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SCIENCE MEDICINES HEALTH

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Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 11-13 July 2017

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

11 July 2017, 09:00-19:00, room 2F

12 July 2017, 08:30-19:00, room 2F

13 July 2017, 08:30-15:00, room 2F

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 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. 23 or more members were present in the room). All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. Adoption of agenda

The agenda for 11-13 July 2017 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 13-15 June 2017 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. - EMA/OD/054/17

Treatment of spinal cord injury

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 4 July 2017, prior to responding to the list of issues.

Notes:

There have been 4 designations for this condition: EMEA/OD/082/07 3-methoxy-pregnenolone, EMEA/OD/059/08 Recombinant human monoclonal antibody to human Nogo-A protein of the IgG4/kappa class, EMEA/OD/042/08 Filgrastim, EMA/OD/119/13 synthetic 12 amino acids peptide designed after subcommissural organ-spondin

2.1.2. Recombinant fragment of human surfactant protein-D - EMA/OD/049/17

Trimunocor Ltd; Prevention of bronchopulmonary dysplasia

COMP coordinator: 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:

- Number of people affected

The sponsor is invited to further discuss the preterm population chosen for the calculation of the population at risk. It is not clear whether the calculations from the sponsor are taking into account all preterm newborns starting with a prematurity cut-off date (currently set by the sponsor at 28 weeks), or if the sponsor targets only very premature babies. The sponsor is reminded that the designation will be targeting all babies at risk of developing bronchopulmonary dysplasia, independently from gestational age.

It is also noted that previously the COMP has determined 32 weeks of gestational age as the cut-off for applications for prevention of bronchopulmonary dysplasia.

In the written response, and during an oral explanation before the Committee on 11 July 2017, the sponsor recalculated the incidence of the condition based on 32 weeks of gestational age.

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

The intention to prevent the condition with the medicinal product containing recombinant fragment of human surfactant protein-D was considered justified based on preclinical data in models of the condition showing improvement of lung histology and reduction of lung inflammation with the proposed product.

The condition is life-threatening and chronically debilitating due to inflammation and scarring in the lungs, resulting in necrotizing bronchiolitis and alveolar septal injury, which compromises the oxygenation of blood.

The population of patients eligible for prevention of the condition was estimated to be less than 2 in 10,000 persons in the European Union, at the time the application was made.

A positive opinion for recombinant fragment of human surfactant protein-D, for prevention of bronchopulmonary dysplasia, was adopted by consensus.

2.1.3. Itraconazole - EMA/OD/056/17

Mayne Pharma UK Limited; Treatment of naevoid basal-cell carcinoma syndrome (Gorlin syndrome)

COMP coordinator: Bożenna Dembowska-Bagińska/Ingrid Wang

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

- Number of people affected

The sponsor has submitted a calculation based on publications which range from the 1980s and current dates. There are available national registries such as for example in the Netherlands, France, Italy and Germany which should be consulted to further enhance the limited publication data the sponsor alludes to. The sponsor should recalculate the prevalence taking into consideration these additional sources.

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

- Significant benefit

The sponsor is proposing a product which has a similar mode of action to that of a product already used to treat the condition.

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

In the written response, the sponsor submitted a revised prevalence calculation where they consulted many different national registries in Europe. The sponsor highlighted that the registries do not distinguish Gorlin Syndrome from the broader condition of basal cell carcinoma and proposed the most recent publication from a survey conducted in the UK that offered the most comprehensive and up-to-date information of the prevalence in Europe. The COMP accepted the most conservative estimate of this publication, which translates into a prevalence of 0.3 in 10,000 in the EU.

The sponsor also submitted additional preliminary clinical data showing that the product offers significant benefit in patients who no longer respond to currently approved treatments.

The written responses were considered satisfactory and the COMP cancelled the oral hearing and issued a positive opinion.

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of naevoid basal-cell carcinoma syndrome (Gorlin syndrome).

The Committee agreed that the condition, naevoid basal-cell carcinoma syndrome (Gorlin syndrome), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing itraconazole was considered justified based on pre-clinical in vivo and preliminary clinical data which showed a reduction in tumour size and clinically a stabilisation of jaw cysts.

The condition is chronically debilitating due to the occurrence of multiple basal cell carcinomas of the skin, potentially invading vital tissues and leading to different types of deformities.

The condition was estimated to be affecting approximately 0.3 in 10,000 persons in the European Union, at the time the application was made.

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 itraconazole will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a

reduction in tumour size in patients who are refractory to authorised treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for itraconazole, for treatment of naevoid basal-cell carcinoma syndrome (Gorlin syndrome), was adopted by consensus.

2.1.4. - EMA/OD/057/17

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 if there exists a scientific rationale for the development of the proposed product for treatment of glioma, the sponsor should further elaborate on:

- the relevance of the pre-clinical model used for the treatment of glioma, and the interpretation of the results obtained in the experiments,
- the methodology used in the pre-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 are based on the new mechanism of action and the potential improved efficacy in the condition.

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

In the written response, and during an oral explanation before the Committee on 12 July 2017, the sponsor clarified the findings in the pre-clinical *in vivo* data. The data showed a reduction in tumour mass but did not establish any improvement in survival and did not take into consideration the use of temozolomide or carmustine which are used first line in the treatment of these patients. The COMP was of the opinion that there were insufficient data to support the grounds for significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 July 2017, prior to final opinion.

2.1.5. - EMA/OD/036/17

Treatment of sickle cell disease

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 sponsor was asked to provide a discussion on significant benefit *versus* Siklos in the patient population above 2 years of age.

In addition, the sponsor was asked to provide a data driven significant benefit argumentation *versus* magistral/officinal formulations used across Europe, e.g. as outlined for the UK on the NICE BNF website.

In the written response, and during an oral explanation before the Committee on 12 July 2017, the sponsor proposed additional arguments to support the significant benefit. The COMP concluded that the available officinal/ magistral formulations for the treatment of sickle cell disease are considered to be satisfactory methods in the EU and that at this point in time there was insufficient evidence to support a clinically relevant advantage or major contribution to patient care in the context of such formulations.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 13 July 2017, prior to final opinion.

2.1.6. Asunercept - EMA/OD/050/17

Apogenix AG; Treatment of myelodysplastic syndromes

COMP coordinator: 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 arguments on significant benefit are based on the new mechanism of action and the potentially improved efficacy in the condition. The attention of the sponsor is drawn to the fact that a novel mechanism of action *per se* would not be considered without a discussion of how this translates into a clinically relevant advantage or major contribution to patient care.

The sponsor is invited to provide a comparative discussion *versus* authorised products in the treatment of the proposed condition, in order to justify a clinically relevant advantage or major contribution to patient care. A discussion *versus* azacitadine, decitabine, lenalidomide and imatinib is expected.

In the written response, the sponsor further discussed the significant benefit and explained that the authorised products target a different population than the ones under study. The COMP accepted this comparative discussion and considered in particular that the preliminary data support haematological responses in low or intermediate risk MDS patients, most of whom were non-del(5q) patients. The Committee accepted these arguments and the oral hearing was cancelled.

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

The intention to treat the condition with the medicinal product asunercept was considered justified based on preliminary clinical observations in transfusion dependent patients with low or intermediate risk myelodysplastic syndromes, supporting a reduction in transfusion dependency.

The condition is life-threatening and chronically debilitating in particular due to anaemia, thrombocytopenia, neutropenia, as well as transformation into acute myeloid leukaemia.

The condition was estimated to be affecting less than 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing asunercept will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical observations that support haematological improvements in low or intermediate risk myelodysplastic syndromes patients, most of whom were non-del(5q) patients. This compares favourably to the currently authorised products, which are targeting different myelodysplastic syndromes populations. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for asunercept, for treatment of myelodysplastic syndromes, was adopted by consensus.

2.1.7. - EMA/OD/003/17

Treatment of N-acetylglutamate synthase deficiency

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 28 June 2017, prior to responding to the list of issues.

Notes:

There has been 1 designation for this condition: EMA/OD/185/16 sodium benzoate

2.1.8. Odiparcil - EMA/OD/043/17

Inventiva; Treatment of mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome)

COMP coordinator: Ingeborg Barisic/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:

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action with the proposed product being a substrate reduction therapy. However, an alternative mechanism of action *per se* would not suffice for the justification of significant benefit.

The sponsor is expected to provide a comparative discussion based on either preclinical or preliminary clinical observations, to justify a clinically relevant advantage or a major contribution to patient care.

In the written response, the sponsor demonstrated that based on indirect comparisons in preclinical models of the condition, the candidate orphan product is expected to exert beneficial effects in manifestations not addressed by the current treatment, such as corneal and cartilage GAG accumulation. These effects are attributed to improved kinetics of the proposed product. The sponsor supported this with additional information from data from a preclinical study showing effects in corneal epithelium thickness and number of cell layers. Overall the significant benefit was considered acceptable on the basis of the product targeting aspects not addressed by the authorised treatment, such as ocular manifestations of the condition. The oral explanation was hence cancelled.

The Committee agreed that the condition, mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing odiparcil was considered justified based on data from a preclinical model of the condition, supporting increased secretion of glycosaminoglycans followed by improvement of histology and motility.

The condition is chronically debilitating and life-threatening due to bone dysplasia, joint restriction, organomegaly, heart disease, and corneal clouding, among several other problems, and reduced life span with death occurring in general up to the fifth decade of life.

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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing odiparcil will be of significant benefit to those affected by the condition. The sponsor has provided data in a preclinical model of the condition supporting that treatment with the product improves manifestations of the condition not targeted by the authorised enzyme replacement therapy, such as ocular manifestations. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for odiparcil, for treatment of mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome), was adopted by consensus.

2.1.9. - EMA/OD/044/17

Treatment of lung allograft dysfunction associated with lung transplantation

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 Committee is of the opinion that the indication of this application would need to be changed into 'treatment in solid organ transplantation', according to recent designations.

To establish correctly if there exists a scientific rationale for the development of the proposed product, the sponsor should further elaborate on the *in vitro* experiments presented in this application.

In addition the sponsor is invited to provide additional data on the lung transplanted patient that was presented as clinical case to support the medical plausibility. This would need to include data on the concomitant treatment, such as e.g. medicinal products preventing/and or treating rejection, antibiotics and antifungals, and timelines of such concomitant treatments.

The sponsor is also reminded that clinical cases where the product was used in diseases other than the proposed condition would not usually be considered supporting the medical plausibility.

- Number of people affected

Since the condition would have to be changed into 'treatment in solid organ transplantation' according to recent COMP designations, the sponsor is invited to re-calculate the prevalence accordingly.

- Significant benefit

Since the designation would be for 'treatment in solid organ transplantation', for which a number of products are authorised, the sponsor is invited to discuss the significant benefit of the proposed product.

Claims of significant benefit should be supported by data showing advantages (clinically relevant advantage and/or major contribution to patient care) of the proposed product in relation to the medicinal products already authorised for the treatment of the condition.

In the written response, and during an oral explanation before the Committee on 12 July 2017, the sponsor further discussed the clinical case, including concomitant treatments and timelines of the clinical response. The COMP was of the opinion that one single clinical case in absence of any other preclinical and/or clinical proof of concept in the condition was not sufficient to support the medical plausibility and significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 13 July 2017, prior to final opinion.

2.1.10. - EMA/OD/327/16

Treatment in cardiopulmonary by-pass

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:

- Condition

The proposed condition pertains to the medical technique of "cardiopulmonary by-pass" (CPB). The sponsor should compare and contrast the specificity of pulmonary complications in the proposed modality compared to other surgical procedures, and major trauma.

- Intention to diagnose, prevent or treat

The sponsor is developing a product for managing pulmonary complications in patients subjected to cardiopulmonary by-pass, and the mechanism of action revolves around restoration of depleted urea cycle intermediates. The sponsor is invited to elaborate on the specificity of urea cycle intermediates depletion in cardiopulmonary by-pass in comparison to other surgical procedures or trauma.

- Life-threatening and debilitating nature of the condition

The sponsor should further elaborate on the life-threatening or chronically debilitating nature of the condition as proposed for designation. From the data provided and the sponsor's arguments it is not well substantiated that the condition can be defined as being life-threatening or chronically debilitating.

- 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 Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

The condition remains to be justified as a valid condition for designation, and the sponsor should recalculate following a consideration of the points above and a possible amendment of the condition.

In case cardiopulmonary by-pass is retained, it is noted that the sponsor has excluded part of the population affected, and should re-calculate the prevalence estimate based on relevant studies.

Given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor should also perform a sensitivity analysis of the reported calculations.

In the written response, and during an oral explanation before the Committee on 13 July 2017, the sponsor further discussed the mechanism of action of the product but it did not appear that such mechanisms were specific for cardiopulmonary by-pass. Similarly, the applicant discussed the specificities of the potential complications of cardiopulmonary by-pass but the COMP considered that it would be difficult to detach them from other aspects of the cardiothoracic procedure. The COMP was of the opinion that the sponsor did not justify the condition, its seriousness, and the number of people affected.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 13 July 2017, prior to final opinion.

2.1.11. - EMA/OD/053/17

Treatment of primary mitochondrial myopathy

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

For the purpose of orphan medicinal product designation, the COMP considers primary mitochondrial myopathy as an unacceptable umbrella of distinct medical entities. The sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

The sponsor proposed an umbrella condition defined by a combination of heterogeneous pathology leading to mitochondrial disease and one unifying clinical characteristic, myopathy. There is, however substantial heterogeneity even in the identified group of conditions. Therefore, the sponsor should split this application into several applications, for each individual condition within the umbrella.

The sponsor presented pooled data from a short clinical trial in a variety of patients with mitochondrial disorders. No individual patient data were presented and only a very short-term follow-up was included in the study, which may have little relevance for a chronic condition.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of primary mitochondrial myopathy, the sponsor should further elaborate on:

- the results obtained in individual patients (affected by the condition as applied for) enrolled in the clinical study,
 - the methodology used in the clinical study as well as the results from this study and their relevance for the development of the product in the condition. Longer term follow up would be informative for a condition of chronic and often progressive nature,
 - alternatively, any existing non-clinical data with the use of the product in valid models of the condition (as applied for), demonstrating functional improvement.
- Number of people affected

The sponsor should re-calculate the prevalence estimate based on relevant epidemiological studies and registers for each orphan condition separately.

In the written response, and during an oral explanation before the Committee on 13 July 2017, the sponsor focused on myopathy as a prominent symptom unifying all, genetically and clinically diverse underlying conditions, and pointed out that the clinical management of patient with primary mitochondrial myopathy is centred on managing individual symptoms, hence it would make sense to group conditions together independent of underlying genotype. The committee questioned the sponsor on the heterogeneity of pathophysiology and clinical character of various primary mitochondrial myopathy types. The committee also pointed out that focusing on only one symptom present in a group of complex conditions falling under the primary mitochondrial myopathy umbrella does not fit the regulatory considerations used to define a distinct medical entity for the purpose of an orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 13 July 2017, prior to final opinion.

2.1.12. [N-{2-\[\(6-\[\(2,6Dichloro3,5dimethoxyphenyl\)carbonyl\]\(methyl\)amino\)pyrimidin-4-yl\)amino\]-5-\(4-ethylpiperazin-1-yl\)phenyl}prop-2-enamide - EMA/OD/052/17](#)

Eisai Europe Limited; Treatment of hepatocellular carcinoma

COMP coordinator: 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:

- 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 Calculation and Reporting of a Prevalence of a Condition for Orphan Designation”](#).

The current prevalence estimate is based on GLOBOCAN data only. The sponsor is invited to revise the prevalence estimate taking into consideration EU member state cancer registries on term ICD-C22 (Germany, UK, NORDCAN, Netherlands Cancer Registry and Rarecare), which are reporting on a higher prevalence of HCC of approximately 1.5 per 10,000.

In the written response, the sponsor provided additional 5-year partial prevalence data of cancer registries in Germany, the Netherlands and from NORCAN. At this point in time a 5-year partial prevalence figure was considered acceptable. The COMP accepted the

prevalence calculation of 1.5 per 10,000 based on the most conservative estimate provided by registry data.

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

The intention to treat the condition with the medicinal product containing N-{2-[(6-[(2,6-dichloro-3,5-dimethoxyphenyl)carbamoyl](methyl)amino)pyrimidin-4-yl)amino]-5-(4-ethylpiperazin-1-yl)phenyl}prop-2-enamide was considered justified based on preclinical *in vivo* data demonstrating tumour volume reduction upon treatment.

The condition is life-threatening and chronically debilitating due to increased mortality and liver dysfunction. Median survival without therapy can be greater than 36 months for stage 0 and A, 16 months for stage B, 4-8 months for stage C and less than 4 months for stage D.

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.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing N-{2-[(6-[(2,6-dichloro-3,5-dimethoxyphenyl)carbamoyl](methyl)amino)pyrimidin-4-yl)amino]-5-(4-ethylpiperazin-1-yl)phenyl}prop-2-enamide will be of significant benefit to those affected by the condition. The sponsor has provided preclinical *in vivo* data comparing the product to the authorised product, which demonstrate that the product inhibits tumour growth to a higher degree. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for N-{2-[(6-[(2,6-dichloro-3,5-dimethoxyphenyl)carbamoyl](methyl)amino)pyrimidin-4-yl)amino]-5-(4-ethylpiperazin-1-yl)phenyl}prop-2-enamide, for treatment of hepatocellular carcinoma, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/079/17

Treatment of primary sclerosing cholangitis

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 September meeting.

2.2.2. Adeno-associated viral vector serotype Anc80 containing the truncated human *ATP7B* gene under the control of the human alpha-1 antitrypsin promoter - EMA/OD/084/17

Vivet Therapeutics SAS; Treatment of Wilson's disease

COMP coordinator: Martin Možina/Fernando Méndez Hermida/Kerstin Westermark

Following review of the application by the Committee, it was agreed to broaden/rename the active substance to adeno-associated viral vector serotype Anc80 containing the truncated human *ATP7B* gene under the control of the human alpha-1 antitrypsin promoter.

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

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype Anc80 containing the truncated human ATP7B gene under the control of the human alpha-1 antitrypsin promoter was considered justified based on non-clinical data in a model of the condition demonstrating normalisation of liver copper levels, alanine aminotransferase and ceruloplasmin levels as well as normalisation of liver histology.

The condition is chronically debilitating and can be life-threatening due to the toxic effects of copper, first accumulating in the liver and later in the brain. The liver disease can present symptoms ranging from mildly elevated transaminases to acute liver failure or liver cirrhosis. Around 5% of all patients are diagnosed only when they develop fulminant acute liver failure, sometimes fatal.

The condition was estimated to be affecting approximately 0.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated viral vector serotype Anc80 containing the truncated human *ATP7B* gene under the control of the human alpha-1 antitrypsin promoter will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate that the use of the product in a model of the condition results in maintained expression of human *ATP7B* in the liver resulting in therapeutic lasting effect (at least 6 months post initial treatment). This compares favourably to existing medicinal products, which have to be administered daily. The product has also a potential to reverse pre-existing liver damage in the condition, an aspect of the condition which is not treated by existing authorised medicines. The Committee considered that this constitutes major contribution to patient care and a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype Anc80 containing the truncated human *ATP7B* gene under the control of the human alpha-1 antitrypsin promoter, for treatment of Wilson's disease, was adopted by consensus.

2.2.3. Antisense oligonucleotide targeting exon 13 in the USH2A gene - EMA/OD/094/17

ProQR Therapeutics IV BV; Treatment of retinitis pigmentosa

COMP coordinator: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing antisense oligonucleotide targeting exon 13 in the USH2A gene was considered justified based on preliminary pre-clinical *in vivo* data, which showed an improvement of retinal function as shown through a recovery of the electroretinogram amplitude.

The condition is chronically debilitating due to the development of nyctalopia and tunnel vision that progress to total blindness.

The condition was estimated to be affecting approximately 3.7 in 10,000 persons in the European Union, at the time the application was made.

A positive opinion for antisense oligonucleotide targeting exon 13 in the *USH2A* gene, for treatment of retinitis pigmentosa, was adopted by consensus.

[2.2.4. - EMA/OD/076/17](#)

Treatment of infantile spasms

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 September meeting.

[2.2.5. - EMA/OD/088/17](#)

Treatment of growth hormone deficiency

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 September meeting.

[2.2.6. - EMA/OD/097/17](#)

Treatment of Neurodegeneration with Brain Iron Accumulation (NBIA)

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 September meeting.

[2.2.7. - EMA/OD/090/17](#)

Treatment of glioblastoma

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 September meeting.

[2.2.8. - EMA/OD/059/17](#)

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 respond in writing before the Committee September meeting.

[2.2.9. - EMA/OD/039/17](#)

Treatment of partial deep dermal and full thickness burns

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

[2.2.10. - EMA/OD/035/17](#)

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 September meeting.

2.2.11. Picropodophyllin - EMA/OD/068/17

Axelar AB; Treatment of glioma

COMP coordinator: Brigitte Blöchl-Daum/Dinko Vitezic
The Committee agreed that the condition, glioma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing picropodophyllin was considered justified based on preclinical data in models of the condition supporting inhibition of tumour growth, and preliminarily clinical observations reporting imaging responses in affected patients.

The condition is life-threatening due to symptoms caused by the tumour compressing the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality and cognitive impairment. The condition is also life-threatening, with poor 5-year survival of less than 5% for glioblastoma multiform patients.

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 has provided sufficient justification for the assumption that the medicinal product containing picropodophyllin will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data supporting responses to treatment in relapsed on refractory patients who have previously been treated with standard treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for picropodophyllin, for treatment of glioma, was adopted by consensus.

2.2.12. Purified, pasteurized and freeze-dried cell-wall fragments from *Mycobacterium tuberculosis* strain RUTI - EMA/OD/098/17

Archivel Farma S.L.; Treatment of tuberculosis

COMP coordinator: Nikolaos Sypsas

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

The intention to treat the condition with the medicinal product containing purified pasteurised and freeze-dried cell-wall fragments from *Mycobacterium tuberculosis* strain RUTI was considered justified based on pre-clinical *in vivo* data showing reduction in bacterial load as well as preliminary clinical data showing improved response to antibiotic treatment.

The condition is chronically debilitating and life-threatening due to haemoptysis, bronchiectasis, diffuse pulmonary destruction, and the possibility of extra-pulmonary infection.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing purified pasteurised and freeze-dried cell-wall fragments from *Mycobacterium tuberculosis* strain RUTI will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data demonstrating improved response to isoniazide when their product is used in combination with this antibiotic in the treatment of patients with latent tuberculosis. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for purified pasteurised and freeze-dried cell-wall fragments from *Mycobacterium tuberculosis* strain RUTI, for treatment of tuberculosis, was adopted by consensus.

2.2.13. Recombinant adeno-associated viral vector serotype 5 carrying the gene for the human frataxin protein - EMA/OD/093/17

Voisin Consulting S.A.R.L.; Treatment of Friedreich's ataxia

COMP coordinator: Armando Magrelli/Fernando Méndez Hermida

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

The intention to treat the condition with the medicinal product containing recombinant adeno-associated viral vector serotype 5 carrying the gene for the human frataxin protein was considered justified based on non-clinical data demonstrating increase of expression of frataxin in a model of the condition.

The condition is chronically debilitating and life threatening due to ataxia, progressive disability that requires the use of wheelchair, and cardiac involvement in the form of hypertrophic cardiomyopathy.

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

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

A positive opinion for recombinant adeno-associated viral vector serotype 5 carrying the gene for the human frataxin protein, for treatment of Friedreich's ataxia, was adopted by consensus.

2.2.14. - EMA/OD/091/17

Treatment of growth hormone deficiency

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 September meeting.

2.2.15. - EMA/OD/292/16

Treatment of ATTR amyloidosis

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 September meeting.

2.2.16. Recombinant truncated N-terminal fragment of human lens epithelium-derived growth factor - EMA/OD/086/17

Dorian Regulatory Affairs BV; Treatment of retinitis pigmentosa

COMP coordinator: Armando Magrelli

For the purpose of orphan designation, the Committee for Orphan Medicinal Products considered that the active substance should be renamed as "recombinant truncated N-terminal fragment of human lens epithelium-derived growth factor".

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

The intention to treat the condition with the medicinal product containing recombinant truncated N-terminal fragment of human lens epithelium-derived growth factor was considered justified based on preclinical data from a valid disease model demonstrating that treatment improved electroretinography measures.

The condition is chronically debilitating due to the development of nyctalopia and tunnel vision progressing to total blindness.

The condition was estimated to be affecting approximately 3.7 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 recombinant truncated N-terminal fragment of human lens epithelium-derived growth factor, for treatment of retinitis pigmentosa, was adopted by consensus.

2.2.17. - EMA/OD/087/17

Treatment of mastocytosis

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

2.2.18. - EMA/OD/060/17

Treatment of Leber congenital amaurosis

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 September meeting.

2.2.19. *Salmonella typhi* Ty21a strain transfected with a plasmid vector encoding for the human vascular endothelial growth factor receptor 2 - EMA/OD/069/17

Vaximm GmbH; Treatment of glioma

COMP coordinator: Brigitte Blöchl-Daum

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

The intention to treat the condition with the medicinal product containing *Salmonella typhi* Ty21a strain transfected with a plasmid vector encoding the human vascular endothelial growth factor receptor 2 was considered justified based on data demonstrating anti-tumour efficacy in preclinical models and in patients affected by the condition.

The condition is chronically debilitating due to symptoms caused by compression of the tumour on the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality and cognitive impairment. The condition is life-threatening, with poor survival of less than 5% for glioblastoma multiform patients.

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 has provided sufficient justification for the assumption that the medicinal product containing *Salmonella typhi* Ty21a strain transfected with a plasmid vector encoding the human vascular endothelial growth factor receptor 2 will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate clinical response in patients affected by the condition, who have failed current best standard of care including authorised treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for *Salmonella typhi* Ty21a strain transfected with a plasmid vector encoding the human vascular endothelial growth factor receptor 2, for treatment of glioma, was adopted by consensus.

2.2.20. Sirolimus - EMA/OD/047/17

Best Regulatory Consulting Ltd; Treatment of tuberous sclerosis

COMP coordinator: Daniel O'Connor/Violeta Stoyanova

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

The intention to treat the condition with the medicinal product containing sirolimus was considered justified based on preliminary clinical data from the published literature demonstrating that a topical formulation of sirolimus is able to improve angiofibroma symptoms in patients affected by the condition.

The condition is chronically debilitating due to facial disfigurement and severe neurological symptoms and life-threatening due to the formation of multiple tumours.

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 sirolimus will be of significant benefit to those affected by the condition. The sponsor has provided evidence of improved formulation characteristics, which might lead to improved clinical efficacy compared to current available topical magistral/officinal formulations of sirolimus. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for sirolimus, for treatment of tuberous sclerosis, was adopted by consensus.

2.2.21. Sodium 2-hydroxylinoleate - EMA/OD/078/17

Ability Pharmaceuticals SL; Treatment of pancreatic cancer

COMP coordinator: Brigitte Blöchl-Daum

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 sodium 2-hydroxylinoleate was considered justified based on preclinical data in valid disease models demonstrating that the product is able to reduce tumour growth.

The condition is chronically debilitating because of pain in the upper abdomen, loss of appetite, nausea, vomiting, weight loss, jaundice, fatigue, weakness and depression, and life-threatening with a median survival of about 6 months.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing sodium 2-hydroxylinoleate will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate that the product is able to reduce tumour growth when used on top of authorised products paclitaxel and gemcitabine. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for sodium 2-hydroxylinoleate, for treatment of pancreatic cancer, was adopted by consensus.

2.2.22. Tacrolimus - EMA/OD/099/17

Vivus B.V.; Treatment of Pulmonary Arterial Hypertension

COMP coordinator: Eva Malikova/Martin Možina

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

The intention to treat the condition with the medicinal product containing tacrolimus was considered justified based on preclinical data and preliminary clinical data showing improvement of endpoints relevant to pulmonary arterial hypertension.

The condition is chronically debilitating and life threatening due to progressive dyspnoea and right heart failure, leading to death in approximately 3 years after diagnosis.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing tacrolimus will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data from compassionate use showing clinical and cardiovascular improvement in patients that did not respond to previous treatment with some of the currently authorised products for pulmonary arterial hypertension. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for tacrolimus, for treatment of pulmonary arterial hypertension, was adopted by consensus.

2.2.23. Teicoplanin - EMA/OD/085/17

Neupharma S.r.l.; Treatment of cystic fibrosis

COMP coordinator: Robert Nistico

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

The intention to treat the condition with the medicinal product containing teicoplanin was considered justified based on preclinical data showing increased survival with the proposed product in models of infection with methicillin resistant *staphylococcus aureus* (MRSA) from cystic fibrosis patients.

The condition is chronically debilitating and life-threatening due to the recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure.

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 teicoplanin will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing improved survival in models of methicillin resistant *staphylococcus aureus* (MRSA) infection relapsing from previous treatment with some of the currently authorised products. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for teicoplanin, for treatment of cystic fibrosis, was adopted by consensus.

2.2.24. - EMA/OD/089/17

Treatment of pulmonary arterial 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 September 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 coordinators

COMP coordinators were appointed for 24 applications submitted.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 7 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of acute hepatic porphyria

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

3.1.2. -

Treatment of Prader-Willi syndrome

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

3.1.3. -

Treatment in solid organ transplantation

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

3.1.4. -

Treatment of 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 myasthenia gravis

The finalised letter was circulated for information.

3.2.2. -

Treatment of mercury toxicity

The finalised letter was circulated for information.

3.2.3. -

Treatment of plasminogen deficiency

The finalised letter was circulated for information.

3.2.4. -

Treatment of graft-versus-host disease

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of paroxysmal nocturnal haemoglobinuria

The new request was noted.

3.3.2. -

Treatment of congenital factor VII deficiency

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. Soliris - eculizumab – Type II variation - EMEA/OD/062/14, EU/3/14/1304, EMEA/H/C/000791/II/0090

Alexion Europe SAS - France; Treatment of myasthenia gravis

COMP coordinator: Violeta Stoyanova / Armando Magrelli; CHMP rapporteur: Jorge Camarero Jiménez

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

The sponsor has not provided a systematic literature search on relevant primary literature sources on all forms of myasthenia gravis. The provided literature has limitations on its predictability for prevalence. In addition, there are reports on general underestimation and rising prevalence. Therefore, the sponsor should provide a literature discussion to confirm that the prevalence criterion is still met.

In its written response, the sponsor presented an in depth discussion on prevalence of myasthenia gravis based on epidemiological reports from individual European regions and across Europe, and published reviews suggesting a trend of increasing prevalence over time. By applying the most conservative approach the sponsor concludes on a final prevalence estimate of 3.63 per 10,000 in 2017. The COMP accepted this prevalence estimate.

The COMP concluded that:

The proposed therapeutic indication, treatment of Refractory generalized Myasthenia Gravis (gMG) patients who are antiacetylcholine receptor (AChR) antibody-positive falls entirely within the scope of the orphan indication of the designated orphan medicinal product, treatment of myasthenia gravis.

The prevalence of myasthenia gravis (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be 3.7 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating due to recurrent crisis characterised by muscle weakness affecting in particular muscles that control eye and eyelid movement, facial expressions, chewing, talking, and swallowing. Crisis can also affect muscles that control breathing, resulting in life-threatening respiratory impairment.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, Soliris is of significant benefit to the subset of the orphan condition as defined in the granted therapeutic indication. The efficacy of Soliris treatment was established in myasthenia gravis patients, who received background therapy including currently authorised products and who were refractory to best standard of care including currently authorised products.

An opinion recommending not to remove Soliris, Eculizumab (EU/3/14/1304) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion will be endorsed for publication on the EMA website.

[Post-meeting note: The COMP adopted the opinion by written procedure following its June meeting and upon adoption of CHMP opinion.]

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

4.2.1. Adcetris - Brentuximab vedotin – Type II variation - EMA/OD/100/11, EU/3/11/939, EMEA/H/C/002455/II/0048

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

CHMP rapporteur: Paula Boudewina van Hennik; CHMP co-rapporteur: Jan Mueller-Berghaus

The status of the procedure at CHMP was noted.

4.2.2. Rydapt - midostaurin – EMEA/H/C/004095

Novartis Europharm Ltd;

a) Treatment of mastocytosis, EMA/OD/016/10, EU/3/10/765

b) Treatment of acute myeloid leukaemia, EMEA/OD/028/04, EU/3/04/214

COMP coordinator: Katerina Kopečková / Frauke Naumann-Winter

As agreed during the previous meeting, a list of issues was sent to the sponsor for response.

a) Treatment of mastocytosis, EMA/OD/016/10, EU/3/10/765. The sponsor was asked to elaborate on the following issues:

- Prevalence

The sponsor produces an estimate on the basis of a 14-year partial prevalence figure in adults, by assuming that approximately 65% of cases occur in children. The sponsor is invited to discuss the duration of the proposed condition and provide a point-prevalence estimate. A sensitivity analysis of any assumptions made is also expected.

In its written response, and during an oral explanation before the Committee on 11 July 2017, the sponsor proposed a revised 2.45 per 10.000 estimate on the basis of Rarecare complete prevalence data with the following assumptions: a) that since 2008 the prevalence has increased at up to approx. 3-fold, b) that systemic advanced mastocytosis is as low as 2% of all mastocytosis cases.

The COMP concluded that:

The proposed therapeutic indication falls entirely within the scope of the orphan indications of the designated Orphan Medicinal Product.

The prevalence of mastocytosis (hereinafter referred to as “the condition”) is estimated to remain below 5 in 10,000 and was concluded to be approximately 2.5 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating due to symptoms such as flushing, tachycardia, pruritus, abdominal cramping, peptic ulcers and diarrhoea, and life-threatening due to bone marrow failure, hepatomegaly, splenomegaly, and poor survival with 5-year rates of around 60% in patients with systemic mastocytosis.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Rydapt will be of potential significant benefit to those affected by the orphan condition still holds. The clinical data presented demonstrate improved survival in treated patients with advanced systemic mastocytosis. This is in contrast to the authorised treatments, which only target specific symptoms of the disease. The Committee considered that this constitutes a clinically relevant advantage.

An opinion recommending not to remove Rydapt (EU/3/10/765) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion will be endorsed for publication on the EMA website.

b) Treatment of acute myeloid leukaemia, EMEA/OD/028/04, EU/3/04/214. The sponsor was asked to elaborate on the following issues:

- Significant Benefit

The sponsor argues a clinically relevant advantage by adding midostaurin on top of standard of care, for first line induction (daunorubicin and cytarabine) and consolidation (cytarabine), followed by maintenance treatment with midostaurin versus placebo. The applicant is invited to discuss the products authorised for populations similar to the proposed therapeutic indication of Rydapt, including azacitidine.

The sponsor is expected to compare and contrast the product versus all authorised counterparts in the proposed indication, and present data to confirm a clinically relevant advantage or major contribution to patient care.

In its written response, and during an oral explanation before the Committee on 11 July 2017, the sponsor provided a comparative discussion versus different classes of products authorised for different therapeutic indications overlapping with the indications of Rydapt. The comparators for the discussion included other anthracyclines, antimetabolite hypomethylating agents and histamine. The COMP was in agreement with the arguments of the sponsor for significant benefit, which were also based on indirect comparisons.

The COMP concluded that:

The proposed therapeutic indication falls entirely within the scope of the orphan indications of the designated orphan medicinal product.

The prevalence of acute myeloid leukaemia (hereinafter referred to as “the condition”) is estimated to remain below 5 in 10,000 and was concluded to be approximately 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating in particular due to bone marrow dysfunction and life-threatening due to its rapid progression and poor survival with 5 year rates of approximately 20%.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Rydapt will be of potential significant benefit to those affected by the orphan condition still holds. The clinical data presented demonstrate improved survival in combination with standard induction/consolidation chemotherapy followed by single-agent continuation therapy in FLT3-positive AML patients. In contrast, other authorised treatments target different patient populations. The COMP considered that this constitutes a clinically relevant advantage.

An opinion recommending not to remove Rydapt (EU/3/04/214) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion will be endorsed for publication on the EMA website.

[Post-meeting note: The COMP adopted the opinion by written procedure following its July meeting and upon adoption of CHMP opinion.]

4.2.3. Verkazia - ciclosporin – EMEA/OD/106/05, EU/3/06/360, EMEA/H/C/004411

Santen Oy; Treatment of vernal keratoconjunctivitis

COMP coordinator: Frauke Naumann-Winter / Armando Magrelli

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

- Prevalence

The sponsor provided a prevalence conclusion based on data from 6 European countries. Since there is a known variability of prevalence of vernal keratoconjunctivitis (VKC) across regions in Europe the sponsor is requested to provide a recalculation and sensitivity analysis to account for the prevalence of VKC in the European Union.

- Significant Benefit

The sponsor's arguments for significant benefit over magistral/officinal preparations of Ciclosporin A (CsA) are based on improved availability, safety and efficacy. No data to support the limitations of availability, safety and efficacy of current CsA formulations were provided. The sponsor is requested to elaborate on the data from the pivotal study and historical data regarding existing formulations of CsA in support of argument for significant benefit.

In its written response, and during an oral explanation before the Committee on 13 June 2017, the sponsor acknowledged that the use of hospital preparations of ciclosporin is widespread across the EU but argued that hospital preparations are not used or easily available in some EU member states and should not be considered as a satisfactory method of treatment of vernal keratoconjunctivitis. The COMP noted that the use of CsA in the treatment of severe vernal keratoconjunctivitis is acknowledged in treatment guidelines and in-hospital/magistral preparation of CsA is not technically challenging and it is widely available. Assumptions of better safety proposed by the sponsor were not supported by the

available clinical data, which are very limited, and the clinical study performed with the use of Verkazia did not include an active CsA comparator. The third argument presented by the sponsor related to limited evidence of the efficacy of ciclosporin hospital preparations. Published clinical trials presented by the sponsor were difficult to compare to the VEKTIS trial data due to limited information on published studies and variability of endpoints measured. No conclusions on the comparison of efficacy of hospital preparations and Verkazia could be made to establish which is more efficacious.

The COMP concluded that:

The proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.

The prevalence of vernal keratoconjunctivitis (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be 3.2 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating, in particular due to potential visual loss and steroid-induced eye complications.

The significant benefit of Verkazia over authorised products such as anti-histamines and corticosteroids was considered justified. The Committee also considered magistral/officinal preparations of ciclosporin, which are widespread and commonly used in the EU for the treatment of vernal keratoconjunctivitis. The sponsor did not provide sufficient data to demonstrate that Verkazia would be of improved efficacy, safety or major contribution to patient care compared to these magistral/officinal preparations. The assumption of improved safety due to reduced ciclosporin concentration in Verkazia was not confirmed by clinical observations. The assumption of major contribution to patient care due to improved availability of the product was also not accepted due to widespread use of magistral/officinal preparations of ciclosporin in the vast majority of EU member states. Thus, the assumption that Verkazia may be of potential significant benefit to those affected by the orphan condition does not hold.

An opinion recommending the removal of Verkazia (EU/3/06/360) from the EC Register of Orphan Medicinal Products was adopted by consensus.

[Post-meeting note: The COMP adopted the opinion by written procedure following its July meeting and upon adoption of CHMP opinion.]

4.2.4. Xermelo - telotristat ethyl – EMEA/OD/047/09, EU/3/09/661, EMEA/H/C/003937

Ipsen Pharma; Treatment of carcinoid syndrome

COMP coordinator: Katerina Kopečková / Frauke Naumann-Winter

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

- Prevalence

The sponsor is invited to recalculate the prevalence as more sources of information than those submitted are available, i.e. national cancer registries and reports regarding the incidence and survival of patients with carcinoid syndrome.

In its written response, the sponsor provided a more robust and thorough prevalence calculation taking into consideration registries and more recent publications on the condition in Europe, resulting in a range from 0.21 to 1.24 in 10,000 with the upper value being the most conservative. In their text a correction factor was introduced which was highlighted by the COMP coordinators establishing the prevalence at 1 in 10,000.

The COMP concluded that:

The proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.

The prevalence of carcinoid syndrome (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;

The condition is chronically debilitating due to flushing and diarrhoea, and, less frequently, life-threatening due to heart failure and bronchoconstriction;

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Xermelo is of significant benefit to those affected by the orphan condition still holds. This is based on a clinically relevant reduction in bowel movement frequency in adult patients with carcinoid syndrome who are inadequately controlled by somatostatin analogue therapy.

An opinion recommending not to remove Xermelo (EU/3/09/661) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion will be endorsed for publication on the EMA website.

[Post-meeting note: The COMP adopted the opinion by written procedure following its July meeting and upon adoption of CHMP opinion.]

4.2.5. [Lutathera - lutetium 177Lu dotatate – EMEA/OD/093/07, EU/3/07/523, EMEA/H/C/004123](#)

Advanced Accelerator Applications; Treatment of gastro-entero-pancreatic neuroendocrine tumours

COMP coordinator: Kateřina Kopečková / Brigitte Blöchl-Daum

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

The sponsor is requested to provide further details and background to the prevalence calculation regarding the specific data sources, the RARECARE data, and the duration of the disease and if the proposed partial prevalence can be considered justified.

In its written response, the sponsor presented further details on the prevalence estimate, including scientific literature on disease duration from 2008-2012. According to the literature, the age-adjusted incidence of all GEP-NETs has steadily increased in the last four decades, increasing in the time interval 1973–2007 by 3.8- to 4.8-fold in Europe. The COMP accepted the arguments of the sponsor and issued a positive opinion.

The COMP concluded that:

The proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.

The prevalence of gastro-entero-pancreatic neuroendocrine tumours (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be 3.8 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is life-threatening with poor prognosis in patients with localised advanced or metastatic disease, and chronically debilitating due to the occurrence of symptoms including diarrhoea, jaundice, flushing, peptic ulcers, diabetes, glucose intolerance, abdominal pain, or weight loss.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Lutathera is of significant benefit to the subset of the orphan condition as defined in the granted therapeutic indication still holds. It was demonstrated that Lutathera treatment improved the progression free survival of patients with midgut gastro-entero-pancreatic tumours, who receive concomitant treatment with authorised somatostatin analogue. Regarding other sub-types of gastro-entero-pancreatic-neuroendocrine tumours, indirect comparisons were provided to demonstrate that the observed progression free survival compared favourably against treatment effects of other authorised treatments including somatostatin analogues, everolimus and sunitinib.

An opinion recommending not to remove Lutathera (EU/3/07/523) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion will be endorsed for publication on the EMA website.

[Post-meeting note: The COMP adopted the opinion by written procedure following its July meeting and upon adoption of CHMP opinion.]

4.2.6. Bavencio – avelumab – EMA/OD/150/15, EU/3/15/1590, EMEA/H/C/004338

Merck Serono Europe Limited; Treatment of Merkel cell carcinoma

COMP coordinator: Bożenna Dembowska-Bagińska / Pauline Evers

The COMP concluded that:

The proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.

The prevalence of Merkel cell carcinoma (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be approximately 0.4 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is life-threatening with a median survival of approximately 3.6 years for local disease, 2.0 years for regional disease and 1.2 years for distant disease.

There is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

An opinion recommending not to remove Bavencio (EU/3/15/1590) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion will be endorsed for publication on the EMA website.

[Post-meeting note: The COMP adopted the opinion by written procedure following its July meeting and upon adoption of CHMP opinion.]

4.3. Appeal

4.3.1. Cuprior - trientine tetrahydrochloride – EMEA/H/C/004005/000, EMA/OD/001/15, EU/3/15/1471

GMP-Orphan SA; Treatment of Wilson's disease

COMP coordinator: Kerstin Westermark / Daniel O'Connor

In its grounds for appeal, and during an oral explanation before the Committee on 11 July 2017, the sponsor presented tabulated summaries of information, which was collected via surveys from health authorities, prescribing physicians, and Wilson's disease patient organisations. The results of the COMP survey demonstrating the existence of regulatory import mechanisms in at least 26 of 28 Member States were also included (appendix 1 of appeal documentation). The sponsor agreed with the COMP's assessment that the majority of countries have an established regulatory access pathway to trientine. The COMP considered that the sponsor had not provided additional evidence on a systematic shortage of supply issue of trientine. Furthermore, the COMP concluded that the sponsor had not provided sufficient justification to determine that Wilson's disease patients in the EU are not adequately managed with currently authorised products including European regulatory access routes for trientine, which are in accordance with Article 5(1) of Directive 2001/83/EC.

The COMP concluded that:

The proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.

The prevalence of Wilson's disease (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating and can be life-threatening due to the toxic effects of copper, first accumulating in the liver and later on in the brain. The liver disease can present with symptoms ranging from mildly elevated transaminases to acute liver failure or liver cirrhosis. Around 5% of all patients are diagnosed only when they develop fulminant acute liver failure, sometimes fatal.

Satisfactory methods of treatment of the condition have been authorised in the European Union; however, the assumption that Cuprior may be of potential significant benefit to those affected by the orphan condition does not hold. The analysis performed by the sponsor to substantiate the lack of availability of trientine in the EU was not satisfactory. In addition, the sponsor's claim of significant benefit due to improved compliance was rejected because of the methodology used by the sponsor to support this claim, as no patients had actually received the improved formulation of trientine - Cuprior. In the absence of data with the use of the product it is not possible to confirm the assumption of improved compliance.

An opinion recommending the removal of Cuprior (EU/3/15/1471) from the EC Register of Orphan Medicinal Products was adopted by consensus.

[Post-meeting note: The COMP formally adopted the final opinion by written procedure following its July meeting.]

4.4. On-going procedures

COMP co-ordinators were appointed for 2 applications.

4.5. Public Summary of Opinions

The draft public summary of the COMP opinion adopted last month was endorsed for publication on the EMA website.

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

5.2.1. Blincyto (blinatumomab) - Type II variation – EMEA/OD/029/09, EU/3/09/650, EMEA/H/C/003731/II/0018

Amgen Europe BV - The Netherlands; Treatment of acute lymphoblastic leukaemia

CHMP rapporteur: Alexandre Moreau

The COMP agreed that a formal review of the maintenance of the orphan designation for the applied indication is needed.

5.3. Appeal

None

5.4. On-going procedures

Documents were circulated in MMD.

Document(s) tabled:

Review of orphan designation for OMP for MA extension - On-going procedures

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. COMP Strategic Review & Learning meeting, 19-21 September 2017, Lisbon, Portugal

Draft agenda and a presentation including practical information for the meeting were circulated in MMD.

7.1.2. Protocol Assistance Working Group

The working group on Protocol Assistance met on 11 July 2017.

7.1.3. Prevalence Working Group

The working group on Prevalence met on 12 July 2017.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendations on eligibility to PRIME – report from CHMP

Documents were circulated in MMD.

Document(s) tabled:

PRIME eligibility requests - list of adopted outcomes June 2017

7.2.2. PDCO/COMP Working Group

Cancelled

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

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

PCWP/HCPWP joint meeting - 15 March 2017

Documents were circulated in MMD.

Document(s) tabled:

Minutes PCWP/HCPWP joint meeting – 15 March (EMA/182189/2017)

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)

Documents were circulated in MMD

Document(s) tabled:

Draft Agenda of EMA/FDA teleconference on Orphan Medicines June 20, 2017

Notes:

Monthly teleconference

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. The 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

Documents were circulated in MMD.

Document(s) tabled:

COMP Work Plan 2017

7.8. Planning and reporting

7.8.1. List of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2017

An updated list of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2017 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. Publication of review of orphan criteria report

The newly proposed procedure for publication of Orphan Maintenance Assessment Report was presented.

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 11-13 July 2017 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bruno Sepodes	Chair	Expert recommended by EMA	No interests declared	
Brigitte Blöchl-Daum	Member	Austria	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No restrictions applicable to this meeting	
Ioannis Kkolos	Member	Cyprus	No interests declared	
Katerina Kopeckova	Member	Czech Republic	No restrictions applicable to this meeting	
Jens Ersbøll	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Nikolaos Sypas	Member	Greece	No restrictions applicable to this meeting	
Melinda Sobor	Member	Hungary	No interests declared	
Sigurdur B. Thorsteinsson	Member	Iceland	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member	Italy	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	
Violeta Stoyanova-Beninska	Member	Netherlands	No interests declared	
Ingrid Wang	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Fernando Mendez Hermida	Member	Spain	No interests declared	
Dan Henrohn	Member	Sweden	No restrictions applicable to this meeting	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Lesley Greene	Member (Vice-Chair)	Patients' Organisation Representative	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Virginie Hivert	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	
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.

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/