20 February 2020
EMA/COMP/33629/2020
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 20-22 January 2020

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

20 January 2020, 09:30-19:00, room 2A

21 January 2020, 08:30-18:15, room 2A

22 January 2020, 09:00-13:30, room 2A

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).

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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.

The COMP was pleased to welcome Mrs Cécile Dop replacing Dr Annie Lorence as member for France.

1.2. Adoption of agenda

The agenda for 20-22 January 2020 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 3-5 December 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. reldesemtiv - EMA/OD/0000010743

Pharma Gateway AB; Treatment of amyotrophic lateral sclerosis

COMP Rapporteur: Robert Nistico

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

- Intention to diagnose, prevent or treat

The sponsor presented data from a phase 2 study, which showed small effects in slow vital capacity (SVC), amyotrophic lateral sclerosis functional rating scale (ALSFRS-R) and muscle strength but did not achieve the expected effect sizes. The mechanism of action of the

product suggested that it could work as a symptomatic treatment in specific subgroups of patients, who still have some motor neurons preserved. The optimal target population was however not clear, in view of the study presented.

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of amyotrophic lateral sclerosis the sponsor was requested to further elaborate on:

a) the clinical relevance of the effects observed in the clinical study,

b) the intended study population in the future clinical development and justification thereof.

In the written response, the sponsor provided additional explanation of the data and provided information about the perceived clinical relevance of the changes observed in the presented clinical study. The slowing of the decline on ALSFRS-R scale of 25% was considered relevant and the COMP accepted the sponsor's explanation. The COMP also acknowledged that the future clinical development was discussed with the Agency as part of a scientific advice procedure. The written responses were considered satisfactory and the oral explanation was cancelled.

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 reldesemtiv was considered justified based on clinical data in patients showing improvements in ALSFRS-R score and slow vital capacity compared to placebo 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 reldesemtiv will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that the use of the product may slow down the deterioration of the motor function in patients. The product can also be used in combination with the current standard of care. The Committee considered that this constitutes a clinically relevant advantage.

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

2.1.2. autologous skin equivalent graft composed of keratinocytes and fibroblasts genetically corrected by CRISPR/Cas9-mediated excision of mutation-carrying exons within *COL7A1* collagenous domain - EMA/OD/0000013899

Consorcio Centro de Investigación Biomédica en Red, M.P.; Treatment of epidermolysis bullosa

COMP Rapporteur: Armando Magrelli

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 application encompassed more than one product (requiring more than one orphan designation application), as the targeting of different exons would require different sets of guide RNAs. The COMP would consider each targeted exon as relating to a separate medicinal product and noted that most of the data pertained to a product targeting exon 80.

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of epidermolysis bullosa the sponsor was requested to further elaborate on:

a) the characteristics of the specific product proposed for designation, including the guide RNAs and targeted exon(s),

b) confirm to which product the non-clinical data presented corresponds.

In the written response, and during an oral explanation before the Committee on 20 January 2020, the sponsor presented more details of different guide RNAs used for the generation of grafts. The sponsor clarified that they would accept receiving a first designation for "autologous skin equivalent graft composed of keratinocytes and fibroblasts genetically corrected by CRISPR/Cas9-mediated excision of mutation-carrying COL7A1 exon 80. The COMP considered that that would be the appropriate product to designate on the basis of the presented data. Based on the provided justifications pertaining to the exon-80 edited graft, the medical plausibility was considered acceptable.

Following review of the application by the Committee, it was agreed to rename the active substance to "Autologous skin equivalent graft composed of keratinocytes and fibroblasts genetically corrected by CRISPR/Cas9-mediated excision of mutation-carrying COL7A1 exon 80".

The Committee agreed that the condition, treatment of epidermolysis bullosa, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing Autologous skin equivalent graft composed of keratinocytes and fibroblasts genetically corrected by CRISPR/Cas9-mediated excision of mutation-carrying COL7A1 exon 80 is justified based on data in an in vivo model supporting expression of collagen VII and functional integrity of the graft.

The condition is life-threatening and chronically debilitating due to blister formation in response to minor friction or trauma, leading to the development of multiple complications including life-threatening infections, failure to thrive, and predisposition to the development of squamous cell carcinoma.

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

The sponsor 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 skin equivalent graft composed of keratinocytes and fibroblasts genetically corrected by CRISPR/Cas9-mediated excision of mutation-carrying

COL7A1 exon 80, for treatment of treatment of epidermolysis bullosa, was adopted by consensus.

2.1.3. combination of three adeno-associated viral vectors of serotype 8 containing the 5'-, the body- and the 3'- coding sequences of human CEP290 fused to inteins - EMA/OD/0000018285

Fondazione Telethon; Treatment of Leber's congenital amaurosis

COMP Rapporteur: Tim Leest

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

According to the COMP, the proposed orphan condition should be broadened to: treatment of inherited retinal dystrophies. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention was drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

In case of disagreement, the sponsor was asked to justify 'Leber's congenital amaurosis' as a distinct medical entity or a valid subset for the purpose of orphan designation.

- Prevalence

The sponsor was requested to amend the prevalence calculation to include all types of inherited retinal dystrophies to reflect the amended indication.

In the written response, the sponsor agreed to rename the condition to 'treatment of inherited retinal dystrophies'. The sponsor provided a new prevalence calculation and proposed it to be 2.6 in 10,000 persons in the EU based on a Norwegian publication from 2019. The COMP acknowledged uncertainties regarding the prevalence and decided to designate 'less than 3 in 10,000 persons in the EU' also taking into consideration previous opinions for this indication.

The written responses were considered satisfactory and the oral explanation was cancelled.

Following review of the application by the Committee, it was agreed to rename the indication to treatment of inherited retinal dystrophies.

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

The intention to treat the condition with the medicinal product containing combination of three adeno-associated viral vectors of serotype 8 containing the 5'-, the body- and the 3'-coding sequences of human CEP290 fused to inteins was considered justified based on non-clinical data demonstrating improved light sensitivity and preserved thickness of the retinal outer nuclear layer.

The condition is chronically debilitating due to loss of sight.

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.

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 combination of three adeno-associated viral vectors of serotype 8 containing the 5'-, the body- and the 3'- coding sequences of human CEP290 fused to inteins will be of significant benefit to those affected by the condition. The sponsor provided non-clinical data that demonstrate that the product will be used in patients affected by CEP290 mutations. There was no other product specifically addressing the needs of these patients. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for combination of three adeno-associated viral vectors of serotype 8 containing the 5'-, the body- and the 3'- coding sequences of human CEP290 fused to inteins, for treatment of inherited retinal dystrophies, was adopted by consensus.

2.1.4. - EMA/OD/0000018682

Treatment of cerebral hypoxia-ischaemia reperfusion injury after return of spontaneous circulation in cardiac arrest patients

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

Treatment of cerebral hypoxia-ischaemia reperfusion injury after return of spontaneous circulation in cardiac arrest patients should be further justified as an orphan condition. The current application did not sufficiently justify the proposed condition. Specifically, the restriction of the condition to "cerebral" hypoxia-ischaemia reperfusion injury, the restriction to patients "after return of spontaneous circulation", and the restriction to "cardiac arrest" patients, needed additional justification 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).

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of cerebral hypoxia-ischaemia reperfusion injury after return of spontaneous circulation in cardiac arrest patients the sponsor was asked to further elaborate on the presented non-clinical and clinical observations.

a) To discuss how the non-clinical models that have been used reflect the pathophysiology of the proposed condition and how the results can predict clinical efficacy in patients affected by the condition.

b) To clarify if other endpoints have been measured to understand the effect on brain injury.

c) To provide external historical control to the provided mortality analysis. If context is provided by unpublished data only, the COMP requests more detail on the characteristics and validity of the external dataset.

d) To provide up-to-date results of the currently ongoing clinical study.

- Number of people affected or at risk

In light of the above discussion and the requirement for further justification of the condition, the sponsor was requested to revise the prevalence accordingly.

In the written response, and during an oral explanation before the Committee on 21 January 2020, the sponsor elaborated on the identified COMP issues.

The sponsor considered to amend the proposed condition to 'ischaemia reperfusion injury associated with cardiac arrest'.

Regarding the provided non-clinical data, the sponsor argued that the non-clinical occlusion models that had been performed were valid for the condition and that the outcome could predict clinically relevant effects on ischaemia-reperfusion of the brain. The sponsor acknowledged that there were cardiac arrest models that could address the full pathophysiology of the proposed condition.

Regarding the preliminary clinical data and the presented mortality analysis, the sponsor could not provide further detail on the unpublished external historical control. The sponsor provided literature data instead. The COMP was of the opinion that the provided data on mortality was immature and the provided external controls were not adequate to contextualise the proposed treatment effect in the single arm study.

The COMP concluded that the presented non-clinical and preliminary clinical evidence was not sufficient to support the intention to treat for the purpose of orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 21 January 2020, prior to final opinion.

2.1.5. - EMA/OD/0000019103

Treatment of acute lymphoblastic leukaemia (ALL)

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 product for treatment of acute lymphoblastic leukaemia the sponsor was asked to further elaborate on any available data with the product as proposed for designation. The stage of development of the proposed formulation should be clearly presented.

- 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 asked to re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition and given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor should perform a sensitivity analysis of the reported calculations.

- Significant benefit

The arguments on significant benefit were based on an assumption of a major contribution to patient care. Clinical data to justify the claims were expected.

The sponsor was also invited to further elaborate on the comparison versus all authorised products in the target indication, to justify a clinically relevant advantage or major contribution to patient care.

In the written response, and during an oral explanation before the Committee on 21 January 2020, the sponsor did not provide any data from any ongoing or completed studies with the proposed product but instead referred to planned studies that would generate data in the future. In the absence of data documenting the perceived problems and showing how these problems could be overcome with the current proposal, no progress had been made regarding the raised issues. In that regard, the COMP did not consider that the criteria for orphan designation could be justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 22 January 2020, prior to final opinion.

2.1.6. - EMA/OD/0000019108

Treatment of glioma

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

- 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 glioma the sponsor was asked to provide any data available with the specific product as proposed for designation.

- Significant Benefit

The arguments were based on a major contribution to patient care, clinical data to justify the claims were expected.

The sponsor was requested to further discuss the arguments provided with reference to any studies with the proposed product.

In the written response, and during an oral explanation before the Committee on 21 January 2020, the sponsor did not provide any data from any ongoing or completed studies with the proposed product but instead referred to planned studies that would generate data in the future. In the absence of data documenting the perceived problems in the application and showing how these problems could be overcome with the current proposal, no progress has been made regarding the raised issues. In that regard, the COMP did not consider that the criteria for orphan designation could be justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 22 January 2020, prior to final opinion.

2.1.7. - EMA/OD/0000019154

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 proposed prevalence estimate from the sponsor appeared to be limited to one source namely the AIRTUM National Registry. The sponsor was asked to re-calculate the prevalence estimate based on a more extensive data source to reflect the variability there could be in different Member States.

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".

- 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 preliminary clinical study submitted to justify the assumption of significant benefit over European Union authorised medicinal products for the proposed orphan condition. In particular, the sponsor was invited to further elaborate on the previous lines of therapy and the relapsed/refractory nature of the patients.

In the written response, and during an oral explanation before the Committee on 21 January 2020, the sponsor provided an adequate response regarding the question on significant benefit. The sponsor provided additional information on the inclusion of patients who were treated with Gazyvaro before they received the sponsor's product.

The sponsor provided an updated estimate of the prevalence of 4.5 in 10,000. The COMP discussed the provided methodology, which used a 'completeness index' described by Dankert et al., in a very recent publication from 2019 in the context of complete prevalence reported for the Nordic countries. The COMP considered that it was impossible to conclude if the prevalence was below 5 in 10,000 given that the sponsor did not provide confirmation of this figure through an independent second method/sensitivity analysis.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 22 January 2020, prior to final opinion.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/0000005680

Treatment of short-bowel 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 February meeting.

2.2.2. autologous human T-cells genetically modified ex-vivo with a lentiviral vector encoding a chimeric antigen receptor for B-cell maturation antigen - EMA/OD/0000013921

Janssen-Cilag International N.V.; Treatment of multiple myeloma

COMP Rapporteur: Karri Penttila

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

The intention to treat the condition with the medicinal product containing Autologous human T-cells genetically modified ex-vivo with a lentiviral vector encoding a chimeric antigen receptor for B-cell maturation antigen was considered justified based on clinical data demonstrating a high overall response rate.

The condition is chronically debilitating due to the development of hypercalcemia, renal insufficiency, anaemia, bone lesions, and life-threatening with a reduced life expectancy.

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 provided sufficient justification for the assumption that the medicinal product containing Autologous human T-cells genetically modified ex-vivo with a lentiviral vector encoding a chimeric antigen receptor for B-cell maturation antigen will be of significant benefit to those affected by the condition. The sponsor provided clinical data that demonstrate that patients who were heavily pre-treated with regimens including immunomodulators, proteasome inhibitors and anti-CD38 antibody, achieved high overall response rates including a high proportion of complete responses. The Committee considered that this constitute a clinically relevant advantage.

A positive opinion for Autologous human T-cells genetically modified ex-vivo with a lentiviral vector encoding a chimeric antigen receptor for B-cell maturation antigen, for treatment of multiple myeloma, was adopted by consensus.

2.2.3. - EMA/OD/0000014446

Treatment of cryopyrin-associated periodic syndromes

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. adeno-associated virus serotype rh74 containing the human micro-dystrophin gene - EMA/OD/0000016347

Sarepta Therapeutics Ireland Limited; Treatment of Duchenne muscular dystrophy

COMP Rapporteur: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing adeno-associated virus serotype rh74 containing the human micro-dystrophin gene was considered justified based on non-clinical data showing increase of muscle strength in valid models of the condition, and on preliminary clinical data showing a beneficial effect on measures of neuromuscular function.

The condition is life-threatening and chronically debilitating due to progressive muscle weakness eventually affecting all voluntary muscles. This is followed by dilated cardiomyopathy and cardiac output decrease, leading to terminal respiratory or cardiac failure often by late adolescence. Patients rarely live beyond the age of 30 years.

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.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor provided sufficient justification for the assumption that the medicinal product containing adeno-associated virus serotype rh74 containing the human micro-dystrophin gene will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data showing improvement in muscle function in children with Duchenne muscular dystrophy treated with the proposed product, as compared to standard of care. In addition, the proposed product offers the potential to treat children with all types of dystrophin gene mutations as compared to the currently authorized product Translarna, which targets only nonsense mutations. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for adeno-associated virus serotype rh74 containing the human micro-dystrophin gene, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

2.2.5. - EMA/OD/0000019066

Treatment of non-squamous non-small cell lung cancer

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

2.2.6. artesunate - EMA/OD/0000019513

YES Pharmaceutical Development Services GmbH; Treatment of malaria

COMP Rapporteur: Bruno Sepodes

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

The intention to treat the condition with the medicinal product containing artesunate was considered justified based on clinical data showing efficacy in severe malaria.

The condition is life-threatening due to the possibility of severe systemic complications such as cerebral malaria, cardiogenic shock, acute renal failure, coagulation disorders and pulmonary oedema. The overall mortality rate of imported *Plasmodium falciparum* malaria in Europe is 0.4%.

The condition was estimated to be affecting approximately 0.12 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 provided sufficient justification for the assumption that the medicinal product containing artesunate will be of significant benefit to those affected by the condition. This appears justified by the improved clinical efficacy of artesunate administered intravenously as monotherapy in the treatment of severe malaria as compared to quinine, the only currently authorized product for intravenous use in the EU.

A positive opinion for artesunate, for treatment of malaria, was adopted by consensus.

2.2.7. - EMA/OD/0000020079

Treatment of chronic myeloid leukaemia

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.

2.2.8. - EMA/OD/0000020769

Treatment of intracerebral hemorrhage

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.

2.2.9. - EMA/OD/0000020844

Treatment of eumycetoma

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.

2.2.10. luspatercept - EMA/OD/0000020912

Celgene Europe B.V.; Treatment of myelofibrosis

COMP Rapporteur: Frauke Naumann-WinterThe Committee agreed that the condition, myelofibrosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing luspatercept was considered justified based on preliminary clinical observations showing improvements in anaemia in affected patients.

The condition is chronically debilitating and life-threatening due to anaemia, splenomegaly, extramedullary haematopoiesis, constitutional symptoms such as fatigue, night sweats and fever, cachexia and leukaemic progression.

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 provided sufficient justification for the assumption that the medicinal product containing luspatercept will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data that support that treatment with the proposed product in addition to ruxolitinib, improves anaemia compared to ruxolitinib alone. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for luspatercept, for treatment of myelofibrosis, was adopted by consensus.

2.2.11. - EMA/OD/0000020924

Treatment of biliary tact cancer

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

2.2.12. 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide monohydrate - EMA/OD/0000020929

IQVIA RDS Ireland Limited; Treatment of myelofibrosis

COMP Rapporteur: Frauke Naumann-Winter

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

The intention to treat the condition with the medicinal product containing 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[C]isoxazolo[4,5-e]azepin-4-yl)acetamide monohydrate was considered justified based on clinical data demonstrating reduced spleen volume, achievement of transfusion independence and improvement of total symptom score.

The condition is life-threatening and chronically debilitating due to anaemia, splenomegaly, extramedullary haematopoiesis, constitutional symptoms such as fatigue, night sweats and fever, cachexia and leukemic progression.

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 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[C]isoxazolo[4,5-e]azepin-4-yl)acetamide monohydrate will be of significant benefit to those affected by the condition. The sponsor provided clinical data that demonstrate that patients who were not adequately treated with ruxolitinib, and who were either treated with the proposed product alone or as an add on to ruxolitinib, achieved promising improvement of total symptom score, spleen volume reduction, achievement of transfusion independence as well as reduced bone marrow fibrosis score. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[C]isoxazolo[4,5-e]azepin-4-yl)acetamide monohydrate, for treatment of myelofibrosis, was adopted by consensus.

2.2.13. - EMA/OD/0000020976

Treatment of pancreatic cancer

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

2.2.14. sintilimab - EMA/OD/0000021070

Parexel International GmbH; Treatment of extranodal NK/T-cell lymphoma, nasal type

COMP Rapporteur: Bozenna Dembowska-Baginska

Following review of the application by the Committee, it was agreed to rename the indication to treatment of "peripheral T-cell lymphoma".

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 sintilimab was considered justified based on preliminary clinical data showing anti-tumour activity in patients affected by the condition.

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 sintilimab will be of significant benefit to those affected by the condition. The sponsor 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 sintilimab, for treatment of peripheral T-cell lymphoma, was adopted by consensus.

2.2.15. - EMA/OD/0000021072

Treatment of viral associated haemorrhagic cystitis

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.

2.2.16. - EMA/OD/0000021100

Treatment of chronic myeloid leukaemia (CML)

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.

2.2.17. adeno-associated viral vector serotype 8 encoding human alpha-galactosidase AcDNA - EMA/OD/0000021153

Freeline Therapeutics (Ireland) Limited; Treatment of Fabry disease

COMP Rapporteur: Dinah Duarte

Following review of the application by the Committee, it was agreed to rename the active substance to "adeno-associated viral vector serotype S3 encoding human alpha-galactosidase A cDNA".

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

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype S3 encoding human alpha-galactosidase A cDNA was considered justified based on non-clinical data in a relevant model of the condition showing improved

galactosidase activity and reduced accumulation of glycosphingolipids in plasma and various tissues.

The condition is chronically debilitating due to recurrent episodes of severe pain that do not respond to standard analgesic, and life-threatening due to renal failure, cardiovascular and cerebrovascular complications.

The condition was estimated to be affecting approximately 2.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor provided sufficient justification for the assumption that the medicinal product containing adeno-associated viral vector serotype S3 encoding human alpha-galactosidase A cDNA will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate that one dose of the product leads to long-term alpha-galactosidase A activity increase, which would obviate the need for regular treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype S3 encoding human alpha-galactosidase A cDNA, for treatment of Fabry disease, was adopted by consensus.

2.2.18. sutimlimab - EMA/OD/0000021157

Celerion Austria GmbH; Treatment of immune thrombocytopenic purpura

COMP Rapporteur: Lyubina Racheva Todorova

Following review of the application by the Committee, it was agreed to rename the indication to treatment of immune thrombocytopenia.

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

The intention to treat the condition with the medicinal product containing sutimlimab was considered justified based on preliminary clinical data showing clinically relevant increase in platelet counts in patients affected by the condition.

The condition is life-threatening and chronically debilitating due to bleeding, which may occur without an obvious precipitating event and can involve the skin, oral cavity and gastrointestinal tract, as well as manifest with intracranial haemorrhage.

The condition was estimated to be affecting 2.4 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 sutimlimab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing that the proposed product results in a clinically relevant improvement of platelet counts in patients affected by the condition who did not respond to previous treatment with at least two of the currently authorised medicinal products. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for sutimlimab, for treatment of immune thrombocytopenia, was adopted by consensus.

2.2.19. adeno-associated virus serotype 8 containing the human RdCVF sequence and the human RdCVFL sequence - EMA/OD/0000021161

SparingVision; Treatment of inherited retinal dystrophies

COMP Rapporteur: Tim Leest

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

The intention to treat the condition with the medicinal product containing adeno-associated virus serotype 8 containing the human RdCVF sequence and the human RdCVFL sequence was considered justified based on improvement of visual acuity in a model of retinitis pigmentosa, which is relevant for the condition applied for.

The condition is chronically debilitating due to loss of vision.

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 adeno-associated virus serotype 8 containing the human RdCVF sequence and the human RdCVFL sequence will be of significant benefit to those affected by the condition. The sponsor has provided nonclinical data in a non-RPE65 model of retinitis pigmentosa supporting improved visual acuity, which therefore targets a different population than the one covered by the authorised product(s). The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated virus serotype 8 containing the human RdCVF sequence and the human RdCVFL sequence, for treatment of inherited retinal dystrophies, 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 coordinators were appointed for twenty applications.

2.7. Evaluation on-going

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

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of haemophilia A

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 glioma

The finalised letter was circulated for information.

3.2.2. -

Treatment of eosinophilic esophagitis

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Prevention of ischaemia reperfusion injury associated with solid organ transplantation

The new request was noted.

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

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

None

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

4.2.1. Givlaari – Givosiran - EMEA/H/C/004775/0000, EMA/OD/125/16, EU/3/16/1731, EMA/OD/0000013235

Accelerated assessment

Alnylam Netherlands B.V.; Treatment of acute hepatic porphyria

An opinion recommending not to remove Givlaari, givosiran, EU/3/16/1731 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.]

4.2.2. - treprostinil sodium – EMEA/H/C/005207/0000, EMA/OD/154/12, EU/3/13/1103, EMA/OD/0000025710

SciPharm Sarl; Treatment of chronic thromboembolic pulmonary hypertension

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.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for applications.

4.5. Orphan Maintenance Reports

5. Documents were tabled for information.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. Adcetris - brentuximab vedotin - Type II variation – EMEA/H/C/002455/II/0070 - EMEA/OD/072/08, EU/3/08/595, EMA/OD/0000007448

Takeda Pharma A/S; Treatment of peripheral T-cell lymphoma

CHMP rapporteur: Paula Boudewina van Hennik

The status of the procedure at CHMP was noted.

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 meeting – joint COMP/CAT/PDCO, 21-22 November 2019, Helsinki, Finland

The COMP adopted the minutes of the Strategic Review & Learning meeting which was held on 21-22 November in Helsinki.

7.1.2. Strategic Review & Learning meeting – COMP, 12-14 February 2020, Zagreb, Croatia

The agenda for the SRLM to be held on 12-14 February 2020 in Zagreb was agreed.

7.1.3. Protocol Assistance Working Group (PAWG)

The meeting of the working group on Protocol Assistance was cancelled.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendation on eligibility to PRIME – report from CHMP

The documents were tabled for information.

7.2.2.

7.2.3. Kick-off meeting – COMP-CAT Working group

The COMP agreed to nominate 5 members to participate in the COMP-CAT WG. The Kick-off meeting will take place on the 19 February 2020.

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

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

The documents were tabled for information.

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

The 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 work plan was discussed and agreed. The document will be available on the EMA website.

7.8. Planning and reporting

7.8.1. List of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2020

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2020 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

8.1.1. EU NTC Training curriculum - Pharmacoepidemiology - from Real-world data to Real-world evidence

The COMP received a presentation on Training Curriculum in Pharmacoepidemiology - EU Network Training Centre. COMP comments are expected by 14th February.

8.1.2. Survey

The survey was tabled for information.

8.1.3. Letter from EC

8.1.4. COMP members nominated on EMA's recommendation

A call for expression of interest was circulated. Candidates should submit they candidature by 14th February.

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 20-22 January 2020 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)	Italy	No interests declared	
Brigitte Schwarzer-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	
Nectaroula Cooper	Member	Cyprus	No interests declared	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Cecile Dop	Member	France	No interests declared	
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	
Irena Rogovska	Member	Latvia	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 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	Slovakia	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	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Bruno Sepodes	Member	Expert recommended by EMA	No interests declared	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Angelo Loris Brunetta	Member	Patients' Organisation Representative	No participation in discussion, final deliberations and voting on:	2.2.10 luspatercept - EMA/OD/0000020912
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Koenraad Norga	Chair of PDCO	Belgium	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
Carla Herberts	CAT Member in person	Netherlands	No interests declared	
Virginie Hivert	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Annie Lorence	Expert - in person*	France	No interests declared	
A representative 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.