4 September 2014
EMA/COMP/357442/2014
Procedure Management and Business Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes of the 8-10 July 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/357448/2014

The agenda was adopted with no amendments.

1.2 Adoption of the minutes of the previous meetings, 13-14 May 2014 EMA/COMP/220006/2014 and 10-12 June 2014 EMA/COMP/295834/2014.

It was agreed to adopt the documents via written procedure.

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:

- B. Bloechl-Daum declared a potential conflict of interest on agenda point 2.2.24.
- J. Isla declared a potential conflict of interest on agenda point 2.2.10.
- EGAN received a grant from the sponsors of the product under agenda point 2.2.8, 2.2.22 and 5.2.2. 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 adrenal insufficiency - EMA/OD/060/14
[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 fulfil the requirements for orphan designation the condition should be justified as a distinct medical entity or a valid subset. This is for the purposes of orphan medicinal product designation and the sponsor's 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 in patients with the condition and why adult patients should be excluded, taking into account that currently authorised 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

[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).

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.

In the written response, and during an oral explanation before the Committee on 8 July 2014, the sponsor elaborated on the target condition and its prevalence, and discussed the age-appropriateness of the formulation of the proposed product in particular for the paediatric population. The committee considered that without data with the specific product as applied for designation, it would be difficult to draw conclusions in particular with respect to the comparison versus authorised counterparts and consequently to justify significant benefit.

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

2.1.2 **Recombinant human apolipoprotein A-I in a complex with phospholipids** for treatment of Apolipoprotein A-I (apoA-I) deficiency, Cerenis Therapeutics Holding SA - EMA/OD/064/14

[COMP co-ordinator: F. Saleh]

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for the treatment of the proposed conditions, the sponsor is invited to further elaborate on the available preliminary clinical data.

- Seriousness

The sponsor is requested to provide as far as possible quantified morbidity and mortality data.

- 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 the condition subject of this application.

In the written response, and during an oral explanation before the Committee on 8 July 2014, the sponsor further elaborated on the available clinical observations in patients affected by the condition. The sponsor also provided the requested clarifications on the seriousness and prevalence of the proposed condition.

The Committee agreed that the condition, apolipoprotein A-I deficiency, 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 apolipoprotein A-I in a complex with phospholipids was considered justified based on preliminary

clinical data showing improvement of biochemical measurements in the plasma, and decrease in the thickness of large vessels by imaging after treatment

The condition is life-threatening and chronically debilitating in particular due to the development of atherosclerosis.

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

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

A positive opinion for Recombinant human apolipoprotein A-I in a complex with phospholipids, for treatment of apolipoprotein A-I deficiency, was adopted by consensus.

2.1.3 **Recombinant human apolipoprotein A-I in a complex with phospholipids** for treatment of ATP-Binding Cassette Transporter A1 (ABCA1) deficiency, Cerenis Therapeutics Holding SA - EMA/OD/063/14

[COMP co-ordinator: F. Saleh]

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for the treatment of the proposed conditions, the sponsor is invited to further elaborate on the available preliminary clinical data.

- Seriousness

The sponsor is requested to provide as far as possible quantified morbidity and mortality data.

- 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 the condition as applied for designation.

In the written response, and during an oral explanation before the Committee on 8 July 2014, the sponsor further elaborated on the available clinical observations in patients affected by the condition. The sponsor also provided the requested clarifications on the seriousness and prevalence of the proposed condition.

The Committee agreed that the condition, ATP-binding cassette transporter A1 deficiency, 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 apolipoprotein A-I in a complex with phospholipids was considered justified based on preliminary clinical data showing improvement of biochemical measurements in the plasma, and decrease in the thickness of large vessels by imaging after treatment.

The condition is life-threatening and chronically debilitating in particular due to the development of atherosclerosis that may lead to coronary artery disease.

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

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

Post-meeting note:

A positive opinion for Recombinant human apolipoprotein A-I in a complex with phospholipids, for treatment of ATP-binding cassette transporter A1 deficiency, was adopted by consensus via written procedure on 21 July 2014.

2.1.4 Product for treatment of Lecithin Cholesterol Acyltransferase (LCAT) deficiency - EMA/OD/066/14
[COMP co-ordinator: F. Saleh]

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for the treatment of the proposed conditions, the sponsor is invited to further elaborate on the available preliminary clinical data in patients affected by the condition as applied for designation.

- Seriousness

The sponsor was requested to further elaborate on the seriousness of the proposed 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".

The sponsor should provide a clear overall conclusion for the condition as proposed for designation.

In the written response, and during an oral explanation before the Committee on 8 July 2014, the sponsor presented data from one patient affected by the condition. The committee noted the fact that only one patient has been treated and the unclear trends in the observations observed, and considered it is difficult to extrapolate the available data to draw conclusions for the condition as applied for designation.

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

2.1.5 Product for treatment of paroxysmal nocturnal haemoglobinuria - EMA/OD/056/14
[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:

- 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.

In the written response, and during an oral explanation before the Committee on 8 July 2014, the sponsor elaborated on the possibility of home self-administration of the proposed product, which would compare favourably versus the currently authorised IV formulated product that is administered at the hospital. The COMP considered that at least in some member states the existing treatment may be administered at home, and that there are no data presented with the specific product to justify the consequences of the claimed improvement in the formulation.

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

2.1.6 Product for treatment of glioma - EMA/OD/055/14

[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

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 results from the presented literature to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

In the written response, and during an oral explanation before the Committee on 8 July 2014, the sponsor further elaborated on the cited bibliography and argued that the novel mechanism of action may result in by-passing resistance to temozolomide. The Committee considered that there is a lack of data with regards to the medical plausibility and significant benefit, and also became aware that preliminary clinical observations may exist with the product that has not been presented by the sponsor. The COMP considered that it would be difficult to deliberate based on the paucity of data that have so far been presented.

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

2.1.7 17α,21-dihydroxy-16α-methyl-pregna-1,4,9(11)-triene-3,20-dione for treatment of Duchenne muscular dystrophy, NDA Group AB - EMA/OD/049/14
[COMP co-ordinator: P. Evers]

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

- Intention to diagnose, prevent or treat

In order to justify the medical plausibility of the proposed product 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, 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 while prednisolone showed the strongest effect among all treatments on normalized grip strength;
- the lack of a dose-response in the parameters, and the clinical relevance of the changes in *in vitro* force contractions.

In the written response, and during an oral explanation before the Committee on 8-10 July 2014, the sponsor further discussed the available data and argued in particular that while literature only supports a positive effect of corticosteroids on specific (normalized to body weight) muscle force, the proposed product positively affects both absolute and specific muscle force. 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 17α,21-dihydroxy-16α-methyl-pregna-1,4,9(11)-triene-3,20-dione was considered justified based on preclinical data showing increased muscle strength in a relevant model 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 less than 0.8 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 17α,21-dihydroxy-16α-methyl-pregna-1,4,9(11)-triene-3,20-dione, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

2.1.8 Product for treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis - EMA/OD/050/14

[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

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.

In the written response, and during an oral explanation before the Committee on 8 July 2014, the sponsor referred to the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides, stressed the lack of a broadly acceptable alternative and argued that the proposal was in line with the candidate drug's efficacy profile and extra-European designation in the US. The COMP considered that the proposed nomenclature is not a classification system and that it would not suffice to justify a distinct entity for the purpose of orphan designation. As such the proposed indication might encompass several distinct medical entities. It was also considered that potential therapeutic indications are distinct concepts compared to orphan indications, as per the ENTR/6283/00 guideline.

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

2.1.9 **Gevokizumab** for treatment of Schnitzler Syndrome, Les Laboratoires Servier - EMA/OD/053/14

[COMP co-ordinator: A. Andrić]

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 Schnitzler Syndrome, the sponsor is invited to further elaborate on any updated results from the ongoing 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.

In the written response, and during an oral explanation before the Committee on 9 July 2014, the sponsor further elaborated on the available data and provided an updated prevalence calculation as requested.

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

The intention to treat the condition with the medicinal product containing gevokizumab was considered justified based on a preliminary clinical study in patients affected by the condition, who responded to treatment by improvement of symptomatology and inflammatory markers.

The condition is life-threatening and chronically debilitating due to chronic urticarial rash, fever, arthralgia or arthritis, bone pain, and lymphadenopathy, while common complications include the development of severe anaemia and AA (amyloid A) amyloidosis and about 20% of patients will develop a lymphoproliferative disorder.

The condition was estimated to be affecting approximately 0.02 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for Gevokizumab, for treatment of Schnitzler syndrome, was adopted by consensus.

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

[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

The sponsor should provide the study reports of the FVIII knockout murine 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.

In the written response, and during an oral explanation before the Committee on 9 July 2014, the sponsor presented the requested animal model reports and further elaborated on the issue of significant benefit. Based on preliminary clinical observations showing a 1.5-fold improvement in half-life, the sponsor proposed a twice weekly administration scheme which would compare favourably to an administration of every 2-3 days of the authorised products, in the context of a potentially improved compliance. The COMP considered that even though the sponsor discussed the importance of compliance, no data were presented to demonstrate that this would be improved with a change in administration of such an extent as the one proposed. In the absence of data with the product on such clinical consequences, it would be difficult to consider justification of significant benefit.

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

2.1.11 **Recombinant factor VIIa modified with three terminal repeats derived from the β chain of human chorionic gonadotropin** for treatment of congenital factor VII deficiency, Richardson Associates Regulatory Affairs Ltd - EMA/OD/057/14

[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:

- 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 authorised plasma-derived FVII products.

In the written response, and during an oral explanation before the Committee on 9 July 2014, the sponsor further elaborated on the issue of significant benefit of the proposed product, and argued improvements with regards to the number of injections at longer intervals by self or carer administration, earlier discharge from in-patient care and removal of the need for establishing and maintaining central venous access.

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

The intention to treat the condition with the medicinal product containing recombinant factor VIIa modified with three terminal repeats derived from the β chain of human chorionic gonadotropin was considered justified based on the mechanism of action which is substitution of the deficient activated factor VII together with preclinical data supporting the prothrombotic effects of the product.

The condition is chronically debilitating due to recurrent bleedings in joints, gastrointestinal tract or other organs and tissues, as well as in surgery. These bleedings may be life-threatening in some patients, in particular in case of an intracranial bleeding.

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 recombinant factor VIIa modified with three terminal repeats derived from the B chain of human chorionic gonadotropin may be of significant benefit to those affected by the condition. The sponsor has provided preclinical pharmacokinetic data that suggest less frequent need for administration for the patients. This assumption is currently supported by data showing extended half-life of the product in preclinical setting. The Committee considered that this may translate into a major contribution to patient care, if supported by data at the time of marketing authorisation.

A positive opinion for Recombinant factor VIIa modified with three terminal repeats derived from the β chain of human chorionic gonadotropin, for treatment of congenital factor VII deficiency, was adopted by consensus.

2.1.12 Recombinant factor VIIa modified with three terminal repeats derived from the β chain of human chorionic gonadotropin for treatment of haemophilia A, Richardson Associates Regulatory Affairs Ltd - EMA/OD/069/14

[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:

- 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.

In the written response, and during an oral explanation before the Committee on 9 July 2014, the sponsor further elaborated on the issue of significant benefit of the proposed product, and argued improvements with regards to the number of injections at longer intervals by self or carer administration, earlier discharge from in-patient care and removal of the need for establishing and maintaining central venous access.

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 recombinant factor VIIa modified with three terminal repeats derived from the β chain of human chorionic gonadotropin was considered justified based on in vitro and in vivo preclinical data using rFVIIa as a comparator for biological activity.

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

The condition was estimated to be affecting approximately 0.7 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 recombinant factor VIIa modified with three terminal repeats derived from the B chain of human chorionic gonadotropin may be of significant benefit to those affected by the condition. The sponsor has provided preclinical pharmacokinetic data that suggest less frequent need for administration for the patients. This assumption is currently supported by data showing extended half-life of the product in preclinical setting. The Committee considered that this may translate into a major contribution to patient care, if supported by data at the time of marketing authorisation.

A positive opinion for Recombinant factor VIIa modified with three terminal repeats derived from the β chain of human chorionic gonadotropin, for treatment of haemophilia A, was adopted by consensus.

2.1.13 Recombinant factor VIIa modified with three terminal repeats derived from the β chain of human chorionic gonadotropin for treatment of haemophilia B, Richardson Associates Regulatory Affairs Ltd - EMA/OD/073/14

[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:

- 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.

In the written response, and during an oral explanation before the Committee on 9 July 2014, the sponsor further elaborated on the issue of significant benefit of the proposed product, and argued improvements with regards to the number of injections at longer intervals by self or carer administration, earlier discharge from in-patient care and removal of the need for establishing and maintaining central venous access

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 recombinant factor VIIa modified with three terminal repeats derived from the β chain of human chorionic gonadotropin was considered justified based on in vitro and in vivo preclinical data using rFVIIa as a comparator for biological activity.

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

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant factor VIIa modified with three terminal repeats derived from the B chain of human chorionic gonadotropin may be of significant benefit to those affected by the condition. The sponsor has provided preclinical pharmacokinetic data that suggest less frequent need for administration for the patients. This assumption is currently supported by data showing extended half-life of the product in preclinical setting. The Committee considered that this may translate into a major contribution to patient care, if supported by data at the time of marketing authorisation.

A positive opinion for Recombinant factor VIIa modified with three terminal repeats derived from the β chain of human chorionic gonadotropin, for treatment of haemophilia B, was adopted by consensus.

2.1.14 Product for treatment of retinopathy of prematurity - EMA/OD/040/14
[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 retinopathy of prematurity, the sponsor should further elaborate on:

- the preclinical data 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 a different formulation seem to be mainly from stage II ROP which can regress 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.

In the written response, and during an oral explanation before the Committee on 9 July 2014, the sponsor attributed the discrepancy in the two literature studies on the different genetic strains of the models used, and elaborated on the issue of formulation of the proposed product. The COMP considered that the limitations pointed out in the list of issues were not addressed, in particular given the lack of data with the specific product as proposed for designation

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

2.1.15 Sodium ascorbate and menadione sodium bisulfite for treatment of autosomal dominant polycystic kidney disease, JJGConsultancy Ltd - EMA/OD/042/14
[COMP co-ordinator: A. Corrêa Nunes]

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

- Number of people affected

The proposed calculation appears to be 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.

In the written response, and during an oral explanation before the Committee on 9 July 2014, the sponsor further elaborated on the methodology used for the calculation of the prevalence estimate, based on literature and registry search. A very limited number of publications were used in the calculation and it was noted that in the cited paper by Neumann and co-workers it is stated that "currently nobody will be able to define the true prevalence of ADPKD, since complete population screening, for example by renal ultrasonography, is impossible for practical and privacy reasons. Since ADPKD becomes symptomatic in the vast majority of patients and since ultrasonography is so widely used by practitioners, internists and nephrologist in our catchment area, it is highly likely that the data for the 50-59 age group, where maximal penetrance is achieved, represent the prevalence data very close to the truth". The COMP considered that the prevalence is 5.7 in 10,000 for this age group which would be above the provisioned threshold. It was also considered that the sponsor did not adequately address the issue of penetrance of the phenotypic form thereby making it difficult to establish the real difference in prevalence between the genotypic and phenotypic forms of the condition. It is was also noted that the genotypic prevalence is much higher than 5 in 10,000, which could be up to 0.2% of the population as per the available literature. As the variability in penetrance was not adequately discussed and the most recent publication points to a 5.7 per 10,000 prevalence, the COMP concluded that the prevalence calculation was inadequate and recommended that designation is not granted.

The Committee agreed that the condition, autosomal dominant polycystic kidney disease, is not a distinct medical entity for orphan designation.

The intention to treat the condition with the medicinal product containing sodium ascorbate and menadione sodium bisulfite was considered justified based on preliminary pre-clinical in vivo data valid models showing a reduction in the hepatic and renal cystic and fibrotic scores and weights.

The condition is chronically debilitating and life-threatening in particular due to the development of kidney failure, cardiovascular abnormalities and diverticulitis.

Having examined the application, the COMP considered that the sponsor has not established that the condition is affecting not more than 5 in 10,000 people at the time the application is made.

The COMP was of the opinion that the prevalence calculation presented by the sponsor was based on a limited number of publications and the methodology used was not sufficiently adequate to encompass all the necessary considerations. Of concern was the lack of clarity regarding the actual level of phenotypic penetration of the genotypes. It is also understood that the genotypes have a prevalence above 5 in 10,000 and that the actual estimation of phenotypic prevalence varies depending on how the phenotype is identified.

The product is intended for treatment of a life-threatening and seriously debilitating condition; however the sponsor did not submit the application on the basis of the second paragraph of Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products, and did not provide any data with the application that would allow an evaluation of a potential claim of insufficient return of the investment without incentives.

Based on the above considerations, and having examined the application and the answers to the list of questions provided by the sponsor in writing and during the oral explanation, 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.

In the light of the overall data submitted and the discussion with the sponsor, the Committee expressed a negative trend on the application.

Post-meeting note:

A negative opinion on orphan medicinal product designation for Sodium ascorbate and menadione sodium bisulfite, for treatment of autosomal dominant polycystic kidney disease, was adopted by consensus via written procedure on 21 July 2014.

2.1.16 Sodium ascorbate and menadione sodium bisulfite for treatment of autosomal dominant polycystic liver disease, JJGConsultancy Ltd - EMA/OD/043/14
[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 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.

In the written response, and during an oral explanation before the Committee on 9 July 2014, the sponsor elaborated on the relevance of the model used, that would allow extrapolation of observations to allow conclusions to be made for the specific condition subject of this application.

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

The intention to treat the condition with the medicinal product containing sodium ascorbate and menadione sodium bisulfite was considered justified based on preliminary pre-clinical in vivo data valid models showing a reduction in the hepatic and renal cystic and fibrotic scores and weights.

The condition is life-threatening and/or chronically debilitating due to experience severe dysfunction of organs around the liver due to the increased hepatic volume or when one or more cysts get torted, infected or develop intra-cystic hemorrhages.

The condition was estimated to be affecting approximately 0.02 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for Sodium ascorbate and menadione sodium bisulfite, for treatment of autosomal dominant polycystic liver disease, was adopted by consensus.

2.1.17 Lumacaftor and ivacaftor fixed-dose combination for treatment of cystic fibrosis, Vertex Pharmaceuticals (U.K.) Limited - EMA/OD/032/14
[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:

- 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, the fixed dose combination of ivacaftor and lumacaftor.

The sponsor is also invited to further elaborate on the extrapolation of the results obtained with the two separate products used in combination treatment to the FDC product.

In the written response, and during an oral explanation before the Committee on 8-10 July 2014, the sponsor further elaborated on the extrapolation of the efficacy results of the combination use of ivacaftor and lumacaftor to the fixed dose combination. In particular the sponsor presented bioavailability studies showing superimposable plasma concentration time profiles for co-dosing versus co-formulation. Similar results were obtained when comparing Cmax and AUCs of the co-dosing and the co-formulation. The sponsor also clarified that a clinical trial using the fixed combination is ongoing in the sought for indication. The doses used in the fixed combination study are the ones that showed the highest efficacy in the existing clinical trials of co-dosing.

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 lumacaftor and ivacaftor fixed-dose combination was considered justified based on preliminary clinical data showing efficacy of the proposed product on relevant clinical endpoints in cystic fibrosis.

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 0.8 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 lumacaftor and ivacaftor fixed-dose combination may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing improvement of lung function when the two products used in combination were added to the standard of care treatment of F508D mutated cystic fibrosis. The Committee considered that this constitutes a clinically relevant advantage for patients affected by cystic fibrosis.

A positive opinion for lumacaftor and ivacaftor fixed-dose combination, for treatment of cystic fibrosis, was adopted by consensus.

2.1.18 Product for treatment of pigmented villonodular synovitis / giant cell tumour of the tendon sheath - EMA/OD/058/14
[COMP co-ordinator: D. O'Connor] [Expert: A. Flanagan]

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 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; the sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

- Number of people affected

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".

In the written response, and during an oral explanation before the Committee on 10 July 2014, the sponsor proposed to amend the condition to "tenosynovial giant cell tumour (TGCT), localized and diffuse type" and revised upwards the prevalence estimation to 1.28 per 10 000 persons. The COMP, taking into account the revised indication and the data presented for the justification of the medical plausibility, raised concerns with regards to the limited preliminary clinical observations to draw conclusions for the treatment of the proposed condition.

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

2.1.19 Ulinastatin for treatment of acute pancreatitis, BSV BioScience GmbH - EMA/OD/072/14
[COMP co-ordinator: A. Corrêa Nunes]

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 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; the sponsor's 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 the condition, the sponsor should indicate on which population the prevalence calculation is based on.

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

In the written response, and during an oral explanation before the Committee on 10 July 2014, the sponsor elaborated on the differences of acute and chronic pancreatitis, that may allow considering them distinct entities for the purpose of orphan designation. The Committee agreed that the condition, acute pancreatitis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing ulinastatin was considered justified based on preliminary clinical data in patients with the condition showing better survival than the control group.

The condition is life-threatening and chronically debilitating due to the need for hospitalisation associated with severe acute pancreatitis. Necrotising pancreatitis a consequence of the condition is often associated with a high morbidity and mortality.

The condition was estimated to be affecting approximately 4.5 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 ulinastatin, for treatment of acute pancreatitis, was adopted by consensus.

2.1.20 Retinol for prevention of bronchopulmonary dysplasia, Dr Philipp Heinrich Novak - EMA/OD/018/14
[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

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

survival 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.

In the written response, and during an oral explanation before the Committee on 10 July 2014, the sponsor further elaborated on the issues raised, and agreed that from a clinical point of view the product could be used also in premature neonates of higher weight than ELBW. The sponsor accepted to have the indication amended to "prevention of bronchopulmonary dysplasia". Regarding the population at risk, the sponsor agreed with previous estimates reporting a rather wide range (1 to 3 in 10,000) due to different practice and outcomes of rescuing of premature neonates across the EU.

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

The intention to prevent the condition with the medicinal product containing retinol was considered justified based on clinical data from published literature showing reduced incidence of manifestations and consequences of bronchopulmonary dysplasia with the proposed product.

The condition is life-threatening and chronically debilitating due to inflammation and scarring in the lungs, resulting in necrotizing bronchiolitis and alveolar septal injury, which compromises the oxygenation of blood.

The population of patients eligible for prevention of the condition was estimated to be between 1 and 3 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of prevention that has been authorised in the European Union for patients at risk of the condition.

A positive opinion for retinol, for treatment of bronchopulmonary dysplasia, was adopted by consensus.

2.1.21 (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 Fabry disease, Genzyme Europe BV - EMA/OD/052/14

[COMP co-ordinator: A. Corrêa Nunes]

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

- Number of people affected

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

The sponsor should justify the inclusion/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.

In the written response, the prevalence was recalculated in the range of 0.04 (Patients with classic FD) – 1.36 (Carriers of any GLA variant) per 10,000 people in the EU. It was noted by the sponsor that the high end of the range is likely an overestimate as it includes all known GLA variants, including classic mutations, those that are incompletely penetrant or potentially non-pathogenic, as well as all uncharacterized genotypes, some of which may also be non-pathogenic. The COMP considered that its previous opinions of less than 2.3 may be accepted for this procedure as well.

The Committee agreed that the condition, Fabry 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 studies in a model of the condition. In that model, concentration of globotriaosylceramide in plasma, urine, kidney and heart tissues was reduced after 9 months of treatment;

The condition is chronically debilitating due to recurrent episodes of severe pain that do not respond to standard analgesics, and life-threatening due to renal failure, cardiovascular and cerebrovascular complications;

The condition was estimated to be affecting less than 2.3 in 10,000 people 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.

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. The sponsor has provided preclinical studies in a model of the condition supporting the assumption that the product may offer improved efficacy when used in combination with enzyme replacement therapy. The Committee considered 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}carbamate, for treatment of Fabry disease, was adopted by consensus.

2.1.22 **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 myelodysplastic syndromes, IDEA Innovative Drug European Associates Limited - EMA/OD/048/14

[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:

- 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.

In the written response the sponsor further elaborated on the prevalence of the proposed condition based on databases such as EUCAN and literature and using both direct prevalence data as well as indirect calculations based on incidence multiplied by the duration of the disease.

The Committee agreed that the condition, myelodysplastic syndromes, 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 dose-dependent increase in hemoglobin in treated patients affected by the condition.

The condition is life-threatening and chronically debilitating due to the development of anemia, thrombocytopenia, neutropenia and progression to acute myelogenous leukaemia.

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 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 committee considered that the product acts through a novel mechanism of action, which may allow for the treatment of anaemia as a prominent symptom of the proposed condition 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 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 myelodysplastic syndromes, was adopted by consensus.

2.1.23 Product for treatment of Duchenne muscular dystrophy - EMA/OD/067/14
[COMP co-ordinator: V. Stoyanova]

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 June 2014, prior to responding to list of issues.

2.2. For discussion / preparation for an opinion

2.2.1 Product for treatment of Pemphigus - EMA/OD/091/14
[COMP co-ordinator: 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 Pemphigus, the sponsor should further elaborate on:

  - the fact that several preclinical models for Pemphigus have been described in the literature and are absent in the present application;

- Number of people affected

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

The sponsor should re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition, using the most conservative incidence figures and taking into consideration the lifelong duration of the condition.

- Significant benefit

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

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on how the results in the chosen preclinical model justify the assumption of significant benefit in the proposed condition. The sponsor is further requested to justify the assumption of significant benefit over all 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 of current authorised medicinal products for the same condition.

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

2.2.2 Product for treatment of Leigh syndrome - EMA/OD/068/14

[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 pancreatic cancer, the sponsor should further elaborate on:

  - the results of the rotarod measurements seemingly showing faster time to fall in treated versus untreated subjects in the wild-type group. The sponsor is also invited to elaborate on the clinical relevance of the increase in time to fall in treated *vs*. untreated of NDUFS4-/- subjects;

  - the relevance of the preclinical NDUFS4-/- preclinical model to the proposed 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".

The sponsor should justify the proposed prevalence estimate of the condition, critically assess sources and justify the methodology used for the prevalence calculation.

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

2.2.3 (Z)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)-N'-(pyrazin-2-yl)acrylohydrazide for treatment of diffuse large B cell lymphoma, Clinipace GmbH - EMA/OD/071/14

[COMP co-ordinator: F. Naumann-Winter]

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

The intention to treat the condition with the medicinal product containing (Z)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)-N'-(pyrazin-2-yl)acrylohydrazide (Chemical) was considered justified based on preliminary clinical data showing anti-cancer activity in patients affected by the condition.

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

The condition was estimated to be affecting approximately 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 (Z)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)-N'-(pyrazin-2-yl)acrylohydrazide may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing a favourable response in 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 (Z)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)-N'-(pyrazin-2-yl)acrylohydrazide, for treatment of diffuse large B cell lymphoma, was adopted by consensus.

2.2.4 (Z)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)-N'-(pyrazin-2-yl)acrylohydrazide for treatment of acute myeloid leukemia, Clinipace GmbH - EMA/OD/061/14

[COMP co-ordinator: F. Naumann-Winter]

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

The intention to treat the condition with the medicinal product containing (Z)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)-N'-(pyrazin-2-yl)acrylohydrazide was considered justified based on preclinical and preliminary clinical data showing anti-cancer activity.

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

The condition was estimated to be affecting approximately 1.1 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 (Z)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)-N'-(pyrazin-2-yl)acrylohydrazide may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing a favourable response in patients with acute myeloid leukaemia 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 acute myeloid leukaemia.

A positive opinion for (Z)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)-N'-(pyrazin-2-yl)acrylohydrazide, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.2.5 [5-Amino-1-(4-fluoro-phenyl)-1H-pyrazol-4-yl]-[3-(2,3-dihydroxy-propoxy)-phenyl]-methanone for treatment of pancreatic cancer, Synovo GmbH - EMA/OD/085/14

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

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

The intention to treat the condition with the medicinal product containing [5-amino-1-(4-fluoro-phenyl)-1H-pyrazol-4-yl]-[3-(2,3-dihydroxy-propoxy)-phenyl]-methanone was considered justified based on a valid pre-clinical in vivo model of the condition showing an improved survival and reduction in the number of metastasis.

The condition is life-threatening due to a 1-year relative survival rate estimated to be 25%, and the 5-year survival is estimated as less than 5% to 6% after diagnosis.

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 [5-amino-1-(4-fluoro-phenyl)-1H-pyrazol-4-yl]-[3-(2,3-dihydroxy-propoxy)-phenyl]-methanone may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical data that demonstrate that an alternative mode of action provides an improvement in survival and reduction in metastasis associated with the condition. The Committee considered that this constitutes a clinically relevant advantage.

Post-meeting note:

A positive opinion for [5-amino-1-(4-fluoro-phenyl)-1H-pyrazol-4-yl]-[3-(2,3-dihydroxy-propoxy)-phenyl]-methanone, for treatment of pancreatic cancer, was adopted by consensus via written procedure on 21 July 2014.

2.2.6 2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethylsulfamide for treatment of small cell lung cancer, DualTpharma B.V. - EMA/OD/086/14

[COMP co-ordinator: K. Kubáčková]

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

The intention to treat the condition with the medicinal product containing 2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethylsulfamide was considered justified based on pre-clinical in vivo data based on a valid model which showed improved survival when compared with the control group.

The condition is chronically debilitating and life threatening due to the advanced disease at diagnosis in most cases, and rapid progression in the other cases. Overall survival at 5 years is 5-10% of those patients diagnosed.

The condition was estimated to be affecting approximately 1.12 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethylsulfamide may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical data that demonstrate that when their product is used in combination with radiotherapy a reduction in the rate of tumour growth as well as the increase in the survival was seen when compared to controls. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethylsulfamide, for treatment of small cell lung cancer, was adopted by consensus.

2.2.7 Product for treatment of Cushing's syndrome - EMA/OD/099/14

[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 treatment of Cushing's syndrome, the sponsor should further elaborate on any available data in patients with Cushing's syndrome apart from Cushing's disease (ACTH-secreting pituitary adenoma).

- Significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit based on available data to justify the assumption of significant benefit over all 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 September meeting.

2.2.8 4-{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid for treatment of acute myeloid leukaemia, Roche Registration Limited - EMA/OD/100/14

[COMP co-ordinator: F. Naumann-Winter]

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

The intention to treat the condition with the medicinal product containing 4-{[(2R,3S,4R,5S)-4-(4-chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid was considered justified based on preclinical and preliminary clinical data showing anti-cancer activity.

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

The condition was estimated to be affecting approximately 1.2 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 4-{[(2R,3S,4R,5S)-4-(4-chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing responses in patients with previously untreated and advanced disease. The Committee considered that this constitutes a clinically relevant advantage for patients affected by acute myeloid leukaemia.

A positive opinion for 4-{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.2.9 **Adeno-associated viral vector serotype 8 containing the human *UGT1A1* gene** for treatment of Crigler-Najjar syndrome, Fondazione Telethon - EMA/OD/082/14

[COMP co-ordinator: A. Corrêa Nunes]

The Committee agreed that the condition, Crigler-Najjar syndrome, 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 *UGT1A1* gene was considered justified based on a pre-clinical in vivo valid model which shows a normalisation of the bilirubin serum levels.

The condition is chronically debilitating and life threatening due to development of kernicterus.

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 Adeno-associated viral vector serotype 8 containing the human *UGT1A1* gene, for treatment of Crigler-Najjar syndrome, was adopted by consensus.

2.2.10 Product for treatment of Dravet syndrome - EMA/OD/083/14

[COMP co-ordinator: I. Bradinova]

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 Dravet syndrome, the sponsor should further elaborate on:

- the methodology used in the preclinical studies as well as the results from these studies and discuss their relevance for the development of the product in the condition as applied for designation.
- the methodology used in the preliminary clinical studies and specifically discuss the Dravet syndrome patients with regards to the treatments received before and during the study and the assessments performed. Any further available preliminary clinical data in Dravet patients should be presented to the COMP.

- 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 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.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. The sponsor is invited to substantiate these claims with any data that may be available. A significant benefit justification versus all authorised products, including stiripentol, should be further elaborated.

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

2.2.11 Product for treatment of neuromyelitis optica - EMA/OD/089/14

[COMP co-ordinator: A. Magrelli]

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

- Intention to diagnose, prevent or treat

The sponsor is advised that without data with the specific product as applied for designation in either relevant preclinical models or patients affected by the condition, the medical plausibility may not be considered justified. In the absence of such data the medical plausibility cannot be established.

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

- the absence of any data with the product in neuromyelitis optica as applied for designation;
- the unpublished case report with regards to previous treatments and assessments;
- the improvements argued in this patient vis a vis the natural course of the condition.

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

2.2.12 Product for treatment of limbal stem cell deficiency - EMA/OD/109/14
[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 limbal stem cell deficiency, the sponsor should further elaborate on:

  - the results from the on-going clinical study performed by the sponsor are unclear. The sponsor is invited to further provide available data on the preliminary results in those patients treated highlighting the parameters relevant to the condition.

- Number of people affected

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

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

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

2.2.13 Product for treatment of cystinosis - EMA/OD/106/14
[COMP co-ordinator: B. Bloechl-Daum]

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

- Significant benefit

The sponsor is invited to state the stage of development of the product they are proposing namely the development of the sponsor's formulation of the ocular solution of cyteamine as it is acknowledged by the COMP that there is variability in the response to therapy due to the variability in the concentrations of cysteamine used in off-licence formulations prepared in the hospitals for patients with the condition.

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

Post-meeting note:

The COMP adopted the list of issues via written procedure on 16 July 2014.

2.2.14 Product for treatment of systemic-onset juvenile idiopathic arthritis - EMA/OD/108/14
[COMP co-ordinator: A. Corrêa Nunes]

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 systemic-onset juvenile idiopathic arthritis, the sponsor should further elaborate on:

  - the mechanism of action of the product,

- the relevance of the preclinical model used for the treatment of systemic-onset juvenile idiopathic arthritis, and the interpretation of the results obtained in the experiments,
- discuss any further available data in either relevant models or preliminary clinical settings, in patients affected by the condition.

- Significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from any studies 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 September meeting.

2.2.15 Humanised IgG1 monoclonal antibody against human KIR3DL2 for treatment of cutaneous T-cell lymphoma, Innate Pharma S.A. - EMA/OD/084/14
[COMP co-ordinator: K. Kubáčková]

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

The intention to treat the condition with the medicinal product containing humanised IgG1 monoclonal antibody against human KIR3DL2 was considered justified based on preclinical data showing killing of cancer cells from patients affected by the condition.

The condition is chronically debilitating due to ulceration and erythroderma. The condition is life threatening in the most aggressive forms due to the risk of further malignant transformations.

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 humanised IgG1 monoclonal antibody against human KIR3DL2 may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing killing of cancer cells from patients affected by the condition, with a mechanism of action different from the currently authorized products, offering the possibility of use in combination. The Committee considered that this constitutes a clinically relevant advantage for patients affected by cutaneous T-cell lymphoma.

A positive opinion for Humanised IgG1 monoclonal antibody against human KIR3DL2, for treatment of cutaneous T-cell lymphoma, was adopted by consensus.

2.2.16 Product for treatment of pancreatic cancer - EMA/OD/081/14
[COMP co-ordinator: 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 pancreatic cancer, the sponsor should further elaborate on:

- the preliminary clinical results presented by the sponsor from an on-going Phase I/II study in patients who have refractory-relapsed pancreatic cancer. The sponsor was also invited to further elaborate on the response seen in patients who have received the treatment

- Significant benefit

The sponsor has proposed that their product offers a more targeted as well as alternative mode of action which will offer a clinically relevant advantage. The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the preliminary results from the Phase I/II study 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 September meeting.

Post-meeting note:

The COMP adopted the list of issues via written procedure on16 July 2014.

2.2.17 Lentiviral vector containing the human liver and erythroid pyruvate kinase (*PKLR*) gene for treatment of Pyruvate Kinase Deficiency, Center for Biomedical Network Research on Rare Diseases (CIBERER) - EMA/OD/102/14

[COMP co-ordinator: A. Magrelli]

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

The intention to treat the condition with the medicinal product containing lentiviral vector containing the human liver and erythroid pyruvate kinase (*PKLR*) gene was considered justified based on preclinical in vivo data showing a stable correction of the phenotype in a preclinical model of the condition;

The condition is chronically debilitating and life-threatening due to symptoms of chronic haemolytic anaemia and sequelae of periodic red blood cell transfusions, comprising fatigue, shortness of breath, splenomegaly, cholecystolithiasis, heart failure, as well as compromised immune function and thromboembolic complications after splenectomy. The condition is also life-threatening due to aggravation of haemolytic anaemia during pregnancy and aplastic crisis during viral infections, as well as hydrops fetalis and perinatal death.

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

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

A positive opinion for Lentiviral vector containing the human liver and erythroid pyruvate kinase (*PKLR*) gene, for treatment of pyruvate kinase deficiency, was adopted by consensus.

2.2.18 Macromolecular conjugate of heparin sodium on a polymer backbone for prevention of ischemia / reperfusion injury associated with solid organ transplantation, Corline Systems AB - EMA/OD/090/14
[COMP co-ordinator: K. Westermark]

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

The intention to prevent the condition with the medicinal product containing macromolecular conjugate of heparin sodium on a polymer backbone was considered justified based on pre-clinical in vivo data based on a preclinical model of the condition which showed better survival and functionality of the transplanted organ.

The condition is chronically debilitating and life threatening due to delayed graft function following transplantation.

The population of patients eligible for prevention of the condition was estimated to be approximately 0.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of prevention of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing macromolecular conjugate of heparin sodium on a polymer backbone may be of significant benefit to the population at risk of developing the condition. The sponsor has provided pre-clinical data that demonstrate that when the transplanted organ survival was better than the control group. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for Macromolecular conjugate of heparin sodium on a polymer backbone, for treatment of, ischaemia reperfusion injury associated with solid organ transplantation, was adopted by consensus.

2.2.19 Product for treatment of cytomegalovirus (CMV) infections in patients following allogeneic stem cell transplantations - EMA/OD/096/14
[COMP co-ordinator: B. Dembowska-Bagińska]

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

- Intention to diagnose, prevent or treat

Cytomegalovirus infections following allogeneic stem cell transplantation should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00). The sponsor is therefore invited to further justify sub-setting the broader condition of impaired cell-mediated immunity and restricting the use of the product only to patients who received HSCT.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of cytomegalovirus infections following allogeneic stem cell transplantation, the sponsor should further elaborate on:

- the timing of administration of the proposed product, with particular attention to whether the use would be preventive or for treatment;

- the feasibility of the intended clinical use of the product, linked to the need of the primary HSC donor to be available when needed for the leukapheresis. In this respect the sponsor is also asked to clarify what the immune status of the donor should be with respect to the three targeted viruses.
- the extrapolation of the results obtained with products different from the one subject of this application.
- the relative composition of the final product and the role of these two different lymphocyte populations in the therapeutic action of the product.

In addition the sponsor is invited to propose a different name that better describes the nature of the product

- Number of people affected

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

The sponsor states that all recipients of HSCT could suffer from a viral infection during the course of one calendar year. However this seems to reflect the population at risk rather than the target group for treatment. The sponsor is therefore asked to provide an estimate of the population target of the treatment indication, based on existing data sources, and the definition of the population to be treated in relation to the specific condition (e.g. viremic and/or symptomatic population?)

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

Post-meeting note:

The COMP adopted the list of issues via written procedure on 16 July 2014.

2.2.20 Product for treatment of Epstein-Barr Virus infections in patients following allogeneic stem cell transplantations - EMA/OD/095/14
[COMP co-ordinator: B. Dembowska-Bagińska]

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

- Intention to diagnose, prevent or treat

Epstein Barr virus infections following allogeneic stem cell transplantation should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00). The sponsor is therefore invited to further justify sub-setting the broader condition of impaired cell-mediated immunity and restricting the use of the product only to patients who received HSCT.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of EBV infections following allogeneic stem cell transplantation, the sponsor should further elaborate on:

- the timing of administration of the proposed product, with particular attention to whether the use would be preventive or for treatment;

- the feasibility of the intended clinical use of the product, linked to the need of the primary HSC donor to be available when needed for the leukapheresis. In this respect the sponsor is also asked to clarify what the immune status of the donor should be with respect to the three targeted viruses;
- extrapolation of the results obtained with products different from the one subject of this application;
- the relative composition of the final products and the role of these two different lymphocyte populations in the therapeutic action of the product.

In addition the sponsor is invited to propose a different name that better describes the nature of the product

- Number of people affected

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

The sponsor states that all recipients of HSCT could suffer from a viral infection during the course of one calendar year. However this seems to reflect the population at risk rather than the target group for treatment. The sponsor is therefore asked to provide an estimate of the population target of the treatment indication, based on existing data sources, and the definition of the population to be treated in relation to the specific condition (e.g. viremic and/or symptomatic population?)

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

Post-meeting note:

The COMP adopted the list of issues via written procedure on 16 July 2014.

2.2.21 Product for treatment of adenovirus infections in patients following allogeneic stem cell transplantations - EMA/OD/094/14
[COMP co-ordinator: B. Dembowska-Bagińska]

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

- Intention to diagnose, prevent or treat

Adenovirus infections following allogeneic stem cell transplantation should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00). The sponsor is therefore invited to further justify sub-setting the broader condition of impaired cell-mediated immunity and restricting the use of the product only to patients who received HSCT.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of adenovirus infections following allogeneic stem cell transplantation, the sponsor should further elaborate on:

- the timing of administration of the proposed product, with particular attention to whether the use would be preventive or for treatment;

- the feasibility of the intended clinical use of the product, linked to the need of the primary HSC donor to be available when needed for the leukapheresis. In this respect the sponsor is also asked to clarify what the immune status of the donor should be with respect to the three targeted viruses;
- the extrapolation of the results obtained with products different from the one subject of this application
- the relative composition of the final products and the role of these two different lymphocyte populations in the therapeutic action of the product.

In addition the sponsor is invited to propose a different name that better describes the nature of the product

- Number of people affected

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

The sponsor states that all recipients of HSCT could suffer from a viral infection during the course of one calendar year. However this seems to reflect the population at risk rather than the target group for treatment. The sponsor is therefore asked to provide an estimate of the population target of the treatment indication, based on existing data sources, and the definition of the population to be treated in relation to the specific condition (e.g. viremic and/or symptomatic population?)

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

Post-meeting note:

The COMP adopted the list of issues via written procedure on 16 July 2014.

2.2.22 Obinutuzumab for treatment of diffuse large B-cell lymphoma, Roche Registration Limited - EMA/OD/092/14
[COMP co-ordinator: B. Dembowska-Bagińska]

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

The intention to treat the condition with the medicinal product containing obinutuzumab was considered justified based on preclinical and preliminary clinical data showing anti tumour activity in the proposed condition.

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

The condition was estimated to be affecting approximately 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 obinutuzumab may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing favourable response in patients with refractory

or relapsing disease. The Committee considered that this constitutes a clinically relevant advantage for patients affected by diffuse large B-cell lymphoma.

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

2.2.23 Product for treatment of short bowel syndrome - EMA/OD/080/14
[COMP co-ordinator: D. Krievins]

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

- Intention to diagnose, prevent or treat

The sponsor is advised that without data with the specific product as applied for designation in either relevant preclinical models or patients affected by the condition, the medical plausibility may not be considered justified. In the absence of such data the medical plausibility cannot be established.

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

  - the relevance of the preclinical model used for the treatment of short bowel syndrome, and the interpretation of the results obtained in the experiments, in particular with regards to how the disturbed intestinal environment associated with short-bowel syndrome would affect the product;

- Significant benefit

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

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on any available data of the product in the proposed condition and results from 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 for a written response and during an oral explanation before the Committee at the September meeting.

2.2.24 Recombinant human diamine oxidase for treatment of mastocytosis, Medical University of Vienna - EMA/OD/075/14
[COMP co-ordinator: J. Torrent-Farnell]

The Committee agreed that the condition, mastocytosis, 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 diamine oxidase was considered justified based on preclinical data showing degradation of histamine by the proposed product.

The condition is chronically debilitating due to symptoms caused by release of histamine and tryptase by the tumour cells, including flushing, tachycardia, pruritus, abdominal cramping, peptic ulcer disease, and diarrhoea. Infiltration of various organs by malignant cells in aggressive forms can be life-

threatening, due to bone marrow failure, hepatomegaly with ascites and impaired liver function, splenomegaly with hypersplenism. Five-year survival rate is around 61% in systemic mastocytosis.

The condition was estimated to be affecting less 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 recombinant human diamine oxidase may be of significant benefit to those affected by the condition. Due to its mechanism of action the product offers the potential of degrading large quantities of histamine differently from the authorized products that act on the binding of histamine to its receptors. The sponsor supported the assumption of significant benefit with preclinical data showing significant reduction of histamine levels in plasma from patients with mastocytosis .The Committee considered that this constitutes a clinically relevant advantage for patients affected by mastocytosis.

A positive opinion for Recombinant human diamine oxidase, for treatment of mastocytosis, was adopted by consensus.

2.2.25 Product for treatment of pigmented villonodular synovitis - EMA/OD/107/14
[COMP co-ordinator: A. Corrêa Nunes]

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

- Condition

The sponsor should revise the proposed indication in accordance to the current WHO classification to "treatment of tenosynovial giant cell tumour, localised and diffused type".

- Seriousness

In light of an amended indication, this section should be amended accordingly.

- Prevalence

In light of an amended indication, this section should be amended accordingly.

The COMP adopted a list of issues for a written response before 18 August 2014.

2.2.26 Product for treatment of Merkel cell carcinoma - EMA/OD/079/14
[COMP co-ordinator: 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 Merkel cell carcinoma, the sponsor should further elaborate on:

  - the relevance of the preclinical model used for the treatment of Merkel cell carcinoma, and the interpretation of the results obtained in the experiments,
  - the absence of any data in specific disease settings with the specific product as applied for designation. In the absence of data with the specific product in pre- clinical models of the

specific condition as applied for designation or in patients affected by the condition, the medical plausibility may not be considered acceptable

- Number of people affected

  The sponsor is invited to propose a conclusion based on EU studies and by addressing the identified incidence increase of Merkel cell carcinoma at the time the application is made.

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

The sponsor should re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition.

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

2.2.27 S3,S13-cyclo(D-tyrolsyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-aspartyl-L-tryptophyl-N-methyl-L-glycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-N-methyl-L-isoleucinamide) for treatment of paroxysmal nocturnal hemoglobinuria, Amyndas Pharmaceuticals S.A. - EMA/OD/098/14
[COMP co-ordinator: A. Magrelli]

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

The intention to treat the condition with the medicinal product containing S3,S13-cyclo(D-tyrolsyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-aspartyl-L-tryptophyl-N-methyl-L-glycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-N-methyl-L-isoleucinamide) was considered justified based on preclinical data showing lack of haemolysis of red cells from patients affected by the condition.

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

The condition was estimated to be affecting approximately 0.1 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 S3,S13-cyclo(D-tyrolsyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-aspartyl-L-tryptophyl-N-methyl-L-glycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-N-methyl-L-isoleucinamide) may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing that the product acts on the complement cascade at a different site as compared to the authorized product for the treatment of the condition, offering the potential of efficacy also in extravascular haemolysis, and in patients not responding to the current treatment. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for S3,S13-cyclo(D-tyrolsyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-aspartyl-L-tryptophyl-N-methyl-L-glycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-N-

methyl-L-isoleucinamide) (AMY-101), for treatment of paroxysmal nocturnal hemoglobinuria, was adopted by consensus.

2.2.28 Variant of recombinant human fibroblast growth factor 19 for treatment of primary biliary cirrhosis, Diamond BioPharm Limited - EMA/OD/101/14
[COMP co-ordinator: A. Corrêa Nunes]

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

The intention to treat the condition with the medicinal product containing variant of recombinant human fibroblast growth factor 19 was considered justified based on pre-clinical in vivo data using a valid model of the condition which showed a normalisation of bile serum levels.

The condition is chronically debilitating and life-threatening due to progressive hepatic dysfunction, with development of portal hypertension and hepatic failure, and the increased risk of developing hepatocellular cancer. Common findings include pruritus which may be very distressing, usually occurring at night, hyperlipidaemia, hypothyroidism, deficiency of fat-soluble vitamins and osteopaenia.

The condition was estimated to be affecting approximately 3.9 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing variant of recombinant human fibroblast growth factor 19 may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical in vivo data using a valid model of the condition that demonstrate a normalisation of serum bilirubin levels. The Committee considered that this constitutes a clinically relevant advantage.

Post-meeting note:

A positive opinion for Variant of recombinant human fibroblast growth factor 19, for treatment of primary biliary cirrhosis, was adopted by consensus via written procedure on 21 July 2014.

2.2.29 Vector based on an adeno-associated virus serotype 2 backbone, pseudo-serotyped with a type 8 capsid, which carries the coding sequence of the human *TYMP* gene under the control of the human thyroxine binding globulin promoter for treatment of mitochondrial neurogastrointestinal encephalomyopathy, Vall d'Hebron Insitute of Research - EMA/OD/093/14
[COMP co-ordinator: J. Torrent-Farnell]

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

The intention to treat the condition with the medicinal product containing vector based on an adeno-associated virus serotype 2 backbone, pseudo-serotyped with a type 8 capsid, which carries the coding sequence of the human *TYMP* gene under the control of the human thyroxine binding globulin promoter was considered justified based on studies in a preclinical model of the condition, where treatment with the product resulted in restoration of thymidine phosphorylase activity in the liver, resulting in the normalisation of systemic levels of thymidine and deoxyuridine.

The condition is chronically debilitating and life threatening, in particular due to gastrointestinal dysmotility, peripheral neuropathy, leukoencephalopathy and reduced life expectancy, with most patients not surviving beyond the 4th decade of life.

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

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

A positive opinion for Vector based on an adeno-associated virus serotype 2 backbone, pseudo-serotyped with a type 8 capsid, which carries the coding sequence of the human *TYMP* gene under the control of the human thyroxine binding globulin promoter, for treatment of mitochondrial neurogastrointestinal encephalomyopathy, was adopted by consensus.

2.3. Revision on the COMP opinion adopted via written procedure

2.3.1. 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 [COMP co-ordinator: A. Moraiti]

2.4. Evaluation on-going

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

2.5. Validation on-going

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

3. Requests for protocol assistance

3.1 Product for treatment of glioma.

The protocol assistance letter was discussed for adoption via written procedure.

4. Overview of applications

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

COMP co-ordinators were appointed for 1 application submitted and 34 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

None.

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)

5.2.2 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H- pyrazolo [3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one; Janssen-Cilag International N.V.

a) for treatment of mantle cell lymphoma (EU/3/13/1115)

b) for treatment of chronic lymphocytic leukaemia (EU/3/12/984)

Post-meeting note:

The COMP adopted the list of issues via written procedure on 21 July 2014.

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

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

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

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

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

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

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

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

5.3.15 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)

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

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

5.3.18 Tasimelteon for treatment of non-24-hour sleep-wake disorder in blind people with no light perception; Vanda Pharmaceuticals Limited (EU/3/10/841)

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

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

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

5.3.22 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine, hydrochloride for treatment of narcolepsy; Bioprojet (EU/3/07/459)

6. Any other business

6.1 Update on the EURORDIS Summer School and EUPATI training

M. Mavris from Eurordis presented the topic.

Date of next COMP meeting: 2-4 September 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
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
Dainis Krievins	Latvia
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
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

Observers:

Maria Mavris	Eurordis

Virginie Hivert	Eurordis
Julian Isla	Dravet Syndrome Foundation

Visiting Experts:

Adrienne Flanagan