22 October 2015
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Procedure Management and Committees Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 1-3 September 2015

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

01 September 2015, 09:00-19:30, room 2F

02 September 2015, 08:30-19:30, room 2F

03 September 2015, 08:30-13:15, room 2F

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Of note, the agenda/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 agenda/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

Pre-meeting list of participants and restrictions in relation to declarations of interests applicable to the items of the agenda for the COMP plenary session to be held 1-3 September 2015. See September 2015 COMP minutes (to be published post October 2015 COMP meeting).

1.2. Adoption of agenda

COMP agenda for 1-3 September 2015 was adopted with no amendments.

1.3. Adoption of the minutes

COMP minutes for 14-16 July 2015 were adopted with no amendments.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. Ovine specific immunoglobulin (Fab) fragments raised against Vipera berus venom - EMA/OD/062/15

MicroPharm Limited; Treatment of snakebite envenomation

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

It is not completely clear on which grounds the sponsor claims the significant benefit of the proposed product, since they compare it to Zagreb, however reporting that Zagreb is no longer available.

In order to justify the significant benefit of the proposed product the sponsor is invited:

- to further elaborate on the advantage of the proposed product in relation to vipera species other than *V. berus* in the frame of the direct comparison with Zagreb;

- to further discuss any available data comparing the proposed product with Viperfab and any other antisera authorized in the EU.

To this purpose the sponsor is also invited to further clarify the regulatory and availability status of the existing products for the treatment of vipera envenomation in the EU.

In the written response, and during an oral explanation before the Committee on 1 September 2015, the sponsor presented pre-clinical in vivo data showing that the product was effective against venoms of snakes in the EU and also showed improved effects to currently available products.

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

The intention to treat the condition with the medicinal product containing ovine-specific immunoglobulin (Fab) fragments raised against *Vipera berus* venom was considered justified based on preclinical data showing protection from lethal outcome with the proposed product.

The condition is life-threatening and chronically debilitating due to the possible development of severe local reactions that can lead to tissue necrosis, and of systemic reactions including lethargy, hypotension, tachypnea, severe tachycardia, internal bleeding, altered sensorium, kidney failure, and respiratory failure.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ovine-specific immunoglobulin (Fab) fragments raised against *Vipera berus* venom may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing higher effect of the proposed product as compared to the authorized ones. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for ovine-specific immunoglobulin (Fab) fragments raised against *Vipera berus* venom, for treatment of snakebite envenomation, was adopted by consensus.

2.1.2. - EMA/OD/083/15

Treatment of cervical cancer

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

- Number of people affected

The prevalence calculation proposed by the sponsor is based on the EUCAN database and involves incidence rates rather than prevalence. The sponsor should present data on prevalence, taking into consideration duration of the condition, the number of people affected by cervical cancer in the EU and the epidemiological index used.

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.

- Significant benefit

The argument to support clinically relevant advantage of the product is based on the indirect comparison of historical published data with comparator treatments versus data from the Phase 2 clinical trial with the product. The sponsor should further elaborate on the

comparability of these studies with regards to the populations studied, treatments received and results obtained.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from Phase 2 study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

It is well known that extrapolation from preclinical or early clinical studies cannot predict the safety of a product in its clinical setting, thus more relevant data is mandatory to justify safety arguments in most cases.

In the written response, and during an oral explanation before the Committee on 1 September 2015, the sponsor proposed that stage I ovarian cancer would not be appropriate for the calculation of prevalence. Moreover the sponsor presented an indirect comparison vis a vis literature studies for the purpose of significant benefit, claiming improved effects in survival.

The COMP considered that all stages of the proposed condition should be taken into consideration for the purpose of calculating the number of people affected. This would result in the prevalence surpassing the statutory threshold of 5 in 10,000.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 1 September 2015, prior to final opinion.

2.1.3. - EMA/OD/079/15

Treatment of retinal artery occlusion

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

Retinal Artery occlusion should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

The sponsor should discuss why the proposed condition cannot be viewed as a common manifestation of other underlying diseases, as the different aetiologies suggest that this is not a distinct entity for the purpose of designation. Exclusions of other vascular occlusive diseases should be also 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.

As it seems that the sponsor has excluded part of the population affected by condition; the sponsor should indicate on which population the prevalence calculation is based.

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.

In the written response, and during an oral explanation before the Committee on 1 September 2015, the sponsor outlined the diagnosis and treatment of the proposed entity, and acknowledged it may be a manifestation of several underlying diseases. It was also discussed that while the proposed active substance might have an effect in other neurological ischemic conditions, it would be difficult to deliver the required high concentrations in other sites.

As for the prevalence calculations, the applicant argued that since the ideal treatment window is no longer than 6.5 hours, then incidence is to be used as an appropriate index, and did not provide an updated prevalence conclusion.

The COMP considered that the sponsor has identified a specific group of patients, but not a distinct rare disease that would be valid for the purpose of the designation. Furthermore, the assumptions regarding the prevalence calculation have not been amended to reflect the specific target patient population.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 2 September 2015, prior to final opinion.

2.1.4. Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor - EMA/OD/077/15

Kite Pharma UK, Ltd; Treatment of mantle 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:

- 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 mantle cell lymphoma, the sponsor should further elaborate on:

- the bridging of the results obtained in vivo with cells expressing chimeric antigen receptors other than the ones subject of this application, to draw conclusions for the product in question;

- the relevance of the preclinical model used for the treatment of mantle cell lymphoma, and the interpretation of the results obtained in the experiments;

- the bridging of the results obtained in other haematological malignancies to draw conclusions for MCL as applied for designation;

- the availability on any data specific for mantle cell lymphoma with the product as applied for designation.

- Significant benefit

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

The sponsor is requested to further discuss the arguments provided for significant benefit with reference to any data specific for the proposed condition as applied for designation.

In the written response the sponsor further produced preliminary clinical data in patients with MCL which supplemented the data submitted for the medical plausibility and significant benefit. The sponsor has provided preliminary clinical data that showed radiological responses in relapsed patients with B-cell neoplasias, including mantle cell lymphoma.

The Committee agreed that the condition, 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 autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor was considered justified based on preliminary clinical data supporting responses in patients affected by the condition.

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.

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 autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate radiological responses in relapsed patients with B-cell neoplasias, including mantle cell lymphoma. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor, for treatment of mantle cell lymphoma, was adopted by consensus.

2.1.5. Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor - EMA/OD/078/15

Kite Pharma UK, Ltd; Treatment of primary mediastinal 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:

- Intention to diagnose, prevent or treat

Primary mediastinal B-cell lymphoma should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

The sponsor is particularly requested to discuss whether the condition is distinct from diffuse large B-cell lymphoma.

- Significant benefit

The sponsor is requested to provide a significant benefit justification versus product authorised for broader indications that may encompass the proposed indication (such as Non Hodgkin lymphoma or Diffuse Large B-cell lymphoma).

In the written response the sponsor stressed the different codes in the WHO classification and elaborated on the differences between PMBCL and DLBCL in in terms of epidemiology (PMBCL affects younger patients and has a female predominance) and B-cell immonuphenotype. With regards to the significant benefit issue, the sponsor discussed the available preliminary clinical data in relapsed/refractory patients.

The Committee agreed that the condition, primary mediastinal 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 autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor was considered justified based on preliminary clinical data in patients affected by the condition who responded to treatment with the product as assessed by imaging.

The condition is life-threatening due to relapses in 20-30% of patients who have poor prognosis and chronically debilitating in particular due to superior vena cava syndrome, night sweats, fever and weight loss.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate radiological responses in relapsed/refractory patients with B-cell neoplasias, including primary mediastinal B-cell lymphoma. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor, for treatment of primary mediastinal B-cell lymphoma, was adopted by consensus.

2.1.6. - EMA/OD/066/15

Treatment of Dravet Syndrome

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 11 August 2015, prior to responding to the list of issues.

2.1.7. - EMA/OD/065/15

Treatment of Lennox-Gastaut Syndrome

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 11 August 2015, prior to responding to the list of issues.

2.1.8. - EMA/OD/073/15

Treatment of pulmonary hypertension associated with idiopathic interstitial pneumonia

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 25 August 2015, prior to responding to the list of issues.

2.1.9. Synthetic peptide L-Cysteine, L-cysteinylglycyl-L-glutaminyl-L-arginyl-L-.alpha.-glutamyl-L-threonyl-L-prolyl-L-.alpha.-glutamylglycyl-L-alanyl-L-.alpha.-glutamyl-L-alanyl-L-lysyl-L-prolyl-L-tryptophyl-L-tyrosyl-, cyclic (1.fwdarw.17)-disulfide - EMA/OD/071/15

Apeptico Forschung und Entwicklung GmbH; Treatment of primary graft dysfunction following lung transplantation

COMP coordinator: Kerstin Westermark

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 discuss any internationally accepted classification to define the proposed condition as a distinct medical entity. Of note that the cited ICD-10 code of T86 does not correspond to the articulated indication.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of primary graft dysfunction following lung transplantation, the sponsor should further elaborate on:

- the relevance of the preclinical model used for the treatment of primary graft dysfunction following lung transplantation, and the interpretation of the results obtained in the experiments,

- the methodology used in the preliminary clinical studies as well as the results from these studies and their relevance for the development of the product in the condition.

In the written response, and during an oral explanation before the Committee on 2 September 2015, the sponsor proposed that there was a different pathophysiology supporting their proposed indication as a distinct medical entity. The sponsor also discussed the importance of the primary end-point regarding establishing the medical plausibility in the absence of long-term data.

The Committee agreed that the condition, primary graft dysfunction following lung transplantation, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing synthetic peptide L-cysteine, L-cysteinylglycyl-L-glutaminyl-L-arginyl-L-.alpha.-glutamyl-L-threonyl-L-prolyl-L-.alpha.-glutamylglycyl-L-alanyl-L-.alpha.-glutamyl-L-alanyl-L-lysyl-L-prolyl-L-tryptophyl-

L-tyrosyl-, cyclic (1.fwdarw.17)-disulfide was considered justified based on preliminary clinical data showing improved oxygenation in patients affected by the condition.

The condition is life-threatening and chronically debilitating due to developing bronchiolitis obliterans syndrome and an increased risk of acute rejection.

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 synthetic peptide L-cysteine, L-cysteinylglycyl-L-glutaminyl-L-arginyl-L-.alpha.-glutamyl-L-threonyl-L-prolyl-L-.alpha.-glutamylglycyl-L-alanyl-L-.alpha.-glutamyl-L-alanyl-L-lysyl-L-prolyl-L-tryptophyl-L-tyrosyl-, cyclic (1.fwdarw.17)-disulfide, for treatment of primary graft dysfunction following lung transplantation, was adopted by consensus.

2.1.10. Nimodipine - EMA/OD/088/15

Dr Stefan Blesse; Treatment of aneurysmal subarachnoid hemorrhage (aSAH)

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 diagnose, prevent or treat

In the application, the sponsor has provided data on the effects that the administration of the product has in angiographic vasospasms in a dog model of subarachnoid haemorrhage, thus in a broader indication that seems to include also non-aneurysmal subarachnoid haemorrhage.

The COMP invites the sponsor to justify that aneurysmal subarachnoid haemorrhage is a distinct medical entity or a valid subset, based on the characteristics of the proposed condition and the mechanism of action of the proposed product.

- 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".

When a broader condition than aneurysmal subarachnoid haemorrhage is to be considered as the most appropriate condition for designation, the sponsor should provide prevalence estimates for the broader condition.

- Significant benefit

The arguments on significant benefit are based on the potential improved efficacy in the condition.

The sponsor is invited to further elaborate on any available preclinical and clinical data supporting the significant benefit of the proposed product in relation to all existing formulations of nimodipine, particularly with regards to formulations for intravenous use.

In the written response, and during an oral explanation before the Committee on 2 September 2015, the sponsor further elaborated on aneurysmal subarachnoid haemorrhage being a distinct medical entity from subarachnoid haemorrhage. The sponsor also provided preliminary clinical data showing improved effect of the proposed formulation over current available formulations.

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

The intention to treat the aneurysmal subarachnoid haemorrhage with the medicinal product containing nimodipine was considered justified based on the pre-clinical proof-of-concept data demonstrating an anti-vasospasm mode of action, and on phase 1/2a clinical data demonstrating favourable outcome.

The condition is life-threatening and chronically debilitating due to cerebral ischemia, hydrocephalus, intracerebral haemorrhage, interventricular haemorrhage, left ventricular systolic dysfunction, subdural hematoma, seizures, increased intracranial pressure or myocardial infarction. The condition has a high mortality rate which is at 5 years between 65-70%.

The condition was estimated to be affecting approximately 1 in 10,000 persons in the European Union, at the time the application was made, based on a review of scientific literature.

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 nimodipine may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that a single administration of the sustained release formulation of nimodipine intrathecally through the external ventricular drain leads to more a favourable outcome compared to oral nimodipine. Both oral and intravenous nimodipine, which are authorized for the treatment of aneurysmal subarachnoid haemorrhage have to be continuously administered over up to 21 days, therefore the proposed new formulation would offer a simpler dosing regimen. The Committee considered that this constitutes a major contribution to patient care.

A positive opinion for nimodipine, for treatment of aneurysmal subarachnoid haemorrhage, was adopted by consensus.

2.1.11. - EMA/OD/067/15

Treatment of progressive supranuclear palsy

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 progressive supranuclear palsy, the sponsor should further elaborate on:

- the validity of the chosen surrogate endpoint “number of viable neurons” for predicting clinical outcome in PSP;

- the extent of evidence gathered. Has the sponsor collected data on tau aggregation or more clinically relevant functional outcome data, *e.g.* motor function?

In the written response, and during an oral explanation before the Committee on 2 September 2015, the sponsor provided further argumentation regarding the acceptability of neuronal survival as a surrogate endpoint; the sponsor acknowledged that definitive evidence on enhanced neuronal survival as a valid biomarker for amelioration of clinical symptoms in PSP patients is lacking. Nevertheless, it was emphasised that this is a key pathological feature and that findings in patients and models establish a causal relationship between the accumulation of abnormal tau protein, neuronal loss, and a range of clinical manifestations.

Regarding the amount of evidence for the proof of concept, the sponsor discussed that the main objective of the model study to address inhibition of tau-induced neuronal loss in PSP. Furthermore, the sponsor aimed at evaluating the effects of the product at the early stages of the pathogenic process, which could be believed to be the most relevant for the human setting.

The COMP considered that there is a difference between the demonstration of a pharmacodynamic effect versus a clinically relevant outcome. It was considered that other more clinically relevant outcomes and at different time points could have been studied. It was the view of the COMP, that the sponsor did not justify the medical plausibility for the treatment of the proposed condition.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 3 September 2015, prior to final opinion.

2.1.12. Recombinant human IgG1 kappa light chain monoclonal antibody targeting plasma kallikrein - EMA/OD/075/15

Dyax Ltd; Treatment of hereditary angioedema

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 sponsor is invited to better clarify the significant benefit in relation to all the existing authorized products for hereditary angioedema. The discussion should be as much as possible supported by any available preclinical and/or clinical data.

In the written response, and during an oral explanation before the Committee on 2 September 2015, the sponsor provided further clarification regarding the findings in the preliminary clinical data where their product was studied in the context of the treatment of these patients.

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

The intention to treat the condition with the medicinal product containing recombinant human IgG1 kappa light chain monoclonal antibody targeting plasma kallikrein was

considered justified based on preliminary clinical data showing reduction of angioedema attack rates in treated patients.

The condition is life-threatening and chronically debilitating due to recurrent attacks of oedema in various parts of the body that may cause airway obstruction leading to asphyxia.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant human IgG1 kappa light chain monoclonal antibody targeting plasma kallikrein may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing a reduction in angioedema attack rates comparing favourably with the data reported for existing products. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by hereditary angioedema.

A positive opinion for recombinant human IgG1 kappa light chain monoclonal antibody targeting plasma kallikrein, for treatment of hereditary angioedema, was adopted by consensus.

2.1.13. Synthetic hepcidin - EMA/OD/092/15

Emas Pharma Ltd; Treatment of chronic iron overload requiring chelation therapy

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

The COMP was of the opinion that chronic iron overload requiring chelation therapy should be modified to reflect a distinct medical entity to e.g. beta thalassaemia intermedia and major which appears more adequate regarding the product's mode of action. 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

The sponsor should change the proposed indication to e.g. beta thalassaemia intermedia and major and recalculate the prevalence to reflect the thalassemias. 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 re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the revised proposed orphan condition.

- Significant benefit

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

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the pre-clinical in vivo data in β-thalassemia 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 3 September 2015, the sponsor amended the proposed condition to beta thalassaemia intermedia and major.

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of beta thalassaemia intermedia and major.

The Committee agreed that the condition, beta thalassaemia intermedia and major, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing synthetic hepcidin was considered justified based on pre-clinical data which shows a reduction in the iron overload.

The condition is life-threatening and chronically debilitating due to the severe anaemia, the need for blood transfusions, and the complications related to these, in particular in beta-thalassaemia major patients.

The condition was estimated to be affecting approximately 2.5 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 synthetic hepcidin may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical data that demonstrate that there was a reduction in iron overload through an alternative mode of action to currently used and approved treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for synthetic hepcidin, for treatment of beta thalassaemia intermedia and major, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. 2-(2-chlorophenyl)-4-[3-(dimethylamino)phenyl]-5-methyl-1H-pyrazolo[4,3-C]pyridine-3,6(2H,5H)-dione - EMA/OD/105/15

GenKyoTex Innovation S.A.S; Treatment of systemic sclerosis

COMP coordinator: Josep Torrent-Farnell

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

The intention to treat systemic sclerosis with the medicinal product containing 2-(2-chlorophenyl)-4-[3-(dimethylamino)phenyl]-5-methyl-1H-pyrazolo[4,3-C]pyridine-3,6(2H,5H)-dione was considered justified based on in vitro and in vivo preclinical data demonstrating antifibrotic effects.

The condition is chronically debilitating and life-threatening due to the deposition of collagen in the skin and in internal organs such as kidneys, heart, lungs and gastrointestinal tract, leading to severe complications such as pulmonary hypertension, progressive dysphagia, sclerodermal renal crisis and cardiac failure.

The condition was estimated to be affecting less than 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 2-(2-chlorophenyl)-4-[3-(dimethylamino)phenyl]-5-methyl-1H-pyrazolo[4,3-C]pyridine-3,6(2H,5H)-dione may be of significant benefit to those affected by the condition. There are no treatments authorised for systemic sclerosis that could stop the build-up of collagen and development of fibrosis. Bosentan was authorised in the EU specifically to treat patients with systemic sclerosis who have pulmonary arterial hypertension or digital ulcers and is unlikely to have an effect on fibrosis. The sponsor has provided preclinical data that demonstrate an antifibrotic effect of the proposed product, which translates into improved histopathology and survival. The Committee considered that this constitutes a clinically relevant advantage to those affected by systemic sclerosis.

A positive opinion for 2-(2-chlorophenyl)-4-[3-(dimethylamino)phenyl]-5-methyl-1H-pyrazolo[4,3-C]pyridine-3,6(2H,5H)-dione, for treatment of systemic sclerosis, was adopted by consensus.

2.2.2. 2-Chloro-N6-(3-iodobenzyl) adenosine-5'-Nmethyluronamide - EMA/OD/118/15

PBS Regulatory Consulting Group Limited; Treatment of hepatocellular carcinoma

COMP coordinator: Bożenna Dembowska-Bagińska

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

The intention to treat the condition with the medicinal product containing 2-chloro-N6-(3-iodobenzyl)adenosine-5'-N-methyluronamide was considered justified based on preclinical data demonstrating anti-tumour activity upon treatment compared to vehicle control, and preliminary clinical data showing stabilisation of disease after treatment.

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

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 2-chloro-N6-(3-iodobenzyl)adenosine-5'-N-methyluronamide may be of significant benefit to those affected by the condition. The sponsor has provided clinical data of patients treated with the product that demonstrate that patients, who failed management with previous authorised medicinal products remain on stable disease. Furthermore, there is evidence that patients treated with the product and

having failed authorised treatments have increased survival. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 2-chloro-N6-(3-iodobenzyl)adenosine-5'-N-methyluronamide, for treatment of hepatocellular carcinoma, was adopted by consensus.

2.2.3. 3-pentylbenzeneacetic acid sodium salt - EMA/OD/072/15

ProMetic BioTherapeutics Ltd; Treatment of idiopathic pulmonary fibrosis

COMP coordinator: Josep Torrent-Farnell

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

The intention to treat the condition with the medicinal product containing 3-pentylbenzeneacetic acid sodium salt was considered justified based on preclinical data showing improvement of lung histology with the proposed treatment in a relevant model of the condition.

The condition is chronically debilitating due to progressive dyspnoea and loss of lung function, heavily limiting exercise capability and decreasing quality of life of the affected patients and leading in many cases within months or a few years to the need of oxygen therapy. Median survival is less than five years. Death ultimately occurs due to respiratory failure.

The condition was estimated to be affecting not more than 3 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 3-pentylbenzeneacetic acid sodium salt may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing higher effect of the proposed product on lung tissue fibrosis than the currently authorized products. Furthermore the anti-fibrotic effect was further enhanced when the proposed product was used in combination with the currently authorised products. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by idiopathic pulmonary fibrosis.

A positive opinion for 3-pentylbenzeneacetic acid sodium salt, for treatment of idiopathic pulmonary fibrosis, was adopted by consensus.

2.2.4. - EMA/OD/115/15

Treatment of focal segmental glomerulosclerosis

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 October meeting.

2.2.5. A highly purified formulation of Staphylococcal aureus protein A - EMA/OD/111/15

Coté Orphan Consulting UK Limited; Treatment of immune thrombocytopenia

COMP coordinator: Bożenna Dembowska-Bagińska

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

The intention to treat the condition with the medicinal product containing a highly purified formulation of *Staphylococcus aureus* protein A was considered justified based on pre-clinical in vivo data based on a valid model of the condition showing an improvement in platelet count.

The condition is life-threatening and chronically debilitating due to an increased risk of fatal haemorrhage such as intracranial haemorrhage.

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 a highly purified formulation of *Staphylococcus aureus* protein A may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical data that could support the potential use in refractory/relapsed patients. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for a highly purified formulation of *Staphylococcus aureus* protein A, for treatment of immune thrombocytopenia, was adopted by consensus.

2.2.6. Ataluren - EMA/OD/110/15

PTC Therapeutics International Limited; Treatment of aniridia

COMP coordinator: Josep Torrent-Farnell

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

The intention to treat the condition with the medicinal product containing ataluren was considered justified based on a pre-clinical in vivo data showing an improvement in visual acuity.

The condition is chronically debilitating due to foveal hypoplasia with reduced visual acuity and the appearance of progressive sight-threatening complications include keratopathy, cataract and glaucoma.

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 ataluren, for treatment of aniridia, was adopted by consensus.

2.2.7. - EMA/OD/108/15

Treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma

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 October meeting.

2.2.8. - EMA/OD/107/15

Treatment of acute lymphoblastic leukaemia

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 October meeting.

2.2.9. - EMA/OD/098/15

Treatment nasopharyngeal carcinoma

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 October meeting.

2.2.10. Delta-9-tetrahydrocannabinol and cannabidiol - EMA/OD/113/15

GW Pharma Ltd; Treatment of glioma

COMP coordinator: Brigitte Bloechl-Daum

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

The intention to treat the condition with the medicinal product containing dronabinol and cannabidiol was considered justified based on results of studies with the product in a valid xenograft model of glioma demonstrating tumour volume reduction and increased survival.

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 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 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 dronabinol and cannabidiol may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate a beneficial effect on tumour volume reduction and survival when the proposed product was added to radiation therapy and temozolomide, which is currently authorised for the treatment of glioma. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by glioma.

A positive opinion for dronabinol and cannabidiol, for treatment of glioma, was adopted by consensus.

2.2.11. - EMA/OD/120/15

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 respond in writing before the Committee at the October meeting.

2.2.12. - EMA/OD/119/15

Prevention of graft-versus-host disease

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

2.2.13. - EMA/OD/091/15

Treatment of adrenal insufficiency

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 October meeting.

2.2.14. - EMA/OD/117/15

Treatment of intestinal malabsorption in pre-term infants

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 October meeting.

2.2.15. - EMA/OD/093/15

Treatment of Middle East respiratory 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 October meeting.

2.2.16. Mazindol - EMA/OD/002/15

NeuroLifeSciences; Treatment of narcolepsy

COMP coordinator: Flavia Saleh

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

The intention to treat the condition with the medicinal product containing mazindol was considered justified based on clinical observations that report improvement in excessive sleepiness and cataplexy in treated patients affected by the condition.

Condition is chronically debilitating in particular due to excessive daytime sleepiness and cataplexy episodes, as well as life-threatening with a 1.5-fold excess mortality in narcolepsy patients relative to those without narcolepsy.

The condition was estimated to be affecting less than 4 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing mazindol may be of significant benefit to those affected by the condition. The sponsor has provided clinical observations showing responses in patients that were resistant to treatment with available products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for mazindol, for treatment of narcolepsy, was adopted by consensus.

2.2.17. N-(2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)ethyl)-2-hydroxybenzamide - EMA/OD/109/15

FGK Representative Service GmbH; Treatment of Duchenne muscular dystrophy

COMP coordinator: Pauline Evers

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

The intention to treat the Duchenne muscular dystrophy with the medicinal product containing n-(2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)ethyl)-2-hydroxybenzamide was considered justified based on efficacy of NF-kB inhibition and reduction of inflammation in vitro in human cells and in vivo models of the disease, leading to functional improvement.

The condition is life-threatening and chronically debilitating due to progressing motor disability, weakness of cardiac and respiratory muscles and consequently reduced life expectancy.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing n-(2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)ethyl)-2-hydroxybenzamide may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data supporting improved histological and performance outcomes which are not limited to a specific mutation, thereby targeting a broader patient population. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for n-(2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)ethyl)-2-hydroxybenzamide, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

2.2.18. - EMA/OD/097/15

Treatment of idiopathic hypersomnia

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 October meeting.

2.2.19. Recombinant adeno-associated viral vector expressing human CNGA3 - EMA/OD/096/15

TMC Pharma Services Ltd; Treatment of achromatopsia caused by mutations in the *CNGA3* gene

COMP coordinator: Armando Magrelli

Following review of the application by the Committee, it was agreed to rename the active substance to recombinant adeno-associated viral vector containing human *CNGA3* gene.

The Committee agreed that the condition, achromatopsia caused by mutations in the *CNGA3* gene, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing recombinant adeno-associated viral vector containing human CNGA3 gene was considered justified based on preclinical in vivo data that demonstrates that gene therapy with various CGNA3 containing AAV vectors can restore cone functionality, visual acuity and behavioural aspects of the disease in two different relevant disease models.

The condition is seriously debilitating due to the serious impairment of visual acuity in daylight, which is associated with limitations in normal day activities. Additional symptoms can be severe photophobia, nystagmus, small central scotoma, eccentric fixation and reduced or complete loss of colour discrimination.

The condition was estimated to be affecting less than 0.3 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 adeno-associated viral vector containing human *CNGA3* gene, for treatment of achromatopsia caused by mutations in the *CNGA3* gene, was adopted by consensus.

2.2.20. - EMA/OD/069/15

Treatment of glioma

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 October meeting.

2.2.21. - EMA/OD/064/15

Treatment of blastic plasmacytoid dendritic cell neoplasm

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 October meeting.

2.2.22. Recombinant human interleukin-3 truncated diphtheria toxin fusion protein - EMA/OD/112/15

Spector Consulting SAS; Treatment of acute myeloid leukaemia

COMP coordinator: Jens Ersbøll

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

The intention to treat the condition with the medicinal product containing recombinant human interleukin-3 truncated diphtheria toxin fusion protein was considered justified based on preclinical data in models of the condition and preliminary clinical data in patients affected by the condition who responded to treatment with the product.

The condition is life-threatening and chronically debilitating due to the consequences of the bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes,

disseminated intravascular coagulation, and the risk of severe infections. The condition progresses rapidly and is fatal within days to weeks or a few months if left untreated. The overall 5-year relative survival with the currently available treatments is approximately 22%.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant human interleukin-3 truncated diphtheria toxin fusion protein may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data reporting responses in patients who were relapsed or refractory to previous treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for recombinant human interleukin-3 truncated diphtheria toxin fusion protein, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.2.23. Sirolimus - EMA/OD/100/15

Desitin Arzneimittel GmbH; Treatment of tuberous sclerosis

COMP coordinator: Josep Torrent-Farnell and Giuseppe Capovilla

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

The intention to treat the condition with the medicinal product containing sirolimus was considered justified based on published clinical studies of topical formulations of sirolimus demonstrating positive clinical outcomes on cutaneous angiofibromas.

The condition is chronically debilitating and life threatening due to the formation of multiple tumours and severe neurodevelopmental symptoms.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing sirolimus may be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that the topical formulation of the proposed product targets the cutaneous manifestations of the condition, as compared to other currently authorised formulations for systemic administration. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.24. Three chimeric human/murine monoclonal antibodies against the Ebola (Zaire) surface glycoprotein - EMA/OD/102/15

Dr Stefan Blesse; Treatment for Ebola virus disease

COMP coordinator: Josep Torrent-Farnell

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

The intention to treat the condition with the medicinal product containing three chimeric human/murine monoclonal antibodies against the Ebola (Zaire) surface glycoprotein was considered justified based on preclinical and preliminary clinical data showing improved survival with the proposed product.

The condition is life-threatening due to severe, fluid-depleting diarrhoea leading to hypotension and shock, with diffuse haemorrhage in the severe forms of the disease.

The condition was estimated to be affecting less than 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 three chimeric human/murine monoclonal antibodies against the Ebola (Zaire) surface glycoprotein, for treatment of Ebola virus disease, was adopted by consensus.

2.2.25. - EMA/OD/081/15

Treatment of diffuse large B-cell lymphoma

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 October meeting.

2.3. Amendment of an existing orphan drug designation

2.3.1. Sialic acid – EMA/OD/126/11

Ultragenyx UK Limited - United Kingdom; Treatment of hereditary inclusion body myopathy

COMP coordinator: Michel Hoffmann

The Committee agreed that the condition, GNE myopathy, is a distinct medical entity and meets the criteria for orphan designation.
The intention to treat the amended condition with the medicinal product containing sialic acid was considered justified based on preclinical data showing reduction of muscle weakness with the proposed product.

The condition is chronically debilitating due to progressive limb muscle weakness leading to difficulties climbing stairs or getting up from sitting, and weakness of the hands and shoulder muscles. The condition usually causes complete functional impairment over 10–20 years, 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 sialic acid, for treatment of GNE myopathy, was adopted by consensus.

2.4. COMP opinions adopted via written procedure following previous meeting

2.4.1. Lanreotide acetate - EMA/OD/027/15

Prof. Dr R.T.Gansevoort; Treatment of autosomal dominant polycystic kidney disease

COMP coordinator: Josep Torrent-Farnell

COMP noted that the revised COMP opinion was adopted by written procedure.

2.5. Appeal

2.5.1. Autologous human peripheral blood Vdelta1+ T lymphocytes activated in vitro by cytokine and monoclonal antibody treatment – EMA/OD/006/15

Lymphact - Lymphocyte Activation Technologies S.A. - Portugal; Treatment of chronic lymphocytic leukaemia/ small lymphocytic lymphoma

COMP coordinator: Frauke Naumann-Winter

In the written grounds and during an oral explanation before the Committee on 1 September 2015, the sponsor presented an analysis of the existing data on the incidence and prevalence of CLL/SLL; in order to estimate the worst case scenario prevalence, the sponsor assumed an average duration of disease of 20 years.

The sponsor also used worst case approaches in relation to estimate of the proportion of CLL/SLL cases within total leukaemia incidence using data from international cancer registries.

The Committee agreed that the condition, 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 autologous human peripheral blood Vdelta1+ T lymphocytes activated in vitro by cytokine and monoclonal antibody treatment was considered justified based on pre-clinical in vivo data showing a reduction in tumour size.

The condition is chronically debilitating and life-threatening due to development of anaemia, neutropenia, thrombocytopenia, lymphadenopathy, splenomegaly, hepatomegaly and impaired production of normal immunoglobulins leading to increased susceptibility to infections.

The condition was estimated to be affecting approximately 4.8 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 autologous human peripheral blood Vdelta1+ T lymphocytes activated in vitro by cytokine treatment may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical in vivo data

that demonstrate that the product can induce tumour regression. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous human peripheral blood Vdelta1+ T lymphocytes activated in vitro by cytokine and monoclonal antibody treatment, for treatment of chronic lymphocytic leukaemia / small lymphocytic lymphoma, was adopted by consensus.

2.6. Nominations

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

COMP coordinators were appointed for 4 applications submitted and 26 upcoming applications.

2.7. Evaluation on-going

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

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of sickle cell disease

3.1.2. -

Treatment of systemic sclerosis

3.1.3. -

Treatment of acromegaly

3.2. Finalised letters

3.2.1. -

Treatment of graft-versus-host disease

The finalised letter was circulated for information.

3.2.2. -

Treatment of Urea Cycle Disorders:

a) treatment of ornithine transcarbamylase deficiency;

b) treatment of carbamoyl-phosphate synthase-1 deficiency;

c) treatment of citrullinaemia type 1;

d) treatment of argininosuccinic aciduria;

e) treatment of hyperargininaemia;

f) treatment of N-acetylglutamate synthetase (NAGS) deficiency;

g) treatment of citrullinaemia type 2;

h) treatment of ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria (HHH) syndrome).

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of ovarian cancer

The new request was noted.

3.3.2. -

Treatment of Prader-Willi syndrome

The new request was noted.

3.3.3. -

Treatment of glycogen storage disease type II (Pompe's disease)

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. Cresemba - isavuconazole – EMEA/H/C/002734

Basilea Medical Ltd;

COMP coordinators: Nikolaos Sypsas / Sigurdur Thorsteinsson

a) treatment of invasive aspergillosis (EMA/OD/009/14, EU/3/14/1284)

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

In view of the nature and the design of the pivotal study versus voriconazole the sponsor is requested to further elaborate on the clinically relevant advantage by discussing comparative data in patients affected by the proposed indication.

In particular, data supporting a clear advantage over voriconazole with regards to nephrotoxicity are expected. A discussion of the seriousness and outcome of the adverse effects observed is also expected.

In its written response, and during an oral explanation before the Committee on 1 September 2015, the sponsor further elaborated on the argument of improved safety over voriconazole. It was noted that the Summary of Product Characteristics of voriconazole raises caution in patients affected by moderate to severe renal dysfunction. The sponsor also further elaborated regarding renal complications in a limited number of patients with low glomerular filtration rate from their main clinical study. However, the COMP considered that the limited number of observations make it difficult to document the sought improved safety with regards to renal toxicity.

On the other hand, significant differences in TEAE's between voriconazole and isavuconazole have been documented as per the CHMP assessment report for the following system organ classes (SOCs): skin disorders, eye disorders and hepatobiliary disorders. In particular, the COMP was of the opinion that the potential to use the product with a minimal risk of hepatotoxicity was of major importance in the treatment of these patients since a major concern with the other currently approved treatment is hepatotoxicity.

The COMP concluded that:

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

The prevalence of invasive aspergillosis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 2 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is life-threatening due to progressive dyspnoea, pleuritic chest pain, haemoptysis, and due to dissemination of the infection to several organs including the brain. Mortality rates are up to 70–95% in recipients of bone marrow transplant.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Cresemba may be of potential significant benefit to those affected by the orphan condition still holds. This is based on clinical data showing improved safety for example in hepatotoxicity. The committee considers that this constitutes a clinically relevant advantage.

An opinion not recommending the removal of Cresemba, isavuconazonium sulfate for treatment of invasive aspergillosis (EU/3/14/1284) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

b) treatment of mucormycosis (EMA/OD/010/14, EU/3/14/1276)

The COMP concluded that:

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

The prevalence of mucormycosis (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be approximately 0.06 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is life-threatening due to possible fungal invasion of the vascular network which results in thrombosis and death of surrounding tissue in different organs.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Cresemba may be of potential significant benefit to those affected by the orphan condition still holds. This is based on clinical data supporting the use of the product in patients that are not eligible for treatment with amphotericin B. The committee considers that this constitute a clinically relevant advantage.

An opinion not recommending the removal of Cresemba, isavuconazonium sulfate for treatment of mucormycosis (EU/3/14/1276) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

4.1.2. Obizur - susoctocog alfa – EMEA/H/C/002792, EMA/OD/043/10, EU/3/10/784

Baxalta Innovation GmbH; Treatment of haemophilia A

COMP coordinator: Karri Penttilä

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 was requested to discuss the arguments for the justification of significant benefit versus all authorised products indicated for the treatment of acquired haemophilia.

In particular with regards to the comparison of efficacy outcomes versus bibliographic data, the sponsor was asked to elaborate onto the comparability of patients and settings, taking into consideration the design and uncontrolled nature of the main efficacy study.

In its written response, and during an oral explanation before the Committee on 1 September 2015, the sponsor stated that there have been no comparative trials conducted with Obizur and authorised products due to the rarity of the disease and the heterogeneity of this population, which does not allow a practical statistical relevant comparison. They further mentioned that Study OBI-1-301/OBI-1-301a could be considered to be the 1st prospective, interventional clinical trial in acquired haemophilia.

In order to justify significant benefit, the sponsor produced two tables comparing and contrasting the findings from their study with literature for rFVIIa and FEIBA products, discussing baseline characteristics, demographics and clinical outcomes:

With regards to efficacy, studies for FEIBA and rVIIa relied on data from observational studies or registries. The sponsor came to the conclusion that Obizur had 100% positive clinical response on bleeding episodes at 24 hours whereas the authorised agents had 81%-100% response. It was considered that since in some studies the comparators showed high

control of bleeding episodes, reaching even 100% in some studies, the claim of improved efficacy could not be accepted based on the data presented.

With regards to safety, it was stated that in contrast to many studies with the authorised agents, there were no product-related thrombotic events in the Obizur study. No thromboembolic events have been observed with Obizur in clinical trials, and in 17 acquired haemophilia A patients treated in the post-marketing period in the US. According to the sponsor, this seems to indicate a low risk for thromboembolic events with treatment and thus a favourable safety profile of the product. The COMP considered that this claim had not been documented, given the low number of patients referred to.

The sponsor also discussed the possibility of tailoring the dose of their product on the basis of factor VIII levels achieved post-infusion in patients' plasma as a claim for significant benefit over currently authorised products, where this is not possible. The sponsor discussed such titration in two patients of their study, and expected that this titration would result in more effective bleeding control. The COMP understood that such an improved effective bleeding control has not been shown, and in the absence of data to document this claim, the argument could not be accepted.

The Sponsor also claimed that there was a better safety profile than other currently authorised products used in acquired haemophilia A and that the risk of contamination with virus was significantly less. The COMP considered that in the absence of data on confirmed infections with the counterparts this safety argument could not be considered.

The COMP concluded that:

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

The prevalence of haemophilia A (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in to be approximately 0.7 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 spontaneous bleeding episodes as well as substantially prolonged bleeding upon injury. Approximately 80-85% of bleeding episodes occur in the muscles and joints of the elbows, knees and ankles, causing acute haemarthrosis and synovitis. Recurrent bleeds in the same location lead to chronic arthropathy, muscular atrophy and deformities. In young children with severe haemophilia, spontaneous bleeds occur within the first 2 years of life, after the child starts to walk. Rare but life-threatening bleeds also occur in the central nervous system, throat, neck, and gastrointestinal tract.

In relation to the existence of satisfactory methods of treatment of the condition that are authorised in the European Union, the assumption that Obizur is of significant benefit to those affected by the orphan condition is not confirmed.

An indirect comparison was performed by the sponsor between their case-series clinical study and literature studies for the authorised products for the specific therapeutic indication, namely prothrombin complex concentrates and activated FVII; this comparison did not confirm improved efficacy or safety; moreover the argued potential for improved titration and monitoring that was proposed by the sponsor was not supported by data with regards to leading to improved bleeding control. The COMP concluded that the sponsor did

not justify a clinically relevant advantage or major contribution to patient care over the existing methods of treatment for the proposed indication.

An opinion recommending the removal of Obizur, susoctocog alfa for treatment of haemophilia A (EU/3/10/784) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

4.2.1. Blincyto – Blinatumomab - EMA/OD/029/09, EU/3/09/650, EMEA/H/C/003731

Amgen Europe B.V.; Treatment of acute lymphoblastic 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 October meeting.

4.2.2. Elocta - Efmoroctocog alfa – EMA/OD/030/10, EU/3/10/783, EMEA/H/C/003964

Biogen Idec Ltd; Treatment of haemophilia A

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 October meeting.

4.2.3. Kyprolis - Carfilzomib – EMEA/OD/120/07, EU/3/08/548, EMEA/H/C/003790

Amgen Europe B.V.; 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 October meeting.

4.2.4. Orkambi - Lumacaftor / ivacaftor – EMA/OD/032/14, EU/3/14/1333, EMEA/H/C/003954

Vertex Pharmaceuticals (U.K.) Ltd.; Treatment of cystic 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 October meeting.

4.2.5. RAVICTI - Glyceryl tri-(4-phenylbutyrate) – EMEA/H/C/003822

Horizon Therapeutics Limited;

a) treatment of carbamoyl-phosphate synthase-1 deficiency (EMA/OD/124/09, EU/3/10/733)

b) treatment of ornithine carbamoyltransferase deficiency (EMA/OD/002/10, EU/3/10/734)

c) treatment of citrullinaemia type 1 (EMA/OD/003/10, EU/3/10/735)

d) treatment of argininosuccinic aciduria (EMA/OD/004/10, EU/3/10/736)

e) treatment of hyperargininaemia (EMA/OD/005/10, EU/3/10/737)

f) treatment of ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria (HHH) syndrome) (EMA/OD/006/10, EU/3/10/738)

g) treatment of citrullinaemia type 2 (EMA/OD/007/10, EU/3/10/739

Status of the procedure at CHMP was noted.

4.3. On-going procedures

4.3.1. List of on-going procedures

COMP co-ordinators were appointed for 3 applications.

4.4. COMP opinions adopted via written procedure following previous meeting

4.4.1. Strensiq - asfotase alfa - EMEA/H/C/003794, EMA/OD/071/08, EU/3/08/594

Alexion Europe SAS; Treatment of hypophosphatasia

The COMP noted that the COMP opinion was adopted via written procedure

5. Organisational, regulatory and methodological matters

5.1. Mandate and organisation of the COMP

5.1.1. Strategic Review & Learning meetings

COMP/PDCO Strategic Review & Learning Meeting under the Luxembourg Presidency to be held on 15-16 October 2015 in Bonn

The discussion was postponed.

5.1.2. Election of Chair and Vice-Chair – 6 October 2015

The elections of the COMP Chair and Vice-Chair will take place on Tuesday 6th October at 9:00. COMP members were asked to arrive on time to not delay the elections.

Candidatures should submit their resumes and letter of motivation to the COMP secretariat by 21 September 2015.

5.2. Coordination with EMA Scientific Committees or CMDh-v

None.

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

5.3.1. Significant Benefit Working Group

The working group on Significant Benefit met on 3 September 2015.

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

EMA Human Scientific Committees' Working Parties with Patients' and Consumers' Organisations (PCWP) and Healthcare Professionals' Organisations (HCPWP) joint meeting minutes were circulated for information. The agenda of the PCWP and HCPWP joint workshop on risk minimisation measures was circulated for information.

5.3.3. Biologics Working Party (BWP)

The document was circulated for information.

5.4. Cooperation within the EU regulatory network

5.4.1. European Commission

The COMP was informed that on the occasion of the 50th anniversary of the adoption of the first EU legislation on human medicines, the European Commission is organising a conference on "50 Years of EU Pharma legislation: Achievements and future perspectives", that will take place on 28 September 2015 in Brussels, at the Charlemagne Building, Rue de la Loi 170.

Note: more information on the Conference can be found at:
http://ec.europa.eu/health/human-use/events/ev_20150928_en.htm

5.4.2. Review of the 2003 Communication on Orphan Medicinal Products

The COMP was updated on the principles to be followed by the Commission when reviewing the EC 2003 Communication on Orphan Medicinal Products. The COMP members were invited to send comments in writing to the EC representative.

5.4.3. The European Network of Centres for Pharmacoepidemiology & Pharmacovigilance (ENCePP)

The Chair reminded COMP members of the call for expression of interest for the appointment of a COMP representative to the ENCePP Steering Group. Volunteers have to submit their candidature to the COMP Secretariat by 21 September 2015 for decision at the October COMP meeting.

5.5. Cooperation with International Regulators

5.5.1. Food and Drug Administration (FDA)

EMA/FDA teleconference on Orphan Medicines – 21 July 2015

The agenda was circulated for information.

5.5.2. Update on the status of the IMI2 project ADAPT-SMART

The EMA introduced the ADAPT-SMART IMI2 project to the COMP and clarified the purpose of the project compared to other ongoing initiatives. Members of EMA Committees are

invited to contribute to the project individually or as a group. Meetings will start in September.

Brigitte Blöchl-Daum and Pauline Evers volunteered.

5.5.3. Update on recent confidentiality arrangements with third country regulators and organisations

COMP was informed that two confidentiality arrangements have been concluded by the European Commission DG SANTE and EMA in July and September 2015 respectively; the first with Swissmedic and the second with the WHO. Both arrangements are concluded for an initial period of 5 years, and may be renewed. Confidentiality agreements were already in place between EMA and the following international partners: USFDA, Japan PMDA/MHLW, Health Canada and TGA Australia.

Under the terms of confidentiality or working arrangements, the parties to the arrangement agree not to disclose non-public information, which means that product related information can be shared between the parties. The arrangements also facilitate ad hoc participation at product related discussions in response to specific requests.

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

None.

5.7. COMP work plan

None.

5.8. Planning and reporting

5.8.1. List of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2015

An updated list of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2015 was circulated.

5.8.2. Overview of orphan marketing authorisations/applications

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

5.8.3. Meeting dates

The COMP discussed the 2016 COMP meeting dates that were presented during the July meeting.
COMP members who are also SAWP members stressed the difficulties they face when SAWP and COMP meetings overlap and advocate that the dates are modified to avoid as much as possible that COMP takes place in parallel with SAWP. The COMP agreed that the dates should be revised.

[*Post-meeting note:* COMP meeting dates for 2016 were moved to the week between SAWP and CHMP whenever possible. The meeting calendars for 2017 and 2018 will be revised accordingly]

6. 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 1-3 September 2015 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	
Andri Andreou	Member	Cyprus	No interests declared	
Katerina Kubacková	Member	Czech Republic	No restrictions applicable to this meeting	
Jens Ersbøll	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Nikolaos 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	
Dainis Krievins	Member	Latvia	No restrictions applicable to this meeting	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Violeta Stoyanova	Member	Netherlands	No interests declared	
Bożenna	Member	Poland	No restrictions	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Dembowska-Bagińska			applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Martin Možina	Member	Slovenia	No interests declared	
Josep Torrent-Farnell	Member	Spain	No interests declared	
Kerstin Westermark	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	Eurordis	Observer	No restrictions applicable to this meeting	
Petronella Ottevanger	Expert - via telephone*		Involvement only in discussions with respect to procedures involving the relevant medicinal product, i.e. no part in final deliberations and voting as appropriate as regards the medicinal product.	2.1.2. Product for treatment of cervical cancer
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the product(s) they have been invited to talk about.