17 December 2015
EMA/COMP/734238/2015
Procedure Management and Committees Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 10-12 November 2015

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

10 November 2015, 09:00-19:45, room 3E

11 November 2015, 08:30-19:30, room 3E

12 November 2015, 08:30-17:50, room 3E

Disclaimers

Some of the information contained in this set of minutes is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scopes listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also vary during the course of the review. Additional details on some of these procedures will be published in the COMP meeting reports once the procedures are finalised and start of referrals will also be available.

Of note, this set of minutes is a working document primarily designed for COMP members and the work the Committee undertakes.

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

Note on access to documents

Some documents mentioned in the 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 and experts and based on the topics in the agenda of the current meeting, the Chair announced that restrictions in the involvement of meeting participants 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. Dr Katerina Kubáčková declared a conflict for topic 2.2.4.

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 10-12 November 2015 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 6-8 October 2015 were adopted with amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. Sirolimus - EMA/OD/142/15

Rare Partners srl Impresa Sociale; Treatment of beta-thalassemia intermedia and major

COMP coordinator: Karri Penttila

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of beta-thalassemia intermedia and major, the sponsor should further elaborate on:

– The results obtained *in vitro* on beta-thalassemia intermedia and major cell lines and to further elaborate on why alternative pre-clinical in-vivo models of beta-thalassemia intermedia and major were not adequate,

– 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.

- Significant benefit

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

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from *in vitro* 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 10 November 2015, the sponsor has provided further information of the results obtained *in vitro*, and discussed further literature data in an *in vivo* model of thalassaemia, where treatment with rapamycin resulted in improvement of haematological parameters. The Committee agreed that the condition, treatment of beta thalassaemia intermedia and major, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing sirolimus was considered justified based on pre-clinical data showing an increase in haemoglobin F levels.

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

The condition was estimated to be affecting approximately 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 sirolimus may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical data that demonstrate an alternative mode of action that can lead to an increase in HbF. The Committee considered that this constitutes a clinically relevant advantage.

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

2.1.2. - EMA/OD/138/15

Treatment of cystic fibrosis

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

- Intention to diagnose, prevent or treat

In order to justify the medical plausibility of the proposed product the sponsor is invited to further discuss:

– The activity of the product when used alone *in vitro* in mutations other than F508D, and the potential links between such activity and the potential clinical activity of the product in cystic fibrosis.

– The relevance of the *in vitro* settings used to draw conclusions for the *in vivo* use of the product.

- Significant benefit

The sponsor is requested to further discuss the arguments for significant benefit by providing a comparative discussion of the potential advantages of the proposed product as compared to the currently authorized products for the treatment of cystic fibrosis. This includes elaborating on any available results supporting an assumption of clinically relevant advantage over authorised medicinal products.

Furthermore, it would be useful to obtain more information on the ongoing study/planned clinical development, since the preclinical data point towards a use in combination with lumacaftor, currently not authorized for the treatment of cystic fibrosis.

In the written response, and during an oral explanation before the Committee on 10 November 2015, the sponsor discussed the *in vitro* activity of the compound in different CFTR class mutations and assay formats, and presented a correlation between the CFTR channel function *in vitro* and the expected clinical change in FEV1. Based on this correlation it was assumed that for G551D patients an FEV1 improvement of approximately 15% may be expected. Furthermore, significant benefit was argued on the basis of the potential combination with other existing treatments, and in particular triple combinations.

The COMP reflected on the *in vitro* extrapolations and considered that it is difficult to assume significant benefit based on the *in vitro* data presented. A discussion also ensued with regards to whether any *in vivo* models of CF may be used, with the sponsor responding that CFTR modulators may not be tested in knockout models due to their mechanism of action.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 November 2015, prior to final opinion.

2.1.3. - EMA/OD/133/15

Treatment of pancreatic cancer

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

- Medical plausibility

As regards the *in vivo* models that the sponsor is using to justify the intention to treat the condition, the sponsor is invited to:

– Elaborate on the settings and the results from these studies;

– Clarify the absence of statistical analyses in the results observed, including survival and tumour growth;

– Discuss the high toxicity observed in these studies.

- Significant benefit

In line with the comments above, the sponsor is invited to elaborate on the argued add-on effects of the proposed compound, and clarify any statistically significant differences observed.

The sponsor is invited to further elaborate on how the assumption of significant benefit compared to existing therapies has been demonstrated.

In the written response, and during an oral explanation before the Committee on 10 November 2015, the sponsor provided a review of the results obtained in the preclinical studies presented in the application, in two models of the proposed condition, accompanied by a statistical analysis. Based on these models, tumour growth inhibition could be confirmed, but the add-on effects to other existing products/combinations were less clear. In particular, the COMP considered that the significant benefit of the proposed active substance has not been supported by data, in particular because there were no confirmed add-on effects on top of gemcitabine combinations.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 November 2015, prior to final opinion.

2.1.4. - EMA/OD/140/15

Treatment of Duchenne muscular dystrophy

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 20 October 2015, prior to responding to the list of issues.

2.1.5. - EMA/OD/127/15

Treatment of amyotrophic lateral sclerosis

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 amyotrophic lateral sclerosis, the sponsor should further elaborate on:

– The absence of data in either ALS preclinical models, or ALS patients

– The extrapolation from heart failure and myasthenia models to draw conclusions for the condition as proposed for designation

- Significant benefit

The arguments on significant benefit are based on the improvement of respiratory function in ALS patients, which is not targeted by authorised medicines. In absence of data in ALS models or patients affected by the condition, the sponsor is requested to present any proof of concept that would support this argument.

In the absence of data with the proposed active substance in either preclinical models of the condition or in affected patients, the criteria for orphan designation cannot be assessed.

In the written response, and during an oral explanation before the Committee on 10 November 2015, the sponsor argued that the use of a myasthenia gravis model would be relevant to draw conclusions for ALS. The applicant drew parallels between the degeneration of lower motor neurons in ALS, and the blocking of the neuromuscular junctions in MG, with regards to the common outcome of postsynaptic dysfunction in otherwise healthy muscles.

The COMP reflected on the bridging attempted by the applicant, and discussed the particularities of the proposed condition (in the context of the natural course of the disease) and proposed mechanism of action. It was reiterated to the applicant that without data in any of the available models of the condition, it would be difficult to extrapolate observations in other conditions. Consequently, the criteria for designation could not be considered met.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 10 November 2015, prior to final opinion.

2.1.6. Variant of recombinant human fibroblast growth factor 19 - EMA/OD/139/15

Diamond BioPharm Limited; Treatment of primary sclerosing cholangitis

COMP coordinator: Josep Torrent-Farnell

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

- Number of people affected

The sponsor estimates the prevalence of the primary sclerosing cholangitis based on one study from the Netherlands.

The sponsor should justify the choice of the source selected for the estimation of the prevalence of the condition. The sponsor should describe and justify the methodology used for the prevalence calculation, especially with regards to extrapolation of estimates from one region to the whole of the EU and the exclusion of other epidemiological 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 re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition, and given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor should perform a sensitivity analysis of the reported calculations.

- Significant benefit

The sponsor is invited to discuss the arguments in favour of significant benefit of the proposed product over ursodeoxycholic acid, which is authorized for the treatment of primary sclerosing cholangitis in most European Union countries. The sponsor should detail the results of any data they have to support the significant benefit assumption in the context of the current therapeutic management of patients.

In the written response, the sponsor provided a new calculation of the prevalence taking into consideration a number of publications from a number of EU member states, and revised upwards the prevalence estimate. In response to the question regarding the significant benefit the sponsor discussed an *in vivo* model of cholangiopathy where the product showed reduced inflammation and biliary fibrosis. Additionally, the sponsor has studied the effects of the product on patients with primary biliary cirrhosis who were unresponsive to ursodeoxycholic acid and obtained promising results in terms of reduced liver inflammation and bile acids synthesis. These patients have a similar bile acid mediated cholestatic injury as those suffering from primary sclerosing cholangitis, therefore this result was deemed relevant.

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

The intention to treat the condition with the medicinal product containing variant of recombinant human fibroblast growth factor 19 was considered justified based on preclinical *in vivo* data showing a reduction of hepatic inflammation and fibrosis.

The condition is chronically debilitating and life-threatening due to progressive hepatic dysfunction, with development of portal hypertension and hepatic failure, and the increased risk of developing hepatocellular cancer. Common findings include pruritus, hyperlipidaemia, hypothyroidism, deficiency of fat-soluble vitamins and osteopenia.

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

In addition, although satisfactory methods of 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 variant of recombinant human fibroblast growth factor 19 may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical data that demonstrate an attenuation of biliary fibrosis, which was not achieved by ursodeoxycholic acid. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for variant of recombinant human fibroblast growth factor 19, for treatment of treatment of primary sclerosing cholangitis, was adopted by consensus.

2.1.7. - EMA/OD/099/15

Treatment of gastric cancer

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 16 October 2015, prior to responding to the list of issues.

2.1.8. - EMA/OD/094/15

Treatment of Primary Sjogren's syndrome

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:

- Proposed indication

The sponsor is requested to explain why the condition should be limited to pSS only since there doesn't seem to exist a generally accepted classification clearly separating this condition from sSS.

In case this is considered as a subset of Sjogren syndrome, and given that the product would work as well in sSS, the sponsor is requested to justify this restriction in the context of the updated guideline (ENTR/6283/00 R04)

- Number of people affected

The sponsor should elaborate further on the grounds for prevalence calculation of pSS by providing a sensitivity analysis of the calculation and elaborating on the basis of excluding relevant epidemiological sources.

The sponsor is also requested to consider the whole population of Sjögren's syndrome and recalculate the prevalence accordingly.

- Significant benefit

The sponsor is requested to present any available comparative data (direct or indirect) between the product as applied for and authorized treatments for the proposed condition.

- Stage of development

The application completely relies on bibliographical data. The Annexes referred to in the text are however lacking so no information as to the sponsor's own experiences are available. The sponsor is invited to present the missing information.

In the written response, and during an oral explanation before the Committee on 11 November, the sponsor drew parallels to a previous designation for another condition, in order to justify that primary Sjogren should be viewed as a distinct entity for the purpose of designation. The sponsor also reviewed the studies that they have used for the prevalence of primary Sjogren disease and discusses that there are no data to support an argument of significant benefit.

The COMP considered that a regulatory extrapolation from a different condition is not a valid method to justify a distinct medical entity. Instead the whole of Sjogren syndrome patients, including secondary Sjogren should have been taken into consideration. It was noted again that the distinction between pSS and sSS was recently removed from a more recent attempt to update these AECG criteria by The American College of Rheumatology and The Sjögren's International Collaborative Clinical Alliance (Shiboski et al, Arthritis Care Res. 2012 Apr; 64(4): 475–487). Moreover, even within the primary subset alone, the prevalence calculations challenge the statutory threshold, if the sensitivity analyses are taken into consideration. Finally, no data had been presented for the justification of significant benefit.

Therefore, the COMP considered that the criteria for designation could not be considered met.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 November 2015, prior to final opinion.

2.1.9. - EMA/OD/128/15

Treatment of activated PI3Kdelta syndrome (APDS); p110delta-activating mutation causing senescent T Cells, lymphadenopathy and immunodeficiency (PASLI)

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:

- General Comment

The COMP considers that in the absence of data with the proposed product in relevant disease models for the proposed condition as applied for designation, the criteria for designation cannot be assessed.

- Proposed condition

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

The sponsor is requested to compare and contrast the aetiology, the pathophysiology, the histopathology, and the clinical characteristics of the proposed condition vis a vis other primary immunodeficiencies.

The sponsor is also requested to provide any internationally accepted classification that would encompass the proposed condition.

- Intention to diagnose, prevent or treat

The above mentioned guideline expects data in relevant disease models or in patients affected by the condition. Without data to justify the medical plausibility the criteria for designation cannot be considered met.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of activated PI3Kdelta syndrome (APDS); p110delta-activating mutation causing senescent T Cells, lymphadenopathy and immunodeficiency (PASLI), the sponsor should further elaborate on:

– Any results obtained *in vivo* in relevant models for the proposed condition, or in preliminary clinical settings in affected patients

– The relevance of the *in vitro* and cell free studies to draw conclusions for the treatment of the condition as applied for designation.

- Life-threatening and debilitating nature of the condition

The sponsor should further quantify the life-threatening or chronically debilitating nature of the condition. Data on morbidity and mortality are expected.

- Number of people affected

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

The sponsor should justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition.

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

- Significant benefit

The sponsor is requested to provide a significant benefit section versus medicines authorised for broader indications that encompass the targeted patients of this submission.

In the written response, and during an oral explanation before the Committee on 11 November, the sponsor acknowledged that "developing a new medicinal product in parallel to the discovery and characterisation of a new condition also raises a number of challenges both from a clinical development perspective but also regulatory perspective", and elaborated on the basis of Orphanet and OMIM classification codes.

Regarding the medical plausibility the sponsor added a) a dose dependent tumour growth inhibition in an *in vivo* model using transfected fibroblasts with overactivated PI3K b) a treated patient showing reduction of pAkt levels after treatment in blood cells.

With regards to prevalence, the sponsor further elaborated on the estimate and included an additional recently published article, while on the issue of significant benefit it was stated that treatment is currently limited to symptomatic management and/or replacement therapy with IVIG.

The COMP reflected on the pathophysiology of the proposed condition, the signalling resulting from an overactivated PI3Kinase, the specificity of the proposed product and the position of the entity in the context of other primary immunodeficiencies. It was also noted that there was an absence of data in the proposed condition, supporting clinically relevant outcomes.

It was considered hat the sponsor had at some extent advanced its position on the definition of the condition, but the latter still however has to find its place in international classification systems. More importantly, the applicant would have to produce some clinically relevant data (at this point there is only Akt phosphorylation in the blood cells of one patient) to justify the intention to treat the condition. Therefore, the criteria for designation had not been justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 November 2015, prior to final opinion.

2.1.10. - EMA/OD/106/15

Treatment of ascites

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

Ascites should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00). This also includes justifying the reasons why the sponsor excludes malignant ascites. The

sponsor is reminded of the definition of a distinct medical entity or a valid subset from the Guideline where it is stated that populations where a product is assumed to have a positive benefit/risk would not qualify as a valid subset.

- Number of people affected

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

It is not clear which sources the sponsor used to establish the prevalence of ascites in conditions other than cirrhosis and how the proposed value was calculated. The sponsor should justify the search methodology and provide a history of the calculations leading to the estimation of the prevalence of the condition.

It seems that the sponsor has excluded part of the population affected by the condition; therefore the sponsor should indicate on which population the prevalence calculation is based on and why ascites from malignancy seems to be excluded from the final prevalence estimate.

In conclusion the sponsor should re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed condition, specifying all sub-populations contributing to the final estimate. Given the wide range provided and substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor is also invited to perform a sensitivity analysis of the reported calculations.

- Significant benefit

In order to justify the significant benefit of the product the sponsor is first of all invited to search the European formularies for any product authorized in the EU for the treatment of ascites. This is needed in order to have a clear view of the products towards which the sponsor needs to justify the significant benefit with a comparative discussion.

Further the sponsor should detail the results of any available data supporting the significant benefit assumption of using dodecanoyl tri-(S)-lysyl terlipressin in the context of the current therapeutic management of patients.

In the written response, and during an oral explanation before the Committee on 11 November, the applicant stressed that all types of ascites are included in the proposal, referred to the ICD-10 code R18 and clarified the envisioned therapeutic indication which would be targeting those patients with ascites due to cirrhosis that cannot be managed or failed to respond to diuretics. An updated prevalence calculation was also submitted, taking into consideration two additional causes of ascites. As regards significant benefit, the centrally approved Catumaxomab for malignant ascites, and several nationally approved diuretics have been considered, and the argument of the applicant was based on targeting the patients who are untreatable with diuretics, for whom there are no approved products.

The COMP considered that the proposed condition can be viewed as a common complication of several underlying distinct medical entities, and as such not a valid condition for designation. In the absence of a valid condition for designation, the criteria for designation cannot be considered justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 November 2015, prior to final opinion.

2.1.11. (R)-1-[1-(4-Acetoxy-3,3-dimethyl-2-oxo-butyl)-2-oxo-5-(pyridin-2-yl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-(3-Methylamino-phenyl)-urea - EMA/OD/147/15

Trio Medicines Ltd; Treatment of gastric neuroendocrine tumours

COMP coordinator: Bożenna Dembowska-Bagińska

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

- Intention to diagnose, prevent or treat

The sponsor is invited to amend the proposed condition to treatment of gastro-entero-pancreatic neuroendocrine tumours in line with previous COMP opinions, or justify the proposed condition as a distinct medical entity or a valid subset. A discussion on the aetiology, pathophysiology, histopathology and clinical characteristics supported by international classification systems is expected. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

- Number of people affected

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

The sponsor is invited to re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the amended orphan condition.

- Significant benefit

The sponsor is requested to discuss the arguments provided for significant benefit and to elaborate on the results from early clinical studies to justify the assumption of significant benefit over authorised medicinal products for the gastro-entero-pancreatic neuroendocrine tumours. It should be noted that the discussion of significant benefit would be required also for gastric neuroendocrine tumours, which constitute a subset of the GEP-NETs, hence are included in this treatment indication.

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

In the written response, the sponsor discussed the anatomical location of the tumours and the mechanism of action of the proposed product. In the view of the committee, the pathology and progression of gastro-entero-pancreatic neuroendocrine tumours seems to cross anatomical boundaries, while it was also noted that the Gastric NETs have not yet been classified as distinct by international classification systems. After communication of this view to the applicant, it was agreed to broaden the proposed condition and the sponsor submitted a new estimate of the prevalence based on a number of review publications. The proposed estimate of 3.5 in 10,000 was accepted by the committee and is in line with previous designations for this condition. Additionally, in the written explanation the sponsor

submitted arguments for the significant benefit. Preliminary clinical data with a surrogate product support that the proposed active may have a disease modifying efficacy in gastric NETs. In contrast the authorized counterparts are mostly targeting symptoms.

Following review of the application by the Committee, it was agreed to rename the indication to treatment of gastro-entero-pancreatic neuroendocrine tumours.

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

The intention to treat the condition with the medicinal product containing (R)-1-[1-(4-Acetoxy-3,3-dimethyl-2-oxo-butyl)-2-oxo-5-(pyridin-2-yl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-(3-methylamino-phenyl)-urea was considered justified based on clinical data in patients affected by the condition demonstrating effects on tumour size and number of metastases.

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

The condition was estimated to be affecting approximately 3.5 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 (R)-1-[1-(4-acetoxy-3,3-dimethyl-2-oxo-butyl)-2-oxo-5-(pyridin-2-yl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-(3-methylamino-phenyl)-urea may be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that gastrin-driven tumours show reduction in size and number of metastases. This compares favourably to the authorized treatments which target symptoms of the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (R)-1-[1-(4-Acetoxy-3,3-dimethyl-2-oxo-butyl)-2-oxo-5-(pyridin-2-yl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-(3-methylamino-phenyl)-urea, for treatment of gastro-entero-pancreatic neuroendocrine tumours, was adopted by consensus.

2.1.12. - EMA/OD/263/14

Treatment of myotonic dystrophy

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

- Intention to diagnose, prevent or treat

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

– The similarities and differences of the surrogate product used in the application for the medical plausibility studies and the proposed product;

– How the results obtained in studies with other products can be extrapolated to the proposed efficacy of the product for designation.

- Significant benefit

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

The sponsor is requested to further discuss the provided arguments for significant benefit and to justify with data the assumption of significant benefit over authorised medicinal products regarding the effects on myotonia and/or other disease manifestations.

In the written response, and during an oral explanation before the Committee on 11 November, the sponsor stressed that the surrogate product had the same delivery and mechanism of action, and presented the differences in terms of chemical modifications, that would only affect the degradation of the product and do not influence its efficacy. Based on this it was argued that extrapolations from one product to the other would be possible.

However, the COMP considered that the active substance of the product for designation is not the same as the active substance of the product that has been used in the studies to demonstrate medical plausibility, and that there is are distinct differences in terms of the binding site. Moreover the COMP considered that there were too many uncertainties regarding the studied endpoints and noted that the sponsor should have performed adequate preclinical studies with the specific product for designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 November 2015, prior to final opinion.

2.1.13. - EMA/OD/125/15

Prevention of mercury toxicity

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

- Intention to diagnose, prevent or treat

In order to establish the medical plausibility of the proposed product the sponsor is invited to further clarify:

– Whether the intended clinical use of the product would be for primary prevention or for secondary prevention (post-exposure prophylaxis), which would be considered as treatment by the COMP;

– The relevance of the data in post-exposure prophylaxis, such as the preclinical study where the product was administered 25 minutes after the exposure, to the prevention indication as sought for;

– The data on the second preclinical model cited in a preventive setting.

– The clinical relevance and real-life applicability of a product preventing mercury toxicity, which is mainly accidental.

- 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 better clarify the methodology used for the population at risk calculation, and to describe figures accounting for all types and causes of mercury toxicity.

In primary prevention it is assumed that the population at risk would be higher than the population that needs treatment in a year, and such population needs to be identified with a robust and understandable methodology. So far it seems that the figures presented by the sponsor would apply to a treatment use rather than preventive use, therefore the sponsor needs to provide figures of the population at risk.

- Significant benefit

There are no treatment currently authorized for the prevention of mercury toxicity, however it seems that the proposed product would be targeting post-exposure prophylaxis, which has been considered as treatment by the COMP, for which medicines are authorized in the EU.

In the written response, and during an oral explanation before the Committee on 12 November, the sponsor clarified that they were seeking designation for primary prevention, and elaborated with regards to the target population, consisting primarily of first responders firefighters in fires and industrial accidents, as well as military personnel in combat zones. The applicant also discussed the relevance of presenting data in a therapeutic setting, and clarified that the details of the second cited model were not available. A (revised downwards) calculation for prevalence was also submitted and no authorised treatments were identified that would require a justification of significant benefit.

The COMP considered that in the absence of data in the preventive setting, the medical plausibility could not be considered justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 November 2015, prior to final opinion.

2.1.14. - EMA/OD/154/14

Treatment of Wilson'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

In order to justify the medical plausibility of the proposed product the sponsor is invited to further discuss:

- the relevance of the endpoints and settings of the preclinical model used;

- the effect of the product on hepatic copper levels;

- Significant benefit

The sponsor is reminded that in absence of a robust medical plausibility the significant benefit of the product cannot be assessed.

The sponsor is invited to discuss and present any data supporting the clinically relevant advantage or major contribution to patient care of the proposed product versus the currently authorized treatments for the condition in the EU.

In the written response, and during an oral explanation before the Committee on 12 November, the sponsor agreed with the limitations of the low number of subjects in the *in vivo* settings studied, and discussed the difficulty to draw conclusions regarding the effect on hepatic copper levels.

The COMP considered that in the absence of data with the proposed product in a relevant model of the condition showing improved effects in a clinically relevant endpoint, the criteria for designation cannot be considered justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 November 2015, prior to final opinion.

2.1.15. 2-amino-2-[2-[2-chloro-4-[[3-(phenylmethoxy)phenyl]thio]phenyl]ethyl]-1,3-propanediol hydrochloride - EMA/OD/131/15

Novartis Europharm Limited; Prevention of graft-versus-host disease

COMP coordinator: Karri Penttila

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for prevention of graft-versus-host disease, the sponsor should further elaborate on:

– The relevance of the preclinical model used for the prevention of graft-versus-host disease, and the interpretation of the results obtained in the experiments;

– 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;

– An overview of the Phase I study in patients covering the aim and methodology as well as the results of the interim analysis.

- Number of people affected

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

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

- Significant Benefit

The sponsor is proposing that their product offers an alternative mode of action which would offer a significant benefit in the prevention of graft vs host disease.

The sponsor should further elaborate on the interim results obtained from the Phase Ib study where the product is being studied in patients with the condition.

In the written response, the sponsor provided information of the preclinical model used for the prevention of graft-versus-host disease and adequate descriptions of both haploidentical and mismatched mouse models of GVHD used in the pre-clinical studies. Regarding the preliminary clinical study, data from 10 individuals who underwent hematopoietic stem cell transplantation were discussed. A recalculation of prevalence was also provided.

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

The intention to prevent the condition with the medicinal product containing 2-amino-2-[2-[2-chloro-4-[[3-(phenylmethoxy)phenyl]thio]phenyl]ethyl]-1,3-propanediol hydrochloride was considered justified based on pre-clinical *in vivo* data which showed improved survival.

The condition is chronically debilitating and life-threatening in particular 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 population of patients eligible for prevention of the condition was estimated to be less than 1 in 10,000 persons in the European Union, at the time the application was made, at the time the application was made.

In addition, although satisfactory methods of prevention 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-amino-2-[2-[2-chloro-4-[[3-(phenylmethoxy)phenyl]thio]phenyl]ethyl]-1,3-propanediol hydrochloride may be of significant benefit to the population at risk of developing the condition. The sponsor has provided clinical data that demonstrate improved outcome in the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 2-amino-2-[2-[2-chloro-4-[[3-(phenylmethoxy)phenyl]thio]phenyl]ethyl]-1,3-propanediol hydrochloride, for treatment of prevention of graft-versus-host disease, was adopted by consensus.

2.1.16. Recombinant human nerve growth factor - EMA/OD/143/15

Dompé farmaceutici S.p.A.; Treatment of neurotrophic keratitis

COMP coordinator: Geraldine O'Dea

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

- Number of people affected

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

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

As it seems that the sponsor has excluded part of the population affected by condition, the sponsor should further elaborate on why they did this. An expanded list of underlying aetiologies (Semeraro et al 2014) should be taken into consideration for the purpose of calculating prevalence. It has been noted that the incidence of this condition increases with ageing which does not seem to have been addressed.

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

In the written response, and during an oral explanation before the Committee on 12 November 2015, the sponsor addressed the issues raised and pointed out that the methodology for calculating the prevalence has been previously considered acceptable by the COMP for another procedure.

The COMP discussed the basis of the submission of the prevalence calculation which was identical to a previous submission by another sponsor, which received a positive opinion at the end of 2014. It was acknowledged that the assumptions made in that submission had been based on a dated review article on the aetiology of the condition. This article is at variance with a more up-to-date article by Semararo et al from 2014. The sponsor questioned the validity of the COMP's decision to base the assessment on prevalence on this more up-to-date article informing the committee that there was no clear European position on what are all the fundamental causes of the condition. Although the Semararo et al article included more causes which can lead to the condition this was still an area for debate amongst experts. The committee took these considerations into account and reviewed the data submitted by this sponsor. The committee recognised the precedence set by the positive opinion from the end of 2014. Based on these considerations the COMP was positive to the designation.

At the time of review of the orphan designation at marketing authorisation the COMP will be vigilant to any changes to the prevalence adopted in this designation. The sponsor dismissed Adie's Syndrome and ageing as potential causes of the condition and did not include them in this calculation. The sponsor proposed an additional refinement to the prevalence assumption regarding diabetic and herpetic causes of the condition. These assumptions indicated that the real rate of neurotrophic keratitis could actually be lower than that which was reported in the only positive opinion that was discussed. This produced a lower calculation of 4.2 in 10,000.

The Committee agreed that the condition, treatment of neurotrophic keratitis, 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 nerve growth factor was considered justified based on preliminary clinical data in patients with the condition showing corneal improvement.

The condition is chronically debilitating due to progressive damage of corneal epithelium and stroma leading to loss of vision. Corneal ulceration, infection and perforation can also occur.

The condition was estimated to be affecting approximately 4.2 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 recombinant human nerve growth factor, for treatment of neurotrophic keratitis, was adopted by consensus.

2.1.17. Combretastatin A1-diphosphate - EMA/OD/144/15

Diamond BioPharm Limited; Treatment of acute myeloid leukaemia

COMP coordinator: Frauke Naumann-Winter

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

- Medical plausibility

In order to further justify the medical plausibility of the proposed product the sponsor is invited to further discuss the lack of efficacy of cytarabine monotherapy in the preclinical studies presented in this application.

- Significant benefit

The sponsor reports safety data from a phase I study started in 2011 in patients with relapsed and/or refractory AML, however no efficacy data are presented.

In order to establish the significant benefit of the proposed product the sponsor is invited to present a comparative discussion of any available preclinical and clinical data supporting the clinical advantage of the proposed product versus the medicinal products already authorized for the condition. This includes any available efficacy data from the phase I study.

In the written response, and during an oral explanation before the Committee on 12 November 2015, the sponsor described the settings and results of the *in vivo* models studied and clarified that the cytarabine resistance of the cell line used *in vivo* has been previously described in the literature. However, the aim of the experiments was for the proposed product to be used in combination with cytarabine to investigate add-on effects.

The sponsor also addressed the question on significant benefit, discussing the preliminary results from the phase I trial in relapsed/refractory AML and myelodysplastic syndromes. The trial was mainly targeted at safety however the sponsor presented some preliminary clinical results showing favourable responses in the treated patients. The COMP considered that this preliminary clinical favourable response in a relapsed population, together with the preclinical data presented by the sponsor, can support the significant benefit at the present stage of development. Protocol assistance for confirmation of significant benefit at marketing authorization was strongly recommended.

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

The intention to treat the condition with the medicinal product containing combretastatin A1-diphosphate was considered justified based on preclinical and clinical data showing antitumor efficacy.

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

progresses rapidly and is fatal within days to weeks or a few months if left untreated. The overall 5-year relative survival with the currently available treatments is approximately 22%.

The condition was estimated to be affecting less than 1.8 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing combretastatin A1-diphosphate may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing efficacy when used in combination with an authorised product and preliminary clinical data showing favourable response in patients relapsing from previous treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for combretastatin A1-diphosphate, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.1.18. - EMA/OD/095/15

Treatment of short bowel syndrome

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 short bowel syndrome, the sponsor should further elaborate on:

– How the presented results can be extrapolated to the proposed product with the active substance being a recombinant fusion protein, providing a detailed discussion on the assumptions.

– The efficacy on the weaning off parenteral nutrition and how this efficacy could compare to a historic control of untreated patients or patients on standard of care.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. The sponsor is requested to further discuss the arguments provided for significant benefit over teduglutide, supported by data. In this context, the sponsor is invited to provide data to support the significant benefit assumptions in the context of the current therapeutic management of patients with teduglutide.

In the written response, and during an oral explanation before the Committee on 10 November 2015, the sponsor further elaborated on the grounds of extrapolation of the effects of another surrogate product, to draw conclusions on the proposed product for designation. The applicant based this extrapolation on the mechanism of action. At the oral explanation the COMP noted that in the absence of data with the specific active substance as applied for designation, the medical plausibility could not be considered justified.

With regards to the significant benefit discussion in the context of authorised teduglutide, the sponsor discussed the envisaged direct benefits of the product versus teduglutide on the basis of data generated with a different active substance and not the product under review.

At the oral explanation the COMP clarified the difficulty to establish significant benefit for a product that has not been tested in a relevant disease model or in patients affected by the condition.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 November 2015, prior to final opinion.

2.1.19. - EMA/OD/137/15

Treatment of adrenal insufficiency

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

- Number of people affected

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

The sponsor is invited to

a) Clarify if all causes of adrenal insufficiency are included in the calculation, including tertiary insufficiency

b) Provide a sensitivity analysis of all assumptions based on worst case scenarios;

c) Discuss any epidemiological changes since the time of the referred studies.

- Significant benefit

In order to justify the significant benefit the sponsor is invited to discuss the potential advantages of the proposed formulation in the adult population *versus* the currently authorized products in the EU. This applies even though the applicant intends to develop the product in children only.

In the written response, and during an oral explanation before the Committee on 12 November 2015, the sponsor clarified that all forms of the condition had been included in the prevalence calculation and provided a sensitivity analysis of a worse-case scenario below the statutory threshold. Significant benefit was argued on the basis of an improved formulation and dosing with a particular benefit for the paediatric population and those patients with difficulties in swallowing tablets. The COMP considered that the prevalence criterion was not justified and that no data to support the significant benefit had been presented with the product vis a vis the authorised treatments for the proposed condition.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 November 2015, prior to final opinion.

2.2. For discussion / preparation for an opinion

2.2.1. [4-aminobutanoic acid-glycyl-L-glutaminyl-L-arginyl-L-.alpha.-glutamyl-L-threonyl-L-prolyl-L-.alpha.-glutamylglycyl-L-alanyl-L-.alpha.-glutamyl-L-alanyl-L-lysyl-L-prolyl-L-tryptophyl-L-tyrosyl-L-aspartyl](cyclo 1-Dgamma17) - EMA/OD/153/15

Apeptico Forschung und Entwicklung GmbH; Treatment of pseudohypoaldosteronism type 1B

COMP coordinator: Vallo Tillmann

The Committee agreed that the condition, treatment of pseudohypoaldosteronism type 1B, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing [4-aminobutanoic acid-glycyl-L-glutaminyl-L-arginyl-L-.alpha.-glutamyl-L-threonyl-L-prolyl-L-.alpha.-glutamylglycyl-L-alanyl-L-.alpha.-glutamyl-L-alanyl-L-lysyl-L-prolyl-L-tryptophyl-L-tyrosyl-L-aspartyl](cyclo 1-Dgamma17) was considered justified based on pre-clinical data showing an improvement in amiloride-sensitive epithelial sodium channel (ENaC) function which is associated with the condition.

The condition is life-threatening and chronically debilitating due to episodes of salt loss, dehydration, hyperkalemia, electrolyte disturbances, gastrointestinal symptoms, respiratory infections and other respiratory problems.

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.

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

A positive opinion for [4-aminobutanoic acid-glycyl-L-glutaminyl-L-arginyl-L-.alpha.-glutamyl-L-threonyl-L-prolyl-L-.alpha.-glutamylglycyl-L-alanyl-L-.alpha.-glutamyl-L-alanyl-L-lysyl-L-prolyl-L-tryptophyl-L-tyrosyl-L-aspartyl](cyclo 1-Dgamma17), for treatment of pseudohypoaldosteronism type 1B, was adopted by consensus.

2.2.2. 2-(2-chlorobenzylidene)hydrazinecarboximidamide acetate - EMA/OD/170/15

Inflectis Bioscience; Treatment of Charcot-Marie-Tooth Disease

COMP coordinator: Giuseppe Capovilla

The Committee agreed that the condition, treatment of Charcot-Marie-Tooth Disease, 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-chlorobenzylidene) hydrazinecarboximidamide acetate was considered justified based on preclinical *in vivo* data showing improved myelination and motor function.

The condition is chronically debilitating due to the progressive deterioration of peripheral motor and sensory nerves which leads to functional impairment, pain, progressive disability and a reduction in the quality of life.

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

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

A positive opinion for 2-(2-chlorobenzylidene)hydrazinecarboximidamide acetate, for treatment of Charcot-Marie-Tooth Disease, was adopted by consensus.

2.2.3. Adeno-associated virus vector serotype rh10 encoding human factor IX - EMA/OD/172/15

Pharma Gateway AB; Treatment of hemophilia B

COMP coordinator: Martin Možina

Following review of the application by the Committee, it was agreed to rename the active substance to adeno-associated viral vector serotype rh10 containing the human factor IX gene.

The Committee agreed that the condition, treatment of haemophilia B, 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 rh10 containing the human factor IX gene was considered justified based on preclinical data in a relevant model of the condition where treatment with the product resulted in a sustained expression of factor IX and restoration of its activity.

The condition is chronically debilitating and life-threatening, in particular due to spontaneous bleeding episodes as well as substantially prolonged bleeding upon injury.

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 adeno-associated virus vector serotype rh10 encoding human factor IX may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data in a model of the condition that support long term restoration of factor IX. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype rh10 containing the human factor IX gene, for treatment of haemophilia B, was adopted by consensus.

2.2.4. - EMA/OD/166/15

Treatment of ovarian cancer

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

2.2.5. Bilayer, engineered, collagen hydrogel-based skin graft composed of autologous keratinocytes and fibroblasts - EMA/OD/163/15

Voisin Consulting S.A.R.L.; Treatment of partial deep dermal and full thickness burns

COMP coordinator: Armando Magrelli

The Committee agreed that the condition, treatment of partial deep dermal and full thickness burns, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing bilayer engineered collagen hydrogel-based skin graft composed of autologous keratinocytes and fibroblasts was considered justified based on preclinical studies and preliminary clinical observations supporting grafting of the product and reconstitution of a stratified epidermal structure in the area of burn.

The condition is chronically debilitating due to formation of extensive scarring that causes disfigurement, pain, itching, impairment of mobility and need for surgery. The condition is also life-threatening due to multi-organ failure and sepsis.

The condition was estimated to be affecting less than 2.9 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 bilayer engineered collagen hydrogel-based skin graft composed of autologous keratinocytes and fibroblasts may be of significant benefit to those affected by the condition. The sponsor has provided preclinical studies and preliminary clinical observations supporting grafting of the product and reconstitution of a stratified epidermal structure in the area of burn. This targets a different aspect of the management of the condition versus the authorised medicinal products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for bilayer engineered collagen hydrogel-based skin graft composed of autologous keratinocytes and fibroblasts, for treatment of partial deep dermal and full thickness burns, was adopted by consensus.

2.2.6. - EMA/OD/164/15

Treatment of non-infectious uveitis

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 December meeting.

2.2.7. Glibenclamide - EMA/OD/149/15

AMMTeK; Treatment of monogenic diabetes

COMP coordinator: Vallo Tillmann

Following review of the application by the Committee, it was agreed to rename the indication to treatment of neonatal diabetes.

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

The intention to treat the condition with the medicinal product containing glibenclamide was considered justified based on preliminary data in paediatric patients with the condition showing improved glycaemic control without increasing hypoglycaemia risk.

The condition is life-threatening and chronically debilitating due to hyperglycemia which includes symptoms such as thirst, frequent urination, and dehydration. In severe cases this is associated with ketoacidosis which can lead to death.

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

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

A positive opinion for glibenclamide, for treatment of neonatal diabetes, was adopted by consensus.

2.2.8. - EMA/OD/116/15

Treatment of acute myeloid leukemia

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 December meeting.

2.2.9. - EMA/OD/148/15

Treatment of interstitial lung disease in children

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 December meeting.

2.2.10. - EMA/OD/155/15

Treatment of myelodysplastic syndromes

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 December meeting.

2.2.11. Imetelstat sodium - EMA/OD/154/15

Janssen-Cilag International N.V.; Treatment of primary myelofibrosis

COMP coordinator: Frauke Naumann-Winter

Following review of the application by the Committee, it was agreed to rename the indication to treatment of myelofibrosis.

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

The intention to treat the condition with the medicinal product containing imetelstat sodium was considered justified based on early clinical data in affected patients demonstrating the potential to reverse fibrosis.

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

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing imetelstat sodium may be of significant benefit to those affected by the condition. The sponsor has provided early clinical data that demonstrate reversal of fibrosis, which is not achieved by any authorized treatments. This is attributed to the novel mechanism of action which inhibits the clonal expansion of malignant cells. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for imetelstat sodium, for treatment of myelofibrosis, was adopted by consensus.

2.2.12. Live attenuated listeria monocytogenes bioengineered with a chimeric human epidermal growth factor receptor 2 fused to a truncated form of the Lm protein Listeriolysin O - EMA/OD/162/15

Coté Orphan Consulting UK Limited; Treatment of osteosarcoma

COMP coordinator: Bożenna Dembowska-Bagińska

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

The intention to treat the condition with the medicinal product containing live attenuated *Listeria monocytogenes* bioengineered with a chimeric human epidermal growth factor receptor 2 fused to a truncated form of the Lm protein listeriolysin O was considered justified based on preliminary pre-clinical *in vivo* data showing improved survival.

The condition is chronically debilitating due to the potential of limb amputation and life-threatening with a less than a 20% long-term survival rate following recurrence.

The condition was estimated to be affecting approximately 2.8 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing live attenuated *Listeria monocytogenes* bioengineered with a chimeric human epidermal growth factor receptor 2 fused to a truncated form of the Lm protein listeriolysin O may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical data that demonstrate that where metastatic disease was present improved survival was noted when the sponsor's product was used. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for live attenuated listeria monocytogenes bioengineered with a chimeric human epidermal growth factor receptor 2 fused to a truncated form of the Lm protein Listeriolysin O, for treatment of osteosarcoma, was adopted by consensus.

2.2.13. - EMA/OD/168/15

Treatment of pancreatic cancer

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

2.2.14. Live attenuated *Listeria monocytogenes* delta *actA*/delta *inlB* strain expressing human mesothelin - EMA/OD/157/15

Medpace Germany GmbH; Treatment of malignant mesothelioma

COMP coordinator: Katerina Kubáčková

The Committee agreed that the condition, treatment of 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 live attenuated *Listeria monocytogenes* delta *actA*/delta *inlB* strain expressing human mesothelin was considered justified based on preliminary clinical data in patients with the condition that show response to treatment and improved progression free survival after add-on treatment to authorised products.

The condition is life-threatening and chronically debilitating 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 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 live attenuated *Listeria monocytogenes* delta *actA*/delta *inlB* strain expressing human mesothelin may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that the add-on treatment to the current authorised standard of care resulted in improvements regarding treatment response and progression free survival. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for live attenuated *Listeria monocytogenes* delta *actA*/delta *inlB* strain expressing human mesothelin, for treatment of malignant mesothelioma, was adopted by consensus.

2.2.15. Recombinant human monoclonal IgG1 antibody against Programmed Death Ligand-1 - EMA/OD/150/15

Merck KGaA; Treatment of Merkel cell carcinoma

COMP coordinator: Bożenna Dembowska-Bagińska

The Committee agreed that the condition, treatment of Merkel cell carcinoma, 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 monoclonal IgG1 antibody against programmed death ligand-1 was considered justified based on preliminary clinical data in patients with metastatic disease, who responded to treatment with the proposed product in terms of tumour volume.

The condition is chronically debilitating with median survival of about a year reported in patients with advanced disease state.

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

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

A positive opinion for recombinant human monoclonal IgG1 antibody against programmed death ligand-1, for treatment of Merkel cell carcinoma, was adopted by consensus.

2.2.16. - EMA/OD/160/15

Treatment of soft tissue sarcoma

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

2.2.17. Sodium (2R,3S,5R)-5-(4-amino-2-oxo-1,3,5-triazin-1(2H)-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl ((2R,3S,5R)-5-(2-amino-6-oxo-1H-purin-9(6H)-yl)-3-hydroxytetrahydrofuran-2-yl)methyl phosphate - EMA/OD/165/15

Otsuka Pharmaceutical Europe Ltd; Treatment of acute myeloid leukaemia

COMP coordinator: Jens Ersbøll

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

The intention to treat the condition with the medicinal product containing sodium (2R,3S,5R)-5-(4-amino-2-oxo-1,3,5-triazin-1(2H)-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl ((2R,3S,5R)-5-(2-amino-6-oxo-1H-purin-9(6H)-yl)-3-hydroxytetrahydrofuran-2-yl)methyl phosphate was considered justified based on preclinical and preliminary clinical data showing antileukaemic activity of the proposed product.

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

The condition was estimated to be affecting approximately 1.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing sodium (2R,3S,5R)-5-(4-amino-2-oxo-1,3,5-triazin-1(2H)-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl ((2R,3S,5R)-5-(2-amino-6-oxo-1H-purin-9(6H)-yl)-3-hydroxytetrahydrofuran-2-yl)methyl phosphate may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing favourable responses with the proposed product in patients relapsing

from treatment with some of the currently authorized products for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by acute myeloid leukaemia.

A positive opinion for sodium (2R,3S,5R)-5-(4-amino-2-oxo-1,3,5-triazin-1(2H)-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl ((2R,3S,5R)-5-(2-amino-6-oxo-1H-purin-9(6H)-yl)-3-hydroxytetrahydrofuran-2-yl)methyl phosphate, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.2.18. - EMA/OD/123/15

Treatment of arginase deficiency

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 December meeting.

2.2.19. - EMA/OD/124/15

Treatment of argininosuccinate lyase deficiency

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 December meeting.

2.2.20. Synthetic peptide L-Cysteine, L-cysteinylglycyl-L-glutaminyl-L-arginyl-L-.alpha.-glutamyl-L-threonyl-L-prolyl-L-.alpha.-glutamylglycyl-L-alanyl-L-.alpha.-glutamyl-L-alanyl-L-lysyl-L-prolyl-L-tryptophyl-L-tyrosyl-, cyclic (1.fwdarw.17)-disulfide - EMA/OD/151/15

Apeptico Forschung und Entwicklung GmbH; Treatment of pseudohypoaldosteronism type 1B

COMP coordinator: Vallo Tillmann

The Committee agreed that the condition, treatment of pseudohypoaldosteronism type 1B, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing synthetic peptide L-cysteine, L-cysteinylglycyl-L-glutaminyl-L-arginyl-L-.alpha.-glutamyl-L-threonyl-L-prolyl-L-.alpha.-glutamylglycyl-L-alanyl-L-.alpha.-glutamyl-L-alanyl-L-lysyl-L-prolyl-L-tryptophyl-L-tyrosyl-, cyclic (1.fwdarw.17)-disulfide was considered justified based on based on pre-clinical data showing an improvement in amiloride-sensitive epithelial sodium channel (ENaC) channel function which is associated with the condition.

The condition is life-threatening and chronically debilitating due to due to episodes of salt loss, dehydration, hyperkalemia, electrolyte disturbances, gastrointestinal symptoms, respiratory infections and other respiratory problems.

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.

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

A positive opinion for synthetic peptide L-cysteine, L-cysteinylglycyl-L-glutaminyl-L-arginyl-L-.alpha.-glutamyl-L-threonyl-L-prolyl-L-.alpha.-glutamylglycyl-L-alanyl-L-.alpha.-glutamyl-

L-alanyl-L-lysyl-L-prolyl-L-tryptophyl-L-tyrosyl-, cyclic (1.fwdarw.17)-disulfide, for treatment of pseudohypoaldosteronism type 1B, was adopted by consensus.

2.2.21. - EMA/OD/169/15

Treatment of pancreatic cancer

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

2.2.22. - EMA/OD/122/15

Treatment of post cardiac arrest 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 December meeting.

2.2.23. - EMA/OD/152/15

Treatment of pulmonary arterial hypertension

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 December meeting.

2.3. Revision of the COMP opinions

None

2.4. COMP opinions adopted via written procedure following previous meeting

None

2.5. Appeal

None

2.6. Nominations

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

COMP coordinators were appointed for 12 submitted applications and 9 upcoming applications.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 18 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of ovarian cancer

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

3.1.2. -

Treatment of amyotrophic lateral sclerosis

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

3.1.3. -

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

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

3.1.4. -

Treatment of growth hormone deficiency

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

3.1.5. -

Treatment of Prader-Willi syndrome

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

3.2. Finalised letters

3.2.1. -

Treatment of systemic sclerosis

The finalised letter was circulated for information.

3.2.2. -

Treatment of acromegaly

The finalised letter was circulated for information.

3.2.3. -

Treatment of sickle cell disease

3.3. New requests

3.3.1. -

Prevention of oral mucositis in head and neck cancer patients undergoing radiation therapy

The new request was noted.

3.3.2. -

Treatment of Niemann-Pick disease, type C

The new request was noted.

3.3.3. -

Treatment of cytomegalovirus disease in patients with impaired cell mediated immunity

The new request was noted.

3.3.4. -

Treatment of advanced ovarian cancer

The new request was noted.

3.3.5. -

Treatment of acute myeloid leukaemia

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. Heparesc - human heterologous liver cells - EMEA/H/C/003750

Cytonet GmbH&Co KG;

a) treatment of carbamoyl-phosphate synthase-1 deficiency (EMA/OD/108/10, EU/3/10/821)

b) treatment of ornithine-transcarbamylase deficiency (EMEA/OD/042/07, EU/3/07/470)

c) treatment of citrullinaemia type 1 (EMA/OD/105/10, EU/3/10/818)

d) treatment of hyperargininaemia (EMA/OD/106/10, EU/3/10/819)

e) treatment of argininosuccinic aciduria (EMA/OD/107/10, EU/3/10/820)

The CHMP negative opinion was noted by the COMP.

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

4.2.1. - Dexamethasone acetate – EMEA/H/C/004071

LABORATOIRES CTRS; Treatment of multiple myeloma

The status of the procedure at the CHMP was noted by the COMP.

4.2.2. Spectrila - recombinant l-asparaginase – EMA/OD/063/04, EU/3/04/258, EMEA/H/C/002661

Medac Gesellschaft fuer klinische Spezialpraeparate mbH; Treatment of acute lymphoblastic leukaemia

The status of the procedure at the CHMP was noted by the COMP.

4.2.3. 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

The status of the procedure at the CHMP was noted by the COMP.

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

Bioprojet; Treatment of narcolepsy

The status of the procedure at the CHMP was noted by the COMP.

4.3. On-going procedures

4.3.1. List of on-going procedures

COMP co-ordinators were appointed for 5 applications.

5. Organisational, regulatory and methodological matters

5.1. Mandate and organisation of the COMP

5.1.1. Strategic Review & Learning meetings

Joint COMP- PDCO Joint Strategic Review & Learning Meeting held in Bonn on 14-16 October 2015

The joint COMP-PDCO session started with presentations on each Committee's missions and supporting Legislations. In particular, the concept of significant benefit and how it is used by both groups was clarified. Both COMP and PDCO were of the view that discussions on relative effectiveness should involve HTAs and start earlier to agree on comparators and endpoints. There was a presentation on areas where the impact of the two legislations affects each other. The area regarding the differences and similarities of the conditions was particularly highlighted. Finally, the attendees discussed a proposal from PDCO to prepare a document focussed on the identification of criteria to select paediatric rare disease to be prioritised for EU funding. Two case studies were presented that emphasized that the approach followed by the two Committees might slightly differ mainly in terms of establishment of significant therapeutic benefit. All participants agreed that the discussions were very informative and that the COMP-PDCO collaboration should be strengthen via the already existing COMP-PDCO working group.

The COMP session was dedicated to significant benefit. Having analysed a few PA cases, the group agreed on standards topics to be included in the answer to a question on significant benefit.

Strategic Review & Learning Meetings organised during the term of the European Presidency:
- Organisational aspects
- Clarification on responsibility for handling of declared interests and on involvement of external (non NCA) speakers

EMA presented a set of guiding principles for the organisation of Strategic Review & Learning meetings. The involvement of the Scientific Coordination Board in proposing key priority areas and topics for inclusion on future agendas as well as potential clustering of committees was highlighted. Subject to the request of the hosting Member State, the EMA can provide support in the development of the meeting agenda and in providing support for the participation of certain committee members (e.g. civil society committee members) according to agreed criteria.

The Chair welcomed the presented principles and highlighted the importance of allowing the participation of EMA staff involved in COMP activities in the Strategic Review & Learning meetings.

5.2. Coordination with EMA Scientific Committees or CMDh-v

5.2.1. Committee for Medicinal Products for Human Use (CHMP)

Public consultation comments on the CHMP Guideline concerning Conditional Marketing Authorisation

EMA presented an updated version of the draft CHMP Guideline on Conditional Marketing Authorisation following comments received from COMP and during the public consultation.

The draft guideline will be presented to the CHMP plenary in November for agreement.

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

5.3.1. Significant Benefit Working Group

The working group on Significant Benefit met on 12 November 2015.

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

Work plan for the European Medicines Agency Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (PCWP) 2016

The Committee noted the PCWP work plan.

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

Work plan for the European Medicines Agency Human Scientific Committees' Working Party with Healthcare Professionals' Organisations (HCPWP) 2016

The Committee noted the HCPWP work plan.

5.4. Cooperation within the EU regulatory network

None

5.5. Cooperation with International Regulators

None

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

None

5.7. COMP work plan

5.7.1. Draft COMP Work Plan 2016

The Chair presented the draft COMP work plan 2016 to the committee and asked for volunteers for the tasks listed in the work plan. A few comments were received on the proposals. The work plan will be updated and presented again in December for adoption.

5.8. Planning and reporting

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

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

5.8.2. Overview of orphan marketing authorisations/applications

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

6. Any other business

6.1.1. Mogamulizumab for treatment of peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated); ProStrakan Limited (EMA/OD/104/11, EU/3/11/943)

Sponsor's clarification request of 4 November 2015

The COMP discussed the scope of the designated indication.

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 10-12 November 2015 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bruno Sepodes	Chair	Expert recommended by EMA	No interests declared	
Brigitte Blöchl-Daum	Member	Austria	No interests declared	
Irena Bradinova	Member	Bulgaria	No interests declared	
Adriana Andrić	Member	Croatia	No interests declared	
Andri Andreou	Member	Cyprus	No interests declared	
Katerina Kubacková	Member	Czech Republic	No participation in final deliberations and voting	2.2.15 2.2.4
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	
Dainis Krievins	Member	Latvia	No restrictions applicable to this	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			meeting	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Violeta Stoyanova-Beninska	Member	Netherlands	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Zuzana Batova	Member	Slovak Republic	No interests declared	
Martin Možina	Member	Slovenia	No interests declared	
Josep Torrent-Farnell	Member	Spain	No interests declared	
Kerstin Westermark	Member	Sweden	No restrictions applicable to this meeting	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Lesley Greene	Member (Vice-Chair)	Patients' Organisation Representative	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Antonio Blazquez	Expert - in person*	Spain	No restrictions applicable to this meeting	

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 restrictions applicable to this meeting	
Dan Henrohn	Observer	Sweden - MPA	No restrictions applicable to this meeting	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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