13 November 2014
EMA/COMP/575359/2014
Procedure Management and Business Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes of the 7-9 October 2014 meeting

Some documents mentioned in the agenda/minutes cannot be released at present within the framework of Regulation (EC) No 1049/2001 on access to documents because 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 Adoption of the agenda, EMA/COMP/545527/2014

The agenda was adopted with no amendments.

1.2 Adoption of the minutes of the previous meeting, 2-4 September 2014 EMA/COMP/427307/2014

The minutes were adopted with no amendments.

1.3 Conflicts of Interest

The Chair asked the Committee members to declare their potential conflict of interest.

The COMP secretariat was informed of the following:

- EGAN received a grant from the sponsors of the product under agenda point 2.2.3, 5.1.1 and 5.2.3. Nevertheless, no direct conflicts of interest have been identified for P. Evers (EGAN), Patient Representative in the COMP.

2. Applications for orphan medicinal product designation[1]

2.1. For opinion

2.1.1 1-(6-benzothiazolylsulfonyl)-5-chloro-1H-indole-2-butanoic acid for treatment of systemic sclerosis, Inventiva - EMA/OD/129/14
[COMP co-ordinator: K. Westermark]

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of systemic sclerosis, the sponsor was asked to further elaborate on:

  - the relevance of the results of the bleomycin study taking into account the timing of administration of the product in relation to the bleomycin challenge, and the relevance of the observations in preventing bleomycin-induced skin fibrosis for the proposed indication;
  - any further available data in either relevant preclinical models, or preliminary clinical settings, with the specific product as applied for designation.

- Significant benefit

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the available preclinical studies to justify the assumption of significant benefit over authorised medicinal products for the proposed indication.

[1] The procedures under assessment discussed by the COMP are considered confidential. COMP meeting reports and subsequent minutes will contain additional details on these procedures once these are finalised. Access to documents in relation to these procedures is possible after marketing authorisation is granted according to the Agency policy on access to documents (EMA/127362/2006).

It was noted that in absence of any data supporting the medical plausibility of the product in treating the proposed condition the significant benefit cannot be assessed.

In the written response, and during an oral explanation before the Committee on 7 October 2014, the sponsor submitted further preclinical data in curative settings to justify the medical plausibility. In a modified bleomycin fibrosis model, assessments of the relative number of α-SMA-positive myofibroblasts, collagen content and dermal thickness, showed that the product was effective at reversing the effect of bleomycin. The significant benefit was also further elaborated versus bosentan, and the sponsor contrasted the vasodilatory effect of bosentan with the anti-fibrotic effects shown by the sponsor in preclinical settings.

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

The intention to treat the condition with the medicinal product containing 1-(6-benzothiazolylsulfonyl)-5-chloro-1H-indole-2-butanoic acid was considered justified based on preclinical data in models of the condition showing a reduction in collagen content.

The condition is chronically debilitating due to extensive fibrosis of the skin and internal organs, and life-threatening with main causes of mortality being cardiac complications, interstitial pulmonary disease, pulmonary hypertension, and renal complications.

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 1-(6-benzothiazolylsulfonyl)-5-chloro-1H-indole-2-butanoic acid may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing that the product may reduce fibrosis in models of the condition, which would compare favourably with the existing product that targets another manifestation of the disease. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 1-(6-benzothiazolylsulfonyl)-5-chloro-1H-indole-2-butanoic acid, for treatment of treatment of systemic sclerosis, was adopted by consensus.

2.1.2 **1-(6-benzothiazolylsulfonyl)-5-chloro-1H-indole-2-butanoic acid** for treatment of idiopathic pulmonary fibrosis, Inventiva - EMA/OD/130/14

[COMP co-ordinator: J. Torrent-Farnell]

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of idiopathic pulmonary fibrosis, the sponsor was asked to further elaborate on the relevance of the results of the bleomycin preclinical model taking into account the timing of administration of the product in relation to the bleomycin challenge.

In the written response, and during an oral explanation before the Committee on 7 October 2014, the sponsor further discussed the preclinical data provided in the initial application and added new data regarding the anti-fibrotic activity of the proposed product, in a curative setting of bleomycin induced

fibrosis. In these experiments the use of the product resulted in reduction of collagen deposition measured by hydroxyproline and in reduction of fibrosis measured at immunohistochemistry.

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

The intention to treat the condition with the medicinal product containing 1-(6-benzothiazolylsulfonyl)-5-chloro-1H-indole-2-butanoic acid was considered justified based on reduction of collagen deposition and of pro-fibrotic mediators with the proposed product in models of pulmonary fibrosis.

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

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 1-(6-benzothiazolylsulfonyl)-5-chloro-1H-indole-2-butanoic acid may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing an effect on endpoints relevant to pulmonary fibrosis, such as collagen deposition. The mechanism of action of the proposed product, different from the currently authorized product for the treatment of idiopathic pulmonary fibrosis, offers the potential of using the product in combination. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by idiopathic pulmonary fibrosis.

A positive opinion for 1-(6-benzothiazolylsulfonyl)-5-chloro-1H-indole-2-butanoic acid, for treatment of idiopathic pulmonary fibrosis, was adopted by consensus.

2.1.3 Product for treatment of cleft lip and palate - EMA/OD/136/14

[COMP co-ordinator: A. Magrelli]

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

- Intention to diagnose, prevent or treat

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

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of cleft lip and palate, the sponsor was asked to further elaborate on:

  - any available data in either relevant models of the condition or preliminary clinical data in patients affected by the condition;
  - the expected therapeutic benefit, in particular at what age the product would be administered and how this would fit into or affect the current standard of care.

- 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 has excluded part of the population affected by condition; the sponsor was asked to re-calculate the prevalence estimate for the proposed orphan condition, or a valid subset, based on relevant epidemiological studies and registers using the correct epidemiologic indices.

In the written response, and during an oral explanation before the Committee on 7 October 2014, the sponsor elaborated on the rationale of the proposed orphan condition based on embryonic development of the craniofacial skeleton and discussed the divergences in the classification of cleft-related conditions of the head and neck. The sponsor proposed a subset of cleft patients who have lip clefts with alveolar bony defects, namely cleft lip and palate with alveolar cleft defect, and provided updated calculations of prevalence accordingly.

The sponsor further elaborated on their preclinical results and clinical experience with the product but no data with the proposed product in the specific condition as applied for orphan designation was presented. The COMP considered that it would be difficult to regard the proposed indication as a distinct medical entity appropriate for orphan designation and that, for the medical plausibility, data in the specific indication would be required.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 October 2014, prior to final opinion.

2.1.4 A combination of two synthetic peptides: H-Lys-Lys-Gly-Pro-Arg-Cys(SH)-Leu-Thr-Arg-Tyr-Tyr-Ser-Ser-Phe-Val-Asn-Met-Glu-Gly-Lys-Lys-OH / H-Lys-Lys-Gly-Asp-Asn-Ile-Met-Val-Thr-Phe-Arg-Asn-Gln-Ala-Ser-Arg-Pro-Tyr-Gly-Lys-Lys-OH for treatment of haemophilia A, Apitope International NV - EMA/OD/123/14

[COMP co-ordinator: L. Gramstad]

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 haemophilia A, the sponsor was asked to further elaborate on:

  - the relevance of the preclinical model used for the treatment of haemophilia A, and the interpretation of the results obtained in the experiments;
  - the reasons why haemophilic preclinical models have not been used.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential for improved efficacy in the condition, as well as improved safety versus authorised products. In addition, arguments are provided for improvement in patient care, since the product is intended for intradermal administration. The sponsor also mentions arguments that lie outside of the orphan framework, such as cost benefits, which cannot be considered and should not be further commented.

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

The comparison should be made on the basis of data and a comparative discussion versus the authorised products.

In addition, extrapolation from preclinical or early clinical studies cannot predict the safety of a product in its clinical setting, thus more relevant data is necessary to justify safety arguments. The sponsor was asked to further elaborate on the potential risks with the product and how this compares with the safety profile of current authorised medicinal products for the same condition.

In the written response, and during an oral explanation before the Committee on 7 October 2014, the sponsor further elaborated on the suitability of the preclinical model used, discussing that inhibitor development in this model more closely resembles the formation of inhibitors in human HA patients. With regards to the significant benefit the sponsor discussed the limitations of the currently used methods of induction of immune tolerance.

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

The intention to treat the condition with the medicinal product containing a combination of H-Lys-Lys-Gly-Pro-Arg-Cys(SH)-Leu-Thr-Arg-Tyr-Tyr-Ser-Ser-Phe-Val-Asn-Met-Glu-Gly-Lys-Lys-OH and H-Lys-Lys-Gly-Asp-Asn-Ile-Met-Val-Thr-Phe-Arg-Asn-Gln-Ala-Ser-Arg-Pro-Tyr-Gly-Lys-Lys-OH was considered justified based on preclinical data supporting induction of immunotolerance to human coagulation factor VIII.

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

The condition was estimated to be affecting approximately 0.7 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing a combination of H-Lys-Lys-Gly-Pro-Arg-Cys(SH)-Leu-Thr-Arg-Tyr-Tyr-Ser-Ser-Phe-Val-Asn-Met-Glu-Gly-Lys-Lys-OH and H-Lys-Lys-Gly-Asp-Asn-Ile-Met-Val-Thr-Phe-Arg-Asn-Gln-Ala-Ser-Arg-Pro-Tyr-Gly-Lys-Lys-OH may be of significant benefit to those affected by the condition. The sponsor has provided data in a preclinical model supporting induction of immunotolerance to human coagulation factor VIII. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for A combination of two synthetic peptides H-Lys-Lys-Gly-Pro-Arg-Cys(SH)-Leu-Thr-Arg-Tyr-Tyr-Ser-Ser-Phe-Val-Asn-Met-Glu-Gly-Lys-Lys-OH and H-Lys-Lys-Gly-Asp-Asn-Ile-Met-Val-Thr-Phe-Arg-Asn-Gln-Ala-Ser-Arg-Pro-Tyr-Gly-Lys-Lys-OH, for treatment of haemophilia A, was adopted by consensus.

2.1.5 4-[[(1S,4S)-5-[[4-[4-(Oxazol-2-yl)phenoxy]phenyl]methyl]-2,5-diazabicyclo[2.2.1]hept-2-yl]methyl]benzoic acid for treatment of cystic fibrosis, Coté Orphan Consulting UK Limited - EMA/OD/131/14

[COMP co-ordinator: J. Eggenhofer]

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

In order to justify the plausibility of the proposed product the sponsor was invited to further elaborate on the data presented in this application and in particular:

- the results of the in vitro chemotaxis assay where absolute values of neutrophil migration have not been provided;
- the clinical meaningfulness of the changes in the levels of leukotriene B4 in the sputum in the phase I study;
- the relevance of the changes in serum C Reactive Protein to the treatment of cystic fibrosis.

The sponsor was also invited to present quantitative results and figures from the two animal models presented to support of the medical plausibility of the proposed product.

In the written response, and during an oral explanation before the Committee on 7-08 October 2014, the sponsor further discussed the data presented to support the medical plausibility, including the doses of the product used in the preclinical studies and the biomarker measurements in the preliminary clinical observations.

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

The intention to treat the condition with the medicinal product containing 4-[[(1S,4S)-5-[[4-[4-(oxazol-2-yl)phenoxy]phenyl]methyl]-2,5-diazabicyclo[2.2.1]hept-2-yl]methyl]benzoic acid was considered justified based on preclinical and preliminary clinical data showing the anti-inflammatory activity of the proposed product.

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

The condition was estimated to be affecting approximately 0.7 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 4-[[(1S,4S)-5-[[4-[4-(oxazol-2-yl)phenoxy]phenyl]methyl]-2,5-diazabicyclo[2.2.1]hept-2-yl]methyl]benzoic acid may be of significant benefit to those affected by the condition. This appears justified based on an alternative mechanism of action of the proposed product targeting neutrophilic inflammation in cystic fibrosis, which offers the potential of using the proposed product in combination with currently authorized products. This is supported by preclinical and preliminary clinical data. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by cystic fibrosis

A positive opinion for 4-[[(1S,4S)-5-[[4-[4-(oxazol-2-yl)phenoxy]phenyl]methyl]-2,5-diazabicyclo[2.2.1]hept-2-yl]methyl]benzoic acid, for treatment of cystic fibrosis, was adopted by consensus.

2.1.6 Donor T lymphocytes depleted ex vivo of host alloreactive T cells using photodynamic treatment for treatment of acute myeloid leukaemia, Kiadis Pharma Netherlands B.V - EMA/OD/103/14

[COMP co-ordinator: B. Bloechl-Daum]

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 was asked to further elaborate on the target condition and how the product directly treats it as it would appear that the product is specific for a treatment modality used in AML. This could imply a change in the condition. The COMP noted that the sponsor has an Orphan Designation for the prevention of Graft versus Host Disease and asked the sponsor to further elaborate on the lack of overlapping between this new proposed application and the earlier designation.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of acute myeloid leukaemia, the sponsor was asked to further elaborate on:

- all the cell populations contained in the proposed product, and clarify as far as possible the role of each one of them in the assumed mechanism of action of the product in the settings of the proposed condition;
- why the product cannot also be used in non-haploidentical allogeneic HSCT;
- AML relapses and survival observed in the preliminary clinical studies *vis a vis* those outcomes that would be expected by the HSCT procedure alone;
- any available immune reconstitution endpoints in the preliminary clinical patients, in the context of HSCT;
- the available preliminary clinical studies in detail, including patient characteristics, endpoints studies and results in detail for the proposed condition as applied for designation.

- 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 was asked to 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 was asked to perform a sensitivity analysis of the reported calculations.

- 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 was asked to elaborate, based on data on the effects of the products versus non-ATIR treated standard of care, including HSCT alone.

In the absence of relevant data in the condition as applied for, significant benefit cannot be assessed at this time.

In the written response, and during an oral explanation before the Committee on 8 October 2014, the sponsor presented several lines of additional evidence, and in particular discussed data from AML patients treated with haploidentical stem cell transplantation alone. Based on these data the sponsor reported higher OS probability and TRM mortality if the transplantation was performed without the addition of the proposed product. The Committee agreed that the condition, acute myeloid leukaemia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing donor T lymphocytes depleted ex vivo of host alloreactive T cells using photodynamic treatment was considered justified based on preliminary clinical data supporting immune reconstitution and preservation of Graft-versus-leukaemia effect.

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

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing donor T lymphocytes depleted ex vivo of host alloreactive T cells using photodynamic treatment may be of significant benefit to those affected by the condition/to the population at risk of developing the condition. The sponsor has provided data in preliminary clinical settings supporting the assumption of immune reconstitution and preservation of Graft-versus-leukaemia effect. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for Donor T lymphocytes depleted ex vivo of host alloreactive T cells using photodynamic treatment, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.1.7 Product for treatment of erythropoietic protoporphyria - EMA/OD/127/14

[COMP co-ordinator: L. Greene]

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of erythropoietic protoporphyria, the sponsor was asked to further elaborate on:

  - the relevance of the ex vivo clinical model used for the treatment of erythropoietic protoporphyria, and the interpretation of the results obtained in the experiments within the context of the target patient population;
  - any pre-clinical in vivo data they may have in a relevant model of the condition.

In the written response, and during an oral explanation before the Committee on 8 October 2014, the sponsor discussed the available in vitro data in the context of the pathophysiology of the condition as applied for designation, and reported that a specific in vivo model of the condition was not yet available. The COMP considered that it would be difficult to establish the medical plausibility in the absence of in vivo data in a specific model of the condition

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 9 October 2014, prior to final opinion.

2.1.8 **mexiletine hydrochloride** for treatment of myotonic disorders, Temmler Pharma GmbH & Co. KG - EMA/OD/074/14

[COMP co-ordinator: D. O'Connor]

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

- Significant benefit

The sponsor has proposed that significant benefit is based on a major contribution to patient care.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the current supply situation in Europe regarding the availability of authorised treatments for patients with myotonic disorders.

In the written response, and during an oral explanation before the Committee on 8 October 2014, the sponsor submitted data regarding the licencing status of authorised treatments for the condition in the Member States as well as the number of patients who were receiving this product for myotonic disorders. This was contrasted with the total number of patients.

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

The intention to treat the condition with the medicinal product containing mexiletine hydrochloride was considered justified based on a bibliographic compilation of clinical studies which have reported the effect of this product in the proposed condition.

The condition is chronically debilitating due to pain with muscle stiffness associated with disability. The muscle stiffness can be very debilitating leading to falls associated with fractures and serious injury.

The condition was estimated to be affecting approximately 2 in 10,000 persons in the European Union, at the time the application was made; this was based on a literature search which was conducted by the sponsor.

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 mexiletine hydrochloride may be of significant benefit to those affected by the condition. The satisfactory methods of treatment authorised include mexiletine hydrochloride being authorised in two EU Member States, which due to its limited coverage does not offer sufficient access for patients affected by the condition. The potential increased availability through a centralised authorisation is accepted as a justification for a significant benefit based on a major contribution to patient care.

A positive opinion for mexiletine hydrochloride, for treatment of myotonic disorders, was adopted by consensus.

2.1.9 **Recombinant human Pentraxin-2** for treatment of primary myelofibrosis, FGK Representative Service GmbH - EMA/OD/140/14

[COMP co-ordinator: B. 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

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of primary myelofibrosis, the sponsor was asked to further elaborate on the results obtained in the preliminary clinical study, by discussing the results obtained separately for primary, post PV, and post ET myelofibrosis patients.

- Significant benefit

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

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

With regards to the safety argument, extrapolation from preclinical or early clinical studies cannot predict the safety of a product in its clinical setting, thus more relevant data is necessary to justify safety arguments.

In the written response the sponsor discussed the available preliminary clinical data specifically in patients with the condition as proposed for designation, and reported symptom and bone marrow responses in the treated patients. As regards the issue of significant benefit, the sponsor also reported some anaemia and platelet responses.

The Committee agreed that the condition, primary myelofibrosis, 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 pentraxin-2 was considered justified based on preliminary clinical data in affected patients supporting decrease of fibrosis, spleen size and symptom response.

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 survivals of approximately 1.3 years for patients with high-risk disease.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant human pentraxin-2 may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in patients affected by the condition including pretreated patients, showing clinically meaningful responses. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for recombinant human pentraxin-2, for treatment of primary myelofibrosis, was adopted by consensus.

2.1.10 Recombinant human Pentraxin-2 for treatment of post-polycythaemia vera myelofibrosis, FGK Representative Service GmbH - EMA/OD/139/14
[COMP co-ordinator: B. 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

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of post-polycythaemia vera myelofibrosis, the sponsor was asked to further elaborate on

the results obtained in the preliminary clinical study, by discussing the results obtained separately for primary, post PV, and post ET myelofibrosis patients.

- Significant benefit

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

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

With regards to the safety argument, extrapolation from preclinical or early clinical studies cannot predict the safety of a product in its clinical setting, thus more relevant data is necessary to justify safety arguments.

In the written response, and during an oral explanation before the Committee on 8 October 2014, the sponsor discussed the available preliminary clinical data specifically in patients with the condition as proposed for designation, and reported symptom and bone marrow responses in the treated patients. As regards the issue of significant benefit, the sponsor also reported some anaemia and platelet responses.

The Committee agreed that the condition, post-polycythaemia vera myelofibrosis, 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 pentraxin-2 was considered justified based on preliminary clinical data in affected patients supporting decrease of fibrosis, spleen size and symptom response.

The condition is life-threatening with a reduced survival depending on risk factors, and chronically debilitating due to anaemia, splenomegaly, extramedullary haematopoiesis, constitutional symptoms such as fatigue, night sweats and fever, cachexia and leukemic progression.

The condition was estimated to be affecting less than 0.15 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant human pentraxin-2 may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in patients affected by the condition including pretreated patients, showing clinically meaningful responses. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for recombinant human pentraxin-2, for treatment of post-polycythaemia vera myelofibrosis, was adopted by consensus.

2.1.11 Recombinant human Pentraxin-2 for treatment of post-essential thrombocythaemia myelofibrosis, FGK Representative Service GmbH - EMA/OD/116/14
[COMP co-ordinator: B. 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

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of post-essential thrombocythaemia myelofibrosis, the sponsor was asked to further elaborate on the results obtained in the preliminary clinical study, by discussing the results obtained separately for primary, post PV, and post ET myelofibrosis patients.

- Significant benefit

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

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

With regards to the safety argument, extrapolation from preclinical or early clinical studies cannot predict the safety of a product in its clinical setting, thus more relevant data is necessary to justify safety arguments.

In the written response, and during an oral explanation before the Committee on 8 October 2014, the sponsor discussed the available preliminary clinical data specifically in patients with the condition as proposed for designation, and reported symptom and bone marrow responses in the treated patients. As regards the issue of significant benefit, the sponsor also reported some anaemia and platelet responses. The Committee agreed that the condition, post-essential thrombocythaemia myelofibrosis, 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 pentraxin-2 was considered justified based on preliminary clinical data in affected patients supporting decrease of fibrosis, spleen size and symptom response.

The condition is life-threatening with reduced survival depending on risk factors, and chronically debilitating due to anaemia, splenomegaly, extramedullary haematopoiesis, constitutional symptoms such as fatigue, night sweats and fever, cachexia and leukemic progression.

The condition was estimated to be affecting less than 0.15 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant human pentraxin-2 may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data supporting improvements in anaemia and thrombocytopenia. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for recombinant human pentraxin-2, for treatment of post-essential thrombocythaemia myelofibrosis, was adopted by consensus.

2.1.12 Selinexor for treatment of refractory and/or relapsed Richter's transformation, Clinipace GmbH - EMA/OD/078/14
[COMP co-ordinator: J. Torrent-Farnell]

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

- Intention to diagnose, prevent or treat

The name of the condition should be justified as a distinct medical entity or a valid subset. The COMP considers that Richter's transformation is a stage of the broader condition Chronic Lymphocytic Leukaemia/lymphoma or DLBCL and asked the sponsor to further elaborate why they believe that it is a distinct condition. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention was drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of refractory and/or relapsed Richter's transformation, the sponsor was asked to further elaborate on:

  - the results obtained in the preliminary clinical study in patients with the chronic lymphoblastic lymphoma/leukaemia and patients with Richter's transformation.

- Number of people affected

As there is concern regarding the proposed condition Richter's transformation, the sponsor was asked to consider recalculating the prevalence regarding the broader condition the COMP believes would correspond more accurately with the regulation.

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 was asked to justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor was asked to describe and justify the methodology used for the prevalence calculation.

- 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 was asked to detail the results of the Phase I clinical data they have to support the significant benefit assumption in the context of the current therapeutic management of patients.

In the written response, and during an oral explanation before the Committee on 8 October 2014, the sponsor elaborated on the raised issues, but accepted the committees view to change the condition from treatment of Richter's transformation to treatment of chronic lymphocytic leukaemia / small lymphocytic lymphoma. The sponsor revised the submitted documents before the end of the meeting by changing the condition and revising the prevalence. The Committee agreed that the condition, chronic lymphocytic leukaemia / small lymphocytic lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing selinexor was considered justified based on preliminary clinical data showing responses in heavily pretreated patients with the condition.

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

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing selinexor may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing favourable responses in heavily pretreated patients including patients with Richter's transformation. The Committee considered that this constitutes a clinically relevant advantage.

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

2.1.13 Selinexor for treatment of plasma cell myeloma, Clinipace GmbH - EMA/OD/087/14
[COMP co-ordinator: F. Naumann-Winter]

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of plasma cell myeloma, the sponsor was asked to further elaborate on:

  - the results from pre-clinical studies, in particular the variability of responses in the different models 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 was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the ongoing clinical study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication. In particular, the sponsor was asked to discuss patients' characteristics and prior treatments with regards to the duration of responses to the product.

In the written response, and during an oral explanation before the Committee on 8 October 2014, the sponsor further elaborated on the issues raised. As regards the medical plausibility, the sponsor justified the variability in tumour growth inhibition seen in the preclinical xenograft models by pointing out the different doses used. For the issue of significant benefit, the sponsor presented new data suggesting a synergistic effect of the product and dexamethasone in preclinical models. The sponsor also presented preliminary clinical data from an ongoing phase I study. In that study, patients with heavily pretreated relapsed/refractory plasma cell myeloma were treated with the product and the overall response rate was reported to be 60%.

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

The intention to treat the condition with the medicinal product containing selinexor was considered justified based on preclinical data and preliminary clinical data showing anti-cancer activity in patients affected by the condition.

The condition is chronically debilitating in particular due to the development of hypercalcaemia, renal insufficiency, anaemia and bone lesions, and life-threatening with an overall survival of up to approximately 45 months for newly diagnosed patients.

The condition was estimated to be affecting approximately 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 selinexor may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing a favourable response in heavily pretreated patients with progressive disease who are refractory or intolerant to alternative treatment options. The Committee considered that this constitutes a clinically relevant advantage for patients affected by the condition.

A positive opinion for selinexor, for treatment of plasma cell myeloma, was adopted by consensus.

2.1.14 Product for treatment of acute peripheral arterial occlusion - EMA/OD/117/14
[COMP co-ordinator: D. Krievins]

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of acute peripheral arterial occlusion, the sponsor was asked to further elaborate on the relevance of the preclinical studies and in particular:

  - the clinical relevance of the methodology and results of the animal mesenterial artery study assessing reperfusion injury inhibition to the treatment of acute peripheral artery occlusion, taking into account the different pathophysiology of the two conditions. The discussion should also include further elaboration on the dosage used to show an effect, which appears to be 10 fold higher than the assumed therapeutic dose, and efficacious only when used in addition to high doses of thrombolytic agents;
  - the methodology and results of the experimental coronary artery occlusion/thrombolysis preclinical model in relation to the proposed condition;
  - the relevance of reducing viscosity to the medical plausibility of using the product in acute peripheral arterial occlusion;

- Significant benefit

In order to establish the significant benefit of the proposed product the sponsor was invited to further discuss the potential advantage of the proposed product in relation to all possible current standards of care, including the combination of two or those, e.g. thrombolysis plus heparin, which is often the treatment of choice. Such discussion should be as much as possible supported by data.

In the written response, and during an oral explanation before the Committee on 8 October 2014, the sponsor further elaborated on the raised issues and discussed results in a mesenteric artery reperfusion model, a peripheral limb ischemia model and an occlusion/thrombolysis model. The sponsor also commented on the dosage of thrombolytic agents in the studies presented based on

earlier studies, and pointed out that a rheologic agent can be expected to facilitate thrombolysis both by increasing the delivery of plasminogen activators and by increasing removal of fibrin degradation products.

With regards to the significant benefit, the sponsor pointed out that both mechanical and pharmacological therapies are effective for restoring perfusion, but both are limited by reperfusion injury, and no-reflow in the microcirculation. The sponsor did not present any data but asserted that the alternative mechanism of action of the product may translate into improved efficacy as it may be additive or synergistic to current standard of care.

The COMP was of the opinion that it is difficult to extrapolate the potential clinical use of the product based on the findings in different models and on the mechanism of action of the product mainly tackling viscosity, particularly in relation to what the significant benefit of the proposed product could be versus the current standard of care of the condition. It was also difficult to consider the acceptability of the proposal in particular with regards to the absence of data to justify the assumption of significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 9 October 2014, prior to final opinion.

2.1.15 Product for treatment of systemic lupus erythematosus - EMA/OD/097/14
[COMP co-ordinator: J. Torrent-Farnell]

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of systemic lupus erythematosus, the sponsor was asked to further elaborate on:

  - the results obtained in vitro on the melanoma cell line the treatment of systemic lupus erythematosus,
  - the relevance of the preclinical model used for the treatment of systemic lupus erythematosus, and the interpretation of the results obtained in the experiments.

- Number of people affected

The condition appears to have a higher prevalence than the one proposed by the sponsor and there are data in the public domain suggesting prevalence higher than the threshold of 5 in 10,000.

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 was asked to justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition, 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 was asked to indicate on which population the prevalence calculation is based on.

- 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 was asked to further elaborate on the clinically

relevant advantage using data generated with the product in either pre-clinical in vivo models of the condition and/or preliminary clinical data in patients affected by the condition. Results should be discussed within the context of the current authorised medicines and standard of care.

In the written response, and during an oral explanation before the Committee on 8 October 2014, the sponsor presented preclinical results from literature studies with surrogate products targeting the same signalling pathway, provided an updated review of epidemiologic literature and elaborated on the significant benefit on the basis of the product targeting inflammation and local damage in target organs, thereby having an effect in late manifestations of the disease. In particular with regards to the prevalence calculations, the sponsor discussed that most (14 of 19) of the epidemiological studies identified indicate prevalence below the orphan threshold

The committee considered in particular that the level of uncertainty in the prevalence calculations does not ensure that the provisioned threshold is respected. Limitations were also identified in the absence of data with the product as applied for in the condition subject of the application. In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 October 2014, prior to final opinion.

2.1.16 Imatinib for treatment of acute respiratory distress syndrome, Numedicus Limited - EMA/OD/110/14
[COMP co-ordinator: M. Možina]

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

- Number of people affected

The sponsor was invited to provide a sensitivity analysis of the estimated affected population including a worst case scenario, taking into account the change in classification that includes all ranges of severity including the cases previously classified as ALI.

In the written response the sponsor discussed the evolution in the classification of ARDS and ALI that could impact the current estimates of the incidence of the condition. As previously reported, the current classification (Berlin consensus 2012) does not distinguish between ALI and ARDS anymore but limits the classification to ARDS, divided in three stages: mild, moderate and severe, with the mild stage overlapping with the functional definition of what was considered as ALI. Taking this into consideration, the sponsor re-examined the literature already reported in the initial application and provided population-adjusted estimates of what was previously the ALI incidence (ALIAECC) using geometric means.

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

The intention to treat the condition with the medicinal product containing imatinib was considered justified based showing attenuation of lung vascular leakage and pulmonary oedema in preclinical models relevant to the disease, and in two clinical cases.

The condition is life-threatening due to progressive damage of the lung vasculature and parenchima with fatality rate of approximately 40%; in survivors the condition can be chronically debilitating due to sequelae such as lung fibrosis and persistent functional impairment.

The condition was estimated to be affecting less than 5 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for imatinib, for treatment of acute respiratory distress syndrome, was adopted by consensus.

2.1.17 Product for treatment of essential thrombocythemia - EMA/OD/124/14
[COMP co-ordinator: M. Možina]

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 22 September 2014, prior to responding to list of issues.

2.1.18 Product for prevention of angioedema - EMA/OD/115/14
[COMP co-ordinator: M. Možina]

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 15 September 2014, prior to responding to list of issues.

2.2. For discussion / preparation for an opinion

2.2.1 (2R,3S)-2-(4-Cyclopentylaminophenyl)-1-(2-fluoro-6-methylbenzoyl)piperidine-3-carboxylic acid(4-methyl-3-trifluoromethylphenyl)amide for treatment of microscopic polyangiitis, ChemoCentryx Limited - EMA/OD/149/14
[COMP co-ordinator: D. Krievins]

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

The intention to treat the condition with the medicinal product containing (2R,3S)-2-(4-cyclopentylaminophenyl)-1-(2-fluoro-6-methylbenzoyl)piperidine-3-carboxylic acid(4-methyl-3-trifluoromethylphenyl)amide was considered justified based on preclinical data in a relevant model of the disease and preliminary clinical data in patients with the condition indicating improvement in renal disease.

The condition is chronically debilitating due to the progressive affection of the respiratory tract and kidneys and life-threatening due to the risk of renal- and respiratory failure, as well as infections and malignancies as a consequence of available treatments.

The condition was estimated to be affecting not more than 1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (2R,3S)-2-(4-cyclopentylaminophenyl)-1-(2-fluoro-6-methylbenzoyl)piperidine-3-carboxylic acid(4-methyl-3-trifluoromethylphenyl)amide may be of significant benefit to those affected

by the condition. The sponsor has provided preliminary clinical data that demonstrate that the product improved parameters of renal function in patients affected by the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (2R,3S)-2-(4-cyclopentylaminophenyl)-1-(2-fluoro-6-methylbenzoyl)piperidine-3-carboxylic acid(4-methyl-3-trifluoromethylphenyl)amide, for treatment of microscopic polyangiitis, was adopted by consensus.

2.2.2 (2R,3S)-2-(4-Cyclopentylaminophenyl)-1-(2-fluoro-6-methylbenzoyl)piperidine-3-carboxylic acid(4-methyl-3-trifluoromethylphenyl)amide for treatment of granulomatosis with polyangiitis, ChemoCentryx Limited - EMA/OD/150/14

[COMP co-ordinator: D. Krievins]

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

The intention to treat the condition with the medicinal product containing (2R,3S)-2-(4-cyclopentylaminophenyl)-1-(2-fluoro-6-methylbenzoyl)piperidine-3-carboxylic acid(4-methyl-3-trifluoromethylphenyl)amide was considered justified based on preliminary clinical data in patients with the condition indicating improvement in renal disease and reduced overall vasculitis activity.

The condition is chronically debilitating due to progressive affection of the respiratory tract and kidneys and life-threatening due to the risk of renal- and respiratory failure, as well as infections and malignancies as a consequence of available treatments.

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 (2R,3S)-2-(4-cyclopentylaminophenyl)-1-(2-fluoro-6-methylbenzoyl)piperidine-3-carboxylic acid(4-methyl-3-trifluoromethylphenyl)amide may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that the product improved parameters of renal function in patients affected by the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (2R,3S)-2-(4-Cyclopentylaminophenyl)-1-(2-fluoro-6-methylbenzoyl)piperidine-3-carboxylic acid(4-methyl-3-trifluoromethylphenyl)amide, for treatment of granulmatosis with polyangiitis, was adopted by consensus.

2.2.3 (3S)-1-azabicyclo[2.2.2]oct-3-yl {2-[2-(4-fluorophenyl)-1,3-thiazol-4-yl]propan-2-yl}carbamate for treatment of Gaucher disease, Genzyme Europe BV - EMA/OD/152/14

[COMP co-ordinator: A. Corrêa Nunes]

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

The intention to treat the condition with the medicinal product containing (3S)-1-azabicyclo[2.2.2]oct-3-yl{2-[2-(4-fluorophenyl)-1,3-thiazol-4-yl]propan-2-yl}carbamate was considered justified based on preclinical data in a model of the condition showing improvement of survival in treated subjects.

The condition is chronically debilitating in particular due to hepatosplenomegaly, thrombocytopenia, anemia, bone disease, as well as neurological manifestations in the neuronopathic form of the condition, and life-threatening with reduced life expectancy.

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 (3S)-1-azabicyclo[2.2.2]oct-3-yl{2-[2-(4-fluorophenyl)-1,3-thiazol-4-yl]propan-2-yl}carbamate may be of significant benefit to those affected by the condition. This was considered justified based on preclinical studies reporting crossing of the blood-brain barrier, that may translate in into improved efficacy in particular for patients affected by the neuronopathic form of the condition. The Committee considers that this constitutes a clinically relevant advantage.

A positive opinion for (3S)-1-azabicyclo[2.2.2]oct-3-yl{2-[2-(4-fluorophenyl)-1,3-thiazol-4-yl]propan-2-yl}carbamateas, for treatment of Gaucher disease, was adopted by consensus.

2.2.4 Product for treatment of Huntington's disease - EMA/OD/114/14

[COMP co-ordinator: V. Stoyanova]

The Committee considered that the following issues require clarification by the sponsor:

- Medical plausibility

The medical plausibility of the proposal has not been supported with data confirming that treatment with the specific product as proposed for designation may result in beneficial effects on any aspect of the condition (cognitive, motor or behavioural) neither in relevant animal models nor in patients. The sponsor was requested to further elaborate on the clinical relevance of the endpoints studied in the preclinical experiments and present any further available data with the product as applied for designation.

- Significant benefit

The arguments on significant benefit are based on a new mechanism of action and the potentially improved efficacy in the condition. The sponsor was requested to specifically elaborate on the consequences of a novel mechanism and demonstrate any improved effects in relevant models of the condition.

With regards to safety, extrapolation from preclinical or early clinical studies cannot predict the safety of a product in its clinical setting, thus more relevant data is necessary to justify safety arguments.

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

2.2.5 Adeno-associated viral vector serotype 8 containing the human *MD1* microdystrophin gene for treatment of Duchenne muscular dystrophy, Généthon - EMA/OD/166/14

[COMP co-ordinator: P. Evers]

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

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 8 containing the human *MD1* gene was considered justified based on data generated in two valid pre-clinical models of the condition.

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

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated viral vector serotype 8 containing the human *MD1* gene may be of significant benefit to those affected by the condition. The sponsor has provided preclinical in vivo data that demonstrate that the alternative mode of action through a gene replacement therapy can restore muscle function in an alternative manner to Translarna and offers the possibility of treating patients independently of the type of mutation causing DMD. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype 8 containing the human *MD1* gene, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

2.2.6 Product for treatment of Mucopolysaccharidosis type IIIA (Sanfilippo A syndrome)- EMA/OD/164/14

[COMP co-ordinator: A. Magrelli]

The Committee considered that the following issues require clarification by the sponsor:

- 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 Mucopolysaccharidosis type IIIA (Sanfilippo A syndrome), the sponsor was asked to elaborate on any further available endpoints studied in the preclinical models used, such as primary and secondary accumulation products (HS-derived oligosaccharides, GM3 and unesterified cholesterol) or any neurological assessments.

The sponsor was also invited to further elaborate on the rationale for the modification of the vector used.

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

2.2.7 Product for prevention of graft-versus-host disease - EMA/OD/163/14

[COMP co-ordinator: K. Westermark]

The Committee considered that the following issues require clarification by the sponsor:

- 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 was asked to further elaborate on the three clinical cases presented and particularly on:

- the reasons for concluding that the proposed product enhances engraftment of the HSCT in these three cases and which, among the data provided, support this conclusion;
- the clinical details, including follow-up, of the three cases and of any other available patients;
- the clinical relevance of the occurrence of GvHD in one out of two mismatched HSCT to the proposed clinical use of the product.

The sponsor was also invited to present any additional available preclinical or clinical data supporting the medical plausibility. Whenever preclinical data are not available, the sponsor was invited to justify the reasons for not producing this type of data in support to the plausibility, including e.g. discussion on the use and limitations of models of the condition.

- 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".

In this case the sponsor has provided estimates of the incidence/prevalence of GvHD rather than providing an estimate of the population at risk. As the product is proposed in preventive use, the estimated population at risk is expected to include all patients undergoing bone marrow/haematopoietic stem cell transplantation.

The sponsor was therefore invited to provide an estimate of the population at risk of GvHD.

- Significant benefit

In absence of an established medical plausibility the significant benefit is difficult to evaluate.

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

2.2.8 **Arimoclomol citrate** for treatment of Niemann-Pick's disease, type C, Orphazyme ApS - EMA/OD/158/14

[COMP co-ordinator: A. Corrêa Nunes]

The Committee agreed that the condition, Niemann-Pick disease, type C, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing arimoclomol citrate was considered justified based on preclinical data in a relevant model of the disease that show that treatment with the product improves disease-relevant behavioral phenotypes and reduces lysosomal accumulation of glycosphingolipids.

The condition is chronically debilitating and life-threatening in particular due to complications such as neurological degeneration, splenomegaly, hepatomegaly and reduced life expectancy. The majority of patients with Niemann-Pick disease type C die before the age of 20.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing arimoclomol citrate may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data in a valid model of the disease that demonstrate that the product may be of significant benefit based on its alternative mode of action. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for arimoclomol citrate, for treatment of Niemann-Pick disease, type C, was adopted by consensus.

2.2.9 Ataluren for treatment of mucopolysaccharidosis type I, PTC Therapeutics, Limited - EMA/OD/165/14
[COMP co-ordinator: J. Torrent-Farnell]

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

Having examined the application, the COMP considered that the sponsor has established the following:

The intention to treat the condition with the medicinal product containing ataluren was considered justified based on reduction of glycosaminoglycan levels shown in several tissues of a preclinical model of the condition.

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

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ataluren may be of significant benefit to those affected by the condition. This was considered justified on the basis of preclinical studies supporting effects in symptoms of the disease that are not adequately addressed by the currently authorised treatment such as CNS manifestations. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for ataluren, for treatment of mucopolysaccharidosis type I, was adopted by consensus.

2.2.10 Product for treatment of mantle cell lymphoma - EMA/OD/151/14
[COMP co-ordinator: F. Naumann-Winter]

The Committee considered that the following issues require clarification by the sponsor:

- Significant benefit

In order to justify the significant benefit the sponsor was invited to further discuss the relevance of the preclinical results obtained in the in vivo studies to the potential clinical use of the product vs. the currently authorized products for the condition, taking into account:

  - the lack of any positive control group reflecting the current standards of care;

- the toxicity episodes leading to withdrawal of some subjects from the study and to the suspension of the treatment for a few days;
- the relevance of the *sc* administration to the expected administration and dosing in humans, in view of the absence of clinical experience at the present stage.

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

2.2.11 Bazedoxifene acetate for treatment of hereditary haemorrhagic telangiectasia, Consejo Superior de Investigaciones Cientificas (CSIC) - EMA/OD/144/14
[COMP co-ordinator: A. Lhoir]

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

The intention to treat the condition with the medicinal product containing bazedoxifene acetate was considered justified based on preliminary data in patients with the condition showing improvements in epistaxis.

The condition is chronically debilitating and life threatening, especially due to haemorrhagic, shunting and space occupying complications of mucocutaneous and visceral arterio-venous malformations.

The condition was estimated to be affecting approximately 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 bazedoxifene acetate, for treatment of hereditary haemorrhagic telangiectasia, was adopted by consensus.

2.2.12 Chloroquine for treatment of glioma, DualTpharma B.V. - EMA/OD/159/14
[COMP co-ordinator: K. Kubáčková]

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

The intention to treat the condition with the medicinal product containing chloroquine was considered justified based on preclinical data showing inhibition of tumour volume progression in relevant xenotransplantation models when the product was used in combination with radiotherapy.

The condition is chronically debilitating, in particular due to compression and invasion of the surrounding brain structures leading to neurological deficits, and life-threatening with poor overall survival. Survival for glioblastoma multiforme patients is less than 5% at 5 years post diagnosis.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 7-Chloro-4[[4-(diethylamino)-1-methylbutyl]amino] quinoline phosphate (1:2) may be of significant benefit to those affected by the condition. This is based mainly on a preliminary

clinical data showing improved survival when the product was used in pretreated patients. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by glioma.

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

2.2.13 Dantrolene sodium for treatment of malignant hyperthermia, Eagle Laboratories Ltd - EMA/OD/162/14
[COMP co-ordinator: I. Bradinova]

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

The intention to treat the condition with the medicinal product containing dantrolene sodium was considered justified based on literature data showing that the active substance can effectively prevent death in around 90% of treated patients.

The condition is life-threatening due to tachycardia and other arrhythmias, acidosis, muscle rigidity, and hyperkalaemia. If untreated, the condition is fatal in more than 90% of cases.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing dantrolene sodium may be of significant benefit to those affected by the condition. This is based on a much shorter administration time of the proposed product compared the currently authorized formulation of dantrolene, offering the potential to reduce the morbidity and mortality associated with treatment delay. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by malignant hyperthermia.

A positive opinion for dantrolene sodium, for treatment of malignant hyperthermia, was adopted by consensus.

2.2.14 Diaspirin Cross-linked Haemoglobin for treatment of hepatocellular carcinoma, New B Innovation (UK) Limited - EMA/OD/160/14
[COMP co-ordinator: A. Magrelli]

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

The intention to treat the condition with the medicinal product containing diaspirin cross-linked haemoglobin was considered justified based on preclinical data showing antitumor activity on relevant endpoints.

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

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing diaspirin cross-linked haemoglobin may be of significant benefit to those affected by the condition. This is supported by preclinical data showing significantly improved survival and reduced formation of metastases when the product was used in addition to the currently authorized product sorafenib. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by hepatocellular carcinoma.

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

2.2.15 Product for treatment of familial cerebral cavernous malformations- EMA/OD/161/14
[COMP co-ordinator: V. Stoyanova]

The Committee considered that the following issues require clarification by the sponsor:

- 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 familial cerebral cavernous malformations, the sponsor was asked to further elaborate on:

  - the rationale and relevance of the preclinical CCM3 -/- model used for the treatment of familial cerebral cavernous malformations that is caused by any of the three genes CCM1, CCM2, CCM3, and the interpretation of the results obtained in the experiments.

- 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 based their prevalence calculation on the available literature on both, spontaneous and familial forms of cerebral cavernous malformations, and reports from genetic databases. Given the wide range of the proposed prevalence and the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor was asked to recalculate the prevalence estimate and perform a sensitivity analysis of the reported calculations.

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

2.2.16 Product for treatment of pancreatic cancer - EMA/OD/143/14
[COMP co-ordinator: K. Kubáčková]

The Committee considered that the following issues require clarification by the sponsor:

- 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 pancreatic cancer, the sponsor was asked to further elaborate on:

  - the clinical relevance of a polyclonal stimulation of T lymphocytes, such as the one demonstrated with the proposed product, for the intended specific use in pancreatic cancer;

- the lack of conclusive results from similar approaches such as the stimulation with BCG;
- the results from the preclinical study, showing no effect on survival when the product was used alone or in combination with gemcitabine. For this study the sponsor was also invited to clarify how metastatisationwas defined.

- Significant benefit

The sponsor was requested to further discuss the arguments provided for significant benefit, and in particular the suggested use of the product in combination with currently authorized products, taking into account the lack of effect in the preclinical models on survival when the product was used in combination with gemcitabine.

The sponsor was also invited to present any results available from the randomised, open-label, proof-of-concept, Phase II trial where the recruitment was concluded in July 2013.

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

2.2.17 Product for treatment of acute myeloid leukaemia- EMA/OD/156/14
[COMP co-ordinator: K. Kubáčková]

The Committee considered that the following issues require clarification by the sponsor:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of acute myeloid leukaemia, the sponsor was asked to further elaborate on:

- the results obtained in vitro on AML cell lines from patients;
- 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 as proposed for designation.

In the absence of data with the specific product in a specific (in vivo) model of the proposed condition as applied for designation, the intention to treat cannot be considered justified.

- Significant benefit

The sponsor proposes an alternative mode of action which may offer a clinically relevant advantage of improved efficacy over current therapies.

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

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

2.2.18 Humanized IgG1 monoclonal antibody against human eotaxin-2 for treatment of systemic sclerosis, CBR Biotech Strategies GmbH - EMA/OD/148/14
[COMP co-ordinator: B. Bloechl-Daum]

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

The intention to treat the condition with the medicinal product containing humanised IgG1 monoclonal antibody against human eotaxin-2 was considered justified based on preliminary pre-clinical in vivo data in a valid model of the condition.

The condition is chronically debilitating due to the deposition of collagen in the skin and, less commonly, in the kidneys, heart, lungs and stomach. This deposition presents in two forms: diffuse scleroderma which affects the skin as well as the heart, lungs, gastrointestinal tract and kidneys and localized scleroderma which affects the skin of the face, neck, elbows and knees and late in the disease causes isolated pulmonary hypertension. Common complications seen with the diffuse form are pulmonary hypertension, reflux esophagitis and dysphagia, as well as the appearance of sclerodermal renal crisis. The condition is also life-threatening due to a 5-year survival which has been reported to be decreased. The main causes of mortality in patients with systemic sclerosis are cardiac complications, interstitial pulmonary disease, pulmonary hypertension, and renal manifestations.

The condition was estimated to be affecting approximately 3.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing humanised IgG1 monoclonal antibody against human eotaxin-2 may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical in vivo data that demonstrate that there is reduction in collagen accumulation which is associated with the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for humanised IgG1 monoclonal antibody against human eotaxin-2, for treatment of systemic sclerosis, was adopted by consensus.

2.2.19 Olaptesed pegol for treatment of glioma, Noxxon Pharma AG - EMA/OD/132/14
[COMP co-ordinator: D. O'Connor]

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

The intention to treat the condition with the medicinal product containing olaptesed pegol was considered justified based on preclinical models of the condition showing improved survival in treated subjects.

The condition is chronically debilitating, in particular due to compression and invasion of the surrounding brain structures leading to neurological deficits, and life-threatening with poor overall survival. Survival for glioblastoma multiforme patients is less than 5% at 5 years post diagnosis.

The condition was estimated to be affecting approximately 2.2 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 olaptesed pegol may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that support the potential of improved activity versus currently available products. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.20 Palovarotene for treatment of fibrodysplasia ossificans progressiva, Medpace Germany GmbH - EMA/OD/145/14
[COMP co-ordinator: J. Torrent-Farnell]

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

The intention to treat the condition with the medicinal product containing palovarotene was considered justified based on data showing that the product is capable of preventing heterotopic bone formation in relevant preclinical models of the condition.

The condition is chronically debilitating due to episodes of painful tumour-like soft-tissue swellings followed by the development of extra bone throughout the body and across joints causing progressive impairment of movement. The condition is life-threatening due to complications of thoracic insufficiency syndrome as a consequence of ankyloses in the thorax that lead to premature death around 50 years of age.

The condition was estimated to be affecting approximately 0.006 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 Palovarotene, for treatment of fibrodysplasia ossificans progressiva, was adopted by consensus.

2.2.21 Pentosan polysulfate sodium for treatment of mucopolysaccharidosis type I, Plexcera Therapeutics EU Limited - EMA/OD/121/14
[COMP co-ordinator: I. Bradinova]

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

The intention to treat the mucopolysaccharidosis type I with the medicinal product containing pentosan polysulfate sodium was considered justified based on relevant in vivo preclinical models and preliminary clinical data showing improved vascular histology and inflammatory biomarkers.

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

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing pentosan polysulfate sodium may be of significant benefit to those affected by the condition. The sponsor has provided preclinical and clinical data demonstrating improvements in vascular diameter, inflammation and the musculoskeletal system function. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for pentosan polysulfate sodium, for treatment of mucopolysaccharidosis type I, was adopted by consensus.

2.2.22 Pro-Pro-Thr-Val-Pro-Thr-Arg for treatment of xeroderma pigmentosum, Prof Alain Taieb - EMA/OD/155/14
[COMP co-ordinator: F. Naumann-Winter]

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

The intention to treat the condition with the medicinal product containing pro-Pro-Thr-Val-Pro-Thr-Arg was considered justified based on preclinical data.

The condition is chronically debilitating because rigorous photoprotective measures limit daytime activities and impact socio-psychological development, and because of neurodegenerative symptoms affecting 25% of patients The condition is life-threating due to a multiple times increased risk for melanomas and non-melanoma skin cancers at young age.

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

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

A positive opinion for containing pro-Pro-Thr-Val-Pro-Thr-Arg, for treatment of xeroderma pigmentosum, was adopted by consensus.

2.2.23 Product for treatment of pleural infection - EMA/OD/125/14
[COMP co-ordinator: S. Thorsteinsson]

The Committee considered that the following issues require clarification by the sponsor:

- Intention to diagnose, prevent or treat

Pleural infection 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 was drawn to the Orphan regulations and guidelines to clarify this (especially guideline ENTR/6283/00, and the "Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation").

Pleural infection is described as a stage of infections of the pleural space rather than a distinct condition or a valid subset, see e.g. the British Thoracic Society pleural disease guideline 2010: *"….Most forms of pleural infection represent a progressive process that transforms a 'simple' self-resolving parapneumonic pleural effusion into a 'complicated' multiloculated fibrinopurulent collection associated with clinical and/or biochemical features of sepsis".*

The sponsor was therefore invited to justify on which basis the proposed condition should be considered a distinct medical entity or a valid subset rather than a stage of infections of the pleural space.

- 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 was asked to justify the choice of the sources selected for the estimation of the incidence of the condition, since it appears that most of the cited articles include only patients below 18 years of age.

The sponsor was asked to therefore describe and justify the methodology used for the prevalence calculation, and in particular the scarcity of the references provided in adult population versus paediatric, and the justifications for assuming a similar incidence of the condition in these populations. In this respect the sponsor was also invited to better clarify which population(s) the final estimated incidence is based on.

In addition, given the substantial uncertainty about many of the assumptions regarding the incidence, the sponsor was asked to perform a sensitivity analysis of the reported calculations.

The sponsor was also reminded that should the proposed indication be revised, the estimated incidence should be amended accordingly.

- Significant benefit

A number of antibiotics are authorized in the European Union for the treatment of pleural infection.

The sponsor was invited to discuss the significant benefit of the proposed product in relation to the standard of care, including antibiotics.

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

2.2.24 Siponimod for treatment of dermatomyositis, Novartis Europharm Limited - EMA/OD/146/14
[COMP co-ordinator: F. Naumann-Winter]

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

The intention to treat the condition with the medicinal product containing siponimod was considered justified based on preliminary clinical data in patients with the condition showing improved muscle function and improvements in skin lesions.

The condition is life-threatening and chronically debilitating due to skin lesions, cardiac impairment, and progressively debilitating muscle weakness and increased risk of malignancy.

The condition was estimated to be affecting approximately 1.7 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing siponimod may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate improvement in muscle function and skin lesions in refractory patients. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for siponimod, for treatment of dermatomyositis, was adopted by consensus.

2.2.25 Siponimod for treatment of polymyositis, Novartis Europharm Limited - EMA/OD/147/14
[COMP co-ordinator: F. Naumann-Winter]

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

The intention to treat the condition with the medicinal product containing siponimod was considered justified based on preliminary clinical data showing improvements in muscle function.

The condition is life-threatening and chronically debilitating due to cardiac impairment and progressively debilitating muscle weakness.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing siponimod may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate an improvement in muscle function in refractory patients. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for siponimod, for treatment of polymyositis, was adopted by consensus.

2.2.26 Product for treatment of myasthenia gravis - EMA/OD/119/14
[COMP co-ordinator: V. Stoyanova]

The Committee considered that the following issues require clarification by the sponsor:

- 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 myasthenia gravis, the sponsor was asked to further elaborate on:

  - the proposed mechanism of action, by providing any available data to document the argued induction of apoptosis specifically in cells involved in immune response against the acetylcholine receptor;
  - the preventive settings of the preclinical model used for the purpose of medical plausibility, and the relevance of this model for the treatment of the condition;
  - any further available data in either relevant models of the proposed condition or in patients affected by the condition.

- Significant benefit

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

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

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

2.3. Appeal procedure

None.

2.4. Evaluation on-going

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

2.5. Validation on-going

The Committee was informed that validation was on-going for nineteen applications for orphan designation.

3. Requests for protocol assistance

3.1 For treatment of mantle cell lymphoma [Coordinator: A. Magrelli]

The Committee was briefed on the significant benefit issues. The protocol assistance letter was adopted via written procedure on 21 October 2014.

3.2 For treatment of gastro-entero-pancreatic neuroendocrine tumours [Co-ordinator: B. Bloechl-Daum]

The Committee was briefed on the significant benefit issues. The protocol assistance letter was adopted.

4. Overview of applications

4.1 Update on applications for orphan medicinal product designation submitted/expected

COMP co-ordinators were appointed for 2 application(s) submitted and 38 upcoming applications.

4.2 Update on orphan applications for Marketing Authorisation

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

5. Review of orphan designation for orphan medicinal products for Marketing Authorisation

5.1. Orphan designated products for which CHMP opinions have been adopted

5.1.1 Cyramza (ramucirumab) for treatment of gastric cancer; Eli Lilly Nederland B.V. (EU/3/12/1004) [COMP co-ordinator: B. Bloechl-Daum]

The COMP noted the CHMP opinion on MA adopted 22-25 September 2014 meeting.
As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to elaborate on the following issues:

- Proposed indication

The sponsor was invited to justify whether adenocarcinoma of the gastroeosophageal junction falls within the distinct medical entity as designated. The sponsor was asked to compare and contrast gastric cancer and cancer of the gastroesophageal junction in terms of classification, pathogenesis, etiology and clinical characteristics.

- Prevalence

The sponsor was requested to provide an updated prevalence calculation for gastric cancer at the time of the review of criteria for designation.

- Justification of significant benefit

In the maintenance document provided at this point in time, the sponsor provides a general discussion without any data and asserts that that the product as a single agent constitutes a clinically relevant advantage due to a different and more tolerable safety profile than other agents used.

Instead, the sponsor was hereby requested to provide data from the available clinical studies (monotherapy or in combination with paclitaxel) to document a clinically relevant advantage (such as improved efficacy or improved safety) or major contribution to patient care, in the context of the current standard of care guidelines for the gastric cancer population for which marketing authorisation is sought.

In particular with regards to the RAINBOW study: the sponsor was asked to discuss the clinical relevance of the extent of the OS improvement, as well as the results in the secondary endpoints studied, for the purpose of justifying significant benefit.

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

5.1.2 Ketoconazole HRA (ketoconazole) for treatment of Cushing's syndrome; Laboratoire HRA (EU/3/12/965) [COMP co-ordinator: K. Westermark]

The COMP noted the CHMP opinion on MA adopted 22-25 September 2014 meeting.

The COMP concluded that:

The proposed therapeutic indication "treatment of Cushing's syndrome" falls entirely within the scope of the orphan indication of the designated orphan medicinal product of Ketoconazole HRA, ketoconazole.

The COMP concluded that:

The proposed therapeutic indication "treatment of Cushing's syndrome" falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.

The prevalence of Cushing's syndrome (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 0.9 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is life-threatening and chronically debilitating due to the consequences of hypercortisolism, including cardiovascular disease, diabetes, clotting disorders, muscular weakness and osteoporosis, and psychiatric disturbances.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that ketoconazole may be of potential significant benefit to those affected by the orphan condition still holds. The significant benefit appears justified based on relevant data showing improved control of cortisol levels when ketoconazole was added to the treatment of patients who were not completely controlled with other products currently authorized for the condition. The COMP considers that this represents a clinically relevant advantage for the patients affected by Cushing's syndrome.

An opinion not recommending the removal of Ketoconazole HRA, ketoconazole, (EU/3/12/965) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion (EMA/COMP/609790/2014) was adopted for publication on the EMA website.

5.1.3 Signifor (pasireotide) for treatment of agromegaly – extension of MA indication; Novartis Europharm Limited (EU/3/09/670) [COMP co-ordinator: K. Westermark]

The COMP noted the CHMP opinion on MA adopted 22-25 September 2014 meeting.

The COMP concluded that:

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

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

The condition is life-threatening and chronically debilitating due the local mass effect of the tumour causing the condition, and to the consequences of chronic hypersecretion of growth hormone, including bone deformation, metabolic complications such as hyperinsulinaemia, diabetes, and dyslipidaemia, hypertension, cardiac myopathies, and respiratory complications.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that pasireotide may be of potential significant benefit to those affected by the orphan condition still holds. This is supported by data from an active comparator controlled phase 3 clinical trial showing improved reduction of growth hormone levels in patients inadequately controlled with the currently authorized somatostatin analogues.

An opinion not recommending the removal of Signifor, pasireotide (EU/3/09/670) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion (EMA/COMP/621067/2014) was adopted for publication on the EMA website.

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

5.2.1 Olaparib for treatment of ovarian cancer; AstraZeneca AB (EU/3/07/501) [COMP co-ordinator: B. Bloechl-Daum]

The COMP considered that the following issue requires clarification by the sponsor:

- Proposed indication

The sponsor was asked to compare and contrast ovarian cancer, fallopian tube and primary peritoneal cancer with regards to aetiology, classification, pathophysiology and clinical characteristics, to justify the inclusion of fallopian and peritoneal patient populations in the orphan designated indication.

- Significant benefit

The sponsor was invited to further elaborate on the significant benefit and justify based on data a clinically relevant advantage or major contribution to patient care versus all authorised counterparts, for the population the marketing authorisation is sought.

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

5.2.2 Nle4, D-Phe7]-alfa-melanocyte stimulating hormone for treatment of erythropoietic protoporphyria; Clinuvel (UK) Limited (EU/3/08/541) [COMP co-ordinator: L. Gramstad]

For information.

5.3. On-going procedures

5.3.1 Autologous tumour-derived immunoglobulin idiotype coupled to keyhole limpet haemocyanin for treatment of follicular lymphoma; Biovest Europe Ltd (EU/3/06/394)

5.3.2 (1R,2R)-octanoic acid[2-(2',3'-dihydro-benzo[1,4] dioxin-6'-yl)-2-hydroxy-1-pyrrolidin-1-ylmethyl-ethyl]-amide-L-tartaric acid salt for treatment of Gaucher disease; Genzyme Europe BV (EU/3/07/514)

5.3.3 Mifepristone for treatment of hypercortisolism (Cushing's syndrome) of endogenous origin; FGK Representative Service GmbH (EU/3/11/925)

5.3.4 Cysteamine hydrochloride for treatment of cystinosis; Orphan Europe S.A.R.L. (EU/3/08/578)

5.3.5 Panobinostat for treatment of multiple myeloma; Novartis Europharm Limited (EU/3/12/1063)

5.3.6 Human heterologous liver cells (for infusion); Cytonet GmbH&Co KG

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

b) treatment of ornithine-transcarbamylase deficiency (EU/3/07/470)

c) treatment of citrullinaemia type 1 (EU/3/10/818)

d) treatment of hyperargininaemia (EU/3/10/819)

e) treatment of argininosuccinic aciduria (EU/3/10/820)

5.3.7 Tasimelteon for treatment of non-24-hour sleep-wake disorder in blind people with no light perception; Vanda Pharmaceuticals Limited (EU/3/10/84)

5.3.8 Ex vivo expanded autologous human corneal epithelium containing stem cells for treatment of corneal lesions, with associated corneal (limbal) stem cell deficiency, due to ocular burns; Chiesi Farmaceutici S.p.A. (EU/3/08/579)

5.3.9 Ruxolitinib for treatment of polycythaemia vera; Novartis Europharm Limited (EU/3/14/1244)

5.3.10 Tolvaptan for treatment of autosomal dominant polycystic kidney disease; Otsuka Pharmaceutical Europe Ltd (EU/3/13/1175)

5.3.11 Ketoconazole for treatment of Cushing's syndrome; Agenzia Industrie Difesa-Stabilimento Chimico Farmaceutico Militare (EU/3/12/1031)

5.3.12 Lenvatinib; Eisai Ltd

a) treatment of papillary thyroid cancer (EU/3/13/1121)

b) treatment of follicular thyroid cancer (EU/3/13/1119)

5.3.13 Susoctocog alfa for treatment of haemophilia A; Baxter AG (EU/3/10/784)

5.3.14 Nintedanib for treatment of idiopathic pulmonary fibrosis; Boehringer Ingelheim International GmbH (EU/3/13/1123)

5.3.15 Levofloxacin hemihydrate for treatment of cystic fibrosis; Aptalis Pharma SAS (EU/3/08/566)

5.3.16 Glyceryl tri-(4-phenylbutyrate); Hyperion Therapeutics Limited

a) treatment of carbamoyl-phosphate synthase-1 deficiency (EU/3/10/733)

b) treatment of ornithine carbamoyltransferase deficiency (EU/3/10/734)

c) treatment of citrullinaemia type 1 (EU/3/10/735)

d) treatment of argininosuccinic aciduria (EU/3/10/736)

e) treatment of hyperargininaemia (EU/3/10/737)

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

g) treatment of citrullinaemia type 2 (EU/3/10/739)

5.3.17 Idebenone for treatment of Leber's hereditary optic neuropathy; Santhera Pharmaceuticals (Deutschland) GmbH (EU/3/07/434)

5.3.18 L-Asparaginase for treatment of acute lymphoblastic leukaemia; medac Gesellschaft fuer klinische Spezialpraeparate mbH (EU/3/04/258)

5.3.19 Asfotase alfa for treatment of hypophosphatasia; Alexion Europe SAS (EU/3/08/594)

5.3.20 Chimeric monoclonal antibody against GD2 for treatment of neuroblastoma; United Therapeutics Europe Ltd (EU/3/11/879)

5.3.21 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine, hydrochloride for treatment of narcolepsy; Bioprojet (EU/3/07/459)

5.3.22 Herpes simplex 1 virus-thymidine kinase and truncated low affinity nerve growth factor receptor transfected donor lymphocytes for adjunctive treatment in haematopoietic cell transplantation; MolMed S.p.A. (EU/3/03/168)

6. Procedural aspects

6.1 Significant Benefit ad hoc Working Group

EMA presented the topic.

6.2 EMA Human Scientific Committees' Working Parties with Patients' and Consumers' Organisations (PCWP) and Healthcare Professionals' Organisations (HCPWP) joint meeting Workshop on benefit-risk communication

Agenda of the 17 September 2014 meeting was circulated for information.

7. Any other business

7.1 SAWP/COMP interaction

EMA presented the updated PA/SB procedure.

7.2 Comparative analysis – COMP Orphan Designation versus PDCO PIP condition

EMA presented the topic.

7.3 Informal CHMP/CAT/COMP meeting to be held on 28-30 October 2014 in Rome

Updated Agenda was circulated for information.

7.4 Strategy paper on registries

EMA presented the topic.

Date of next COMP meeting: 11-13 November 2014

List of participants

Chair:

Bruno Sepodes

Vice-Chair:

Lesley Greene	Patient representative for Eurordis

COMP Members:

André Lhoir	Belgium
Irena Bradinova	Bulgaria
Kateřina Kubáčková	Czech Republic
Jens Ersbøll	Denmark
Frauke Naumann-Winter	Germany
Vallo Tillmann	Estonia
Geraldine O'Dea	Ireland
Nikolaos Sypsas	Greece
Josep Torrent Farnell	Spain
Annie Lorence	France
Adriana Andrić	Croatia
Sigurdur B. Thorsteinsson	Iceland
Armando Magrelli	Italy
Elena Kaisis	Cyprus
Dainis Krievins	Latvia
Aušra Matulevičienė	Lithuania
Henri Metz	Luxembourg
Judit Eggenhofer	Hungary
Albert Vincenti	Malta
Violeta Stoyanova-Beninska	The Netherlands
Lars Gramstad	Norway
Brigitte Blöchl-Daum	Austria
Bożenna Dembowska-Bagińska	Poland
Ana Corrêa-Nunes	Portugal
Flavia Saleh	Romania
Martin Možina	Slovenia
Zuzana Batová	Slovak Republic
Kerstin Westermark	Sweden
Daniel O'Connor	United Kingdom
Birthe Byskov Holm	Patient representative for Eurordis
Pauline Evers	Patient representative representing the EGAN

Aikaterini Moraiti	Member nominated by the European Commission on the EMA's recommendation
Ingeborg Barisic	Member nominated by the European Commission on the EMA's recommendation
Giuseppe Capovilla	Member nominated by the European Commission on the EMA's recommendation

Observers:

Virginie Hivert	Eurordis