to demonstrate '*less benefit'* compared to the standard of care. This rating has been included into '*additional benefit not proved'*.

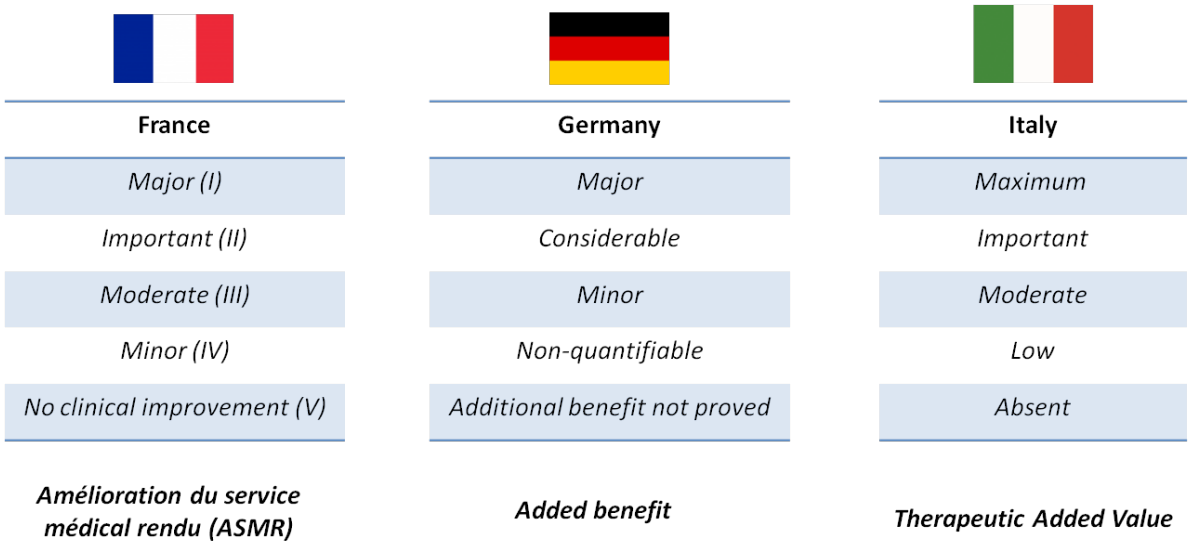

Figure 2. Results of comparison among national opinions in terms of "*added therapeutic value*".

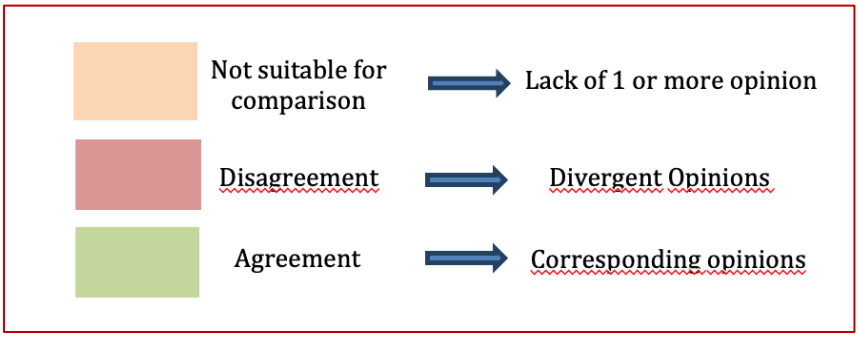

Figure 3. Grouping the ratings into "*higher added value*" (H) and "*lower or no added value*" (L) as previously reported. The G-BA's "non-quantifiable" rating was not considered in the analysis.

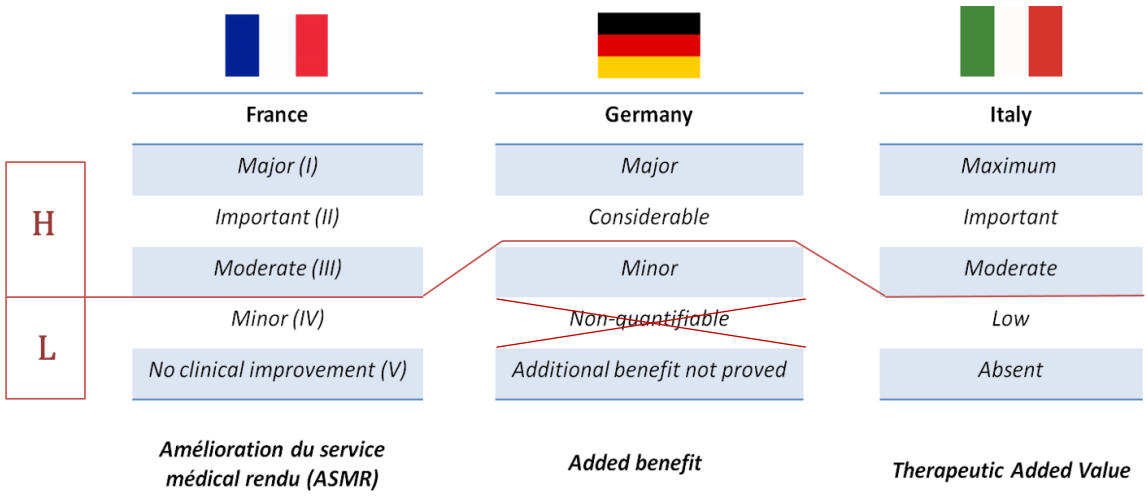

Figure 4. Interpretation of Cohen's kappa

VALUE OF K	STRENGTH OF AGREEMENT
≤ 0	Poor/none
0.01 - 0.20	Slight
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Substantial
0.81 - 1.00	Almost perfect

Table 1. Drugs with neurological indication approved in Europe in the reference period (2011-2021)

N	Medicine name	Active substance	Therapeutic area	ATC code	Marketing authorisation date
1	***Skysona®***	***elivaldogene autotemcel***	***Adrenoleukodystrophy***	***N07***	***16/07/2021***
2	Ontozry®	cenobamate	Epilepsy	N03AX	26/03/2021
3	Byfavo®	remimazolam	Conscious Sedation	N05CD	26/03/2021
4	***Evrysdi®***	***Risdiplam***	***Muscular Atrophy, Spinal***	***M09AX10***	***26/03/2021***
5	Fintepla®	Fenfluramine hydrochloride	Epilepsies, Myoclonic	N03	18/12/2020
6	***Libmeldy®***	***atidarsagene autotemcel***	***Leukodystrophy, Metachromatic***	***N07***	***17/12/2020***
7	Exparel liposomal®	bupivacaine	Acute Pain	N01BB01	16/11/2020
8	Zynrelef®	bupivacaine, meloxicam	Pain, Postoperative	N01B	24/09/2020
9	Gencebok®	Caffeine citrate	Apnea	N06BC01	19/08/2020
10	***Zolgensma®***	***onasemnogene abeparvovec***	***Muscular Atrophy, Spinal***	***M09AX09***	***18/05/2020***
11	Sunosi®	solriamfetol hydrochloride	Narcolepsy; Sleep Apnea, Obstructive	N06BA14	16/01/2020
12	Inbrija®	levodopa	Parkinson Disease	N04BA01	19/09/2019
13	Epidyolex®	Cannabidiol	Lennox Gastaut Syndrome; Epilepsies, Myoclonic	N03AX	19/09/2019
14	Lacosamide UCB®	lacosamide	Epilepsies, Partial	N03AX18	26/08/2019
15	Sixmo®	Buprenorphine hydrochloride	Opioid-Related Disorders	N07BC01	19/06/2019
16	***Ajovy®***	***fremanezumab***	***Migraine Disorders***	***N02***	***28/03/2019***
17	Buvidal®	buprenorphine	Opioid-Related Disorders	N07BC01	20/11/2018

18	***Emgality®***	***Galcanezumab***	***Migraine Disorders***	***N02***	***14/11/2018***
19	Kigabeq®	vigabatrin	Spasms, Infantile; Epilepsies, Partial	N03AG04	20/09/2018
20	Slenyto®	melatonin	Sleep Initiation and Maintenance Disorders; Autistic Disorder	N05CH01	20/09/2018
21	***Onpattro®***	***patisiran sodium***	***Amyloidosis, Familial***	***N07***	***27/08/2018***
22	***Aimovig®***	***erenumab***	***Migraine Disorders***	***N02CX07***	***26/07/2018***
23	***Tegsedi®***	***inotersen sodium***	***Amyloidosis***	***N07***	***6/07/2018***
24	Dzuveo®	sufentanil citrate	Pain	N01AH03	25/06/2018
25	Zubsolv®	Buprenorphine hydrochloride, Naloxone hydrochloride dihydrate	Opioid-Related Disorders	N07BC51	10/11/2017
26	***Spinraza®***	***nusinersen sodium***	***Muscular Atrophy, Spinal***	***M09***	***30/05/2017***
27	Ongentys®	opicapone	Parkinson Disease	N04	24/06/2016
28	Wakix®	pitolisant	Narcolepsy	N07XX11	31/03/2016
29	Briviact (in Italy: Nubriveo)®	Brivaracetam	Epilepsy	N03AX23	13/01/2016
30	Zalviso®	sufentanil	Pain, Postoperative	N01AH03	18/09/2015
31	Hetlioz®	tasimelteon	Sleep Disorders, Circadian Rhythm	N05CH	3/07/2015
32	Xadago®	safinamide methanesulfonate	Parkinson Disease	N04B	23/02/2015
33	Rasagiline ratiopharm®	rasagiline	Parkinson Disease	N04BD02	12/01/2015
34	Duloxetine Lilly®	duloxetine	Neuralgia; Diabetic Neuropathies; Depressive Disorder, Major	N06AX21	8/12/2014
35	Pregabalin Pfizer®	pregabalin	Anxiety Disorders; Epilepsy	N03AX16	10/04/2014

36	Corbilta® (previously Levodopa/Carbidopa/Entacapone Sandoz)	levodopa, carbidopa, entacapone	Parkinson Disease	N04BA03	11/11/2013
37	Selincro®	Nalmefene hydrochloride dihydrate	Alcohol-Related Disorders	N07BB05	24/02/2013
38	Memantine Merz®	memantine hydrochloride	Alzheimer Disease	N06DX01	22/11/2012
39	Fycompa®	perampanel	Epilepsies, Partial	N03AX22	23/07/2012
40	***Vyndaqel®***	***tafamidis***	***Amyloidosis***	***N07XX08***	***16/11/2011***
41	Dexdor®	dexmedetomidine hydrochloride	Conscious Sedation	N05CM18	15/09/2011
42	Buccolam®	midazolam	Epilepsy	N05CD08	4/09/2011
43	Levodopa/Carbidopa/Entacapone Orion®	levodopa, carbidopa, entacapone	Parkinson Disease	N04BA03	23/08/2011
44	Entacapone Orion®	entacapone	Parkinson Disease	N04BX02	18/08/2011
45	Fampyra®	Fampridine	Multiple Sclerosis	N07XX07	20/07/2011
46	Leganto®	rotigotine	Restless Legs Syndrome; Parkinson Disease	N04BC09	16/06/2011

Table 2: Innovative drugs with neurological indication approved in Europe in the reference period (2011-2021) and approval details.

N	Product	Active substance	ATC code	Type	Therapeutic indication	Conditional approval	Exceptional circumstances	Accelerated assessment	Orphan medicine	MA date
1	***Skysona®***	elivaldogene autotemcel	N07	Gene replacement therapy	Treatment of early cerebral adrenoleukodystrophy in patients less than 18 years of age, with an *ABCD1* genetic mutation, and for whom a HLA matched sibling HSC donor is not available.	No	No	No	Yes	16/07/21
2	***Evrysdi®***	risdiplam	M09AX10	Small molecule	Treatment of 5q SMA in patients 2 months of age and older, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with 1 to 4 SMN2 copies	No	No	Yes	Yes	26/03/21
3	***Libmeldy®***	atidarsagene autotemcel	N07	Gene replacement therapy	Treatment of MLD characterized by biallelic mutations in the ARSA gene leading to a reduction of the ARSA enzymatic activity: - in children with late infantile or early juvenile forms, without clinical manifestations of the disease, - in children with the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline	No	No	Yes	Yes	17/12/20
4	***Zolgensma®***	onasemnogene abeparvovec	M09AX09	Gene replacement therapy	Treatment of patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene.	Yes	No	No	Yes	18/05/20
5	***Ajovy®***	fremanezumab	N02	Monoclonal antibody	Prophylaxis of migraine in adults who have at least 4 migraine days per month	No	No	No	No	28/03/19
6	***Emgality®***	galcanezumab	N02	Monoclonal antibody	Prophylaxis of migraine in adults who have at least 4 migraine days per month	No	No	No	No	14/11/18
7	***Onpattro®***	patisiran	N07	siRNA	Treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy	No	No	Yes	Yes	27/08/18
8	***Aimovig®***	erenumab	N02CX07	Monoclonal antibody	Prophylaxis of migraine in adults who have at least 4 migraine days per month	No	No	No	No	26/07/18
9	***Tegsedi®***	inotersen	N07	ASO	Treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis	No	No	Yes	Yes	06/07/18
10	***Spinraza®***	nusinersen	M09	ASO	Treatment of 5q SMA	No	No	Yes	Yes	30/05/17
11	***Vyndaqel®***	tafamidis	N07XX08	Small molecule	Treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment	No	Yes	No	Yes	16/11/11

Antisense oligonucleotide = ASO; arylsulfatase A = ARSA; haematopoietic stem cell = HSC; hereditary transthyretin-mediated amyloidosis = hATTR amyloidosis; human leukocyte antigen = HLA; marketing authorization = MA; metachromatic leukodystrophy = MLD; small interfering ribonucleic acid = siRNA; spinal muscular atrophy = SMA

Accelerated assessment is granted by the European Medicines Agency (EMA) for product of major interest for public health and therapeutic innovation. This procedure allows to reduce the timeframe for review a marketing-authorisation application (from up to 210 days to 150 days).

A conditional marketing authorisation may be granted with less comprehensive clinical data than normally required for medicines that address unmet medical needs, where the benefit outweighs the risk inherent in the fact that additional data are still needed. For this procedure, marketing approval is granted provided that the sponsor will provide missing data within an agreed timeframe.

EMA may also grant a marketing authorisation under exceptional circumstances when comprehensive data cannot be obtained even after authorization, because the condition is rare, or collection of full data is not possible or unethical.

Table 3. Data from clinical trials for innovative drugs approved in Europe in the reference period.

Product	Clinical trial	Study design	N. of patients	Primary Outcome	Follow-up	Results
***Skysona*®**(100)	ALD-102	Open-label, single-arm prospective phase 2/3 study	32	Month 24 MFD-free survival (Major Functional Disabilities) = loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, or complete loss of voluntary movement.	24-months	Twenty-seven out of 30 patients (90%, 95% CI: 73.5, 97.9) achieved Month 24 MFD-free survival. Most patients (26/27, 96.3%) remained alive and maintained their MFD-free status through their last follow-up on study, including 14 patients with 5 or more years of follow-up
	ALD-104 (ongoing)	Open-label, single-arm phase 3 study	19 (35 planned)	Month 24 MFD-free survival (Major Functional Disabilities) = loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, or complete loss of voluntary movement.	24-months	No subjects have completed the month-24 Visit
***Evrysdi*®**(101)	BP39056 (FIREFISH)	Open-label, 2-part study (Part 1 was the dose-finding part of the study; Part 2 the confirmatory study)	21 (part 1) 41 (part 2)	Proportion of patients with the ability to sit without support for at least 5 seconds (Sitting without support is never achieved in untreated patients with Type 1 SMA)	24 months	After 12 months of treatment with risdiplam, 29.3% of patients in Part 2 were sitting without support. This proportion is significantly higher than the pre-defined performance criterion of 5% based on natural history data ($p<0.0001$).
	BP39055 (SUNFISH)	Part 1 was the exploratory dose-finding portion and Part 2 was the randomized, double-blind, placebo-controlled confirmatory portion	51 (part 1) 180 (part 2)	Change from baseline score at Month 12 on the Motor Function Measure-32 (MFM32)	12 months	The primary analysis for SUNFISH Part 2 showed a clinically meaningful and statistically significant difference between patients treated with Evrysdi and placebo. Change from baseline in MFM32 total score showed an improvement in the risdiplam group [change from baseline, LS means: 1.36 (95% CI: 0.61-2.11)], compared to a worsening observed in the PBO group [-0.19 (95% CI-1.22, 0.84)].
***Libmeldy*®**(102)	Study 201222	Open-label, non-randomized, single-arm, prospective, comparative (non-concurrent control), Phase I/II study	20	Co-primary endpoints: • Gross Motor Function Measure (GMFM): An improvement of >10% of the total GMFM score in treated patients, when compared to the GMFM scores in the age-matched, untreated historical control, evaluated at Year 2 after treatment, and • ARSA activity: A significant (≥2 SD) increase in residual ARSA activity as compared to pretreatment values,	4.0 years (range 0.6 - 7.5 years)	Early-onset MLD patients treated before the onset of overt symptoms showed normal motor development, stabilisation, or delay in the rate of progression of motor dysfunction as measured by GMFM total score. A statistically significant increase in ARSA activity in PBMCs was also observed at Year 2 post-treatment compared to pre-treatment baseline in both pre-symptomatic patients (20.0-fold increase; $p<0.001$) and early symptomatic patients (4.2-fold increase; $p=0.004$)

				measured in peripheral blood mononuclear cells (PBMC) at Year 2 after treatment		
	Study 205756	Open-label, single-arm study	6	• Gross Motor Function Measure (GMFM) • ARSA activity	0.87 year (range: 0.0 to 1.47 years)	Preliminary data on GMFM total score showed that gross motor function for all 4 subjects was within the range of gross motor function observed in a healthy cohort of children from of similar chronological age. ARSA activity levels were detectable and within the normal range at Month 3 in all three subjects with available data.
Zolgensma®(103)	CL-303	Phase III, open label, single arm	22	Event-free survival (event = death or permanent ventilation)	18 months	90.9% (95% CI: 79.7%, 100.0%) event-free survival at 14 months
	CL-101	Phase I, open-label, dose-escalation	15	1. Requirement of respiratory assistance per day continuously for ≥2 weeks in the absence of an acute reversible illness, or 2. death.	24 months	All treated patients had statistically significant improved survival without permanent ventilation
	CL-302 (ongoing)	Phase III, open-label, single-arm,	33	Achievement of developmental milestone	18 months	The primary efficacy endpoint “independent sitting for at least 10 seconds at any time up to 18 months of age was met by 6 of the 32 patients (18.8%)
	CL-304 (ongoing)	Phase III, open-label, single-arm	At least 44 (as of the 31 DEC 2019 data cut-off, 29 patients were enrolled)	Achievement of developmental milestone	As of the efficacy data cut-off date of 31 DEC 2019, patients in cohort 1 had been in the study for an average of 10.5 months (range: 5.1-18 months). Patients in cohort 2 had been in the study for an average of 8.74 months (range: 2-13.9 months).	All patients in the study were alive and free of permanent ventilation at the data cut-off.

Ajovy®*(104)*	Study 1(TEV-48125-30050)	Randomised, double-blind, placebocontrolled phase III studies	875	Mean change from baseline in the monthly average number of migraine days	12-weeks	Both monthly and quarterly dosing regimens of fremanezumab demonstrated statistically significant and clinically meaningful improvement from baseline compared to placebo
	Study 2 (TEV-48125-30049)	Randomised, double-blind, placebo-controlled phase III studies	1,130	Mean change from baseline in the monthly average number of headache days of at least moderate severity	12-weeks	Both monthly and quarterly dosing regimens of fremanezumab demonstrated statistically significant and clinically meaningful improvement from baseline compared to placebo
	Study 30051	Long-term study	Patients who completed the pivotal efficacy studies+ approximately 300	Safety	15 months	For all episodic and chronic migraine patients, efficacy was sustained for up to 12 additional months. No safety signal was observed during the 15-month combined treatment period.
Emgality®(105)	EVOLVE-1	Phase 3, randomized, placebo-controlled, double-blind studies	843	overall mean change from baseline in number of monthly Migraine Headache Days (MHDs)	6 months	Both galcanezumab 120 mg and 240 mg treatment groups demonstrated statistically significant and clinically meaningful improvements from baseline compared to placebo on mean change in MHD
	EVOLVE-2	Phase 3, randomized, placebo-controlled, double-blind studies	896	overall mean change from baseline in number of monthly Migraine Headache Days (MHDs)	6 months	Both galcanezumab 120 mg and 240 mg treatment groups demonstrated statistically significant and clinically meaningful improvements from baseline compared to placebo on mean change in MHD
	REGAIN	Phase 3, randomized, placeboc-ontrolled, double-blind studies	1,085	overall mean change from baseline in number of monthly Migraine Headache Days (MHDs)	12 months	Both galcanezumab 120 mg and 240 mg treatment groups demonstrated statistically significant and clinically meaningful improvements from baseline compared to placebo on mean change in MHD
	Study CGAJ	Phase 3, long-term, randomized study	270	The overall mean reduction from baseline in the number of monthly MHDs	12 months	The overall mean reduction from baseline in the number of monthly MHDs averaged over the treatment phase was 5.6 days for the 120 mg dose group and 6.5 days for the 240 mg dose group.
Onpattro®(106)	APOLLO (ALN-TTR02-004)	Phase 3, randomised, double-blind, placebo-controlled study	225	change from baseline in modified Neuropathy Impairment Score +7 (mNIS+7).	18 months	A statistically significant benefit in mNIS+7 with Onpattro relative to placebo was observed at 18 months. Benefits relative to placebo were also observed across all mNIS+7 components.
	Study 003	Multicenter, Phase 2, open-label, extension study	27	Mean change from baseline in the mNIS+7	Up to 2 years	The mean change from baseline in the mNIS+7 at 24 months was -6.95 (2.03) points

	Study 006	Multicentre, multinational, open-label extension study	184	Week 52 mNIS+7	52 Weeks	Week 52 mNIS+7 efficacy data were available for 64 patients
***Aimovig*®**(107)	Study 20120295	Phase 2 randomised, multicentre, placebo-controlled, double-blind study	667	Change in mean monthly migraine days (MMD)	12-weeks 52-week open-label extension	Reduction in mean monthly migraine days from placebo was observed in a monthly analysis from Month 1 and in a follow-up weekly analysis an onset of erenumab effect was seen from the first week of administration. Efficacy was sustained for up to 1 year in the open-label extension.
	Study 20120296	Phase 3, randomised, multicentre, placebo-controlled, double-blind study	955	Change from baseline in mean monthly migraine days	24-weeks 52-week active re-randomisation part	Patients treated with erenumab had a clinically relevant and statistically significant reduction from baseline in the frequency of migraine days from Months 4 to 6 compared to patients receiving placebo. Efficacy was sustained up to 1 year in the active re-randomisation part
	Long-term follow-up study	Open-label treatment phase	383	/	5 years	Of the 383 patients, 168 (43.9%) discontinued with the most common reasons being patient request (84 patients; 21.9%), adverse events (19 patients; 5.0%), lost to follow-up (14 patients; 3.7%) and lack of efficacy (12 patients; 3.1%). The results indicate that efficacy was sustained for up to 5 years in the open-label treatment phase of the study
***Tegsedi*®**(108)	Pivotal Study: CS2 (ISIS 420915-CS2)	Phase 2/3 multicentre, double-blind, placebo-controlled trial	172	Change from baseline in the modified Neuropathy Impairment Score + 7 tests (mNIS+7) composite score and in the Norfolk Quality of Life – Diabetic Neuropathy (QoL-DN) questionnaire total score	Week 66	The changes from baseline in both primary endpoints (mNIS+7 and Norfolk QoL-DN) demonstrated statistically significant benefit in favour of inotersen treatment at Week 66. The differences were large with -19.73 (95% CI: -26.43, -13.03; p=0.00000004) for the mNIS+7 Score (maximum score 346) and -11.68 (95% CI: -18.29, -5.06; p<0.0006) for the Norfolk QoL-DN (maximum score 156)
	CS3 (ISIS 420915-CS3)	Phase 3 Open-Label Extension Study	114	Safety	5 years	The results obtained with the open label extension study corroborated the results obtained with CS2 study and efficacy was maintained throughout the whole duration of the study
***Spinraza*®**(109)	Study CS3B (ENDEAR)	Phase 3, randomized, double-blind, sham-procedure controlled study	121	Proportion of motor milestone responders Time to death or permanent ventilation (≥ 16 hours ventilation/day continuously for > 21 days in the absence of an acute reversible event or tracheostomy)	14 months	There were 21 (41%) subjects in the nusinersen group with a motor mile response at their last possible visit (day 183, 302 or 394 depending on the date they were treated), compared to 0/27 patients on control. This was highly statistically significant (p<0.0001). In the final analysis, this percentage improved; 51% of subjects in the nusinersen group achieved a response compared to 0% in the control group (p<0.0001)

						There were 27/80 (34%) patients who died or required permanent ventilation on nusinersen compared to 20/41 (49%) on control. There were 12/80 (15%) deaths on nusinersen, compared to 13 (32%) on control. Overall, there was a 47% reduction in the risk of death or permanent ventilation compared to control: the risk of death was 62.8% lower in nusinersen-treated subjects than in those who received the sham procedure; the risk of permanent ventilation was 34% lower in nusinersen-treated subjects.
	Study CS11 (SHINE)	Phase 3, open label extension study	89+125	Number of participants experiencing Adverse events (AEs) and/or Serious Adverse Events (SAEs)	8 years	/
	Study CS3A	Open-label Phase 2 study	20	Proportion of patients who improved in one or more categories in motor milestones	2 years	Twelve out of 20 patients (60%) in the study met the primary endpoint with improvement in mean motor milestone achievement over time
	Study CS4 (CHERISH)	Phase 3, randomised, double-blind, sham-procedure controlled study	126	Change from baseline in Hammersmith Functional Motor Scale – Expanded (HFMSE) score	15 months	Subjects treated intrathecally with nusinersen achieved sustained and clinically meaningful benefits compared with a control group of subjects who received a sham procedure. A statistically significant change from baseline in HFMSE score was observed in the nusinersen group (4.0 (95% CI: 2.9-5.1)) compared to the sham control group (-1.9 (95% CI: -3.8-0.0)) (p=0.0000002)
	Study CS7 (EMBRACE)	Phase 2, randomized, double-blind, sham-procedure study followed by a long-term open label extension phase (Part 2)	21	Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)	day 422	EMBRACE was terminated early due to positive results from other nusinersen trials, and patients were moved into the extension phase of EMBRACE (ongoing). Due to early termination, only six patients (43%) in the nusinersen group completed Part 1 (assessment visit day 422) while none of the control group reached the 422-assessment visit day.
	Study CS5 (NURTURE)	Phase 2, open-label, multicentre, single-arm study	17	Time to death or respiratory intervention (defined as invasive or non-invasive ventilation for ≥6 hours/day continuously for ≥7 consecutive days OR tracheostomy)	Efficacy data were available for 13 subjects at Day 64, 10 subjects at Day 183, and 5 subjects at Day 302.	No subjects died or had respiratory intervention (defined as either invasive or non-invasive ventilation for ≥6 hours/day continuously for ≥7 consecutive days or tracheostomy).
***Vyndaqel*®**(110)	Study Fx-005	Phase II/III, multicentre, randomised, double-	128	Neuropathy Impairment Score of the Lower Limb (NIS-LL – a physician assessment of the neurologic exam of the	18 months	More tafamidis meglumine-treated patients were NIS-LL Responders (change of less than 2 points on NIS-LL) Outcomes for the pre-specified analyses. At the primary

		blind, placebo-controlled study.		lower limbs) and the Norfolk Quality of Life - Diabetic Neuropathy (Norfolk QOL-DN – a patient reported outcome, total quality of life score [TQOL]).		timepoint (Month 18), 45.3% of patients in the tafamidis group had an increase in the NIS-LL of <2, compared to 29.5% patients in the placebo group, but the differences between groups were not statistically significant (p=0.068).
	Fx-006	Open-label extension study	71	Long-term safety and tolerability	12 months	The rate of change in the NIS-LL was similar to that observed in those patients randomised and treated with tafamidis in the previous double blind 18 months period. The placebo-treated patients in the ITT population had progressively worse TQOL scores than tafamidis-treated patients, but the differences between groups were not statistically significant (7.2 versus 2.0, p-value=0.1).
	Fx1A-201	Open-label, multicentre, single-arm study	21	Transthyretin stabilisation at steady state, as measured by a validated immunoturbidimetric assay, in patients with non V30M TTR amyloidosis.	12 months	Treatment with tafamidis over 12 months in a mixed genotype population of patients with ATTR-PN resulted in TTR stabilization in 95% of patients by week 6 and 100% of patients at months 6 and 12, supporting persistence of TTR stabilization with chronic dosing of tafamidis.

Table 4. Agreement among opinions about therapeutic added value issued by Member States

Product	*Italy*	*France*	*Germany*
Skysona®	*/*	*/*	*/*
Evrysdi®	*/*	*III^(111)*	*Hint of a non-quantifiable added benefit^^ (IV)/ Additional benefit not proven (V)^^^(112)*
Libmeldy®	*/*	*III*(113)*	*/*
Zolgensma®	*Important (II)(114)*	*III**/V***(115)*	*Additional benefit not proven (V)(116)*
Ajovy ®	*Low (IV)(117)*	*V(118)*	*Additional benefit not proven° (V)/ Hint for a considerable additional benefit°° (II)(119)*
Emgality ®	*Low (IV)(120)*	*V(121)*	*Additional benefit not proven° (V)/ Hint for a considerable additional benefit°° (II)(122)*
Onpattro®	*Important (II)(123)*	*III(124)*	*Considerable additional benefit (II)(125)*
Aimovig®	*Low (IV)(126)*	*V(127)*	*Additional benefit not proven° (V)/ Hint for a considerable additional benefit°° (II)(128)*
Tegsedi ®	*/*	*IV(129)*	*Non-quantifiable (IV)(130)*
Spinraza®	*Important (II)(52)*	*III/V[§](131)*	*Major additional benefit[§§] (I)/ Hint for a considerable additional benefit[#a] (II)(132)*
Vyndaqel ®	*/*	*IV(133)*	*Additional benefit not proven[b] (V)(134)*

*^SMA 2, like nusinersen, and SMA 3 patients, not moving; ^^infantile form (SMA 1) versus nusinersen; ^^^SMA 2 and 3 and presyntomatic; *Asymptomatic children without clinical manifestation; **SMA 1, pre-symptomatic with a genetic diagnosis of SMA (bi-allelic mutation of the SMN1 gene) and 1 to 2 copies of the SMN2 gene; ***SMA 2,pre-symptomatic patients with a genetic diagnosis of SMA (bi-allelic mutation of the SMN1 gene) and 3 copies of the SMN2 gene; °Untreated adult patients and patients who have responded inadequately to at least one prophylactic medication, or are unable to tolerate or are unsuitable for at least one prophylactic medication or patients who are not responsive to or are unsuitable to or do not tolerate the medicinal therapies/active ingredient classes metoprolol, propranolol, flunarizine, topiramate, and amitriptyline; °°patients who are not responsive to or unsuitable for or do not tolerate the medicinal therapies/active ingredient metoprolol, propranolol, flunarizine, topiramate, amitriptyline, valproic acid or Clostridium botulinum toxin type A; [a]assessment updated on May 2021; [§§]5q-SMA 1 versus BSC; #pre-symptomatic children 5q-SMA versus BSC; [b]assessment updated on May 2021 comparing tafamidis to patisiran; [§]III for SMA 1 and 2 and pre-symptomatic infants and children with 5q SMA with 2 to 3 copies of the SMN2 gene; V for SMA 3*

Table 5. Drugs approved in Europe in the reference period for multiple sclerosis and approval details.

Active substance	ATC code	Type	Therapeutic Indication	Additional monitoring	Conditional approval	Exceptional circumstances	Accelerated assessment	Orphan medicine	MA date
ponesimod	L04	SM	Adult with RMS with active disease defined by clinical or imaging features.	yes	no	no	no	no	19/05/2021
ofatumumab	L04	mAb	Adults with RMS with active disease defined by clinical or imaging features	yes	no	no	no	no	26/03/2021
ozanimod hydrochloride	L04	SM	Adults with RRMS with active disease as defined by clinical or imaging features.	yes	no	no	no	no	20/05/2020
siponimod fumaric acid	L04	SM	Adults with SPMS with active disease evidenced by relapses or imaging features of inflammatory activity.	yes	no	no	no	no	13/01/2020
ocrelizumab	L04	mAb	Adults with RMS with active disease defined by clinical or imaging features. Adults with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.	yes	no	no	no	no	8/01/2018
cladribine	L04	SM	Adults with highly active RMS as defined by clinical or imaging features.	no	no	no	no	no	22/08/2017
peginterferon beta-1a	L03	Biologic	Adults with RRMS.	no	no	no	no	no	17/07/2014
dimethyl fumarate	L04	SM	Adults with RRMS.	no	no	no	no	no	30/01/2014
alemtuzumab	L04	mAb	Adults with RRMS with active disease defined by clinical or imaging features.	yes	no	no	no	no	12/09/2013
teriflunomide	L04	SM	Adult and pediatric patients aged 10 years and older with RRMS	no	no	no	no	no	26/08/2013
fingolimod hydrochloride	L04	SM	As single DMT in highly active RRMS for adults and pediatric patients aged 10 years and older: with highly active disease despite a full and adequate course of treatment with at least 1 DMT or with rapidly evolving severe RRMS defined by 2 or more disabling relapses in 1 year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.	no	no	no	no	no	17/03/2011

MA = marketing authorization; RMS = relapsing forms of multiple sclerosis; RRMS = relapsing remitting multiple sclerosis; SM = small molecule; SPMS = secondary progressive multiple sclerosis; PPMS = primary progressive multiple sclerosis; EDSS = Expanded Disability Status Scale; DMT = disease-modifying therapy

Table 6. Agreement among opinions about therapeutic added value issued by Member States

Active substance	Italy	France	Germany
ponesimod	/	V*(67)	Additional benefit not proven (V)**/ Hint for a considerable additional benefit (II)***(135, 136)
ofatumumab	/	III°/ V°°(137)	/
ozanimod hydrochloride	/	V(138)	Low additional benefit (III)[§]/ Additional benefit not proven (V)[§§](139)
siponimod fumaric acid	/	Not applicable(79)	Additional benefit not proven (V)(80)
ocrelizumab	Low (IV)[#](86)	V[##]/ III[###]/ V[####](64)	Low additional benefit (III)[a]/ Additional benefit not proven(V)[aa]/ Low additional benefit (III)[aaa](88)
cladribine	Low (IV)(140)	V(71)	Additional benefit not proven (V)(72)
peginterferon beta-1a	/	V(141)	/
dimethyl fumarate	/	V(76)	Additional benefit not proven (V)(77)
alemtuzumab	/	V(142)	/
teriflunomide	/	V(143, 144)	Additional benefit not proven (V)(145, 146)
fingolimod hydrochloride	Important (II)(95)	IV(97)	Additional benefit not proven (V)[b]/ Non-quantifiable (IV)[bb]/ Non-quantifiable (IV) [bbb]/ Additional benefit not proven (V)[bbbb](98)

*Compared to ozanimod
**Adult patients with RMS with highly active disease despite DMT; comparator: - alemtuzumab or fingolimod or natalizumab; adults with active RMS without prior DMT or adults with prior DMT whose disease is not highly active (EDSS > 3.5); comparator: IFN-β 1a or IFN-β 1b or glatiramer acetate or dimethyl fumarate or teriflunomide or ocrelizumab
***Adults with active RMS without prior DMT or adults with prior DMT whose disease is not highly active (EDSS ≤ 3.5); comparator: IFN-β 1a or IFN-β 1b or glatiramer acetate or dimethyl fumarate or teriflunomide or ocrelizumab
°compared to teriflunomide in patients with early-stage RRMS in terms of disease duration and inflammatory activity; °°no clinical added value in the care pathway for patients with highly active or severe RMS in the same way as ocrelizumab
[§]RRMS with active disease who have not previously received DMT or adult patients previously treated with DMT whose disease is not highly active; comparator: Interferon beta-1a or interferon beta-1b or glatiramer acetate;
[§§]RRMS with highly active disease in spite of prior treatment with DMT; comparator: alemtuzumab or fingolimod or natalizumab

[#]PPMS at an early stage in terms of duration of illness and level of disability, with typical radiological characteristics of inflammatory activity
[##]PPSM
[###]versus interferon ß-1a in patients with RRMS at an early stage in terms of disease duration and inflammatory activity
[####]for patients with very active or severe RMS
[a]RMS with active disease who have not yet received DMT or adult patients with DMT who are not highly active; comparator: Interferon beta-1a or interferon beta-1b or glatiramer acetate under
[aa]RMS with highly active disease despite treatment with DMT; comparator: alemtuzumab or fingolimod or natalizumab or, if appropriate, changes within the basic therapeutics (interferon beta-1a or interferon beta-1b or glatiramer acetate)
[aaa]Early PPMS, characterized by disease duration and degree of disability, and with imaging characteristics typical of inflammatory activity; comparator: Best supportive care Indication of a low additional benefit
[b] Children and adolescents ≥ 10 and < 18 years of age with highly active RRMS despite treatment with at least one DMT for whom escalation of therapy is indicated; comparator: therapy according to the doctor's instructions; [bb] Children and adolescents ≥ 10 and < 18 years of age with highly active RRMS despite treatment with at least one DMT for whom a change within the basic therapeutics is indicated; comparator: Interferon beta-1a or interferon beta-1b or glatiramer acetate; [bbb] Children and adolescents ≥ 10 and < 18 years of age with rapidly evolving severe RRMS defined by two or more disabling relapses in one year and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI who have not yet received DMT; comparator: Interferon beta-1a or interferon beta-1b or glatiramer acetate; [bbbb] Children and adolescents ≥ 10 and < 18 years of age with rapidly evolving severe RRMS defined by two or more disabling relapses in one year and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI despite DMT; comparator: Therapy according to the doctor's instructions

Table 7: Grouping the ratings into "*higher added value*" (H) and "*lower or no added value*" (L).

Product	Active substance	Italy	France	Germany
Skysona®	elivaldogene autotemcel	/	/	/
Evrysdi®	risdiplam	L	H	L
Libmeldy®	atidarsagene autotemcel	/	H	/
Zolgensma®	onasemnogene abeparvovec	H	H/L	L
Ajovy®	fremanezumab	L	L	L/H
Emgality®	galcanezumab	L	L	L/H
Onpattro®	patisiran	H	H	H
Aimovig®	erenumab	L	L	L/H
Tegsedi®	inotersen	/	L	
Spinraza®	nusinersen	H	H/L	H/H
Vyndaqel®	tafamidis	/	L	L
Ponvory®	ponesimod	/	L	L/H
Kesimpta®	ofatumumab	/	H/L	/
Zeposia®	ozanimod hydrochloride	/	L	L/L
Mayzent®	siponimod fumaric acid	/	NA	L
Ocrevus®	ocrelizumab	L	L/H/L	L/L/L
Mavenclad®	cladribine	L	L	L
Plegridy®	peginterferon beta-1a	/	L	/
Tecfidera®	dimethyl fumarate	/	L	L
Lemtrada®	alemtuzumab	/	L	/
Aubagio®	teriflunomide	/	L	L
Gilenya®	fingolimod hydrochloride	H	L	L/L

Table 8: Concordance on added therapeutic value assessmen

s among HTA bodies.

	Italy vs France	**Italy vs Germany**	**France vs Germany**
Both judges agree to include	1	2	1
Both judges agree to exclude	4	3	6
Only the first judge wants to include	4	4	3
Only the second judge wants to include	3	2	2
Cohen's k	**- 0.23**	**- 0.06**	**0**
Interpretation	***No agreement***	***No agreement***	***No agreement***

Table 9: ongoing clinical trials available on *clinicaltrials.gov* for multiple sclerosis (MS) as '*condition or disease'*, including only those with the following status: '*not yet recruiting*', '*recruiting'*, '*enrolling by invitation*', '*active, not recruiting*', and excluding those without therapeutic intervention (update February 2023).

Indication	N. of studies
MS (overall)	467
RRMS	76
PPMS	22
SPMS	27
Funded by company	150
Phase 1	20
Phase 2	33
Phase 3	59
Phase 4	27
Other funders	322
Phase 1	33
Phase 2	40
Phase 3	14
Phase 4	13
Including children/ adolescents	28
Funded by company	11

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