19 March 2020
EMA/COMP/86291/2020
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 18-20 February 2020

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

18 February 2020, 09:00-19:15, room 2A

19 February 2020, 09:00-17:55, room 2A

20 February 2020, 09:00-11:15, 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.

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
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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 that no restriction in the involvement of meeting participants in upcoming discussions was identified as included in the pre-meeting list of participants and restrictions.

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

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

In view of the UK's withdrawal from the European Union on 1 February 2020, persons representing, appointed by, or nominated by the UK can no longer participate in EMA meetings. The EMA secretariat would like to thank the member from the UK Daniel O'Connor for his involvement in the Agency's scientific and regulatory activities and for his contribution to the Committee.

The COMP was pleased to welcome Mr Vasileios Loutas replacing Nectaroula Cooper as member for Cyprus.

1.2. Adoption of agenda

The agenda for 18-20 February 2020 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 20-22 January 2020 were adopted and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. - EMA/OD/0000005680

Treatment of short-bowel 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:

- Significant benefit

The arguments on significant benefit were based on a major contribution to patient care as the dosing proposed is twice a week and not daily as is the case for the currently authorised product.

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

In the written response, and during an oral explanation before the Committee on 18 February 2020, the sponsor claimed major contribution to patient care associated with the pharmacokinetic properties of the sponsor's product and the dosing once or twice a week. Associated with this was the reduction in the number of adverse events and the ease of use of the autoinjector used to deliver the proposed product, as opposed to the several steps needed for the administration of a comparator. The COMP questioned the robustness of the clinical findings to support the major contribution to patient care. During the discussion the rates of reduction of parenteral feeding as well as its total cessation in the more severe patients was raised. The sponsor highlighted that in their clinical experience the more severe patients became parenteral feeding free sooner than what is currently seen with a comparator. The data available at the oral explanation was, however, insufficient to support a reduction in parenteral feeding. The impact on the reduction or elimination of parenteral nutrition was noted to be potentially better from the clinical experience of the company's invited clinical expert. The COMP stated that this was an interesting finding and that the sponsor should consider resubmitting the application once the data to support this claim is appropriately summarised.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 February 2020, prior to final opinion.

2.1.2. allogeneic multi-virus specific T-lymphocytes targeting BK virus, cytomegalovirus, human herpesvirus-6, Epstein-Barr virus and adenovirus - EMA/OD/0000021072

TMC Pharma (EU) Limited; Treatment of viral associated haemorrhagic cystitis

COMP Rapporteur: Ingeborg Barisic

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 focused on a complication seen in HSCT (hematopoietic stem cell transplantation). Viral associated haemorrhagic cystitis should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

The sponsor is invited to provide any available data regarding:

- The potential effects of the product in other HSCT complications (such as BKV nephropathy);
- The potential effects of the product outside HSCT settings.

In the written response, the sponsor revised the condition applied for designation to "treatment in haematopoietic stem cell transplantation". This was considered acceptable

taking also into consideration that the product was matched to both recipient and donor and its assumed function in the condition.

The applicant also submitted a revised prevalence calculation for the new indication, however the premises (e.g. limiting to allogeneic procedures) on which this was done were not clear. With reference to the EBMT activity survey of 2017, 45418 HSCT procedures were performed on 41,100 patients. Based on this data the COMP has previously accepted the prevalence of 'less than 1 per 10,000'.

With regards to the significant benefit, the provided details of the inclusion criteria of the study. The responses seen in the included patients were considered supportive of a clinically relevant advantage of improved efficacy.

The COMP therefore considered the written responses sufficient for a positive opinion and cancelled the oral explanation.

Following review of the application by the Committee, it was agreed to rename the indication to treatment in haematopoietic stem cell transplantation.

The Committee agreed that the condition, treatment in haematopoietic stem cell transplantation, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing allogeneic multi-virus specific T lymphocytes targeting BK virus, cytomegalovirus, human herpesvirus-6, Epstein-Barr virus and adenovirus was considered justified based on clinical data supporting an improvement in the treatment of viral haemorrhagic cystitis in HSCT recipients.

The condition is life-threatening due to the consequences of bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition is also associated with complications such as graft-versus-host disease.

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 allogeneic multi-virus specific T lymphocytes targeting BK virus, cytomegalovirus, human herpesvirus-6, Epstein-Barr virus and adenovirus will be of significant benefit to those affected by the condition. The sponsor has provided clinical data supporting an improvement in the treatment of viral haemorrhagic cystitis in HSCT recipients, compared to standard antiviral treatment. The Committee considered that this constitutes a clinically relevant advantage.

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

A positive opinion for allogeneic multi-virus specific T lymphocytes targeting BK virus, for treatment in haematopoietic stem cell transplantation, was adopted by consensus.

2.1.3. fosgemcitabine palabenamide - EMA/OD/0000020924

Pharma Gateway AB; Treatment of biliary tract cancer

COMP Rapporteur: Maria Elisabeth Kalland

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

- 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 biliary tract cancer the sponsor should further elaborate on the presented preliminary clinical data. The sponsor was asked to further elaborate on the results (responses and PFS) of the 7 refractory/relapsed patients that have been treated with monotherapy of the proposed product. Furthermore, the sponsor was requested to discuss the results in combination with cisplatin and critically discuss the contribution of each compound to the overall activity and justify the validity of the presented indirect comparison.

In the written response, and during an oral explanation before the Committee on 18 February 2020, the sponsor provided additional information on the presented clinical evidence in patients in the relapsed/refractory and first line setting.

The COMP noted that there was very limited evidence with the proposed product in monotherapy in the relapsed/refractory setting. Hence the focus of the discussion with the COMP was on the provided data from a study in first line setting, where the proposed product was administered in combination with cisplatin. In order to better understand the contribution of the proposed product to the efficacy of the combination therapy, the sponsor provided literature studies to contextualise the clinical outcome through indirect comparisons. The sponsor justified the validity of these indirect comparisons and the COMP was of the opinion that the compared patient populations and studies were sufficiently similar to accept the provided indirect comparisons for the purpose of initial orphan designations. The indirect comparisons suggested that the proposed product in combination with cisplatin is able to induce anti-tumour response in first line therapy of biliary tract cancer patients. The COMP considered that there was sufficient evidence to support the intention to treat for the purpose of initial orphan designation.

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

The intention to treat the condition with the medicinal product containing fosgemcitabine palabenamide was considered justified based on preliminary clinical data demonstrating anti-tumour responses in treatment naïve patients affected by the condition when fosgemcitabine palabenamide was provided in combination with cisplatin.

The condition is life-threatening and chronically debilitating due to the development of liver insufficiency, cholestasis, cholangitis, weight loss and cachexia. Patients with unresectable tumours die between 6- and 12 months following diagnosis. Death usually occurs from liver failure or infectious complications accompanying the progressive biliary obstruction.

The condition was estimated to be affecting approximately 1.5 in 10,000 persons in the European Union, at the time the application was made.

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

2.1.4. 2-hydroxy-N,N,N-trimethylethan-1-aminium (Z)-4-(5-((3-benzyl-4-oxo-2-thioxothiazolidin-5-ylidene)methyl)furan-2-yl)benzoate - EMA/OD/0000020976

MWB Consulting S.A.R.L.; Treatment of pancreatic cancer

COMP Rapporteur: Brigitte Schwarzer-Daum

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

- Number of people affected

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

The sponsor was asked to re-calculate the prevalence estimate based on relevant epidemiological studies from the EU and registers for the proposed orphan condition and should complement these with crude incidence data for the proposed condition (see e.g. ECIS: European Cancer Information System).

In the written response, the sponsor clarified the data used to provide the prevalence calculation and the use of ECIS and age-adjusted criteria. The duration of pancreatic cancer which has been increasing to one year was discussed with the COMP because it was not discussed thoroughly in the sponsor's submission. The COMP considered that although patient survival has improved from 6 months with many surviving up to 9 months on average the prevalence estimate based on incidence was still acceptable. It was noted that the sponsor's calculation presented the progressive increase that has been noted over the last 10 years with the current proposed ratio of 2 in 10,000 acceptable as current.

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

The intention to treat the condition with the medicinal product containing 2-hydroxy-N,N,N-trimethylethan-1-aminium (Z)-4-(5-((3-benzyl-4-oxo-2-thioxothiazolidin-5-ylidene)methyl)furan-2-yl)benzoate was considered justified based on non-clinical in vivo data which showed improved survival when the product was used in combination with gemcitabine and paclitaxel.

The condition is life-threatening and chronically debilitating due to early dissemination of the tumour to distant sites including brain, bone, soft tissues, and lungs.

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

A positive opinion for 2-hydroxy-N,N,N-trimethylethan-1-aminium (Z)-4-(5-((3-benzyl-4-oxo-2-thioxothiazolidin-5-ylidene)methyl)furan-2-yl)benzoate, for treatment of pancreatic cancer, was adopted by consensus.

2.1.5. - EMA/OD/0000019066

Treatment of non-squamous non-small cell lung cancer

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 31 January 2020, prior to responding to the list of issues.

2.1.6. - EMA/OD/0000021100

Treatment of chronic myeloid leukaemia (CML)

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 12 February 2020, prior to responding to the list of issues.

2.1.7. asciminib - EMA/OD/0000020079

Novartis Europharm Limited; Treatment of chronic myeloid leukaemia

COMP Rapporteur: Karri Penttila

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

- Significant benefit

The COMP did not agree with the focus of the sponsor on bosutinib. Hence, the sponsor was requested to discuss significant benefit over all currently authorised therapies in relapsed/refractory (R/R) patients: dasatinib, nilotinib, bosutinib, ponatinib.

In this context, the sponsor was requested to elaborate on the results from the study in order to support significant benefit:

- To justify the argument of improved efficacy over bosutinib by justifying the validity of the presented indirect comparison.
- To present more details specifically on patients that have failed (some or all) currently authorised therapies.
- To present more details on patients that have received concomitant therapy with authorised products.

In the written response, the sponsor elaborated on the preliminary clinical data that was available from the currently ongoing clinical development and clinical trial enrolled patients that have failed all currently authorised therapies. Three out of 12 patients who received all available therapies (imatinib, dasatinib, nilotinib, bosutinib and ponatinib) achieved major molecular response. The COMP considered that this level of evidence was sufficient to justify significant benefit over all authorised therapies in the R/R setting of chronic myeloid leukaemia for the purpose of initial orphan designation. The sponsor was recommended to request protocol assistance to discuss the clinical development and the plans for the demonstration of significant benefit at the time of marketing authorisation.

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

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

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

The condition was estimated to be affecting approximately 1.2 in 10,000 persons in the European Union, at the time the application was made.

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

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

2.1.8. benzyl benzoate, beta-caryophyllene, cineole, cinnamaldehyde, cinnamyl acetate, linalool, trans-2-methoxycinnamaldehyde - EMA/OD/0000020844

Septeos S.A.S.; Treatment of eumycetoma

COMP Rapporteur: Eva Malikova

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 with the use of the product in a non-clinical model of the condition. The statistical evaluation of the results was not submitted and the relevance of the improved activity over itraconazole was not supported by data.

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

  - The relevance of the non-clinical model used for the treatment of eumycetoma, and the interpretation of the results obtained in the experiments,
  - The methodology and statistical evaluation used in the non-clinical studies, as well as the results from these studies and its relevance for the development of the product in the condition.

- 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 mentioned the direct activity of the product on the membranes and non-growing fungi. No data to support these claims was presented. The comparison to itraconazole was not clearly explained, which would help to understand the potential clinical relevance of the results presented.

The sponsor was asked to further discuss all arguments to support the significant benefit and to provide data to support those claims. The sponsor was asked also to clarify the intended positioning of the product in the current standard of care.

In the written response, and during an oral explanation before the Committee on 19 February 2020, the sponsor provided further justification of the choice of non-clinical model used to support medical plausibility. The sponsor also elaborated on the details of the methodology, statistical evaluation as well as conclusions drawn from the results. The use of the proposed product resulted in a statistically significant but marginal effect on survival in

the model studied when compared to vehicle and itraconazole. The sponsor attempted to explain the possible clinical relevance of the results observed, by extrapolating from one non-clinical model to another and then to human (indirect extrapolation), and by mentioning translatability of the effects of posaconasole when used in the same non-clinical model and in human. The latter data was not included in the written documents submitted to the Committee and thus could not be verified. The sponsor proposed that the product may lead to a curative effect either alone or in combination with the standard of care. However, data to support either assumption were not convincing because of the primitive nature of the model used and because combination treatment was not trialled yet. The Committee accepted the data presented in the non-clinical model in support of medical plausibility despite identified weaknesses of the model. However, in view of the unclear translatability of the results observed to a meaningful clinical advantage, the Committee was negative on the assumption of significant benefit over itraconazole. In addition, the arguments presented by the sponsor did not address the significant benefit over amphotericin B and posaconazole.

The intention to treat the condition was considered justified based on non-clinical data in a model of the condition showing a small improvement in survival upon treatment with the proposed product as compared to either vehicle or the standard first line treatment, itraconazole.

Eumycetoma (hereinafter referred to as "the condition") was estimated to be affecting approximately 0.01 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has established that the condition is chronically debilitating and/or life-threatening.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has not provided sufficient justification for the assumption that the medicinal product containing benzyl benzoate, beta-caryophyllene, cineole, cinnamaldehyde, cinnamyl acetate, linalool, trans-2-methoxycinnamaldehyde will be of significant benefit to those affected by the condition. Although the non-clinical model used was considered as valid for the purpose of supporting medical plausibility in eumycetoma, the data produced in this model were not found sufficient to support the significant benefit. The sponsor has shown that the treatment with the proposed product leads to a marginal improvement in survival in the non-clinical model when compared to the treatment with itraconazole. However, the sponsor failed to support the claim that such improvement is clinically relevant. In addition, the sponsor has not established the significant benefit over other authorised, satisfactory methods of treatment- amphotericin B and posaconazole.

A negative opinion for benzyl benzoate, beta-caryophyllene, cineole, cinnamaldehyde, cinnamyl acetate, linalool, trans-2-methoxycinnamaldehyde, for treatment of eumycetoma, was adopted by consensus.

[Post-meeting note: This negative opinion was revised and adopted in the March 2020 meeting. The sponsor will have 90 days to appeal from the COMP decision.]

2.1.9. melatonin - EMA/OD/0000020769

Worphmed S.r.l.; Treatment of intracerebral hemorrhage

COMP Rapporteur: Giuseppe Capovilla

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 used terms "intracerebral haemorrhage" and "haemorrhagic stroke" interchangeably. However, the application is for treatment of "intracerebral haemorrhage". Therefore, the sponsor was requested to justify the condition of intracerebral haemorrhage as a distinct medical entity or a valid subset.

The sponsor was asked to specify the inclusion criteria and clarify whether the following subsets of patients were included in the proposed condition:

- subarachnoid haemorrhage,
- other non-traumatic intracerebral haemorrhage,
- haemorrhagic transformation after ischemic stroke.

In case of exclusion of any of those subsets, the arguments supporting the use of the proposed medicine only in the condition "intracerebral haemorrhage" should be presented.

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

- Number of people affected

The sponsor was asked to specify which patients were included in the sources used for the calculation of the intracerebral haemorrhage incidence; and if needed, to provide an updated calculation including all relevant subsets of patients affected by cerebrovascular disease.

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

In the written response, and during an oral explanation before the Committee on 19 February 2020, the sponsor clarified that subarachnoid haemorrhage, other non-traumatic intracerebral haemorrhage, and haemorrhagic transformation after ischemic stroke are specifically excluded from the proposed orphan indication 'treatment of intracerebral haemorrhage'. The sponsor confirmed that this is a subset of stroke and considered this subset valid based on the fact that data to support medical plausibility was generated in an adequate experimental model of intracerebral haemorrhage. The Committee considered the proposed subset of patients sufficiently defined, however disagreed that the data presented are sufficient to justify sub-setting in this case. According to the 'Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another' (ENTR/6283/00 Rev 4) a subset can only be considered valid for an orphan designation if patients in that subset present distinct and unique characteristics related to the condition and if the product does not have pharmacodynamic properties outside of that subset in absence of these characteristics. The sponsor was not able to provide any evidence to support the specificity of melatonin to the proposed subset of stroke.

In addition, the sponsor did not discuss the inclusion criteria in the two epidemiological studies included to support the prevalence estimate. The Committee considered that the prevalence was not comprehensively presented and therefore it could not be confirmed that the estimate presented by the sponsor is a good approximation of the true prevalence of the proposed condition. Consequently, it remains unclear if the proposed condition meets the orphan criteria of not affecting more than 5 in 10,000 persons.

In light of the above, the Committee expressed a negative opinion that the criteria for orphan designation had been satisfied based on the unjustified sub-setting of a common condition and lack of comprehensive prevalence estimate.

The sponsor proposed that 'intracerebral haemorrhage' is a valid subset of stroke and therefore considered it an appropriate orphan condition for a designation. The sponsor failed to provide data to demonstrate the specificity of the product to the proposed subset only. Therefore, the condition 'treatment of intracerebral haemorrhage' as defined by the sponsor could not be accepted as valid subset for the purpose of the orphan designation.

The sponsor has not provided a comprehensive estimation of the prevalence of the proposed orphan condition and therefore has not established that the condition affects not more than 5 in 10,000 persons in the European Union at the time the application was made.

The sponsor has established that the condition is chronically debilitating and life-threatening.

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

A negative opinion for melatonin, for treatment of intracerebral haemorrhage, was adopted by consensus.

[Post-meeting note: This negative opinion was revised and adopted in the March 2020 meeting. The sponsor will have 90 days to appeal from the COMP decision.]

2.1.10. - EMA/OD/0000014446

Treatment of cryopyrin-associated periodic syndromes

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 29 January 2020, prior to responding to the list of issues.

2.2. For discussion / preparation for an opinion

2.2.1. losmapimod - EMA/OD/0000015410

Pharma Gateway AB; Treatment of facioscapulohumeral muscular dystrophy

COMP Rapporteur: Michel Hoffmann

The Committee agreed that the condition, facioscapulohumeral 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 losmapimod was considered justified based on non-clinical data suggesting that the proposed product is able to affect main molecular pathways associated with the pathology of the condition.

The condition is chronically debilitating due to progressive severe weakness of skeletal muscles, leading to impaired mobility, chronic fatigue and pain, visual and hearing impairment. Patients with infantile onset disease have a reduced life-expectancy.

The condition was estimated to be affecting less than 1.5 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for losmapimod, for treatment of facioscapulohumeral muscular dystrophy, was adopted by consensus.

2.2.2. trifarotene - EMA/OD/0000015613

Premier Research Group S.L.; Treatment of autosomal recessive congenital ichthyosis

COMP Rapporteur: Ingeborg Barisic

The Committee agreed that the condition, autosomal recessive congenital ichthyosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing trifarotene was considered justified based on early clinical data in patients treated with the product used as a topical cream who showed improvements in investigator's global assessment and total sum score in scaling and roughness.

The condition can be life-threatening and is chronically debilitating in particular due to manifestations such as collodion babies, the development of scales, an impairment of the epidermal barrier resulting in infections and trans epithelial water loss, hyperkeratosis interfering with sweat gland function, ectropion, conductive hearing loss, hair loss, palmoplantar and nail abnormalities, as well as the development of skin malignancies.

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 provided sufficient justification for the assumption that the medicinal product containing trifarotene will be of significant benefit to those affected by the condition. The sponsor provided clinical data that demonstrate that patients who were not adequately managed with the use of oral retinoid treatment, improved when topically treated with the proposed product in addition to oral retinoids. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for trifarotene, for treatment of autosomal recessive congenital ichthyosis, was adopted by consensus.

2.2.3. - EMA/OD/0000019167

Treatment of ovarian 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 March meeting.

2.2.4. - EMA/OD/0000020629

Treatment of small cell lung cancer (SCLC)

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 March meeting.

2.2.5. - EMA/OD/0000021732

Treatment of hepatocellular carcinoma

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

2.2.6. - EMA/OD/0000022351

Prevention of graft versus host disease

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

2.2.7. - EMA/OD/0000022586

Treatment of von Hippel-Lindau disease

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

2.2.8. - EMA/OD/0000022633

Prevention of retinopathy of prematurity

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 March meeting.

2.2.9. - EMA/OD/0000022802

Treatment of acute 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 March meeting.

2.2.10. - EMA/OD/0000022808

Treatment of intrahepatic cholestasis of pregnancy

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 March meeting.

2.2.11. - EMA/OD/0000022918

Treatment of myasthenia gravis

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 March meeting.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

None

2.6. Nominations

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

COMP rapporteurs were appointed for 15 applications.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 16 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Prevention of ischaemia reperfusion injury associated with solid organ transplantation

The discussion was postponed.

3.2. Finalised letters

Treatment of haemophilia A

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of naevoid basal-cell carcinoma syndrome (Gorlin syndrome)

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. Trepulmix - 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

COMP rapporteurs: Elisabeth Johanne Rook / Eva Malikova

An opinion recommending not to remove Trepulmix, treprostinil sodium, EU/3/13/1103 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.

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

4.2.1. - isatuximab – EMEA/H/C/004977, EMA/OD/198/13, EU/3/14/1268, EMA/OD/0000019553

Sanofi-Aventis Groupe; Treatment of plasma cell myeloma

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.

4.2.2. - pexidartinib – EMEA/H/C/004832, EMA/OD/279/14, EU/3/15/1457, EMA/OD/0000021360

Daiichi Sankyo Europe GmbH; Treatment of tenosynovial giant cell tumour, localised and diffuse type

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 March meeting.

4.2.3. - bulevirtide – EMEA/H/C/004854, EMA/OD/329/14, EU/3/15/1500, EMA/OD/0000018086

Accelerated assessment

MYR GmbH; Treatment of hepatitis delta virus infection

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 March meeting.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for four applications.

4.5. Orphan Maintenance Reports

Documents were tabled for information.

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

None

5.3. Appeal

None

5.4. On-going procedures

COMP co-ordinators were appointed for one application.

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 – COMP, 12-14 February 2020, Zagreb, Croatia

The Chair debriefed the Committee on the discussions taken during the SRLM held on 12-14 February in Zagreb.

7.1.2. Protocol Assistance Working Group (PAWG)

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

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendation on eligibility to PRIME – report from CHMP

Documents were tabled for information.

7.2.2. Kick-off meeting – COMP-CAT Working Group

Proposed meeting time on 19 February 2020 at 18:30 in room 1B.

Feedback was provided from the discussions in the kick-off meeting. COMP noted the proposal to meet on a monthly basis to discuss the orphan ATMPs under evaluation.

The first meeting will take place on 18 March 2020. The COMP core-members and the Rapporteur of the ATMP identified for discussion will be invited.

7.2.3. SAWP/COMP joint membership

COMP agreed to nominate the following COMP members as SAWP members/alternates: Dr Karri Pentila, Prof. Brigitte Schwarzer-Daum, Dr Eva Malikova, Dr Dinah Duarte, Prof. Robert Nisitico and Dr Armando Magrelli.

7.2.4. COMP members nominated on EMA's recommendation

The call for nomination of COMP members on EMA’s recommendation was tabled for information.

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

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

The documents were tabled for information.

7.4. 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

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 2020

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2020 was 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 EU NTC training Curriculum in Pharmacoepidemiology was presented. The Committee was invited to send comments until the 14th February.

8.1.2. Update on EMA organisational aspects

The EMA updated the Committee on the new organisational structure of the Huma medicines division and the new EMA operating model.

8.1.3. UK withdrawal from the EU - Update

The EMA updated the Committee on the practical aspects of the UK's withdrawal from the EU.

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 18-20 February 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	
Vasileios Loutas	Member	Cyprus	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	
Cecile Dop	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Zsofia Gyulai	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No interests declared	
Elisabeth 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	
Bruno Sepodes	Member	Expert recommended by EMA	No interests declared	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Angelo Loris Brunetta	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	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.