18 October 2016
EMA/COMP/590983/2016
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 06-08 September 2016

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

06 September 2016, 09:00-19:00, room 2F

07 September 2016, 08:30-19:00, room 2F

08 September 2016, 08:30-17:30, room 2F

Disclaimers

Some of the information contained in this agenda 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 agenda is a working document primarily designed for COMP members and the work the Committee undertakes.

Further information with relevant explanatory notes can be found at the end of this document.

Note on access to documents

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

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1. Introduction

1.1. Welcome and declarations of interest of members and experts

In accordance with the Agency's policy on handling of declarations of interests of scientific committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced that no restriction in the involvement of meeting participants in upcoming discussions was identified as included in the pre-meeting list of participants and restrictions.

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

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

1.2. Adoption of agenda

COMP agenda for 6-8 September 2016 was adopted with no amendments.

1.3. Adoption of the minutes

COMP minutes for 11-13 July 2016 were adopted with no amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. Lutetium-177(3+), S2,S7-cyclo[N-{4,7,10-Tricarboxymethyl-1,4,7,10-tetraaza-cyclododecan-1-yl-acetyl}-4-chloro-L-phenylalanyl-D-cysteinyl-4-[(4S)-2,6-dioxo-1,3-diazinane-4-carboxamido]-L-phenylalanyl-4-(carbamoylamino)-D-phenylalanyl-L-lysyl-L-threonyl-L-cysteinyl-D-tyrosinamide] - EMA/OD/089/16

Ipsen Pharma; Treatment of gastroenteropancreatic neuroendocrine tumours

COMP coordinator: Katerina Kopečková

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 presented data to support the potential efficacy of the proposed

product in patients. No data on treatment received by patients prior to the study was presented. The outcomes observed were not discussed in the context of the current expected outcome for patients with advanced inoperable disease.

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

The sponsor should elaborate on the treatment the patients receive prior to the study and on the results of clinical study to support the significant benefit assumption in the context of the current therapeutic management of patients.

In the written response, and during an oral explanation before the Committee on 6 September 2016, the sponsor provided details of patient characteristics as well and responses in patients who received the proposed treatment so far. Patients who were suffering from GEP-NETs were not pre-treated with somatostatin analogues. The committee inquired why patients did not receive somatostatin analogues, which are authorised as a first line treatment. The sponsor explained that the use of somatostatin analogues is only recommended in patients presenting with symptoms, such as carcinoid syndrome. Since neither of the two patients in the study had symptoms, they did not require such treatment. The committee acknowledged these reasons and considered that at present none of the available products are authorised as anti-tumour treatments in broad GEP-NET population. Since the proposed product offers a possibility of inducing tumour remission, this would constitute a clinically relevant advantage.

The Committee agreed that the condition, 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 lutetium-177(3+),S^2,S^7-cyclo[N-{4,7,10-tricarboxymethyl-1,4,7,10-tetraaza-cyclododecan-1-yl-acetyl}-4-chloro-L-phenylalanyl-D-cysteinyl-4-[(4S)-2,6-dioxo-1,3-diazinane-4-carboxamido]-L-phenylalanyl-4-(carbamoylamino)-D-phenylalanyl-L-lysyl-L-threonyl-L-cysteinyl-D-tyrosinamide] was considered justified based on clinical data demonstrating partial remissions or stable disease.

The condition is chronically debilitating and life-threatening, in particular due to the debilitating symptoms and the poor prognosis in patients with localised advanced or metastatic disease.

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

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 lutetium-177(3+),S^2,S^7-cyclo[N-{4,7,10-tricarboxymethyl-1,4,7,10-tetraaza-cyclododecan-1-yl-acetyl}-4-chloro-L-phenylalanyl-D-cysteinyl-4-[(4S)-2,6-dioxo-1,3-diazinane-4-carboxamido]-L-phenylalanyl-4-(carbamoylamino)-D-phenylalanyl-L-lysyl-L-threonyl-L-cysteinyl-D-tyrosinamide] will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients with advanced, progressive, inoperable disease achieved stable disease and partial remission, which is not expected in palliative care using authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for lutetium-177(3+),S^2,S^7-cyclo[N-{4,7,10-tricarboxymethyl-1,4,7,10-tetraaza-cyclododecan-1-yl-acetyl}-4-chloro-L-phenylalanyl-D-cysteinyl-4-[(4S)-2,6-dioxo-1,3-diazinane-4-carboxamido]-L-phenylalanyl-4-(carbamoylamino)-D-phenylalanyl-L-lysyl-L-threonyl-L-cysteinyl-D-tyrosinamide], for treatment of gastro-entero-pancreatic neuroendocrine tumours, was adopted by consensus.

2.1.2. Autologous mononuclear cells derived from human cord blood - EMA/OD/099/16

BrainRepair UG (haftungsbeschränkt); Treatment of periventricular leukomalacia

COMP coordinator: Dinah Duarte

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 if the proposed condition is a distinct medical entity for orphan designation, the sponsor is invited to provide a discussion of similarities and distinctions between the proposed condition and hypoxic-ischaemic encephalopathy (HIE) based on pathophysiology, histopathology, clinical characteristics and classification systems.

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

- the results obtained in the cerebral ischaemia model and how the results could predict a clinically meaningful efficacy;
- the relevance of the preclinical model and how the results could predict a clinically meaningful efficacy;
- the availability of other preclinical models as described in the literature;
- the outcome of clinical case reports of patients that received the 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".

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 clarify how prevalence has been established from the reported incidence figures and how the disease duration has been accounted for.

In the written response, and during an oral explanation before the Committee on 6 September 2016, the sponsor discussed the clinical data available and the delineation of the condition from hypoxic-ischaemic encephalopathy (HIE) based on differences in pathophysiology, histopathology and clinical characteristics. Regarding the medical plausibility, the COMP acknowledged the available data, which included outcomes from preclinical hypoxia models and patients with hypoxic-ischaemic lesions. In totality, the outcomes suggest improvements in the neurological and developmental sequelae that are associated with the condition. The COMP therefore considered that there was sufficient evidence to support the assumption of medical plausibility for the purpose of orphan

designation. The COMP strongly recommended the sponsor to request protocol assistance on the future development.

Regarding the prevalence, the COMP acknowledged that the condition could be described as acute and therefore accepted the proposed prevalence estimate that was based on incidence figures of the condition.

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

The intention to treat the condition with the medicinal product containing autologous mononuclear cells derived from human cord blood was considered justified based on preclinical data and preliminary clinical data suggesting improvements in the neurological and developmental sequelae associated with the condition.

The condition is life-threatening and chronically debilitating due to the risk of developing deficits in cognition, vision, behaviour, attention, socialisation, motor function and cerebral palsy.

The condition was estimated to be occurring in approximately 0.3 in 10,000 persons per year 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 autologous mononuclear cells derived from human cord blood, for treatment of periventricular leukomalacia, was adopted by consensus.

2.1.3. N-[(2S)-5-{[(1R, 2S)-2-(4-fluorophenyl)cyclopropyl] amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt - EMA/OD/115/16

Imago BioSciences Ltd.; Treatment of myelofibrosis

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 sponsor presented data from preclinical model of the condition, where an analogue of the active substance was used instead of the intended product. Although the choice of this alternative product has been justified by the pharmacokinetics considerations, no data to support comparable pharmacodynamics was presented. The comparability of the two substances should be further discussed.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of myelofibrosis, the sponsor should further elaborate on the results obtained *in vitro* to support comparative inhibitory activity of the two products used. The sponsor is invited to explain the choice of the molecule for future clinical development.

In the written response, the sponsor submitted data on comparability of the proposed product and its analogue, which was used for preclinical studies. The two substances were shown to have similar inhibitory activity and the choice of the proposed product was

supported by the pharmacokinetic properties of the substance in man. The committee considered the written responses satisfactory and that there was no need for an oral hearing, which was subsequently cancelled.

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

The intention to treat the condition with the medicinal product containing N-[(2S)-5-{[(1R,2S)-2-(4-fluorophenyl)cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt was considered justified based on preclinical data demonstrating reversal of bone marrow fibrosis and a reduction of spleen volume.

The condition is chronically debilitating due to anaemia, splenomegaly, extramedullary haematopoiesis, constitutional symptoms such as fatigue, night sweats and fever, cachexia and leukaemic progression. The condition is also life-threatening with median survival of approximately 1.3 years for patients with high-risk disease.

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 N-[(2S)-5-{[(1R,2S)-2-(4-fluorophenyl)cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate a reduction in spleen volume and a reversal of bone marrow fibrosis in a valid model of the condition treated with the proposed product. Reduction of bone marrow fibrosis cannot be achieved by the authorised product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for N-[(2S)-5-{[(1R,2S)-2-(4-fluorophenyl)cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt, for treatment of myelofibrosis, was adopted by consensus.

2.1.4. - EMA/OD/113/16

Treatment of retinitis pigmentosa

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 order to justify the medical plausibility of the proposed product the sponsor is invited to further discuss how the *in vitro* data showing antioxidant effects and increased survival of retinal cells would translate into clinical efficacy of the proposed product.

The sponsor discussed the disadvantages of using models of retinitis pigmentosa. To support medical plausibility the sponsor used data from a model of a different condition. The sponsor is invited to justify the use of the acute glaucoma model as the basis for the medical plausibility in the present application.

In the written response, and during an oral explanation before the Committee on 6 September 2016, the sponsor further clarified the preclinical data presented in the application. The COMP considered that in absence of data in a specific model of the condition it is not possible to establish the medical plausibility of the proposed product..

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 7 September 2016, prior to final opinion.

2.1.5. - EMA/OD/084/16

Treatment of short bowel syndrome

Action: For information

Documents tabled:
Withdrawal request of 9 August 2016

2.1.6. Mogamulizumab - EMA/OD/091/16

Kyowa Kirin Limited; Treatment of cutaneous T-cell lymphoma

COMP coordinator: Katerina Kopečková

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

In order to justify the significant benefit of the proposed product, based on relapsing cutaneous T-cell lymphoma, the sponsor is invited to provide more details on the previous treatments of the patients enrolled in the two clinical studies presented in this application.

In the written response, the sponsor further detailed the patient population of the phase I/II study that was presented to support the medical plausibility. The sponsor adequately addressed the questions of the COMP regarding previous treatments and responses of the patients in the clinical studies, which allowed the Committee to put the results in a perspective for signficant benefit. The COMP was of the opinion that the favourable clinical responses shown in the studies so far in pretreated patients constitute sufficient grounds for the significant benefit of mogamulizumab and an oral explanation was not necessary. The sponsor was invited to apply for protocol assistance on order to discuss the maintenance of significant benefit at the time of marketing authorization.

The Committee agreed that the condition, 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 mogamulizumab was considered justified based on preclinical data showing reduction of tumour size, and on preliminary clinical data.

The condition is chronically debilitating due to the development of cutaneous lesions, generalised erythroderma, and lymphadenopathy. Ulceration of tumours, with secondary bacterial infections, is linked to morbidity and death. The overall five-year survival rates vary between 24% and 68% according to the subtype of cutaneous T-cell lymphoma.

The condition was estimated to be affecting approximately 2.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing mogamulizumab 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. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

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

2.1.7. (6aR, 10aR)-3-(1',1'-dimethylheptyl)- Δ8-tetrahydro-cannabinol-9-carboxylic acid - EMA/OD/100/16

TMC Pharma Services Ltd; Treatment of cystic fibrosis

COMP coordinator: Judith Eggenhofer

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for the treatment of cystic fibrosis, the sponsor should further elaborate on the potential different effects of the product on CB1 vs CB2 receptors, and the impact of this on the intended pharmacological activity.

- Significant benefit.

In order to justify the significant benefit of the proposed product the sponsor is invited to further discuss the potential advantages that the product would bring to the current treatment of cystic fibrosis. This would require a comparative discussion in relation to all existing authorized products for the treatment of cystic fibrosis.

The sponsor is reminded that any claim of significant benefit should be as much as possible supported by data.

In the written response, and during an oral explanation before the Committee on 7 September 2016, the sponsor further clarified the expected activity of the proposed product in relation to CB1 and CB2 receptors. In order to support the receptor selectivity the sponsor presented supportive preclinical studies. The COMP considered that the sponsor sufficiently elucidated the mechanism of action of the proposed product, including its effect on the two different CB receptors.

In relation to significant benefit, the sponsor argued that none of the currently authorized products for the treatment of CF is characterised by the same mechanism of action. Even though these data are preliminary and no comparison was performed with any of the existing products, the COMP considered that the different mechanism of action of the proposed product in relation to what already authorized offers the potential for a use in combination that may justify at the present stage an assumption of significant benefit.

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

The intention to treat the condition with the medicinal product containing (6aR,10aR)-3-(1',1'-dimethylheptyl)-delta-8-tetrahydrocannabinol-9-carboxylic acid was considered justified based on preclinical data showing reduction of lung inflammation and of the burden of Pseudomonas aeruginosa infection with the proposed product.

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

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (6aR,10aR)-3-(1',1'-dimethylheptyl)-delta-8-tetrahydrocannabinol-9-carboxylic acid will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing that the proposed product reduced lung inflammation and increased clearance of *Pseudomonas aeruginosa* infection in valid models of the condition. The product acts with a different mechanism of action than the currently authorised treatments for the condition, offering the potential to be used in combination. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for (6aR,10aR)-3-(1',1'-dimethylheptyl)-delta-8-tetrahydrocannabinol-9-carboxylic acid, for treatment of cystic fibrosis, was adopted by consensus.

2.1.8. - EMA/OD/202/15

Treatment of variegate porphyria

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

- Intention to diagnose, prevent or treat

The sponsor presented clinical data in patients with erythropoietic protoporphyria (EPP). The sponsor extrapolates the medical plausibility of the product to variegate porphyria (VP) based on some aspects of molecular pathology that are shared by these two conditions. The sponsor does not comment on the differences in pathophysiology in variegate porphyria and does not discuss the fact that one of these conditions is chronic and the other is acute.

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

– the relevance and validity of extrapolating the clinical data in erythropoietic protoporphyria for the treatment of variegate porphyria, and the interpretation of the clinical results;

– the comparative pathophysiology and clinical presentations of erythropoietic protoporphyria and variegate porphyria and a discussion on the expected use of the product, which is a controlled release implant, in an acute hepatic porphyria;

– any available data in a model of the condition to support the medical plausibility.

- 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 argues that the product will be of significant benefit because it targets a different aspect of the condition and can be used in combination with hemin.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from clinical study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication. In the absence of data in the condition the significant benefit cannot be established.

In the written response, and during an oral explanation before the Committee on 7 September 2016, the sponsor provided a side to side comparison of erythropoietic protoporphyria with variegate porphyria. Differences and similarities of skin presentations were discussed. Similar aetiology related to the build-up of protoporphyrin in the skin was highlighted. Since EPP is acute in nature and VP skin lesions are more chronic, the COMP questioned the applicability of the controlled-release formulation for conditions with such different dynamics and the sponsor explained the long term maintained effects of the application of the drug. Nevertheless, the COMP felt it was necessary to support the application with some data in the condition. This is because variegate porphyria is more complex and the localisation of porphyrin in the skin is different to that in erythropoietic porphyria.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 7 September 2016, prior to final opinion.

2.1.9. - EMA/OD/112/16

Treatment of narcolepsy

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

In order to justify the significant benefit of the proposed product over existing authorised medicinal products for narcolepsy, the sponsor is invited to further justify:

– how data obtained in the preclinical model would support the assumed clinical advantage of the proposed product in narcoleptic patients *versus* the currently authorized products;

– the relevance of the results on DREM phases in the preclinical model of the condition to the intended significant benefit of the proposed product;

– the clinical relevance of the results showed in healthy sleep deprived subjects to the demonstration of significant benefit in narcoleptic patients.

In the written response, and during an oral explanation before the Committee on 7 September 2016, the sponsor further clarified the preclinical and clinical data presented in

the application. The COMP considered that at the present stage there was not sufficient evidence to support an assumption of significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 September 2016, prior to final opinion.

2.1.10. A non-covalent trimer of tumor necrosis factor fused to an antibody specific to the extra-domain B of fibronectin in single-chain variable fragment format - EMA/OD/108/16

Philogen S.p.A.; Treatment of soft tissue sarcoma

COMP coordinator: Katerina Kopečková

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 results obtained with F8muTNF and how they can be extrapolated to the proposed product;

– the methodology of the *in vivo* xenograft model and why doxorubicin did not reduce tumour growth;

– the results of PH-L19TNFDOXO-01/12, and how the observed effects can be contextualised in order to understand the treatment effect of the proposed product versus doxorubicin.

- Significant benefit

The sponsor is invited to discuss the target patient population (naïve or recurrent) and where their treatment fits into the current ESMO treatment guideline. Furthermore, the sponsor is invited to clarify the significant benefit in the envisaged target patient population and discuss those products that are considered authorised for the envisaged patient population.

In the written response, the sponsor provided additional preliminary clinical data from the ongoing clinical development with the product, where it is used in combination with doxorubicin. The data demonstrated that patients, who failed previous treatments including authorised doxorubicin and ifosfamide, responded to treatment. Furthermore progression free survival data compared favourably with published literature on patients receiving doxorubicin alone. In conclusion, the COMP considered that this is sufficient evidence to support the assumption of medical plausibility for the purpose of orphan designation. The COMP also established that this preliminary clinical data was sufficient to support the assumption of significant benefit in patients who failed previous treatments including authorised treatments. The COMP strongly recommends the sponsor to request protocol assistance and consult the COMP with a significant benefit question.

Following review of the application by the Committee, it was agreed to broaden/rename the active substance to a non-covalent trimer of tumour necrosis factor fused to an antibody specific to the extra-domain B of fibronectin in single-chain variable fragment format.

The Committee agreed that the condition, 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 a non-covalent trimer of tumour necrosis factor fused to an antibody specific to the extra-domain B of fibronectin in single-chain variable fragment format was considered justified based on preliminary clinical data demonstrating responses and improvements in progression-free survival in patients affected by the condition that had received previous treatments.

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 2.8 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 a non-covalent trimer of tumour necrosis factor fused to an antibody specific to the extra-domain B of fibronectin in single-chain variable fragment format will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data demonstrating responses and improvements in progression-free survival in patients affected by the condition that had received previous treatments including authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for a non-covalent trimer of tumour necrosis factor fused to an antibody specific to the extra-domain B of fibronectin in single-chain variable fragment format, for treatment of soft tissue sarcoma, was adopted by consensus.

2.1.11. - EMA/OD/105/16

Treatment of progressive multifocal leukoencephalopathy

Action: For information

Documents tabled:
Withdrawal request of 11 August 2016

2.1.12. Radio-iodinated (131I) anti-CD45 murine monoclonal antibody - EMA/OD/090/16

Wainwright Associates Ltd; Treatment in haematopoietic stem cell transplantation

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 sponsor could consider amending the indication to “treatment in haematopoietic stem cell transplantation”, especially if development is not only foreseen in acute myeloid

leukaemia. In this context, the sponsor is asked to place the product into consensus treatment algorithms.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of acute myeloid leukaemia, the sponsor should further contextualise the outcome data of clinical study to support the assumption of medical plausibility. The sponsor is asked to provide a discussion of the published literature and compare to the 1 year outcomes of the trial.

- Significant benefit

The sponsor should provide further information on the enrolled patient population of clinical study, especially with regards the eligibility for non-intensive treatment regimens.

In the written response, and during an oral explanation before the Committee on 7 September 2016, the sponsor agreed to the proposal of the COMP to amend the orphan indication to “treatment in haematopoietic stem cell transplantation” based on the mechanism of action. Regarding the medical plausibility, the sponsor provided a literature overview on survival of patients that are similar to the patients enrolled in the presented clinical trials. The overall survival outcome of the patients receiving the proposed product compared favourably to the overall survival that was reported in the literature. The COMP considered this to be sufficient evidence to support medical plausibility for the purpose of orphan designation.

In addition, the sponsor clarified that the presented clinical trial has enrolled patients that are considered non-eligible for intensive conditioning treatments above 50 years of age as this is established as the upper limit for the eligibility for allogeneic stem cell transplantation. The COMP accepted the argumentation as sufficient to establish significant benefit on the grounds of clinically relevant advantage in patients receiving allogeneic stem cell transplantation and non-myeloablative conditioning regimens. For the demonstration of significant benefit at the time of marketing authorisation, the COMP strongly recommended the sponsor to request protocol assistance with the consultation of the COMP on significant benefit.

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

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

The intention to treat the condition with the medicinal product containing radio-iodinated (131I) anti-CD45 murine monoclonal antibody was considered justified based on treatment-related improvements in survival of patients affected by the condition.

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

The condition was estimated to be occurring in approximately 1 in 10,000 persons per year 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 radio-iodinated (^{131}I) anti-CD45 murine monoclonal antibody will be of significant benefit to those affected by the condition. The

sponsor has provided preliminary clinical data that demonstrate improvement in overall survival in relapsed and refractory patients after the product is added to the current best standard of non-myeloablative care previous to haematopoietic stem cell transplantation. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for radio-iodinated (^{131}I) anti-CD45 murine monoclonal antibody, for treatment in haematopoietic stem cell transplantation, was adopted by consensus.

2.1.13. Xenon - EMA/OD/109/16

Neuroprotexeon Ltd; Treatment of ischaemia reperfusion injury associated with cardiac arrest

COMP coordinator: Martin Možina

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

- Intention to treat

In order to more clearly define the proposed condition, the sponsor is invited to further elaborate on the multi-organ dimension of the condition and on the pathophysiology of the condition in relation to the ischemia and reperfusion phases.

- Number of people affected

In order to justify the proposed incidence of the condition the sponsor should further elaborate on the incidence of in-hospital cardiac arrest.

In the written response, the sponsor supported the multi-organ dimension of the proposed condition with published data and the main pathogenic events following cardiac arrest and resuscitation in relation to ischemic and reperfusion damage. As the scope of the question asked to the sponsor was to justify the definition of ischemia reperfusion injury and to demonstrate that the damage is widespread rather than just neurological, the COMP was satisfied with the answer.

The sponsor presented additional data from the literature and from registries from three European countries, concluding with an estimate of incidence of 1.58 in 10,000. Including the out of hospital cardiac arrest incidence, previously reported, the COMP concluded that with the currently available data, the incidence of ischemia reperfusion injury associated with cardiac arrest can be estimated to be less than 4 in 10,000.

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of ischaemia reperfusion injury associated with cardiac arrest.

The Committee agreed that the condition, ischaemia reperfusion injury associated with cardiac arrest, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing xenon was considered justified based on clinical data showing improvement of neurological damage measured by brain magnetic resonance in patients treated with the proposed product used in combination with hypothermia. In addition improved survival was shown in a clinically relevant sub-population of treated patients.

The condition is life-threatening and chronically debilitating due to the damage of multiple organs including brain, heart and kidney, among others. Mortality in patients resuscitated

from cardiac arrest can be up to 50% and a significant amount of patients remain comatose.

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

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

A positive opinion for xenon, for treatment of ischaemia reperfusion injury associated with cardiac arrest, was adopted by consensus.

2.1.14. - EMA/OD/126/16

Treatment of Duchenne muscular dystrophy

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 provided bibliographical application on the product for the treatment of DMD is considered to be incomplete. To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Duchenne muscular dystrophy, the sponsor should provide an appropriate literature overview of all preclinical and clinical data that discusses the efficacy of the product in the proposed condition. Please specifically comment on the published literature that contradicts the findings of presented preclinical study.

- Significant benefit

Significant benefit cannot be established without a demonstration of medical plausibility. As described above, the sponsor should provide an appropriate literature overview of all preclinical and clinical data that discusses the efficacy and/or significant benefit of the product in the proposed condition.

In the written response, and during an oral explanation before the Committee on 7 September 2016, the sponsor presented bibliographical data and discussed the shortcomings of the studies in which the product did not show efficacy. The COMP considered that the bibliographical evidence to support medical plausibility for the treatment of DMD with the product was not sufficient at the time of submission. The sponsor was recommended to generate further data to support medical plausibility in the future. In light of these issues, significant benefit was not further discussed.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 September 2016, prior to final opinion.

2.1.15. (E)-(6-((N-methyl-((3-methylbenzofuran-2-yl) methyl)amino)-3-oxoprop-1-en-1-yl)-2-oxo-3,4-dihydro- 1,8-naphthyridin-1(2H)-yl)methyl phosphate, bis ethanolamine salt - EMA/OD/123/16

Voisin Consulting S.A.R.L.; Treatment of osteomyelitis

COMP coordinator: Dinko Vitezic

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

- Intention to diagnose, prevent or treat

The sponsor presented data to support the use of a product, which is expected to work only in osteomyelitis caused by Staphylococcus infections. The sponsor presented a brief description of *in vitro* data to support product specificity and preclinical *in vivo* data to demonstrate the efficacy in the condition. Detailed information on the nature of resistant strains screened was not included. With regards to *in vivo* studies, information on bacterial load in the bone and functional, clinically relevant endpoints were not included.

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

– the results obtained *in vitro* on Staphylococcal and non-Staphylococcal bacterial stains and the nature of resistances screened,

– the results obtained in preclinical models of osteomyelitis, and the interpretation of the results obtained in the experiments.

- Number of people affected

The sponsor estimated the incidence of osteomyelitis based on hospital registries and literature. It is, however, not clear, whether all types of osteomyelitis, including non-infectious osteomyelitis was included in this calculation.

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".

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

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.

- Significant benefit

The sponsor presented data to demonstrate the improved efficacy of the product compared to vancomycin. Other antibiotics authorised for the treatment of the condition were not discussed and no data about the incidence of resistance to these alternative options was included.

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

In the written response, and during an oral explanation before the Committee on 8 September 2016, the sponsor provided additional data including details of resistant bacterial clones that were successfully targeted by the proposed product. The sponsor clarified that the product would only be expected to have activity in staphylococcal infection and would not inhibit the growth of other families of bacteria. The sponsor also provided additional evidence to support the notion that the active substance penetrates into the bone. With

regards to the prevalence calculation the sponsor provided a sensitivity analysis, which was methodologically sound and further supported the original prevalence estimate. Further, the sponsor clarified that the product is intended as first line treatment in methicillin-resistant *Staphylococcus Aureus* and other multi-resistant *Staphylococcus* infection related osteomyelitis. The committee was satisfied with the written responses and the oral hearing was cancelled.

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

The intention to treat the condition with the medicinal product containing (E)-(6-((N-methyl-((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-2-oxo-3,4-dihydro-1,8-naphthyridin-1(2H)-yl)methyl phosphate, bis ethanolamine salt was considered justified based on preclinical data in a model of the condition demonstrating significant reduction of bacterial counts in infections caused by methicillin-resistant *Staphylococcus aureus*.

The condition is life-threatening due to sepsis and chronically debilitating due to infectious destruction of the bone leading to disability.

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 (E)-(6-((N-methyl-((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-2-oxo-3,4-dihydro-1,8-naphthyridin-1(2H)-yl)methyl phosphate, bis ethanolamine salt will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate that the product inhibits the growth of resistant strains of bacteria and is more potent than the authorised first line therapy for the treatment of osteomyelitis caused by methicillin resistant *Staphylococcus aureus*. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (E)-(6-((N-methyl-((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-2-oxo-3,4-dihydro-1,8-naphthyridin-1(2H)-yl)methyl phosphate, bis ethanolamine salt, for treatment of osteomyelitis, was adopted by consensus.

2.1.16. Venetoclax - EMA/OD/121/16

Abbvie Ltd.; Treatment of multiple myeloma

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:

- Number of people affected

The sponsor has provided a partial prevalence for the condition. The COMP no longer accepts partial prevalence for this condition so they should calculate the point prevalence.

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.

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 proposed significant benefit based on a clinically relevant advantage in patients who are relapsed/refractory to first line treatment. 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 Phase I study to justify the assumption of significant benefit over authorised medicinal products in the same patient population for the proposed orphan indication.

The sponsor should also further elaborate on the importance of treatment considerations regarding the multiple myeloma population with the t(11;14) that was described as responding in the Phase I study.

In the written response, and during an oral explanation before the Committee on 8 September 2016, the sponsor provided a revised, more conservative prevalence calculation. The COMP accepted this higher estimate for the prevalence of multiple myeloma.

Regarding the significant benefit the COMP discussed the merits of the results in the multiple myeloma patients with t(11;14) translocations and whether this could constitute a clinically relevant advantage. Recently published data indicate that MM cells with the t(11;14) translocation are particularly sensitive to BCL-2 inhibition, as these cells have an affinity to have higher BCL-2 and low MCL-1 levels (Bodet 2011; Touzeau 2014). The COMP rejected this argument as it was felt that the target patient population identified represents a medium risk and not a high risk group. The COMP however felt that preliminary clinical data could support the assumption of a clinically relevant advantage in patients who were relapsed refractory to previous heavy pre-treatment. The COMP strongly advised the sponsor to come for Protocol Assistance and seek guidance regarding significant benefit as there have been many new products authorised for use in this condition.

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

The intention to treat the condition with the medicinal product containing venetoclax was considered justified based on preliminary clinical data where patients who were relapsed/refractory to multiple myeloma showed a response.

The condition is chronically debilitating and life threatening due to the poor survival of patients with relapsed or refractory disease.

The condition was estimated to be affecting approximately 3.2 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 venetoclax will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate a

response in heavily pre-treated relapsed/refractory patients. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for venetoclax, for treatment of multiple myeloma, was adopted by consensus.

2.1.17. Synthetic 15 amino acid macrocyclic peptide acylated with a polyethyleneglycol palmitoylated linker - EMA/OD/107/16

Ra Europe Limited; Treatment of paroxysmal nocturnal haemoglobinuria

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:

- Number of people affected

It appears that the sponsor retrieved only very limited information on the prevalence of the condition. In addition the sponsor has not provided a final prevalence as a figure in 10,000 in the EU.

The sponsor is therefore invited to re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition covering as many as possible EU regions, and to provide a final figure.

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 claims a potential better efficacy of the proposed product vs. eculizumab however no data are presented to support this claim. The sponsor should clarify on which bases a better efficacy of the proposed product could be assumed, and to present and discuss any data supporting this assumption.

The sponsor showed the results of an *in vitro* assay where the proposed product significantly reduced *ex vivo* haemolysis of red blood cells from a patient with eculizumab resistance. More details should be provided on this case, possibly including data showing the lack of inhibition of haemolysis by eculizumab in this patient.

Finally, the sponsor also claims a major contribution to patient care based on the subcutaneous administration route of the proposed product vs. the intravenous administration of eculizumab. However in order to translate into a major contribution to patient care, a potential advantage linked to subcutaneous administration should be put in perspective with other aspects influencing the burden of care, such as dosing schedule, and a comparable efficacy of eculizumab. The sponsor is therefore invited to further discuss the claims of major contribution to patient care.

In the written response, the sponsor elaborated on the assumed significant benefit of the proposed product vs. eculizumab, currently authorized for the treatment of the condition. The sponsor also recalculated the prevalence of the condition. The arguments for significant benefit were discussed and the COMP found the arguments of improved efficacy due to reduction of breakthrough haemolysis unsupported at this stage. The argument of major

contribution to patient care was, however accepted based on the outcome of the survey and literature demonstrating patient preference of a self-administered product over infused one. In addition, a possibility of using the product in patients non-responding to eculizumab was appreciated. The COMP found the written responses sufficient and the oral explanation was cancelled.

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

The intention to treat the condition with the medicinal product containing synthetic 15-amino-acid macrocyclic peptide acylated with a polyethyleneglycol palmitoylated linker was considered justified based on studies showing ex vivo inhibition of complement-mediated red cell lysis with the proposed product.

The condition is chronically debilitating due to the complications of the chronic haemolysis such as abdominal pain, infection, cytopenia, and kidney malfunction, and due to the occurrence of thrombosis and haemorrhage in different organs.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing synthetic 15-amino-acid macrocyclic peptide acylated with a polyethyleneglycol palmitoylated linker will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing protection from haemolysis in a patient resistant to the currently authorised treatment. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition. In addition the product offers the possibility of self-administration while the current treatment is administered intravenously. The Committee considered that this may constitute a major contribution to patient care for the patients affected by the condition.

A positive opinion for synthetic 15-amino-acid macrocyclic peptide acylated with a polyethyleneglycol palmitoylated linker, for treatment of paroxysmal nocturnal haemoglobinuria, was adopted by consensus.

2.1.18. - EMA/OD/092/16

Treatment of haemophilia B

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 proposing significant benefit based on major contribution to patient care and improved safety.

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

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 8 September 2016, the sponsor did not submit any additional data to support the claim for significant benefit. The sponsor discussed the bridging exercise with the data submitted in a parallel submission for haemophilia A. The COMP was of the opinion that the proposed rationale was insufficient to support the significant benefit and that preliminary pre-clinical or clinical data was needed to support the basis of the claim by the sponsor.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 September 2016, prior to final opinion.

2.1.19. Human monoclonal IgG1 antibody against tissue factor pathway inhibitor - EMA/OD/093/16

Pfizer Limited; Treatment of haemophilia A

COMP coordinator: Armando Magrelli

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

- Significant benefit

The sponsor is proposing significant benefit based on major contribution to patient care and improved safety.

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

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 8 September 2016, the sponsor elaborated the major contribution to patient care of using a subcutaneous delivery system within the context of a similar efficacy profile to products which have recently been authorised in the EU. Currently authorised products are intravenous formulations and even with recently authorised products with extended half-life dosing is done to 2-3 times per week. The COMP considered that the assumption of a major contribution to patient care could be made based on data indicating that the projected efficacious concentration can be maintained on a once weekly subcutaneous dosing schedule.

The Committee agreed that the condition, 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 human monoclonal IgGI antibody against tissue factor pathway inhibitor was considered justified based on pre-clinical *in vivo* data in a valid mouse model of the condition showing improved bleeding times.

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

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing human monoclonal IgGI antibody against tissue factor pathway inhibitor will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate the effectiveness of a sub-cutaneous formulation in the treatment of the condition. The Committee considered that this constitutes a major contribution to patient care.

A positive opinion for human monoclonal IgGI antibody against tissue factor pathway inhibitor, for treatment of haemophilia A, was adopted by consensus.

2.1.20. 2-(1, 5-Dimethyl-3-phenyl-1H-pyrrol-2-yl)- N-{4-[4-(5-fluoro-pyrimidin-2-yl) piperazin- 1-yl]-phenyl}-2-oxo-acetamide - EMA/OD/104/16

F2G Ltd; Treatment of invasive aspergillosis

COMP coordinator: Olimpia Neagu

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

- Number of people affected

The sponsor should re-calculate the prevalence estimate as it appears to be an underestimate of the incidence. 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.

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 provided a revised prevalence calculation and the COMP accepted the new estimate for the purpose of designation.

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

The intention to treat the condition with the medicinal product containing 2-(1,5-dimethyl-3-phenyl-1H-pyrrol-2-yl)-N-{4-[4-(5-fluoro-pyrimidin-2-yl)piperazin-1-yl]-phenyl}-2-oxo-acetamide was considered justified based on pre-clinical *in vivo* data showing response in a model of the condition using azole resistant aspergillosis.

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.

The condition was estimated to be affecting approximately 1.7 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 2-(1,5-dimethyl-3-phenyl-1H-pyrrol-2-yl)-N-{4-[4-(5-fluoro-pyrimidin-2-yl)piperazin-1-yl]-phenyl}-2-oxo-acetamide will be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical *in vivo* data that demonstrate a response in invasive aspergillosis infections which were resistant to azoles. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 2-(1,5-dimethyl-3-phenyl-1H-pyrrol-2-yl)-N-{4-[4-(5-fluoro-pyrimidin-2-yl)piperazin-1-yl]-phenyl}-2-oxo-acetamide, for treatment of invasive aspergillosis, was adopted by consensus.

2.1.21. Autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19 - EMA/OD/087/16

Novartis Europharm Limited; Treatment of diffuse large B cell lymphoma

COMP coordinator: Jens Ersbøll

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

According to recent sources the prevalence of diffuse large B cell lymphoma would appear higher than what was provided by the sponsor.

The sponsor should therefore re-calculate the prevalence estimate based on relevant recent epidemiological studies and registers for the proposed orphan condition, and taking into account the maximum duration of the disease at the present time.

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 addressed the COMP request for recalculating the prevalence taking into account longer duration of the disease than the five-year survival point. The sponsor concluded with 10-year prevalence, which was accepted by the COMP and approximated to less than 4.5 in 10,000.

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

The intention to treat the condition with the medicinal product containing autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19 was considered justified based on preclinical data and preliminary clinical data showing antitumor activity of the proposed product.

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

The condition was estimated to be affecting less than 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 autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19 will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing favourable responses in patients affected by the condition relapsing from previous treatments. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19, for treatment of diffuse large B-cell lymphoma, was adopted by consensus.

2.1.22. Venetoclax - EMA/OD/122/16

Abbvie Ltd.; Treatment of diffuse large B-cell 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:

- Number of people affected

The sponsor appears to have provided an under-estimation of the prevalence of the condition at 10yrs. The sponsor should re-calculate the prevalence estimate based on relevant epidemiological studies such as the Smith et al. publication from HMRN 2015 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, and during an oral explanation before the Committee on 6 September 2016, the sponsor submitted a recalculation of the prevalence. The COMP decided to accept the new estimate and approximated the value to 4 in 10,000 for the purpose of orphan designation.

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

The intention to treat the condition with the medicinal product containing venetoclax was considered justified based on clinical data in patients who had complete or partial response.

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

The condition was estimated to be affecting approximately 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 venetoclax will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate a response in patients who were relapsed and refractory to first line medicines. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for venetoclax, for treatment of diffuse large B-cell lymphoma, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/132/16

Treatment of X-linked adrenoleukodystrophy

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.

2.2.2. Acebutolol hydrochloride - EMA/OD/128/16

Therapicon Srl; Treatment of Smith-Magenis syndrome

COMP coordinator: Ingeborg Barisic/Giuseppe Capovilla

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

The intention to treat the condition with the medicinal product containing acebutolol hydrochloride was considered justified based on data from the published literature reporting improvement in sleep disturbances of patients affected by the condition when used in combination with melatonin.

The condition is chronically debilitating due to failure to thrive, mental retardation, sleep disturbance, craniofacial and skeletal anomalies, self-injurious and attention-seeking behaviours, and speech and motor delay.

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.

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 acebutolol hydrochloride, for treatment of Smith-Magenis syndrome, was adopted by consensus.

2.2.3. Adeno-associated viral vector serotype 5 containing the human *RLBP1* gene - EMA/OD/146/16

HORAMA SAS; Treatment of retinitis pigmentosa

COMP coordinator: Armando Magrelli

Following review of the application by the Committee, it was agreed to broaden/rename the indication from retinitis punctata albescens to treatment of retinitis pigmentosa.

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

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 5 containing the human RLBP1 gene was considered justified based on preclinical data showing improvement in measures of visual response in valid models of the condition.

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

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.

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 adeno-associated viral vector serotype 5 containing the human *RLBP1* gene, for treatment of retinitis pigmentosa, was adopted by consensus.

2.2.4. - EMA/OD/133/16

Treatment of Crigler-Najjar syndrome

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

2.2.5. Adeno-associated virus serotype 2/2 vector containing a gene encoding the channelrhodopsin-2 protein - EMA/OD/158/16

Alacrita LLP; Treatment of retinitis pigmentosa

COMP coordinator: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 2/2 containing a gene encoding the channelrhodopsin-2 protein was considered justified based on literature data in preclinical models of the condition showing restoration of normal response to light stimuli with the proposed product.

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

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.

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 adeno-associated viral vector serotype 2/2 containing a gene encoding the channelrhodopsin-2 protein, for treatment of retinitis pigmentosa, was adopted by consensus.

2.2.6. - EMA/OD/151/16

Treatment of cytomegalovirus infection in patients with impaired cell-mediated immunity

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.

2.2.7. - EMA/OD/149/16

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.

2.2.8. - EMA/OD/167/15

Treatment of acquired Factor Xa coagulopathy associated with severe, life threatening bleeding in a critical organ or compartment

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.

2.2.9. - EMA/OD/141/16

Treatment of hypoxic-ischaemic encephalopathy

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. - EMA/OD/139/16

Treatment of IgA nephropathy

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.

2.2.11. Carbamazepine - EMA/OD/148/16

University of Newcastle upon Tyne; Treatment of metaphyseal chondrodysplasia, Schmid type

COMP coordinator: Ingeborg Barisic

The Committee agreed that the condition, metaphyseal chondrodysplasia, Schmid type, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing carbamazepine was considered justified based on preclinical data showing improvement of skeletal dysplasia in valid models of the condition.

The condition is chronically debilitating due to the development of hip and knee deformity with associated pain and waddling gait leading in some cases to the need of surgical procedures.

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 carbamazepine, for treatment of metaphyseal chondrodysplasia, Schmid type, was adopted by consensus.

2.2.12. Chemically modified human recombinant sulfamidase - EMA/OD/142/16

Swedish Orphan Biovitrum AB (publ); Treatment of mucopolysaccharidosis type IIIA (Sanfilippo A syndrome)

COMP coordinator: Dinah Duarte/Armando Magrelli

The Committee agreed that the condition, mucopolysaccharidosis type IIIA (Sanfilippo A syndrome), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing chemically modified human recombinant sulfamidase was considered justified based on preclinical data demonstrating improvement of motor function, reduction of heparan sulphate levels and improved brain histology.

The condition is life-threatening and chronically debilitating due to frequent infections and neurocognitive delay which progresses to profound mental disability and vegetative state. The survival of the patients is limited to 20-30 years.

The condition was estimated to be affecting approximately 0.1 in 10,000 persons in the European Union, at the time the application was made.

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 chemically modified human recombinant sulfamidase, for treatment of mucopolysaccharidosis type IIIA (Sanfilippo A syndrome), was adopted by consensus.

2.2.13. - EMA/OD/103/16

Treatment of ovarian cancer

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

2.2.14. Crenolanib besylate - EMA/OD/129/16

Arog Pharmaceuticals Europe Ltd; Treatment of soft tissue sarcoma

COMP coordinator: Brigitte Bloechl-Daum

The Committee agreed that the condition, 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 crenolanib besylate was considered justified based on clinical data in patients with the condition.

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 2.8 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 crenolanib besylate will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that in pretreated patients with advanced soft tissue sarcoma a response can be achieved. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for crenolanib besylate, for treatment of soft tissue sarcoma, was adopted by consensus.

2.2.15. Crenolanib besylate - EMA/OD/147/16

Arog Pharmaceuticals Europe Ltd; Treatment of acute myeloid leukemia

COMP coordinator: Bożenna Dembowska-Bagińska

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 crenolanib besylate was considered justified based on preliminary clinical data in patients with the condition.

The condition is life-threatening due to its rapid progression and its 5 year survival of approximately 22% with current treatments and chronically debilitating due to the consequences of bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections.

The condition 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 crenolanib besylate will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that the sponsor's product can provide a complete response in patients with relapsed/refractory acute myeloid leukaemia. Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for crenolanib besylate, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.2.16. - EMA/OD/157/16

Treatment of ovarian cancer

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

2.2.17. Exendin (9-39) - EMA/OD/065/16

Eiger Biopharmaceuticals Europe Limited; Treatment of noninsulinoma pancreatogenous hypoglycaemia syndrome

COMP coordinator: Martin Možina

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

The intention to treat the condition with the medicinal product containing exendin (9-39) was considered justified based on clinical data in patients with the condition.

The condition is life-threatening and chronically debilitating due to the repetitive nature of the associated hypoglycaemia which can be severe leading to neuroglycopenia resulting in dangerous and life-threatening outcomes, such as seizures, loss of consciousness and brain damage.

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

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

A positive opinion for exendin (9-39), for treatment of noninsulinoma pancreatogenous hypoglycaemia syndrome, was adopted by consensus.

2.2.18. Fenretinide - EMA/OD/131/16

Clinipace GmbH; Treatment of non-cutaneous mature T/NK-cell lymphoma

COMP coordinator: Katerina Kopečková

The Committee agreed that the condition, peripheral 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 demonstrating that patients affected by the condition responded to treatment.

The condition is life-threatening and chronically debilitating due to poor response to therapy and high rate of relapses. Clinical presentation and course vary from an indolent clinical behaviour for years in milder subtypes, to fulminant disease in aggressive sub-types.

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 fenretinide will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients, who failed previous treatments including authorised products, responded to treatment. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.19. Hematopoietic stem cells modified with a lentiviral vector containing the *CD18* gene - EMA/OD/154/16

Centro de Investigación Biomédica en Red (CIBER); Treatment of leukocyte adhesion deficiency type I

COMP coordinator: Armando Magrelli

Following review of the application by the Committee, it was agreed to broaden/rename the active substance to haematopoietic stem cells modified with a lentiviral vector containing the *CD18* gene.

The Committee agreed that the condition, leukocyte adhesion deficiency type I, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing haematopoietic stem cells modified with a lentiviral vector containing the CD18 gene was considered justified based on a valid pre-clinical *in vivo* model which shows an improvement in CD18 expression and restoration of neutrophil migration in inflammation models, which is the main reason for the immunodeficiency.

The condition is life-threatening and chronically debilitating due to the fact that approximately 75% of children with the severe form of the condition die before the age of 2 years because of extensive bacterial infections, unless they receive successful haematopoietic stem cell transplantation. Prognosis is better for patients with a moderate form of the condition. In those patients recurrent acute infections can be managed with antibiotics, but for some patients, a prophylactic and continuous administration of antibiotics is required. Nevertheless, quality of life remains poor and only 25% of patients survive to the age of 40 years.

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 haematopoietic stem cells modified with a lentiviral vector containing the *CD18* gene, for treatment of leukocyte adhesion deficiency type I, was adopted by consensus.

2.2.20. - EMA/OD/136/16

Treatment of cutaneous T-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.

2.2.21. - EMA/OD/135/16

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 October meeting.

2.2.22. - EMA/OD/160/16

Treatment of Merkel cell carcinoma

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

2.2.23. - EMA/OD/083/16

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 October meeting.

2.2.24. Melatonin - EMA/OD/127/16

Therapicon Srl; Treatment of Smith-Magenis syndrome

COMP coordinator: Ingeborg Barisic/Giuseppe Capovilla

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

The intention to treat the condition with the medicinal product containing melatonin was considered justified based on data from the published literature reporting improvement in sleep disturbances of patients affected by the condition when used in combination with acebutolol hydrochloride.

The condition is chronically debilitating due to failure to thrive, mental retardation, sleep disturbance, craniofacial and skeletal anomalies, self-injurious and attention-seeking behaviours, and speech and motor delay.

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.

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

A positive opinion for melatonin, for treatment of Smith-Magenis syndrome, was adopted by consensus.

2.2.25. - EMA/OD/145/16

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.

2.2.26. - EMA/OD/138/16

Treatment of acute pancreatitis

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.

2.2.27. - EMA/OD/137/16

Treatment of opioid poisoning

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.

2.2.28. - EMA/OD/140/16

Treatment of spinal cord injury

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.

2.2.29. P-ethoxy growth factor receptor-bound protein 2 (Grb2) antisense oligonucleotide - EMA/OD/155/16

Clinical Network Services (UK) Ltd; Treatment of acute myeloid leukaemia

COMP coordinator: Frauke Naumann-Winter

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 P-ethoxy growth factor receptor-bound protein 2 antisense oligonucleotide was considered justified based on preclinical data showing increased survival with the proposed product.

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

The condition was estimated to be affecting approximately 1.5 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 P-ethoxy growth factor receptor-bound protein 2 antisense oligonucleotide will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing favourable responses in combination with a current treatment regimen in patients relapsing from previous treatments. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by acute myeloid leukaemia.

A positive opinion for P-ethoxy growth factor receptor-bound protein 2 antisense oligonucleotide for treatment of acute myeloid leukaemia, was adopted by consensus.

2.2.30. - EMA/OD/114/16

Treatment of sudden sensorineural hearing loss

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.

2.2.31. Recombinant adeno-associated viral vector encoding a human micro-dystrophin gene under the control of a muscle specific promoter - EMA/OD/161/16

Pharma Gateway AB; Treatment of Duchenne muscular dystrophy

COMP coordinator: Giuseppe Capovilla/Armando Magrelli

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 condition with the medicinal product containing recombinant adeno-associated viral vector encoding a human micro-dystrophin gene under the control of a muscle specific promoter was considered justified based on preclinical data demonstrating improved muscle function.

The condition is life-threatening and chronically debilitating due to progressive weakness occurring throughout the proximal musculature affecting the muscles of the hips, thighs, pelvic area and shoulders and eventually affecting all voluntary muscles. This is followed by dilated cardiomyopathy and cardiac output decrease, leading to terminal respiratory or cardiac failure often by late adolescence. Patients rarely live beyond the age of 30 years.

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 adeno-associated viral vector encoding a human micro-dystrophin gene under the control of a muscle specific promoter will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data *in vivo* models of the disease that demonstrate that the use of the product caused a durable improvement of muscle function. The mechanism of action of the active substance should allow treatment independently of the specific type of mutation leading to the disease. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for recombinant adeno-associated viral vector encoding a human micro-dystrophin gene under the control of a muscle specific promoter, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

2.2.32. Self-complementary AAV9 vector containing the *SGSH* gene - EMA/OD/164/16

Ser-mes Planificación SL; Treatment of Mucopolysaccharidosis type IIIA (Sanfilippo A syndrome)

COMP coordinator: Ingeborg Barisic

Following review of the application by the Committee, it was agreed to broaden/rename the active substance to self-complementary adeno-associated viral vector serotype 9 containing the *SGSH* gene.

The Committee agreed that the condition, mucopolysaccharidosis type IIIA (Sanfilippo A syndrome), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing self-complementary adeno-associated viral vector serotype 9 containing the SGSH gene was considered justified based on pre-clinical *in vivo* data showing improvement in neurological symptoms and survival.

The condition is chronically debilitating and life-threatening, in particular due to neurologic involvement leading to poor development of language and motor skills, hyperactivity, overall delay in development and reduction of life expectancy.

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 self-complementary adeno-associated viral vector serotype 9 containing the *SGSH* gene, for treatment of mucopolysaccharidosis type IIIA (Sanfilippo A syndrome), was adopted by consensus.

2.2.33. - EMA/OD/144/16

Treatment of sickle cell 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.

2.2.34. Tadekinig alfa - EMA/OD/150/16

Coté Orphan Consulting UK Limited; Treatment of haemophagocytic lymphohistiocytosis

COMP coordinator: Bożenna Dembowska-Bagińska

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

The intention to treat the condition with the medicinal product containing tadekinig alfa was considered justified based on preclinical data demonstrating an improvement in liver histology and reduction of inflammation.

The condition is life-threatening and debilitating due to poor overall survival (21% 5-year), pancytopenia and neurocognitive deficits.

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.

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 tadekinig alfa, for treatment of haemophagocytic lymphohistiocytosis, was adopted by consensus.

2.2.35. Tetrofosmin - EMA/OD/143/16

ProActina; Diagnosis of glioma

COMP coordinator: Michel Hoffmann/Ingrid Wang

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

The intention to diagnose the condition with the medicinal product containing tetrofosmin was considered justified based on clinical data identifying patients with recurrent glioma.

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

In addition, although satisfactory methods of 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 tetrofosmin will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate additional imaging capacity in advanced recurrent glioblastoma patients. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for tetrofosmin, for diagnosis of glioma, was adopted by consensus.

2.2.36. Ubiquinol - EMA/OD/153/16

Centro de Investigación Biomédica en Red (CIBER); Treatment of coenzyme Q10 deficiency syndrome

COMP coordinator: Irena Bradinova/Pauline Evers

The Committee agreed that the condition, primary coenzyme Q_{10} deficiency syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing ubiquinol was considered justified based on preclinical data in a valid model of the disease showing improvement in physical activity and increased coenzyme Q10 concentration in muscles and liver. Further clinical data showing increased plasma levels of coenzyme Q10 and improvement in the ataxia score in patients responding poorly to ubiquinone was provided.

The condition is life-threatening and chronically debilitating due to the progressive nature of the disorder causing renal failure and encephalopathy.

The condition was estimated to be affecting approximately 0.1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ubiquinol will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that ubiquinol has a higher bioavailability compared to the authorised treatment. This higher bioavailability allows for the administration of lower oral doses which may translate into improved compliance. In addition the product can be used in patients not responding to the authorised product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for ubiquinol, for treatment of primary coenzyme Q_{10} deficiency syndrome, was adopted by consensus.

2.2.37. - EMA/OD/159/16

Treatment of ovarian cancer

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

2.2.38. - EMA/OD/162/16

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 respond in writing before the Committee at the October 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 30 applications submitted.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 24 applications for orphan designation.

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

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of soft tissue sarcoma

The Committee was briefed on the significant benefit issues.

[Post-meeting note: The COMP adopted the proposed answers by written procedure following its September meeting.]

3.1.2. -

Treatment of tuberculosis

The discussion was postponed.

3.2. Finalised letters

3.2.1. –

Treatment of microscopic polyangiitis

The finalised letter was circulated for information.

3.2.2. -

Treatment of granulomatosis with polyangiitis

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment in haematopoietic stem cell transplantation

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. Onivyde - irinotecan - EMA/OD/051/11, EU/3/11/933, EMEA/H/C/004125

Baxter Innovations GmbH; Treatment of pancreatic cancer

COMP coordinator: Josep Torrent-Farnell / Brigitte Bloechl-Daum

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

The sponsor is invited to further discuss the significant benefit, including providing additional details and discussion on the previous treatments of the patients in study NAPOLI-1. The clinical relevance of the OS improvement in absolute terms should also be addressed with regards to the benefit this brings to the patients.

In its written response, and during an oral explanation before the Committee on 7 September 2016, the sponsor discussed the grounds for the significant benefit of Onivyde in pancreatic cancer. The main argument of the sponsor was based on the results of the NAPOLI I trial in patients who had progressed following gemcitabine therapy, showing that the combination of Onivyde with 5-FU/LV resulted in a median 1.9 month survival benefit in favour of the experimental arm (6.1 vs 4.2 months, HR 0.67, p=0.0122) as compared to the 5-FU/LV regimen alone. The improvement in survival was accepted as clinically meaningful by the CHMP as part of the assessment for granting the marketing authorisation of Onivyde. The COMP discussed whether such change would be considered relevant for the purpose of significant benefit. The sponsor supported the improved efficacy with data showing that there were no detrimental effects on quality of life during the prolonged survival period obtained with Onivyde. The COMP took into account the fact that Onivyde is the first product authorised for patients who progressed following gemcitabine therapy, which per se may constitute an advantage for this patient population. It was also noted that the 1.9 months represented a nearly 33% relative increase in survival which was regarded as significant for patients.

The COMP concluded that:

The proposed therapeutic indication, treatment of metastatic adenocarcinoma of the pancreas, in combination with 5 fluorouracil (5 FU) and leucovorin (LV), in adult patients who have progressed following gemcitabine based therapy falls entirely within the scope of the orphan indication of the designated orphan medicinal product, treatment of pancreatic cancer.

The prevalence of pancreatic cancer (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be approximately 1.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

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

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that nanoliposomal irinotecan may be of potential significant benefit to those affected by the orphan condition still holds. This is based on the results of a phase III clinical trial showing statistically significant improvement of overall survival in patients treated with the proposed product in combination with 5-fluorouracil and leucovorin, who have progressed following gemcitabine based therapy. No medicinal products are currently authorised for this patient population.

An opinion not recommending the removal of Onivyde, nanoliposomal irinotecan (EU/3/11/933) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

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

4.2.1. Lartruvo – olaratumab – EMA/OD/266/14, EU/3/15/1447, EMEA/H/C/004216

Eli Lilly Nederland B.V.; Treatment of soft tissue sarcoma

COMP coordinator: Brigitte Bloechl-Daum; CHMP rapporteur: Aranzazu Sancho-Lopez; CHMP co-rapporteur: Daniela Melchiorri

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 October meeting.

[*Post-meeting note: CHMP opinion was adopted in September 2016*]

4.2.2. Ocaliva - obeticholic acid – EMEA/OD/073/09, EU/3/10/753, EMEA/H/C/004093

Intercept Italia s.r.l; Treatment of primary biliary cirrhosis

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.

Notes:
Status of the procedure at the CHMP: Expected Opinion in October 2016

4.2.3. SomaKit-TOC - edotreotide – EMA/OD/219/14, EU/3/15/1450, EMEA/H/C/004140

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

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. Venclyxto - venetoclax – EMA/OD/124/12, EMEA/H/C/004106, EU/3/12/1080

AbbVie Ltd.; Treatment of chronic lymphocytic 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.

[*Post-meeting note: CHMP Opinion postponed to October 2016*]

4.2.5. - cediranib - EMEA/H/C/004003, EU/3/14/1303, EMA/OD/059/14

AstraZeneca AB; Treatment of ovarian cancer

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

[*Post-meeting note: the marketing authorisation application was withdrawn on 19 September 2016. The product will therefore not be discussed at COMP*]

4.2.6. NINLARO - ixazomib - EMEA/H/C/003844, EU/3/12/1060, EMA/OD/110/12

Takeda Pharma A/S; Multiple myeloma

COMP coordinator: Josep Torrent-Farnell / Dinah Duarte; Re-examination Rapporteur: Sinan B. Sarac, Re-examination Co-Rapporteur: Tuomo Lapvetelainen

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.

[*Post-meeting note: CHMP re-examination opinion was adopted in September 2016*]

4.2.7. - parathyroid hormone – EMA/OD/102/13, EU/3/13/1210, EMEA/H/C/003861

NPS Pharma Holdings Limited; Treatment of hypoparathyroidism

The status of the procedure at CHMP was noted.

4.2.8. Chenodeoxycholic acid - chenodeoxycholic acid – EMA/OD/196/14, EU/3/14/1406, EMEA/H/C/004061

Sigma-tau Arzneimittel GmbH; Treatment of inborn errors of primary bile acid synthesis

COMP coordinator: Geraldine O'Dea/Ingeborg Barisic/Josep Torrent-Farnell; CHMP rapporteur: Robert James Hemmings; CHMP co-rapporteur: George Aislaitner

The sponsor will be invited to an oral explanation before the Committee at the October meeting.

[*Post-meeting note: the COMP adopted a list of issues in June 2016, the CHMP opinion was adopted in September 2016*]

4.3. On-going procedures

COMP co-ordinators were appointed for 2 applications.

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

None

6. Organisational, regulatory and methodological matters

6.1. Mandate and organisation of the COMP

6.1.1. Protocol Assistance Working Group

The working group on Protocol Assistance met on 7 September 2016.

Document(s) tabled:
Draft agenda

Draft minutes from July meeting

6.1.2. COMP Drafting Group

Cancelled

6.1.3. Preclinical Models Working Group

Cancelled

6.1.4. Recommendation on criteria for competence and expertise of COMP members

The Committee endorsed the proposal for criteria for experience and expertise of COMP members. Some additional areas of expertise were identified. The proposed criteria will be added as an annex to the nomination invitation letters to the nominating authorities. An overview of the expertise of the current committee will be prepared.

6.1.5. COMP Membership

The COMP welcomed Robert Nistico as new member representing Malta.

6.2. Coordination with EMA Scientific Committees or CMDh-v

6.2.1. PDCO/COMP Working Group

Cancelled

6.2.2. Recommendations on eligibility to PRIME – report from CHMP

Documents were circulated in MMD.

Document tabled:
PRIME eligibility requests - list of adopted outcomes July 2016

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

6.3.1. Patients' and Consumers' Organisations (PCWP) and Healthcare Professionals' Organisations (HCPWP) joint meetings

EMA workshop with patient and healthcare professional representatives about communication on medicines - 8 March 2016

EMA Human Scientific Committees 'Working Parties with Patients' and Consumers' Organisations (PCWP) and Healthcare Professionals' Organisations (HCPWP) joint meeting - 9 March 2016

EMA Human Scientific Committees 'Working Parties with Patients' and Consumers' Organisations (PCWP) and Healthcare Professionals' Organisations (HCPWP) joint meeting – Workshop on social media – 19 September 2016

EMA Human Scientific Committees 'Working Parties with Patients' and Consumers' Organisations (PCWP) and Healthcare Professionals' Organisations (HCPWP) joint meeting – 20 September 2016

Documents were circulated in MMD.

Document(s) tabled:
Report of a joint EMA workshop with patient and healthcare professional representatives about communication on medicines - 8 March 2016 (EMA/194543/2016)
Minutes of the PCWP and HCPWP joint meeting - 9 March 2016 (EMA/183905/2016
Agenda – PCWP and HCPWP joint meeting – Workshop on social media – 19 September 2016 (EMA/825257/2015)
Draft Agenda – PCWP and HCPWP joint meeting – 20 September 2016 (EMA/428004/2016)

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

EMA Human Scientific Committees' Working Parties with Patients' and Consumers' Organisations (PCWP) meeting – 14 June 2016

EMA Human Scientific Committees' Working Parties with Patients' and Consumers' Organisations (PCWP) 10th Anniversary meeting – 14 June 2016

Documents were circulated in MMD.

Document(s) tabled:
Agenda – PCWP meeting – 14 June (EMA/ 274681/2016)
Minutes - PCWP meeting – 14 June 2016 (EMA/419205/2016)
Agenda - PCWP 10th Anniversary meeting – 14 June 2016 (EMA/ 392315 /2016)

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

EMA Human Scientific Committees' Working Parties with Healthcare Professionals' Organisations (HCPWP) meeting – 15 June

Documents were circulated in MMD.

Document(s) tabled:
Agenda - HCPWP meeting – 15 June (EMA/285607/2016)
Minutes HCPWP meeting – 15 June (EMA/418148/2016)

6.4. Cooperation within the EU regulatory network

6.4.1. European Commission

None

6.5. Cooperation with International Regulators

6.5.1. Food and Drug Administration (FDA)

None

6.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

6.5.3. The Therapeutic Goods Administration (TGA), Australia

None

6.5.4. Health Canada

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

6.7.1. COMP Work Plan 2016

Documents were circulated in MMD.

Document tabled:
COMP Work Plan 2016
6-7-1 COMP Work plan tracking tool 2016

6.7.2. COMP Work Plan 2017

Documents were circulated in MMD.

Document tabled:
COMP draft Work Plan 2017

6.8. Planning and reporting

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

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

6.8.2. Overview of orphan marketing authorisations/applications

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

7. Any other business

7.1. EMA organisational adjustments presentation

EMA informed COMP on the internal organisational adjustments. The COMP noted the changes in EMA organisation.

7.2. EMA Business Pipeline activity and Horizon scanning

Documents were circulated in MMD.

7.3. EMA Workshop on scientific and regulatory challenges of genetically modified cell-based cancer immunotherapy products

The workshop will take place on 15-16 November 2016 at the EMA.

Notes:
More information available on the following links:
http://www.ema.europa.eu/docs/en_GB/document_library/Agenda/2016/08/WC500212061.pdf
http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2016/08/WC500212063.docx

7.4. Defining orphan conditions – COMP Workshop

The workshop will take place on 9 December 2016 at the EMA. The draft agenda can be found in MMD.

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 6-8 September 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	
Irena Bradinova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No restrictions applicable to this meeting	
Katerina Kopeckova	Member	Czech Republic	No restrictions applicable to this meeting	
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 *via TC*	Member	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No interests declared	
Violeta Stoyanova-Beninska	Member	Netherlands	No interests declared	
Ingrid Wang	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Martin Možina	Member	Slovenia	No interests declared	
Josep Torrent-Farnell	Member	Spain	No interests declared	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Lesley Greene	Member (Vice-Chair)	Patients' Organisation Representative	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Virginie Hivert	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Julian Isla	Expert - in person*	Patients' Organisation Representative	No interests declared	
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the agenda topics or activities they participated in.

Explanatory notes

The notes below give a brief explanation of the main sections and headings in the COMP agenda and should be read in conjunction with the agenda or the minutes.

Abbreviations / Acronyms

CHMP: Committee for Medicinal Product for Human Use
COMP: Committee for Orphan Medicinal Products
EC: European Commission
OD: Orphan Designation
PA: Protocol Assistance
PDCO: Paediatric Committee
PRAC: Pharmacovigilance and Risk Assessment Committee
SA: Scientific Advice
SAWP: Scientific Advice Working Party

Orphan Designation (*section 2 Applications for orphan medicinal product designation*)

The orphan designation is the appellation given to certain medicinal products under development that are intended to diagnose, prevent or treat rare conditions when they meet a pre-defined set of criteria foreseen in the legislation. Medicinal products which get the orphan status benefit from several incentives (fee reductions for regulatory procedures (including protocol assistance), national incentives for research and development,10-year market exclusivity) aiming at stimulating the development and availability of treatments for patients suffering from rare diseases.

Orphan Designations are granted by Decisions of the European Commission based on opinions from the COMP. Orphan designated medicinal products are entered in the Community Register of Orphan Medicinal Products.

Protocol Assistance (*section 3 Requests for protocol assistance with significant benefit question*)

The protocol assistance is the help provided by the Agency to the sponsor of an orphan medicinal product, on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product in view of the submission of an application for marketing authorisation.

Sponsor

Any legal or physical person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product.

Maintenance of Orphan Designation (*section 4 Review of orphan designation for orphan medicinal products for marketing authorisation*).

At the time of marketing authorisation, the COMP will check if all criteria for orphan designation are still met. The designated orphan medicinal product should be removed from the Community Register of Orphan Medicinal Products if it is established that the criteria laid down in the legislation are no longer met.

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu/