21 September 2016
EMA/COMP/478805/201
Procedure Management and Committees Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 11-13 July 2016

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

11 July 2016, 09:00-19:00, room 2F

12 July 2016, 08:30-19:00, room 2F

13 July 2016, 08:30-16:00, 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.

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

The agenda for 11-13 July 2016 was adopted with amendments.

1.3. Adoption of the minutes

The 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. Valproic Acid - EMA/OD/073/16

Vall d'Hebron Institute of Research; Treatment of McArdle disease

COMP coordinator: Michel Hoffmann

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

- Intention to diagnose, prevent or treat

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

- the results obtained in vitro on skeletal cells lines in a preclinical model of the condition in the treatment of McArdle disease and the relevance with the patient setting as patient cells were not used;
- why the sponsor has not conducted pre-clinical in vivo work in the model, from which the cells were derived;
- the relevance of the preclinical model used for the treatment of McArdle disease in vivo, and the interpretation of the results obtained in the experiments, in particular the lack of measureable functional outcomes;
- the methodology used in the pre-clinical studies as well as the results from these studies and its relevance for the development of the product in the condition.

In the written response, and during an oral explanation before the Committee on 11 July 2016, the sponsor elaborated on the difficulties in creating the clinical signs and symptoms associated with the condition in the pre-clinical models submitted. It was highlighted that it was very difficult to reproduce physical exertion in vivo in such a manner that skeletal symptoms would appear. The COMP accepted this explanation and agreed that Orphan Designation could be recommended for this application.

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

The intention to treat the condition with the medicinal product containing valproic acid was considered justified based on pre-clinical in vivo data showing improved glycogen use in skeletal muscle.

The condition is life-threatening due to acute rhabdomyolysis and chronically debilitating due to exercise intolerance consisting of acute early fatigue crises, muscle stiffness and contractures. This is sometimes accompanied by rhabdomyolysis and myoglobinuria. Acute rhabdomyolysis carries a mortality of 8%.

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 valproic acid, for treatment of McArdle's disease, was adopted by consensus.

2.1.2. - EMA/OD/059/16

Treatment of argininosuccinic aciduria

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 argininosuccinic aciduria, the sponsor should provide data to demonstrate efficacy with the product as single therapy in patients affected by the condition. The sponsor is also invited to present more details and/or outcomes of the named patient program in Germany. Otherwise medical plausibility cannot be established.

- Significant benefit

The sponsor has not provided evidence to support a significant benefit versus the authorised product Ravicti. The sponsor is invited to clarify, which patient population would be treated with the proposed product and how the significant benefit versus Ravicti can be established.

In the written response, and during an oral explanation before the Committee on 11 July 2016, the sponsor presented two reports from the published scientific literature concerning patients with argininosuccinic aciduria (Kalkan-Uçar 2015, Grioni 2011). The publication that reported on hyperammonaemia reported on one patient that was originally managed with the product but had to be switched to alternative treatment. The second publication reported on epilepsy in argininosuccinic aciduria patients and did not report on hyperammonaemia outcomes of patients that were treated with the product. In totality, the COMP considered that a higher level of evidence was necessary to support the medical plausibility. The COMP noted that additional case reports of argininosuccinic aciduria patients receiving the product as single treatment and reporting on hyperammonaemia should be available for a resubmission.

As a result of the medical plausibility assessment, the COMP considered that significant benefit cannot be established.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 July 2016, prior to final opinion.

2.1.3. Sodium benzoate - EMA/OD/056/16

Lucane Pharma SA; Treatment of ornithine translocase deficiency

COMP coordinator: Annie Lorence

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 ornithine translocase deficiency, the sponsor should provide data to demonstrate efficacy with the product as single nitrogen scavenger therapy in patients affected by the condition. The sponsor is also invited to present more details and/or outcomes of the named patient program in Germany. Otherwise medical plausibility cannot be established.

- Significant benefit

The sponsor has not provided evidence to support a significant benefit versus the authorised product Ravicti. The sponsor is invited to clarify, which patient population would be treated with the proposed product and how the significant benefit versus Ravicti can be established.

In the written response, and during an oral explanation before the Committee on 11 July 2016, the sponsor presented one case report in the literature concerning one patient with ornithine translocase deficiency (Al Hassnan 2008). The 4 year old patient presented recurrent Reyelike episodes, hypotonia, and multiple stroke-like lesions on brain MRI. Biochemical and molecular analysis confirmed that she had hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome. She significantly improved on protein restriction and sodium benzoate treatment. The sponsor presented the graph showing

improvements in hyperammonaemia after treatment. The COMP considered that this one case report on single nitrogen scavenger treatment with sodium benzoate was sufficient to establish medical plausibility for the purpose of orphan designation.

The COMP considered that the assumption of significant benefit on improving nitrogen scavenging efficacy when used in combination with sodium phenylbutyrate can be supported. This assumption is supported by treatment guidelines for the treatment of urea cycle disorders from the British Inherited Metabolic Diseases Group (BIMDG) and the suggested guidelines for the diagnosis and management of urea cycle disorders (Häberle et al. Orphanet Journal of Rare Diseases 2012, 7:32). This level of evidence was considered sufficient for the purpose of orphan designation.

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

The intention to treat the condition with the medicinal product containing sodium benzoate was considered justified based on published case reports demonstrating that sodium benzoate could normalise serum ammonia.

The condition is life-threatening and chronically debilitating due to the consequences of metabolic decompensation leading to developmental delay, mental disability, and other types of neurological damage.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing sodium benzoate will be of significant benefit to those affected by the condition. This is based on the potential of the product to be used in combination with the currently authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for sodium benzoate, for treatment of ornithine translocase deficiency, was adopted by consensus.

2.1.4. Sodium benzoate - EMA/OD/055/16

Lucane Pharma SA; Treatment of lysinuric protein intolerance

COMP coordinator: Annie Lorence

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 lysinuric protein intolerance, the sponsor should provide data to demonstrate efficacy with the product as single nitrogen scavenger therapy in patients affected by the condition. The sponsor is invited to present more details and/or outcomes of the named patient program in Germany. Otherwise medical plausibility cannot be established.

In the written response, and during an oral explanation before the Committee on 11 July 2016, the sponsor presented one case report from the published scientific literature concerning one patient with lysinuric protein intolerance (Ko et al 2012). For acute management of hyperammonaemia the patient received oral arginine supplementation and intravenous sodium benzoate infusion. After the level of ammonia was normalized and the diagnosis of lysinuric protein intolerance was confirmed, low protein diet (1.5 g/kg/day) and oral supplementation of sodium benzoate (200 mg/kg/day), citrulline (100 mg/kg/day) and L-carnitine (50 mg/kg/day) were maintained. During the follow-up period of 12 months, there was no acute episode of metabolic decompensation, and anaemia and leukopenia were resolved. The COMP considered that this one case report on single nitrogen scavenger treatment with sodium benzoate was sufficient to establish medical plausibility for the purpose of orphan designation.

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

The intention to treat the condition with the medicinal product containing sodium benzoate was considered justified based on published case reports demonstrating that the sodium benzoate could normalise serum ammonia.

The condition is life-threatening and chronically debilitating due to the consequences of metabolic decompensation leading to developmental delay, mental disability, and other types of neurological damage.

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

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

A positive opinion for sodium benzoate, for treatment of lysinuric protein intolerance, was adopted by consensus.

2.1.5. - EMA/OD/054/16

Treatment of N-acetylglutamate synthase deficiency

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor 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 N-acetylglutamate synthase deficiency, the sponsor should provide data to demonstrate efficacy with the product as single nitrogen scavenger therapy in patients affected by the condition. The sponsor is invited to present more details and/or outcomes of the named patient program in Germany. Otherwise medical plausibility cannot be established.

- Significant benefit

The sponsor has not provided evidence to support a significant benefit versus the authorised product Carbaglu. The sponsor is invited to clarify, which patient population would be treated with the proposed product and how the significant benefit versus carglumic acid can be established.

In the written response, and during an oral explanation before the Committee on 11 July 2016, the sponsor failed to identify additional case reports or data on the product as single nitrogen scavenger treatment in N-acetylglutamate synthase deficiency. The COMP considered that a higher level of evidence was necessary to support the medical plausibility. The COMP noted that additional case reports of N-acetylglutamate synthase deficiency patients receiving sodium benzoate as single nitrogen scavenger treatment reporting on hyperammonaemia should be available for a resubmission.

As a result of the medical plausibility assessment, the COMP considered that significant benefit cannot be established. In this condition Carbaglu is authorised, which deems nitrogen scavenger treatment unnecessary. The sponsor argued that N-acetylglutamate synthase deficiency patients that do not receive Carbaglu might need a nitrogen scavenger treatment with the product. The sponsor failed to demonstrate the significance and unmet medical need of this patient population.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 July 2016, prior to final opinion.

2.1.6. - EMA/OD/080/16

Treatment of graft versus host disease

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

- Significant benefit

The sponsor presented data from preclinical models of islets transplantation to support the argument of significant benefit. This model is not relevant to the proposed condition, which is associated with the hematopoietic stem cell transplantation.

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition when used in combination with cyclosporin or rapamycin.

The sponsor is requested to further discuss the arguments for significant benefit and to elaborate on the relevance of the preclinical model and the results from preclinical studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication

In the written response, and during an oral explanation before the Committee on 12 July 2016, the sponsor presented publications to support the mechanism of action of the product and to enforce a notion that GvHD and solid transplants rejection share many molecular similarities. The sponsor was questioned about the positioning of the product in the treatment regimen of patients. The pre-clinical model used to support medical plausibility represented chronic GvHD only. No data in a model of acute GvHD was provided. The sponsor explained the positioning of the product in the context of acute GvHD treatment guideline. The COMP considered that positioning of the product in the context of acute GvHD would not be supported by the pre-clinical data and a higher level of evidence would be required to support significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 July 2016, prior to final opinion.

2.1.7. - EMA/OD/078/16

Treatment of idiopathic dilated cardiomyopathy

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:

- Orphan indication

The sponsor is invited to discuss the grounds on which idiopathic dilated cardiomyopathy could be considered a distinct medical entity with respect to the broader group of dilated cardiomyopathy, based on up to date classifications of dilated cardiomyopathies, and on the specific aetiology, pathophysiology and clinical features of the proposed condition.

- Prevalence

The sponsor is invited to further discuss the prevalence calculations, including the reasons for excluding the worst case incidence scenario. In this respect it also seems that the highest estimate of overall incidence in the study from Rakar et al is 6.95 rather than 4.5. In addition it appears that the duration of disease can be estimated to be higher than 10 years for some patient groups.

In view of the possibility of enlarging the condition to dilated cardiomyopathy as a whole, the sponsor is also invited to provide a prevalence estimate of dilated cardiomyopathy.

In revising the prevalence calculations, the sponsor is invited to take into account existing disease registries besides literature sources.

- Significant benefit

The sponsor states that no medicinal products are authorised for the treatment of idiopathic dilated cardiomyopathy. However a number of products are authorized for dilated cardiomyopathy and heart failure in the EU that are also part of the treatment algorithm of the idiopathic forms. Indeed the clinical trial performed by the sponsor studied patients that were being treated with ACE inhibitors, beta blockers and diuretics, among others.

The sponsor is therefore requested to elaborate on the results from their study to justify the assumption of significant benefit in the context of the current therapeutic management of patients.

In this view the sponsor is also invited to further elaborate on the advantage of using the proposed product in patients in NYHA class II-IV, in whom existing treatments have shown to be able to positively influence clinical course and prognosis.

In the written response, and during an oral explanation before the Committee on 11 July 2016, the sponsor discussed idiopathic dilated cardiomyopathy (IDCM) as a distinct medical entity, highlighting the diagnostic process and differences with other forms of dilated cardiomyopathy. At present there are no known etiologic, pathophysiologic or clinical characteristics that are specific only of IDCM and allow differentiating it from secondary forms of IDCM and the treatment of secondary forms of dilated cardiomyopathy is usually the same. As such at the present time it would be difficult to consider IDCM as a distinct medical entity.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 July 2016, prior to final opinion.

2.1.8. Recombinant protein derived from the saliva of the Ornithodoros moubata tick - EMA/OD/077/16

Akari Therapeutics Plc; Treatment of paroxysmal nocturnal haemoglobinuria

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 proposed calculation appears to be high with other reported calculations in the public domain.

The sponsor should justify the inclusion and 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 submitted a revised calculation of the prevalence estimate. The revised calculation was substantially lower proposing 0.2 in 10,000. The COMP accepted this calculation.

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 recombinant protein derived from the saliva of the Ornithodoros moubata tick was considered justified based on preliminary clinical data where a reduction in complement activation was noted.

The condition is life-threatening and chronically debilitating due to the complications of the chronic haemolysis such as abdominal pain, infection, cytopenia, and kidney malfunction, and due to occurrence of thrombosis and haemorrhage in different organs. Vascular complications at the level of the central nervous system are the most common cause of death.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant protein derived from the saliva of the *Ornithodoros moubata* tick will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that their product could be used in eculizumab resistant patients. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for recombinant protein derived from the saliva of the *Ornithodoros moubata* tick, for treatment of paroxysmal nocturnal haemoglobinuria, was adopted by consensus.

2.1.9. - EMA/OD/050/16

Treatment of Huntington's disease

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

- 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 Huntington's disease, the sponsor should further elaborate on how the results obtained in valid disease models could predict clinically meaningful outcome in patients affected by the condition. In this context, the sponsor is invited to provide any additional data on functional outcomes in valid disease models with their product. Additionally, the sponsor should discuss the effect of the product on wild type huntingtin expression. If no appropriate data can be presented, significant benefit cannot be established.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. The sponsor is invited to provide evidence how this novel mechanism of action can be translated into a significant benefit in the context of already authorised products. If no appropriate data can be presented, significant benefit cannot be established.

In the written response, and during an oral explanation before the Committee on 12 July 2016, the sponsor discussed preliminary clinical data of similar products published in the scientific literature. The sponsor outlined, that the proposed product in development differed substantially from the one used in publications. The COMP expressed concerns about these differences. While the sponsor has demonstrated that the product can reduce levels of HTT, there is no evidence as of yet to understand potential side effects. Additionally, in the view of a lack of functional outcomes in valid preclinical models the COMP considered the application to be too premature to conclude on medical plausibility. The sponsor outlined that appropriate studies to measure functional outcomes in valid preclinical models are currently ongoing and planned. The COMP encouraged the sponsor to reapply, once further evidence is available.

The significant benefit was not discussed in full detail, as medical plausibility was of primary concern.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 July 2016, prior to final opinion.

2.1.10. - EMA/OD/051/16

Treatment of West Nile virus infection

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 23 June 2016, prior to responding to the list of issues.

2.1.11. 3-(3-Methanesulfonyl-phenyl)-1-propyl-piperidine Hydrochloride - EMA/OD/079/16

A. Carlsson Research AB; Treatment of narcolepsy

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:

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of narcolepsy, the sponsor should further elaborate on the methodology of the preclinical studies.

This is particular in relation to the experimental conditions that increase the methylphenidate-induced psychomotor activity and those that dampen it, since it does not appear clear from the data provided how the same doses of both methylphenidate and the proposed product in combination could at the same time enhance and dampen the effects of methylphenidate.

In addition the sponsor is invited to better describe the clinical cases presented, including the methodology used for measuring the reported clinical improvements.

The sponsor is reminded that in absence of convincing level of evidence the medical plausibility cannot be justified.

- Number of people affected

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

The sponsor is invited to conclude on a prevalence estimate as a figure in 10,000. This should be based on relevant and up to date sources and on the critical appraisal of such sources. The sponsor should also describe and justify the methodology used for the prevalence calculations.

- Significant benefit

The sponsor is requested to further elaborate on the results from the clinical cases in order to justify the significant benefit of the proposed product in the context of the authorized medicinal products and the current therapeutic management of patients affected by narcolepsy.

In the written response, and during an oral explanation before the Committee on 12 July 2016, the sponsor presented an additional preclinical experiment and further discussed the existing clinical experience with the proposed product in narcolepsy.

Regarding the medical plausibility of the proposed product in combination with methylphenidate, the sponsor presented an additional preclinical study showing the effects on methylphenidate-induced psychomotor activation. However, the preclinical model is not usually used to study narcolepsy. As such the potential translation of the results to the intended clinical use in narcolepsy was questionable according to the COMP. In the clinical study on narcoleptic patients, the proposed product showed only very modest effects at the

end of the study period, with significant improvement only in the mental fatigue score among a number of endpoints studied.

The sponsor claimed significant benefit on grounds of better efficacy, safety, and major contribution to patient care. The outcome of this discussion is captured in the grounds for the opinion below. In addition the sponsor used arguments for the ease of use of the proposed product, which were not relevant because the position of the product in the treatment algorithm of narcolepsy is not known at this stage.

The COMP having examined the application concluded that:

The medical plausibility of 3-(3-methanesulfonyl-phenyl)-1-propyl-piperidine hydrochloride for treatment of narcolepsy is not justified at this stage.

All the preclinical studies presented by the sponsor were performed in a model that is not usually used to study narcolepsy. In relation to the potential use of the product as monotherapy the results of these studies showed only modest effect on one endpoint of psychomotor function with the proposed product as monotherapy. In a clinical study on seven narcoleptic patients, the proposed product showed only very modest effects, with significant improvement only observed for mental fatigue score among a number of endpoints studied.

Similarly the COMP was of the opinion that the medical plausibility of the proposed product in combination with methylphenidate, as proposed by the sponsor, is not justified at the present stage. The preclinical data presented by sponsor showed reinforcement by the proposed product of the stimulating effects of low doses methylphenidate on one psychomotor endpoint, and reduction of the effects of higher doses methylphenidate. The potential to translate this preclinical information into clinical activity does not appear founded so far, including how modulating the dosing of methylphenidate could be achieved in its therapeutic use in patients in order to achieve the effects showed in the preclinical setting, and the clinical consequences of the different potential dosing of methylphenidate. Indeed it appears from the oral explanations that only one clinical case was treated with the combination so far and no details on this case were provided that could help clarifying this issue.

In relation to prevalence the sponsor did not provide a conclusive estimate showing that the condition was estimated to be affecting not more than 5 in 10,000 persons in the European Union, at the time the application was made.

As satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has to be provided that the proposed product may be of significant benefit to those affected by the condition. The sponsor claimed significant benefit on grounds of better efficacy, safety, and major contribution to patient care.

In relation to efficacy, the results of the study performed by the sponsor on seven patients over approximately 20 weeks, showing only significant improvement of mental fatigue score among a range of neurocognitive measures performed was not considered by the COMP sufficient to assume better efficacy of the proposed product over the currently authorized ones for the treatment of narcolepsy.

The COMP was also of the opinion that any claim of better safety of the proposed product as compared to the currently authorised ones cannot be accepted. Claims of better safety would be considered when a proposed product offers the potential of a comparable efficacy

to the currently authorised medicinal products, which the sponsor has not demonstrated. In addition in consideration of the limited clinical experience with the proposed product in the treatment of narcolepsy, no conclusions can be clearly drawn on its safety profile.

Similarly, the argument of the sponsor of a major contribution to patient care versus sodium oxybate was not substantiated by sufficient discussion or reasoning on documented difficulties with the administration of sodium oxybate, and any type of data that would allow assuming a comparable efficacy of the two products are also missing.

A negative opinion for 3-(3-methanesulfonyl-phenyl)-1-propyl-piperidine hydrochloride, for treatment of narcolepsy, was adopted by consensus. The sponsor will have 90 days to appeal from the COMP decision.

2.1.12. Masitinib mesilate - EMA/OD/081/16

AB Science; Treatment of amyotrophic lateral sclerosis

COMP coordinator: Violeta Stoyanova; Expert: Mário Miguel Rosa

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

- Intention to diagnose, prevent or treat

In the application, the sponsor has provided preclinical data in a valid model of the condition and data from an interim analysis of a phase2/3 clinical study. Nevertheless the pre-clinical data do not entail any functional endpoints other than the calculation of survival probability. Clinically relevant endpoints have been included in the clinical study. However, it is difficult to interpret the data due to limited information regarding the study design and the methodology used for the analysis.

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

- the methodology used in the pre-clinical studies as well as the results from these studies and their relevance for the clinical development of the product in the condition;
- the design of the clinical study and the methodology used in the interim analysis and the relevance of analysis of patient subsets.

- Significant benefit

The sponsor presented results of the interim analysis of the on-going phase 2/3 clinical study.

The arguments on significant benefit are based on the potential improved efficacy in the condition when used in combination with riluzole.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the study design, the methodology used and results from clinical study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition. Without clarity with regards to the clinical study results the assumption of significant benefit cannot be made.

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

In the written response and during an oral explanation before the Committee on 12 July 2016, the sponsor clarified the preclinical data obtained to date and explained the mechanism of action, which is proposed to involve the inhibition of gliosis. The COMP found the data presented insufficient for elucidation of the exact mechanism of action of the product. The sponsor also admitted that no functional data was collected in the preclinical model tested.

Furthermore, the sponsor clarified the assumptions and design features of the Phase 2/3 clinical study. . The sponsor was asked to explain the relevance of the post-hoc analysis of the results of the study and the methodology used in the study. The COMP questioned the placebo outcomes in the post-hoc analyses. The expert assisting the COMP questioned a surprisingly fast functional decline in the placebo arm, which is not normally expected for a population, such as the one enrolled in the study.

The sponsor confirmed that all patients in the study were treated with riluzole in line with the latest ALS treatment guideline recommendations.

Although many questions remained open and the COMP had concerns about the interpretation of the clinical data, the COMP considered that the medical plausibility of the product in the condition is supported by the clinical data. The assumptions that were made would need to be confirmed at the time of marketing authorisation and the COMP was concerned about the apparent plan of the sponsor to submit a marketing authorisation application shortly after orphan designation. The sponsor was warned about the potential difficulty during maintenance of the orphan drug designation procedure should no additional data become available until that time.

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

The intention to treat the condition with the medicinal product containing masitinib mesilate was considered justified based on clinical data demonstrating a clinical effect on the amyotrophic lateral sclerosis functional rating scale.

The condition is life-threatening and chronically debilitating due to progressive degeneration of motor neurons, ultimately leading to paralysis and respiratory failure. The survival of patients is usually limited to 2-3 years.

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 masitinib mesilate will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate an added effect of the proposed product on the amyotrophic lateral sclerosis functional rating scale when used in combination with the authorised product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for masitinib mesilate, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.1.13. Autologous mesenchymal stromal cells on a decellularised tracheal scaffold from a cadaveric donor - EMA/OD/069/16

Videregen Ltd; Treatment of tracheal stenosis

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:

- 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 tracheal stenosis, the sponsor should further elaborate on the methodology of the preclinical studies and on the basis for bridging the results of these studies to the intended product in its clinical use in humans.

In relation to the clinical cases, it is noted that the sponsor reported two successful cases but did not mention a number of cases where the clinical course after surgery resulted in early death of the operated patients. The sponsor is invited to provide a comprehensive overview of all cases reported in the literature and discuss the different outcomes of these cases.

In addition the sponsor is invited to discuss how the results of successful clinical cases in which different methods were used would allow bridging with the potential clinical efficacy of the proposed product.

In the written response, and during an oral explanation before the Committee on 12 July 2016, the sponsor clarified the issues raised by the COMP in relation to the medical plausibility of the proposed product.

First the sponsor clarified the primary aims of the preclinical studies presented. It appears that these aims were achieved in the experiment, which may be sufficient to support the medical plausibility of the proposed product in clinical setting.

The COMP acknowledged the difficulties in performing preclinical studies with the proposed product. The company also clarified the inclusion criteria of the future clinical studies. In relation to existing clinical data, the sponsor presented results of all existing clinical cases, some of which were missing in the first submission.

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

The intention to treat the condition with the medicinal product containing autologous mesenchymal stromal cells on a decellularised tracheal scaffold from a cadaveric donor was considered justified based on preclinical data showing successful engraftment of a functional trachea in models of the condition.

The condition is life-threatening and chronically debilitating due to the development of progressive dyspnoea, cyanosis, wheezing, persistent croup and pneumonia. Dysphagia may occur and may be accompanied by apnoea or cyanotic spells during attempts to swallow solid food.

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

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 mesenchymal stromal cells on a decellularised tracheal scaffold from a cadaveric donor, for treatment of tracheal stenosis, was adopted by consensus.

2.1.14. Zoledronic acid - EMA/OD/067/16

Laboratorio Italiano Biochimico Farmaceutico Lisapharma S.p.A.; Treatment of glioma

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:

- Number of people affected

The sponsor presented data from EUCAN database without reference to the epidemiological index or other valid sources.

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

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

In the written response, the sponsor submitted a recalculation of the prevalence. Based on EUCAN database and a revision of values, which were previously misread, the sponsor stated that the prevalence was amounting to 0.87 per 10,000, assuming 5-year prevalence index. This estimate is lower, but in line with the prevalence values from Crocetti et al, 2012. Additionally, the sponsor commented that malignant glial tumours are a fraction of the prevalent brain and central nervous system cancers, meaning that the prevalence value for the condition applied to designation is lower than previously calculated. In accordance to all data collected the sponsor proposed the prevalence of the condition to be in a range between 0.83 and 1.0 per 10,000 persons in the EU. The COMP considered this calculation acceptable and agreed to adopt a more conservative end of the range.

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

The intention to treat the condition with the medicinal product containing zoledronic acid was considered justified based on preclinical in vivo data demonstrating reduction of the tumour burden.

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

The condition was estimated to be affecting 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 zoledronic acid will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate that the administration of the product in a model of glioblastoma multiforme leads to a significant reduction of tumour burden, which compared favourably to the efficacy of temolozomide in the same model. The Committee considered that this constitutes a clinically relevant advantage.

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

2.1.15. Naltrexone - EMA/OD/035/16

Able AB; Treatment of fibromyalgia

COMP coordinator: Dinah Duarte/Martin Možina

As agreed during the May 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 naltrexone for treatment of fibromyalgia (FM), the sponsor should further elaborate on:

- the mechanism of action and proof of concept regarding the use of low-dose naltrexone in the proposed condition.
- the representativeness of the published studies to support the efficacy of the product in the proposed condition as it has been noted that similar products have recently shown a lack of efficacy in clinical studies in the target condition.

The sponsor is invited to present scientifically relevant data to support the potential pharmacologic activity and a plausible effect of low-dose naltrexone in patients with fibromyalgia.

- Life-threatening, seriously debilitating or serious and chronic nature of the condition

It was also noted by the COMP that in article 3(2)a second paragraph of the Orphan Regulation No(EC) 141/2000 if the applicant is seeking OD based on return of investment the condition should be life-threatening, seriously debilitating or serious and chronic. Studies show that at 2 years after diagnosis 47% no longer fulfil the ACR FM criteria, and remission is objectively identified in approx. 25% of the assessed patients (ref Granges G et al J Rheum 1994). This is data from adult FM. In paediatric FM similar data exist demonstrating only 51% continue to fulfil FM criteria at 6 years FU (ref Kashikar-Zuck S et al Paediatrics 2014). The notice on better prognosis in paediatric FM is also described by Gedalia A et al Clin Exp Rheum 2000. The sponsor should further elaborate on the life-threatening, seriously debilitating or serious and chronic nature of the condition. From the data provided and the sponsor's arguments it is not well substantiated that the condition can be defined as life-threatening, seriously debilitating or serious and chronic.

- Insufficient return of the investment

The sponsor should further elaborate on the proposed insufficient return of the investment without incentives as the assumptions proposed only focus primarily on net present value

(NPV) and do not consider the fact that this is a repurposed product as well as the impact of small to medium enterprise status at the EMA incentives which are linked to orphan designation. The COMP would also require more clarity regarding the impact of discounting and the expected pre-licencing costs and the expected return over the 10yrs of Market Exclusivity with and without the effects of the exclusivity. The sponsor should show estimated costs and sales per year before and after licensing. The sponsor should also clarify the value of the proposed prevalence as the COMP has noted that it is up to 8% of the population in the EU, in order to clarify the expected return, based on the sales for the proposed indication.

- Significant benefit

As it is accepted that there are well-established standard of care in the management of these patients the sponsor is asked to further elaborate what the significant benefit would be of using their product including nonpharmacological interventions.

The written responses and those given during the oral explanation before the Committee on 15 June 2016 have been described in the Minutes from June 2016 COMP meeting.

The COMP, having examined the application, concluded that:

Limited bibliographical data has been submitted to establish the medical plausibility. The number of patients and trial design used to establish the medical plausibility of naltrexone in the condition was considered insufficient to establish the proposed efficacy in the condition. During the oral explanation no additional data was presented by the sponsor.

The sponsor has failed to established that the condition is life-threatening, seriously debilitating or a serious and chronic condition.

The sponsor has failed to establish that the expected revenues from marketing of the product in the EU are unlikely to generate sufficient return to justify the necessary investment.

In addition, the sponsor has not provided sufficient justification for the assumption that the medicinal product containing naltrexone will be of significant benefit to those affected by the condition. The Committee considered that it has not been sufficiently established if the product could be considered of a clinically relevant advantage or major contribution to patient care.

A negative opinion for naltrexone, for treatment of fibromyalgia, was adopted by consensus. The sponsor will have 90 days to appeal from the COMP decision.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/113/16

Treatment of retinitis pigmentosa

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

2.2.2. - EMA/OD/100/16

Treatment of cystic fibrosis

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

2.2.3. - EMA/OD/123/16

Treatment of osteomyelitis

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

2.2.4. 2-((2-ethyl-6-(4-(2-(3-hydroxyazetidin-1-yl)-2-oxoethyl)-piperazin-1-yl)-8-methylimidazo[1,2-α]pyridin-3-yl)-(methyl)amino)-4-(4-fluorophenyl)-thiazole-5-carbonitrile - EMA/OD/088/16

Galapagos NV; Treatment of idiopathic pulmonary fibrosis

COMP coordinator: Geraldine O'Dea

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

The intention to treat the condition with the medicinal product containing 2-((2-ethyl-6-(4-(2-(3-hydroxyazetidin-1-yl)-2-oxoethyl)-piperazin-1-yl)-8-methylimidazo[1,2-alpha]pyridin-3-yl)-(methyl)amino)-4-(4-fluorophenyl)-thiazole-5-carbonitrile was considered justified based on preclinical data showing reduction of lung fibrosis with the proposed product in valid models of the condition.

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

The condition was estimated to be affecting approximately 3.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 2-((2-ethyl-6-(4-(2-(3-hydroxyazetidin-1-yl)-2-oxoethyl)-piperazin-1-yl)-8-methylimidazo[1,2-alpha]pyridin-3-yl)-(methyl)amino)-4-(4-fluorophenyl)-thiazole-5-carbonitrile will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing higher activity on lung fibrosis in comparison to pirfenidone, currently authorised for the condition, and increased antifibrotic activity when used in combination with nintedanib, also authorised for the treatment of the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by idiopathic pulmonary fibrosis.

A positive opinion for 2-((2-ethyl-6-(4-(2-(3-hydroxyazetidin-1-yl)-2-oxoethyl)-piperazin-1-yl)-8-methylimidazo[1,2-alpha]pyridin-3-yl)-(methyl)amino)-4-(4-fluorophenyl)-thiazole-5-carbonitrile, for treatment of idiopathic pulmonary fibrosis, was adopted by consensus.

2.2.5. 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/106/16

F2G Ltd; Treatment of scedosporiosis

COMP coordinator: Nikolaos Sypsas

The Committee agreed that the condition, scedosporiosis, 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 data showing susceptibility of the microorganism and improvement in survival.

The condition is life-threatening due to disseminated infection and chronically debilitating due to skin and soft tissue infections that can lead to osteomyelitis, endocarditis, and meningitis.

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

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 reduction in infections associated with azole resistance. 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 scedosporiosis, was adopted by consensus.

2.2.6. - EMA/OD/104/16

Treatment of invasive aspergillosis

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 September meeting.

2.2.7. 6'-(R)-Methyl-5-O-(5-amino-5,6-dideoxy-α-L-talofuranosyl)- paromamine sulfate - EMA/OD/119/16

Coté Orphan Consulting UK Limited; Treatment of mucopolysaccharidosis type I

COMP coordinator: Dinah Duarte

The Committee agreed that the condition, mucopolysaccharidosis 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 6'-(R)-methyl-5-O-(5-amino-5,6-dideoxy-alpha-L-talofuranosyl)-paromamine sulfate was considered justified based on pre-clinical in vivo data in a valid model of the condition showing increased alpha-L-iduronidase activity in organs affected by the condition.

The condition is chronically debilitating due to facial dysmorphism, hepatosplenomegaly, upper airway obstruction, skeletal deformity, cardiomyopathy, central nervous system manifestations and life-threatening with death ensuing by adolescence if the severe form of the disease is left untreated.

The condition was estimated to be affecting approximately 0.02 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 6'-(R)-methyl-5-O-(5-amino-5,6-dideoxy-alpha-L-talofuranosyl)-paromamine sulfate will be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical in vivo data that demonstrate an increase in alpha-L-iduronidase activity without the need for enzyme replacement therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 6'-(R)-methyl-5-O-(5-amino-5,6-dideoxy-alpha-L-talofuranosyl)-paromamine sulfate, for treatment of mucopolysaccharidosis type I, was adopted by consensus.

2.2.8. - EMA/OD/108/16

Treatment of soft tissue sarcoma

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

2.2.9. Adeno-associated viral vector serotype 9 containing the human mini-dystrophin gene - EMA/OD/096/16

Advanced Biotherapeutics Consulting SARL; 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 adeno-associated viral vector serotype 9 containing the human mini-dystrophin gene was considered justified based on data in valid preclinical in vivo models of the disease showing a restoration of muscle strength and endurance in a dose-dependent manner.

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 approximately 0.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated viral vector serotype 9

containing the human mini-dystrophin gene will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data in pre-clinical in vivo models of the disease that demonstrate the restoration of muscle strength in a broader patient population. 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 adeno-associated viral vector serotype 9 containing the human mini-dystrophin gene, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

2.2.10. Adenovirus associated viral vector serotype 5 containing the human RPGR gene - EMA/OD/102/16

Athena Vision Ltd; Treatment of retinitis pigmentosa

COMP coordinator: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing adenovirus associated viral vector serotype 5 containing the human RPGR gene was considered justified based on preclinical in vivo data demonstrating improved survival of photoreceptor cells and improved retinal function.

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

The condition was estimated to be affecting approximately 3.3 in 10,000 persons in the European Union, at the time the application was made.

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

2.2.11. - EMA/OD/202/15

Treatment of variegate porphyria

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

2.2.12. - EMA/OD/099/16

Treatment of periventricular leukomalacia

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

2.2.13. - EMA/OD/087/16

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 September meeting.

2.2.14. Cannabidiol - EMA/OD/110/16

Richardson Associates Regulatory Affairs Ltd; Treatment of graft versus host disease

COMP coordinator: Jens Ersbøll/Martin Možina

The Committee agreed that the condition, graft-versus-host disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing cannabidiol was considered justified based on preliminary clinical data in patients affected by the condition showing that treatment with the proposed product reduced the incidence and the time to onset of acute graft-versus-host disease.

The condition is life-threatening and chronically debilitating due to intestinal inflammation causing diarrhoea, abdominal pain, nausea and vomiting, as well as due to hepatotoxicity, skin and mucosal damage, sicca syndrome, cholestasis, arthritis, obliterative bronchiolitis and the need for immunosuppression that increases susceptibility to infections.

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 cannabidiol will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that the treatment with the proposed product on top of standard of care, including already authorised products, was able to reduce the incidence and time to onset of acute graft-versus-host disease. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for cannabidiol, for treatment of graft-versus-host disease, was adopted by consensus.

2.2.15. Cisplatin - EMA/OD/101/16

PlumeStars s.r.l.; Treatment of malignant mesothelioma

COMP coordinator: Daniel O'Connor/Bożenna Dembowska-Bagińska

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

The intention to treat the condition with the medicinal product containing cisplatin was considered justified based on a pre-clinical in vivo model of the condition showing a reduction in tumour nodules.

The condition is life-threatening due to the invasion of the pleura leading to pleural effusions, dyspnoea and malignant ascites. Local invasion may also result in obstruction of the superior vena cava, cardiac tamponade, and spinal cord compression. Patients with pleural mesothelioma usually die due to increasing tumour bulk that gradually fills the hemithorax causing progressive respiratory compromise (“incarceration” of the lungs),

pneumonia, or myocardial dysfunction with arrhythmias. In patients with peritoneal mesothelioma, distension due to ascites, abdominal pain, and organ impairment such as bowel obstruction are observed.

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 cisplatin will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate a reduction in pleural tumour nodules which may translate into improved management of local residual disease. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for cisplatin, for treatment of malignant mesothelioma, was adopted by consensus.

2.2.16. - EMA/OD/105/16

Treatment of progressive multifocal leukoencephalopathy

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

2.2.17. Fimaporfin (in combination with gemcitabine) - EMA/OD/111/16

PCI Biotech AS; Treatment of cholangiocarcinoma

COMP coordinator: Katerina Kopečková/Dinko Vitezic

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

The intention to treat the condition with the medicinal product containing fimaporfin was considered justified based on clinical data in patients who achieved stable disease, partial responses and improved survival.

The condition is life-threatening and chronically debilitating due to biliary obstruction, late diagnosis and a median survival of less than 24 months.

The condition was estimated to be affecting less than 1.3 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for fimaporfin, for treatment of cholangiocarcinoma, was adopted by consensus.

2.2.18. - EMA/OD/112/16

Treatment of narcolepsy

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

2.2.19. - EMA/OD/092/16

Treatment of haemophilia B

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

2.2.20. - EMA/OD/093/16

Treatment of haemophilia A

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

2.2.21. L-Pyr-L-Glu-L-Gln-L-Leu-L-Glu-L-Arg-L-Ala-L-Leu-L-Asn-L-Ser-L-Ser - EMA/OD/094/16

Araim Pharma Europe Ltd; Prevention of graft loss in pancreatic islet transplantation

COMP coordinator: Frauke Naumann-Winter

The Committee agreed that the condition, graft loss in pancreatic islet transplantation, is a distinct medical entity and meets the criteria for orphan designation.

The intention to prevent the condition with the medicinal product containing l-Pyr-L-Glu-L-Gln-L-Leu-L-Glu-L-Arg-L-Ala-L-Leu-L-Asn-L-Ser-L-Ser was considered justified based on two valid pre-clinical in vivo models which show an improvement in blood glucose levels and graft survival.

The condition is life-threatening and chronically debilitating due to the increased risk of morbidity when loss of the transplanted islets occurs.

The population of patients eligible for prevention of the condition was estimated to be 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 prevention that has been authorised in the European Union for the population at risk of developing the condition.

A positive opinion for l-Pyr-L-Glu-L-Gln-L-Leu-L-Glu-L-Arg-L-Ala-L-Leu-L-Asn-L-Ser-L-Ser, for treatment of graft loss in pancreatic islet transplantation, was adopted by consensus.

2.2.22. - EMA/OD/089/16

Treatment of gastroenteropancreatic 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 September meeting.

2.2.23. Methotrexate - EMA/OD/086/16

aimAKU (Associazione Italiana Malati di Alcaptonuria); Treatment of alkaptonuria

COMP coordinator: Dinah Duarte

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

The intention to treat the condition with the medicinal product containing methotrexate was considered justified based on early clinical data demonstrating reduction of serum amyloid A and improvement of symptoms such as pain and joint mobility.

The condition is life-threatening due to oxidative haemolysis and methaemoglobinaemia and chronically debilitating due to spondyloarthropathy, rupture of ligaments/muscle/tendons, valvular heart disease, aortic stenosis and renal stones.

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 methotrexate, for treatment of alkaptonuria, was adopted by consensus.

2.2.24. - EMA/OD/091/16

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 September meeting.

2.2.25. - EMA/OD/115/16

Treatment of myelofibrosis

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

2.2.26. - EMA/OD/126/16

Treatment of Duchenne muscular dystrophy

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

2.2.27. Nintedanib - EMA/OD/095/16

Boehringer Ingelheim International GmbH; Treatment of systemic sclerosis

COMP coordinator: Josep Torrent-Farnell

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

The intention to treat the condition with the medicinal product containing nintedanib was considered justified based on in vivo preclinical data demonstrating antifibrotic effects.

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

The condition was estimated to be affecting less than 3.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing nintedanib will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate an antifibrotic effect of the proposed product which is directly associated with the condition and not targeted by the currently authorised treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for nintedanib, for treatment of systemic sclerosis, was adopted by consensus.

2.2.28. - EMA/OD/090/16

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 September meeting.

2.2.29. Recombinant human acid alpha-glucosidase conjugated with mannose-6-phosphate analogues - EMA/OD/098/16

NanoMedSyn; Treatment of glycogen storage disease type 2 (Pompe disease)

COMP coordinator: Dinah Duarte

The Committee agreed that the condition, glycogen storage disease type II (Pompe's disease), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing recombinant human acid alpha-glucosidase conjugated with mannose-6-phosphate analogues was considered justified based on preclinical data showing improvement of motor function and restoration of muscle fibres in valid models of the condition.

The condition is life-threatening and chronically debilitating due to accumulation of glycogen in muscle and nerve cells leading to progressive skeletal myopathy, cardiomyopathy, and respiratory insufficiency, leading to death within two years of birth in the infantile forms, and in the fourth decade of life in forms with later onset.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant human acid alpha-glucosidase conjugated with mannose-6-phosphate analogues will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data in valid models

of the condition showing better responses on motor function and muscle regeneration compared to Myozyme, currently authorised for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by glycogen storage disease type 2 (Pompe's disease).

A positive opinion for recombinant human acid alpha-glucosidase conjugated with mannose-6-phosphate analogues, for treatment of glycogen storage disease type II (Pompe's disease), was adopted by consensus.

2.2.30. Recombinant human interleukin 12 - EMA/OD/116/16

Coté Orphan Consulting UK Limited; Treatment of acute radiation syndrome

COMP coordinator: Martin Možina

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

The intention to treat the condition with the medicinal product containing recombinant human interleukin-12 was considered justified based on preclinical data demonstrating that treatment improved survival.

The condition is life-threatening due to haematopoietic, gastrointestinal, neurological and vascular symptoms associated with multiple organ dysfunction leading to multiple organ failure and carcinogenesis.

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

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

A positive opinion for recombinant human interleukin-12, for treatment of acute radiation syndrome, was adopted by consensus.

2.2.31. Recombinant human monoclonal antibody against human complement component C5a - EMA/OD/118/16

Alexion Europe SAS; Treatment of graft-versus-host disease

COMP coordinator: Frauke Naumann-Winter

The Committee agreed that the condition, graft-versus-host disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing recombinant humanised monoclonal antibody against human complement component C5a was considered justified based on preliminary clinical data demonstrating that patients affected by the condition respond to treatment.

The condition is life-threatening and chronically debilitating due to intestinal inflammation causing diarrhoea, abdominal pain, nausea and vomiting, as well as due to hepatotoxicity, skin and mucosal damage, sicca syndrome, cholestasis, arthritis, obliterative bronchiolitis and the need for immunosuppression that increases susceptibility to infections.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant humanised monoclonal antibody against human complement component C5a will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that patients receiving the proposed product as add-on to best standard of care, including authorised products, respond to treatment. The response rate compared favourably to response rates reported in the published scientific literature. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for recombinant humanised monoclonal antibody against human complement component C5a, for treatment of graft-versus-host disease, was adopted by consensus.

2.2.32. - EMA/OD/107/16

Treatment of paroxysmal nocturnal haemoglobinuria

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

2.2.33. Synthetic double-stranded siRNA oligonucleotide directed against delta-aminolevulinic acid synthase 1 mRNA, that is covalently linked to a ligand containing three N-acetylgalactosamine residues - EMA/OD/125/16

Alnylam UK Limited; Treatment of acute hepatic porphyria

COMP coordinator: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing synthetic double-stranded siRNA oligonucleotide directed against delta-aminolevulinic acid synthase 1 mRNA covalently linked to a ligand containing three N-acetylgalactosamine residues was considered justified based on preclinical data demonstrating a significant reduction of levels of aminolevulinic acid and porphobilinogen in the serum.

The condition is life-threatening due to paralysis and respiratory arrest during an attack and chronically debilitating due to attacks, which are causing pain, nausea, seizures and skin blistering.

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 synthetic double-stranded siRNA oligonucleotide directed against delta-aminolevulinic acid synthase 1 mRNA covalently linked to a ligand containing three N-acetylgalactosamine residues will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that

demonstrate a faster downregulation of the neurotoxic intermediate metabolites, aminolevulinic acid and porphobilinogen, in the serum as compared to the authorised product. Additionally, a single administration of the product resulted in a lasting response, which is not achievable by the use of the authorised product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for synthetic double-stranded siRNA oligonucleotide directed against delta-aminolevulinic acid synthase 1 mRNA covalently linked to a ligand containing three N-acetylgalactosamine residues, for treatment of acute hepatic porphyria, was adopted by consensus.

2.2.34. - EMA/OD/084/16

Treatment of short bowel syndrome

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

2.2.35. Synthetic ribonucleic acid oligonucleotide directed against superoxide dismutase 1 messenger ribonucleic acid - EMA/OD/120/16

Biogen Idec Limited; Treatment of amyotrophic lateral sclerosis

COMP coordinator: Josep Torrent-Farnell

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

The intention to treat the condition with the medicinal product containing synthetic ribonucleic acid oligonucleotide directed against superoxide dismutase 1 messenger ribonucleic acid was considered justified based on improvements in motor function and survival upon treatment in a valid preclinical model of the condition.

The condition is life-threatening and chronically debilitating due to progressive degeneration of motor neurons, ultimately leading to paralysis and respiratory failure. The survival of the patients is usually limited to 2-3 years.

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 synthetic ribonucleic acid oligonucleotide directed against superoxide dismutase 1 messenger ribonucleic acid will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data which demonstrate that treatment improved motor function. The currently authorised product does not have a therapeutic effect on motor function. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for synthetic ribonucleic acid oligonucleotide directed against superoxide dismutase 1 messenger ribonucleic acid, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.2.36. Temozolomide - EMA/OD/085/16

Double Bond Pharmaceutical AB; Treatment of glioma

COMP coordinator: Katerina Kopečková

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

The intention to treat the condition with the medicinal product containing temozolomide was considered justified based on preliminary clinical data demonstrating that treatment improved overall survival of patients affected by the condition.

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

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing temozolomide will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that treatment improved overall survival of patients affected by the condition. The overall survival compared favourably to historic data on the survival of patients receiving the best standard of care including currently authorised products. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.37. - EMA/OD/121/16

Treatment of multiple myeloma

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

2.2.38. - EMA/OD/122/16

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 September meeting.

2.2.39. - EMA/OD/109/16

Treatment of global ischaemic reperfusion Injury

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 September meeting.

2.3. Revision of the COMP opinions

2.3.1. Melatonin - EMA/OD/001/16

Therapicon Srl; Treatment of necrotising enterocolitis

COMP coordinator: Vallo Tillmann

Following the adoption, in May 2016, of a COMP positive opinion for melatonin for the treatment of necrotising enterocolitis, the Commission asked for further information on the reasoning supporting medical plausibility and requested confirmation that necrotising enterocolitis could be considered as a distinct medical entity. COMP confirmed that necrotising enterocolitis is a distinct medical entity and noted that the level of evidence provided by the sponsor to support medical plausibility is in line and consistent with what is generally required for comparable designations. A response reflecting the discussion will be addressed to the Commission.

[Post-meeting note: The response letter was tabled in MMD for information]

2.4. COMP opinions adopted via written procedure following previous meeting

None (EMA/OD/035/16 was moved under section 2.1.15)

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 38 applications submitted.

2.7. Evaluation on-going

The Committee noted that there was no evaluation on-going for applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of microscopic polyangiitis

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

3.1.2. -

Treatment of granulomatosis with polyangiitis

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

3.1.3. -

Treatment of soft tissue sarcoma

The Committee was briefed on the significant benefit issues in preparation of the September meeting.

3.2. Finalised letters

3.2.1. -

Treatment of acute myeloid leukaemia

The finalised letter was circulated for information.

3.2.2. -

Treatment of growth hormone deficiency

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of tuberculosis

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

MolMed SpA; Adjunctive treatment in haematopoietic cell transplantation

COMP coordinator: Armando Magrelli and Violeta Stoyanova; CAT rapporteur: Johannes H. Ovelgönne; CAT co-rapporteur: Sol Ruiz

The COMP report on review of orphan medicinal product designation adopted by written procedure after the June meeting was circulated.

4.1.2. Revlimid – lenalidomide - Type II variation - EMA/OD/078/11, EU/3/11/924, EMEA/H/C/000717/II/0079

Celgene Europe Limited; Treatment of mantle cell lymphoma

COMP coordinator: Jens Ersbøll and Daniel O'Connor; Patient's expert: Guy Bouguet; CHMP rapporteur: Pierre Demolis; CHMP co-rapporteur: Filip Josephson

The COMP report on review of Orphan Medicinal Product Designation adopted by written procedure after the June meeting was circulated.

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

4.2.1. 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

The status of the procedure at CHMP was noted. The oral explanation at COMP was postponed.

[*Post-meeting note: CHMP discussion on similarity is planned in September 2016*]

4.2.2. - 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.

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

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

The status of the procedure at CHMP was noted.

Notes:
Status of the procedure at the CHMP: Expected opinion in September 2016

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

Baxter Innovations GmbH; Treatment of pancreatic cancer

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

4.3. On-going procedures

COMP co-ordinators was appointed for 1 application.

4.4. Public Summary of Opinion

The draft public summaries of the COMP opinions adopted last month were endorsed for publication on the EMA website.

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

None

6. Organisational, regulatory and methodological matters

6.1. Mandate and organisation of the COMP

6.1.1. Strategic Review & Learning meetings

Strategic Review & Learning meeting in Utrecht (NL), 31 May-1 June 2016

The minutes were circulated for information.

6.1.2. Protocol Assistance Working Group

The working group on Protocol Assistance met on 12 July 2016.

6.1.3. COMP Drafting Group

The COMP Drafting group met on 12 July 2016.

6.2. Coordination with EMA Scientific Committees or CMDh-v

6.2.1. PDCO/COMP Working Group

The PDCO/COMP working group took place on 13 July 2016 by teleconference.

6.2.2. Recommendations on eligibility to PRIME – report from CHMP

In June 2016, CHMP granted eligibility to PRIME to two products out of eight. One of the eligible products is orphan.

EMA informed COMP members that for orphan designated products, COMP members previously involved in the evaluation of the OD applications will be systematically invited to the PRIME kick-off meetings (if still COMP member). COMP members who were not coordinators for the product are welcome to attend any kick-off meetings they are interested in.

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

6.3.1. Scientific Advice Working Party (SAWP)

Revised SAWP Mandate

The revised document was circulated for information and EMA presented the main changes.

6.4. Cooperation within the EU regulatory network

6.4.1. Commission Expert Group on Rare Diseases

The report from the Commission Expert Group on Rare Diseases 7th meeting held on 5-6 April 2016 was circulated for information.

6.5. Cooperation with International Regulators

6.5.1. Food and Drug Administration (FDA)

The draft agenda of the monthly teleconference with FDA held on 21 June 2016 is available in MMD for information.

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

The 2016 COMP Work Plan and tracking tool were tabled in MMD for information.

6.7.2. COMP Work Plan 2017

The discussion on COMP work plan 2017 was postponed due to time constraints. The COMP draft work plan 2017 is tabled in MMD.

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. Request for COMP opinion on therapeutic indication proposed for upcoming MAA

The COMP discussed a sponsor's request for COMP opinion on whether the therapeutic indication proposed in an upcoming Marketing Authorisation Application (MAA) in the EU is considered to be included within the designated orphan conditions held by the Sponsor.

COMP discussed the request and was of the view that the patient population proposed by the sponsor in the therapeutic indication was broader than the patient populations within the orphan designation cluster and would recommend limiting the MA application to the orphan conditions granted to the product.

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 11-13 July 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	
Andri Andreou	Member	Cyprus	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	Member	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	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	
Dan Henrohn	Member	Sweden	No restrictions applicable to this meeting	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Lesley Greene	Member (Vice-Chair)	Patients' Organisation Representative	No interests declared	
Mario Ricciardi	Member	Patients' Organisation Representative	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Marcela Vostarkova	Observer	Czech Republic	No interests declared	
Mário Miguel Rosa	Expert - via telephone*	Expert recommended by EMA	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

Explanatory notes

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

Abbreviations / Acronyms

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

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

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

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

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

Sponsor

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

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

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

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