8 October 2013
EMA/COMP/432621/2013
Human Medicines Development and Evaluation

Committee for Orphan Medicinal Products (COMP)

Minutes of the 3 - 4 September 2013 meeting

Note on access to documents

Documents under points 1.1 and 2 to 7 cannot be released at present as they are currently in draft format or are classified as confidential. They will become public when adopted in their final form 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/432619/2013

The agenda was adopted with a minor correction to point 1.4.

B. Dembowska-Bagińska informed that the conflict of interest indicated on the agenda for 2.1.2 is incorrect and should be deleted.

1.2 Adoption of the minutes of the previous meeting, 9 - 11 July 2013 EMA/COMP/366326/2013

The minutes were adopted with minor corrections to points 2.2.10, 2.2.16 and the list of participants.

1.3 Conflicts of Interest

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

The COMP secretariat was informed as follows:

- EGAN received grants from the sponsors of a product under agenda point 5.2.8. Nevertheless, no direct conflicts of interest have been identified for P. Evers, who represents EGAN in the COMP.
- K. Kubáčková declared a conflict of interest for 2.2.10 and 2.2.11.

2. Applications for orphan medicinal product designation[1]

2.1. For opinion

2.1.1 Product for treatment of glioma - EMA/OD/033/13
[Co-ordinators: D. O'Connor / S. Mariz]

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

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of glioma, the sponsor was asked to further elaborate on the relevance of the results obtained with the product in the *in vitro* glioblastoma cell line studies that have been presented to the clinical condition.

Non-clinical data should be discussed in full in particular the sponsor should further discuss the concentrations of the proposed product used and how this corresponds to the potential doses which could have an effect in the clinical setting.

The sponsor was also asked to discuss how a combination of the proposed product with copper could be translated into use in the clinical setting.

The lack of data from a relevant *in vivo* model (reference to Guideline) should be justified by the sponsor.

[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).

- Prevalence

The sponsor was asked to re-calculate the prevalence estimate based on additional more extensive use of relevant epidemiological studies and registers for the proposed orphan condition.

- Justification of significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the *in vitro* studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

In the written response, and during an oral explanation before the Committee on 3 September 2013, the sponsor has further elaborated on the relevance of the *in vitro* studies that were submitted to support the medical plausibility. The sponsor also gave further information on the expected doses in man and discussed the place of using copper supplementation. The Committee was critical that no pharmacodynamic *in vivo* study was presented to support the medical plausibility. The COMP was of the opinion that the in vitro data was not robust enough to support medical plausibility at this stage.

The sponsor has recalculated the prevalence and has included the GLOBOCAN 2008 database in addition to the EUCAN database. The presented recalculation was considered acceptable by the Committee.

The sponsor argued that the treatment has a new mechanism of action compared to the current treatment modalities. The Committee was of the view, that as the current support for medical plausibility is weak, the assumption of the significant benefit could not be accepted at the present time.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 3 September 2013, prior to final opinion.

2.1.2 **Recombinant fusion protein linking coagulation factor VIIa with albumin** for treatment of congenital factor VII deficiency, CSL Behring GmbH - EMA/OD/051/13

[Co-ordinators: L. Gramstad / S. Tsigkos]

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:

- Justification of significant benefit

The arguments on significant benefit are based on improved pharmacokinetics compared to the authorised counterparts. The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the clinical benefit of the proposed improved pharmacokinetics with regards to the potential dosing scheme for patients affected by the condition, in the context of the current treatment practice of factor VII deficiency.

In the written response, and during an oral explanation before the Committee on 3 September 2013, the sponsor further elaborated the justification of significant benefit.

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 fusion protein linking coagulation factor VIIa with albumin was considered justified based on the mechanism of action

which is substitution of the deficient factor VII together with preclinical data supporting the prothrombotic effects of the product. In addition, the experience of the product in healthy volunteers supports the activity of the product.

The condition is chronically debilitating due to recurrent bleedings in joints, gastrointestinal tract or 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 not more than 0.1 in 10,000 people in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant fusion protein linking coagulation factor VIIa with albumin may be of significant benefit to those affected by the condition. The sponsor has provided pharmacokinetic data that suggest less frequent need for administration for the patients. This assumption is currently supported by pre-clinical and clinical data. 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 fusion protein linking coagulation factor VIIa with albumin, for treatment of congenital factor VII deficiency, was adopted by consensus.

2.1.3 Recombinant human monoclonal IgM antibody targeting glucose regulated protein 78

for treatment of plasma cell myeloma, Patrys GmbH - EMA/OD/072/13
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of recombinant human monoclonal IgM antibody targeting glucose regulated protein 78 for treatment of plasma cell myeloma, the sponsor was asked to further elaborate on:

- the detailed results obtained *in vitro* showing synergistic/additive effects to other medicinal products with regards to plasma cell apoptosis.

- the details of the murine preclinical model used for the treatment of plasma cell myeloma, and the results from this study

- the so far available data form the on-going phase 1/2 dose escalation clinical study, in patients with plasma cell myeloma.

- Justification of significant benefit

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

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the preclinical study claiming a possible synergy in addition to other medicinal products.

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

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 also mandatory to justify the safety claims.

In the written response, and during an oral explanation before the Committee on 3 September 2013, the sponsor provided additional *in vitro* data on the effects of the product in combination with other compounds. The sponsor also elaborated the information provided with regards to the *in vivo* model. Finally the sponsor reported two stable patients out of 8 evaluated patients from the ongoing dose escalation clinical study.

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

The intention to treat the condition with the medicinal product containing recombinant human monoclonal IgM antibody targeting glucose regulated protein 78 was considered justified based on preliminary clinical data showing a reduction of tumour cells in the bone marrow.

The condition is chronically debilitating in particular due to the development of hypercalcaemia, renal insufficiency, anaemia and bone lesions, and life-threatening with an overall survival of up to approximately 45 months for newly diagnosed patients. The condition was estimated to be affecting approximately 1.8 in 10,000 people in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant human monoclonal IgM antibody targeting glucose regulated protein 78 may be of significant benefit to those affected by the condition. This is based on the novel mechanism of action that might result in improved efficacy as supported by preclinical data of the product in disease models. In addition, preliminary clinical data in resistant patients support the assumption that the product either alone or in combination may improve the outcome of the patients or reverse the previous resistance to other products.

A positive opinion for recombinant human monoclonal IgM antibody targeting glucose-regulated protein 78, for treatment of plasma cell myeloma, was adopted by consensus.

2.1.4 Product for treatment of cervical insufficiency - EMA/OD/085/13

[Co-ordinators: K. Westermark / S. Tsigkos]

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

- Proposed indication

The sponsor was invited to provide an **internationally established and agreed upon definition** (emphasis added) of the proposed condition as applied for designation. Without such a definition of a valid condition for designation, the Committee cannot consider whether the criteria for orphan designation are fulfilled.

- Medical plausibility

The sponsor defends the medical plausibility on the basis of clinical studies showing protection against preterm birth in patients with ‘short cervix’ compared to placebo.

To establish correctly if there exists a scientific rationale for the development of progesterone for treatment of cervical insufficiency, the sponsor was asked to further elaborate on the use of ‘short

cervix' measured with trans vaginal ultrasound as a surrogate to draw conclusions for the proposed condition as applied for designation, which is cervical insufficiency.

Moreover the sponsor was asked to clarify if the product is proposed for the treatment of short cervix, treatment of cervical insufficiency, or prevention of preterm birth.

- Prevalence

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

a. The sponsor was asked to further elaborate on the duration of the proposed condition as applied for designation.

b. The sponsor was asked to elaborate on the epidemiological consequences of the fact that there is no agreed definition of the condition as applied for designation, and discuss alternative calculations based on different approaches that focus on structural or functional aspects.

c. The sponsor was asked to provide an additional calculation based on the sum of underlying disorders that cause the condition.

The sponsor withdrew the application on 16 August 2013, prior to responding to the list of questions.

2.1.5 **L-Pyr-L-Glu-L-Gln-L-Leu-L-Glu-L-Arg-L-Ala-L-Leu-L-Asn-L-Ser-L-Ser** for treatment of chronic sarcoidosis, Araim Pharma Europe Ltd - EMA/OD/081/13

[Co-ordinators: L. Gramstad / L. Fregonese][Expert: B. Quadder]

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

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of L-Pyr-L-Glu-L-Gln-L-Leu-L-Glu-L-Arg-L-Ala-L-Leu-L-Asn-L-Ser-L-Ser for treatment of chronic sarcoidosis, the sponsor was asked to elaborate on:

- the reasons for seeking the designation of chronic sarcoidosis rather than sarcoidosis as a whole;

- the relevance of the results obtained in animal models of sciatic crush injury, spared nerve injury, and neuro-inflammation induced by Freund's adjuvant to the specific neuro-inflammation described in sarcoidosis;

- the relevance of neuropathic pain to the clinical setting of sarcoidosis;

- the relevance of the endpoints of the phase II clinical trial to the treatment of sarcoidosis;

- any results other than on neurological endpoints from the phase II study.

- Justification of significant benefit

The sponsor was invited to further discuss the grounds supporting significant benefit, i.e. the clinically relevant advantage or major contribution to patient care that the proposed product would bring in comparison to what is already authorised for the treatment of the proposed condition.

In this respect the sponsor was also invited to further discuss the methodology and results of the phase II trial, including the use of concomitant treatments.

In the written response, and during an oral explanation before the Committee on 4 September 2013, the sponsor elaborated the information provided on the disease, medical plausibility and the justification on significant benefit. With regards to the medical plausibility, the role of the small fiber neuropathy in sarcoidosis was clarified.

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

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

The intention to treat the condition with the medicinal product containing L-Pyr-L-Glu-L-Gln-L-Leu-L-Glu-L-Arg-L-Ala-L-Leu-L-Asn-L-Ser-L-Ser was considered justified based on preliminary clinical data in patients with the condition where improvement was seen in corneal nerve density, allodynia and other neuropathic manifestations.

The condition is life-threatening and chronically debilitating due to progressive tissue damage from active inflammation. Common organ targets are the lung, skin, eye, and peripheral nervous system. Involvement of these diverse organ systems can lead to marked reduction in functional capacity and quality of life. Mortality is increased due mainly to cardiovascular failure. The condition was estimated to be affecting approximately 2 in 10,000 people in the European Union, at the time the application was made; the sponsor conducted a literature search to establish the prevalence.

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 L-Pyr-L-Glu-L-Gln-L-Leu-L-Glu-L-Arg-L-Ala-L-Leu-L-Asn-L-Ser-L-Ser may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical and clinical data that demonstrate that improvements were seen in signs and symptoms associated with the condition such as allodynia, 6min walking test, neuropathic pain and corneal nerve fibers. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for L-Pyr-L-Glu-L-Gln-L-Leu-L-Glu-L-Arg-L-Ala-L-Leu-L-Asn-L-Ser-L-Ser, for treatment of sarcoidosis, was adopted by consensus.

2.1.6 **Mexiletine Hydrochloride** for treatment of myotonic disorders, Agenzia Industrie Difesa-Stabilimento Chimico Farmaceutico Militare - EMA/OD/069/13

[Co-ordinators: I. Bradinova / S. Mariz]

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

- Proposed indication

In the sponsor's application, it is asserted that: "…Dystrophia myotonica [Steinert], Myotonia congenita and Paramyotonia congenita are subgroups of the myotonic disorders. Dystrophia myotonica is characterised by the presence of myotonic phenomenon and muscular dystrophy, whereas in myotonia and paramyotonia congenita muscular dystrophy is absent or very limited and secondary to the persistence of the myotonic phenomenon…"

Therefore more than one distinct medical entity is considered in this application. At this point, the attention of the sponsor was drawn to the updated guideline ENTR/6283/00 Rev 03 that states that "If more than one indication is applied for the same product, separate applications should be submitted for each indication".

The sponsor was hence invited to amend the proposed indication by submitting two separate applications for a) treatment of dystrophic myotonia and b) treatment of non-dystophic myotonia. The sponsor was asked to submit updated application forms and scientific annexes for the abovementioned indication, including inter alia a *separate prevalence estimate* (emphasis added) for each of them.

In the written response, and during an oral explanation before the Committee on 3 September 2013, the sponsor further elaborated the information provided on the classification of myotonic disorders. The sponsor argued that the existing classifications do not take into account the aetiology and that they are not clinically homogenous. Therefore, the Committee finally accepted the indication that is also recognised in the ICD10-classification, as proposed by the sponsor.

The Committee agreed that the condition, myotonic disorders, is a valid condition for orphan designation.

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

The condition is chronically debilitating due to pain with muscle stiffness associated with disability. The muscle stiffness can be very debilitating leading to falls associated with fractures and serious injury. The condition was estimated to be affecting approximately 2 in 10,000 people in the European Union, at the time the application was made; this was based on a literature search which was conducted by the sponsor.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing mexiletine hydrochloride may be of significant benefit to those affected by the condition. The satisfactory methods of treatment authorised include mexiletine being authorised in two EU Member States, which due to its limited coverage does not offer sufficient access for patients affected by the condition. The potential increased access through a centralised authorisation is accepted as a justification for a significant benefit based on a major contribution to patient care.

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

2.1.7 Product for treatment of parathyroid carcinoma - EMA/OD/080/13

[Co-ordinators: B. Dembowska-Bagińska / S. Aarum]

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

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development in the treatment of parathyroid carcinoma, the sponsor should clarify the following issues:

- the composition of the product in particular certain components where there are known safety concerns, and

- the activity of the specific products' constituents in parathyroid carcinoma

- Freund's adjuvant is a toxic compound and described to cause at least severe local reactions. The sponsor should clarify the possible activity of Freund's adjuvant. The information provided with regards to the 15 treated patients should be elaborated. The sponsor was asked to provide more details of the patients (such as a compassionate use program report) clarifying the medical history and clinical evaluation especially with regards to the other treatments (e.g. calcimimetics), tumour and antibody responses, taking into account any possible bias that may have affected the results.

- to provide more details of the reliability of the method used to evaluate tumour responses.

- to discuss the reliability of the measured endpoints in patients with parathyroid carcinoma administered with the product.

- Justification of significant benefit

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

The sponsor was requested to further discuss the capability of the product to treat hypercalcaemia and to elaborate on the information from the compassionate use program to justify the assumption of significant benefit over authorised product for the proposed orphan indication.

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

The Committee was informed that the sponsor withdrew the application on 8 August 2013, prior to responding to the list of questions.

2.2. For discussion / preparation for an opinion

2.2.1 Product for treatment of neurotrophic keratitis - EMA/OD/184/12
[Co-ordinators: K. Westermark / S. Tsigkos]

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

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of neurotrophic keratitis, the sponsor should further elaborate on the relevance of the preclinical model used for the treatment of neurotrophic keratitis, and the interpretation of the results obtained in the experiments

- Prevalence

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

The sponsor should re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition. Given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor should perform a sensitivity analysis of the reported calculations. The sponsor is also invited to provide information regarding the numerous conditions that could cause the condition as presented in Table 1 (Bonini et al, 2003).

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

2.2.2 Product for treatment of acromegaly - EMA/OD/082/13
[Co-ordinators: V. Tillmann / S. Aarum]

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

- Medical plausibility

In the application, the sponsor has provided *in vitro* data on the receptor binding capability of the applied product. In addition, the *in vitro* effects of the product on inhibition of GH and prolactin release have been studied using cultured pituitary cells obtained from Wistar rats.

Nevertheless, the current evidence on the activity of the product in acromegaly is limited.

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

- the methodology used in the pre-clinical studies as well as the results from these studies and their relevance for the development of the product in acromegaly;

- to provide any other new data or information (such as effects on IGF-1) that may exist to support the efficacy of the product in the applied condition.

- Justification of significant benefit

With the limited data presented to support the efficacy of the product in acromegaly, the sponsor is requested to further discuss the arguments provided for significant benefit over existing authorised products, and to elaborate on the results to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

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

2.2.3 **3,5-Diiodothyropropionic Acid** for treatment of the Allan-Herndon-Dudley Syndrome, CATS Consultants GmbH - EMA/OD/089/13
[Co-ordinators: F. Saleh / S. Mariz]

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

The intention to treat the condition with the medicinal product containing 3,5-diiodothyropropionic acid was considered justified based on preclinical data using MCT8 knock-out mice and preliminary clinical data in patients with the condition where there was a normalisation of serum thyroid hormones and increase in body weight.

The condition is life-threatening and chronically debilitating due to hypotonia, muscle hypoplasia, severe mental retardation, poor head control, dysarthria and athetoid movements. Patients have a hypermetabolic state, failure to thrive, and an inability to gain weight. Survival is limited in most patients. The condition was estimated to be affecting approximately 0.2 in 10,000 people in the European Union, at the time the application was made; this is based on a literature search conducted by the sponsor.

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 3,5-diiodothyropropionic acid, for treatment of Allan-Herndon-Dudley syndrome, was adopted by consensus.

2.2.4 Antisense oligonucleotide targeting the F508delta mutation of CFTR for treatment of cystic fibrosis, ProQR Therapeutics BV - EMA/OD/096/13
[Co-ordinators: J. Eggenhofer / L. Fregonese]

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 antisense oligonucleotide targeting the F508delta mutation of CFTR was considered justified based preclinical results supporting the activity of the product in restoring the function of the CFTR protein 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 0.7 in 10,000 people in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing antisense oligonucleotide targeting the F508delta mutation of CFTR may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that support the activity of the product in modifying the disease in cystic fibrosis patients carrying the F508delta mutation of CFTR. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for antisense oligonucleotide targeting the F508delta mutation of CFTR, for treatment of cystic fibrosis, was adopted by consensus.

2.2.5 Product for treatment of glioma - EMA/OD/086/13
[Co-ordinators: A. Magrelli / S. Tsigkos]

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

- Proposed active substance

The sponsor is invited to further elaborate on the populations of leukocytes contained in the proposed product regarding their anti-tumour characteristics.

- Prevalence

The sponsor is invited to provide additional estimates based on 5-year prevalence, and given the uncertainty about the assumptions used in the calculation, to perform a sensitivity analysis in particular by varying the ratio of gliomas versus all intracranial tumours.

- Justification of significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the implicit argument of improved efficacy versus authorised products or other therapies (e.g. neurosurgical intervention) for the treatment of the condition.

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

2.2.6 Product for prevention of graft versus host disease - EMA/OD/103/13
[Co-ordinators: K. Westermark / S. Mariz]

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

- Medical plausibility

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

- the relevance of the methodology and results of the in vitro models used to show the effects in the prevention of graft-versus-host disease, in particular the relevance of the endothelial in vitro data with autologous HSCT;

- the relevance of the clinical data. More details are needed with regards to a post hoc analysis performed. More information on the therapeutic approach used, including background treatment, greater detail regarding the target patient population and the extent of HLA mismatch (or other relevant risk factor for GvHD) is required.

- Justification of significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from in vitro studies and the patient population as well as the standard of care used in the clinical post hoc analysis submitted to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

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

2.2.7 **Naproxcinod** for treatment of Duchenne muscular dystrophy, NicOx - EMA/OD/090/13
[Co-ordinators: P. Evers / S. Mariz]

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 naproxcinod was considered justified based on pre-clinical data using a valid model which showed an effect on relevant parameters used to measure therapeutic effect.

The condition is life-threatening and chronically debilitating due to an inexorable progressive weakness occuring 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 respiratory and cardiac muscle strength decline, forced vital capacity and cardiac output decrease, leading, often by late adolescence, to terminal respiratory or cardiac failure. Patients rarely live beyond the age of 30

years. The condition was estimated to be affecting approximately 0.5 in 10,000 people in the European Union, at the time the application was made; this was based on an extensive literature search.

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 naproxcinod, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

2.2.8 Product for treatment of Fabry disease - EMA/OD/100/13
[Co-ordinators: P. Evers / S. Aarum]

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

- Justification of significant benefit

The sponsor is of the opinion that the applied product may be of significant benefit based on greater enzyme stability and longer plasma half-time *in vivo* than the authorised treatment.

However, the sponsor is requested to further discuss the arguments provided for significant benefit taking into account both authorised products, in order to justify the assumption of significant benefit for the proposed orphan indication.

The sponsor should also clarify the intended clinical use of the product in the future in comparison to the already existing products. In particular, the sponsor is requested to comment on how significant benefit will be achieved.

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

2.2.9 Product for treatment of mucopolysaccharidosis type II (Hunter's syndrome - EMA/OD/091/13
[Co-ordinators: V. Saano / S. Aarum]

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

- Prevalence

The sponsor has concluded a prevalence of 0.08 in 10,000. It is not clear how this figure is established from the available data. Also, the sponsor has also calculated a considerably higher figure (1.45 in 10,000) when using incidence and duration of the disease.

The sponsor should explain how the final conclusion is drawn from the available data, and to clarify the discrepancy. If considered relevant, a re-calculation of the prevalence should be provided.

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

2.2.10 Product for treatment of follicular thyroid cancer - EMA/OD/092/13
[Co-ordinators: K. Westermark / S. Aarum]

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

- Prevalence

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

The sponsor has concluded a prevalence of 0.64 in 10,000 using a calculation with many percentages that may potentially insert uncertainties into the calculation. Also, the conclusion given by the sponsor is higher than that previously accepted by the Committee.

The sponsor should better explain and justify the methodology used for the prevalence calculation.

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

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

2.2.11 Product for treatment of papillary thyroid cancer - EMA/OD/093/13
[Co-ordinators: K. Westermark / S. Aarum]

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

- Prevalence

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

The sponsor has concluded a prevalence of 2.56 in 10,000 using a calculation with many percentages that may potentially insert uncertainties into the calculation. Also, the conclusion is higher than what is the current knowledge of the Committee.

The sponsor should better explain and justify the methodology used for the prevalence calculation.

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

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

2.2.12 Autologous CD34+ cells transduced with a lentiviral vector containing the human Wiskott-Aldrich syndrome gene for treatment of Wiskott-Aldrich-Syndrome, Généthon - EMA/OD/104/13
[Co-ordinators: A. Magrelli / L. Fregonese]

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

The intention to treat the condition with the medicinal product containing autologous CD34+ cells transduced with a lentiviral vector containing the human Wiskott-Aldrich syndrome gene was considered justified based on preclinical data showing restoration of the function of several cell types affected by Wiskott Aldrich syndrome when the proposed gene therapy is administered. The sponsor also presented some preliminary clinical reports supporting the intention to treat, showing clinically significant improvement in haematologic and functional parameters.

The condition is life-threatening and chronically debilitating due to thrombocytopenia leading to prolonged bleeding episodes, immunodeficiency leading to recurrent infections that may result in sepsis, autoimmunity resulting in cytopenias, as well as due to the development of haematologic malignancies. The condition was estimated to be affecting approximately 0.01 in 10,000 people in the European Union, at the time the application was made; this was based on data from the literature and from international registries.

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

A positive opinion for autologous CD34+ cells transduced with a lentiviral vector containing the human Wiskott-Aldrich syndrome gene, for treatment of Wiskott-Aldrich syndrome, was adopted by consensus.

2.2.13 Product for treatment of Adult Onset Still's Disease- EMA/OD/099/13
[Co-ordinators: A. Corrêa Nunes / S. Mariz]

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

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of adult onset Still's disease, the sponsor should further elaborate on the relevance of the pre-clinical and clinical data submitted to support the effects of the product in the target condition as this data is derived from rheumatoid arthritis animal models, healthy volunteers and patients with rheumatoid arthritis and psoriasis.

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

2.2.14 Product for treatment of *Pseudomonas aeruginosa* infection in cystic fibrosis - EMA/OD/101/13
[Co-ordinators: J. Eggenhofer / L. Fregonese]

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

- Medical plausibility

In order to establish the medical plausibility of treating the proposed condition with the proposed product, the sponsor is invited to further discuss:

- the extrapolation of the *in vitro* results on biofilms to the clinical manifestations of CF;

- the expected doses when translating *in vitro* results to the clinical setting.

- Prevalence

The sponsor should provide as final estimate of the prevalence of the condition.

- Justification of significant benefit

The sponsor is invited to elaborate on the advantages of administering the two products in a fixed combination rather than separately, taking into account:

- the proposed mechanism of action at the base of the expected clinical effects of one of the components in cystic fibrosis;

- the position of this combination in the current treatment algorithm of the disease;

- the possibility of increasing antibiotic resistances;

- the applicability of the inhalation route of a product The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the October meeting.

2.2.15 Zoledronic acid for treatment of complex regional pain syndrome, Axsome Therapeutics Limited - EMA/OD/088/13
[Co-ordinators: B. Bloechl-Daum / S. Tsigkos]

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

The intention to treat the condition with the medicinal product containing zoledronic acid was considered justified based on the assumption, that zoledronic acid could treat the underlying cause of the condition, which was demonstrated by the reduction of symptoms and signs observed in a preclinical model of the proposed condition. This assumption is also supported by literature studies with other products containing substances with a similar mechanism of action that suggested improvement in patients affected by the condition.

The condition is chronically debilitating due to symptoms such as pain, hyperesthesia or allodynia, oedema, weakness, tremor, dystonia, as well as skin trophic changes. The condition was estimated to be affecting less than 3 in 10,000 people 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 zoledronic acid, for treatment of complex regional pain syndrome, was adopted by consensus.

2.3. Evaluation on-going

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

2.4. Validation on-going

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

3. Requests for protocol assistance

3.1 Product for treatment of systemic sclerosis

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

3.2 Product for treatment of acromegaly

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

3.3 Product for treatment of anaplastic thyroid cancer

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

3.4. Product for treatment of primary myelofibrosis

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

3.5 Product for treatment of peripheral T-cell lymphoma (nodal, other extranodal and leukemic/disseminated)

The Committee was briefed on the significant benefit issues.

3.6 Product for treatment of graft-versus-host disease

The Committee was briefed on the significant benefit issues.

3.7 Product for treatment of chronic lymphocytic leukaemia

The Committee was briefed on the significant benefit issues.

3.8 Product for treatment of Fabry disease

The Committee was briefed on the significant benefit issues.

3.9 Product for treatment of ovarian cancer

The Committee was briefed on the significant benefit issues.

3.10 Product for treatment of mercury toxicity

The COMP was informed that a list of issues was adopted at the July SAWP. Postponed to October COMP meeting.

4. Overview of applications

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

COMP co-ordinators were appointed for 9 applications submitted and 37 upcoming applications.

4.2 Update on orphan applications for Marketing Authorisation

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

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

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

5.1.1 Defitelio (Defibrotide) for treatment of hepatic veno-occlusive disease; Gentium S.p.A. (EU/3/04/212) [Co-ordinators: J. Torrent-Farnell / S. Mariz]

The COMP concluded that:

The proposed therapeutic indication "Treatment of severe hepatic veno-occlusive disease (VOD), also known as sinusoidal obstructive syndrome (SOS), in haematopoietic stem-cell transplantation therapy (HSCT)" falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.

The prevalence of hepatic veno-occlusive disease was estimated to remain below 5 in 10,000 at the time of the review of the designation criteria. The condition is chronically debilitating due to weight gain, tender hepatomegaly, ascites, and increased bilirubin. It often is associated with renal failure. Between 20 to 50% of patients die from hepatic veno-occlusive disease. The main causes of death are, hepatic failure directly due to veno-occlusive disease, renal failure due to hepatorenal syndrome, respiratory failure due to pulmonary veno-occlusive disease, interstitial pneumonitis (infectious or noninfectious), pulmonary haemorrhage, gastrointestinal bleeding and congestive heart failure.

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

An opinion not recommending the removal of Defitelio (defibrotide) (EU/3/04/211) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion (EMA/COMP/536533/2013) was adopted for publication on the EMA website.

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

5.2.1 Cholic Acid FGK for treatment of inborn errors of primary bile acid synthesis responsive to treatment with cholic acid; FGK Representative Service GmbH (EU/3/09/683) [Co-ordinators: A. Magrelli / S. Tsigkos]

The Committee was informed that a standing Committee will be organised shortly by the European Commission.

5.2.2 Cometriq [Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L)-malate salt] for treatment of medullary thyroid carcinoma; TMC Pharma Services Ltd (EU/3/08/610) [Co-ordinators: B. Bloechl-Daum / S. Aarum]

Discussion is postponed until update on progress of the MA procedure.

5.2.3 Masican N-(methyl-diazacyclohexyl-methylbenzamide)-azaphenyl-aminothiopyrrole for treatment of malignant gastrointestinal stromal tumours; AB Science (EU/3/04/251) [Co-ordinators: D. O'Connor / S. Mariz]

Discussion is postponed until update on progress of the MA procedure.

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

Discussion is postponed until update on progress of the MA procedure.

5.2.5 Neoforderx (Dexamethasone (40 mg tablet) for treatment of multiple myeloma; Laboratoires CTRS (Cell Therapies Research & Services) (EU/3/10/745) [Co-ordinators: D. O'Connor / S. Aarum]

Discussion is postponed until update on progress of the MA procedure.

5.2.6 Opsumit (Macitentan) for treatment of pulmonary arterial hypertension; Actelion Registration Ltd. (EU/3/11/909), [Co-ordinators: V. Saano / L. Fregonese]

The Committee considered that the justification of significant benefit issue requires clarification by the sponsor. The sponsor is invited to further discuss and support as much as possible with data the significant benefit of Opsumit in relation to currently authorised therapies, in particular endothelin receptor antagonists.

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

5.2.7 PAS-GR (Para-aminosalicylic acid) for treatment of tuberculosis; Lucane Pharma SA (EU/3/10/826) [Co-ordinators: V. Stoyanova / S. Mariz]

Discussion is postponed until update on progress of the MA procedure.

5.2.8 Sirturo [Bedaquiline ((1R,2S) 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-(1-naphthyl)-beta-phenyl-3-quinolineethano)] for treatment of tuberculosis; Janssen-Cilag International N.V. (EU/3/05/314) [Co-ordinators: N. Sypsas / L. Fregonese]

Discussion is postponed until update on progress of the MA procedure.

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

Discussion is postponed until update on progress of the MA procedure.

5.3. On-going procedures

5.3.1 Adempas (Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinyl(methyl)carbamate) for treatment of pulmonary arterial hypertension including treatment of chronic thromboembolic pulmonary hypertension; Bayer Pharma AG (EU/3/07/518)

5.3.2 Folcepri (N-[4-[[(2-amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-D-gamma-glutamyl-(2S)-2-amino-beta-alanyl-L-alpha-aspartyl-L-cysteine to be used with folic acid) for diagnosis of positive folate receptor status in ovarian cancer; Endocyte Europe, B.V. (EU/3/12/1043)

5.3.3 Gazyva (Obinutuzumab) for treatment of chronic lymphocytic leukemia; Roche Registration Limited (EU/3/12/1054)

5.3.4 Holoclar (former name: GPLSCD01) (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)

5.3.5 Neocepri (Folic acid to be used with N-[4-[[(2-amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-D-gamma-glutamyl-(2S)-2-amino-beta-alanyl-L-alpha-aspartyl-L-cysteine) for diagnosis of positive folate receptor status in ovarian cancer; Endocyte Europe, B.V. (EU/3/12/1044)

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

5.3.7 Vantobra, Tobramycin (inhalation use) for treatment of P*seudomonas Aeruginosa* lung infection in cystic fibrosis; PARI Pharma GmbH (EU/3/09/613)

5.3.8 Vimizim (Recombinant human N-acetylgalactosamine-6-sulfatase) for treatment of mucopolysaccharidosis, type IVA (Morquio A syndrome); BioMarin Europe Ltd (EU/3/09/657)

5.3.9 Vynfinit (Vincaleukoblastin-23-oic acid, O4-deacetyl-2-[(2-mercaptoethoxy)carbonyl]hydrazide, disulfide with N-[4-[[(2-amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-L-gamma-glutamyl-L-alpha-aspartyl-L-arginyl-L-alpha-aspartyl-L-alpha-aspartyl-L-cysteine) for treatment of ovarian cancer; Endocyte Europe, B.V. (EU/3/12/959)

5.3.10 Winfuran (-)-17(cyclopropylmethyl)-1,14 ß-dihydroxy-4,5 alpha-epoxy-6ß-[N-methyl-trans-3-(3-furyl) acrylamido] morphinan hydrochloride for treatment of uremic pruritus; Toray International U.K. Limited (EU/3/02/115).

6. Procedural aspects

6.1 Proposal for improvement of the COMP procedures

The new summary report template was presented to the Committee.

6.2 Autologous regulatory T cells with an immunophenotype of CD4+CD25hiFoxP3+ for prevention of graft rejection following solid organ transplantation, iReg Medical AB - EMA/OD/043/13 [Co-ordinators: K. Westermark / L. Fregonese]

The revised grounds of the COMP opinion adopted in the July 2013 meeting were adopted by consensus.

6.3 PCWP/HCPWP joint meeting 25 September 2013

The draft agenda was circulated for information.

6.4 Workshop on patient's voice in the evaluation of medicines 26 September 2013

The draft agenda was circulated for information.

7. Any other business

7.1 Projects on adaptive licensing

The Committee was briefed on the on-going project by P. Evers. The Committee expressed their opinion about the project and will prepare a letter on this topic to the adaptive licensing group.

7.2 Proposal for a publication strategy (including book on rare diseases)

The Committee postponed this topic to the next COMP meeting.

7.3 Results on the survey on orphan medicinal products development

The Committee postponed this topic to the next COMP meeting.

7.4 Workshop with the PDCO on a definition of conditions for haematological malignancies

The Committee was informed of the upcoming workshop in October.

7.5 Grounds of major contribution to patient care

The Committee postponed this topic to the next COMP meeting.

7.6 Similarity group

The Committee postponed this topic to the next COMP meeting.

7.7 Scientific Coordination Board

The Committee postponed this topic to the next COMP meeting.

7.8 Eurordis Summer School(s)

A presentation was given by M. Mavris.

7.9 Public consultation on the guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another

The topic was discussed.

Date of next COMP meeting: 8 – 9 (10) October 2013

List of participants

Chair:

Bruno Sepodes

Vice-Chair:

Lesley Greene	Volunteer patient representative for Eurordis

COMP Members:

Irena Bradinova	Бълга̀рия
Kateřina Kubáčková	Česká Republika
Vacant	Danmark
Frauke Naumann-Winter	Deutschland
Vallo Tillmann	Eesti
Geraldine O'Dea	Éire/Ireland
Nikolaos Sypsas	Ελλάδα
Annie Lorence	France
Adriana Andric	Hrvatska
Sigurdur B. Thorsteinsson	Iceland
Armando Magrelli	Italia
Ioannis Kkolos	Κύπρος
Dainis Krievins	Latvija
Aušra Matulevičienė	Lietuva
Henri Metz	Luxembourg
Judit Eggenhofer	Magyarország
Albert Vincenti	Malta
Violeta Stoyanova-Beninska	Nederland
Lars Gramstad	Norway
Brigitte Blöchl-Daum	Österreich
Bożenna Dembowska-Bagińska	Polska
Ana Corrêa-Nunes	Portugal
Flavia Saleh	România
Martin Možina	Slovenija
Vacant	Slovensko
Veijo Saano	Suomi/Finland
Kerstin Westermark	Sverige
Daniel O'Connor	United Kingdom
Pauline Evers	Patient representative representing the European Genetic Alliances Network
Aikaterini Moraiti	CHMP Representative
Vacant	EMA Representative
Vacant	EMA Representative

Observers:

Maria Mavris	Eurordis

European Commission:

Agnès Mathieu	DG Health and Consumers

EMA:

Jordi Llinares Garcia	Head of Orphan Medicines
Stiina Aarum	Scientific Administrator
Segundo Mariz	Scientific Administrator
Nacho Mbaeliachi	Scientific Administrator (for 5.1.1)
Cinzia N'Diamoi	Assistant
Frederique Dubois	Assistant

Apologies

Members:

André Lhoir	België/Belgique/Belgien
Josep Torrent Farnell	España
Birthe Byskov Holm	Volunteer patient representative for Eurordis

Observers:

Antonio Blazquez	Agencia Española de Medicamentos y Productos Sanitarios