EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 April 2013
EMA/COMP/83433/2013
Human Medicines Development and Evaluation

Committee for Orphan Medicinal Products (COMP)

Minutes of the 12 - 13 March 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).

Contents

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1. Introduction

1.1 Adoption of the agenda, EMA/COMP/83429/2013

The agenda was adopted with no amendments.

1.2 Adoption of the minutes of the previous meeting held on 5 - 6 February 2013 EMA/COMP/18213/13

The minutes were adopted.

1.3 Conflicts of Interest

The Chair asked the Committee members to declare their potential conflicts of interest. No conflict of interest was declared.

2. Applications for orphan medicinal product designation[1]

2.1. For opinion

2.1.1 For treatment of non-small-cell lung cancer in patients expressing HLA-A2 - EMA/OD/168/12 *[Co-ordinators: B. Bloechl-Daum / L. Fregonese]*

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:

- Orphan indication

The sponsor was invited to justify "non-small-cell lung cancer in patients expressing HLA-A2" as a valid subset having distinct aetiologic, histopathologic and clinical characteristics as compared to the broader condition "non-small cell lung cancer".

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of non-small-cell lung cancer in patients expressing HLA-A2, the sponsor was invited to further elaborate on:

  - the specific mechanism of action of the product in the proposed condition;
  - the methodology and results of the phase I study, where it appears that 6 NSCLC subjects were studied; however, the immunologic response was evaluated in patients affected by colon cancer. The sponsor was invited to discuss the reasons why the immunologic response of the NSCLC patients is not shown and how the response of colon cancer patients can be extrapolated to NSCLC;
  - the use of the immunologic response as proxy of clinical efficacy;
  - the lack of response in a number of subjects of this study- what is meant by "the vaccine was immunogenic and effective at inducing strong and broad CTL responses in a high frequency of patients". The sponsor is invited to provide figures of such response;

[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).

- the methodology and the results of the phase II study, including discussion on the survival figures presented. In this respect, it would be important to know among others, if the survival curves include all patients treated with the proposed product or only the responders. Possible reasons for non-responding should be also addressed.

- Prevalence

The sponsor was invited to re-calculate the provided estimate based on complete prevalence rather than 5-year prevalence.

- Justification of significant benefit

The sponsor was invited to discuss the grounds of significant benefit, including reasoning on why the product would constitute a clinically relevant advantage or major contribution to patient care as compared to what is already authorised for the treatment of the condition. The reasoning should be as much as possible supported by data.

In the written response, and during an oral explanation before the Committee on 12 March 2013, the sponsor defended the choice of subset as applied for designation, on the grounds of the specific activity of the product which is linked to immunological restriction. It was stressed that HLA-A2 expression would be an absolute requirement to obtain a T cell response against the targeted tumour. In addition, it was argued that the serological HLA-A2 cell surface marker is described with prognostic significance on survival in numerous cancers (NSCLC, endometrial, ovarian, prostatic), exemplifying the role of the cellular immune system. The sponsor also elaborated on the clinical studies presented in the application, the use of IFN-γ responses as measured by ELISPOT assays to monitor cytotoxic responses against specific epitopes, the choice of immunological response as a proxy of clinical responses, and the results observed in patients. An updated prevalence calculation was also submitted for the proposed indication based on complete prevalence as requested by the Committee. Moreover, the sponsor argued on a significant benefit based on a novel mechanism of action that might have the potential of improved efficacy. This was argued based on the preliminary clinical data in NSCLC patients of advanced stage treated with the product, which showed an encouraging survival profile compared to historical data (i.e. published studies with authorised medicinal products).

The Committee emphasized that the choice of the subset as proposed for designation was a major concern for orphan designation. As per the Guideline on the format and content of the applications (ENTR6283/00 Rev 03), the subset should inter alia have a "*plausible link to the condition*" and be "*closely linked to the pharmacological action of the medicinal product in such a way that the absence of these characteristics will render the product ineffective in the rest of the population*". The Committee stressed that in particular the first of the abovementioned requirements was not fulfilled, even though the second one had been addressed. It was discussed that HLA-A2 pertained to the immune system of the individual and was not a characteristic of the condition for which the proposed product is applied for designation. Patients expressing HLA-A2 were classified based on their immune system and not the condition that they were affected with. Therefore the subset of NSCLC as proposed for designation was not considered acceptable. In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 March 2013, prior to final opinion.

2.1.2 **Lenvatinib** for treatment of differentiated thyroid cancer, Eisai Europe Limited - EMA/OD/173/12

[Co-ordinators: K. Westermark / L. Fregonese]

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:

- Orphan indication

Differentiated thyroid cancer might be perceived as a stage of the disease rather than a distinct medical entity from the perspective of the legal basis of the orphan designation.

Differentiated thyroid cancer should be justified as a distinct medical entity or the application should be split in two separate applications for papillary thyroid cancer and follicular thyroid cancer. The latter is assumed to include also Hürtle cell carcinoma.

- Prevalence

The sponsor was invited to calculate the prevalence according to the possible splitting of the indication into papillary thyroid cancer and follicular thyroid cancer, i.e. providing one prevalence estimate for each of these two conditions.

In addition the sponsor was invited to provide complete prevalence rather than 5-year prevalence of the proposed condition(s), taking into account the duration of the disease.

- Significant benefit

In order to justify the preliminary evidence of a significant benefit, the sponsor was invited to provide more details on the phase II study, in particular regarding the number of patients who were treated, as from the investigator brochure it would appear that 117 subjects were recruited, however only 58 are mentioned in the current application. The number of patients affected by FTC and PTC should also be reported.

The sponsor requested that the proposed orphan indication "treatment of differentiated thyroid cancer" be split into two separate indications and submitted two updated application forms accordingly for the following indications: treatment of papillary thyroid cancer (the present application: EMA/OD/173/12) and treatment of follicular thyroid cancer (EMA/OD/019/13) .

In the written response, and during an oral explanation before the Committee on 12 March 2013, the sponsor agreed to amend the proposed indication and split "treatment of differentiated thyroid cancer" (DTC) into "treatment of papillary thyroid cancer" (PTC) and "treatment of follicular thyroid cancer" (FTC). As requested, the sponsor also split the prevalence of the two conditions and the methodology (mainly based on international cancer registries, including the ones assessed in the project RareCARE).

Regarding significant benefit, the sponsor clarified the number of treated subjects in the Phase II study on ^{131}I refractory differentiated thyroid cancer, explaining that the study was composed of two cohorts. Fifty-eight subjects (the ones mentioned by the sponsor in the original application for DTC) were affected by PTC and FTC (35 and 23, respectively) and the second cohort consisted of 59 patients affected by medullary thyroid cancer, which is not part of this application. In the 58 subjects of the first cohort treatment with lenvatinib resulted in stable disease in 40% of the subjects and in partial response in approximately 50% of the subjects, with a median progression free survival of 15.9 months in PTC and 10.8 months in FTC.

For the purpose of orphan designation, the COMP agreed that the indication should be split into "treatment of papillary thyroid cancer" and "treatment of follicular thyroid cancer".

a) treatment of papillary thyroid cancer, EMA/OD/173/12

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

Papillary thyroid cancer as estimated to be affecting less than 1 in 10,000 people in the European Union, at the time the application was made; the prevalence calculations were based on data from international cancer registries including Globocan and the RARECare project. The intention to treat the condition with the proposed product is justified by preclinical data showing reduction of tumour growth in xenograft models, and by early clinical data showing survival benefit in patients with ^{131}I refractory disease. The condition is chronically debilitating due to the local symptoms such as hoarseness, difficulties in swallowing, neck and throat pain, and to symptoms due to the presence of metastasis. The condition can be life-threatening due to the progression of the tumour in case of no response to first-line treatment with surgery and ^{131}I treatment, and in case of development of metastasis with wide spread of the tumour.

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 lenvatinib may be of significant benefit to those affected by the condition. This appears justified based on early clinical data in patients refractory to ^{131}I treatment. In this patient population, treatment with lenvatinib resulted in a partial response in half of the patients and in stable disease in an additional 40% of patients. This is assumed to translate in a clinically relevant advantage for the patients affected by papillary thyroid cancer.

A positive opinion for Lenvatinib, for treatment of papillary thyroid cancer, was adopted by consensus.

b) treatment of follicular thyroid cancer, EMA/OD/019/13

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

Follicular thyroid cancer was estimated to be affecting less than 0.2 in 10,000 people in the European Union, at the time the application was made; the prevalence calculations were based on data from international cancer registries including Globocan and the RARECare project. The intention to treat the condition with the proposed product is justified by preclinical data showing reduction of tumour growth in xenograft models, and by early clinical data showing survival benefit in patients with ^{131}I refractory disease. The condition is chronically debilitating due to the local symptoms such as hoarseness, difficulties in swallowing, neck and throat pain, and to symptoms due to the presence of metastasis. The condition can be life-threatening due to the progression of the tumour in case of no response to first-line treatment with surgery and ^{131}I treatment, and in case of development of metastasis with wide spread of the tumour.

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 lenvatinib may be of significant benefit to those affected by the condition. This appears justified based on early clinical data in patients refractory to treatment with ^{131}I. In these patient population, treatment with lenvatinib resulted in a partial response in half of the patients and in stable disease in an additional 40% of patients. This is assumed to translate in a clinically relevant advantage for the patients affected by follicular thyroid cancer.

A positive opinion for lenvatinib, for treatment of follicular thyroid cancer, was adopted by consensus.

2.1.3 For treatment of osteonecrosis of the femoral head - EMA/OD/176/12
[Co-ordinators: K. Westermark / L. Fregonese]

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

Osteonecrosis of the femoral head should be justified as a distinct medical entity or a valid subset or the application should be changed accordingly. The sponsor was invited to justify the restriction of the use of the product in osteonecrosis of the femoral head. This should not be based on a potential envisioned therapeutic indication but on the definition of a subset (distinct aetiologic, histopathological and clinical characteristics) as compared to the broader condition, in this case osteonecrosis. Thus the sponsor should justify why the product would not work outside the proposed subset of osteonecrosis of the femoral head.

- Prevalence

The sponsor should recalculate the prevalence according to the revised condition

In the written response, and during an oral explanation before the Committee on 12 March 2013, the sponsor stressed that the rationale for justifying osteonecrosis of the femoral head as a distinct medical entity or a valid subset, was based on the three-dimensional structure of the investigational medicinal product which was particularly suitable for this specific indication as it can support the mechanical force to promote bone remodelling and avoid collapse. In addition, the sponsor did not recalculate the prevalence of the proposed condition as the indication was not amended, but instead provided further justifications by referring to the number of total hip arthroplasties in the different EU countries.

The Committee considered that the sponsor had not excluded that the product might exert pharmacodynamic effects when used in osteonecrosis outside the proposed location in the femur, and as such the proposed subset limiting the indication to the femoral head would not be valid for the purpose of an orphan indication.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 March 2013, prior to final opinion.

2.1.4 For treatment of neuroendocrine tumours - EMA/OD/185/12
[Co-ordinators: B. Dembowska-Bagińska / 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

The sponsor has proposed that bibliographical data where other types of therapies have been used support the use of their product for treatment of neuroendocrine tumours. The sponsor has not presented any data that they may have generated on their own with their product in the proposed condition. The sponsor was therefore invited to further elaborate on the relevance of using the proposed bibliographical data to support the medical plausibility.

- Prevalence

The sponsor should justify the sources of the prevalence data and describe the methodology used for the prevalence calculation. The sponsor should indicate on which population the prevalence calculation is based on. In this case the COMP would need to see all forms of neuroendocrine tumours as currently defined in current publications. The sponsor was invited to re-calculate the prevalence calculation based on relevant epidemiological studies and registries for the proposed orphan condition in this case is neuroendocrine tumours.

- 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. This is based on extrapolation from bibliographical data with other therapies. The sponsor has not submitted any data of their own which would support the significant benefit with the current therapeutic algorithms and comparison to currently approved therapies in this condition. The sponsor should further elaborate on this.

- Development of Medicinal Product

The sponsor should clarify if the product applied for will be developed, and provide detailed information and update the Committee on the current stage of development of the product.

In the written response, and during an oral explanation via teleconference on 12 March 2013, the sponsor discussed the position of the product in the management of the condition, based on bibliographical references of other products with a similar principle of action, but not with the product proposed for designation. The same level of evidence was proposed to justify the potential of improved efficacy over authorised products in the context of significant benefit. Moreover, with regards to the prevalence calculation, the sponsor discussed the available epidemiological data and provided conclusions for the prevalence of neuroendocrine tumours, based on the Rarecare Technical report. Finally the sponsor briefed the Committee on the current stage of development.

The Committee did not accept the extrapolations proposed by the sponsorfor the justification of significant benefit, since the differences proposed for the product under evaluation are expected to result in a different efficacy and safety profile.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 13 March 2013, prior to final opinion.

2.1.5 For diagnosis of neuroendocrine tumours - EMA/OD/181/12

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

The COMP noted a withdrawal of the application prior to responding to the COMP List of questions adopted at the February meeting.

2.1.6 For treatment of chronic inflammatory demyelinating polyneuropathy - EMA/OD/169/12

[Co-ordinators: H. Metz / 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 the proposed product for the treatment of the proposed condition, the sponsor should further elaborate on the relevance of the in vitro model used for the treatment of chronic inflammatory demyelinating polyneuropathy, and the interpretation of the results obtained in the experiments.

In particular the sponsor has shown that the proposed product abrogates induced CXCL10 expression in Schwann cell cultures. The sponsor is requested to discuss any further available data in relevant models of CIDP or in preliminary clinical settings.

- Justification of significant benefit

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

In the written response, and during an oral explanation before the Committee on 12 March 2013, the sponsor further discussed the relevance of the in vitro model by stressing that Schwann cells and CXCL10 are both key elements in the proposed condition. The sponsor also drew parallels to multiple sclerosis and models of experimental autoimmune encephalitis, while also reported some further anti-inflammatory cellular activityin vitro. With regards to the justification of medical plausibility the sponsor argued based on preliminary clinical data that the expected administration scheme would consist of one monthly infusion, which would compared favourably to the current treatment scheme of every 3 weeks over 2 or 4 days. The sponsor also referred to two past examples of shortages of intravenous immunoglobulins , and discussed that the safety profile has been favourable up to date.

The Committee considered that the observations from the in vitro data provided, could not be extrapolated to draw conclusions for the treatment of patients affected by the proposed condition, because the model used was not a model of the condition as proposed for designation. Moreover, the significant benefit could not be considered justified because the dosing scheme in the condition remains to be determined and the impact of such changes compared to intravenous immunoglobulin were not further discussed and documented. In addition, the safety profile of the product is currently unknown and there were no documented and recurrent shortages in intravenous immunoglobulin that resulted in patients with the condition not having access to the authorised product.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 March 2013, prior to final opinion.

2.1.7 For treatment of epidermolysis bullosa - EMA/OD/180/12

[Co-ordinators: D. Krievins / S. Tsigkos] [Experts: J. Hinchlife, E. Pillay]

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

The proposed mechanism is described in generic terms. None of these claims with regards to the mechanism of action is either specified or supported by any data presented in the application. Whatever more, the sponsor asserts that the product "…has no pharmacological effect in itself". Therefore the proposed mechanism of action remains at least assumptive. The sponsor was invited to

further elaborate whether the proposed product has a mechanical or pharmacological effect mode of action.

In addition, the sponsor was invited to further elaborate on:

- the proposed mechanism of action based on data in relevant models;
- any further available data to support the proof of concept in either preclinical models or preliminary clinical settings.

- Prevalence

The sponsor should justify the sources of the prevalence data and describe the methodology used for the prevalence calculation. A clear overall conclusion is expected for the time the application is made.

In the written response, and during an oral explanation via teleconference on 12 March 2013, the sponsor clarified that the product binds to components of the extracellular matrix and growth factors, protecting them against degradation and allowing them to exert their physiological roles. The sponsor also further discussed the medical plausibility by discussing four clinical cases with epidermolysis bullosa treated with the proposed product and the products' effect over pain and wound size as observed in these patients. With regards to prevalence, the sponsor did not present a final figure as requested, but asserted that based on different approaches the threshold of orphan designation is respected.

The Committee considered that the proposed mechanism of action remained assumptive and incompletely understood, and that non-mechanical aspects might be included in the pharmacodynamics of the product. A major issue was identified in the medical plausibility justification, which was mainly based on four case reports in patients with the proposed condition. The Committee considered that the clinical results observed could not be attributed to the product due to the uncontrolled nature of the treatment, the variability and heterogeneity of the clinical presentation of the condition and its natural course. Optimum wound care might have had the same effects as the ones described, and the absence of information about prior treatments received was also pointed by the Committee as potentially confounding the results . Therefore, the medical plausibility was not considered justified.

The experts appointed by the Committee questioned the clinical results presented by the sponsor and its validity to justify the product's medical plausibility.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 13 March 2013, prior to final opinion.

2.1.8 4-[2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxamide monohydrate for treatment of Glioma, Eli Lilly Nederland B.V. - EMA/OD/170/12

[Co-ordinators: B. Bloechl-Daum / 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

The sponsor was requested to further elaborate on the particulars of the dose escalating phase I study with regards to the population and the results obtained.

- Justification of significant benefit

The justification of significant benefit is based on a novel mechanism of action that may result in improved efficacy as a clinically relevant advantage compared to authorised products.

The sponsor was requested to further elaborate on the clinical data with regards to any previous treatments received by the respondents, as well as to better quantify the observed responses.

In the written response the sponsor provided the information requested by the Committee. It was clarified that the population studied pertained to patients that "have histological or cytological evidence of relapsed malignant glioma (such as glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligodendroglioma) for which no treatment of higher priority exists." The sponsor also described the treatments received, the previous background and the definition of responses seen in the first in human clinical trial as requested. The Committee considered that the observations of clinically relevant responses in glioma patients who have relapsed following treatment with currently available methods can be accepted for the medical plausibility and considered as a clinically relevant advantage for the justification of significant benefit.

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

The intention to treat the condition with the product was considered justified on the grounds of preclinical and preliminary clinical data. In the preclinical data, treatment with the product resulted in inhibition of tumour volume progression in relevant xenotransplantation models. In the preliminary clinical data, treatment of patients with relapsed malignant glioma resulted in clinically relevant responses with regards to tumour size. The condition is chronically debilitating, in particular due to compression and invasion of the surrounding brain structures leading to neurological deficits, and life-threatening with poor overall survival. Survival for glioblastoma multiforme patients is less than 5% at 5 years post diagnosis. The condition was estimated to be affecting approximately 2.2 in 10,000 people in the European Union, at the time the application was made; the Rarecare registry and European epidemiological publications found in the public domain were used to calculate 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 4-[2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxamide monohydrate may be of significant benefit to those affected by the condition. The sponsor has presented preliminary clinical data in glioma patients who have relapsed following treatment with currently available methods. In these patients, the sponsor has reported clinically relevant responses to treatment with regards to tumour size. This might suggest a potentially improved efficacy. The committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 4-[2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxamide monohydrate, for treatment of glioma, was adopted by consensus.

2.1.9 For treatment of Pseudomonas aeruginosa infection in cystic fibrosis - EMA/OD/179/12
[Co-ordinators: J. Eggenhofer / L. Fregonese]

The COMP noted a withdrawal of the application prior to responding to the COMP List of questions adopted at the February meeting.

2.1.10 For treatment of pancreatic cancer - EMA/OD/178/12
[Co-ordinators: B. Bloechl-Daum / S. Tsigkos]

The COMP noted a withdrawal of the application prior to responding to the COMP List of questions adopted at the February meeting.

2.2. For discussion / preparation for an opinion

2.2.1 (S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one for treatment of chronic lymphocytic leukaemia, Voisin Consulting S.A.R.L. - EMA/OD/196/12
[Co-ordinators: B. Bloechl-Daum / S. Tsigkos]

Following review of the application by the Committee, it was agreed to rename the indication to "treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma", in line with the current World Health Organization classification of tumours of haematopoietic and lymphoid tissue.

The Committee agreed that the condition, chronic lymphocytic leukaemia/small lymphocytic lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing (S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one was considered justified based on preliminary clinical data showing partial responses in refractory or relapsed patients affected by the condition. The condition is life-threatening and chronically debilitating due to development of cytopenias (anaemia, neutropenia, and thrombocytopenia), lymphadenopathy, splenomegaly, hepatomegaly and impaired production of normal immunoglobulin leading to increased susceptibility to infections. The condition was estimated to be affecting less than 3.5 in 10,000 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 (S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one may be of significant benefit to those affected by the condition. The sponsor has presented preliminary clinical data showing responses in patients previously relapsed or refractory to available treatments. The Committee considered that this constitutes a clinically relevant advantage.

Post-meeting note:

A positive opinion for (S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one, for treatment of treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma was adopted via written procedure on 20 March 2013.

2.2.2 2-hydroxypropyl-β-cyclodextrin for treatment of Niemann-Pick disease type C, International Niemann-Pick Disease Alliance (INPDA) - EMA/OD/191/12
[Co-ordinators: L. Greene/ G. O'Dea / S. Tsigkos]

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

The intention to treat the condition with the medicinal product containing 2-hydroxypropyl-B-cyclodextrin is considered justified based on preclinical models of the condition, that show that treatment with the product results in improvements in cellular accumulation of cholesterol and

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

The condition was estimated to be affecting approximately 0.1 in 10,000 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 2-hydroxypropyl-β-cyclodextrin may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data of improved survival when the product is used in combination with the authorised treatment. The Committee considered that this could constitute a clinically relevant advantage.

A positive opinion for 2-hydroxypropyl- β-cyclodextrin, for treatment of Niemann-Pick disease, type C, was adopted by consensus.

2.2.3 For treatment of drug-induced ototoxicity - EMA/OD/193/12

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

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

- Medical Condition

Drug-induced ototoxicity should be justified as a distinct medical entity or a valid subset. This should be put within the context of all forms of ototoxicity. There appears to be several classifications of ototoxicity which are conflicting such as the classification presented by the sponsor and the ICD-10 code. This renders interpretation of the condition as a distinct medical entity difficult.

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of the product for treatment of drug-induced ototoxicity, the sponsor should further elaborate on:

- the results obtained in two in vitro cell lines studies to support the medical plausibility of the product in the treatment of drug-induced ototoxicity.

The sponsor should further elaborate on the lack of non-clinical in vivo data to support the medical plausibility of the product in the condition.

- Indication

In view of the mode of action and the condition the sponsor is invited to discuss the use of the product in the prevention of drug-induced ototoxicity. Please make a comparative analysis of the treatment indication versus prevention.

- Prevalence

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. For example the data provided by the four experts that were used may not represent the total population subject of the submission. The sponsor should also further elaborate on the relevance of the hospital admission data used in estimating the prevalence of the condition.

The sponsor should also prepare a prevalence calculation to estimate the prevalence of patients where the product would be used in the prevention of ototoxicity.

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 April meeting

2.2.4 For treatment of Graft versus Host Disease - EMA/OD/197/12
[Co-ordinators: K. Westermark/ D. Meyer / L. Fregonese]

The Committee considered that the prevalence requires clarification by the sponsor. The sponsor is invited to revise this section providing prevalence rather than incidence data, in consideration of the fact that GvHD is considered to include also chronic cases.

The sponsor therefore is invited to take into account in the revised calculation the cases of chronic GvHD, based on the up to date definition of chronic GvHD. The sponsor is invited to support the prevalence calculation with relevant data from registries and from the literature related to allogeneic haematopoietic stem cell transplantation.

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

2.2.5 For treatment of ovarian cancer - EMA/OD/192/12
[Co-ordinators: B. Bloechl-Daum / S. Aarum]

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 product for the treatment of ovarian cancer, the sponsor should further elaborate on the clinical results obtained so far. In particular, more details such as effect size and duration of response with regards to all patients administered with the product in the cited clinical study should be discussed.

The sponsor is also asked to provide an update on the results since the cut-off date of October 2012.

- Justification of significant benefit

The sponsor is requested to further elaborate on the significant benefit. In particular, the sponsor is requested to further elaborate on the consequences of the proposed new mechanism of action and support these consequences by any available data. In addition, the sponsor should further elaborate on the available preliminary clinical data with regards to the features of the population studied including previous and concomitant treatments received

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 April meeting.

2.2.6 For treatment of B-cell acute lymphoblastic leukaemia - EMA/OD/194/12
[Co-ordinators: B. Dembowska-Bagińska / L. Fregonese]

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

- Orphan indication

The COMP has previously designated ALL as a whole rather than B-cell lymphoblastic leukaemia/ lymphoma. The sponsor is invited to revise the indication considering the current WHO classification.

- Prevalence

It seems that the sponsor reported the complete prevalence of all precursor B/T lymphoblastic leukaemia/lymphoblastic lymphoma (including Burkitt leukaemia/lymphoma) rather than ALL. This results in a prevalence estimate of ALL of 3.22 (2.25 for B-ALL) that is much higher than previous designations for this condition by the COMP, and not reflecting the true prevalence of ALL. The sponsor is invited to recalculate the prevalence estimate of the orphan condition as currently defined in the WHO classification

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 April meeting.

2.2.7 For treatment of invasive aspergillosis - EMA/OD/189/12
[Co-ordinators: N. Sypsas / S. Tsigkos]

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

- Medical plausibility

To establish if there exists a scientific rationale with the proposed product as applied for in the treatment of invasive aspergillosis the sponsor is invited to elaborate on the choice of the preclinical in vivo model used and its relevance to the condition as applied for designation, as well as to discuss in detail the results obtained in this model.

- Justification of significant benefit

The arguments on significant benefit are mainly based on the formulation, antifungal spectrum and safety profile in comparison to other azoles. The sponsor is requested to further elaborate on these claims by providing:

- any available data showing effects of the product as proposed for designation in aspergillus strains resistant to voriconazole;

- any data to support serious and documented limitations with the current formulations of azoles, including data showing that these can be overcome by the proposed formulation; it is important to consolidate and quantify the proposed limitations;

- data clarifying the conversion of the product as proposed for designation to the active moiety and discussing the potential effects of the by-products of the conversion;

- a comparison of the safety profile of the product versus azoles and in particular voriconazole, including the currently described adverse reaction profile. 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 that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the April meeting.

2.2.8 For treatment of zygomycosis/mucormycosis - EMA/OD/190/12
[Co-ordinators: S. Thorsteinsson / S. Tsigkos]

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

- Proposed indication

The sponsor should revise the proposed indication to "treatment of mucormycosis".

- Medical Plausibility

In order to justify the intention to treat the mucormycosis, the sponsor is requested to further elaborate on the preclinical in vitro data presented in the application. In particular, the sponsor should comment on the levels of the minimal inhibitory concentrations as observed, and discuss the clinical relevance of these observations.

The sponsor is also requested to comment on the absence of any relevant preclinical in vivo models for the proposed indication as applied for.

- Justification of significant benefit

The arguments on significant benefit are based on the alternative mechanism of action and the formulation of the product.

The sponsor is requested to further discuss the profile of the product versus authorised amphotericin with regards to: a) the clinical consequences of the alternative mechanism of action, b) the potential efficacy of the product versus amphotericin B, c) a comparison of safety, d) document any serious limitations with amphotericin-B formulations and how this compares to the formulation of the proposed 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 April meeting.

2.2.9 For treatment of Non Dystrophic Myotonia - EMA/OD/182/12
[Co-ordinators: V. Stoyanova / S. Mariz]

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

- Medical condition

Non-dystrophic myotonia should be justified as a distinct medical entity or a valid subset. The proposed condition submitted by the sponsor appears to be at variance with other descriptions of myotonia and the ICD-10 classification. The sponsor should further elaborate on similarities and differences of their definition of the condition with other classifications of myotonia.

- Life-threatening and debilitating nature of the condition

The sponsor should further elaborate on the life-threatening or chronically debilitating nature of the condition. From the data provided and the sponsor's arguments it is not well substantiated that the condition can be defined as being life-threatening or chronically debilitating.

- Medical Plausibility

The sponsor should further elaborate on the relevance of the bibliographical data submitted as this is in a variety of different myotonic conditions and how this can be extrapolated to the proposed condition.

Post meeting note:

Due to lack of the quorum the COMP adopted a list of issues via written procedure on 21 March 2013. The sponsor will be invited to an oral explanation before the Committee at the April meeting.

2.2.10 For treatment of adrenocortical carcinoma - EMA/OD/195/12
[Co-ordinators: B. Dembowska-Bagińska / S. Mariz]

The Committee considered that the justification of significant benefit issue requires clarification by the sponsor. The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. The sponsor should further elaborate on how the product will bring significant benefit within the context of the current standard of care for this 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 April meeting.

2.2.11 Nintedanib for treatment of idiopathic pulmonary fibrosis, Boehringer Ingelheim International GmbH - EMA/OD/186/12
[Co-ordinators: V. Saano / L. Fregonese]

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

The intention to treat the condition with the medicinal product containing nintedanib was considered justified based on data showing activity on fibroblast cells and in preclinical models of lung fibrosis. Furthermore the intention to treat the condition was supported by early clinical data showing improvement of lung function and quality of life, and reduction of exacerbations in patients affected by idiopathic pulmonary fibrosis. The condition is chronically debilitating due to progressive dyspnoea and loss of lung ventilator function, heavily limiting exercise capability and decreased quality of life of the affected patients and leading in many cases within months or a few years to the need of oxygen therapy. Pulmonary hypertension usually develops. Median survival is less than five years. Death ultimately occurs due to respiratory failure. The condition was estimated to be affecting not more than 3 in 10,000 people in the European Union, at the time the application was made. The conclusions of the sponsor were based on an extensive literature search.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing nintedanib may be of significant benefit to those affected by the condition. The sponsor has provided Phase II proof of concept clinical data showing improvement of the primary endpoint of lung function. Even with the limitations of the early phase of this trial, the extent of the improvement of lung function obtained with nintedanib within 52 weeks appears to be not inferior to the one induced by pirfenidone within 72 weeks, as assessed with indirect comparisons. In addition nintedanib showed significant reduction of exacerbations, and improvement in quality of life of patients affected by IPF. The Committee considered that this constitutes a valid assumption of improved clinical efficacy with the potential to translate into a clinically relevant advantage for the patients affected by the condition.

A positive opinion for nintedanib, for treatment of idiopathic pulmonary fibrosis, was adopted by consensus.

2.2.12 For treatment of polycythemia vera - EMA/OD/188/12
[Co-ordinators: L. Gramstad / S. Aarum]

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

- Medical plausibility

In the application, the sponsor has provided data in primary and secondary myelofibrosis, including post polycythaemia vera myelofibrosis. Nevertheless, the applicability of these results to the applied indication has not been adequately justified.

Therefore, to establish correctly if there exists a scientific rationale for the development of the product for treatment of polycythemia vera, the sponsor should further elaborate on:

- the relevance of the preclinical models used for the treatment of polycythaemia vera, since the provided data are mainly focused on myelofibrosis. The sponsor should also clarify how the preclinical results obtained are relevant for the treatment of patients with polycythaemia, and not only for myelofibrosis;

- the details and results of the patients with polycythaemia vera administered the product, if such data are available.

- Justification of significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potentially improved efficacy especially in patients who are resistant or intolerant to hydroxyurea.

The sponsor should provide more details on the natural history and size of this polycythaemia vera patient subgroup.

The sponsor is further requested to elaborate on the arguments provided for the justification of significant benefit for the polycythaemia vera patients being resistant or intolerant to hydroxyurea, as well as to discuss the possible assumptions of significant benefit for other patients with polycythaemia vera. This discussion should be supported by available data, as far as possible

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 April meeting.

2.2.13 For treatment of hepatocellular carcinoma - EMA/OD/187/12
[Co-ordinators: D. O'Connor / S. Mariz]

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

- Medical plausibility

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

- the relevance of the results of the two preclinical studies in supporting the medical plausibility in hepatocellular carcinoma;

- the relevance of the preliminary clinical findings from the on-going clinical study in patients with hepatocellular carcinoma.

- Prevalence

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

- Justification of significant benefit

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

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 April meeting.

2.2.14 R,S-O-(3-piperidino-2-hydroxy-1-propyl)-nicotinic acid amidoxime dihydrochloride

for treatment of Duchenne muscular dystrophy, N-GENE Kutatási és Fejlesztési Kf - EMA/OD/183/12
[Co-ordinators: P. Evers / L. Fregonese]

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 R,S-O-(3-piperidino-2-hydroxy-1-propyl)-nicotinic acid amidoxime dihydrochloride was considered justified based on data in relevant preclinical models showing improvement of the dystrophic pathophysiology in both limb and diaphragm muscles, together with improved muscle architecture, whole body strength, and contractile function. In the same studies administration of the product reduced kyphosis and prolonged survival of 27% on average. The condition is chronically debilitating and life-threatening due to progressive muscle weakness with loss of function of voluntary muscles. All voluntary muscles are affected including legs, arms and trunk, and most children affected by Duchenne muscular dystrophy will need a wheel chair before 12 years of age. Respiratory muscles deteriorate also resulting in a forced vital capacity of the lungs less than 25% of normal values, requiring ventilation support. Without ventilation support, a median survival age of 19 years has been reported. Death occurs at median age of 25 years, usually due to respiratory or cardiac failure. The condition was estimated to be affecting approximately 0.3 in 10,000 people in the European Union, at the time the application was made; the estimate of prevalence was based on an extensive literature search and on available registry data from a number of regions in the EU.

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 R,S-O-(3-piperidino-2-hydroxy-1-propyl)-nicotinic acid amidoxime dihydrochloride, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

2.3. Evaluation on-going

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

2.4. Validation on-going

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

3. Requests for protocol assistance

The Committee was briefed on significant benefit issues and adopted the protocol assistance letters for three products with the following indications:

3.1 For prophylaxis and treatment of bleeding episodes in patients with haemophilia A

3.2 For single-agent treatment of advanced gastric adenocarcinoma and -for treatment of advanced gastric adenocarcinoma

3.3 For treatment of ovarian cancer

4. Overview of applications

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

COMP co-ordinators were appointed for two applications submitted and twenty seven 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 Pheburane (Sodium phenylbutyrate); Lucane Pharma, [Co-ordinators: J. Torrent-Farnell / S. Tsigkos]
- for treatment of citrullinaemia type 1 (EU/3/12/949)

- for treatment of ornithine transcarbamylase deficiency (EU/3/12/950)

- for treatment carbamoyl-phosphate synthase-1 deficiency (EU/3/12/951)

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

- Prevalence

The sponsor is asked to provide an update of the prevalence estimates of the three conditions subject to the review of the criteria for orphan designation. In the report submitted by the Sponsor to justify the maintenance of the orphan designation criteria the sponsor presents different estimates to the ones supporting orphan designation without any justification.

- Justification of significant benefit

At the time of the orphan drug designation, the Committee commented in the summary report that:

"..., a significant benefit can be assumed at this orphan designation stage, but the sponsor would have to substantiate this assumption with further data addressing the further clinical consequences (e.g. show improved compliance) stemming from this assumed improved palatability. Therefore it has to be strongly recommended to apply for Protocol Assistance in particular with regards to the significant benefit issues".

In its report on the maintenance of the criteria at the marketing authorisation stage the sponsor has provided data to support that:

1) the new formulation has improved palatability over the currently authorised form of phenylbutyrate

2) there are difficulties in administering the currently authorised form of phenylbutyrate to patients

Nevertheless, the sponsor has not provided data to document that the improved palatability of a new formulation of sodium phenylbutyrate is directly linked to an improvement in treatment compliance.

Without objective data confirming the improved compliance with the new formulation, the Committee cannot evaluate if Pheburane provides a major contribution to patient care. The sponsor is invited to provide any available data to justify an improved compliance

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 April meeting.

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

5.2.1 Defitelio (Defibrotide); Gentium S.p.A. [Co-ordinators: J. Torrent-Farnell / S. Mariz]

- prevention of hepatic veno-occlusive disease (EU/3/04/211)
- treatment of hepatic veno-occlusive disease (EU/3/04/212)

5.3. On-going procedures

5.3.1 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)

5.3.2 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)

5.3.3 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)

5.3.4 Cysteamine bitartrate [Cysteamine bitartrate (gastroresistant)] for treatment of cystinosis; Raptor Pharmaceuticals Europe B.V. (EU/3/10/778)

5.3.5 Delamanid ((R)-2-Methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-b]oxazole) for treatment of tuberculosis; Otsuka Novel Products GmbH (EU/3/07/524)

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

5.3.7 Exjade (4-(3,5-bis(hydroxy-phenyl)-1,2,4) triazol-1-yl) benzoic acid) for treatment of chronic iron overload requiring chelation therapy; Novartis Europharm Limited (OD/061/01, EU/3/02/092)
Type II variation - for the treatment of chronic iron overload due to blood transfusions in patients with beta thalassaemia major aged 6 years and older.

5.3.8 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)

5.3.9 Iclusig (benzamide, 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl]-); ARIAD Pharma Ltd

- treatment of chronic myeloid leukaemia (EU/3/09/716)
- treatment of acute lymphoblastic leukaemia (EU/3/09/715)

5.3.10 Kinaction (Masitinib mesilate) for treatment of pancreatic cancer; AB Science (EU/3/09/684)

5.3.11 Masican N-(methyl-diazacyclohexyl-methylbenzamide)-azaphenyl-aminothiopyrrole for treatment of malignant gastrointestinal stromal tumours; AB Science (EU/3/04/251)

5.3.12 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)

5.3.13 Opsumit (Macitentan) for treatment of pulmonary arterial hypertension; Actelion Registration Ltd. (EU/3/11/909)

5.3.14 PAS-GR (Para-aminosalicylic acid) for treatment of tuberculosis; Lucane Pharma SA (EU/3/10/826)

5.3.15 Pomalidomide Celgene (Pomalidomide) for treatment of multiple myeloma; Celgene Europe Ltd. (EU/3/09/672)

5.3.16 Revlimid (3-(4'aminoisoindoline-1'-one)-1-piperidine-2,6-dione) for treatment of myelodysplastic syndromes; Celgene Europe Limited – UK (EU/3/04/192)
Type II variation - new indication for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without other cytogenetic abnormalities.

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

5.3.18 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)

5.3.19 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)

5.3.20 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)

5.3.21 Vantobra, Tobramycin (inhalation use) for treatment of Pseudomonas Aeruginosa lung infection in cystic fibrosis; PARI Pharma GmbH (EU/3/09/613).

5.4. COMP opinions adopted via written procedure following previous meeting

5.4.1 Bosulif (Bosutinib) for treatment of chronic myeloid leukaemia; Pfizer Limited (OD/160/09, EU/3/10/762) [Co-ordinators: K. Kubackova / S. Tsigkos]

6. Procedural aspects

6.1 European Medicines Agency Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (PCWP)

- Meetings documents

7. Any other business

7.1 COMP Informal meeting on 28 February - 1 March 2013 in Dublin

7.2 Overview articles on the EMA's scientific committees

- Article on the COMP

7.3 Question on cardiotrohpin-1 product classification

7.4 COMP Work Programme 2013-2015

The Committee adopted the Work Programme for 2013-2015.

Date of next COMP meeting: 16 - 17 April 2013

List of participants

Chair:

Bruno Sepodes

Vice-Chair:

Lesley Greene	Volunteer patient representative for Eurordis

COMP Members:

André Lhoir	België/Belgique/Belgien
Irena Bradinova	България
Dorthe Meyer	Danmark
Vacant	Deutschland
Vallo Tillmann	Eesti
Geraldine O'Dea	Éire/Ireland
Nikolaos Sypsas	Ελλάδα
Josep Torrent Farnell	España
Sigurdur B. Thorsteinsson	Iceland
Armando Magrelli	Italia
Ioannis Kkolos	Κύπρος
Aušra Matulevičienė	Lietuva (present on 2nd day only)
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	Romãnia
Martin Možina	Slovenija
Vacant	Slovensko
Veijo Saano	Suomi/Finland
Kerstin Westermark	Sverige
Daniel O'Connor	United Kingdom
Birthe Byskov Holm	Volunteer patient representative for Eurordis
Pauline Evers	Patient representative representing the European Genetic Alliances Network
János Borvendég	CHMP Representative
Aikaterini Moraiti	CHMP Representative
Vacant	EMA Representative

Observers:

Maria Mavris	Eurordis

Experts:

James Hinchcliffe and Elizabeth Pillay	for agenda point 2.1.8

EMA:

Jordi Llinares Garcia	Head of Orphan Medicines
Stiina Aarum	Scientific Administrator
Laura Fregonese	Scientific Administrator
Segundo Mariz	Scientific Administrator
Stylianos Tsigkos	Scientific Administrator
Frederique Dubois	Assistant
Agnieszka Wilk-Kachlicka	Assistant

Apologies

Members:

Kateřina Kubáčková	Česká Republika
Annie Lorence	France
Dainis Krievins	Latvija

Observers:

Antonio Blazquez	Agencia Española de Medicamentos y Productos Sanitarios
Vesna Osrecki	Croatia

European Commission:

Agnès Mathieu	DG Health and Consumers