31 March 2016
EMA/COMP/240468/2016
Procedure Management and Committees Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 16-18 February 2016

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

16 February 2016, 09:00-19:00, room 2F

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

18 February 2016, 09:00-14:00, 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.

Note on access to documents

Some documents mentioned in the minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

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1. Introduction

1.1. Welcome and declarations of interest of members and experts

In accordance with the Agency's policy on handling of declarations of interests of scientific committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of some meeting participants in upcoming discussions as included in the pre-meeting list of participants and restrictions.

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

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure and as included in the list of participants. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 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 16-18 February 2016 was adopted with no amendments. Section 6.1.5 was added post-meeting.

1.3. Adoption of the minutes

COMP minutes for 19-21 January 2016 were adopted with amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. Glucopyranosyl lipid A stable emulsion and recombinant New York esophageal squamous cell carcinoma-1 protein- EMA/OD/159/15

Pharm Research Associates (UK) Limited; Treatment of soft tissue sarcoma

COMP coordinator: Daniel O'Connor

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 soft tissue sarcoma, the sponsor should further elaborate on the relevance of the preliminary clinical data. In particular the sponsor is asked to

discuss the clinical relevance of the results of this study where only one of the three treated patients with sarcoma achieved stable disease.

- Significant benefit

The sponsor is invited to further discuss the available preliminary clinical results and to provide additional information on the clinical studies presented.

In particular the sponsor is invited to provide information on the patient population (stage of disease, previous and concomitant treatments) and to discuss how the results support the clinical use of the proposed combination regimen and a potential clinical advantage of the proposed regimen (e.g. as add-on to current treatments, or in relapsing disease, or other).

In the written response, and during an oral explanation before the Committee on 16 February 2016, the sponsor elaborated on the mechanism of action in combination with a second product (proposed as well for orphan designation) and justified the absence of *in vivo* preclinical data in models of the condition based on cross-species particularities.

The sponsor also further elaborated on the available clinical data and the use of the two proposed products in their intended sequential combination, in particular by providing more details on the immune and clinical responses observed. Results regarding SD responses and PFS at 3 months were presented to the COMP.

Following review of the application by the Committee, it was agreed to rename the active substance to “glucopyranosyl lipid A stable emulsion and recombinant New York esophageal squamous cell carcinoma-1 protein”.

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

The intention to treat the condition with the medicinal product containing glucopyranosyl lipid A stable emulsion and recombinant New York oesophageal squamous cell carcinoma-1 protein was considered justified based on preliminary clinical data showing anti-tumor efficacy.

The condition is chronically debilitating with a high recurrence and metastasis rate, and life-threatening with an overall 5-year survival rate of approximately 60%.

The condition was estimated to be affecting approximately 2.3 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 glucopyranosyl lipid A stable emulsion and recombinant New York oesophageal squamous cell carcinoma-1 protein will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing favourable activity with the proposed product in patients previously treated with other antineoplastic agents. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by soft tissue sarcoma.

A positive opinion for glucopyranosyl lipid A stable emulsion and recombinant New York esophageal squamous cell carcinoma-1 protein, for treatment of soft tissue sarcoma, was adopted by consensus.

2.1.2. Sindbis virus envelope pseudotyped lentiviral vector encoding New York esophageal squamous cell carcinoma-1 protein- EMA/OD/238/15

Pharm Research Associates (UK) Limited; Treatment of soft tissue sarcoma

COMP coordinator: Daniel O'Connor

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 soft tissue sarcoma, the sponsor should further elaborate on the preclinical data generated in models of disease other than soft tissue sarcoma and their applicability and extrapolation to the intended clinical application.

The Sponsor should also discuss the relevance of the clinical data: the best outcome in the clinical data was stable disease or 14% tumour regression in one patient. The sponsor should better explain how the observed duration of stable disease and the clinical picture (NY-ESO positive) compares to the natural history of the disease.

- Significant benefit

The sponsor is invited to further discuss the available preliminary clinical results and to provide additional information on the clinical studies presented. This applies to both products intended to be used as a combination regimen.

In particular the sponsor is invited to provide information on the patient population (stage of disease, previous and concomitant treatments) and to discuss how the results support the clinical use of the proposed combination regimen and a potential clinical advantage of the proposed regimen (e.g. as add-on to current treatments, or in relapsing disease, or other).

In the written response, and during an oral explanation before the Committee on 16 February 2016, the sponsor elaborated on the mechanism of action of the product in combination with a second product (proposed as well for orphan designation) and justified the absence of *in vivo* preclinical data in models of the condition based on cross-species particularities.

The sponsor also further elaborated on the available clinical data and the use of the two proposed products in their intended sequential combination, in particular by providing more details on the immune and clinical responses observed. Results regarding SD responses and PFS at 3 months were presented to the COMP.

Following review of the application by the Committee, it was agreed to rename the active substance to “sindbis virus envelope pseudotyped lentiviral vector encoding New York esophageal squamous cell carcinoma-1 protein”.

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

The intention to treat the condition with the medicinal product containing sindbis virus envelope pseudotyped lentiviral vector encoding New York oesophageal squamous cell carcinoma-1 protein was considered justified based on preliminary clinical data showing anti-tumour efficacy.

The condition is chronically debilitating with a high recurrence and metastasis rate, and life-threatening with overall 5-year survival rate of approximately 60%.

The condition was estimated to be affecting approximately 2.3 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 sindbis virus envelope pseudotyped lentiviral vector encoding New York oesophageal squamous cell carcinoma-1 protein may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing favourable activity with the proposed product in patients previously treated with other antineoplastic agents. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by soft tissue sarcoma.

A positive opinion for sindbis virus envelope pseudotyped lentiviral vector encoding New York esophageal squamous cell carcinoma-1 protein, for treatment of soft tissue sarcoma, was adopted by consensus.

2.1.3. Fosbretabulin tromethamine - EMA/OD/211/15

Diamond BioPharm Limited; Treatment of gastro-entero-pancreatic neuroendocrine tumours

COMP coordinator: Katerina Kubáčková

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

It should be noted that in order to justify the significant benefit of the proposed product some data (preclinical and/or clinical) are needed showing that the product has the potential to result in a clinically relevant advantage and/or a major contribution to patient care in the treatment of the condition.

The sponsor is therefore invited to provide further information on the available studies, in particular in relation to previous treatments, and to the use of the proposed product in combination with currently authorized products.

In relation to the available clinical results the sponsor is also invited to further discuss the clinical relevance of the observed response rates in relation to the existing treatments.

In the written response, the sponsor clarified the protocol of the ongoing clinical study and provided further details of the preliminary results. The study included patients with recurrent or metastatic pancreatic or gastrointestinal neuroendocrine tumours who failed prior therapy, but remain on chronic somatostatin analogue therapy. The endpoints studied included the change in selected biomarker levels from baseline to each study visit, and quality of life.

Overall the data presented by the sponsor supported improvement of relevant biomarkers of the disease including 5-hydroxyindoleacetic acid, serotonin, and chromogranin A. Due to the slow course of most GEP-NET, the use of biomarkers is informative of preliminary efficacy, although the sponsor did not discuss the relevance of the chosen biomarkers nor discussed the effects of the products on biomarkers other than the three ones above mentioned.

The Committee agreed that the condition, treatment of gastro-entero-pancreatic neuroendocrine tumours, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing fosbretabulin tromethamine was considered justified based on anti-tumour activity in a small number of patients treated with the proposed product.

The condition is chronically debilitating and life-threatening, due to the occurrence in a number of cases of debilitating symptoms caused by inappropriate secretion of physiologically active amines, peptides and proteins, and with bad prognosis in the poorly differentiated forms.

The condition was estimated to be affecting approximately 3.5 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 fosbretabulin tromethamine will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate favourable responses in patients previously treated with some of the currently satisfactory methods for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for fosbretabulin tromethamine, for treatment of gastro-entero-pancreatic neuroendocrine tumours, was adopted by consensus.

2.1.4. Ubenimex - EMA/OD/179/15

Eiger Biopharmaceuticals Europe Limited; Treatment of pulmonary arterial hypertension

COMP coordinator: Josep Torrent-Farnell

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 invited to recalculate the prevalence of the proposed condition and in light of the uncertainties regarding the assumptions used, to provide a sensitivity analysis of all assumptions for the calculation of the prevalence estimate.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential add-on effect in the condition.

Instead, the sponsor is expected to provide data with the product, in either preclinical or clinical studies, to support either a clinically relevant advantage or a major contribution to patient care.

The sponsor should detail the results of any preclinical or preliminary clinical data they have to support the significant benefit assumption in the context of the current therapeutic management of patients. In the absence of such data the significant benefit cannot be considered justified.

In the written response, and during an oral explanation before the Committee on 17 February 2016, the sponsor provided an updated prevalence calculation and further elaborated on the issue of significant benefit.

With regards to the issue of significant benefit, new unpublished data were included in an *in vivo* model of the condition, where the outcomes studied included survival, haemodynamics, histology and LTB4 as an inflammatory marker.

The Committee agreed that the condition, treatment of 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 ubenimex was considered justified based on data in preclinical models of the condition showing increased survival and right ventricle function.

The condition is chronically debilitating and life threatening due to progressive dyspnoea and right hearth failure, leading to death in an average period of 2.8 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ubenimex may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate improved survival and right ventricle function compared to sildenafil in a model of the condition. The Committee considered that this constitutes a clinically relevant advantage.

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

2.1.5. EMA/OD/198/15

Treatment of acute myeloid leukaemia

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 27 January 2016, prior to responding to the list of issues.

2.1.6. Acalabrutinib - EMA/OD/196/15

Acerta Pharma, BV; Treatment of chronic lymphocytic leukaemia / small lymphocytic lymphoma

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 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 their Phase I/II study to justify the assumption of

significant benefit over authorised medicinal products such as ibrutinib and idelalisib for the proposed orphan indication. The effect on Richter's transformation should be clarified.

The sponsor should detail the results of any additional clinical data they have to support the significant benefit assumption in the context of the current therapeutic management of patients.

In the written response, the sponsor further elaborated on the result from the ongoing clinical study in particular with regards to the populations studied and the safety aspects. It was stressed that the clinical studies also included subjects who are intolerant to ibrutinib therapy due to adverse effects but were tolerating acalabrutinib therapy.

The Committee agreed that the condition, treatment of chronic lymphocytic leukaemia / small lymphocytic lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing acalabrutinib was considered justified based on preliminary clinical data showing improved survival.

The condition is life-threatening and chronically debilitating due to development cytopaenias (anaemia, neutropaenia, thrombocytopaenia), lymphadenopathy, splenomegaly, hepatomegaly and impaired production of normal immunoglobulin leading to increased susceptibility to infections.

The condition was estimated to be affecting approximately 4.5 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 acalabrutinib may be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate an improved survival. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for acalabrutinib, for treatment of chronic lymphocytic leukaemia / small lymphocytic lymphoma, was adopted by consensus.

2.1.7. EMA/OD/214/15

Treatment of gastro-entero-pancreatic neuroendocrine tumours

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

In the application, the sponsor has provided data demonstrating that the administration of the product decreases the renal absorption and retention of radiolabelled somatostatin analogues. Nevertheless the relationship between these findings and the pathophysiology of the disease has not been adequately justified.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of gastro-entero-pancreatic neuroendocrine tumours, the sponsor should further elaborate on:

- the results obtained with use of the proposed product in the treatment of gastro-entero-pancreatic neuroendocrine tumours;
- the relevance of the clinical data relating to kidney toxicity for the treatment of gastro-entero-pancreatic neuroendocrine tumours, and the interpretation of the results obtained in the studies;
- the justification of the use of the product only in combination with the product developed by the sponsor and not other existing, authorized somatostatin analogues (other PRRT or scintigraphy agents).

- Significant benefit

The arguments on significant benefit are based on the improved safety of the product in the prevention of renal toxicity following the PRRT treatment of the condition.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from clinical studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication, i.e. gastro-entero-pancreatic neuroendocrine tumours.

The sponsor should detail the results of any clinical data they have to support the significant benefit assumption in the context of the current therapeutic management 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 17 February 2016, the sponsor further elaborated on the two issues raised. In particular, it was argued that the product has the potential to improve efficacy used as an add-on during somatostatin analogue treatment, on the grounds of its mechanism of action. The COMP asked for any data supporting such add-on effect, but studies to this end were not available. The COMP considered that in the absence of data in the proposed condition, the criteria for designation could not be considered acceptable.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 February 2016, prior to final opinion.

2.1.8. EMA/OD/209/15

Treatment of graft rejection following solid organ 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

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of graft rejection following solid organ transplantation, the sponsor should further elaborate on

- the clinical relevance of the outcome regarding the transplant glomerulopathy for patients affected by the condition;
- if the treatment is considered as “treatment of antibody-mediated rejection”, or rather “prevention of transplant glomerulopathy”;

- how many patients are affected by transplant glomerulopathy and how these patients are currently managed.

- Number of people affected

The sponsor should re-calculate the prevalence estimate to include data on all types of solid organ transplants, to exclude any non-European data, and to take into account the disease duration of all types of rejection including the chronic rejection.

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 arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition.

The sponsor is invited to provide a discussion on significant benefit taking into consideration the use of corticosteroids in antibody mediated rejection.

Furthermore, the sponsor is invited to provide a discussion on the practical considerations regarding the clear separation of rejections based on antibody mediated or cellular rejection. This discussion aims to establish the need to consider significant benefit versus other authorised products used to treat patients with solid organ rejection.

In the written response, and during an oral explanation before the Committee on 17 February 2016, the sponsor provided an updated prevalence estimate and further elaborated on the issues of medical plausibility and significant benefit. In particular, the sponsor did not provide any new data but emphasised the importance of prevention of transplant glomerulopathy and argued that the primary endpoints presented might not have been met because of the early time-point used.

The COMP discussed that as per the Banff criteria transplant glomerulopathy is considered a feature of antibody mediated rejection but not the sole criterion for diagnosis. It was also considered that various aetiologies are reported for transplant glomerulopathy without the presence of alloantibodies. Previous SAWP/CHMP scientific procedures with regards to glomerulopathy as an endpoint were also discussed. In the absence of relevant data in the condition as proposed for designation the medical plausibility may not be considered met.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 February 2016, prior to final opinion.

2.1.9. EMA/OD/176/15

Treatment of acute lymphoblastic leukemia

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 acute lymphoblastic leukaemia, the sponsor should further elaborate on

a) the complication of bleeding as a characteristic symptom of ALL and

b) the clinical studies presented in the application with regards to

- the acute lymphoblastic leukaemia cases studied
- the design, population, endpoints, assessments, and results obtained in these ALL patients.

- 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 epidemiological index to be used based on the survival of the target population, and provide an updated estimate for the time that the application is made.

- Significant benefit

The applicant is invited to a) describe the standard of care for the bleeding in ALL patient based on consensus or guidelines for the target patient population, b) specify the authorised products and c) position the proposed product in this setting based on any available data, to justify either a clinically relevant advantage or a major contribution to patient care.

In the written response, and during an oral explanation before the Committee on 17 February 2016, the sponsor elaborated on the three issues in writing and during an oral explanation via teleconference.

The sponsor was not in a position to delineate ALL cases in the cited studies, and as such only provides "pooled" AL data. In the absence of data in the proposed condition the medical plausibility and benefit may not be considered justified. With regards to prevalence, the sponsor still proposed 5-year partial prevalence estimates and not point-prevalence calculations. Finally with regards to the significant benefit, notwithstanding the absence of data in the proposed condition, no authorised products for the treatment of bleeding were identified/listed.

The COMP considered that in the absence of data in the proposed condition as applied for designation, the criteria for designation could not be considered met.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 17 February 2016, prior to final opinion.

2.1.10. Florilglutamic acid (^{18}F) - EMA/OD/200/15

Piramal Imaging GmbH; Diagnosis of hepatocellular carcinoma

COMP coordinator: Bożenna Dembowska-Bagińska, Expert: Bjørg Bolstad

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

In order to establish the number of eligible patients per annum, the sponsor uses HCC incidence in conjunction with assumptions on how often patients need further diagnostic

interventions throughout the treatment algorithm. It seems that the sponsor has excluded part of the population eligible for diagnosis.

The sponsor is invited to substantiate the assumptions by literature references. Furthermore, the sponsor is requested to include into its prevalence estimate the number of patients that are candidates for a diagnostic procedure or are candidates for differential diagnosis of HCC. Furthermore, the sponsor was asked to discuss the number of surveillance patients and if they should be included into the prevalence considerations.

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 has not identified authorised products, thus the provided SB argumentation is currently considered to be insufficient. There are authorised products for MRI imaging that are currently authorised for the diagnosis of the proposed condition, eg Primovist UK, MultiHance UK.

The sponsor is invited to search the EU national formularies and provide a complete list of products used for MRI imaging that are authorised for diagnosing the proposed condition. Subsequently, the sponsor is invited to provide a data-driven discussion on assumptions of significant benefit of the proposed product in relation to the identified MRI contrast agents.

In the written response, the sponsor provided an amended prevalence calculation and further elaborated on the issue of significant benefit.

In particular with regards to the justification of significant benefit, the sponsor has submitted a list of MRI contrast agents that are currently authorised and used for the proposed condition. Significant benefit was argued on the basis of an improvement in sensitivity versus MRI imaging. To support this assumption, preliminary clinical data was presented supporting detection of smaller lesions via PET scan that were missed by a previous MRI.

The Committee agreed that the condition, hepatocellular carcinoma, is a distinct medical entity.

The intention to diagnose the condition with the medicinal product containing florilglutamic acid (^{18}F) was considered justified based on preclinical *in vivo* and preliminary clinical data demonstrating the detection of cancer tissue via positron emission tomography.

The condition is life-threatening with survival of approximately 6 to 20 months following diagnosis and chronically debilitating due to abdominal pain, weight loss, ascites, encephalopathy, jaundice and variceal bleeding.

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

In addition, although satisfactory methods of diagnosis of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing florilglutamic acid (^{18}F) may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate the product for positron emission tomography may improve

diagnosis of smaller cancer lesions that are missed by currently authorised products that are used for magnetic resonance imaging. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for florilglutamic acid (^{18}F), for diagnosis of hepatocellular carcinoma, was adopted by consensus.

2.1.11. Florilglutamic acid (^{18}F) - EMA/OD/201/15

Piramal Imaging GmbH; Diagnosis of glioma

COMP coordinator: Katerina Kubáčková; Expert: Bjørg Bolstad

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

In order to establish the number of eligible patients per annum, the sponsor uses glioma incidence in conjunction with assumptions on how often patients need further diagnostic interventions throughout the treatment algorithm. It seems that the sponsor has excluded part of the population at risk of the condition that are candidates for differential diagnosis.

The sponsor is invited to substantiate the assumptions by literature references. Furthermore, the sponsor is requested to include into its prevalence estimate the number of patients that are candidates for a diagnostic procedure or are candidates for differential diagnosis of glioma.

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 currently provided SB discussion focuses on other authorised PET tracers. There are authorised products for MRI imaging that are currently authorised for the diagnosis of the proposed condition, e.g. Primovist UK, MultiHance UK.

The sponsor is invited to search the EU national formularies and provide a complete list of products used for MRI imaging that are authorised for diagnosing the proposed condition. Subsequently, the sponsor is invited to provide a data-driven discussion on assumptions of significant benefit of the proposed product in relation to the identified MRI contrast agents.

In the written response, the sponsor provided a revised prevalence calculation and further elaborated on the issue of significant benefit. The sponsor had already included preclinical data that demonstrate that positron emission tomography imaging with the product achieved higher image sensitivity compared to other currently authorised positron tomography imaging products. The updated significant benefit argumentation was expanded to include all MRI contrast agents that are authorised and used in the diagnostic paradigm of the condition. Literature sources were discussed supporting the benefits of PET scanning versus MRI, in terms of differentiation of viable tumour tissue from treatment-induced non-neoplastic changes, and in terms of a more appropriate estimation of true tumour extension.

The Committee agreed that the condition, glioma, is a distinct medical entity.

The intention to diagnose the condition with the medicinal product containing florilglutamic acid (^{18}F) was considered justified based on preclinical *in vivo* and preliminary clinical data demonstrating the detection of cancer tissue via positron emission tomography.

The condition is life-threatening with poor 5-year survival of less than 5% for glioblastoma multiforme patients and 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 and cognitive impairment.

The population of patients eligible for diagnosis of the condition was estimated to be approximately 1.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of diagnosis of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing florilglutamic acid (^{18}F) may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate that positron emission tomography imaging with the product achieved higher image sensitivity compared to other currently authorised positron tomography imaging products. Furthermore, the sponsor has provided evidence from the published literature that substantiate that the product may improve the detection of viable tumour and true tumour extension compared to currently authorised products that are used for magnetic resonance imaging. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for florilglutamic acid (^{18}F), for diagnosis of glioma, was adopted by consensus.

2.1.12. EMA/OD/181/15

Treatment of monogenic diabetes

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 COMP discussed the proposed condition and was of the opinion that neonatal diabetes mellitus (NDM) and maturity onset diabetes of the young (MODY) should be considered as separate medical entities to the purpose of orphan designation.

The sponsor is therefore invited to discuss the two conditions separately in relation to medical plausibility. In this respect the sponsor is invited to further justify the medical plausibility of NDM, as so far all data presented refer to MODY.

- Prevalence

If the sponsor intends to pursue the designation of both NDM and MODY, separate prevalence calculations should be provided.

- Significant benefit

In order to justify the significant benefit, the sponsor is invited to provide further evidence that the treatment of MODY is not covered by any current authorizations in any EU member states.

Furthermore, it would be useful to obtain more information on the planned development

In the written response, and during an oral explanation before the Committee on 18 February 2016, the sponsor amended the proposed indication to “treatment of maturity onset diabetes of the young” and presented prevalence calculations for this entity alone, estimating the prevalence in the EU at 0.95 in 10,000.

The COMP further reflected on the issue of significant benefit in this new indication, and in particular with regards to the existence of any authorised products for the proposed condition. In particular, it was discussed that there are authorised indications for products containing glyclazide, with some authorisations referring to “type 2 diabetes mellitus”, others to “maturity onset diabetes mellitus”, and others to “non-insulin dependent diabetes mellitus”. Some older licenses also exist where the therapeutic indication is “diabetes” or “diabetes mellitus”. It was considered that a general indication in “non-insulin dependent diabetes mellitus” or broader would not exclude cases of MODY that are not at the stage of insulin dependence.

As such, products containing gliclazide were considered as existing satisfactory methods of treatment for the purpose of orphan designation. In the absence of data to justify significant benefit versus those products for the above indication, the criterion of significant benefit could not be considered met.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 February 2016, prior to final opinion.

2.1.13. Allogeneic Epstein-Barr virus specific cytotoxic T lymphocytes - EMA/OD/210/15

Wainwright Associates Ltd; Treatment of post-transplant lymphoproliferative disorder

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

The sponsor is invited to rename the condition as “Post-transplant lymphoproliferative disorder” or to justify the proposed condition as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor’s attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

- 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 update the prevalence calculation taking into consideration the amended medical condition. The sponsor should describe and justify the methodology used for the prevalence calculation. Additionally, the sponsor should indicate on which population the prevalence calculation is based. Given the substantial uncertainty about assumptions regarding the prevalence, the sponsor should perform a sensitivity analysis of the reported calculations.

In the written response, the sponsor agreed to rename the condition as 'post-transplant lymphoproliferative disorder' (PTLD) and provided an updated calculation of prevalence.

Following review of the application by the Committee, it was agreed to rename the indication to "post-transplant lymphoproliferative disorder".

The Committee agreed that the condition, treatment of post-transplant lymphoproliferative disorder, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing allogeneic Epstein-Barr virus specific cytotoxic T lymphocytes was considered justified based on clinical data demonstrating improved overall survival of persons affected by the condition.

The condition is life-threatening due to fulminant and lethal course of the disease and chronically debilitating due to transplant specific organ dysfunction, malaise, lethargy, weight loss and fever.

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.

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 allogeneic Epstein-Barr virus specific cytotoxic T lymphocytes, for treatment of post-transplant lymphoproliferative disorder, was adopted by consensus.

2.1.14. Fenretinide - EMA/OD/203/15

Clinipace GmbH; Treatment of cutaneous T-cell lymphoma

COMP coordinator: Bożenna Dembowska-Bagińska

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 estimate of the applicant is based on 5-year partial prevalence for non-Hodgkin lymphoma (NHL) and the assumption that cutaneous T-cell lymphoma (CTCL) represents 4% of all NHL.

The sponsor is invited to recalculate the prevalence, by providing a point prevalence estimate for the condition as proposed for designation, and given the uncertainty about the estimation's methodology, provide a sensitivity analysis of all assumptions used.

In the written response, the sponsor provided a new updated prevalence calculation including a sensitivity analysis by varying the assumptions used (ratio of CTCL/NHL up to 15%, all T-cell lymphomas diagnosed as CTCL) and taking into consideration the duration of the condition (median survival up to 24 years).

The Committee agreed that the condition, treatment of cutaneous T-cell lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing fenretinide was considered justified based on preliminary clinical data in patients affected by the condition who responded to treatment with reduction of tumour size.

The condition is chronically debilitating due to ulceration and erythroderma, and life threatening in the most aggressive forms due to the risk of further malignant transformations.

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 fenretinide may be of significant benefit to those affected by the condition. The sponsor has provided clinical data that show responses in relapsed/refractory patients affected by the proposed condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for fenretinide, for treatment of cutaneous T-cell lymphoma, was adopted by consensus.

2.1.15. Synthetic double-stranded siRNA oligonucleotide directed against hydroxyacid oxidase 1 (HAO1) mRNA that is covalently linked to a ligand containing three N-acetylgalactosamine (GalNAc) residues - EMA/OD/195/15

Alnylam UK Limited; Treatment of primary hyperoxaluria

COMP coordinator: Armando Magrelli and Lesley Greene

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 COMP considers primary hyperoxaluria type 1 to be a subset of primary hyperoxaluria (PH) and concluded that the criteria for sub-setting are not fulfilled in this application. The sponsor is requested to broaden the name of the condition to “primary hyperoxaluria”.

- Number of people affected

The COMP invites the sponsor to re-calculate the prevalence estimate of the broader condition “primary hyperoxaluria” based on relevant epidemiological studies and registers for the proposed orphan condition.

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”.

In the written response, the sponsor has accepted the COMP request to broaden the condition of this application to “primary hyperoxaluria” in line with the orphan legislation and provided an appropriately amended prevalence calculation. For the final calculation the sponsor used the estimate established for the type 1, assuming that this represents approximately 80% of the PH population, and adding further 20% to account for type 2 and type 3.

Following review of the application by the Committee, it was agreed to rename the condition to “primary hyperoxaluria” and to rename the active substance to “synthetic double-stranded siRNA oligonucleotide directed against hydroxyacid oxidase 1 mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues”.

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

The intention to treat the condition with the medicinal product containing synthetic double-stranded siRNA oligonucleotide directed against hydroxyacid oxidase 1 mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues was considered justified based on results from valid preclinical *in vivo* disease models showing that the product can reduce deregulated urinary oxalate levels.

The condition is life-threatening and chronically debilitating due to recurrent nephrolithiasis and progressive nephrocalcinosis leading to renal damage. The majority of the patients develop end stage renal disease during the 3rd to 5th decade of life.

The condition was estimated to be affecting approximately 0.05 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 synthetic double-stranded siRNA oligonucleotide directed against hydroxyacid oxidase 1 mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues, for treatment of primary hyperoxaluria, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. Acalabrutinib - EMA/OD/237/15

Acerta Pharma, BV; Treatment of lymphoplasmacytic lymphoma

COMP coordinator: Frauke Naumann-Winter and Jens Ersbøll

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

The intention to treat the condition with the medicinal product containing acalabrutinib was considered justified based on preliminary clinical data showing anti-tumour activity with the proposed product.

The condition is life-threatening and chronically debilitating due to bone marrow dysfunction, lymphadenopathy, splenomegaly and paraproteinaemia resulting in hyperviscosity, autoimmunity, cryoglobulinaemia, coagulopathies and neuropathies.

The condition was estimated to be affecting less than 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 acalabrutinib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing favourable responses in patients relapsing from previous treatments. In addition the preliminary clinical data point towards lower rates of adverse events compared to ibrutinib, currently authorized for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for acalabrutinib, for treatment of lymphoplasmacytic lymphoma, was adopted by consensus.

2.2.2. Acalabrutinib - EMA/OD/231/15

Acerta Pharma, BV; Treatment of mantle cell lymphoma

COMP coordinator: Jens Ersbøll

The Committee agreed that the condition, treatment of mantle 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 acalabrutinib was considered justified based on preliminary clinical data showing anti-tumour activity.

The condition is life-threatening and chronically debilitating due to lymphadenopathy, night sweats, fever, and weight loss. Median survival is 3 to 5 years.

The condition was estimated to be affecting less than 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing acalabrutinib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing activity in patients previously treated with some of the authorized products for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for acalabrutinib, for treatment of mantle cell lymphoma, was adopted by consensus.

2.2.3. Adeno-associated viral vector serotype 5 containing a B-domain deleted variant of human coagulation factor VIII gene - EMA/OD/230/15

BioMarin Europe Ltd.; Treatment of haemophilia A

COMP coordinator: Frauke Naumann-Winter and Armando Magrelli

The Committee agreed that the condition, treatment of haemophilia A, 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 5 containing a B-domain deleted variant of human coagulation factor VIII gene was considered justified based on restoration of bleeding time and reduced bleeding in a preclinical model of the proposed condition.

The condition is chronically debilitating due to recurrent bleedings in joints, gastrointestinal tract or in surgery, which may be also be life-threatening.

The condition was estimated to be affecting approximately 0.7 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 adeno-associated viral vector serotype 5

containing a B-domain deleted variant of human coagulation factor VIII gene will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data in a model of the condition that demonstrate long-term restoration of factor VIII activity after a single administration, which may result in reduction of the need for on-demand and prophylactic treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype 5 containing a B-domain deleted variant of human coagulation factor VIII gene, for treatment of haemophilia A, was adopted by consensus.

2.2.4. Adeno-associated virus serotype 8 vector encoding human ornithine transcarbamylase - EMA/OD/227/15

Pharma Gateway AB; Treatment of ornithine transcarbamylase deficiency

COMP coordinator: Annie Lorence

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

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 8 encoding human ornithine transcarbamylase was considered justified based on pre-clinical data showing a reduction of urinary orotic aciduria a marker of the condition.

The condition is life-threatening and chronically debilitating due to the metabolic decompensation that can lead to irreversible neurological damage.

The condition was estimated to be affecting approximately 0.14 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 adeno-associated viral vector serotype 8 encoding human ornithine transcarbamylase will be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical data that demonstrate a reduction in orotic aciduria which may reduce the need for ammonia scavangers. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated virus serotype 8 vector encoding human ornithine transcarbamylase, for treatment of ornithine transcarbamylase deficiency, was adopted by consensus.

2.2.5. EMA/OD/212/15

Treatment of acute respiratory distress syndrome

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

2.2.6. EMA/OD/234/15

Prevention of Cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk

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

2.2.7. Diaspirin cross-linked haemoglobin - EMA/OD/192/15

New B Innovation (UK) Limited; Treatment of oesophageal cancer

COMP coordinator: Brigitte Bloechl-Daum

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

The intention to treat the condition with the medicinal product containing diaspirin cross-linked haemoglobin was considered justified based on pre-clinical *in vivo* data showing an additive anti-tumour effect of the product when used on top of Cisplatin or 5-Fluorouracil compared to either agent in monotherapy.

The condition is life-threatening due to increased mortality and chronically debilitating due to dysphagia, regurgitation, odynophagia, upper gastrointestinal bleeding, acid indigestion and pain. The 5-year relative survival for localized, regional and distant oesophageal cancer is 40.4%, 21.6% and 4.2% respectively.

The condition was estimated to be affecting approximately 0.75 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 diaspirin cross-linked haemoglobin will be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical *in vivo* data that demonstrate that the product has an additive effect to Cisplatin or 5-Fluorouracil treatment measured as tumour growth reduction, tumour invasiveness reduction and tumour microvessel density reduction. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for diaspirin cross-linked haemoglobin, for treatment of oesophageal cancer, was adopted by consensus.

2.2.8. EMA/OD/204/15

Treatment of pancreatic cancer

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

2.2.9. Exenatide - EMA/OD/187/15

Alan Boyd Consultants Ltd; Treatment of idiopathic intracranial hypertension

COMP coordinator: Giuseppe Capovilla

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

The intention to treat the condition with the medicinal product containing exenatide was considered justified based on pre-clinical *in vivo* data showing a reduction in intracranial hypertension when the sponsor's product was used.

The condition is chronically debilitating due to visual loss and refractory headache.

The condition was estimated to be affecting approximately 1.4 in 10,000 persons in the European Union, at the time the application was made.

A positive opinion for exenatide, for treatment of idiopathic intracranial hypertension, was adopted by consensus.

2.2.10. EMA/OD/215/15

Treatment of soft tissue sarcoma

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

2.2.11. EMA/OD/217/15

Prevention of short bowel syndrome

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

2.2.12. EMA/OD/236/15

Treatment of Smith-Magenis syndrome

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

2.2.13. N-acetyl-D-mannosamine monohydrate - EMA/OD/228/15

Escala Therapeutics Ltd; Treatment of GNE myopathy

COMP coordinator: Violeta Stoyanova

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

The intention to treat the condition with the medicinal product containing n-acetyl-D-mannosamine monohydrate was considered justified based on preclinical *in vivo* data showing improvement of biomarkers and muscle function with the proposed product in models of the condition.

The condition is chronically debilitating due to progressive weakness of proximal leg muscles and of the hands and shoulder muscles. The condition usually progresses to complete functional impairment of the involved muscles over a 10–20 year period, leading to a wheelchair-bound state.

The condition was estimated to be affecting less than 0.1 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 n-acetyl-D-mannosamine monohydrate, for treatment of GNE myopathy, was adopted by consensus.

2.2.14. EMA/OD/235/15

Treatment of osteogenesis imperfecta

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

2.2.15. EMA/OD/233/15

Treatment of acute myeloid leukaemia

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

2.3. 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 22 applications submitted.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 20 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1.

Diagnosis of gastro-entero-pancreatic neuroendocrine tumours

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 Niemann-Pick disease, type C

The finalised letter was circulated for information.

3.2.2.

Treatment of cytomegalovirus disease in patients with impaired cell mediated immunity

The finalised letter was circulated for information.

3.2.3.

Treatment of advanced ovarian cancer

3.3. The Committee was briefed on the significant benefit issues. The COMP adopted updated proposed answers on the significant benefit issues.New requests

Treatment of pyruvate kinase deficiency

The new request was noted with no significant benefit question, therefore the procedure will not be discussed at next COMP meeting.

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. Wakix - 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine, hydrochloride - EMEA/OD/087/06, EU/3/07/459, EMEA/H/C/002616

Bioprojet; Treatment of narcolepsy

COMP coordinators: Michel Hoffmann and Ingeborg Barisic

In its written grounds, and during an oral explanation before the Committee on 16 February 2016, the sponsor discussed the epidemiology of the proposed condition, and further elaborated on the issue of significant benefit. The sponsor highlighted that the performed studies submitted had followed the recommendations from Protocol Assistance and produced data comparing the effect of pitolisant vs modafinil and the use of pitolisant in combination with sodium oxybate. The sponsor also discussed safety and tolerability issues.

The COMP considered that the results from study Harmony 1 supported an improvement in cataplexy versus modafinil, which was considered clinically relevant in the treatment of these patients. As regards the grounds to establish a significant benefit versus sodium oxybate, the COMP considered that the latter is a CNS depressant, prescribed with caution, and requires titration over several weeks. It was also considered that sodium oxybate is administered twice every night due to the short half-life of the drug (Busardo et al, Eur Rev Med Pharmacol Sci. 2015 Dec;19(23):4654-63). Compassionate use data produced by the sponsor confirmed the acceptability of switching from sodium oxybate to pitolisant to treat the cataplexy associated with the condition.

The COMP concluded that:

The proposed therapeutic indication “treatment of narcolepsy with or without cataplexy” falls entirely within the scope of the orphan indication of the designated orphan medicinal product “treatment of narcolepsy”.

The sponsor has established the prevalence of narcolepsy (hereinafter referred to as “the condition”) remains below 5 in 10,000. The applicant has taken into consideration all the available and most recent epidemiological studies and did provide a sensitivity analysis as requested by the Committee.

The condition is chronically debilitating in particular due to excessive daytime sleepiness and cataplexy.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Wakix is of significant benefit to those affected by the orphan condition as defined in the granted therapeutic indication still holds. The sponsor has established that their product offers a clinically relevant advantage to modafinil as it is not associated with the same tolerability issues and has an effect in cataplexy. A major contribution to patient care was seen with Wakix as it is a once-a-day oral administration compared to sodium oxybate which has a complex dosing schedule involving dose titration, medical monitoring and sleep disruption.

An opinion not recommending the removal of Wakix, 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine, hydrochloride, pitolisant hydrochloride, (EU/3/07/459) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

4.1.2. Empliciti - elotuzumab - EMA/OD/061/12, EU/3/12/1037, EMEA/H/C/003967

Bristol-Myers Squibb; Treatment of multiple myeloma

COMP coordinator: Frauke Naumann-Winter and Karri Penttila; Expert: Mr Jacob Hygen 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 basing the revision of estimate on the basis of 2012 data, and partial prevalence indices. Instead the sponsor is requested to provide full point prevalence at the time of the review, taking into consideration the recent advancements in the treatment of multiple myeloma that may have impacted on the duration of the condition.

- Significant benefit

The sponsor is requested to further elaborate on the issue of significant benefit, in particular by providing data to justify a clinically relevant advantage or a major contribution to patient care versus both the authorised proteasome inhibitors for the proposed condition, bortezomib and carfilzomib, as well as versus doxorubicin.

In its written response, and during an oral explanation before the Committee on 16 February 2016, the sponsor further elaborated on the issues raised as follows:

As regards the prevalence recalculation, the sponsor acknowledged that the point prevalence is more appropriate given the increase in survival and revised the prevalence upwards taking into consideration both a) the increased duration of the condition and b) the ratio between cumulative/ 5 year-partial prevalence, as sourced in NORDCAN (1.56 fold) and AIRTUM (1.65 fold). This leads to an estimate of (2.77 up to) 3.96 per 10,000. The COMP considered that a less than 4 per 10,000 figure may be considered for the purpose of this procedure, which is also in line with recent COMP procedures. The prevalence issue was thus considered resolved.

With regards to significant benefit, the sponsor provided further explanations versus bortezomib, carfilzomib and doxorubicin.

In order to demonstrate significant benefit of elotozumab over bortezomib, the sponsor provided indirect comparisons of the results of the registration studies for elotuzumab and bortezomib in multiple myeloma indications. The COMP considered that PFS, ORR and OS from these studies compare favourably for the applicant's product in similar populations.

The situation is different versus carfilzomib, where again the sponsor performed an indirect comparison of the ASPIRE study for carfilzomib, versus study CA204004 for elotuzumab. Three points were made:

- The sponsor argued that the product would be of improved efficacy because in particular subjects, elotuzumab appears to provide a greater risk reduction for progressive disease; in particular this was argued for senior patients (over 65 years), subjects with prior lenalidomide treatment, refractory to prior bortezomib, and those with high risk disease based upon ISS stage and cytogenetic results.

The COMP noted the limitations stemming from the indirect comparisons attempted and importantly also that the overall results of the study appear to favour carfilzomib. With regards to hazard ratios, results are comparable with almost equal figures (0.68 vs. 0.69). It was hence considered that this indirect comparison does not support improved efficacy of elotuzmumab in the overall studied population.

- As a second point the sponsor discussed a safety argument versus carlfizomib, again on the basis of indirect comparisons of the registration studies. It was argued that, elotuzumab in combination with lenalidomide and dexamethasone provides lower rates of ≥ grade 3 adverse events, in particular cardiac failure, hypertension, renal failure and infusion reactions, compared to carlfizomib, lenalidomide and dexamethasone. The COMP considered that the argument of improved safety based on this indirect comparison cannot be accepted because the examination of the control arms supports that the different percentage of AEs may be attributed to the different populations and settings studied and because such an argument should also be weighed in the context of a worse efficacy regarding the survival endpoints in the registration studies.

- A final third point raised by the sponsor is a major contribution to patient care claim, on the grounds that elotuzumab's administration poses a lighter burden for patients with most cycles requiring 2 treatments per month compared to the 6 treatments per month with carfilzomib. The COMP considered that such an improved convenience by itself cannot be considered without data to substantiate the consequences over and above preferences or convenience, such as quality of life, patient reported outcomes, or improved compliance to treatment.

Finally with regards to doxorubicin, an indirect comparison performed provided a 35% improvement in response rate and a 10.5 month extension in the duration of response, almost a doubling of progression free survival and greater overall survival. The COMP accepted this significant benefit over doxorubicin.

The COMP concluded that:

The proposed therapeutic indication "Empliciti is indicated in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy" falls entirely within the scope of the orphan indication of the designated orphan medicinal product "treatment of multiple myeloma".

The prevalence of multiple myeloma (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 chronically debilitating in particular due to the development of hypercalcemia, renal insufficiency, anaemia and bone lesions, and life-threatening with an overall survival of up to approximately 6 years.

Satisfactory methods of treatment have been authorised in the European Union; the assumption that Empliciti may be of potential significant benefit to those affected by the orphan condition does not hold.

In particular, significant benefit versus carfilzomib has not been justified; an indirect comparison of the results from studies CA204004 and ASPIRE pertaining to subgroup analysis, did not justify a clinically relevant advantage, such as improved efficacy or safety in the approved identical indication.

In addition, the argument of reduced frequency of IV dosing proposed by the sponsor is not supported by any data substantiating a claim of major contribution to patient care.

In the absence of data to justify either a clinically relevant advantage or a major contribution to patient care, significant benefit cannot be considered justified.

4.1.3. An opinion recommending the removal of Emplicti, elotuzumab (EU/3/12/1037) from the EC Register of Orphan Medicinal Products was adopted by consensus.Revlimid – Lenalidomide - Type II variation - EMA/OD/078/11, EU/3/11/924, EMEA/H/C/000717/II/0079

Celgene Europe Limited; Treatment of mantle cell lymphoma

COMP coordinators: Katerina Kubáčková and Frauke Naumann-WinterAs 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:

- Significant Benefit

The sponsor should further elaborate the clinically relevant advantage offered by lenalidomide monotherapy with respect to durable responses in mantle cell lymphoma patients who are relapsed or refractory to ibrutinib as presented in MCL-004. The sponsor is invited to present any additional data from additional patients or longer follow up of those reported.

In its written response, and during an oral explanation before the Committee on 16 February 2016, the sponsor further elaborated on the issue of significant benefit. The sponsor argued that although the clinical treatment landscape has evolved, the post-ibrutinib median survival is limited to 2.9 months. The sponsor discussed the results of the MCL-004 study and argued that lenalidomide has a different mode of action to ibrutinib and exploratory analyses revealed that it induces responses in patients with genetic mutations known to confer primary resistance to ibrutinib.

The COMP further discussed the results of study MCL-004 in patients who were relapsed or refractory to ibrutinib. The committee was concerned that the effects seen in combination therapy arms could not be attributed to the proposed active alone. Importantly, in the monotherapy arm there was only one response of only 3 weeks which cannot be regarded as durable. The COMP concluded that:

The proposed therapeutic indication “treatment of adult patients with relapsed or refractory mantle cell lymphoma” falls entirely within the scope of the orphan indication of the designated orphan medicinal product “treatment of mantle cell lymphoma”.

The prevalence of mantle cell lymphoma (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be 0.3 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 3 to 5 years and chronically debilitating due to lymphadenopathy, night sweats, fever, and weight loss.

Satisfactory methods of treatment of the condition have been authorised in the European Union and the assumption that Revlimid may be of significant benefit compared to other approved products authorised for relapsed and refractory mantle cell lymphoma does not hold. The magnitude of the response rate and the duration of response did not support the criteria for significant benefit when compared to ibrutinib which has an identical therapeutic indication. Furthermore, the activity of lenalidomide post ibrutinib was limited, especially in the monotherapy setting. Responses after combination therapy could not be attributed to lenalidomide. Therefore, the COMP did not consider that the significant benefit had been justified.

An opinion recommending the removal of Revlimid, lenalidomide (EU/3/11/924) from the EC Register of Orphan Medicinal Products was adopted by consensus.

4.1.4. Uptravi - selexipag - EMEA/OD/043/05, EU/3/05/316, EMEA/H/C/003774

Actelion Registration Ltd.; Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension

COMP coordinators: Josep Torrent-Farnell, Zuzana Batová and 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:

In order to justify the significant benefit the sponsor is invited to discuss the advantages of selexipag vis a vis the authorized prostacyclin analogues. Such discussion should be as much as possible supported by data showing the clinically relevant advantage or/and major contribution to patient care of the proposed product.

In the written response, and during an oral explanation before the Committee on 16 February 2016, the sponsor further elaborated on the issues of significant benefit. The model of action and formulation were discussed as potential significant benefit. It was argued that the proposed active is a highly selective IP-receptor agonist that allows targeting the prostacyclin pathway without off-target effects and without receptor desensitisation or tachyphylaxis, which is supported by non-clinical studies. It was also argued that the product has only modest effects on platelet aggregation and was not associated with an increased incidence of bleeding events compared with placebo.

The sponsor acknowledged that a detailed comparative discussion versus prostacyclin analogues was difficult, given that approved medicines acting on the prostacyclin pathway have been documented mainly in short-term monotherapy trials focusing on intermediate endpoints, while the selexipag was studied as an add-on treatment and demonstrated benefit on the risk of events of PAH disease progression.

The COMP considered that in the absence of data to justify either a clinically relevant advantage or a major contribution to patient care, the signifincat benefit could not be considered justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the orphan designation from the register of orphan medicinal products, on 17 February 2016, prior to final opinion.

4.1.5. COAGADEX - factor X - EMEA/OD/044/07, EU/3/07/471, EMEA/H/C/003855

BIO PRODUCTS LABORATORY; Treatment of hereditary factor X deficiency

COMP coordinator: Karri Penttilä and Josep Torrent-Farnell

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:

- Significant Benefit

The sponsor should further elaborate on the relevance of their claim that their product has a clinically relevant advantage over currently approved products in Member States (such as Beriplex and Octaplex) for use in the treatment of the condition. As part of this the sponsor

should indicate in which countries mixed coagulation factors (such as Beriplex and Octaplex) are authorised in the European Union.

In its written response, and during an oral explanation before the Committee on 16 February 2016, the sponsor provided a list of authorised product in the EU for the proposed condition, and elaborated on the clinically relevant advantage in the context of the available Haemophilia treatment Guidelines, according to which a "product containing only FIX is more appropriate than prothrombin complex concentrates, which also contain other clotting factors such as factors II, VII, and X, some of which may become activated during manufacture". It was further noted that for the authorised products Beriplex and Octaplex (under 4.1, indication section of the SmPCs) it is clearly stated that they should be used "only when purified specific coagulation factor products are not available".

It was considered that administration of prothrombin complex concentrates (PCCs) containing FX is associated with the risk of thromboembolic complication due to the high concentrations of other coagulation factors, which is not always known or consistent. This could represent a meaningful risk, particularly in patients with severe clinical symptoms, who need frequent infusions or regular prophylaxis.

The COMP concluded that:

The proposed therapeutic indication "treatment and prophylaxis of bleeding in patients with hereditary factor X deficiency" falls entirely within the scope of the orphan indication of the designated orphan medicinal product "treatment of hereditary factor X deficiency".

The prevalence of hereditary factor X deficiency (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in 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 and life threatening due to risk of bleeding including recurrent haemorrhages that can result in chronic and major haemorrhages that carry a direct vital risk.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Coagadex may be of potential significant benefit to those affected by the orphan condition still holds. This was supported by the argument that the sponsor's product was considered safer as it does not contain coagulation factors which could become activated during manufacturing process leading to an increase in predisposition to thromboembolism.

An opinion not recommending the removal of human coagulation factor X, factor X, (EU/3/07/471) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

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

4.2.1. migalastat – EMEA/OD/105/05, EU/3/06/368, EMEA/H/C/004059

Amicus Therapeutics UK Ltd; Treatment of Fabry disease

The status of the procedure at CHMP was noted.

4.2.2. albutrepenonacog alfa – EMEA/OD/117/09, EU/3/09/723, EMEA/H/C/003955

CSL Behring GmbH; Treatment of haemophilia B

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

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

Takeda Pharma A/S; Treatment of multiple myeloma

The status of the procedure at CHMP was noted.

4.2.4. eftrenonacog alfa – EMEA/OD/012/07, EU/3/07/453, EMEA/H/C/004142

Biogen Idec Ltd; Treatment of haemophilia B

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

4.3. On-going procedures

4.3.1. List of on-going procedures

Action: For information

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

5.1.1.

6. Organisational, regulatory and methodological matters

6.1. Mandate and organisation of the COMP

6.1.1. Strategic Review & Learning meetings

None

6.1.2. Significant Benefit Working Group

The working group on Significant Benefit met on 17 February 2016.

6.1.3. Preclinical Models Working Group

The working group on Preclinical Models met on 18 February 2016.

6.1.4. Revised Standard Operating Procedures (SOPs)

3049 SOP – Orphan medicinal product designation EMA/358120/2005

3190 SOP – Review of orphan designation at the time of granting/varying a marketing authorisation EMA/71584/2007

The updated SOPs were circulated for information.

6.1.5. COMP Membership

The COMP welcomed Dinko Vitezic as new member representing Croatia.

6.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

6.3.1. SAWP/COMP joint membership

Call of interest for a SAWP/COMP member

The call of interest was circulated via email on 7th March 2016.

6.3.2. Patients' and Consumers' Working Party (PCWP) and Healthcare Professionals' Working Party (HCPWP) joint meetings

PCWP/HCPWP joint meeting – 17 September 2015

PCWP/HCPWP joint meeting - Session on communication and information on medicines – 08 March 2016

PCWP/HCPWP joint meeting – 09 March 2016

Report on EMA's workshop on risk minimisation measures -Towards optimising risk minimisation measures – 16 Sept 2015

Documents were circulated for information.

6.3.3. Patients' and Consumers' Working Party (PCWP)

PCWP meeting with all eligible organisations – 26 November 2015

The minutes were circulated for information.

6.3.4. Paediatric Committee (PDCO)

Proposed meeting time on 18 February 2016 at time 13:00, room 8A

The COMP was updated on the COMP/PDCO Working Group February meeting.

6.4. Cooperation within the EU regulatory network

6.4.1. European Commission

None

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.

6.8.3. Data Gathering Initiative

The COMP was informed of the second phase of the data gathering initiative and how COMP delegates and EMA Secretariat would be involved in the exercise. The Chair assured the Agency of the COMP's collaboration.

7. Any other business

None

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 16-18 February 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	
Brigitte Blöchl-Daum	Member	Austria	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	
Jens Ersbøll	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Annie Lorence	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Nikolaos Sypsas	Member	Greece	No restrictions applicable to this meeting	
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	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Violeta Stoyanova-Beninska	Member	Netherlands	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Zuzana Batova	Member	Slovak Republic	No interests declared	
Martin Možina	Member	Slovenia	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	
Mario Ricciardi	Member	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	
Eva Malíková	Observer	Slovakia	No interests declared	
Jacob Hygen	Expert - via telephone*	Independent scientific expert	No interests declared	
Giuseppe Plazzi	Expert - via telephone*	Independent scientific expert	Involvement limited to testify and give specialist advice on a specific issue by providing information and replying to any questions only.	4.1.1. Wakix
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.