15 July 2021
EMA/COMP/359170/2021
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 15-17 June 2021

Chair: Violeta Stoyanova-Beninska – Vice-Chair: Armando Magrelli

Disclaimers

Some of the information contained in this set of minutes is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scopes listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also vary during the course of the review. Additional details on some of these procedures will be published in the COMP meeting reports once the procedures are finalised.

Of note, this set of minutes is a working document primarily designed for COMP members and the work the Committee undertakes.

Note on access to documents

Some documents mentioned in the minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

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1. Introduction

1.1. Welcome and declarations of interest of members and experts

The Chairperson opened the meeting by welcoming all participants. Due to the current coronavirus (COVID-19) outbreak, and the associated EMA Business Continuity Plan (BCP), the meeting was held remotely.

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced that no restriction in the involvement of meeting participants in upcoming discussions was identified as included in the pre-meeting list of participants and restrictions.

Participants in this meeting were asked to declare any changes, omissions or errors to their declared interests and/or additional restrictions concerning the matters for discussion. No new or additional interests or restrictions were declared.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure and as included in the list of participants. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 22 or more members were present in the room). All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

Giuseppe Capovilla gave a proxy to Angelo Loris Brunetta to vote on behalf of Giuseppe Capovilla during part of June 2021 COMP meeting.

Lyubina Racheva Todorova gave a proxy to Eva Malikova to vote on behalf of Lyubina Racheva Todorova during June 2021 COMP meeting.

The COMP was pleased to welcome Mr Enrico Costa as new member for Italy.

The COMP was pleased to welcome Mr Armando Magrelli as member appointed by the EC on EMA's recommendation.

The COMP noted that Angelo Loris Brunetta's mandate as COMP member representing Patients' Organisation Representative has ended.

1.2. Adoption of agenda

The agenda for 15-17 June 2021 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 10-12 May 2021 were adopted with no amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. saroglitazar magnesium - EMA/OD/0000053160

Zydus France; Treatment of primary biliary cholangitis (PBC)

COMP Rapporteur: Geraldine O'Dea

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Number of people affected

For the estimation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor was asked to add more recent prevalence sources, e.g., Lv, Tingting & Chen, Sha & Li, Min & Zhang, Dong & Kong, Yuanyuan & Jia, Jenna. (2020). Regional variation and temporal trend of PBC epidemiology: a systematic review and meta-analysis. Journal of gastroenterology and hepatology. 10.1111/jgh.15329.

The sponsor was requested to re-calculate the prevalence estimate based on most recent epidemiological studies and registers for the proposed orphan condition and propose the most likely value based on these sources.

In the written response, the sponsor provided an extended prevalence calculation and added prevalence sources such as Drazilova et al., 2020 and Lv, T et al 2020. By considering the most recent sources, the prevalence of PBC in Europe is proposed to be less than 2.25 per 10,000 persons. The assumptions and methodology were accepted by the COMP and the final estimate prevalence value agreed on was approximately 2 in 10,000 persons in the EU, which is in line with previously accepted estimates for this condition.

The Committee agreed that the condition, primary biliary cholangitis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing saroglitazar magnesium was considered justified based on clinical data showing clinically relevant liver transaminase ALP reductions in patients treated with a combination of ursodeoxycholic acid and saroglitazar magnesium.

The condition is chronically debilitating due to pruritus, fatigue, hyperlipidaemia, hypothyroidism, deficiency of fat-soluble vitamins and osteopenia and life-threatening due to progressive hepatic dysfunction, with development of portal hypertension and hepatic failure, and the increased risk of developing hepatocellular cancer.

The condition was estimated to be affecting approximately 2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing saroglitazar magnesium will be of significant benefit to those

affected by the condition. The sponsor has provided clinical data that demonstrate that patients who have received the product in addition to background therapy with ursodeoxycholic acid achieved improved outcomes in terms of liver transaminase levels. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for saroglitazar magnesium, for treatment of primary biliary cholangitis, was adopted by consensus.

2.1.2. tisagenlecleucel - EMA/OD/0000053899

Novartis Europharm Limited; Treatment of follicular lymphoma (FL)

COMP Rapporteur: Maria Elisabeth Kalland

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Number of people affected

The sponsor had proposed a prevalence which was based on publications and assumptions which do not appear to reflect the current epidemiological knowledge. The sponsor was therefore requested to re-calculate the prevalence estimate based on more relevant and extensive data sources on FL, including ECIS (for indirect estimation), which is the most comprehensive database with EU-wide data on incidence of non-Hodgkin's lymphoma (NHL) from all member states. The suitability of the duration of the condition used for the prevalence was asked to be discussed. Furthermore, sensitivity analyses of the reported calculations were asked to be provided on the proportion of FL cases within NHL to reflect the variability and uncertainties from the different sources used.

For the estimation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

In the written response, the sponsor had discussed thoroughly both the limitations and strengths of the different methods used for the prevalence estimates presented. The prevalence of FL ranged from 2.40 (10-year prevalence; Globocan 2020) to 4.92 (20-year partial prevalence; ECIS 2020) per 10,000 for the limited-duration prevalence estimates, whereas the complete prevalence (ECIS 2020; UK HMRN) was estimated to be 4.56 per 10,000 people. The sponsor stated in the epidemiological report for the updated prevalence estimates that FL accounts for about 11-19% of all prevalent NHL cases in the 4 largest EU member states plus the UK (EU4 [France, Germany, Italy, and Spain] and the UK) and 20-25% in the US (Dulac et al., 2013). The sponsor further concluded that the maximum proportion of incident FL cases among all incident NHL cases in the European Community is approximately 20%. This proportion was obtained from the upper range of proportions of incident cases reported in the published literature, where the proportion of FL among all NHL ranged from 16.3% in Italy (Luminari et al., 2007) to 21.9% in Sweden and France (Ekberg et al., 2020; Le Guyader-Peyrou et al., 2016). This proportion of FL within all NHL cases was then used for the indirect estimate of the complete prevalence. The assumption proposed by the sponsor on a FL proportion of 20% among all NHL cases in the European Community could be considered acceptable based on current knowledge of the COMP. As requested, the sponsor also discussed the observed variability of median survival time reported for FL in population-based studies conducted in various European countries and regions. The sponsor acknowledged that the OS of patients with FL has improved over the

last 25 years, and suggested that the improvement may be a result of the sequential application of effective therapies, including rituximab, and better supportive care (Anderson et al., 1998; Karmali et al., 2018; Salles, 2007; Tan et al., 2013). The reported median OS in the literature studied ranged from around 6 years to 13 years (Dandoit et al., 2015; Krol et al., 2003). In another study conducted in selected Spanish hospitals, the median OS for FL was approximately 19 years (Provencio et al., 2017). The latter source, which reported survival of FL patients in a Spanish population, reflect survival of FL from a more recent period from 1980-2013 and is considered more up-to-date than some of the other sources found. However, the patient population included in this study had only FL grades 1-3a since patients with grade 3b were excluded. In addition, these patients appeared to be rather young with a mean age at diagnosis of 58 years. Consequently, the median OS of 19.25 years reported in this study could be considered to represent the upper range of the survival for FL patients in the European population. The sponsor did not consider any of the proposed prevalence estimates to be more accurate than the others for the current prevalence of FL in Europe. Instead, the sponsor highlighted that the different nature of the supplementary information used for the calculations, despite use of the same starting information, may contribute to the differences in the estimates presented, contrary to what would be expected if the prevalence estimates were calculated using information from only one source and by use of identical methods. This argument was supported. Although both the complete and the 20-year prevalence estimates presented for FL are close to the established orphan designation threshold, the estimates are still below the upper limit of 5 cases per 10,000 people. Hence, based on the data provided, the COMP accepted that the condition currently is not affecting more than 5 in 10,000 people in the European Community. The COMP concluded that the upper conservative estimate of 4.9 in 10,000 could be accepted.

The Committee agreed that the condition, follicular lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing tisagenlecleucel was considered justified based on preliminary clinical data showing that a high proportion of relapsed/refractory patients achieve durable complete responses.

The condition is life-threatening and chronically debilitating due to lymphadenopathy, splenomegaly, bone marrow dysfunction and the potential of transformation to aggressive lymphoma.

The condition was estimated to be affecting approximately 4.9 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing tisagenlecleucel will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate sustained complete responses in a high proportion of heavily pre-treated relapsed/refractory patients who have failed several approved therapies. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for tisagenlecleucel, for treatment of follicular lymphoma, was adopted by consensus.

2.1.3. eftansomatropin alfa - EMA/OD/0000055257

Parexel International (Irl) Limited; Treatment of growth hormone deficiency (GHD)

COMP Rapporteur: Vallo Tillmann

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Number of people affected

For the estimation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor was asked to justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor was asked to describe and justify the methodology used for the prevalence calculation. In addition, due to uncertainties regarding the point prevalence of GHD, a sensitivity analysis was requested.

In the written response, the sponsor provided a revised prevalence estimates which were reported or derived from incidence for Belgium, Catalonia, Denmark, France, Germany, Italy and Spain. For countries reporting incidence only, prevalence was calculated based on incidence rates provided in the cited literature. Based on published information the average duration of adult growth hormone deficiency was assumed to be 26.5 years. For paediatric growth hormone deficiency, the duration of disease for paediatric patients was assumed to be 9.2 years. The EU weighted average of GHD across children and adults, was proposed to be 4.6 per 10,000 persons. The COMP accepted the sources included, the methodology and the proposed estimate.

The Committee agreed that the condition, growth hormone deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing eftansomatropin alfa was considered justified based on early clinical data showing comparable efficacy of the product to the standard of care in both adults and children.

The condition is chronically debilitating due to delayed puberty and deficits in facial, dental and genital development, associated with reduced bone mass with increased risk of developing osteopenia, osteoporosis, and bone fractures. Adult growth hormone deficiency is associated with abdominal obesity, decreased lean body mass, reduced muscle strength and exercise capacity. Patients also experience severe psychosocial problems linked to the very short stature.

The condition was estimated to be affecting approximately 4.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing eftansomatropin alfa will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that the product can be used once weekly or biweekly and still achieve the same clinical efficacy as compared to the standard of care, which consists of once daily injections. This is of value especially in children, for whom no long-acting growth hormone is authorised yet. The Committee considered that this constitutes a major contribution to patient care.

A positive opinion for eftansomatropin alfa, for treatment of growth hormone deficiency, was adopted by consensus.

2.1.4. - EMA/OD/0000045468

Treatment of glioma

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Significant benefit

The arguments on significant benefit were based on the new mechanism of action and the potential improved efficacy in the condition.

The sponsor was requested to further elaborate on the results from the submitted clinical studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition. The sponsor was asked to provide additional patient data from the completed Phase 1 study, especially on the patients with stable disease as well as highlight the previous treatment and clarify the duration of the stable disease.

The sponsor was also asked to provide an update on the ongoing clinical Phase 2 study as the interim analyses do not appear current. As the patients studied were treated in the adjuvant setting, the sponsor was requested to also further elaborate on the comparability with historical controls.

In the written response, and during an oral explanation on 15 June 2021, the sponsor introduced the concept of non-methylated O6-methylguanine-methyltransferase (MGMT) glioblastomas as a specific target for the treatment of patients who did not respond to temozolomide (TMZ) in first line therapy. The sponsor highlighted that one of the main reasons for the failure to respond was due to nonmethylated MGMT which is involved in the DNA repair mechanism of cells. They highlighted that in almost 60% of patients with glioblastoma TMZ was not effective because of this repair mechanism. It was noted that the patient population in the Phase II ongoing trial was made up of these glioblastoma patients. The overall survival rates between the data being generated in this Phase II study was indirectly compared to historical data, but the COMP had doubts about the relevance of the comparative exercise and if the populations were similar enough to compare. This in addition to the emerging nature of nonmethylated MGMT as a marker regarding tumour responsiveness. The clinical benefit has been attributed to the fact that MGMT can remove the damaging alkyl groups from the O6 position of guanine and repairs the DNA damage caused by alkylating agents; MGMT promoter methylation therefore results in compromised DNA repair and promotes tumour cell death. However, it remains an area of debate whether TMZ should be used for MGMT unmethylated patients. While some strongly believe that TMZ is ineffective in this subgroup of glioblastoma (GBM) patients and advocate for omitting TMZ from the treatment of patients with MGMT unmethylated GBM, especially in the elderly population, others have argued that there is insufficient evidence to withhold an approved treatment from those with the poorer prognosis. (Neuro-Oncology Advances2(1), 1–7, 2020). The COMP requested that the sponsor further elaborate on this new emerging argument to establish significant benefit which however they had not come prepared to do. Following the oral explanation, the COMP was of the opinion that insufficient information had been provided regarding this new concept and thus could not satisfy the request for further clarification made by the committee.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 16 June 2021, prior to final opinion.

2.1.5. sirolimus - EMA/OD/0000055663

YES Pharmaceutical Development Services GmbH; Treatment of soft-tissue sarcoma

COMP Rapporteur: Bozenna Dembowska-Baginska

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

The COMP discussed the target condition of perivascular epithelioid cell tumours (PEComas) as a separate orphan condition to soft tissue sarcoma. The sponsor was asked to further discuss perivascular epithelioid cell tumours as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention was drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

- Number of people affected

The COMP considered that the prevalence of perivascular epithelioid cell tumours should be provided as there could be some criteria that support this group of tumours as a standalone orphan condition. The sponsor was requested to describe and justify the methodology used for the prevalence calculation.

For the estimation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

- Significant benefit

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the clinical study to justify the assumption of significant benefit over authorised medicinal products for PEComas and soft tissue sarcomas.

A comparative discussion versus the expected effects with the available treatments in the studied population for either condition was invited towards this end.

In the written response, the sponsor provided adequate answers to the questions. The planned oral explanation was therefore cancelled. It was noted that perivascular epithelioid cell differentiation tumours are a family of mesenchymal tumours consisting of perivascular epithelioid cells (PECs). The cell type from which these tumours originate remains unknown. Genetically, PECs are linked to the tuberous sclerosis genes TSC1 and TSC2, although this link is stronger for angiomyolipoma and lymphangioleiomyomatosis than for other members of the PEComa family. PEComas are included in the WHO classification of tumours of the soft tissue as "Tumours of uncertain differentiation". They are rare and can have myriad features; therefore, they can be confused with carcinomas, smooth muscle tumours, adipocytic tumours, clear cell sarcomas, melanomas and gastrointestinal stromal tumours (GIST). Most are benign but there is a subgroup which are malignant which have a high mortality at 5 years. The sponsor provided a prevalence estimate based on oncology registries and a literature search. The incidence rates were estimated using the Information Network on Rare Cancers (RARECARENet) database and NETSARC (the French Sarcoma

Network's clinical-pathologic registry). This was established to be ≤1/1,000,000. The number of people affected is estimated to be 0.0334 in 10,000 persons. The COMP accepted less than 0.1 in 10,000. The sponsor proposed that significant benefit is supported by targeting malignant PEComas, for which there are currently no authorized medicines. Preliminary clinical data in patients with malignant PEComas was submitted providing 1.5-year of follow-up data after the primary analysis date. It was noted that 7/12 responders were still receiving treatment, and that the median DOR had not been reached after a median follow-up for response of 2.5 years (DOR range 5.6, 47.2+ months). Following their deliberation, the COMP considered that they could recommend granting the orphan designation for this submission.

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of perivascular epithelioid tumours.

The Committee agreed that the condition, perivascular epithelioid tumours, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing sirolimus was considered justified based on responses in treated patients with advanced perivascular epithelioid tumours.

The condition is chronically debilitating and life-threatening in particular with regards to the malignant subtypes of perivascular epithelioid tumours, which have been reported as having a median overall survival of up to approximately 2 years.

The condition was estimated to be affecting less than 0.1 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has provided sufficient justification for the assumption that the medicinal product containing sirolimus will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that patients who have malignant PEComas respond to sirolimus for whom there are currently no authorised medicines. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for sirolimus, for treatment of perivascular epithelioid tumours, was adopted by consensus.

2.1.6. lutetium (^{177}Lu) omburtamab barzuxetan - EMA/OD/0000055340

Y-Mabs Therapeutics A/S; Treatment of medulloblastoma

COMP Rapporteur: Dinko Vitezic

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Significant benefit

The arguments on significant benefit were based on the in vivo anti-tumour activity of 177Lu-DTPA-omburtamab reported in a non-clinical model.

The sponsor was requested to further discuss the arguments provided for significant benefit and to provide any indirect or direct comparisons with authorised medicinal products in the same indication (vincristine and carmustine).

In the written responses, the sponsor argued that it is less relevant to compare the potential clinical benefit of 177Lu-DTPA-omburtamab with carmustine, as the indication for carmustine specifically concerns adult medulloblastoma and adult patients only constitute a small fraction (5-6 %) of those affected by medulloblastoma (Ostrom, 2020). Considering vincristine, it is approved for medulloblastoma and is part of the recommended frontline chemotherapy protocols for paediatric patients with medulloblastoma, combined with either cisplatin and lomustine or cisplatin and cyclophosphamide for average-risk patients and vincristine combined with carboplatin, cisplatin, lomustine, and cyclophosphamide for high-risk patients. In paediatric patients with recurrent or refractory medulloblastoma, the same combination regimens or other exploratory combinations with addition of, e.g., temozolomide and targeted therapies are being used as salvage therapy (International Society for Pediatric Neurosurgery [ISPN] guide to paediatric neurosurgery). According to the sponsor no data on the efficacy of vincristine alone is available from randomised clinical trials in paediatric patients with recurrent or refractory medulloblastoma, but a few reports are available from combination regimens. The sponsor referred to a retrospective study in which vincristine is used as a part of multi-modal regimens (i.e. combination regimens of irinotecan, vincristine, cisplatin, cyclophosphamide, and etoposide) and it was concluded that this regimen may produce objective responses. The sponsor concluded that vincristine is not used or recommended as single-agent treatment in either paediatric or adult patients with medulloblastoma.

The COMP considered the difficulties in performing comparative experiments or studies and taking into account the limited options in recurrent relapsed medulloblastoma (specifically in children) the benefit of Lutetium (^{177}Lu) omburtamab barzuxetan at this stage of development of the product is considered acceptable. The planned oral explanation was therefore cancelled.

The Committee agreed that the condition, medulloblastoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing Lutetium (^{177}Lu) omburtamab barzuxetan was considered justified based on the in vivo anti-tumour activity reported in a non-clinical model of the condition.

The condition is chronically debilitating due to long-term neurocognitive and neuroendocrine sequelae and life-threatening due to poor prognosis of patients with recurrent medulloblastoma.

The condition was estimated to be affecting approximately 0.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing Lutetium (^{177}Lu) omburtamab barzuxetan will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate anti-tumour activity in a model of the condition harbouring relapsing/resistant medulloblastoma. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (^{177}Lu) omburtamab barzuxetan, for treatment of medulloblastoma, was adopted by consensus.

2.1.7. - EMA/OD/0000054743

Treatment of diffuse large B-cell lymphoma

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 17 May 2021, prior to responding to the list of issues.

2.1.8. - EMA/OD/0000056712

Treatment of amyotrophic lateral sclerosis (ALS)

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of ALS the sponsor was requested to discuss the methodology of the study and to discuss its strengths and uncertainties such as: (i) subgrouping approach (ii) statistical significance, (iii) matching selection from PRO-ACT database, (iv) percentage of patients dropping out of the study, (v) how was the score calculated 6 months after treatment (considering that ALSFRS-R was evaluated only at each mesenchymal cells (MSC) administration visit i.e. 0, 2, 4 months.

- Significant benefit

The arguments on significant benefit were based on the new mechanism of action and the potential improved efficacy in the condition. However, assumption of significant benefit could only be justified pending acceptance of the medical plausibility.

In the written responses, and during an oral explanation on 17 June 2021, the sponsor tried to elaborate on the methodological aspects of the published study Barczewska et al. 2020. However, the relevance of the subgrouping approach in defining a subpopulation of responders remained unclear. In fact, it appears that only the female sex and a positive clinical response to the first administration of the proposed product when compared to the matched reference patient is a significant predictor for overall efficacy. In addition, the choice of an "artificial" control group from PRO-act database remains questionable (selection of 67 from more than a thousand of cases) and may contribute to selection bias.

Finally, from the analysis provided, it is still unclear what the net effect of the proposed product over riluzole is, and therefore the justification of significant benefit based on the assumption of the potential disease modifying effect of the proposed product over riluzole cannot be confirmed.

The presented published evidence was not considered sufficient to support the medical plausibility and the significant benefit. In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 17 June 2021, prior to final opinion.

2.1.9. pridopidine hydrochloride - EMA/OD/0000056592

Prilenia Therapeutics B.V.; Treatment of amyotrophic lateral sclerosis (ALS)

COMP Rapporteur: Robert Nistico

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of amyotrophic lateral sclerosis the sponsor was requested to further elaborate on the relevance of the nonclinical endpoints used for the treatment of amyotrophic lateral sclerosis, and the interpretation of the results obtained in the experiments. Extrapolation to functional outcomes, such as muscle strength and motor function may be discussed in ALS experimental settings.

- Significant benefit

The arguments on significant benefit were based on the new mechanism of action and the potential improved efficacy in the condition. The sponsor was requested to further elaborate on the clinical relevance of the studied endpoints in an in vivo model of the condition, in order to justify a comparison versus the authorised product.

In the written responses, the sponsor provided literature-based argumentation linking the observed enhancement of neuromuscular junction (NMJ) innervation functional improvement in ALS. NMJ innervation has been associated with improvement in locomotor activity and speed in models of ALS (Miyoshi et al. EMBO Mol Med 2017) an increase in the number of functioning motor unites and restoration of hind limb grip strength in a model of paralysis (Deshpande et al, Ann Neurol, 2006). The COMP considered that despite the lack of data on behavioural or motor function, the endpoints measured relate to the recovery of muscle function/wasting and are suggestive of improved motor output and could therefore support medical plausibility as well as significant benefit. In concluding on a positive opinion, the COMP cancelled the oral hearing, which was no longer needed.

The Committee agreed that the condition, amyotrophic lateral sclerosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing pridopidine hydrochloride was considered justified based on non-clinical data showing preservation of innervation and function of neuromuscular junctions.

The condition is life-threatening and chronically debilitating due to progressive degeneration of motor neurons, ultimately leading to paralysis and respiratory failure. The survival of the patients is usually limited to 2-3 years.

The condition was estimated to be affecting approximately 1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing pridopidine hydrochloride will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate that treatment with the product leads to the preservation of neuromuscular junction innervation and their function. This was considered supportive of potential preserved motor function, an aspect of the condition which is not improved by treatment with the only authorised

product, riluzole. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for pridopidine hydrochloride, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.1.10. - EMA/OD/0000054015

Treatment of hereditary angioedema (HAE)

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Significant benefit

The arguments on significant benefit were based on potential improved efficacy in the condition.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the non-clinical in vivo study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

The sponsor was asked to provide justification for significant benefit in the treatment and prophylaxis of acute HAE attacks.

In the written responses and during an oral explanation on 16 June 2021, the sponsor only provided a theoretical basis for significant benefit versus the C1-esterase inhibitor concentrates (C1-INH) Cinryze®, Berinert®, and Ruconest®, which are all administered intravenously and are either administered in a health care setting or by a trained carer, in the acute management of a HAE attack particularly in the context of laryngeal oedema. The sponsor postulates that treatment with their oral product would be rapid and therefore of particular benefit in the context of laryngeal oedema. No data was provided on comparative efficacy with C1-INH products in a pre-clinical or clinical setting.

The sponsor then outlined the disadvantages and challenges associated with the administration of lanadelumab SC (Takhzyro) which is authorised for the prevention of HAE attacks. These included the need for refrigeration, training in administration, local administration site reactions, and the potential development of anti-drug antibodies. An advantage was also claimed based on the potential for the proposed product to be used for acute treatment or in prevention. No comparative data showing equivalent or better efficacy compared to Takhzyro was provided, a prerequisite for the discussion on major contribution to patient care.

Based on the mode of action the sponsor postulated that their product may be of use in those very rare cases where patients with HAE have normal plasma levels of C1-INH (HAE-nC1-INH). All forms of angioedema attacks involve the excessive stimulation of the endothelial bradykinin B2 receptor by overproduction of bradykinin and thus ensuring increased microvascular permeability. Thus, in the development of HAE attacks, plasma and tissue derived kallikrein may play a role in the production of kinins. Lanadelumab specifically targets and binds to active plasma kallikrein (Kenniston et al., 2014), but does not inhibit tissue kallikrein (KLK-1). The sponsor postulated that because their product is a potent bradykinin B2 receptor antagonist, with a direct effect at the receptor level, the proposed product should provide more complete prophylaxis and has the potential to be an effective treatment in the broader HAE population. No data was submitted to support this

basis for significant benefit which can only be considered a theoretical advantage. The COMP decided that it could not recommend granting the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 16 June 2021, prior to final opinion.

2.1.11. melatonin - EMA/OD/0000055883

Worphmed S.r.l.; Treatment of nontraumatic spontaneous intracerebral hemorrhage (SICH)

COMP Rapporteur: Martin Mozina

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Proposed condition

The sponsor was requested to clarify whether secondary non-traumatic cases are included in the proposed spontaneous non-traumatic ICH condition.

- Number of people affected

For the estimation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation". In light of the need to reconsider the proposed indication, the sponsor was asked to elaborate on:

a) the choice of prevalence versus annual incidence rates for the purpose of reporting the number of affected individuals,

b) the reference to older studies as more current publications if available,

c) an estimate for the entirety of the population spanned by the proposed condition,

d) a sensitivity analysis based on the percentage of patients with nontraumatic spontaneous intracerebral haemorrhage in the total numbers of stroke in Europe.

When SICH is reported in the literature it seems mainly to refer to both primary and secondary, therefore the COMP agreed that both primary and secondary SICH should be included in the condition. The literature as well as databases supported an incidence of around 3 in 10,000. It was agreed to use the incidence as a proxy for prevalence due to the generally short duration of the actual condition. As the outstanding issues had been resolved the planned oral explanation was cancelled.

The Committee agreed that the condition, non-traumatic spontaneous intracerebral haemorrhage, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing melatonin was considered justified based on non-clinical and clinical data from the literature reporting improved neurological outcomes.

The condition is life-threatening due to a high mortality which reaches approximately 50% within the first 3 months and most survivors are left with severe neurological disabilities.

The condition was estimated to be affecting approximately 3 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for melatonin, for treatment of non-traumatic spontaneous intracerebral haemorrhage, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. zanidatamab - EMA/OD/0000033980

Voisin Consulting; Treatment of biliary tract cancer

COMP Rapporteur: Maria Elisabeth Kalland

The Committee agreed that the condition, biliary tract cancer, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing zanidatamab was considered justified based on early clinical data showing that pre-treated patients with high HER2 expression may achieve durable partial responses.

The condition is life-threatening and chronically debilitating due to late diagnosis, development of hepatic insufficiency, progressive biliary obstruction followed by complications such as infections, and a low overall median survival of less than one year following diagnosis.

The condition was estimated to be affecting approximately 1.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing zanidatamab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that some patients with inoperable, pre-treated biliary tract cancer, with high expression of HER2, achieved durable partial responses. The proposed product targets a different patient population within the proposed orphan condition (patients overexpressing HER2) than the currently authorised product, pemigatinib (patients with FGFR2 mutations). This would offer a treatment option to a new patient population who have no remaining treatment options. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for zanidatamab, for treatment of biliary tract cancer, was adopted by consensus.

2.2.2. - EMA/OD/0000041501

Treatment of pulmonary arterial hypertension (PAH) condition

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

2.2.3. synthetic double-stranded siRNA oligonucleotide directed against apolipoprotein C-III mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues - EMA/OD/0000044658

Pharma Gateway AB; Treatment of familial chylomicronaemia syndrome

COMP Rapporteur: Geraldine O'Dea

The Committee agreed that the condition, familial chylomicronaemia syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing Synthetic double-stranded siRNA oligonucleotide directed against apolipoprotein C-III mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues was considered justified based on clinical data demonstrating clinically relevant reductions in triglycerides in treated patients.

The condition is life threatening and chronically debilitating due to recurrent episodes of pancreatitis which may lead to pancreatic insufficiency resulting in malabsorption, failure to thrive and diabetes mellitus.

The condition was estimated to be affecting approximately 0.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing Synthetic double-stranded siRNA oligonucleotide directed against apolipoprotein C-III mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that the product used at low dose induced lasting and clinically relevant effect by lowering triglyceride levels in patients. This compared favourably to the existing antisense therapy which has to be used at a higher dose and more frequently. The Committee considered that this constitutes a clinically relevant advantage and major contribution to patient care.

A positive opinion for synthetic double-stranded siRNA oligonucleotide directed against apolipoprotein C-III mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues, for treatment of familial chylomicronaemia syndrome, was adopted by consensus.

2.2.4. - EMA/OD/0000053211

Treatment of follicular lymphoma

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

2.2.5. 1-(4-(6-chloropyridazin-3-yl)piperazin-1-yl)-2-(4-cyclopropyl-3-fluorophenyl)ethan-1-one - EMA/OD/0000053228

Premier Research Group S.L.; Treatment of pantothenate kinase-associated neurodegeneration

COMP Rapporteur: Dinah Duarte

The Committee agreed that the condition, pantothenate kinase-associated neurodegeneration, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 1-(4-(6-chloropyridazin-3-yl)piperazin-1-yl)-2-(4-cyclopropyl-3-fluorophenyl)ethan-1-one was considered justified based on in vivo non-clinical data in a valid model of the condition demonstrating improvement in movement and survival.

The condition is chronically debilitating due to progressive neurological degeneration with signs of parkinsonism and dystonia and life-threatening due to secondary complications such as aspiration pneumonia, malnutrition and status dystonicus.

The condition was estimated to be affecting less than 0.1 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for 1-(4-(6-chloropyridazin-3-yl) piperazin-1-yl)-2-(4-cyclopropyl-3-fluorophenyl)ethan-1-one, for treatment of pantothenate kinase-associated neurodegeneration, was adopted by consensus.

2.2.6. 1-(4-(6-chloropyridazin-3-yl)piperazin-1-yl)-2-(4-cyclopropyl-3-fluorophenyl)ethan-1-one - EMA/OD/0000053262

Premier Research Group S.L.; Treatment of propionic acidaemia

COMP Rapporteur: Ingeborg Barisic

The Committee agreed that the condition, propionic acidaemia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 1-(4-(6-chloropyridazin-3-yl)piperazin-1-yl)-2-(4-cyclopropyl-3-fluorophenyl)ethan-1-one was considered justified based on non-clinical data in a model that showed improved survival, and improved C3:C2 carnitine ratio and methylcitrate levels.

The condition is chronically debilitating and life-threatening from the first months of life in most cases, due to failure to thrive and progressive encephalopathy leading to seizures, coma, and death.

The condition was estimated to be affecting approximately 0.04 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 1-(4-(6-chloropyridazin-3-yl)piperazin-1-yl)-2-(4-cyclopropyl-3-fluorophenyl)ethan-1-one will be of significant benefit to those affected by the condition. The sponsor has provided nonclinical data that demonstrate that the proposed product improves survival and reduces C3-carnitine levels on which the medicinal product currently authorized has no effects. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 1-(4-(6-chloropyridazin-3-yl) piperazin-1-yl)-2-(4-cyclopropyl-3-fluorophenyl)ethan-1-one, for treatment of propionic acidaemia, was adopted by consensus.

2.2.7. itolizumab - EMA/OD/0000053328

Biocon Pharma Ireland Limited; Treatment of graft-versus-host disease

COMP Rapporteur: Martin Mozina

The Committee agreed that the condition, graft-versus-host disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing itolizumab was considered justified based on early clinical data in acute Graft versus Host Disease (aGvHD) as add-on to corticosteroids showing high rate of responses which appear to be sustained and allow for corticosteroid dose reduction.

The condition is life-threatening and chronically debilitating due to potential severe multiorgan damage. The organs most commonly affected acutely by GvHD include the skin, liver, and gastrointestinal system.

The condition was estimated to be affecting approximately 0.9 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing itolizumab will be of significant benefit to those affected by the condition. The sponsor has provided early clinical data that demonstrate that the product is likely to be of improved efficacy as add-on to corticosteroids in the treatment of aGvHD. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for itolizumab, for treatment of graft-versus-host disease, was adopted by consensus.

2.2.8. - EMA/OD/0000054695

Treatment of diffuse large B-cell lymphoma

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

2.2.9. vodobatinib - EMA/OD/0000055969

Sun Pharmaceutical Industries Europe B.V.; Treatment of chronic myeloid leukemia

COMP Rapporteur: Karri Penttila

The Committee agreed that the condition, chronic myeloid leukaemia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing vodobatinib was considered justified based on preliminary clinical data demonstrating anti-tumour response in patients affected by the condition.

The condition is life threatening and chronically debilitating due to the consequences of the bone marrow dysfunction, intracranial or gastro-intestinal haemorrhagic episodes and the risk of severe infections.

The condition was estimated to be affecting approximately 1.9 in 10,000 persons in the European Union, at the time the application was made;

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing vodobatinib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data demonstrating anti-tumour response in patients affected by the condition, who have failed all currently authorised therapies. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for vodobatinib, for treatment of chronic myeloid leukaemia, was adopted by consensus.

2.2.10. - EMA/OD/0000056765

Treatment of chronic lymphocytic leukaemia / small lymphocytic lymphoma

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

[Post-meeting note: The sponsor formally withdrew the application for orphan designation on 24 June 2021.]

2.2.11. - EMA/OD/0000056412

Treatment of small cell lung cancer

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

2.2.12. - EMA/OD/0000057079

Treatment of GM2 gangliosidosis

The COMP adopted a list of issues that will be sent to the sponsor. The Committee will discuss the submitted answers to the list of issues at the July meeting.

2.2.13. humanised IgG2k Fc-modified bispecific monoclonal antibody against CD3 and BCMA - EMA/OD/0000057402

Pfizer Europe MA EEIG; Treatment of multiple myeloma

COMP Rapporteur: Maria Elisabeth Kalland

The Committee agreed that the condition, multiple myeloma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing humanised IgG2k Fc-modified bispecific monoclonal antibody against CD3 and BCMA was considered justified based on preliminary clinical data showing that advanced patients with relapsed or refractory multiple myeloma achieved partial or complete responses.

The condition is chronically debilitating and life-threatening due to the development of hypercalcaemia, renal insufficiency, anaemia and bone lesions.

The condition was estimated to be affecting approximately 4.1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing Humanised IgG2k Fc-modified bispecific monoclonal antibody against CD3 and BCMA will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that heavily pre-treated patients with relapsed/refractory multiple myeloma who failed several lines of currently approved therapies achieved partial and stringent complete responses. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for humanised IgG2k Fc-modified bispecific monoclonal antibody against CD3 and BCMA, for treatment of multiple myeloma, was adopted by consensus.

2.2.14. mRNA encoding the human glycogen debranching enzyme - EMA/OD/0000057891

Ultragenyx Germany GmbH; Treatment of glycogen storage disease type III (GSD III)

COMP Rapporteur: Lyubina Racheva Todorova

The Committee agreed that the condition, glycogen storage disease type III, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing mRNA encoding the human glycogen debranching enzyme was considered justified based on non-clinical in vivo data in a model of the condition showing a reduction in hepatic glycogen, increases in fasting serum glucose, and reductions in liver enzymes which correlate with the production of the human glycogen debranching enzyme in hepatocytes.

The condition is chronically debilitating due to liver involvement which presents as ketotic hypoglycemia, hepatomegaly, hyperlipidemia, and elevated hepatic transaminases. Hypertrophic cardiomyopathy develops in childhood. It is asymptomatic in the majority of patients but can evolve to severe cardiac dysfunction and congestive heart failure and can be life-threatening due to end-stage liver failure or conversion to hepatomas and sudden death possibly due to cardiac arrhythmias.

The condition was estimated to be affecting approximately 0.1 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for containing mRNA encoding the human glycogen debranching enzyme, for treatment of glycogen storage disease type III, was adopted by consensus.

2.2.15. adeno-associated viral vector serotype 9 containing the human *SLC13A5* gene - EMA/OD/0000057939

Raremoon Consulting Esp S.L.; Treatment of SLC13A5-epileptic encephalopathy deficiencies

COMP Rapporteur: Giuseppe Capovilla

The Committee agreed that the condition, SLC13A5-epileptic encephalopathy deficiencies, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 9 containing the human *SLC13A5* gene was considered justified based on reduced severity of seizures in a relevant in vivo model of the condition;

The condition is chronically debilitating due to occurrence of pharmaco-resistant epilepsy, severe neurodevelopmental delay resulting in cognitive impairment and motor developmental delay.

The condition was estimated to be affecting less than 0.001 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for adeno-associated viral vector serotype 9 containing the human *SLC13A5* gene, for treatment of SLC13A5-epileptic encephalopathy deficiencies, was adopted by consensus.

2.2.16. - EMA/OD/0000058120

Treatment of upper tract urothelial carcinoma

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 29 June 2021.]

2.2.17. autologous CD34+ hematopoietic stem and progenitor cells genetically modified with the lentiviral vector encoding for the human palmitoyl-protein thioesterase 1 gene - EMA/OD/0000058064

University of Padua; Treatment of neuronal ceroid lipofuscinosis

COMP Rapporteur: Giuseppe Capovilla

The Committee agreed that the condition, neuronal ceroid lipofuscinosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing autologous CD34+ haematopoietic stem and progenitor cells genetically modified with the lentiviral vector encoding for the human palmitoyl-protein thioesterase 1 gene was considered justified based on non-clinical data showing improved survival, motor function and brain histology.

The condition is life-threatening and chronically debilitating due to visual, cognitive, and motor skills decline, speech impediment, behavioural problems, seizures, cerebral atrophy, and ultimately premature death.

The condition was estimated to be affecting approximately 0.1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the

medicinal product containing autologous CD34+ haematopoietic stem and progenitor cells genetically modified with the lentiviral vector encoding for the human palmitoyl-protein thioesterase 1 gene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate that the product used in a non-clinical model of neuronal ceroid lipofuscinosis type 1 (CLN1) improved survival and motor function and brain histology. Since the only authorised medicine for the condition, Brineura, is not designed for patients with CLN1, the proposed treatment would bring significant benefit over Brineura. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous CD34+ haematopoietic stem and progenitor cells genetically modified with the lentiviral vector encoding for the human palmitoyl-protein thioesterase 1 gene, for treatment of neuronal ceroid lipofuscinosis, was adopted by consensus.

2.2.18. infigratinib - EMA/OD/0000058250

YES Pharmaceutical Development Services GmbH; Treatment of achondroplasia

COMP Rapporteur: Dinah Duarte

The Committee agreed that the condition, achondroplasia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing infigratinib was considered justified based on non-clinical in vivo data in a model of the condition showing improvement in long bone lengthening and cranial bone structure following treatment.

The condition is chronically debilitating due to manifestations such as hypotonia, otolaryngeal system dysfunction, and rhizomelic short stature, thoracolumbar kyphosis, spinal stenosis, and foramen magnum stenosis and life-threatening with approximately 10 years shorter life expectancy.

The condition was estimated to be affecting approximately 0.4 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for infigratinib, for treatment of achondroplasia, was adopted by consensus.

2.2.19. - EMA/OD/0000058262

Treatment of myotonic disorders

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

2.2.20. 3,5-diiodothyropropionic acid - EMA/OD/0000058312

Raremoon Consulting Esp S.L.; Treatment of Allan-Herndon-Dudley syndrome

COMP Rapporteur: Dinah Duarte

The Committee agreed that the condition, Allan-Herndon-Dudley syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 3,5-diiodothyropropionic acid was considered justified based on early clinical data showing normalization of serum thyroid hormone, improved body weight, lack of seizures and no need for gastric tube feeding.

The condition is life-threatening due to a risk of sudden cardiac arrest or aspiration pneumonia and chronically debilitating due to cognitive impairment and hypotonia, which evolves to spastic paraplegia. Other symptoms include peripheral hyperthyroidism with increased heart frequency, tremor, weight loss and muscular weakness.

The condition was estimated to be affecting less than 0.1 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for 3,5-diiodothyropropionic acid, for treatment of Allan-Herndon-Dudley syndrome, was adopted by consensus.

2.2.21. adeno-associated viral vector serotype Anc80 containing the 3' portion of human *OTOF* gene, adeno-associated viral vector serotype Anc80 containing the 5' portion of human *OTOF* gene - EMA/OD/0000058314

Boyd Consultants Limited; Treatment of otoferlin gene-mediated hearing loss

COMP Rapporteur: Ingeborg Barisic

The Committee agreed that the condition, otoferlin gene-mediated hearing loss, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype Anc80 containing the human *OTOF* gene was considered justified based on data in a relevant non-clinical model of the condition which showed restoration of the auditory function and physiologic hearing.

The condition is chronically debilitating due to permanent severe-to-profound hearing loss or deafness.

The condition was estimated to be affecting less than 1 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for adeno-associated viral vector serotype Anc80 containing the 3' portion of human *OTOF* gene, adeno-associated viral vector serotype Anc80 containing the 5' portion of human *OTOF* gene, for treatment of otoferlin gene-mediated hearing loss, was adopted by consensus.

2.2.22. recombinant human ectonucleotide pyrophosphatase/phosphodiesterase 1 fused to the Fc fragment of IgG1 - EMA/OD/0000058504

Inozyme Pharma Ireland Limited; Treatment of adenosine triphosphate binding cassette transporter protein subfamily C member 6 deficiency

COMP Rapporteur: Ingeborg Barisic

The Committee agreed that the condition, adenosine triphosphate binding cassette transporter protein subfamily C member 6 deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing recombinant human ectonucleotide pyrophosphatase/phosphodiesterase 1 fused to the fc fragment of IgG1 was considered justified based on non-clinical in vivo data in a model of the condition showing a reduction in calcification in the eyes and vibrissae.

The condition is chronically debilitating due to pathological mineralization and intimal proliferation that manifests in a spectrum of phenotypes. It is associated with a risk of blindness, decreased quality of life and peripheral vascular compromise. As the disease progresses, cardiovascular manifestations can occur and manifest as increased risk of ischemic stroke and early myocardial infarcts, as well as intermittent claudication and hypertension.

The condition was estimated to be affecting approximately 0.5 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for recombinant human ectonucleotide pyrophosphatase/phosphodiesterase 1 fused to the Fc fragment of IgG1, for treatment of adenosine triphosphate binding cassette transporter protein subfamily C member 6 deficiency, was adopted by consensus.

2.2.23. adeno-associated virus vector serotype 1 containing the human *GRN* gene - EMA/OD/0000058488

Pharma Gateway AB; Treatment of frontotemporal dementia

COMP Rapporteur: Robert Nistico

The Committee agreed that the condition, frontotemporal dementia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing adeno-associated virus vector serotype 1 containing the human *GRN* gene was considered justified based on non-clinical in vitro and ex vivo data in a model of the condition showing significantly improved key neuropathological features found in patients with GRN-related neurodegeneration, including prevention of lipofuscin accumulation and a reduction in microglial infiltration.

The condition is life-threatening and chronically debilitating due to neurological and cognitive impairment and limited life-expectancy.

The condition was estimated to be affecting approximately 3.6 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for adeno-associated virus vector serotype 1 containing the human *GRN* gene, for treatment of frontotemporal dementia, was adopted by consensus.

2.2.24. - EMA/OD/0000058580

Treatment of idiopathic pulmonary fibrosis (IPF)

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

[Post-meeting note: The sponsor formally withdrew the application for orphan designation on 28 June 2021.]

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

None

2.6. Nominations

2.6.1. New applications for orphan medicinal product designation - Appointment of COMP rapporteurs

COMP coordinators were appointed for 23 applications.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 1 application for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment in haematopoietic stem cell transplantation

The Committee was briefed on the significant benefit issues.

3.1.2. -

Treatment of pancreatic cancer

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues.

3.1.3. -

Treatment of myelodysplastic syndromes

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues.

3.1.4. -

Treatment of acute myeloid leukemia

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues.

3.2. Finalised letters

3.2.1. -

Treatment of transthyretin-mediated amyloidosis in patients with cardiomyopathy

The finalised letter was circulated for information.

3.2.2. -

Treatment of mucopolysaccharidosis type I

The finalised letter was circulated for information.

3.2.3. -

Treatment of glioma

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of paediatric patients with severe combined immunodeficiency (SCID) receiving allogeneic haematopoietic stem cell transplantation

The new request was noted.

4. Review of orphan designation for orphan medicinal products at time of initial marketing authorisation

4.1. Orphan designated products for which CHMP opinions have been adopted

None

4.2. Orphan designated products for discussion prior to adoption of CHMP opinion

4.2.1. Flynpovi – eflornithine / sulindac - EMEA/H/C/005043/0000, EMA/OD/130/12, EU/3/12/1086, EMA/OD/0000061571

Cancer Prevention Pharma (Ireland) Limited; Treatment of familial adenomatous polyposis

CHMP negative opinion was noted.

4.2.2. Abecma – idecabtagene vicleucel - EMEA/H/C/004662/0000, EU/3/17/1863, EMA/OD/0000035635

Celgene Europe BV; Treatment of multiple myeloma

COMP Rapporteurs: Karri Penttilä; Maria Elisabeth Kalland

An opinion recommending not to remove Abecma, idecabtagene vicleucel, EU/3/17/1863 from the EC Register of Orphan Medicinal Products was adopted by consensus.

The orphan maintenance assessment report will be publicly available on the EMA website.

[Post-meeting note: The COMP adopted the opinion by written procedure following its June 2021 meeting.]

4.2.3. Voxzogo – vosoritide - EMEA/H/C/005475/0000, EMA/OD/149/12, EU/3/12/1094, EMA/OD/0000032549

BioMarin International Limited; Treatment of achondroplasia

COMP Rapporteur: Ingeborg Barisic; Expert: Armando Magrelli

An opinion recommending not to remove Voxzogo, vosoritide, EU/3/12/1094 from the EC Register of Orphan Medicinal Products was adopted by consensus.

The orphan maintenance assessment report will be publicly available on the EMA website.

[Post-meeting note: The COMP adopted the opinion by written procedure following its June 2021 meeting.]

4.2.4. Minjuvi – tafasitamab - EMEA/H/C/005436/0000, EMA/OD/215/14, EU/3/14/1424, EMA/OD/0000047254

Morphosys AG; Treatment of diffuse large B-cell lymphoma

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

4.2.5. – zanubrutinib - EMEA/H/C/004978/0000, EMA/OD/0000004269, EU/3/19/2167, EMA/OD/0000058248

BeiGene Ireland Ltd; Treatment of lymphoplasmacytic lymphoma

The status of the procedure at CHMP was noted.

4.2.6. – avalglucosidase alfa - EMEA/H/C/005501, EU/3/14/1251, EMA/OD/0000048959

Genzyme Europe BV; Treatment of Pompe's disease

The status of the procedure at CHMP was noted.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 4 applications.

4.5. Orphan Maintenance Reports

Documents were tabled for information.

5. Review of orphan designation for authorised orphan medicinal products at time marketing authorisation extension

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

None

5.3. Appeal

None

5.4. On-going procedures

None

6. Application of Article 8(2) of the Orphan Regulation

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. Strategic Review & Learning meetings

None

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely on 11 June 2021.

7.1.3. Election of COMP Vice-Chairperson

Armando Magrelli was elected as COMP Vice-Chair for a second three-year mandate. Furthermore it was agreed that Armando Magrelli will continue to represent COMP in SAWP as alternate.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendation on eligibility to PRIME – report

Documents were tabled for information.

7.2.2. CAT-COMP Working Group

The CAT-COMP Working Group met remotely on 14 June 2021.

7.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups

7.3.1. Working Party with Patients' and Consumers' Organisations (PCWP) and Working Party with Healthcare Professionals' Organisations (HCPWP)

The documents were tabled for information.

7.3.2. Satisfactory Methods Working Group

The COMP noted the manuscript prepared on satisfactory methods of treatment in rare diseases - the EU regulator's perspective.

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

Public consultation for the revision of the Orphan Regulation

The COMP noted the update on the ongoing public consultation.

Updated Q&A related to the assessment of similarity for Advanced Therapy Medicinal products in the context of the orphan legislation

The COMP noted the updated version of the EC Q&A.

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

The document was tabled for information.

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. Therapeutic Goods Administration (TGA), Australia

None

7.5.4. Health Canada

None

7.6. Contacts of the COMP with external parties and interaction with the Interested Parties to the Committee

None

7.7. COMP work plan

None

7.8. Planning and reporting

7.8.1. List of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2021

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2021 were circulated.

7.8.2. Overview of orphan marketing authorisations/applications

An updated overview of orphan applications for Marketing Authorisation was circulated.

8. Any other business

8.1. Horizon Scanning report on Genome Editing

A report on genome editing has been finalised by the EU Innovation network (EU IN; EMA Rapporteur; contributions by experts from the EU Network, Committees and Working parties).

Genome editing, EU-IN Horizon Scanning Report was tabled for information.

8.2. Real World Data use cases

The COMP noted the presentation on real world evidence (RWE) to support committees' decision making, use cases, proof of concept and DARWIN EU. There has been an increase in the use of RWE in the development, authorisation and post-marketing surveillance of medicines to facilitate decision-making. EMA committees can obtain RWE. Currently EMA has access to primary care data from UK (THIN), FR and DE (IMS). From 2013, there have been 98 EMA in-house analyses or full studies performed. PRAC pilot (November 2019 - January 2021) aimed to test the feasibility and usefulness of a process for rapid identification, analysis and reporting of results of epidemiological questions that may arise in the context of regulatory assessments. However there are preparations ongoing for a procurement on having access to additional data sources in order to increase geographical representation and access to hospital prescribing. The aim is to obtain access up to three more data sources. There were 30 studies funded through framework contracts from 2010, which allows accessing different data sources and scientific expertise. However there will be a new framework contract in place in September - DARWIN EU®. This will provide scientific expertise in formulating and executing studies and analysis on behalf of the EMRN and the EMA's scientific committees. Furthermore, it will provide onboarding of data sources and maintenance of a catalogue of known, relevant data sources, continually ensuring the quality of the data held by data holders and conformance to metadata (e.g. maintain the federated network).

For COMP, there were 3 areas identified, where independent RWE could support the assessment during a procedure:

- Support the evaluation of prevalence of diseases (at time of pre-authorisation, during the evaluation, and at the time of review of the maintenance of the orphan designation);
- Clinical management of the disease of interest (generate evidence on the actual clinical standard of care (e.g. are medicines used according to the authorised indication or off-label?)) and characterise severe adverse events occurring in the treated population;
- Natural history of disease (support a better understanding of the disease progression, by generating evidence on disease characteristics (procedures, lab values…) and comorbidities over time)

The COMP work plan 2021 includes the proof of concept on RWE.

As next steps, the call for expression of interest was launched

8.3. EMA Business Pipeline activity and Horizon scanning

The document was tabled for information.

9. List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 15-17 June 2021 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Violeta Stoyanova - Beninska	Chair	Netherlands	No interests declared	
Armando Magrelli	Vice-chair	Expert recommended by EMA	No interests declared	
Brigitte Schwarzer-Daum	Member	Austria	No restrictions applicable to this meeting	
Tim Leest	Member	Belgium	No interests declared	
Dinko Vitezic	Member	Croatia	No interests declared	
Vasileios Loutas	Member	Cyprus	No interests declared	
Lenka Gaidadzi	Member	Czechia	No interests declared	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Cecile Dop	Member	France	No interests declared	
Zsofia Gyulai	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Enrico Costa	Member	Italy	No restrictions applicable to this meeting	
Irena Rogovska	Member	Latvia	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No interests declared	
Elisabeth Johanne Rook	Member	Netherlands	No interests declared	
Maria Elisabeth Kalland	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No restrictions applicable to this meeting	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Gloria Maria Palomo Carrasco	Member	Spain	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Angelo Loris Brunetta	Member	Patients' Organisation Representative	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Virginie Hivert	Expert via WebEx*	Patients' Organisation Representative	No restrictions applicable to this meeting	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	Observer via WebEx*		Confidentiality agreement	
	Observer via WebEx*		Confidentiality agreement	
	Observer via WebEx*		Confidentiality agreement	
	Observer via WebEx*		Confidentiality agreement	
	Observer via WebEx*		Confidentiality agreement	
Johanna Lähteenvuo	CHMP member via WebEx*	Finland	No interests declared	
The representatives from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were evaluated against the agenda topics or activities they participated in.

10. Explanatory notes

The notes below give a brief explanation of the main sections and headings in the COMP agenda and should be read in conjunction with the agenda or the minutes.

Abbreviations / Acronyms

CHMP: Committee for Medicinal Product for Human Use

COMP: Committee for Orphan Medicinal Products

EC: European Commission

OD: Orphan Designation

PA: Protocol Assistance

PDCO: Paediatric Committee

PRAC: Pharmacovigilance and Risk Assessment Committee

SA: Scientific Advice

SAWP: Scientific Advice Working Party

Orphan Designation *(section 2 Applications for orphan medicinal product designation)*

The orphan designation is the appellation given to certain medicinal products under development that are intended to diagnose, prevent or treat rare conditions when they meet a pre-defined set of criteria foreseen in the legislation. Medicinal products which get the orphan status benefit from several incentives (fee reductions for regulatory procedures (including protocol assistance), national incentives for research and development, 10-year market exclusivity) aiming at stimulating the development and availability of treatments for patients suffering from rare diseases.

Orphan Designations are granted by Decisions of the European Commission based on opinions from the COMP. Orphan designated medicinal products are entered in the Community Register of Orphan Medicinal Products.

Protocol Assistance *(section 3 Requests for protocol assistance with significant benefit question)*

The protocol assistance is the help provided by the Agency to the sponsor of an orphan medicinal product, on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product in view of the submission of an application for marketing authorisation.

Sponsor

Any legal or physical person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product.

Maintenance of Orphan Designation *(section 4 Review of orphan designation for orphan medicinal products for marketing authorisation).*

At the time of marketing authorisation, the COMP will check if all criteria for orphan designation are still met. The designated orphan medicinal product should be removed from the Community Register of Orphan Medicinal Products if it is established that the criteria laid down in the legislation are no longer met.

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu/