EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 August 2014
EMA/COMP/295834/2014
Procedure Management and Business Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes of the 10-12 June 2014 meeting

Note on access to documents

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).

Contents

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. Introduction

1.1 Adoption of the agenda, EMA/COMP/296811/2014

The agenda was adopted with no amendments.

1.2 Adoption of the minutes of the previous meetings held on:

- 8-9 April 2014, EMA/COMP/151064/2014

  The minutes were adopted with no amendments.

- 13-14 May 2014, EMA/COMP/220006/2014

  The adoption of the minutes was postponed.

1.3 Conflicts of Interest

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

The COMP secretariat was informed as follows:

- EGAN received a grant from the sponsors of the product under agenda point 2.2.2. 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 Product for treatment of cystinosis - EMA/OD/031/14
[Co-ordinators: 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

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

  - the results obtained in vitro on cell lines the relevance of the preclinical model used for the treatment of cystinosis, and the interpretation of the results obtained in the experiments;
  - the methodology used in the pre-clinical studies as well as the results from these studies and their relevance for the development of the product in the condition.

- Number of people affected

The submitted prevalence calculation appears to be quite high. The sponsor should re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition and resubmit to the COMP.

[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).

- Significant benefit

The arguments on significant benefit are based on a major contribution to patient care.

The sponsor is requested to further discuss the arguments provided for significant benefit and to clarify how the results from the in vitro fibroblast cell study could justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

The sponsor should discuss the place of non-clinical in vivo models which could confirm the in vitro data presented.

In the written response, and during an oral explanation before the Committee on 10 June 2014, the sponsor discussed the preclinical models used in the application, and elaborated on the results seen in healthy and patient-derived cells in vitro, as well as the observations in a healthy preclinical in vivo model with regards to gastric irritation. With regards to the prevalence issue, the sponsor defended its position based on the argument that literature and registers on the epidemiology of cystinosis concur on an incidence of 1 in 100,000 – 1 in 200,000. Finally, the sponsor argued for significant benefit based on improvements in tolerance and safety that may also lead to improved compliance to treatment, thereby offering a major contribution to patient care.

The committee considered that in the absence of data specifically addressing the projected claims for significant benefit the justification of the criteria for designation would be difficult to accept.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 10 June 2014, prior to final opinion.

2.1.2 **Marizomib** for treatment of plasma cell myeloma, Richardson Associates Regulatory Affairs Ltd - EMA/OD/035/14

[Co-ordinators: 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:

- Prevalence

The sponsor is invited to further justify the duration of the condition used for the calculation of prevalence and if necessary recalculate the estimate taking into account the most recent information on the prognosis of these patients.

- Significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit in particular with regards to the authorised proteasome inhibitor.

The sponsor is also invited to elaborate on the background treatments of the relapsed/refractory patients who participated in the preliminary clinical studies presented as part of the application.

In the written response, the sponsor recalculated the prevalence by assuming a 6.1 year duration of the disease based on literature data; the estimate was revised upwards to approximately 3.6/10,000 people in the EU. Moreover, with regards to the phase I preliminary clinical data, it was further elaborated that most subjects were very heavily pretreated and the sponsor presented results confirming responses in patients who have previously been refractory to authorised treatments. 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 marizomib was considered justified based on preclinical and preliminary clinical data in plasma cell myeloma patients showing clinically relevant responses after treatment with the product.

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 3.6 per 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 marizomib may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in patients with plasma cell myeloma who had relapsed or progressed following treatment with available products. In these patients, treatment with the product resulted in clinically relevant responses. The Committee considered that this constitutes a clinically relevant advantage.

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

2.1.3 Product for treatment of Growth Hormone Deficiency in Adults and Children - EMA/OD/030/14

[Co-ordinators: V. Tillmann]

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 is proposing a range for the prevalence for the condition. Previous designations have given a point estimate.

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

- Significant benefit

The sponsor should further elaborate on the differences between their product and the authorised modified release somatropin. The arguments on significant benefit are based on a modified release formulation offering a clinically relevant advantage based on different pharmacokinetic and pharmacodynamic properties.

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

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

The sponsor should further elaborate on the potential risks with the product and how this compares with the safety profile with regards to immunogenicity of current authorised medicinal products for the same condition.

In the written response, and during an oral explanation before the Committee on 11 June 2014, the sponsor further elaborated in the requested issues. The prevalence was recalculated based on separate considerations for child and adult populations, and a 2.94/10,000 figure was proposed. With regards to significant benefit, this was argued on the basis of an improved pharmacokinetic/ pharmacodynamic profile, improved (lower) immunogenicity and injection site tolerability, as well as a major Contribution to Patient Care on the grounds of an improved pharmaceutical presentation.

The COMP considered the data insufficient for the justification of major contribution to patient care as the basis of the significant benefit, and in communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 June 2014, prior to final opinion.

2.1.4 **Carboxy pyrrolidine hexanoyl pyrrolidone carboxylate** for treatment of systemic amyloidosis, GlaxoSmithKline Trading Services Limited - EMA/OD/020/14

[Co-ordinators: 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:

- Proposed condition

As per the 2012 recommendations from the Nomenclature committee of the International Society of Amyloidosis (Sipe *et al* Amyloid 19(4) 167-70) and in line with the opinion of the Committee, the sponsor is requested to apply for the treatment of distinct medical entities.

For the purposes of orphan medicinal product designation attention is drawn to the Orphan regulations and guidelines (especially section A of ENTR/6283/00 Rev04).

- Intention to diagnose, prevent or treat

To establish correctly the medical plausibility, the sponsor should further elaborate on the following issues:

  - the argued obligate partnership between the two products applied for designation (in two separate applications simultaneously submitted), by providing data that shows that neither of these products may have effects alone;
  - any specific data obtained with the product(s) from the on-going studies either in models or in patients affected by the condition;
  - the methodology used in the pre-clinical studies as well as the results from these studies and their relevance for the development of the product in the condition.

- Life-threatening and debilitating nature of the condition

For the amended indication(s), the sponsor should further elaborate on the life-threatening or chronically debilitating nature of the condition.

- Number of people affected

For the amended indication (s), the sponsor should also recalculate the prevalence. For the calculation and presentation of the prevalence estimate it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

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

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential for improved efficacy in the condition. The sponsor is requested to further discuss the arguments provided for significant benefit based on data, and provide a comparative discussion versus authorised counterparts.

The sponsor should also detail the results of any clinical studies 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 11 June 2014, the sponsor further elaborated on the raised issues. With regards to the proposed indication, the sponsor, in light of the concerns raised by the Committee's, amended the indication to treatment of AL-amyloidosis. Updated seriousness and prevalence sections were also submitted. As for the "obligate partnership" of the two products applied for designation, it was emphasised that Carboxy pyrrolidine hexanoyl pyrrolidone carboxylate (CPHPC) treatment alone does not promote amyloid regression and that CPHPC depletes circulating serum amyloid P (SAP) but leaves residual SAP as specific marker of amyloid deposits. At the same time anti-SAP antibody cannot be administered alone because of an unacceptable safety risk. Therefore the partnership composed of administration of CPHPC, is to first deplete circulating SAP, and then administer anti-SAP antibody to target residual SAP in the amyloid deposits. The Committee accepted this notion.

The sponsor also discussed the absence of models for systemic AL amyloidosis. The only distantly relevant model would be a murine model of "amyloidomas" produced by subcutaneous injection of human free immunoglobulin light chains in mice. The sponsor also referred to an AA amyloidosis model, but the COMP considered that even though there are some commonalities between AL, and AA amyloidosis, these are two different entities and extrapolations were difficult to consider. Therefore, the basis of medical plausibility was considered mainly on the basis of the preliminary clinical data.

Moreover, at the oral hearing with the COMP, the preliminary clinical data in a few AL patients were further questioned, especially with regards to an apparent discrepancy between imaging and other endpoints studied such as the liver function tests. The sponsor elaborated on the imaging method in the context of their experience in different forms of amyloidosis, and clarified that the expected changes are not prominent but in line with other observations, such as liver elastography and liver biochemistry.

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

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

The intention to treat the condition with the medicinal product containing carboxy pyrrolidine hexanoyl pyrrolidine carboxylate was considered justified based on preliminary clinical studies showing clinically relevant improvements in treated patients affected by the condition.

The condition is chronically debilitating and life-threatening due to the accumulation of fibril deposits which disrupts normal tissue structure and function, notably in the heart, kidneys, liver, peripheral nervous system, gastrointestinal tract, and soft tissues.

The condition was estimated to be affecting approximately 1.1 in 10,000 persons in the European Union, at the time the application was made; Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

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 Carboxy pyrrolidine hexanoyl pyrrolidine carboxylate, for treatment of AL amyloidosis, was adopted by consensus.

2.1.5 **Recombinant monoclonal antibody to human serum amyloid P component** for treatment of systemic amyloidosis, GlaxoSmithKline Trading Services Limited - EMA/OD/021/14 *[Co-ordinators: 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:

- Proposed condition

As per the 2012 recommendations from the Nomenclature committee of the International Society of Amyloidosis (Sipe *et al* Amyloid 19(4) 167-70) and in line with the opinion of the Committee, the sponsor is requested to apply for the treatment of distinct medical entities.

For the purposes of orphan medicinal product designation attention is drawn to the Orphan regulations and guidelines (especially section A of ENTR/6283/00 Rev04).

- Intention to diagnose, prevent or treat

To establish correctly the medical plausibility, the sponsor should further elaborate on the following issues:

  - the argued obligate partnership between the two products applied for designation (in two separate applications simultaneously submitted) by providing data that shows that neither of these products may have effects alone;
  - any specific data obtained with the product(s) from the on-going studies either in models or in patients affected by the condition;
  - the methodology used in the pre-clinical studies as well as the results from these studies and their relevance for the development of the product in the condition.

- Life-threatening and debilitating nature of the condition

For the amended indication (s), the sponsor should further elaborate on the life-threatening or chronically debilitating nature of the condition.

- Number of people affected

For the amended indication (s), the sponsor should also recalculate the prevalence. For the calculation and presentation of the prevalence estimate it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

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

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential for improved efficacy in the condition. The sponsor is requested to further discuss the arguments provided for significant benefit based on data, and provide a comparative discussion versus authorised counterparts.

The sponsor should also detail the results of any clinical studies 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 11 June 2014, the sponsor further elaborated on the raised issues. With regards to the proposed indication, the sponsor, in light of the concerns raised by the Committee's, amended the indication to treatment of AL-amyloidosis. Updated seriousness and prevalence sections were also submitted. As for the "obligate partnership" of the two products applied for designation, it was emphasised that Carboxy pyrrolidine hexanoyl pyrrolidone carboxylate (CPHPC) treatment alone does not promote amyloid regression and that CPHPC depletes circulating serum amyloid P (SAP) but leaves residual SAP as specific marker of amyloid deposits. At the same time anti-SAP antibody cannot be administered alone because of an unacceptable safety risk. Therefore the partnership composed of administration of CPHPC, is to first deplete circulating SAP, and then administer anti-SAP antibody to target residual SAP in the amyloid deposits. The Committee accepted this notion.

The sponsor also discussed the absence of models for systemic AL amyloidosis. The only distantly relevant model would be a murine model of "amyloidomas" produced by subcutaneous injection of human free immunoglobulin light chains in mice. The sponsor also referred to an AA amyloidosis model, but the COMP considered that even though there are some commonalities between AL, and AA amyloidosis, these are two different entities and extrapolations were difficult to consider. Therefore, the basis of medical plausibility was considered mainly on the basis of the preliminary clinical data.

Moreover, at the oral hearing with the COMP, the preliminary clinical data in a few AL patients were further questioned, especially with regards to an apparent discrepancy between imaging and other endpoints studied such as the liver function tests. The sponsor elaborated on the imaging method in the context of their experience in different forms of amyloidosis, and clarified that the expected changes are not prominent but in line with other observations, such as liver elastography and liver biochemistry.

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

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

The intention to treat the condition with the medicinal product containing recombinant monoclonal antibody to human serum amyloid P component was considered justified based on preliminary clinical studies showing clinically relevant improvements in treated patients affected by the condition.

The condition is chronically debilitating and life-threatening due to the accumulation of fibril deposits which disrupts normal tissue structure and function, notably in the heart, kidneys, liver, peripheral nervous system, gastrointestinal tract, and soft tissues.

The condition was estimated to be affecting approximately 1.1 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 Recombinant monoclonal antibody to human serum amyloid P component, for treatment of AL amyloidosis, was adopted by consensus.

2.1.6 **Sodium acetate salt of the synthetic peptide H-D-Ala-Ser-Pro-Met-Leu-Val-Ala-Tyr-Asp-D-Ala-OH** for treatment for necrotizing soft tissue infections, Dr Ulrich Granzer - EMA/OD/028/14

[Co-ordinators: S. Thorsteinsson]

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

- Proposed condition

"Necrotizing soft tissue infections" should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00 Rev4).

The sponsor should provide any internationally accepted classification or consensus agreement justifying that the condition as proposed for designation is a distinct medical entity, or amend the proposed indication accordingly.

- Intention to diagnose, prevent or treat

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

  - the relevance of the preclinical models used for the treatment of necrotizing soft tissue infections (or in case of an amended indication, the new indication), and the interpretation of the results obtained in the experiments;
  - the basis for restricting the proposed indication to Necrotizing soft tissue infections, and the relevance of the product for other infections and septic syndromes, notwithstanding that the orphan condition should be a distinct medical entity or a valid subset;
  - the methodology used in the preliminary-clinical study as well as the results from this study and their relevance for the development of the product in the condition;

- the discrepancy in the level of effects observed in the preclinical and preliminary clinical settings.

Life-threatening and debilitating nature of the condition.

In case of amended indication, the seriousness of the condition should be readdressed.

- Number of people affected

In case of amended indication, the prevalence of the condition should be readdressed.

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

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potentially improved efficacy in the condition. The sponsor should detail the results of any clinical data they have to support the significant benefit assumption in the context of the current therapeutic management of patients.

In its written response, and during an oral explanation before the committee, the sponsor first discussed the differences of the proposed indication vis a vis other infections and septic syndromes. It was stressed that the main difference pertained to progressive tissue destruction and that the clinical features are characterised by tissue necrosis. The sponsor also referred to treatment guidelines to support the notion that this is a distinct medical entity. The COMP considered that the proposed condition is a distinct medical entity primarily on the basis of the presence of extensive tissue necrosis.

As per the medical plausibility, the sponsor further elaborated on the relevance of the preclinical models for the condition and discussed the results from the available clinical study. In particular with regards to the clinical results, it was argued that all the endpoints studied showed similar trends in favour of the proposed therapy, a consideration which was accepted by the Committee. The Committee focused on these preliminary clinical results which were seen as more relevant than the preclinical experiments for the proposed indication. Given that the preliminary clinical study pertains to use of the product as an add-on to standard of care, the Committee also considered that the alternative mechanism of action may also be translated to improved efficacy allowing the product to be used in addition to available treatments.

The Committee agreed that the condition, necrotizing soft tissue infections, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing sodium acetate salt of the synthetic peptide H-D-Ala-Ser-Pro-Met-Leu-Val-Ala-Tyr-Asp-D-Ala-OH was considered justified based on preclinical data in relevant models and preliminary clinical data in patients affected by the condition that showed clinically relevant improvement upon treatment.

The condition is life-threatening with reported mortality of up to 17% and chronically debilitating due to the need for extensive surgical debridement, and the development of organ dysfunction and sepsis.

The condition was estimated to be affecting less than 1 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 sodium acetate salt of the synthetic peptide H-D-Ala-Ser-Pro-Met-Leu-Val-Ala-Tyr-

Asp-D-Ala-OH may be of significant benefit to those affected by the condition. This assumption was based on an alternative mechanism of action that may translate into improved efficacy, as supported by preliminary clinical data in patients affected by the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for Sodium acetate salt of the synthetic peptide H-D-Ala-Ser-Pro-Met-Leu-Val-Ala-Tyr-Asp-D-Ala-OH, for treatment of necrotising soft tissue infections, was adopted by consensus.

2.1.7 A product for treatment of diffuse large B-cell lymphoma - EMA/OD/029/14
[Co-ordinators: B. Dembowska-Bagińska]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 20 May 2014, prior to responding to the list of issues.

2.1.8 A product for treatment of thrombocytopenia caused by chronic idiopathic thrombocytopenia purpura - EMA/OD/025/14
[Co-ordinators: 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 26 May 2014, prior to responding to the list of issues.

2.2. For discussion / preparation for an opinion

2.2.1 Product for treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis - EMA/OD/050/14
[Co-ordinators: B. Bloechl-Daum]

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

- Intention to diagnose, prevent or treat

There is no clear consensus in the scientific world regarding classification of ANCA-associated vasculitis, e.g. grouping the different forms as the sponsor does, or based on ANCA specificity (MPO/PR3), or with categories for GPA and MPA.

The sponsor is therefore invited to discuss the plausibility of grouping granulomatosis with polyangiitis (GPA) (previously named Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) (previously named Churg Strauss syndrome) under the same orphan designation, taking into account the definition of distinct medical entity as given in guideline ENTR/6283/00, and the target condition(s) and population(s) of the studies presented in this application.

Alternatively the sponsor is invited to target separately one or more of the single distinct forms of vasculititis that have been presented in this application under the umbrella of ANCA-associated vasculitis.

- Number of people affected

Should the sponsor be changing the medical condition(s) object of this application it is expected that prevalence calculations are revised accordingly.

- Life-threatening and chronically debilitating nature of the condition

Should the sponsor be changing the medical condition(s) object of this application it is expected that the paragraphs on seriousness are revised accordingly.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the July meeting.

2.2.2 Product for treatment of Fabry disease - EMA/OD/052/14
[Co-ordinators: A. Corrêa Nunes]

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

- Number of people affected

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

The sponsor should justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor should describe and justify the methodology used for the prevalence calculation. In particular, a discussion of clinical disease versus mutation carriers should be made.

The COMP adopted a list of issues that will be sent to the sponsor for a written response only.

2.2.3 Product for treatment of Duchenne muscular dystrophy - EMA/OD/049/14
[Co-ordinators: P. Evers]

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

- Intention to diagnose, prevent or treat

In order to justify the medical plausibility of the proposed product for the treatment of Duchenne muscular dystrophy the sponsor is invited to discuss more in detail the data of the two animal model studies including:

- the results obtained in the first study, where both the proposed product and prednisolone almost normalized muscle strength, taking into account the lack of clear evidence of an effect of corticosteroids on muscle strength in the published literature so far;
- the great reduction in maximal force exerted with prednisolone in this study- even lower than in the untreated control group - while prednisolone showed the strongest effect among all treatments on forelimb and hindlimb normalized grip strength;
- the lack of a dose-response in the parameters measured in the second study, and the clinical relevance of the changes in *in vitro* force contractions of EDL muscle.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the July meeting.

2.2.4 Product for treatment of pigmented villonodular synovitis/giant cell tumour of the tendon sheath - EMA/OD/058/14
[Co-ordinators: D. O'Connor]

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

- Intention to diagnose, prevent or treat

The proposed condition currently describes two entities (pigmented villonodular synovitis / giant cell tumour of the tendon sheath). The sponsor should revise the condition in line with current classification systems where possible. Note that this is for the purposes of orphan medicinal product designation attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

- Number of people affected

A more detailed discussion of the evidence to support the prevalence claim is required, and will need to be revised in line with the conclusion on the condition.

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

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the July meeting.

2.2.5 Adeno-associated viral vector serotype 9 containing the human cardiac calsequestrin gene for treatment of catecholaminergic polymorphic ventricular tachycardia, Fondazione Salvatore Maugeri Clinica del Lavoro e della Riabilitazione - EMA/OD/037/14
[Co-ordinators: A. Moraiti]

The Committee agreed that the condition, catecholaminergic polymorphic ventricular tachycardia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 9 containing the human cardiac calsequestrin gene was considered justified based on studies in relevant preclinical models.

The condition is chronically debilitating due to syncoptic episodes and life-threatening due to cardiac arrest after emotional or physical stress that may lead to sudden death.

The condition was estimated to be affecting approximately 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 Adeno-associated viral vector serotype 9 containing the human cardiac calsequestrin gene, for treatment of catecholaminergic polymorphic ventricular tachycardia, was adopted by consensus.

2.2.6 Cediranib for treatment of ovarian cancer, AstraZeneca AB - EMA/OD/059/14
[Co-ordinators: B. Bloechl-Daum]

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

The intention to treat the condition with the medicinal product containing cediranib was considered justified based on clinical data in patients with the condition.

The condition is chronically debilitating in particular due to pain, weight loss, ascites and vaginal bleeding, and life-threatening with approximately half of the patients surviving less than five years.

The condition was estimated to be affecting approximately 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 cediranib may be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that their product improves progression free survival and overall survival in patients previously treated with platinum. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for Cediranib, for treatment of ovarian cancer, was adopted by consensus.

2.2.7 Cysteamine bitartrate for treatment of Huntington's disease, Raptor Pharmaceuticals Europe BV - EMA/OD/070/14
[Co-ordinators: V. Stoyanova]

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

The intention to treat the condition with the medicinal product containing cysteamine bitartrate was considered justified based on preliminary clinical data which shows a reduction in the motorloss of the disease.

The condition is chronically debilitating due to severe behavioural and cognitive disturbances, progressive motor dysfunction and potentially fatal complications.

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 cysteamine bitartrate may be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate a decline in the rate of progression of the disease on the motor symptoms when compared to a control group. The Committee considered that this could translate into a clinically relevant advantage.

A positive opinion for Cysteamine bitartrate, for treatment of Huntington's disease, was adopted by consensus.

2.2.8 Product for treatment of glioma - EMA/OD/055/14
[Co-ordinators: B. Bloechl-Daum]

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 glioma, the sponsor should further elaborate on:

  - the relevance of the preclinical model used for the treatment of glioma, and the interpretation of the results obtained in the experiments;
  - the methodology used in the pre-clinical studies as well as the results from these studies and its relevance for the development of the product in the condition.

- Significant benefit

The sponsor has presented their product as having an alternative mode of action in the treatment of glioblastoma multiform resistant to temozolomide. The arguments on significant benefit are based on an alternative mechanism of action and the potential improved efficacy in the condition.

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

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the July meeting.

2.2.9 **Eculizumab** for treatment of myasthenia gravis, Alexion Europe SAS - EMA/OD/062/14

[Co-ordinators: J. Torrent-Farnell]

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

The intention to treat the condition with the medicinal product containing eculizumab was considered justified based on preclinical and preliminary clinical data in patients affected by the condition who responded to treatment.

The condition is chronically debilitating and life-threatening, in particular due to generalised muscle weakness resulting in severe respiratory impairment and reduced overall survival.

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

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 eculizumab may be of significant benefit to those affected by the condition. This assumption was considered on the basis of a novel mechanism of action which may translate into improved efficacy as supported by preclinical and preliminary clinical data in patients affected by refractory myasthenia gravis. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for Eculizumab, for treatment of myasthenia gravis, was adopted by consensus.

2.2.10 Product for treatment of Schnitzler Syndrome - EMA/OD/053/14
[Co-ordinators: A. Andrić]

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 Schnitzler Syndrome, the sponsor is invited to further elaborate on any updated results from the on-going proof of concept study.

The Sponsor should also elaborate on the results presented in the application and in particular discuss the absence of quantified data in the treated patients.

- Prevalence

The sponsor is invited to recalculate the prevalence estimate taking into consideration the underdiagnosis of the condition and the updated diagnostic criteria.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the July meeting.

2.2.11 Humanised anti-alpha v beta 6 monoclonal antibody for treatment of idiopathic pulmonary fibrosis, Biogen Idec Limited - EMA/OD/051/14
[Co-ordinators: M. Možina]

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 humanised anti-alpha v beta 6 monoclonal antibody was considered justified based on preclinical data showing improvement of fibrosis induced by bleomycin and by radiation.

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

The condition was estimated to be affecting not more than 3 in 10,000 persons in the European Union, at the time the application was made. The conclusions of the sponsor were based on a literature search.

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 anti-alpha v beta 6 monoclonal antibody is of significant benefit to those affected by the condition. The sponsor provided preclinical data showing reduction of fibrosis in relevant preclinical models. In addition the product has a different mechanism of action from the authorised pirfenidone, targeting specifically alpha v beta 6. The Committee considered that this may translate into a clinically relevant advantage.

A positive opinion for Humanised anti-alpha v beta 6 monoclonal antibody, for treatment of idiopathic pulmonary fibrosis, was adopted by consensus.

2.2.12 Humanized Recombinant Monoclonal Antibody Against Epidermal Growth Factor Receptor Conjugated to Maleimidocaproyl Monomethylauristatin F for treatment of glioma, AbbVie Ltd - EMA/OD/065/14
[Co-ordinators: B. Bloechl-Daum]

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

The intention to treat the condition with the medicinal product containing humanised recombinant monoclonal antibody against epidermal growth factor receptor conjugated to maleimidocaproyl monomethylauristatin F was considered justified based on preclinical data showing inhibition of tumour growth, as well as preliminary clinical data showing objective responses in patients affected by the condition.

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

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

In addition, although satisfactory methods for 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 recombinant monoclonal antibody against epidermal growth factor receptor conjugated to maleimidocaproyl monomethylauristatin F may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing improved inhibition of tumour growth when the product is added to existing methods, as well as preliminary clinical data in refractory glioma patients who responded to treatment with the proposed product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for Humanized recombinant monoclonal antibody against epidermal growth factor receptor conjugated to maleimidocaproyl monomethylauristatin F, for treatment of glioma, was adopted by consensus.

2.2.13 Product for treatment of adrenal insufficiency - EMA/OD/060/14
[Co-ordinators: K. Westermark]

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

- Intention to diagnose, prevent or treat

The sponsor seeks an orphan designation for a group of conditions. To fulfil the requirements for orphan designation the condition should therefore be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation attention is 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 adrenal insufficiency, the sponsor should further elaborate on why the sponsor has not generated any data with their formulation in patients with the condition and why adult patients should be excluded, taking into account that currently authorised hydrocortisone products do not allow for fine dose adjustments.

- Number of people affected

The sponsor should recalculate the prevalence according to the condition to be treated, including both paediatric and adult patients. For the calculation and presentation of the prevalence estimate it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

- Significant benefit

The sponsor has not submitted any comparison with authorised treatments. There is also a lack of data in the intended population to be treated. As there is no data the sponsor should further elaborate on the significant benefit their product may offer in the target patient population and what the basis of this would be.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the July meeting.

2.2.14 Product for treatment of cystic fibrosis - EMA/OD/032/14
[Co-ordinators: J. Eggenhofer]

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

- Intention to diagnose, prevent or treat

In order to justify the medical plausibility the sponsor is invited to present any available data with the product as applied for designation.

The sponsor is also invited to further elaborate on the extrapolation of the results obtained with the two separate constituents of the product.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the July meeting.

2.2.15 Oxytocin for treatment of Prader-Willi Syndrome, Maïthé Tauber - EMA/OD/054/14
[Co-ordinators: V. Tillmann]

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

The intention to treat the condition with the medicinal product containing oxytocin was considered justified based on preliminary pre-clinical and clinical data in infants and adults showing improvements in feeding and behavioural parameters.

The condition is life-threatening and chronically debilitating, in particular due to cognitive impairment, maladaptive behaviour and morbid obesity.

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 oxytocin may be of significant benefit to those affected by the condition. The

sponsor has provided pre-clinical in vivo and clinical data that demonstrate improvements in feeding and behavioural parameters associated with the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for Oxytocin, for treatment of Prader-Willi syndrome, was adopted by consensus.

2.2.16 Product for treatment of haemophilia A - EMA/OD/024/14

[Co-ordinators: L. Gramstad]

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

- Intention to diagnose, prevent or treat

The sponsor should provide the study reports of the FVIII knockout preclinical in vivo models.

- Significant benefit

The claims for the assumption of significant benefit should be supported by data as far as possible.

The sponsor is requested to further discuss the arguments provided for significant benefit based on data and to elaborate on the compliance issues argued and how these are related to the frequency of the dosing scheme.

The sponsor is also requested to further elaborate on the envisioned dosing scheme of the new product and compare this to the dosing schemes of all authorised products for the treatment of haemophilia A, based on any available data.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the July meeting.

2.2.17 Product for treatment of retinopathy of prematurity - EMA/OD/040/14

[Co-ordinators: 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 treatment of retinopathy of prematurity, the sponsor should further elaborate on:

  - The preclinical data bibliographic are conflicting as the results from one study are positive from one investigative unit. However when a different investigative unit tried to reproduce the results these were negative. The concerns regarding the lack of reproducibility need to be further discussed and clarified.
  - Results from clinical data obtained with an oral formulation, seem to be mainly from stage II ROP which often regresses spontaneously. In addition data from the proposed formulation seem to influence only the superficial layer of the retina. The sponsor's product is under development and so far no studies have been performed. The sponsor is invited to further elaborate on the preliminary clinical data with the eye drops and how this data may support the medical plausibility.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the July meeting.

2.2.18 Product for treatment of congenital factor VII deficiency - EMA/OD/057/14
[Co-ordinators: L. Gramstad]

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

- Significant benefit

The arguments on significant benefit are based on a major contribution to patient care.

The sponsor is requested to further discuss the arguments provided for significant benefit, specifically to elaborate on how the results from preclinical simulations allow for predicting trough levels and therapeutic plasma levels required to achieve and maintain haemostasis to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

The sponsor should also justify the assumption of significant benefit over authorised plasma-derived FVII products.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the July meeting.

2.2.19 Product for treatment of haemophilia A - EMA/OD/069/14
[Co-ordinators: L. Gramstad]

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

- Significant benefit

The arguments on significant benefit are based on a major contribution to patient care in patients with haemophilia A, who developed inhibitory antibodies.

The sponsor is requested to further discuss the arguments provided for significant benefit, specifically to elaborate on how the results from animal simulations allow for predicting trough levels and therapeutic plasma levels required to achieve and maintain haemostasis to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

The sponsor should also justify the assumption of significant benefit over other authorised bypass agents.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the July meeting.

2.2.20 Product for treatment of haemophilia B - EMA/OD/073/14
[Co-ordinators: L. Gramstad]

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

- Significant benefit

The arguments on significant benefit are based on a major contribution to patient care.

The sponsor is requested to further discuss the arguments provided for significant benefit, specifically to elaborate on how the results from animal simulations allow for predicting trough levels and therapeutic plasma levels required to achieve and maintain haemostasis to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

The sponsor should also justify the assumption of significant benefit over other authorised bypass agents.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the July meeting.

2.2.21 Product for treatment of myelodysplastic syndromes - EMA/OD/048/14
[Co-ordinators: J. Torrent-Farnell]

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

- Number of people affected

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

The sponsor should justify the inclusion/choice of the epidemiological index used, elaborate on the duration of the condition, and justify the methodology for the prevalence calculation.

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

The COMP adopted a list of issues that will be sent to the sponsor for a written response only.

2.2.22 Recombinant fusion protein consisting of a modified form of the extracellular domain of human Activin Receptor IIB linked to the human IgG1 Fc domain for treatment of beta-thalassemia intermedia and major, IDEA Innovative Drug European Associates Limited - EMA/OD/047/14
[Co-ordinators: L. Gramstad]

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

The intention to treat the condition with the medicinal product containing recombinant fusion protein consisting of a modified form of the extracellular domain of human activin receptor IIB linked to the human IgG1 Fc domain was considered justified based on preliminary clinical data showing haemoglobin increase in non-transfusion dependent patients affected by the condition.

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

The condition was estimated to be affecting approximately 1in 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 fusion protein consisting of a modified form of the extracellular domain of human Activin Receptor IIB linked to the human IgG1 Fc domain may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing that

treatment of patients with the product may improve anaemia, which is a different aspect to the target of the iron chelation products authorised. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for Recombinant fusion protein consisting of a modified form of the extracellular domain of human activin receptor IIB linked to the human IgG1 Fc domain, for treatment of beta-thalassaemia intermedia and major, was adopted by consensus.

2.2.23 Product for treatment of paroxysmal nocturnal haemoglobinuria - EMA/OD/056/14
[Co-ordinators: J. Torrent-Farnell]

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

- Significant benefit

The arguments on significant benefit are based on an improvement of quality of life on the grounds of a self-administered subcutaneous administration of the product versus the intravenous administration of the authorised counterpart.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the relevance of the cited literature pertaining to different products and disease settings. The claims for significant benefit should be supported with relevant data.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the July meeting.

2.2.24 Product for treatment of Apolipoprotein A-I (apoA-I) deficiency - EMA/OD/064/14
[Co-ordinators: F. Saleh]

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 the treatment of the proposed conditions, the sponsor is invited to further elaborate on the available preliminary clinical data by discussing the effects of treatment separately for each of the three medical entities as applied for designation.

Moreover, the sponsor should justify the grounds on which the proposed product is applicable for all the conditions applied for designation, and comment on the lack of data on preclinical models for each of the conditions.

- Seriousness

The sponsor is requested to provide as far as possible quantified morbidity and mortality data for each of the three medical entities 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 should provide a clear overall conclusion for each of the three medical entities as applied for designation.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the July meeting.

2.2.25 Product for treatment of ATP-Binding Cassette Transporter A1 (ABCA1) deficiency - EMA/OD/063/14
[Co-ordinators: F. Saleh]

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 the treatment of the proposed conditions, the sponsor is invited to further elaborate on the available preliminary clinical data by discussing the effects of treatment separately for each of the three medical entities as applied for designation.

Moreover, the sponsor should justify the grounds on which the proposed product is applicable for all the conditions applied for designation, and comment on the lack of data on preclinical models for each of the conditions.

- Seriousness

The sponsor is requested to provide as far as possible quantified morbidity and mortality data for each of the three medical entities 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 should provide a clear overall conclusion for each of the three medical entities as applied for designation.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the July meeting.

2.2.26 Product for treatment of Lecithin Cholesterol Acyltransferase (LCAT) deficiency - EMA/OD/066/14
[Co-ordinators: F. Saleh]

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 the treatment of the proposed conditions, the sponsor is invited to further elaborate on the available preliminary clinical data by discussing the effects of treatment separately for each of the three medical entities as applied for designation.

Moreover, the sponsor should justify the grounds on which the proposed product is applicable for all the conditions applied for designation, and comment on the lack of data on preclinical models for each of the conditions.

- Seriousness

The sponsor is requested to provide as far as possible quantified morbidity and mortality data for each of the three medical entities 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 should provide a clear overall conclusion for each of the three medical entities as applied for designation.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the July meeting.

2.2.27 Product for prevention of bronchopulmonary dysplasia - EMA/OD/018/14
[Co-ordinators: K. Westermark]

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

- Intention to diagnose, prevent or treat

In order to justify the medical plausibility the sponsor is invited to clarify the stage of development of the product and present any available data with the new formulation in the condition as applied for.

In addition the sponsor should justify why only ELBW neonates would be administered the product to prevent BPD. Although it is understood that ELBW neonates do not benefit from orally administered retinol due to their immature gastrointestinal tract, the sponsor should clarify why the product would not be effective and benefit other neonates included in the definition of BPD (NIHCH 2001 consensus document).

Regarding the bibliographic data presented from the Cochrane review, the sponsor is invited to further discuss the assumption of efficacy on oxygen requirement at 36 weeks of gestational age and on death or oxygen requirement at one month of age, taking into account the heterogeneity of the studies included in the review, and the results showing values of risk ratios close to one. In addition the sponsor is invited to discuss how the studies in the review would support the use of retinol in the chosen therapeutic indication (ELBW neonates).

- Number of people affected

Rather than sub-setting the population of neonates according to the sponsor's intentions to administer the product, the sponsor should discuss the potential population to be administered retinol to prevent BPD. If acceptable to the sponsor, the prevalence should then be recalculated accordingly, taking into account the National Institute of Child Health and Human Development (NICHD) 2001 consensus definition of BPD.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the July meeting.

2.2.28 Rilotumumab for treatment of gastric cancer, Amgen Europe BV - EMA/OD/012/14
[Co-ordinators: B. Bloechl-Daum]

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

The intention to treat the condition with the medicinal product containing rilotumumab was considered justified based on preclinical in vitro and clinical data.

The condition is life-threatening with a poor overall survival.

The condition was estimated to be affecting approximately 2.4 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 rilotumumab may be of significant benefit to those affected by the condition. The sponsor has provided clinical data that support that the product may improve the survival of the patients when used in combination with the standard treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for Rilotumumab, for treatment of gastric cancer, was adopted by consensus.

2.2.29 Riociguat for treatment of systemic sclerosis, Bayer Pharma AG - EMA/OD/044/14
[Co-ordinators: K. Westermark]

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 riociguat was considered justified based on preclinical data from two valid models 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, interstitial pulmonary disease, pulmonary hypertension, and renal manifestations.

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 riociguat may be of significant benefit to those affected by the condition. Based on

the pre-clinical data provided, the product is expected to reduce the fibrotic process which is directly associated with the condition and not targeted by the current authorised treatments. The Committee considered that this is expected to translate into a clinically relevant advantage for the patients.

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

2.2.30 Product for treatment of Duchenne muscular dystrophy - EMA/OD/067/14
[Co-ordinators: 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 Duchenne muscular dystrophy, the sponsor should further elaborate on:

  - The results obtained in vitro on cell lines and cells from DMD patients emphasising reproducibility and extent of dystrophin restoration in different amendable genotypes.
  - The sponsor should further elaborate on the extrapolation from the clinical data presented in the application.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the July meeting.

2.2.31 Product for treatment of autosomal dominant polycystic kidney disease - EMA/OD/042/14
[Co-ordinators: A. Corrêa Nunes]

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

- Number of people affected

The proposed calculation appears to be low as it has been stated in the literature that the prevalence could be 0.2% of the population Abu-Wassel et al 2013. For the calculation and presentation of the prevalence estimate it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

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

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

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the July meeting.

2.2.32 Product for treatment of autosomal dominant polycystic liver disease - EMA/OD/043/14
[Co-ordinators: J. Torrent-Farnell]

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 autosomal dominant polycystic liver disease, the sponsor should further elaborate on:

  - the relevance of the preclinical polycystic kidney disease model used for the treatment of autosomal dominant polycystic liver disease, and the interpretation of the results obtained in the experiments.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the July meeting.

2.2.33 Synthetic double-stranded siRNA oligonucleotide directed against antithrombin mRNA that is covalently linked to a ligand containing three N-acetylgalactosamine residues

for treatment of haemophilia B, Alnylam UK Limited **-** EMA/OD/041/14
[Co-ordinators: A. Magrelli]

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

The intention to treat the condition with the medicinal product containing synthetic double-stranded siRNA oligonucleotide directed against antithrombin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues was considered justified based on preclinical data showing haemostatic clot formation at all sites of injury after treatment with the proposed product in a hemophilia model.

The condition is life-threatening and chronically debilitating due to spontaneous bleeding episodes as well as substantially prolonged bleeding upon injury. Patients with haemophilia B are at risk for severe bleeding, especially in the head, neck, chest, joints, and gastrointestinal and abdominal regions.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing synthetic double-stranded siRNA oligonucleotide directed against antithrombin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues may be of significant benefit to those affected by the condition. The mechanism of action of the product, inducing increased levels of thrombin, is different from that to the current treatment of Haemophilia B, mainly based on replacement of the missing coagulation factor. This offers the potential for use in combination with the currently authorized treatments and for use in patients who develop inhibitors to the standard of care replacement treatment.

The Committee considered that this constitutes a clinically relevant advantage for the patients affected by haemophilia B.

A positive opinion for Synthetic double-stranded siRNA oligonucleotide directed against antithrombin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues, for treatment of haemophilia B, was adopted by consensus.

2.2.34 Synthetic double-stranded siRNA oligonucleotide directed against antithrombin mRNA that is covalently linked to a ligand containing three N-acetylgalactosamine residues for treatment of haemophilia A, Alnylam UK Limited - EMA/OD/039/14
[Co-ordinators: A. Magrelli]

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 synthetic double-stranded siRNA oligonucleotide directed against antithrombin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues was considered justified based on preclinical data showing haemostatic clot formation at all sites of injury after treatment with the proposed product in a hemophilia model.

The condition is life-threatening and chronically debilitating due to spontaneous bleeding episodes as well as substantially prolonged bleeding upon injury. Recurrent bleedings in the same location lead to chronic arthropathy, muscular atrophy and deformities. Life-threatening bleedings may occur in the central nervous system, throat, neck, and gastrointestinal tract.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing synthetic double-stranded siRNA oligonucleotide directed against antithrombin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data supporting the potential of the product to be used also in patients who develop inhibitors to the standard of care replacement treatment with factor VIII. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by haemophilia A.

A positive opinion for Synthetic double-stranded siRNA oligonucleotide directed against antithrombin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues, for treatment of haemophilia A, was adopted by consensus.

2.2.35 Product for treatment of acute pancreatitis - EMA/OD/072/14
[Co-ordinators: A. Corrêa Nunes]

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

- Intention to diagnose, prevent or treat

The proposed indication should be justified as a distinct medical entity or a valid subset within the overall group of different forms of pancreatitis. Note that this is for the purposes of orphan medicinal product designation attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00). The proposed condition appears to be a subset of a larger condition namely pancreatitis. The sponsor is asked to clarify if the product can be used in all forms of pancreatitis.

- Number of people affected

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

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

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

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

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the July meeting.

2.3. Evaluation on-going

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

2.4. Validation on-going

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

3. Requests for protocol assistance

3.1 Letters

3.1.1 Product for treatment of ovarian cancer

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

3.1.2 Product for treatment of chronic non-infectious uveitis

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 3 applications submitted and 27 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 Vantobra (Tobramycin (inhalation use)) for treatment of *Pseudomonas Aeruginosa* lung infection in cystic fibrosis; PARI Pharma GmbH (EU/3/09/613) [Co-ordinator: V. Stoyanova]

The COMP noted the CHMP opinion on MA adopted 19-22 May 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:

"Demonstration of significant benefit at the time of marketing authorisation will need to be supported by data and a critical review of the clinically relevant advantage or major contribution to patient care that the product may offer in the context of the methods authorised for the proposed orphan indication".

The sponsor is therefore invited to discuss the significant benefit of Vantobra in relation to all medicinal products authorised for the treatment of *Pseudomonas aeruginosa* infection in cystic fibrosis (at national or centralised level) and to support the claims of significant benefit with any available data.

In its written response, and during an oral explanation before the Committee on 10 June 2014, the sponsor argued mainly on a clinical benefit compared to other authorised products on the basis of the improved patient convenience of a much shorter nebulization time, an improved dosing scheme and improved tolerability.

The Committee considered that the major contribution to patient care was not supported by data confirming the clinical consequences of the argued benefits.

In communicating to the sponsor the outcome of the discussion, the sponsor requested the removal of the product from the register of orphan medicinal products, on 11 June 2014, prior to final opinion.

5.1.2 Gazyvaro (obinutuzumab) for treatment of chronic lymphocytic leukaemia; Roche Registration Limited (EU/3/12/1054) [Co-ordinator: B. Dembowska-Bagińska]

The COMP noted the CHMP opinion on MA adopted 19-22 May 2014 meeting.

The COMP concluded that:

The proposed therapeutic indication "in combination with chlorambucil is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy" falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.

The prevalence of chronic lymphocytic leukaemia (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 at the time of the review of the designation criteria. The prevalence is estimated to remain approximately 3 in 10,000 in the EU.

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

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Obinutuzumab may be of potential significant benefit to those affected by the orphan condition still holds. This is justified based on clinical data showing that the product used as first-line treatment in combination with the alkylating agent chlorambucil resulted in a statistically significant improvement in progression free survival versus chlorambucil alone and versus a regimen containing chlorambucil and rituximab. This is considered by the Committee a clinically relevant advantage for the patient population affected by chronic lymphocytic leukaemia.

An opinion not recommending the removal of Gazyvaro (obinutuzumab) (EU/3/12/1054) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

5.1.3 Translarna (3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazole-3-yl]-benzoic acid) for treatment of Duchenne muscular dystrophy; PTC Therapeutics Ltd (EU/3/05/278) [Co-ordinator: P. Evers]

The COMP noted the CHMP opinion on MA adopted 19-22 May 2014 meeting.

The COMP concluded that:

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

The prevalence of Duchenne muscular dystrophy (hereinafter referred to as “the condition”) was estimated to be approximately 0.4 in 10,000 and thus remain below 5 in 10,000 at the time of the review of the designation criteria.

The condition is chronically debilitating and life threatening in particular due to progressive weakness of girdle muscles, respiratory and cardiac failure and premature death (late adolescence).

There is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

An opinion not recommending the removal of Translarna (3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazole-3-yl]-benzoic acid) (EU/3/05/278) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

5.1.4 Masiviera (Masitinib mesilate) for treatment of pancreatic cancer; AB Science (EU/3/09/684) [Co-ordinators: B. Bloechl-Daum]

The COMP noted the CHMP negative opinion was adopted at the May 2014 meeting.

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

5.2.1 Dexamethasone (40 mg tablet) for treatment of multiple myeloma; Laboratoires CTRS (Cell Therapies Research & Services) (EU/3/10/745)

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 Ramucirumab for treatment of gastric cancer; Eli Lilly Nederland B.V. (EU/3/12/1004)

5.3.5 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)

5.3.6 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)

5.3.7 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H- pyrazolo [3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one for treatment of mantle cell lymphoma; Janssen-Cilag International N.V. (EU/3/13/1115)

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

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

5.3.10 Ketoconazole for treatment of Cushing's syndrome; Laboratoire HRA (EU/3/12/965)

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

5.3.12 Olaparib for treatment of ovarian cancer; AstraZeneca AB (EU/3/07/501)

5.3.13 [Nle4, D-Phe7]-alfa-melanocyte stimulating hormone for treatment of erythropoietic protoporphyria; Clinuvel (UK) Limited (EU/3/08/541)

5.3.14 Signifor (Pasireotide) for treatment of acromegaly; Novartis Europharm Limited (Type II variation) (EU/3/09/670)

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

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

5.3.17 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 Updated CoI policy

Updated CoI policy was presented by Chief Policy Adviser N. Wathion.

7. Any other business

7.1 6th presentation on the EMA move to 30 Churchill Place

COMP noted the information provided.

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

The Draft Agenda was circulated for information.

7.3. Clarification request

Date of next COMP meeting: 8-10 July 2014

List of participants

Chair:

Bruno Sepodes

Vice-Chair:

Lesley Greene	Patient representative for Eurordis

COMP Members:

André Lhoir	Belgium
Irena Bradinova	Bulgaria
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
Elena Kaisis	Cyprus
Aušra Matulevičienė	Lithuania
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
Pauline Evers	Patient representative representing the European Genetic Alliances Network
Aikaterini Moraiti	EMA Representative

Observers:

Maria Mavris	Eurordis
Virginie Hivert	Eurordis