17 February 2022
EMA/COMP/63104/2022
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 18-20 January 2022

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.

1.2. Adoption of agenda

The agenda for 18-20 January 2022 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 7-9 December 2021 were adopted with amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. EMA/OD/0000068060

Treatment of multiple myeloma

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 considered that the condition the sponsor is targeting is treatment in haematopoietic stem cell transplantation. Note that this is for the purposes of orphan

medicinal product designation; the sponsor's attention is drawn to the orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

If the case the sponsor wishes to maintain multiple myeloma they need to establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of multiple myeloma the sponsor should further elaborate on:

- the relevance of the nonclinical model used for the treatment of multiple myeloma, and the interpretation of the results obtained in the experiments;
- the methodology used in the non-clinical studies as well as the results from these studies and its relevance for the development of the product in the condition.

- Prevalence

The sponsor was requested to provide a revised prevalence estimate for the proposed orphan condition treatment in haematopoietic stem cell transplantation.

For the estimation and presentation of the prevalence estimate the sponsor is 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 arguments on significant benefit were based on an alternative mechanism of action and the 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.

In the written response, and during an oral explanation before the Committee on 18 January 2022, the sponsor accepted the change of the condition to treatment in haematopoietic stem cell transplantation and they have adjusted the prevalence to reflect this change. This also clarified the relevance of the non-clinical in vivo data in order to support the medical plausibility. The Committee therefore felt that the questions regarding the condition, medical plausibility and prevalence had been addressed adequately by the sponsor.

The COMP discussed the sponsor's response regarding significant benefit. The proposed product is suitable candidate for post transplantation immune-cell therapy since this do not induce graft versus host disease. It has also been noted that haploidentical donors can be used as donors with similar clinical outcome using post-transplant cyclophosphamide. The combination of haploidentical transplantation and the proposed product has been reported to be a very attractive and relevant opportunity, since nearly every patient will have a haploidentical donor. The possible advantage of using the proposed product in a haploidentical context was understood by the COMP.

The sponsor argued for the possible effect of the proposed product against multiple myeloma based on in vitro as well as in vivo non-clinical data. The additional data showed that the proposed product could circumvent the low glucose status in bone marrow of patients with multiple myeloma (Ehlers *et al.*, 2021a). They also argued that there could be an advantage to using so-called mismatched part of the proposed product. This may

especially be the case if the proposed product can be combined with a haploidentical donor bone marrow stem cell transplantation, as was also suggested by Sahebi (Sahebi *et al.*, 2019). The sponsor explained that they intend the product to be used in high-risk multiple myeloma patients.

Several concerns associated with significant benefit were discussed by the COMP. The concept of high-risk multiple myeloma patients was noted to be a complex one as there are many treatments currently available, yet many patients continue to progress. The target patient population is therefore difficult to define. The COMP noted that indeed the theoretical potential of using the type of product the sponsor proposes is understood however, the data to contextualise the use within the current standard of care was weak.

Although promising the data submitted was considered insufficient to support the significant benefit. The Committee therefore considered it was unable to 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 20 January 2022, prior to final opinion.

2.1.2. aldesleukin - EMA/OD/0000070454

Iltoo Pharma; Treatment of amyotrophic lateral sclerosis (ALS)

COMP Rapporteur: Elisabeth Johanne Rook

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 and significant benefit

The sponsor was requested to further substantiate that aldesleukin would lead to improvement of clinical symptoms and survival. Based on the pharmacodynamic data provided, it is not clear if or to what extent downregulation of inflammation correlates with clinical improvement. (Preliminary) data from the ongoing Phase 2b study would be helpful to establish medical plausibility and significant benefit.

In the written response, the sponsor stated that efficacy data from the ongoing Phase IIb study will not be available before the end of the first quarter of 2022.

The sponsor presented additional scientific data to support their claim of a correlation between certain inflammatory biomarkers in ALS patients with disease activity and progression. Amongst other data, the sponsor pointed out that:

- CCL2, a small chemokine belonging to C-C subfamily also known as MCP1, has been shown to correlate with the total Norris scale (Nagata T *et al.*, 2007), the revised amyotrophic lateral sclerosis functional rating scale (ALSFRS-R) score (Tanaka *et al.,* 2006) reflecting the severity of ALS and with survival of ALS patients (Gille B *et al.,* 2019);
- ALS patients consistently present a significant decrease in regulatory T cells (Tregs) as compared to controls (Mantovani S *et al.,* 2009; Rentzos M *et al.,* 2012; Henkel JS *et al.,* 2013) and that decreased levels of Tregs were correlated with disease severity. A study investigating a relatively large prospective ALS cohort (n=102), Treg levels predicted progression rates and survival (Henkel JS *et al.,* 2013), with patients in the "low" Treg group (low FoxP3 expression levels) showing a two-fold

increase in rate of progression on a functional assessment and a two-fold increase in risk of death over a 3-year follow-up time, as compared to the "high" Treg group. Also, in a phase Ib open-label trial (Thonhoff JR *et al.* 2018) autologous infusions of expanded Tregs into ALS patients with concomitant subcutaneous low-dose IL-2 administration at early stages (4 doses over 2 months) and later stages (4 doses over 4 months) of disease suggested that the increase of Treg numbers may be linked with a reduction in functional decline. In all patients, the rate of decline of the ALSFRS-R and AALS score slowed during each round of infusions and was correlated with increased Treg suppressive function.

The COMP considered that the existing data is sufficient to support medical plausibility and significant benefit, for the purpose of initial orphan designation. Therefore the oral explanation was cancelled. The totality of data suggests a potential therapeutic benefit of low-dose IL-2 as an add-on therapy to riluzole in the treatment of patients suffering from ALS. The sponsor's plan to seek protocol assistance from EMA upon completion of the ongoing phase IIb study is strongly supported. The sponsor is especially encouraged to include a question on significant benefit in the planned protocol assistance.

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 aldesleukin was considered justified based on exploratory clinical data demonstrating a pharmacodynamic effect of an increment of regulatory T-cells, an effect that has been shown to slow down disease progression and reduce neuro-inflammation in other clinical studies.

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 aldesleukin will be of significant benefit to those affected by the condition. The sponsor has provided exploratory clinical data suggesting a complimentary effect on the reduction of relevant prognostic biomarkers of neuroinflammation when used in combination with the authorized medicinal product. The Committee considered that this constitutes a clinically relevant advantage.

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

2.1.3. gadolinium-chelated polysiloxane nanoparticles - EMA/OD/0000069751

Nh Theraguix; Treatment of pancreatic cancer (PC)

COMP Rapporteur: Brigitte Schwarzer-Daum

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 whether there exists a scientific rationale for the development of the proposed product for treatment of pancreatic cancers the sponsor was requested to further elaborate on the patient population eligible for treatment with the intended product. The sponsor was asked to provide more detailed results of any non-clinical or clinical data to support medical plausibility in this population.

- Significant benefit

The role of the proposed product in the treatment of PC was asked to be discussed in more detail, especially the patient population for which the product is intended. A discussion on significant benefit compared to the standard of care for that population was requested. The sponsor was asked to detail the results of any clinical data to support the significant benefit assumption in the context of the current therapeutic management of patients.

In the written response, and during an oral explanation before the Committee on 19 January 2022, the sponsor confirmed that the patient population for which the product is intended is locally advanced disease and referred to the trial currently ongoing. This is a phase Ib/II trial for the treatment of patients with locally advanced pancreatic cancer, but no clinical data demonstrating the effect of the proposed product on this population are yet available. The preliminary safety data obtained on 3 patients show a good tolerance of the combination of gadolinium-chelated polysiloxane nanoparticles with SBRT (stereotactic body radiation therapy) (total dose of 40 Gy in 5 fractions of 8 Gy).

The plan is also to expand the treatment and include borderline resectable patients for a registration trial.

The position of radiotherapy alone in the treatment of pancreatic cancer can be debated and chemo radiotherapy might be a more common treatment modality. However, as the sponsor was able to show that their product has the ability to improve the efficacy of radiotherapy , as shown in the non-clinical studies, the COMP considered that that could be sufficient proof of significant benefit at the time of orphan designation.

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

The intention to treat the condition with the medicinal product containing gadolinium-chelated polysiloxane nanoparticles was considered justified based on non-clinical in vivo studies showing a reduction in tumour growth and survival benefit when the product was combined with radiotherapy.

The condition is chronically debilitating due to pain in the upper abdomen, loss of appetite, nausea, vomiting, weight loss, jaundice, fatigue, weakness and depression and life-threatening with a markedly reduced life expectancy.

The condition was estimated to be affecting approximately 2.3 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 gadolinium-chelated polysiloxane nanoparticles will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate that combining the product with radiotherapy results in reduction of tumour growth and improved survival as compared to radiation alone. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for gadolinium-chelated polysiloxane nanoparticles, for treatment of pancreatic cancer, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. valemetostat tosilate - EMA/OD/0000061188

Daiichi Sankyo Europe GmbH; Treatment of peripheral T-cell lymphoma

COMP Rapporteur: Bozenna Dembowska-Baginska

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

The intention to treat the condition with the medicinal product containing valemetostat tosilate was considered justified based on preliminary clinical data in relapsed/refractory patients who responded to treatment with valemetostat tosilate monotherapy.

The condition is life-threatening and chronically debilitating due to poor response to therapy and high rate of relapses. Clinical presentation and course vary from an indolent clinical behaviour for years in milder subtypes, to fulminant disease in aggressive sub-types.

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.

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 valemetostat tosilate will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing anti-tumour activity in patients affected by the condition that have failed best standard of care including authorised therapies. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for valemetostat tosilate, for treatment of peripheral T-cell lymphoma, was adopted by consensus.

2.2.2. vatiquinone - EMA/OD/0000063681

PTC Therapeutics International Limited; Treatment of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

COMP Rapporteur: Ingeborg Barisicz

The Committee agreed that the condition, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing vatiquinone was considered justified based on preliminary clinical data suggesting a positive effect in disease symptoms, as compared to patients' baseline values.

The condition is life-threatening and chronically debilitating due to the recurrence of seizures, vomiting and headaches, anorexia, exercise intolerance, proximal limb weakness, sensorineural hearing loss and stroke-like episodes with transient hemiparesis and/or

cortical blindness. The onset of disease is between the age of 2 and 10 years and patients have a reduced life expectancy.

The condition was estimated to be affecting less than 0.5 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 vatiquinone, for treatment of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episode, was adopted by consensus.

2.2.3. - EMA/OD/0000064376

Treatment of incomplete spinal cord injury

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 February meeting.

2.2.4. - EMA/OD/0000068622

Treatment of narcolepsy

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 February meeting.

2.2.5. - EMA/OD/0000068912

Treatment of gastro-entero-pancreatic neuroendocrine tumours

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 February meeting.

2.2.6. pyridoxal 5'-phosphate - EMA/OD/0000069374

Amsterdam UMC; Treatment of pyridoxamine 5'-phosphate oxidase deficiency

COMP Rapporteur: Giuseppe Capovilla

The Committee agreed that the condition, pyridoxamine 5'-phosphate oxidase deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing pyridoxal 5'-phosphate was considered justified based on bibliographical data which suggests sustained seizure control in patients with the condition.

The condition is chronically debilitating due to seizure recurrence and neurocognitive impairment and life-threatening due to intractable seizures which may be fatal.

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 pyridoxal 5'-phosphate, for treatment of pyridoxamine 5'-phosphate oxidase deficiency, was adopted by consensus.

2.2.7. bovactant - EMA/OD/0000069674

Aerogen Pharma Limited; Treatment of respiratory distress syndrome

COMP Rapporteur: Martin Mozina

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

The intention to treat the condition with the medicinal product containing bovactant was considered justified based on clinical data suggesting a reduced need for endotracheal intubation and bolus instillation and a reduced occurrence of bronchopulmonary dysplasia.

The condition is life-threatening due to pulmonary complications leading to high mortality rates and chronically debilitating due to the consequences of hypoxia including encephalopathy and iatrogenic morbidity related to respiratory assistance, such as bronchopulmonary dysplasia and retinopathy of prematurity.

The condition was estimated to be affecting approximately 2.5 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 bovactant will be of significant benefit to those affected by the condition. The sponsor has provided clinical data suggesting a reduced need for endotracheal intubation and bolus instillation and a reduced occurrence of bronchopulmonary dysplasia compared to patients receiving standard of care therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for bovactant, for treatment of respiratory distress syndrome, was adopted by consensus.

2.2.8. [Ala1,3,12,Gln10,Arg11,Trp14]PTH(1-14)/[Ala18,22, Lys26]PTHrP(15-36)COOH - EMA/OD/0000069873

Amolyt Pharma; Treatment of hypoparathyroidism

COMP Rapporteur: Vallo Tillmann

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

The intention to treat the condition with the medicinal product containing [Ala1,3,12,Gln10,Arg11,Trp14]PTH(1-14)/[Ala18,22, Lys26]PTHrP(15-36)COOH was considered justified based on non-clinical data in valid models of the disease which showed sustained normalisation of calcium and phosphate serum levels.

The condition is chronically debilitating due to neuromuscular symptoms, cognitive impairment, abnormal calcium and phosphate metabolism, and reduced bone turnover. The condition may be life-threatening due to risk of hypocalcaemia that may lead to seizures, cardiac arrhythmias, cardiomyopathy and laryngeal spasm if untreated.
The condition was estimated to be affecting approximately 3 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 [Ala1,3,12,Gln10,Arg11,Trp14]PTH(1-14)/[Ala18,22, Lys26]PTHrP(15-36)COOH will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in valid models of the disease that demonstrate sustained normalisation over 24 hours of calcium and phosphate serum levels without hypercalciuria, which cannot be achieved with current standard of care therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for [Ala1,3,12,Gln10,Arg11,Trp14]PTH(1-14)/[Ala18,22, Lys26]PTHrP(15-36)COOH, for treatment of hypoparathyroidism , was adopted by consensus.

2.2.9. 18-mer antisense oligonucleotide complementary to SCN1A mRNA, sodium salt- EMA/OD/0000072303

Insidereg Limited; Treatment of Dravet syndrome

COMP Rapporteur: Giuseppe Capovilla

Action: For discussion/adoption

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

The intention to treat the condition with the medicinal product containing 18-mer antisense oligonucleotide complementary to SCN1A mRNA, sodium salt was considered justified based on data in a valid non-clinical in vivo model of the condition demonstrating significant reduction in seizure occurrence and mortality. In addition, the product was able to prolong latency to the first seizure.

The condition is chronically debilitating due to psychomotor and cognitive impairment and the occurrence of seizures, and life-threatening due to sudden unexpected death in epilepsy.

The condition was estimated to be affecting less than 0.5 in 10000 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 18-mer antisense oligonucleotide complementary to SCN1A mRNA, sodium salt will be of significant benefit to those affected by the condition. The sponsor has provided nonclinical in vivo data that demonstrate that the proposed product can act as a disease modifier with the potential ability to correct the genetic pathway of Dravet syndrome and improved survival which currently authorised medicines do not have in their indication. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 18-mer antisense oligonucleotide complementary to SCN1A mRNA, sodium salt, for treatment of Dravet syndrome, was adopted by consensus.

2.2.10. autologous CD34+ cells edited with CRISPR/CAS9 and transduced with an adeno-associated virus vector serotype 6 containing the codon-optimized version of *PKLR* gene - EMA/OD/0000072308

Consorcio Centro de Investigación Biomédica en Red, M.P.; Treatment of pyruvate kinase deficiency

COMP Rapporteur: Gloria Maria Palomo Carrasco

The Committee agreed that the condition, pyruvate kinase deficiency, 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+ cells edited with CRISPR/Cas9 and transduced with an adeno-associated virus vector serotype 6 containing the codon-optimized version of *PKLR* gene was considered justified based on non-clinical in vivo data in a valid model of the condition showing good engraftment and restoration of ATP production in erythroid cells.

The condition is chronically debilitating and life-threatening due to symptoms of chronic haemolytic anaemia and sequelae of periodic red blood cell transfusions, comprising fatigue, shortness of breath, splenomegaly, cholecystolithiasis, heart failure, as well as compromised immune function and thromboembolic complications after splenectomy. The condition is also life-threatening due to aggravation of haemolytic anaemia during pregnancy and aplastic crisis during viral infections, as well as hydrops fetalis and perinatal death.

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.

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 autologous CD34+ cells edited with CRISPR/Cas9 and transduced with an adeno-associated virus vector serotype 6 containing the codon-optimized version of *PKLR* gene, for treatment of pyruvate kinase deficiency, was adopted by consensus.

2.2.11. epcoritamab - EMA/OD/0000072899

AbbVie Deutschland GmbH & Co. KG; Treatment of diffuse large B-cell lymphoma (DLBCL)

COMP Rapporteur: Frauke Naumann-Winter

The Committee agreed that the condition, diffuse large B-cell lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing epcoritamab was considered justified based on preliminary clinical data showing responses achieved in patients with relapsed/refractory diffuse large B-cell lymphoma.
The condition is chronically debilitating due to involvement of single or multiple nodal or extranodal sites, including the gastrointestinal tract, the central nervous system and bone marrow and life-threatening in patients with relapsed/refractory disease.
The condition was estimated to be affecting approximately 4 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 epcoritamab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data which demonstrated that heavily pre-treated patients with relapsed/refractory diffuse large B-cell lymphoma responded to treatment with the current product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for epcoritamab, for treatment of diffuse large B-cell lymphoma, was adopted by consensus.

2.2.12. enzastaurin hydrochloride - EMA/OD/0000073562

Dlrc Pharma Services Limited; Treatment of Ehlers-Danlos syndrome

COMP Rapporteur: Zsofia Gyulai

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

The intention to treat the condition with the medicinal product containing enzastaurin hydrochloride was considered justified based on data from a valid non-clinical in vivo model of the condition showing an improvement in survival and a reduction of aortic rupture.

The condition is life-threatening and chronically debilitating due to joint instability, chronic musculoskeletal pain, degenerative joint disease, frequent injuries, and spinal deformities which may limit mobility. Patients with blood vessel fragility have a high risk of fatal complications, including spontaneous arterial rupture, which is the most common cause of sudden death.

The condition was estimated to be affecting approximately 0.3 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 enzastaurin hydrochloride, for treatment of Ehlers-Danlos syndrome, was adopted by consensus.

2.2.13. - EMA/OD/0000073624

Prevention of graft versus host disease

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 February meeting.

2.2.14. - EMA/OD/0000073716

Treatment of epidermolysis bullosa

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 February meeting.

[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 03 February 2022.]

2.2.15. cannabidiol - EMA/OD/0000073948

EUDRAC GmbH; Treatment of fragile X syndrome (FXS)

COMP Rapporteur: Dinah Duarte

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

The intention to treat the condition with the medicinal product containing Cannabidiol was considered justified based on clinical data suggesting positive behavioural effects in a subset of patients with fragile X syndrome.

The condition is chronically debilitating due to developmental delay and a range of neurobehavioral and neurocognitive complications.

The condition was estimated to be affecting less than 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 cannabidiol, for treatment of fragile X syndrome, was adopted by consensus.

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 rapporteurs were appointed for 19 applications.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 13 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of cystic fibrosis

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 myasthenia gravis

The finalised letter was circulated for information.

3.2.2. -

Treatment of tuberous sclerosis

The finalised letter was circulated for information.

3.3. New requests

None

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. – artesunate - EMEA/H/C/005718/0000, EMA/OD/043/15, EU/3/15/1521, EMA/OD/0000063220

B And O Pharm; Treatment of malaria

The status of the procedure at CHMP was noted.

4.2.2. AYVAKYT – avapritinib - EMEA/H/C/005208/X/0004/G, EMA/OD/079/18, EU/3/18/2074, EMA/OD/0000071880

Blueprint Medicines (Netherlands) B.V. Treatment of mastocytosis

COMP Rapporteurs: Frauke Naumann-Winter; Tim Leest; CHMP Rapporteur: Blanca Garcia-Ochoa; CHMP Co-Rapporteur: Ingrid Wang

Action: For discussion/adoption

Action: For discussion/adoption

An opinion recommending not to remove Ayvakyt, avapritinib EU/3/18/2074 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 January meeting.]

4.2.3. Breyanzi – lisocabtagene maraleucel - EMEA/H/C/004731/0000

Celgene Europe B.V.

a) Treatment of primary mediastinal large-B-cell lymphoma, EMA/OD/0000001127, EU/3/18/2099, EMA/OD/0000039978

b) Treatment of diffuse large B-cell lymphoma, EMA/OD/045/17, EU/3/17/1890, EMA/OD/0000039934

c) Treatment of follicular lymphoma, EMA/OD/260/17, EU/3/18/2018, EMA/OD/0000039979

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 February meeting.

4.2.4. – tebentafusp - EMEA/H/C/004929/0000, EMA/OD/0000030272, EU/3/21/2397, EMA/OD/0000068646

Accelerated assessment

Immunocore Ireland Limited; Treatment of uveal melanoma

Postponed

4.3. Appeal

4.3.1. Nexviadyme - avalglucosidase alfa - EMEA/H/C/005501/0000, EU/3/14/1251

Genzyme Europe B.V.; Treatment of Pompe's disease

Action: For information, appointment of rapporteurs

The COMP noted the intent to appeal from the applicant. The appeal rapporteurs were appointed

4.3.2. Uplizna – inebilizumab - EMEA/H/C/005818/0000, EMA/OD/267/16, EU/3/17/1856, EMA/OD/0000079956

Viela Bio B.V.; Treatment of neuromyelitis optica spectrum disorders

Action: For information, appointment of rapporteurs

The COMP noted the intent to appeal from the applicant. The appeal rapporteurs were appointed

4.4. On-going procedures

The COMP noted the review of orphan designation for OMP for MA - On-going procedures

COMP co-ordinators were appointed for 3 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

The COMP noted the review of orphan designation for OMP for MA extension - On-going procedures

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. COMP membership

The COMP welcomed Mrs Jana Mazelova as new COMP member representing Czechia. The COMP also welcomed new expert Maria Cavaller-Bellaubi and thanked the previous expert Virginie Hivert for her contributions.

7.1.2. Vote by proxy

None

7.1.3. Strategic Review & Learning meetings

None

7.1.4. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely on 17 January 2022.

7.1.5. Principal Decisions Database

The COMP acknowledged the importance of adding further topics to the database.

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. PRIME – Analysis of the first 5 years' experience

The COMP noted the PRIME analysis of the first 5 years' experience. On the request of COMP, the deadline to provide feedback was extended until 20th January 2022. The COMP discussed and gathered the comments received, which will be further discussed at the upcoming SciCoBo meeting.

7.2.3. COMP-CAT Working Group

The COMP-CAT Working Group met remotely on 17 January 2022.

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

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

Documents were tabled for information.

7.3.2. Working Party with Healthcare Professionals' Organisations (HCPWP)

Documents were tabled for information.

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

None

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

The COMP adopted the work plan.

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 and 2022

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2021 and 2022 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

None

9. List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 18-20 January 2022 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	Member (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	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No interests declared	
Elli Loizidou	Member	Cyprus	No interests declared	
Jana Mazelova	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 restrictions applicable to this meeting	
Frauke Naumann-Winter	Member	Germany	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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 restrictions applicable to this meeting	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No restrictions applicable to this meeting	
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 interests declared	
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	
Darius Matusevicius	Member	Sweden	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
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Ines Alves	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	
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	
Maria Cavaller Bellaubi	Expert via WebEx	Expert	No restrictions applicable to this 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/