29 June 2016
EMA/COMP/339164/2016
Procedure Management and Committees Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 17-19 May 2016

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

17 May 2016, 09:00-19:00, room 2F

18 May 2016, 09:00-19:00, room 2F

19 May 2016, 08:30-12:45, room 2F*

(* Training for new COMP members: 19 May 2016, 13:00-15:00, 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. 22 or more members were present in the room). All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. Adoption of agenda

COMP agenda for 17-19 May 2016 was adopted with no amendments.

1.3. Adoption of the minutes

COMP minutes for 19-21 April 2016 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. Humanised anti-IL-6 receptor monoclonal antibody - EMA/OD/014/16

Chugai Pharma Europe Ltd; Treatment of neuromyelitis optica spectrum disorders

COMP coordinator: Michel Hoffmann

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 neuromyelitis optica, the sponsor should further elaborate on:

– The bridging of bibliographical data pertaining to another antibody to draw conclusions for the product as applied for designation.

– Any further information with this specific antibody proposed for designation in either preclinical or preliminary clinical settings. Any updated information from the ongoing studies should be included in the application to justify the medical plausibility.

In the written response, and during an oral explanation before the Committee on 17 May 2016, the sponsor discussed the role of IL-6 in the pathophysiology of the condition, as well as the mechanism of action of the active substance, which is the same as tocilizumab.

It was clarified that further to the bridging exercise with the clinical effects of tocilizumab, which was based on the same epitope binding domains of the two antibodies, there is data with the proposed active substance in vitro in plasmablasts isolated from NMOSD patients, showing a decrease in cell population. There is also an ongoing clinical study in patients affected by the condition, where a preliminary interim analysis by an un-blinded review committee resulted in continuation of the study.

The COMP reflected on the importance of IL-6 blocking in in context of several pathophysiological aspects of the condition. The commonalities and differences of the two antibodies was also discussed, and the bridging exercise with the clinical effects of tocilizumab was accepted on the basis of the same epitope binding sites, and the preliminary preclinical data of the proposed antibody in plasmabasts isolated from NMOSD patients.

Following review of the application by the Committee, it was agreed to rename the condition to “neuromyelitis optica spectrum disorders” (hereinafter referred to as “the condition”) based on the International Panel for Neuromyelitis Optica Diagnosis (Neurology 2015; 85:1-13).

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

The intention to treat the condition with the medicinal product containing humanised anti-IL-6 receptor monoclonal antibody was considered justified based on the reduction of plasmablast population in cells isolated from patients affected by the condition, in combination with clinical data with a comparable antibody, which improved the annualised relapse rate and the Expanded Disability Status Scale score in patients affected by the condition.

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

The condition was estimated to be affecting approximately 0.4 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for humanised anti-IL-6 receptor monoclonal antibody, for treatment of neuromyelitis optica spectrum disorders, was adopted by consensus.

2.1.2. Citric acid monohydrate - EMA/OD/022/16

CATS Consultants GmbH; Treatment of acute liver failure

COMP coordinator: Martin Možina

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 has identified two products (lactulose and rifaximin) which are authorised for use in acute liver failure namely a subset this being hepatic encephalopathy. The sponsor is proposing an alternative approach to reducing the hyperammonaemia which is a critical symptom of acute liver failure. The citric acid inside the core of liposomes captures the excess ammonia which is different to other approved products.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the preclinical studies 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 17 May 2016, the sponsor highlighted differences in the approach to treating acute liver failure with citric acid liposomes versus the use of lactulose and rifaximin. The sponsor noted the scarcity of clinical data that would demonstrate the efficacy of lactulose. A preliminary report from the United States Acute Liver Failure Study Group (US ALFSG), retrospectively compared patients who received lactulose to a well-matched group of untreated patients; they found an increase in survival time, but no difference in the severity of encephalopathy or in the overall outcome.

Current data suggests that rifaximin is as effective as lactulose in treatment of hepatic encephalopathy and has a better safety profile and tolerability in patients with chronic liver disease. Its possible benefit in lowering ammonia in patients with ALF has not yet been explored.

It was noted that citric acid's potential to reduce hyperammonaemia could be linked to a reduction in brain oedema and supports the liver and kidney functions. Targeting hepatic and extrahepatic organ failure may improve the patients' prognosis and may potentially extend the time to liver transplant. This offers a relevant clinical benefit over lactulose and rifaximin, which do not offer this possibility in the acute liver failure setting. The COMP concluded that this was of significant benefit.

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

The intention to treat the condition with the medicinal product containing citric acid monohydrate was considered justified based on in vivo preclinical models which show a reduction in hyperammonaemia.

The condition is life threatening in particular due to the development of encephalopathy with intracranial hypertension, multi-organ failure and sepsis.

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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing citric acid monohydrate will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate a normalisation of ammonaemia levels which can lead to a prolongation of survival until a liver transplant can be conducted. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for citric acid monohydrate, for treatment of acute liver, was adopted by consensus.

2.1.3. Humanized monoclonal antibody targeting interleukin-15 - EMA/OD/004/16

Dr Alain Vicari; Treatment of eosinophilic oesophagitis

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:

- 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 eosinophilic oesophagitis, the sponsor should further elaborate on:

- the relevance of the preventive settings used in the allergen-induced in vivo model to draw conclusions for a treatment indication as proposed for designation
- the relevance of the in vivo model and the results obtained in that model to draw conclusions for the condition subject of this application

- Number of people affected

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

The sponsor should justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor should describe and justify the methodology used for the prevalence calculation.

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

The sponsor is invited to provide an updated prevalence taking into consideration a) all population regardless of age b) the point in time the application is made and c) the need to establish the number of people affected in the EU.

In the written response, and during an oral explanation before the Committee on 17 May 2016, the sponsor confirmed that the proposed antibody does not cross-react with the murine IL-15 and provided a biochemical assay to support this. The sponsor also pointed out that in the model studied there is no clearly defined induction phase and maintenance phase since a) the antigen is given throughout the experiment and b) there is a steady

increase in IL-15 and IL-15/IL-15Rα levels throughout the study. Finally the sponsor acknowledged that the model is not directly a model of EoE, but it was considered relevant due to the involvement of IL-15 in the pathophysiology of the condition.

Further, the applicant revised the prevalence estimate to a more conservative value of 3.8 per 10,000, based on four publications from the literature, and by assuming that the prevalence doubles every five years. The COMP accepted this conclusion in the absence of direct data in the literature challenging the threshold at the time of the application.

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

The intention to treat the condition with the medicinal product containing humanised monoclonal antibody targeting interleukin-15 was considered justified based on the reduction of eosinophilic infiltration observed in an in vivo model of the condition.

The condition is chronically debilitating due to chronic oesophageal inflammation with development of dysphagia that affects dietary intake, oesophageal stenosis and fragility of the oesophageal wall.

The condition was estimated to be affecting approximately 3.8 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for humanised monoclonal antibody targeting interleukin-15, for treatment of eosinophilic oesophagitis, was adopted by consensus.

2.1.4. Melatonin - EMA/OD/007/16

Therapicon Srl; Treatment of neonatal sepsis

COMP coordinator: Nikolaos Sypsas

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 it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

It seems that the condition can affect neonates of any gestational age up to 28 days after birth. The sponsor is therefore invited to provide an incidence calculation taking into account newborns of any gestational age. The calculation should be based on relevant epidemiological studies and registers for the proposed orphan condition, whenever available, and any other relevant source of information on the condition.

In the written response, the sponsor presented updated prevalence calculation including both pre-term and full term births, and taking into account both early onset sepsis (estimated as those cases of sepsis occurring within 7 days from birth) and late onset sepsis (occurring after 7 days). The sponsor used data from Sweden as reference for the number of premature births before 34 weeks of gestational age. EU-28 data were used for the number of term births. The number of deaths from sepsis was based on an assumption that

50% of cases of sepsis end up with death. The sponsor doubled the number of deaths from sepsis and assumed this to be the number of cases of neonatal sepsis in the EU. The sponsor performed similar calculations considering prematurity based on gestational weight rather than gestational age, since low gestational weight is also widely used as prematurity criterion. The sponsor estimated incidence of neonatal sepsis to be 0.61 in 10,000 in the EU. Similar values of incidence of sepsis in preterm and full term birth were also reported by an expert neonatologist consulted by the COMP. In addition, it was discussed with the expert that also suspected cases of sepsis should be taken into account, since the diagnosis of neonatal sepsis can be difficult and cases with positive outcome may not be recorded. In conclusion it was estimated that the incidence of neonatal sepsis in the EU is approximately 2 in 10,000.

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

The intention to treat the condition with the medicinal product containing melatonin was considered justified based on preclinical data showing increased survival with the proposed product in valid model of sepsis.

The condition is life-threatening due to the development of respiratory distress, shock and multi-organ failure.

The condition was estimated to be affecting approximately 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 melatonin will be of significant benefit to those affected by the condition. The sponsor has provided data from published literature demonstrating clinical improvement of sepsis when the product was used in combination with the standard of care treatment of the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for melatonin, for treatment of neonatal sepsis, was adopted by consensus.

2.1.5. Melatonin - EMA/OD/001/16

Therapicon Srl; Treatment of necrotising enterocolitis

COMP coordinator: Vallo Tillmann

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 it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor is invited to provide a specific figure of the incidence of the condition. The calculation should be based on relevant epidemiological studies and registers for the proposed orphan condition, whenever available, and any other relevant source of

information on the condition. The calculation is expected to take into account all cases of the condition, irrespective of age.

In the written response, the sponsor revised the prevalence calculation by including forms of NEC that can sporadically occur at any age. This included mainly cases occurring in the context of ischemia reperfusion-injury from different causes. The sponsor based the estimate of NEC occurring in ischemia-reperfusion injury on valid literature sources.

The final estimated incidence of 1.2 in 10,000 was accepted by the COMP and the oral explanation was not needed. The COMP approximated the estimated incidence to less than 2 in 10,000 in the EU, based on a conservative approach.

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

The intention to treat the condition with the medicinal product containing melatonin was considered justified based on preclinical data showing improvement of histology and increased survival with the proposed product.

The condition is chronically debilitating due to development of short-bowel syndrome, malnutrition and growth delay, and life-threatening due to bowel perforation, peritonitis, sepsis and mortality reported as high as in 50% of the cases.

The condition was estimated to be affecting less than1.5 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 that has been authorised in the European Union for patients affected by the condition.

A positive opinion for melatonin, for treatment of necrotising enterocolitis, was adopted by consensus.

2.1.6. Allogeneic donor-derived ex-vivo expanded T lymphocytes transduced with a retroviral vector containing inducible caspase 9 and truncated CD19 - EMA/OD/018/16

QRC Consultants Ltd; Treatment of beta thalassaemia intermedia and major

COMP coordinator: Armando Magrelli

Please see 2.1.8.

2.1.7. Allogeneic donor-derived ex-vivo expanded T lymphocytes transduced with a retroviral vector containing inducible caspase 9 and truncated CD19 - EMA/OD/019/16

QRC Consultants Ltd; Treatment of Fanconi anaemia

COMP coordinator: Armando Magrelli

Please see 2.1.8.

2.1.8. Allogeneic donor-derived ex-vivo expanded T lymphocytes transduced with a retroviral vector containing inducible caspase 9 and truncated CD19 - EMA/OD/020/16

QRC Consultants Ltd; Treatment of severe combined immunodeficiency

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:

- Intention to diagnose, prevent or treat

Having acknowledged the partial cluster of orphan designation applications (see 2.1.6, 2.1.7, 2.1.8 and 2.1.9), the COMP invites the sponsor to merge the four indications treatment of beta thalassemia intermedia and major, treatment of Fanconi anaemia, treatment of severe combined immunodeficiency and treatment of Wiskott-Aldrich syndrome into the indication "Treatment in haematopoietic stem cell transplantation". The committee is of the view, that due to exceptional circumstances, where the mechanism of action of the proposed product is closely linked to the treatment modality, irrespective of the underlying condition, the proposed indication may be considered as a distinct condition. Such exceptional case is foreseen by the EC Guideline ENTR/6283/00 Rev3 (Page 7/13).

- Number of people affected

The sponsor is invited to provide a prevalence calculation that reflects the revised orphan indication "Treatment in haematopoietic stem cell transplantation".

For the calculation and presentation of the prevalence estimate it 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 invited to present a list of all products that are authorised for the treatment of patients in haematopoietic stem cell transplantation. Subsequently, the sponsor is requested to discuss arguments for significant benefit and to elaborate on the results from the clinical studies 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 17 May 2016, the sponsor agreed to amend the condition to 'haematopoietic stem cell transplantation'. The sponsor provided a new prevalence calculation, which was derived from the annual incidence of haematopoietic stem cell transplantations in the EU as per the European Society for Blood and Marrow Transplantation (EBMT) registry. The prevalence estimate was proposed to be 0.65 in 10,000 based on data from the year 2015. The COMP adopted a value 'less than 1 in 10,000' based on observed annual fluctuation of numbers over the recent years.

The sponsor provided a comprehensive list of products authorised for treatment in HSCT in the written responses. The arguments for significant benefit were based on reduced number of infections and treatment related mortalities in patients treated with the proposed product. This compared favourably to historical controls receiving standard of care, including authorised products.

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

Ex-vivo expanded T lymphocytes transduced with a retroviral vector containing inducible caspase 9 and truncated CD19 was considered justified based on preliminary clinical data in patients receiving haploidentical haematopoietic stem cell transplantation that demonstrated reduced infection rates and improved survival.

The condition is life-threatening and chronically debilitating due to susceptibility to severe infections and complications such as graft-versus-host disease.

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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing allogeneic donor-derived ex-vivo expanded T lymphocytes transduced with a retroviral vector containing inducible caspase 9 and truncated CD19 will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data demonstrating shorter time to discharge from hospital, fewer hospitalisations, reduced incidence of infections and improved survival of patients treated with the product on top the standard of care, which included authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic donor-derived ex-vivo expanded T lymphocytes transduced with a retroviral vector containing inducible caspase 9 and truncated CD19, for treatment in haematopoietic stem cell transplantation, was adopted by consensus.

2.1.9. Allogeneic donor-derived ex-vivo expanded T lymphocytes transduced with a retroviral vector containing inducible caspase 9 and truncated CD19 - EMA/OD/021/16

QRC Consultants Ltd; Treatment of Wiskott-Aldrich syndrome

COMP coordinator: Armando Magrelli

Please see 2.1.8.

2.1.10. 2'-O-(2-methoxyethyl) phosphorothioate antisense oligonucleotide targeting the growth hormone receptor - EMA/OD/023/16

Coté Orphan Consulting UK Limited; Treatment of acromegaly

COMP coordinator: Vallo Tillmann

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 the treatment of acromegaly, the sponsor should further elaborate on:

– the different responses on IGF-1 levels with the two different dosing regimens (once a week vs. twice a week) in the clinical study presented, and the clinical relevance of the reduction of IGF-1 achieved with the more frequent dosing regimen

- the results on the Growth Hormone Binding Protein, and the clinical relevance of such results

- Significant benefit

In order to justify the significant benefit of the proposed product the sponsor is invited to provide any available data and/or a comparative discussion supporting the claim of an improved outcome when the product would be used in combination with the existing authorised treatments for the condition.

In the written response, the sponsor clarified that when the dose was corrected for body weight, a correlation existed between mg/kg dose and serum levels of insulin-like growth factor (sIGF). The sponsor also commented on the expected efficacy of the product at a lower dose and the expected dosing regimen in the majority of patients. To further support the results, the sponsor also indicated that the study population had very high baseline levels of sIGF compared to other acromegaly studies. The significant reduction of IGF levels measured in these patients can therefore be considered particularly clinically relevant.

The sponsor also presented the data on growth hormone (GH)-binding protein (GHBP). GHBP represents the extracellular portion of the growth hormone receptor, and serum levels of GHBP can be used as a marker of growth hormone receptor (GHR) expression. A decrease in the receptor expression accompanying the effects of the product on sIGF is considered an important signal of the efficacy of the proposed product.

To support the significant benefit, the sponsor produced preclinical data showing that combination of the proposed product with some of the currently authorized products for the condition yielded a higher effect on IGF levels (intrahepatic and serum) than each product used alone.

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

The intention to treat the condition with the medicinal product containing 2'-O-(2-methoxyethyl)phosphorothioate antisense oligonucleotide targeting the growth hormone receptor was considered justified based on preliminary clinical results showing reduction in treated patients of Insulin-like Growth Factor-I, an established marker of efficacy in the condition.

The condition is life-threatening and chronically debilitating due to disproportionate skeletal, tissue, and organ growth, leading to multisystem morbidities and terminal cardiovascular, cerebrovascular, and respiratory disease.

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.

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 2'-O-(2-methoxyethyl)phosphorothioate antisense oligonucleotide targeting the growth hormone receptor will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing higher reduction of Insulin-like Growth Factor-I and growth hormone receptor with the proposed product, as compared to some of the currently authorized products for the condition. The reduction of Insulin-like Growth Factor-I was further enhanced when the proposed product was used in combination with some of the currently authorized products

for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by acromegaly.

A positive opinion for 2'-O-(2-methoxyethyl)phosphorothioate antisense oligonucleotide targeting the growth hormone receptor, for treatment of acromegaly, was adopted by consensus.

2.1.11. Eflornithine - EMA/OD/009/16

Orbus Therapeutics Limited; Treatment of glioma

COMP coordinator: 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 clarify the following issues:

- Significant benefit

The arguments on significant benefit are based on the alternative mechanism of action and the potentially improved efficacy in the condition.

The sponsor is requested to further discuss the arguments provided for significant benefit and to contextualise the results from clinical studies published in 2003 into contemporary treatment algorithms, both with respect to authorised standard treatment (temozolomide) and with the assessment of molecular markers to guide treatment decisions.

In the written response, and during an oral explanation before the Committee on 17 May 2016, the sponsor highlighted the limited efficacy of the existing treatment regimens and the poor overall survival of patients. Standard of care comprises surgery, radiation and chemotherapy (alkylators or combinations of alkylator and vincristine). According to the sponsor, the PCV combination for anaplastic glioma was replaced by temozolomide mainly based on a more predictable safety profile but not due to improved efficacy.

The sponsor referred to chemotherapy as being inconsistent in improving outcome of patients and to the limitation of use of temozolomide, which was reported to stimulate a transformation of WHO grade II and III gliomas to glioblastoma.

The sponsor's product offers a different mode of action vs alkylators. It was already used in combination with alkylating agents and had numerically improved survival. Since the study has been performed a long time ago (published in 2003), the distribution of contemporary markers between study arms, which might also explain differential responses, is not known.

The COMP noted that despite a high number of orphan designations, very few products were introduced to the market – and their efficacy is limited, especially for glioblastoma. The COMP considered that based on the potential efficacy when used in combination with one (of several) authorised alkylator regimens used in anaplastic oligodendroglioma/anaplastic mixed oligoastrocytoma, the product might be of significant benefit to patients.

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 eflornithine was considered justified based on clinical data showing an improvement in survival of patients with the condition.

The condition is chronically debilitating due to symptoms caused by compression by the tumour on the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality change and cognitive impairment. The condition is life-threatening, with poor 5-year survival of less than 5% for glioblastoma multiforme 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing eflornithine will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate an improved survival when the product is used in combination with other authorised medicines. The Committee considered that this constitutes a clinically relevant advantage.

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

2.1.12. Molgramostim - EMA/OD/005/16

Serendex Pharmaceuticals A/S; Treatment of acute respiratory distress syndrome

COMP coordinator: Martin Možina

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 treat

The sponsor is invited to further elaborate on the clinical studies with molgramostin in the sought indication, and discuss the results observed and the populations studied to draw conclusions for the treatment of ARDS;

The formulation of the proposed product should also be further discussed;

- Number of people affected

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

The sponsor should justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor should describe and justify the methodology used for the prevalence calculation.

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

In the written response, and during an oral explanation before the Committee on 18 May 2016, the sponsor elaborated on the three cited clinical studies. It was argued that effects are expected mainly in the ARDS of infectious origin, even though effects in the non-infectious (indirect) ARDS may not be excluded. It was also further explained that the two clinical studies supporting use of rhGM-CSF in ARDS of infectious origin were of small size and only one was a prospective, randomised study. Nevertheless they were able to show

statistically significant improvements in oxygenation. This was considered acceptable for the purpose of justifying the medical plausibility.

Further, the applicant used two methods to estimate annual incidence of ARDS. The first one is derived from population based studies concluded at approximately 3.34/10,000. The second one is an indirect calculation through ICU-admission incidence (three studies reporting from 7% to 19% of ICU admissions). The sponsor used this data to estimate an incidence ranging from 1.56 to 24.53/10,000 (for Germany) with a mean reported to be 3.54.

The COMP considered that the prevalence estimate should only be based on the available population based studies, and accepted approximately 3.3 at the time of the application, while at the same time noting that the prevalence may further evolve in the future and new data may become available at the time of the review of the designation at the stage of marketing authorisation.

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

The intention to treat the condition with the medicinal product containing molgramostim was considered justified based on preliminary clinical data in acute respiratory distress syndrome patients who responded to treatment with the proposed active substance by improving blood oxygenation.

The condition is life-threatening with mortality up to approximately 50% and chronically debilitating due to persistent functional impairment.

The condition was estimated to be affecting approximately 3.3 in 10,000 persons in the European Union, at the time the application was made taking into account population-based epidemiological studies from the literature.

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

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

2.1.13. Donor T lymphocytes depleted ex vivo of host alloreactive T cells using photodynamic treatment - EMA/OD/008/16

Kiadis Pharma Netherlands B.V.; Treatment in haematopoietic stem cell transplantation.

COMP coordinator: 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 clarify the following issues:

- Intention to diagnose, prevent or treat

Having considered the scope of this application, the COMP invites the sponsor to amend the orphan indication from acute lymphoblastic leukaemia to “Treatment in haematopoietic stem cell transplantation”. This is in line with the special consideration section of guideline ENTR/6283/00 Rev 04.

- Seriousness

The sponsor is invited to discuss the morbidity and mortality associated with haematopoietic stem cell transplantation

- Number of people affected

The sponsor is invited to provide a prevalence calculation that reflects the revised orphan indication “Treatment in haematopoietic stem cell transplantation”.

For the calculation and presentation of the prevalence estimate it 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 invited to present a list of all products that are authorised for the treatment of patients in haematopoietic stem cell transplantation. Subsequently, the sponsor is requested to discuss arguments for significant benefit and to elaborate on the results from the clinical studies 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 18 May 2016, the sponsor accepted the recommendation to amend the proposed indication to “treatment in haematopoietic stem cell transplantation”, and argued that the orphan criteria are established on the following grounds:

- the life-threatening nature is argued in particular due to opportunistic infections and graft versus host disease;
- the prevalence criterion was argued on the basis of annual number of HSCT procedures, which was estimated by the applicant to be approximately 40.000 per year (rounded up figure of EBMT survey), or 0.8/10.000;
- the applicant has identified busulfan, figrastim, plerixafor and thiotepa as authorised in the proposed indication;
- significant benefit is argued on targeting a different aspect of the HSCT procedure. It is argued that the authorised products are either part of the conditioning regimen (busulfan and thiothepa) relieve neutropenia, or mobilize the before harvesting the stem cells (filgrastim). Contrary, ATIR101 is being developed as an adjuvant therapy to haploidentical HSCT, and clinical data support improved survival compared to HSCT alone.

The COMP further reflected in particular on the existing methods and the significant benefit issue. It was considered that the applicant had not identified all authorised products in the EU whose indication referred to HSCT, and the list should also refer to antifungals (Voriconazole, Posaconazole, Micafungin, Fluconazole), Antivirals (ganciclovir and acyclovir), Immunoglobulin, Antihaemorrhagics (Revolade), Antithrombotics (Defibrotide), Immunosupresive agents (Ciclosporin, Tacrolimus, Azathioprine, Deflazacort), and cytotoxic agents (brentuximab vedotin, Bortezomib, Bendamustine hydrochloride, doxorubicin hydrochloride, Azacitidine, Melphalan hydrochloride, busulfan, Cyclophosphamide).

However, for the issue of significant benefit, it was considered that the proposed product targeted a different aspect of HSCT, namely early immune reconstitution, and the sponsor has provided clinical data showing improved transplantation related mortality and overall

survival in haploidentical HSCT recipients versus controls receiving standard of care. This was accepted as a clinically relevant advantage.

The Committee agreed that the condition, 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 donor T lymphocytes depleted ex vivo of host alloreactive T cells using photodynamic treatment was considered justified based on preliminary clinical data supporting improved survival in patients receiving haploidentical haematopoeitic stem cell transplantation.

The condition is life-threatening and chronically debilitating due to susceptibility to severe infections and complications such as graft-versus-host disease.

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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing donor T lymphocytes depleted ex vivo of host alloreactive T cells using photodynamic treatment will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that show improved overall survival and transplantation-related mortality in patients subjected to haploidentical haemopoietic stem cell transplantation. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for donor T lymphocytes depleted ex vivo of host alloreactive T cells using photodynamic treatment, for treatment in haematopoietic stem cell transplantation, was adopted by consensus.

2.1.14. - EMA/OD/010/16

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:

- Significant benefit

The sponsor provides a discussion of the efficacy of the product as compared to bevacizumab or sunitinib with or without radiotherapy.

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition compared to products authorised outside of the European Union.

The sponsor is requested to further discuss the arguments for significant benefit and to elaborate on results from preclinical studies to justify the assumption of significant benefit over medicinal products authorised in the EU for treatment of glioma. The sponsor should also elaborate on the intended position of the proposed product in the treatment regimen of patients.

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

In the written response, and during an oral explanation before the Committee on 18 May 2016, the sponsor elaborated on the data obtained in preclinical models, where the product was compared to two comparators alone or in combination with radiation. The sponsor relied on an assumption that the efficacy of the authorised products is limited. Therefore an alternative treatment option with a different mechanism of action would be of significant benefit. The COMP considered that data with presented comparators is not relevant because they are not authorised for the treatment of the condition in the EU. In the absence of comparative data with at least one of authorised chemotherapeutic agents, it is impossible to assume the significant benefit. The sponsor was informed of the negative trend in COMP opinion and encouraged to re-apply once preclinical or preliminary clinical data demonstrating improved efficacy over the standard of care becomes available.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 19 May 2016, prior to final opinion.

2.1.15. 3-(5-amino-2-methyl-4-oxoquinazolin-3(4H)-yl)piperidine-2,6-dione hydrochloride - EMA/OD/016/16

Celgene Europe Limited; Treatment of diffuse large B-cell lymphoma

COMP coordinator: 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 clarify the following issues:

- Prevalence

The sponsor is requested to provide an updated prevalence estimate taking into consideration more current sources for the time the application is made.

In the written response, the sponsor revised upwards the prevalence estimate based on GLOBOCAN 2012 and HMRN database, by assuming a 10 year median duration of the proposed condition. This revision yielded a figure of 4.3 per 10,000 which was considered acceptable by the COMP.

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

The intention to treat the condition with the medicinal product containing 3-(5-amino-2-methyl-4-oxoquinazolin-3(4H)-yl)piperidine-2,6-dione hydrochloride was considered justified based on preliminary clinical studies showing responses in relapsed/refractory patients affected by the condition.

The condition is chronically debilitating due to involvement of single or multiple nodal or extra nodal sites, including the gastrointestinal tract and bone marrow and life-threatening with 5-year survival rates reported as low as 26% for the high risk patients.

The condition was estimated to be affecting approximately 4.3 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 3-(5-amino-2-methyl-4-oxoquinazolin-3(4H)-yl)piperidine-2,6-dione hydrochloride will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical observations in

relapsed/refractory patients with the condition who responded to treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 3-(5-amino-2-methyl-4-oxoquinazolin-3(4H)-yl)piperidine-2,6-dione hydrochloride, for treatment of diffuse large B-cell lymphoma, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/046/16

Treatment of idiopathic pulmonary fibrosis

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 June meeting.

2.2.2. 4,5-bis(hydroxymethyl)-2-methyl-pyridin-3-ol - EMA/OD/034/16

FGK Representative Service Ltd.; Treatment of fragile X syndrome

COMP coordinator: Ingeborg Barisic/Violeta Stoyanova

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

The intention to treat the condition with the medicinal product containing 4,5-bis(hydroxymethyl)-2-methyl-pyridin-3-ol was considered justified based on preclinical data in a valid disease model demonstrating that treatment improved learning, social interaction and spatial working memory.

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

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

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

A positive opinion for 4,5-bis(hydroxymethyl)-2-methyl-pyridin-3-ol, for treatment of fragile X syndrome, was adopted by consensus.

2.2.3. - EMA/OD/028/16

Treatment of retinitis pigmentosa

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 June meeting.

2.2.4. - EMA/OD/043/16

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 June meeting.

2.2.5. - EMA/OD/049/16

Prevention of hereditary angioedema attacks

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 June meeting.

2.2.6. Cyclocreatine - EMA/OD/032/16

Pharma Gateway AB; Treatment of creatine deficiency syndromes

COMP coordinator: Geraldine O'Dea

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

The intention to treat the condition with the medicinal product containing cyclocreatine was considered justified based on preclinical in vivo data in a valid model of the condition showing an improvement in cognitive parameters.

The condition is chronically debilitating due to mental impairment, absence of expressive speech, severe language delay, autistic behaviour, epilepsy, and developmental delay.

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

A positive opinion for cyclocreatine, for treatment of creatine deficiency syndromes, was adopted by consensus.

2.2.7. Diclofenamide - EMA/OD/012/16

Sun Pharmaceutical Industries Europe B.V.; Treatment of periodic paralysis

COMP coordinator: Violeta Stoyanova

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

The intention to treat the condition with the medicinal product containing diclofenamide was considered justified based on preliminary clinical data, supporting a reduction in the number of attacks in patients affected by the condition.

The condition is chronically debilitating, due to permanent weakness and muscle pain in the majority of patients, and the requirement of mobility aids in about half of the patients. The condition may also be life-threatening, in particular due to the risk of cardiac arrhythmias in hypokalaemic periodic paralysis and Andersen-Tawil syndrome.

The condition was estimated to be affecting approximately 0.2 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for diclofenamide, for treatment of periodic paralysis, was adopted by consensus.

2.2.8. - EMA/OD/029/16

Treatment of bullous pemphigoid

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 at the June meeting.

2.2.9. Modified mRNA encoding UGT1A1 protein - EMA/OD/047/16

Alexion Europe SAS; Treatment of Crigler-Najjar syndrome

COMP coordinator: Katerina Kubáčková/Armando Magrelli

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

The intention to treat the condition with the medicinal product containing modified mRNA encoding the UGT1A1 protein was considered justified based on a reduction in bilirubin levels see in a preclinical in vivo model of the condition.

The condition is chronically debilitating due to the development of bilirubin encephalopathy (kernicterus), characterized by extrapyramidal dystonia, choreoathetosis, hearing loss due to auditory neuropathy and oculomotor paresis, and life-threatening with reduced life expectancy for type I patients.

The condition was estimated to be affecting 0.01 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for modified mRNA encoding the UGT1A1 protein, for treatment of Crigler-Najjar syndrome, was adopted by consensus.

2.2.10. - EMA/OD/035/16

Treatment of fibromyalgia

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 June meeting.

2.2.11. - EMA/OD/048/16

Treatment of lymphangioleiomyomatosis

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 June meeting.

2.2.12. - EMA/OD/041/16

Treatment of hyperargininaemia

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 June meeting.

2.2.13. - EMA/OD/042/16

Treatment of Clostridium difficile 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 June meeting.

2.2.14. Recombinant humanised Monoclonal IgG2 lambda antibody against human sclerostin - EMA/OD/052/16

Mereo Biopharma Group Limited; Treatment of osteogenesis imperfecta

COMP coordinator: Ingeborg Barisic/Vallo Tillmann

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

The intention to treat the condition with the medicinal product containing recombinant humanised monoclonal IgG2 lambda antibody against human sclerostin was considered justified based on clinical data demonstrating that treatment improved the bone mineral density of patients affected by the condition.

The condition is chronically debilitating due to fragile bones, multiple fractures and bone deformations leading to persistent physical and functional limitations, pain and restrictions in daily life activities.

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

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

A positive opinion for recombinant humanised monoclonal IgG2 lambda antibody against human sclerostin, for treatment of osteogenesis imperfecta, was adopted by consensus.

2.2.15. Recombinant protein derived from the saliva of the Ornithodoros moubata tick - EMA/OD/030/16

Akari Therapeutics Plc; Treatment of Guillain-Barré syndrome

COMP coordinator: Michel Hoffmann

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

The intention to treat the condition with the medicinal product containing recombinant protein derived from the saliva of the *Ornithodoros moubata* tick was considered justified based on data from preclinical in vivo models demonstrating improved clinical score and reduced neuronal degeneration.

The condition is life-threatening due to respiratory insufficiency and potentially chronically debilitating due to weakness of the extremities, hyporeflexia or areflexia, as well as autonomic dysfunction.

The condition was estimated to be affecting approximately 0.2 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 recombinant protein derived from the saliva of the *Ornithodoros moubata* tick will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate a reduction of symptoms, which may impact the long term recovery. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for recombinant protein derived from the saliva of the *Ornithodoros moubata* tick, for treatment of Guillain-Barré syndrome, was adopted by consensus.

2.2.16. Setmelanotide - EMA/OD/033/16

TMC Pharma Services Ltd; Treatment of Prader-Willi syndrome

COMP coordinator: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing setmelanotide was considered justified based on preclinical studies in valid models of the condition showing normalization of food intake and energy expenditure with the proposed product.

The condition is life-threatening and chronically debilitating, in particular due to cognitive impairment, maladaptive behaviour and morbid obesity leading to increased cardiovascular morbidity and mortality.

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 setmelanotide will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing normalisation of food intake and energy expenditure, aspects of the condition that are not influenced by the currently authorised treatments. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for setmelanotide, for treatment of Prader-Willi syndrome, was adopted by consensus.

2.2.17. - EMA/OD/045/16

Treatment of lymphangioleiomyomatosis

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 June meeting.

2.2.18. Teriparatide - EMA/OD/031/16

Alacrita LLP; Treatment of hypoparathyroidism

COMP coordinator: Vallo Tillmann/Dinah Duarte

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

The intention to treat the condition with the medicinal product containing teriparatide was considered justified based on preliminary clinical data showing normalisation of calcium metabolism with the proposed product.

The condition is chronically debilitating due to neuromuscular symptoms, cognitive impairment, abnormal calcium and phosphate metabolism, and reduced bone turnover. The condition may be life-threatening due to risk of hypocalcaemia that may lead to seizures, cardiac arrhythmias, cardiomyopathy and laryngeal spasm if untreated.

The condition was estimated to be affecting less than 5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing teriparatide will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing better normalisation of calcium metabolism with the proposed product than with calcium supplements, currently used for the condition. In addition the use of the proposed product resulted in significant reduction of the need of calcium supplement that is linked to the development of kidney failure in patients with hypoparathyroidism. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by hypoparathyroidism.

A positive opinion for teriparatide, for treatment of hypoparathyroidism, was adopted by consensus.

2.3. Revision of the COMP opinions

None

2.4. COMP opinions adopted via written procedure following previous meeting

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 2 applications submitted.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 31 applications for orphan designation.

Action: For information

Notes:
Cross reference to other agenda point. See 6.8.1. Table 6. Evaluation Ongoing.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of primary sclerosing cholangitis

The Committee was briefed on the significant benefit issues.

[*Post-meeting note:* The COMP answer was adopted by written procedure following its May meeting.]

3.1.2. -

Treatment of beta thalassaemia intermedia and major

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

[*Post-meeting note:* The COMP answer was adopted by written procedure following its May meeting.]

3.2. Finalised letters

None

3.3. New requests

3.3.1. -

Treatment of microscopic polyangiitis

The new request was noted.

3.3.2. -

Treatment of granulomatosis with polyangiitis

The new request was noted.

3.3.3. -

Treatment of acute myeloid leukaemia

The new request was noted.

3.3.4. -

Treatment of growth hormone deficiency

The new request was noted.

4. Review of orphan designation for orphan medicinal products for marketing authorisation

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

4.1.1. Gazyvaro – obinutuzumab - Type II variation - EMA/OD/013/15, EU/3/15/1504, EMEA/H/C/002799/II/0007

Roche Registration Limited; Treatment of follicular lymphoma

COMP coordinator: Bożenna Dembowska-Bagińska and Frauke Naumann-Winter; CHMP rapporteur: Sinan B. Sarac; CHMP co-rapporteur: Pierre Demolis

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 invited to recalculate the prevalence estimate taking into account the most recent data available on the epidemiology of the condition and the longest average duration of the disease at the present time. It is expected that the estimate provided by the sponsor corresponds to the complete prevalence.

In its written response, the sponsor revised its initial calculation based on 10 year partial prevalence (2.3 in 10.000) upwards to a total prevalence of 3.7 (1.77-4.3) based on mean survival of 10 years. The average survival estimate was derived from the US-American SEER database. It is considered that the EU and the USA have similar survival rates of follicular lymphoma, as similar management and international guidelines are used in both regions.

The COMP concluded that:

The proposed therapeutic indication “Gazyvaro in combination with bendamustine followed by Gazyvaro maintenance is indicated for the treatment of patients with follicular lymphoma who did not respond to or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen” falls entirely within the scope of the orphan indication of the designated orphan medicinal product “treatment of follicular lymphoma”.

The prevalence of follicular lymphoma (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be less than 4 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is life-threatening and chronically debilitating due to lymphadenopathy, splenomegaly, bone marrow dysfunction and the potential of transformation into aggressive lymphoma.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Gazyvaro will be of significant benefit to the subset of the orphan condition as defined in the granted therapeutic indication is confirmed. The significant benefit is mainly based on the results of the pivotal phase III clinical trial showing a statistically significant and clinically meaningful improvement of progression free survival of Gazyvaro plus bendamustine versus bendamustine alone in patients relapsing or refractory to treatment with rituximab. In addition, continuation of treatment with obinutuzumab as maintenance resulted in significant reduction of the risk of disease progression or death in patients with relapsed/refractory follicular lymphoma. These results support the significant benefit of Gazyvaro vs. rituximab, and the advantage of the combination with bendamustine. Ibritumumab and idelalisib are also authorised for the treatment of follicular lymphoma. Ibritumomab is indicated as consolidation therapy after remission induction in previously untreated patients and its benefit following rituximab in combination with chemotherapy has not been established. Idelalisib is indicated as monotherapy for follicular lymphoma relapsing from previous treatments. Its use in combination with other currently authorised medicinal products for follicular lymphoma is at present not supported by the authorised indication. Based on all the above, the COMP is of the opinion that the significant benefit of Gazyvaro is confirmed.

An opinion not recommending the removal of Gazyvaro, obinutuzumab (EU/3/15/1504) 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.

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

4.2.1. NINLARO - ixazomib – EMEA/H/C/003844, EU/3/11/899, EMA/OD/048/11

Takeda Pharma A/S; Treatment of multiple 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 June meeting.

4.2.2. Opsiria - sirolimus – EMA/OD/021/11, EU/3/11/898, EMEA/H/C/003978

Santen Oy; Treatment of chronic non-infectious uveitis

The COMP noted that the Application for Marketing Authorisation for Opsiria had been withdrawn.

4.2.3. Zalmoxis - allogeneic T cells genetically modified to express suicide gene - EMEA/OD/041/03, EU/3/03/168, EMEA/H/C/002801

MolMed SpA; Adjunctive treatment in haematopoietic cell transplantation

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

4.3. On-going procedures

4.3.1. List of on-going procedures

COMP co-ordinators were appointed for 2 applications.

4.4. Public Summary of Opinion

The draft public summaries of COMP opinions adopted last month were endorsed by the COMP and will be published on the EMA website.

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

None

6. Organisational, regulatory and methodological matters

6.1. Mandate and organisation of the COMP

6.1.1. COMP Drafting Group

The COMP Drafting group met on 18 May 2016.

6.1.2. Protocol Assistance Working Group

The working group on Protocol Assistance met on 18 May 2016.

6.1.3. Preclinical Models Working Group

The working Group on Preclinical Models met on 19 May 2016.

6.1.4. Training of new COMP members

The second of the two training sessions for new COMP members took place on 19 May 2016.

6.2. Coordination with EMA Scientific Committees or CMDh-v

6.2.1. PDCO/COMP Working Group

The PDCO/COMP working group met on 19 May 2016.

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

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

On 19 May, the COMP re-nominated Daniel O'Connor as COMP representative in the Patients' and Consumers' Organisations Working Party (PCWP) for a second 3-year term.

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

On 19 May, the COMP re-nominated Kateřina Kopečková (previously Kateřina Kubáčková) as COMP representative in the Healthcare Professionals' Organisations Working Party (HCPWP) for a second 3-year term.

6.4. Cooperation within the EU regulatory network

6.4.1. European Commission

The COMP was informed of the main comments received during the public consultation on the proposed Commission Notice on the application of Articles 3,5 and 7 of Regulation (EC) NO 141/2000 on Orphan Medicinal Products and commented on the updated proposal.

6.5. Cooperation with International Regulators

None

6.6. Contacts of the COMP with external parties and interaction with the Interested Parties to the Committee

None

6.7. COMP work plan

None

6.8. Planning and reporting

6.8.1. List of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2016

An updated list of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2016 were circulated.

6.8.2. Overview of orphan marketing authorisations/applications

An updated overview of orphan applications for Marketing Authorisation was circulated.

7. Any other business

7.1.1. COMP Prevalence Survey

Results of a survey to COMP members on how to deal with various aspects of prevalence during orphan drug designation and at confirmation of orphan status at the time of market authorization were presented to the COMP. The main conclusions and next steps will be discussed later on.

7.1.2. EMA Business Pipeline activity and Horizon scanning

EMA presented the data collection process and an estimation of initial marketing authorisation applications expected in 2017.

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 17-19 May 2016 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	
André Lhoir	Member	Belgium	No interests declared	
Irena Bradinova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No restrictions applicable to this meeting	
Katerina Kopeckova	Member	Czech Republic	No restrictions applicable to this meeting	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Annie Lorence	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Nikolaos Sypsas	Member	Greece	No restrictions applicable to this meeting	
Judit Eggenhofer	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	
Michel Hoffmann	Member	Luxembourg	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Violeta Stoyanova-Beninska	Member	Netherlands	No interests declared	
Ingrid Wang	Member	Norway	No restrictions applicable to this meeting	
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 Možina	Member	Slovenia	No interests declared	
Josep Torrent-Farnell	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/