16 April 2019
EMA/COMP/305701/2019
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 19-21 March 2019

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

19 March 2019, 09:00-19:30, room 0-H

20 March 2019, 08:30-18:00, room 0-H

21 March 2019, 08:30-15:00, room 0-H

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.

Further information with relevant explanatory notes can be found at the end of this document.

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).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction

1.1. Welcome and declarations of interest of members and experts

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 the restricted involvement of some meeting participants in upcoming discussions 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. 23 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 19-21 March 2019 was adopted with no amendments.

1.3. Adoption of the minutes

The COMP minutes for 19-21 February 2019 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. Autologous human bone marrow-derived hematopoietic and mesenchymal stem cells depleted of erythrocytes, monocytes and lymphocytes - EMA/OD/0000002559

Neuroplast B.V.; Treatment of spinal cord injury

COMP rapporteur: Dinah DuarteAs 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 calculation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor was invited to revisit the assumed disease durations that were used to estimate prevalence based on contemporaneous epidemiological literature. The COMP has previously considered longer disease durations for traumatic and non-traumatic forms of the condition.

In the written response, the sponsor updated the previously presented prevalence estimate. The sponsor collected and presented scientific literature on the survival times of patients with traumatic and non-traumatic spinal cord injury respectively. The average survival time for both sub-populations was calculated. The COMP accepted the average survival times of 19.41 years for traumatic spinal cord injury and 7.37 years for non-traumatic spinal cord injury. This resulted in a total prevalence estimate of 4.46 per 10,000 inhabitants (4.04 traumatic and 0.42 non-traumatic) as per formula P=I*D.

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

The intention to treat the condition with the medicinal product containing autologous human bone marrow-derived haematopoietic and mesenchymal stem cells depleted of erythrocytes, monocytes and lymphocytes was considered justified based on non-clinical data suggesting that the proposed product can improve motor function in valid models of the condition.

The condition is chronically debilitating due to sensory and motor loss function in the limbs, and life-threatening with overall reduced life expectancy.

The condition was estimated to be affecting approximately 4.46 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 human bone marrow-derived haematopoietic and mesenchymal stem cells depleted of erythrocytes, monocytes and lymphocytes will be of significant benefit to those affected by the condition. The sponsor has provided nonclinical data that suggest that the proposed product can improve motor function to a higher degree than the currently authorised product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous human bone marrow-derived haematopoietic and mesenchymal stem cells depleted of erythrocytes, monocytes and lymphocytes, for treatment of spinal cord injury, was adopted by consensus.

2.1.2. Balipodect - EMA/OD/0000002563

Takeda Pharma A/S; Treatment of fragile X syndrome

COMP rapporteur: Giuseppe CapovillaAs 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 has provided a prevalence calculation based on one publication only. The COMP considered that the prevalence calculation was very limited and should have included more current publications in order to offer a more complete calculation.

For the calculation and presentation of the prevalence estimate the sponsor is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

In writing, the sponsor further elaborated on the issue of prevalence. FXS prevalence was obtained from a systematic meta-analysis performed by Hunter et al (Am J Med Genet A. 2014 Jul;164A(7):1648-58), i.e. 1.15 per 10,000. In view of the uncertainty inherent in

these calculations, the formal estimate for orphan designation purposes was considered to be not more than 2 per 10,000. The small number of prevalence estimates based on data <20 years old which are not considered by Hunter *et al*. are in line with this estimate.

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 balipodect was considered justified based on data from a non-clinical *in vivo* model of the condition showing a significant attenuation of hyperactivity and a reduction in freezing behavior and in seizure frequency.

The condition is chronically debilitating due to developmental delay, severe neurobehavioural and neurocognitive complications.

The condition was estimated to be affecting approximately 2 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 balipodect, for treatment of fragile X syndrome, was adopted by consensus.

2.1.3. 3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-pyrazol-1-yl)propanoic acid - EMA/OD/0000002526

TMC Pharma (EU) Limited; Treatment of Stargardt's disease

COMP rapporteur: Tim LeestAs 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

Stargardt’s disease should be further discussed as distinct medical entity. The classification and the current clinical and genetic understanding of Stargardt’s disease should be discussed in the context of the broader terms macular degeneration or inherited retinal dystrophies. The Committee noted that this is for the purposes of orphan medicinal product designation; the sponsor’s attention was drawn to the Orphan Regulation and relevant guidelines (especially section A of ENTR/6283/00).

To establish correctly, whether there exists a scientific rationale for the development of the proposed product for treatment of Stargardt's disease, the sponsor was asked to provide additional non-clinical data from valid models of the condition that would suggest improvements regarding ERG or other functional endpoints.

In the written response, and during an oral explanation before the Committee on 19 March 2019, the sponsor discussed the current understanding of Stargardt’s disease within the broader terms “macular degeneration” or “inherited retinal dystrophies”. The sponsor was of the opinion that Stargardt’s disease continues to be a well-established clinical entity based on its genetic basis, the pathophysiology, the clinical presentation and diagnostic features and prognosis. The COMP agreed with the sponsor and designated Stargardt’s disease as the orphan condition for this application.

Regarding medical plausibility, the sponsor justified the absence of more functional or ERG outcomes from valid models at that point in time. The disease model that has been used to

test efficacy of the proposed product shows accelerated light-dependent deposition of A2E (Bis-retinoid *N*-retinyl-*N*-retinylidene ethanolamine) as a major fluorophore of lipofuscin, which is consistent with Stage II-III of the human disease, however the model does not manifest with retinal degeneration, which is not consistent with the human phenotype. Another model was discussed in which retinal degeneration could be tested; however the sponsor argued that this model also shows inherent differences to the human phenotype. Moreover, the sponsor presented further details on the biomarker A2E and its association with disease pathology, even though surrogacy has not yet been established. The COMP outlined that in general a higher level of evidence would be required to demonstrate medical plausibility, i.e. functional endpoints in valid models. Nevertheless, the COMP accepted the sponsor's argumentation and justification to receive orphan designation based on the presented data with the strong recommendation to seek protocol assistance for the future clinical development.

The Committee agreed that the condition, Stargardt's disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-pyrazol-1-yl)propanoic acid was considered justified based on non-clinical data demonstrating that the proposed product can decrease the biomarker A2E, which is associated with the toxic accumulation of lipofuscin.

The condition is chronically debilitating, in particular due to loss of visual acuity and central vision loss, which may progress to complete blindness.

The condition was estimated to be affecting approximately 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-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-pyrazol-1-yl)propanoic acid, for treatment of Stargardt's disease, was adopted by consensus.

2.1.4. EMA/OD/0000002530

Treatment of invasive aspergillosis

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:

- Medical plausibility

To establish correctly, if there exists a scientific rationale for the development of the proposed product for treatment of invasive aspergillosis the sponsor should further elaborate on the model used for the treatment of invasive aspergillosis, and the interpretation of the results obtained in the experiments.

In particular a) the intravenous route of challenge b) the absence of dose response effects and negative controls c) the low number of subjects per group and the absence of statistical analysis, as well as d) the absence of data in more relevant models of the proposed condition are expected to be discussed.

- Prevalence

The sponsor was requested to recalculate the prevalence of the proposed condition and provide a sensitivity analysis of the assumptions made.

- 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 discuss the arguments provided for significant benefit and to elaborate on the results from the non-clinical studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition, taking also into consideration that the strain used in the non-clinical experiments appears to be sensitive to some authorised treatments.

In the written response, and during an oral explanation before the Committee on 19 March 2019, the sponsor further elaborated on the raised issues. With regards to the medical plausibility, it was stressed that the used *in vivo* model is a demanding one, with a virulent strain administered IV (intravenous) and at a late time of treatment. No new data in relevant *in vivo* models of the condition with the specific product as applied for designation was submitted, and the sponsor alluded to the *in vitro* activity in various microbial targets.

The COMP noted the general absence of data in relevant *in vivo* models as well as the limited number of observations and the absence of dose-response effects in the data provided so far. The uncertainties regarding the mechanism of action also did not support the rationale of treating the condition.

Regarding prevalence, the sponsor provided a sensitivity analysis by varying the incidence of the condition in the EU by a 20% margin. After considering different populations at risk, incidence was calculated up to 1.036/10,000. The COMP considered that the proposal was in line with previous considerations for the proposed condition and that the number of affected patients was less than 2 in 10,000.

With regard to the significant benefit, the applicant alluded to an indirect comparison on the basis of the broad antimicrobial spectrum of the proposed product, as well as published studies in invasive pulmonary aspergillosis models where amphotericin and itraconazole did not eradicate the fungus. Such indirect comparisons were not considered acceptable by the COMP, on the grounds of comparability and on the limitations of the submitted *in vivo* data with the product as described above.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 19 March 2019, prior to final opinion.

2.1.5. EMA/OD/0000002735

Treatment of hepatocellular carcinoma

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 08 March 2019, prior to responding to the list of issues.

2.1.6. EMA/OD/0000002861

Treatment of follicular lymphoma

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 provided a calculation of point prevalence, which assumes 10 years disease duration (considering longer survival as evidence of cure) and adjusts for disease cure rate as well as transformation into aggressive NHL (non-Hodgkin lymphoma). In COMP's view the methodology proposed by the sponsor and the assumed disease duration are not acceptable.

For the calculation and presentation of the prevalence estimate the sponsor is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

Follicular lymphoma (FL) is an indolent and incurable disease. Therefore, the sponsor was asked to provide a recalculation based on:

1. Current crude prevalence/incidence data (*e.g.,* estimating FL based on appropriate NHL incidence as reported by Ferlay *et al.* 2018);

2. An estimation of actual disease duration based on current literature (*e.g.*, Provencio *et al*. 2017).

The sponsor was asked to provide a sensitivity analysis in which the main assumptions (current crude incidence, duration of disease, improvement in survival) are varied in order to assure that the proposed prevalence calculation appropriately describes the epidemiology of the disease at the time of designation.

- Significant benefit

The sponsor presented data from a clinical study in which patients were refractory/relapsed after at least two lines of treatment including rituximab and alkylating agents.

The arguments of significant benefit versus other products authorised in the same clinical setting were based on an improved safety profile vs. idelalisib as well as on improved efficacy due to the fact that obinutuzumab + bendamustine and ibritumomab tiuxetan are rarely used in third line of treatment. The safety profile of the proposed product is not considered mature at this point, which makes assumptions of improvement difficult. The sponsor might consider providing post marketing safety data. A comparative discussion of the efficacy of the other two products in third line setting would be expected.

Furthermore, it would be useful to obtain more information on the ongoing study/planned development.

In the written response, and during an oral explanation before the Committee on 20 March 2019, the sponsor provided a new calculation of prevalence using the incidence figure from Globocan 2018 of 1.35 in 10,000, the proportion of FL within NHL of 14,7% and assuming the disease duration of 20 years. The sensitivity analysis provided a range of values resulting from varying the disease duration (between 12.5 – 25 years). The incidence value was questioned by the COMP, because the ECIS (European Cancer Information System) 2018 database (which sources its numbers from the same IARC (International Agency for Research on Cancer) database as GLOBOCAN (Global Cancer Incidence, Mortality and Prevalence) provided a larger crude incidence number. The number provided by the sponsor was closer to the age-standardised incidence in the same database. The COMP therefore did not find the proposed prevalence calculation complete and convincing.

With regards to significant benefit, the COMP acknowledged the safety issues reported for idelalisib, and that the available clinical data suggest an improved safety profile of the proposed product. The sponsor also presented arguments for significant benefit over the combination therapy with obinutuzumab and bendamustine based on indirect comparison of clinical data and the discussion of the respective treatment indications. The COMP considered that the product will be used in a later line of treatment and that the indirect comparison suggests a potential for improved efficacy of the proposed product in the third line setting.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 20 March 2019, prior to final opinion.

2.1.7. EMA/OD/0000002754

Treatment of Mucopolysaccharidosis type III (Sanfilippo syndrome)

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 Mucopolysaccharidosis type III (Sanfilippo syndrome), the sponsor was asked to further elaborate on the medical plausibility, given that valid nonclinical *in vivo* models of the condition are known to exist. The sponsor was asked to explain why these models had not been used to establish the medical plausibility of this product for the treatment of this condition.

In the written response, and during an oral explanation before the Committee on 20 March 2019, the sponsor further elaborated on the raised issue. The COMP highlighted to the applicant that they do not normally accept *in vitro* level evidence, without additional pre-clinical *in vivo* or clinical observations in the sought indication. It was also highlighted that several MPS III *in vivo* models exist, of which some are knock-out models. It was noted that the applicant has not provided any valid explanation for not preforming *in vivo* experiments. The COMP concluded 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 21 March 2019, prior to final opinion.

2.2. For discussion / preparation for an opinion

2.2.1. EMA/OD/0000002397

Treatment of Cushing syndrome

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 April meeting.

2.2.2. Human culture expanded autologous mesenchymal stromal cells - EMA/OD/0000002775

IQVIA RDS Ireland Limited; Treatment of amyotrophic lateral sclerosis

COMP rapporteur: Zsofia GyulaiThe COMP agreed that the condition, amyotrophic lateral sclerosis (ALS), was a distinct medical entity and met the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing human culture expanded autologous mesenchymal stromal cells was considered justified based on clinical observations showing a delay in functional decline as measured by ALS Functional Rating Scale Revised (ALSFRS-R) in treated patients.

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 human culture expanded autologous mesenchymal stromal cells will be of significant benefit to those affected by the condition. The sponsor has provided clinical observations showing a delay in functional decline as measured by ALSFRS-R when the product is added-on to the authorised riluzole treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for human culture expanded autologous mesenchymal stromal cells, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.2.3. EMA/OD/0000003085

Treatment of non-small cell lung cancer with MET alterations

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 April meeting.

2.2.4. EMA/OD/0000003147

Treatment of lichen planopilaris

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 April meeting.

2.2.5. EMA/OD/0000003185

Treatment of Angioimmunoblastic T-cell lymphomas (AITL)

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 April meeting.

2.2.6. EMA/OD/0000003203

Treatment of Enteropathy-associated T-cell lymphoma (EATL)

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 April meeting.

2.2.7. Modified messenger ribonucleic acid encoding human propionyl-coenzyme A carboxylase alpha and beta subunits encapsulated into lipid nanoparticle - EMA/OD/0000003207

Pharma Gateway AB; Treatment of propionic acidaemia

COMP rapporteur: Ingeborg BarisicThe COMP 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 modified messenger ribonucleic acid encoding human propionyl-coenzyme A carboxylase alpha and beta subunits encapsulated into lipid nanoparticle was considered justified based on non-clinical data in valid models of the condition showing reduction of hyperammonaemia and of relevant biomarkers, accompanied by reduction of heart mass.

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. In milder forms of the disease, hypertrophic cardiomyopathy, with consequent arrhythmia and heart failure, is the main cause of 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 modified messenger ribonucleic acid encoding human propionyl-coenzyme A carboxylase alpha and beta subunits encapsulated into lipid nanoparticle will be of significant benefit to those affected by the condition. The administration of the proposed product in non-clinical models resulted in production of functional propionyl CoA carboxylase, the protein defective in the condition. This offers the potential of treating clinical manifestations that are not addressed by the currently authorised product for the condition, which only treats hyperammonaemia. The sponsor has provided non clinical data in models of the condition, showing that the proposed product not only improves hyperammonaemia but also reduces heart mass, on which the medicinal product currently authorised has no effects. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for modified messenger ribonucleic acid encoding human propionyl-coenzyme A carboxylase alpha and beta subunits encapsulated into lipid nanoparticle, for treatment of propionic acidaemia, was adopted by consensus.

2.2.8. Sodium benzoate, sodium phenylacetate - EMA/OD/0000003216

Dipharma B.V.; Treatment of ornithine transcarbamylase deficiency

COMP rapporteur: Martin MozinaThe Committee agreed that the condition, ornithine transcarbamylase deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing sodium benzoate, sodium phenylacetate was considered justified based on clinical data demonstrating improved survival of patients affected by the condition.

The condition is chronically debilitating and life threatening due to the consequences of metabolic decompensation leading to developmental delay, mental disability, and other types of neurological damage.

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 sodium benzoate, sodium phenylacetate will be of significant benefit to those affected by the condition. The sponsor has provided clinical data demonstrating improved survival of patients affected by the condition. The data support that the proposed product can treat patients affected by the condition in the emergency situation of acute hyperammonaemia occurring despite the chronic management of hyperammonaemia with the currently authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for sodium benzoate, sodium phenylacetate, for treatment of ornithine transcarbamylase deficiency, was adopted by consensus.

2.2.9. EMA/OD/0000003229

Treatment in solid organ transplantation

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 April meeting.

2.2.10. EMA/OD/0000003554

Treatment of loculated pleural effusion

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 April meeting.

2.2.11. EMA/OD/0000004269

Treatment of lymphoplasmacytic 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 April meeting.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

2.4.1. Eculizumab – EMA/OD/0000003544

Alexion Europe S.A.S.; Treatment of neuromyelitis optica; Proposed new indication: Treatment of neuromyelitis optica spectrum disorders

COMP rapporteur: Michel Hoffmann

For the purpose of amendment of an existing designation, the COMP considered that the amended condition proposed by the sponsor should be renamed as "treatment of neuromyelitis optica spectrum disorders" (hereinafter referred to as "the condition") based on the current international diagnostic consensus (Wingerchuk *et al.*, Neurology 2015; 85:1-13).

The Committee agreed that the condition, neuromyelitis optica spectrum disorders, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing eculizumab was considered justified based on clinical data supporting a delay of relapse in treated patients.

The condition is chronically debilitating and life-threatening due to neurological impairment such as paraplegia, sensory loss, bladder dysfunction, peripheral pain, and increased 5-year mortality.

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 that has been authorised in the European Union for patients affected by the condition.

A positive opinion for eculizumab, sodium phenylacetate, for treatment of neuromyelitis optica spectrum disorders, was adopted by consensus.

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 20 applications submitted.

2.7. Evaluation on-going

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

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of ATTR amyloidosis

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

3.1.2. -

Treatment of congenital adrenal hyperplasia

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 beta-thalassaemia intermedia and major

The discussion was postponed.

3.1.4. -

Treatment of hyperargininaemia

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

3.1.5. -

Treatment of adenosine deaminase-deficient-severe combined immunodeficiency

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 diffuse large B-cell lymphoma

The finalised letter was circulated for information.

3.2.2. -

Treatment of gastric carcinoid

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of amyotrophic lateral sclerosis

The new request was noted.

3.3.2. -

Treatment of cystinuria

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

4.1.1. Palynziq – Pegvaliase – EMEA/H/C/004744, EMEA/OD/112/09, EU/3/09/708

BioMarin International Limited; Treatment of hyperphenylalaninaemia

A list of issues was adopted on 21 February 2019.

No oral explanation was held.

The Committee confirmed that all issues previously identified in this application had been addressed.

An opinion recommending not to remove Palynziq 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.

4.1.2. Waylivra - volanesorsen – EMEA/H/C/004538, EMA/OD/180/13, EU/3/14/1249

Akcea Therapeutics UK Ltd; Treatment of familial chylomicronemia syndrome

An opinion recommending not to remove Waylivra 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 February meeting.]

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

4.2.1. Zynteglo - Autologous CD34+ haematopoietic stem cells transduced with lentiviral vector encoding the human betaA-T87Q-globin gene – EMEA/H/C/003691, EMA/OD/146/12, EU/3/12/1091

bluebird bio GmbH; Treatment of beta-thalassemia intermedia and major

An opinion recommending not to remove Zynteglo 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 March meeting.]

4.2.2. Pegylated recombinant factor VIII – EMEA/H/C/004883, EMA/OD/144/11, EU/3/12/995

Novo Nordisk A/S; Treatment of haemophilia A

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to respond in writing before the Committee April meeting.

4.2.3. Trientine dihydrochloride – EMEA/H/C/004111, EMEA/OD/043/03, EU/3/03/172

Univar BV; Treatment of Wilson's disease

The status of the procedure at CHMP was noted.

4.2.4. Soliris - eculizumab – Type II variation – EMEA/H/C/000791/II/0105, EMA/OD/087/13, EU/3/13/1185

Alexion Europe SAS; Treatment of neuromyelitis optica spectrum disorder

The status of the procedure at CHMP was noted.

4.2.5. Larotrectinib - EMEA/H/C/004919

Bayer AG;

a) Treatment of salivary gland cancer EMA/OD/213/17, EU/3/18/1995

b) Treatment of soft tissue sarcoma EMA/OD/184/15, EU/3/15/1606

The status of the procedure at CHMP was noted.

4.2.6. Glutamine – EMEA/H/C/004734, EMA/OD/016/12, EU/3/12/1011

Emmaus Medical Europe Limited; Treatment of sickle cell disease

The status of the procedure at CHMP was noted.

4.3. Appeal

None

4.4. On-going procedures

COMP rapporteurs were appointed for 9 applications.

4.5. Orphan Maintenance Reports

Documents were circulated in MMD.

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

5.2.1. Imnovid – pomalidomide – Type II variation – EMEA/OD/053/09, EU/3/09/672, EMEA/H/C/002682/II/0031/G

Celgene Europe Limited; Treatment of multiple myeloma

CHMP rapporteur: Greg Markey;

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to respond in writing before the Committee April meeting.

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 on 19 March 2019.

7.1.3. Non-Clinical Working Group

The working group on Non-Clinical met on 20 March 2019.

7.1.4. Prevalence Working Group

The topic was postponed.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendations on eligibility to PRIME – report from CHMP

Document was circulated in MMD.

Document(s) tabled:
PRIME eligibility requests - list of adopted outcomes February 2019

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

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

Action: For information

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

Action: For information

7.3.3. SAWP/COMP joint membership

Call for interest to replace COMP alternate representative at SAWP - Deadline 8 March 2019

Expression of interest received from Robert Nistico. The Committee agreed that Robert Nistico will become the COMP alternate representative at SAWP.

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.4.2. Handling of confidential information within the EU network

Presentation was given by EMA.

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

Action: For information

Notes: Monthly teleconference

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

Action: For information

Notes: Ad hoc basis meeting

7.5.3. The Therapeutic Goods Administration (TGA), Australia

Action: For information

Notes: Ad hoc basis meeting

7.5.4. Health Canada

Action: For information

Notes: Ad hoc basis meeting

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 2019

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2019 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. EMA Business Pipeline activity and Horizon scanning

Action: For information

Document tabled:
Q1/2019 Update of the Business Pipeline report for the human scientific committees

9. 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/

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 19-21 March 2019 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	
Brigitte Blöchl-Daum	Member	Austria	No interests declared	
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No interests declared	
Lenka Kovarova	Member	Czech Republic	No interests declared	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Annie Lorence	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Nikolaos Sypsas	Member	Greece	No restrictions applicable to this meeting	
Zsofia Gyulai	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member (Vice-Chair)	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Robert Nistico	Member	Malta	No interests declared	
Elizabeth 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	
Fernando Mendez Hermida	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Daniel O'Connor	Member	United Kingdom	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 participation in discussion, final deliberations and voting on:	3.2.1. 5.2.1. Imnovid – pomalidomide – Type II variation – EMEA/OD/053/09, EU/3/09/672, EMEA/H/C/002682/II/0031/G
Bruno Sepodes	Member	Expert recommended by EMA	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	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Virginie Hivert	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	
A representatives from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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