29 May 2013
EMA/COMP/165816/2013
Human Medicines Development and Evaluation

# Committee for Orphan Medicinal Products (COMP)

Minutes of the 16 - 17 April 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




7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
**Telephone** +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
**E-mail** info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union



© European Medicines Agency, 2013. Reproduction is authorised provided the source is acknowledged.

# 1. Introduction

**1.1** Adoption of the agenda, EMA/COMP/163412/2013

The agenda was adopted with no amendments.

**1.2** Adoption of the minutes of the previous meeting, 12 - 13 March 2013 EMA/COMP/83433/2013

The minutes were adopted.

**1.3** Conflicts of Interest

The Chair asked the Committee members to declare their potential conflict of interest. K. Kubackova declared potential conflict of interest for agenda point 2.1.2.

# 2. Applications for orphan medicinal product designation[1]

## 2.1. For opinion

**2.1.1** For treatment of drug-induced ototoxicity - EMA/OD/193/12
*[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 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.

[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 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.

In the written response, and during an oral explanation before the Committee on 16 April 2013, the sponsor defended its position on the condition being a distinct medical entity, by elaborating on the differences between drug-induced ototoxicity and occupational ototoxicity, as well as by discussing the available classification systems. With regards to the medical plausibility issue the sponsor discussed preclinical data in three models arguing on a) up-regulation of neurotrophic factors in vitro in Corti organ cells b) reduction of in vitro cisplatin-induced cell death in neuroblastoma cells c) promotion of transcription and expression of neurotrophin-related genes and increase in transcription of Bcl/Bax ratio in a preclinical model of Parkinson's disease. With regards to the potential use as a prevention treatment, the sponsor commented that the intra-tympanic administration would result of the product being more suitable for treatment in the clinical and not in prevention settings. Finally, the sponsor referred to databases and expert testimonies, who were surveyed about the epidemiology of the condition, in order to justify that the prevalence criterion was met.

The committee considered that data to justify the medical plausibility were limited pertaining mainly to the in vitro model of a neuroblastoma cell line. The committee noted that the settings in this model were relevant to prevention and not treatment, as the product was adminsitered prior to challenge by cisplatin. In addition, the other two models presented were not models of the condition as proposed for desigantion. Therefore the intention to treat the proposed condiiton as applied for desigantion could not be considered acceptable.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 17 April 2013, prior to final opinion.

### **2.1.2** For treatment of ovarian cancer - EMA/OD/192/12

*[Co-ordinators: B. Bloechl-Daum / 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 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 was also asked to provide an update on the results since the cut-off date.

- Justification of significant benefit

The sponsor was requested to further elaborate on the significant benefit. In particular, the sponsor was 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.

In the written response, and during an oral explanation before the Committee on 16 April 2013, the sponsor discussed updated data from the on-going uncontrolled open label phase 1 study in patients affected by the proposed condition, as requested by the committee. The primary endpoint studied was safety and toxicity of the product based on the laboratory analysis of blood samples and occurrence of adverse events, while the secondary endpoint was to determine the immunological response following administration, by induction of tumour-specific T-cell response. Based on this study, the sponsor argued increased levels of tumour-antigen specific T-cells in treated patients.

The sponsor also presented one case study in a patient with the proposed condition, after surgery and receiving chemotherapy. It was reported that the patient became again sensitive to chemotherapy and as per the imaging evaluation the disease remained stable. Cancer antigen-125 levels from this patient were also presented and argued to fluctuate close to the normal levels, and increased levels of tumour-specific T-cells were also reported.

The Committee considered that it is difficult to draw conclusions on any effects of the product based on the uncontrolled nature of the studies presented, the concomitant use of chemotherapy and the assumptive mechanism of action. Hence, the intention to treat the condition and the clinically relevant advantage versus authorised treatments for the condition was not considered justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 17 April 2013, prior to final opinion.

### 2.1.3 **Mexiletine Hydrochloride** for treatment of Non Dystrophic Myotonia, Prof Michael Hanna - EMA/OD/182/12

*[Co-ordinators: V. Stoyanova / 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 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.

In the written response, and during an oral explanation before the Committee on 16 April 2013, the sponsor argued that all experts in this field including several national expert groups (including the World Muscle Society, the British Myology Society, the USA Muscle study group and the UK MRC Centre for Neuromuscular Diseases) agree that non-dystrophic myotonia encompasses three myotonic disorders, namely Myotonia congenita (caused by mutations in the chloride channel gene CLCN1), Paramyotonia congenita (caused by mutations muscle sodium channel gene SCN4A) and Sodium channel myotonia. The sponsor also defended the chronically debilitating nature of the condition on the grounds of severe muscle stiffness and pain, resulting in disability. Moreover, the sponsor elaborated on the relevance of the available bibliographic data to support the medical plausibility, and focused on a double-blind placebo controlled randomized clinical trial conducted in patients with non-dystrophic myotonia which showed statistically significant effects in this group of patients.

The Committee agreed that the condition, non-dystrophic myotonia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing mexiletine hydrochloride was considered justified based on preliminary clinical data. 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 1 in 10,000 people in the European Union, at the time the application was made; this was based on a literature search.

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 sponsor has provided argumentation that there was a lack of supply of the product in Europe and that being able to meet this shortfall would be a major contribution to patient care as the basis for significant benefit. The Committee considered that this constitutes a major contribution to patient care.

A positive opinion for mexiletine hydrochloride, for treatment of non-dystrophic myotonia, was adopted by consensus.

### 2.1.4 N-[2,6-bis(1-methylethyl)phenyl]-N'-[[1-[4-(dimethylamino) phenyl]cyclopentyl]methyl]urea, hydrochloride salt

**N-[2,6-bis(1-methylethyl)phenyl]-N'-[[1-[4-(dimethylamino) phenyl]cyclopentyl]methyl]urea, hydrochloride salt** for treatment of adrenocortical carcinoma, Atterocor Ltd - EMA/OD/195/12
*[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 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.

In the written response, and during an oral explanation before the Committee on 16 April 2013, the sponsor discussed the available in vitro and in vivo data for the proposed product as applied for designation, including studies with human adrenocortical carcinoma xenograft models. The sponsor also provided an indirect comparative discussion of those effects versus published data pertaining to the authorized treatment in the same model.

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

The intention to treat the condition with the medicinal product containing N-[2,6-bis(1-methylethyl)phenyl]-N'-[[1-[4-(dimethylamino) phenyl]cyclopentyl]methyl]urea, hydrochloride salt was considered justified based on pre-clinical data in valid models which showed a reduction of tumour size following treatment with the proposed product. The condition is life-threatening due a median survival between 13 months and 29.5 months. The condition was estimated to be affecting approximately 0.9 in 10,000 people in the European Union, at the time the application was made;

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 N-[2,6-bis(1-methylethyl)phenyl]-N'-[[1-[4-(dimethylamino)-phenyl]cyclopentyl]methyl]urea, hydrochloride salt may be of significant benefit to those affected by the condition. The sponsor has provided relevant preclinical models in the target condition showing effective tumour reduction with the proposed product. This supports the potential effects of a different mode of action to mitotane and therefore offers the potential of another therapy in the condition.

A positive opinion for N-[2,6-bis(1-methylethyl)phenyl]-N'-[[1-[4-(dimethylamino) phenyl]cyclopentyl]methyl]urea, hydrochloride salt, for treatment of adrenocortical carcinoma, was adopted by consensus.

### **2.1.5** For treatment of invasive aspergillosis - EMA/OD/189/12

*[Co-ordinators: N. Sypsas / 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 if there exists a scientific rationale with the proposed product as applied for in the treatment of invasive aspergillosis the sponsor was 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. The sponsor was 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 currently available products, 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.

In the written response, and during an oral explanation before the Committee on 16 April 2013, the sponsor further elaborated on the requested issues.

With regards to the medical plausibility, the sponsor announced that more in vivo studies were on-going and discussed a)preliminary data in a non-neutropenic preclinical model, showing improved survival compared to controls; b) preliminary data from a non-neutropenic preclinical model of pulmonary aspergillosis claiming a correlation between AUC/MIC ratio and the lung fungal burden as assessed by quantitative PCR in tissue homogenate; c) asserted that further research was being conducted but no data is yet available from an invasive pulmonary aspergillosis preclinical model.

With regards to the significant benefit, the sponsor referred to literature data on the in vitro effects of the product. The sponsor also reiterated the known limitations of other antifungal products (such as variability of exposure after per os administration resulting in supra- or sub-optimal exposure, interaction with food, need for cyclodextrin in intravenous formulations that presents limitations for use in impaired kidney function patients). In the antipode the sponsor proposed that per os administration of the proposed product results in high bioavailability, that the plasma exposure is linear with dose, and that there is no influence of food. Moreover, a direct discussion on safety based on a clinical phase 2 study for the proposed product in another indication versus fluconazole was provided.

The committee considered that at this point in time there are no data in either a valid preclinical model or preliminary clinical settings in the condition as applied for designation that could be considered as acceptable to justify the medical plausibility. In addition, a comparative data based discussion versus voriconazole, the authorised standard of care for the proposed condition, had not been provided as requested for the purpose of justifying significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 16 April 2013, prior to final opinion.

### **2.1.6** For treatment of zygomycosis/mucormycosis - EMA/OD/190/12

*[Co-ordinators: S. Thorsteinsson / 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 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 was 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 was 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.

In the written response, and during an oral explanation before the Committee on 16 April 2013, the sponsor with regards to medical plausibility acknowledged on the one hand that the MICs against mucorales are high, but at the same time discussed that the situation is different if pharmacokinetic considerations are also taken in to account, as the AUC/MIC might be better. The absence of in vivo studies was also acknowledged, but the sponsor reported on-going work in two preclinical models that were nevertheless not available for evaluation.

With regards to the significant benefit, the sponsor reiterated the two different mechanisms of action and stressed the known limitations of the effects of the authorised product with high treatment failure and mortality rates. As per the claim of improved efficacy, a single case report was also presented based on a meeting poster which described the use of the product in a patient with AML that had presented amphotericin-related potassium depletion. The case reported a reduction in the size of brain and lung lesions in this patient who was treated with the compound before he died from AML, as well as resolution of skin lesions. As per the claim of safety, the sponsor described some potential advantages against antifungal products that were not authorised for the proposed condition and with regards to the proposed formulation, the sponsor described the need for reconstitution and Iv aseptic infusion for amphotericin, while the proposed product has also the potential to be administered orally.

The committee considered that there is an absence of data in either a relevant model or in preliminary clinical settings, with the most relevant data pertaining to one case report which was inconclusive as the patient never cleared the infection and died from the underlying condition. In absence of data in relevant preclinical models or preliminary clinical settings, the medical plausibility may not be considered acceptable, nor the clinically relevant advantage or a major contribution to patient care versus the authorised counterpart be accepted.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 16 April 2013, prior to final opinion.

### **2.1.7** For treatment of hepatocellular carcinoma - EMA/OD/187/12

*[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 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.

In the written response, and during an oral explanation before the Committee on 17 April 2013, the sponsor discussed the effects of the product in combination with sorafenib, in a preclinical model of hepatocellular carcinoma with regards to tumour volume and hepatic biochemistry endpoints. The sponsor also presented preliminary clinical data from a phase 1 study in patients with primary and secondary liver tumours. In that study, it was discussed that three of the included patients were affected by the condition applied for designation and one patient achieved stable disease. With regards to the prevalence, the sponsor further elaborated and referred to data from the European Society Medical Oncology and the European Congress of Oncology. With regards to the significant benefit, the sponsor defended a clinically relevant advantage based on a novel mechanism of action that may allow for improved efficacy when used in combination with authorised treatments for the condition.

The Committee considered that the effects described in the preclinical model were not significant in particular with regards to tumour volume, and that the preliminary clinical data did not confirm any responses in patients affected by the condition. Therefore the intention to treat and the significant benefit arguments could not be considered acceptable.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 17 April 2013, prior to final opinion.

### **2.1.8** For treatment of polycythaemia vera - EMA/OD/188/12

*[Co-ordinators: L. Gramstad / 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

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 polycythaemia 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 was 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.

In the written response, and during an oral explanation before the Committee on 17 April 2013, the sponsor further elaborated on the issues of medical plausibility and significant benefit.

With regards to the medical plausibility, the sponsor defended the validity of the preclinical models used in the application, on the grounds that they recapitulate the hallmark mutation present in the proposed condition and emulate the phenotype of polycythaemia vera, with reference to increased haematocrit, splenomegaly and extramedullary erythropoiesis. The sponsor also discussed preliminary clinical data from a phase II study in treated patients affected by myelofibrosis and reported that about a third of the population included were diagnosed with myelofibrosis secondary to polycythaemia vera. The sponsor argued that the results in this subgroup were similar to the overall population with regards to the spleen size, and a decrease of about 40% after 6 months of oral treatment with the product had been observed. At the same time the sponsor reported that data from another phase 2 study in patients with polycythaemia vera and essential thrombocytosis were not yet available as regards to efficacy. Commenting on the issue of significant benefit, the sponsor provided a definition of patients with polycythaemia vera that are resistant or intolerant to hydroxyurea, and drew parallels from the published effects of another product with a similar mechanism of action in this population. Finally, the sponsor also commented on the paucity of epidemiological data, in order to justify the methodology used in its application.

The Committee considered that observations regarding the effects of the product in patients with myelofibrosis associated with myeloproliferative neoplasms such as polycythaemia vera, cannot be easily extrapolated to draw conclusions for the treatment polycythaemia vera as such. The Committee considered that in the absence of data in the proposed condition as applied for designation, the intention to treat the condition and the justification of significant benefit may not be considered acceptable.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 17 April 2013, prior to final opinion.

### 2.1.9 **Inotuzumab ozogamicin** for treatment of B-cell acute lymphoblastic leukaemia, Pfizer Limited - EMA/OD/194/12

*[Co-ordinators: B. Dembowska-Bagińska / 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 COMP has previously designated ALL as a whole rather than B-cell lymphoblastic leukaemia/ lymphoma. The sponsor was 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 was invited to recalculate the prevalence estimate of the orphan condition as currently defined in the WHO classification.

In the written response, and during an oral explanation before the Committee on 17 April 2013, the sponsor discussed the World Health Organization classification of precursor lymphoid neoplasms, to the end of discerning B-cell from T-cell neoplasms. The sponsor also defended the proposed indication as applied for designation on the grounds of the mechanism of action of the product which targets CD22, which is expressed only on B-cells and not on normal T-cells or T-cell malignancies. With regards to the requested prevalence revision, an amended calculation of the prevalence of ALL and B-cell ALL was presented to the Committee, based on the EU 5 year-prevalence data of leukaemia derived from the GLOBOCAN database.

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

The intention to treat the condition with the medicinal product containing inotuzumab ozogamicin was considered justified based on pre-clinical studies showing selective inhibition of the growth of leukemic cell lines expressing CD22, the main target of the product which, after binding on the cell surface of B cells induces cell death through the cytotoxic calicheamicin. In addition the plausibility is supported by the demonstration of tumour regression and cure in models of disseminated leukaemia and by early clinical data on patients not responding to previous treatment.

The condition is chronically debilitating and/or life-threatening depending on the response to treatment, with acute leukemic forms being fatal in a few weeks if left untreated. The main manifestations of the disease such as persistent fever, infections, anaemia, fatigue, breathlessness, bone and joint pain, are linked to invasion by the tumour cells of the bloodstream, the bone marrow and/or the lymphnodes and other lymphatic organs, resulting in lack of normal blood cells, bone marrow failure, and specific organ damage. The condition was estimated to be affecting approximately 0.4 in 10,000 people in the European Union, at the time the application was made.

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 inotuzumab ozogamicin may be of significant benefit to those affected by the condition. The selectivity for B cells, due to the restricted expression of CD22 on B cells, offers the potential to eliminate only the cells responsible for the leukaemia while sparing normal cells of the immune system. The preliminary clinical data presented by the sponsor showed favourable responses in B-cell acute lymphoblastic leukaemia patients pre-treated with several different antineoplastic regimens. The above indicates the possibility to use the product in forms of the condition which are resistant and/or relapsing to currently authorised treatments and to direct the treatment specifically to B-cells. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by B-cell acute lymphoblastic leukaemia.

A positive opinion for inotuzumab ozogamicin, for treatment of B-cell acute lymphoblastic leukaemia, was adopted by consensus.

**2.1.10 Allogeneic bone marrow derived mesenchymal cells expanded ex vivo in synthetic media** for treatment of Graft versus Host Disease, Cell2B Advanced Therapeutics, SA - EMA/OD/197/12

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

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The Committee considered that the prevalence requires clarification by the sponsor. The sponsor was 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 was 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 was invited to support the prevalence calculation with relevant data from registries and from the literature related to allogeneic haematopoietic stem cell transplantation.

In the written response, the sponsor provided an amended prevalence calculation. Since there were no available compiled data on the incidence and prevalence of GvHD, the sponsor estimated these parameters using a model based on the number of BMT and published estimates of the percentage of GvHD associated with BMT.

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

The intention to treat the condition with the medicinal product containing allogeneic bone marrow derived mesenchymal cells expanded *ex vivo* in synthetic media was considered justified based on preliminary clinical evidence from the scientific literature, supported by sponsor-generated data in the form of a small case series showing complete response with the proposed treatment in two out of three cases affected by corticosteroid-resistant graft versus host disease.

The condition is chronically debilitating or life-threatening depending on the severity and the response to treatment with corticosteroids and other immunosuppressive agents. The acute forms are characterized mainly by severe intestinal inflammation with diarrhoea, abdominal pain, nausea and vomiting. Severe skin rash is also present, and damage to the mucosa. In the chronic forms also connective tissue and exocrine glands can be affected. Severe infection can occur due to the immunosuppressive agents currently used for the treatment of the condition. Mortality from graft versus host disease can reach 100% in the severe forms non-responding to immunosuppressive treatment. The condition was estimated to be affecting not more than 0.6 in 10,000 people in the EU, at the time the application was made. The prevalence estimate included both acute and chronic forms of graft versus host disease. The calculation was based on a literature search and international databases.

Although satisfactory methods of treatment of the condition have been authorised in the EU, the sponsor has provided sufficient justification for the assumption that the medicinal product containing allogeneic bone marrow derived mesenchymal cells expanded *ex vivo* in synthetic media may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing complete response to the proposed treatment in two out of three subjects who had not responded to the currently authorized immunosuppressant treatment methods. This could translate into a clinically relevant advantage for those subjects affected by the condition who do not respond to the currently authorized treatment methods, if the efficacy of the proposed product is confirmed in larger studies.

A positive opinion for allogeneic bone marrow derived mesenchymal cells expanded *ex vivo* in synthetic media, for treatment of graft-versus-host disease, was adopted by consensus.

## 2.2. For discussion / preparation for an opinion

**2.2.1** For treatment of Alagille syndrome - EMA/OD/007/13
*[Co-ordinators: A. Corrêa Nunes / 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 Alagille syndrome, the sponsor should further elaborate on:

- the relevance of pruritus in the clinical presentation of patients affected by the proposed condition

- the use of serum bile acid levels as a clinical surrogate for cholestatic pruritus

- the absence of any data in either preclinical models or clinical settings in the condition as proposed for designation

- the extent of the clinical effect in the serum concentration by providing further data, as so far there is only a trend of reduction and an absence of a dose-response effect in the data discussed.

- the relevance of the observed effects in serum concentration of bile acids in healthy volunteers for the treatment of pruritus in patients with the proposed condition as applied for designation.

- Prevalence

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

The sponsor should justify in detail the grounds on which the proposed prevalence has been calculated.

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 May meeting.

**2.2.2** For treatment of primary sclerosing cholangitis - EMA/OD/008/13
*[Co-ordinators: A. Corrêa Nunes / S. Tsigkos]*

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

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

- Medical plausibility

- the relevance of pruritus in the clinical presentation of patients affected by the proposed condition

- the use of serum bile acid levels as a clinical surrogate for cholestatic pruritus

- the absence of any data in either preclinical models or clinical settings in the condition as proposed for designation

- the extent of the clinical effect in the serum concentration by providing further data, as so far there is only a trend of reduction and an absence of a dose-response effect in the data discussed

- the relevance of the observed effects in serum concentration of bile acids in healthy volunteers for the treatment of pruritus in patients with the proposed condition as applied for designation.

- Justification of significant benefit

The sponsor is requested to provide a comparative discussion vis a vis any authorised counterparts for the proposed condition as applied for designation in the EU, including ursodeoxycholic acid.

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 May meeting.

**2.2.3** For treatment of primary biliary cirrhosis - EMA/OD/010/13
*[Co-ordinators: A. Corrêa Nunes / 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 primary biliary cirrhosis, the sponsor should further elaborate on:

- the relevance of pruritus in the clinical presentation of patients affected by the proposed condition

- the use of serum bile acid levels as a clinical surrogate for cholestatic pruritus

- the absence of any data in either preclinical models or clinical settings in the condition as proposed for designation

- the extent of the clinical effect in the serum concentration by providing further data, as so far there is only a trend of reduction and an absence of a dose-response effect in the data discussed

- the relevance of the observed effects in serum concentration of bile acids in healthy volunteers for the treatment of pruritus in patients with the proposed condition as applied for designation.

- Justification of significant benefit

The sponsor is requested to provide a comparative discussion in particular with regards to the authorised counterparts for the proposed condition as applied for designation.

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 May meeting.

**2.2.4** For treatment of progressive familial intrahepatic cholestasis - EMA/OD/009/13
*[Co-ordinators: A. Corrêa Nunes / 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 the proposed product for treatment of progressive familial intrahepatic cholestasis, the sponsor should further elaborate on:

- the relevance of pruritus in the clinical presentation of patients affected by the proposed condition

- the use of serum bile acid levels as a clinical surrogate for cholestatic pruritus

- the absence of any data in either preclinical models or clinical settings in the condition as proposed for designation

- the extent of the clinical effect in the serum concentration by providing further data, as so far there is only a trend of reduction and an absence of a dose-response effect in the data discussed

- the relevance of the observed effects in serum concentration of bile acids in healthy volunteers for the treatment of pruritus in patients with the proposed condition as applied for designation.

- Prevalence

The sponsor should justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition, describe and justify the methodology used for the prevalence calculation. The sponsor should justify in detail the grounds on which the proposed prevalence has been calculated.

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 May meeting.

### 2.2.5 5-[1-(2,6-dichlorobenzyl)piperidin-4-ylmethoxy]quinazoline-2,4-diamine dihydrochloride for treatment of 5q spinal muscular atrophy, Repligen Sweden AB - EMA/OD/034/13

*[Co-ordinators: H. Metz / S. Aarum]*

The Committee agreed that the condition, 5q spinal muscular atrophy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 5-[1-(2,6-dichlorobenzyl)piperidin-4-ylmethoxy]quinazoline-2,4-diamine dihydrochloride was considered justified based on results in cells from SMA type I patient and data from two preclinical models. The condition is life-threatening and chronically debilitating due to muscle wasting, weakness, failure to thrive, pulmonary and orthopaedic complications. The condition was estimated to be affecting approximately 0.2 in 10,000 people in the EU, 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 EU for patients affected by the condition.

A positive opinion for 5-[1-(2,6-dichlorobenzyl)piperidin-4-ylmethoxy]quinazoline-2,4-diamine dihydrochloride, for treatment of 5q spinal muscular atrophy, was adopted by consensus.

### 2.2.6 Autologous CD34+ cells transduced with a lentiviral vector containing the human ADA gene (EF1αS-ADA lentiviral vector gene modified autologous CD34+ cells) for treatment of adenosine deaminase deficient-severe combined immunodeficiency (ADA-SCID), Prof. Bobby Gaspar - EMA/OD/014/13

*[Co-ordinators: J. Torrent-Farnell / L. Fregonese]*

The Committee agreed that the condition, adenosine deaminase-deficient severe combined immunodeficiency, 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 ADA gene was considered justified based on *in vitro* studies showing ADA expression in CD34+ cells from ADA-deficient patients as a result of

transduction with the proposed product. The proposed gene therapy product was also shown to engraft in valid pre-clinical models of the disease, resulting in development of immune cells expressing ADA. In addition the off-study compassionate use of the product in two cases with severe ADA-SCID resulted in effective gene transduction and in T cell recovery and metabolic correction to date, at 6 months of observation.

The condition is chronically debilitating and life-threatening due to the repeated and persistent opportunistic bacterial, fungal and viral infections. Pneumonia, diarrhoea and failure to thrive are the main symptoms of the disease, usually appearing around six months of life. The disease is usually fatal within the first two years of life if left untreated. In cases of longer survival, developmental disorders, hearing loss, skeletal dysplasia and costochondral abnormalities, and hepatic and renal dysfunction can develop. The condition was estimated to be affecting less than 0.1 in 10,000 people in the EU, at the time the application was made. The prevalence calculations were mainly based on data from the European Society for Primary Immunodeficiency database.

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

A positive opinion for autologous CD34+ cells transduced with a lentiviral vector containing the human *ADA* gene, for treatment of adenosine deaminase-deficient severe combined immunodeficiency, was adopted by consensus.

### **2.2.7** For treatment of Schnitzler Syndrome - EMA/OD/006/13

*[Co-ordinators: A. Corrêa Nunes / S. Mariz]*

The Committee considered that the medical plausibility issue requires clarification by the sponsor. To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Schnitzler syndrome, the sponsor should present and discuss the data of their own investigations with the product, in a pre-clinical model or in a preliminary clinical setting in 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 May meeting.

### **2.2.8** **Maribavir** for treatment of cytomegaloviral disease, ViroPharma SPRL - EMA/OD/013/13

*[Co-ordinators: K. Kubáčková / L. Fregonese]*

For the purpose of orphan designation, the Committee for Orphan Medicinal Products (COMP) considered that treatment of cytomegaloviral disease originally proposed by the sponsor should be renamed as “treatment of cytomegalovirus disease in patients with impaired cell mediated immunity”.

The Committee agreed that the condition, cytomegalovirus disease in patients with impaired cell mediated immunity, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing maribavir was considered justified based on preclinical data showing anti-cytomegalovirus in vitro activity, and by early clinical data showing serological and clinical resolution of cytomegalovirus infection in patients not responding to previous antiviral treatment.

The condition is life-threatening due to complications such as pneumonitis, hepatitis, inflammation of the gastrointestinal tract and acute graft rejection in transplanted patients. It is the leading viral cause

of morbidity and mortality in patients with human stem cell or solid organ transplantation, with direct damage resulting from viral invasion of different organs, and indirect effects on the immune system that increase the risk of other infections and promote acute graft rejection. The condition can be chronically debilitating in case of the development of long-term sequelae in the affected organs and in case of reduced graft survival. The condition was estimated to be affecting approximately 2 in 10,000 people in the EU, at the time the application was made.

Although satisfactory methods of treatment of the condition have been authorised in the EU, the sponsor has provided sufficient justification for the assumption that the medicinal product containing maribavir may be of significant benefit to those affected by the condition. The sponsor has provided early clinical data in the form of case reports where the product was used in compassionate use in patients not responding to previous antiviral treatment. In this setting maribavir resulted in serological and clinical resolution of cytomegalovirus infection in more than half of the studied patients, indicating the potential to be used in forms of the condition that are resistant to currently authorized antiviral treatments. When confirmed in clinical studies, the Committee considered that this will constitute a clinically relevant advantage for the immunocompromised patients affected by cytomegalovirus disease.

**Post-meeting note:**

Due to lack of the quorum a positive opinion for maribavir, for treatment of cytomegalovirus disease in patients with impaired cell mediated immunity, was adopted formally via written procedure on 23 April 2013.

### 2.2.9 N-methyl-4-({4-[({3-methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide hydrochloride (Reletinib)

**N-methyl-4-({4-[({3-methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide hydrochloride (Reletinib)** for treatment of maligmant mesothelioma, TMC Pharma Services Ltd - EMA/OD/012/13
*[Co-ordinators: B. Dembowska-Baginska / L. Fregonese]*

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

The intention to treat the condition with the medicinal product containing N-methyl-4-({4-[({3-methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide hydrochloride was considered justified based on preclinical *in vitro* data showing anti-tumour activity of the product on malignant mesothelioma cell including cancer stem cells, and preclinical *in vivo* data showing reduction of tumour growth. The condition was estimated to be affecting approximately 0.5 in 10,000 people in the EU, at the time the application was made; the prevalence estimate was based on a search in relevant literature and in international databases, with a good geographic representation of the EU.

The condition is life-threatening due to the invasion of the pleura leading to pleural effusions, dyspnoea and malignant ascites. Local invasion may also result in obstruction of the superior vena cava, cardiac tamponade, and spinal cord compression. Patients with pleural mesothelioma usually die due to increasing tumour bulk that gradually fills the hemithorax causing progressive respiratory compromise (“incarceration” of the lungs), pneumonia, or myocardial dysfunction with arrhythmias. In patients with peritoneal mesothelioma, distension due to ascites, abdominal pain, and organ impairment such as bowel obstruction are observed. The median survival of malignant mesothelioma is 8-12 months.

A positive opinion for N-methyl-4-({4-[({3-methyl(methylsulfonyl)amino]pyrazin-2-yl}methyl)amino]-5-(trifluoromethyl)pyrimidin-2-yl}amino)benzamide hydrochloride, for treatment of malignant mesothelioma, was adopted by consensus.

**2.2.10** For treatment of (localized) neuroendocrine tumours - EMA/OD/002/13
*[Co-ordinators: K. Kubáčková / S. Aarum]*

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

- Medical plausibility

The sponsor has proposed that bibliographical data with other products support the use of their product for treatment of neuroendocrine tumours. The sponsor should present any data that they may have generated on their own with their product in the proposed condition to support the medical plausibility.

- Prevalence

The sponsor should justify the sources of the prevalence data and indicate on which population the prevalence calculation is based. In this case the COMP would need to see all forms of neuroendocrine tumours as currently defined in current publications.

The sponsor is invited to re-calculate the prevalence calculation based on relevant epidemiological studies and registries for the proposed orphan condition neuroendocrine tumours.

- Justification of significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potentially improved efficacy in the condition. This is based on extrapolation from bibliographical data with other products. Since the sponsor has not submitted any data of their own which would support the significant benefit, 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.

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 May meeting.

**2.2.11** For diagnosis of neuroendocrine tumours - EMA/OD/001/13
*[Co-ordinators: K. Kubáčková / S. Aarum]*

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

- Medical plausibility

The sponsor has based their medical plausibility for the proposed product for the diagnosis of neuroendocrine tumours on a hypothesis but has not supported this with any data of their own or bibliographical data. The sponsor is invited to present supporting data either non-clinical and/or, if available clinical data with their product showing the plausibility of using it in the diagnosis of neuroendocrine tumours.

- 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 is invited to re-calculate the prevalence calculation based on relevant epidemiological studies and registries for the proposed orphan condition in this case the diagnosis of neuroendocrine tumours.

- Justification of significant benefit

The sponsor has not established the significant benefit of the using of the product in question as diagnostic for neuroendocrine tumours over OctreoScan® which is a kit for radiopharmaceutical preparation of $^{111}$In-Pentetreotide and is approved in Europe for this purpose. The sponsor is invited to further elaborate on the sensitivity and specificity of the product over the currently approved diagnostic methods in Europe.

- Development of medicinal products

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.

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 May meeting.

**2.2.12 Recombinant human CXCL8 mutant** for treatment of cystic fibrosis, ProtAffin Biotechnologie AG - EMA/OD/005/13
*[Co-ordinators: V. Saano / 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 recombinant human CXCL8 mutant was considered justified based on data in preclinical models showing reduction of neutrophil burden in the lungs after challenge with lipopolysaccharide from Pseudomonas aeruginosa, which mimics the inflammation *in vivo* in cystic fibrosis. The product also resulted in reduced levels of the neutrophil chemoattractant wild-type CXCL8 (interleukin 8) *ex vivo* in sputum from cystic fibrosis patients. The condition is chronically debilitating and life threatening due to the recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure.

The condition was estimated to be affecting approximately 0.8 in 10,000 people in the EU, at the time the application was made, based on data from the literature and from national and European registries and databases.

Although satisfactory methods of treatment of the condition have been authorised in the EU, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant human CXCL8 mutant may be of significant benefit to those affected by the condition. The product acts displacing the wild-type CXCL8 (interleukin 8) from glycosaminoglycans, thereby reducing the recruitment of inflammatory cells from the bloodstream into the lung tissue in cystic fibrosis. In

preclinical studies, this resulted in the reduction of wild-type CXCL8 and inflammatory cells recruitment in the lungs after challenge with bacterial lipopolysaccharide. The different mechanism of action of the recombinant human CXCL8 mutant as compared to the products already authorised for the treatment of the cystic fibrosis, including antibiotics, mucolytics, bronchodilators and one CFTR modifier, supports the potential use of the product in combination with currently authorized products. The benefit of the use in combination will have to be confirmed in clinical studies. If confirmed, the Committee considers that this will constitute a clinically relevant advantage for the patients affected by cystic fibrosis.

A positive opinion for recombinant human CXCL8 mutant, for treatment of cystic fibrosis, was adopted by consensus.

**2.2.13 Recombinant human nerve growth factor** for treatment of retinitis pigmentosa, Dompé S.p.A. - EMA/OD/015/13
*[Co-ordinators: V. Saano / L. Fregonese]*

The Committee agreed that the condition, retinitis pigmentosa, 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 nerve growth factor was considered justified based on pre-clinical data in a relevant model of the condition as well as some preliminary clinical data. The condition is chronically debilitating as it leads to blindness.

The condition was estimated to be affecting approximately 3 in 10,000 people in the EU, at the time the application was made; this was based on a literature search.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the EU for patients affected by the condition/for the population at risk of developing the condition.

A positive opinion for recombinant human nerve growth factor, for treatment of retinitis pigmentosa, was adopted by consensus.

**2.2.14 Recombinant human transglutaminase 1 encapsulated into liposomes** for treatment of transglutaminase 1 deficient autosomal recessive congenital ichthyosis, Westfälische Wilhelms-Universität Münster - EMA/OD/003/13
*[Co-ordinators: V. Tillmann / S. Mariz]*

The Committee agreed that the condition, transglutaminase-1-deficient autosomal recessive congenital ichthyosis, 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 transglutaminase 1 encapsulated into liposomes was considered justified based on a valid pre-clinical model showing improved functionality of the grafted affected skin.

The condition is chronically debilitating due to the functionality of the skin which is compromised and presents as coarse, large, plate-like scales covering the entire body. The scaling is accompanied by chronic skin inflammation that presents as erythema and often cannot be appreciated clinically as the skin is covered by the overlying scaling. Further clinical problems involve generalized pruritus all over the body and a lifelong proneness to skin infections, in particular mycotic infections. The condition was estimated to be affecting approximately 0.04 in 10,000 people in the EU, at the time the application was made; this was done through an extensive literature search.

In addition, although satisfactory methods of treatment of the condition have been authorised in the EU, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant human transglutaminase 1 encapsulated into liposomes may be of significant benefit to those affected by the condition. The sponsor has provided preliminary pre-clinical data using a valid skin graft model and the data demonstrate that the restorative effects of the proposed product offer significant benefit regarding the reduction of water loss when compared to retinoids.

A positive opinion for recombinant human transglutaminase 1 encapsulated into liposomes, for treatment of transglutaminase-1-deficient autosomal recessive congenital ichthyosis, was adopted by consensus.

**2.2.15** For treatment of Stargardt's disease - EMA/OD/004/13
*[Co-ordinators: I. Bradinova/ A. Magrelli / 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 Stargardt's disease, the sponsor should further elaborate on:

- the proposed mechanism of action for the product as applied for designation

- the absence of any model of the proposed condition as applied for designation

- the pre-clinical studies and the results from these studies and their relevance for the development of the product in the condition as proposed for designation.

- Prevalence

The sponsor should justify the sources selected for the estimation of the prevalence of the condition and recalculate the prevalence in line with the abovementioned guideline.

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 May meeting.

## 2.3. COMP opinions adopted via written procedure following previous meeting

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

The COMP was informed that positive opinion agreed on at the March meeting was formally adopted via written procedure on 20 March 2013.

## 2.4. Evaluation on-going

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

### 2.5. Validation on-going

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

## 3. Requests for protocol assistance

The Committee adopted the protocol assistance letters for four products with the following indications:

- treatment of acute myeloid leukaemia
- treatment of diffuse large B cell lymphoma
- treatment of ovarian cancer
- treatment of squamous cell carcinoma of the head and neck in patients undergoing radiotherapy.

The Committee discussed the significant benefit issues for two products with the following indications:

- treatment of peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated)
- treatment of neovascular glaucoma

Relevant protocol asstistance letter will be formally adopted at the May 2013 meeting.

## 4. Overview of applications

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

COMP co-ordinators were appointed for 1 application submitted and 20 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** a) treatment of citrullinaemia type 1

b) treatment of ornithine transcarbamylase deficiency

c) treatment carbamoyl-phosphate synthase-1 deficiency

*[Co-ordinators: J. Torrent-Farnell / S. Tsigkos]*

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

- Prevalence

The sponsor was 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".

The COMP concluded that for the three conditions discussed the criteria for designation as set out in Article 3(1)(b) were not satisfied.

The sponsor was informed about the possibility to appeal.

**5.1.2 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
*[Co-ordinators: K. Kubackova / L. Fregonese]*

a) treatment of acute lymphoblastic leukaemia (EU/3/09/715)

b) treatment of chronic myeloid leukaemia (EU/3/09/716)

The CHMP adopted a positive opinion for Iclusig at their March 2013 meeting. The COMP concluded that:

**5.1.2 (a)** Treatment of acute lymphoblastic leukaemia

The proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product. The prevalence of acute lymphoblastic leukaemia was estimated to remain below 5 in 10,000 at the time of the review of the designation criteria. The sponsor estimated the current prevalence at less than 1 in 10,000 people in the EU, based on a literature search and international cancer databases. The condition is chronically debilitating and/or life-threatening depending on the response to treatment, being fatal in a few weeks if left untreated. The main manifestations of the disease such as persistent fever, infections, anaemia, fatigue, breathlessness, bone and joint pain, are linked to invasion by the leukaemic cells of the bloodstream, the bone marrow and other organs, resulting in lack of normal blood cells, bone marrow failure, and specific organ damage.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that benzamide, 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] is of significant benefit to those affected by the orphan condition still holds. Administration of the product resulted in improved responses in a phase II study in patients with acute lymphoblastic leukaemia who had not responded to previous treatment with dasatinib and nilotinib received in second line or further line. In these studies the product was shown to be particularly beneficial in those patients whose acute lymphoblastic leukaemia harbours the T315I mutation, a mutation of the BCR ABL linked to resistance to the currently authorized thyrosine kinase inhibitors. The aforementioned studies results demonstrate a clinically

relevant advantage for the patient population affected by acute lymphoblastic leukaemia resistant or intolerant to dasatinib and nilotinib, and for those forms of acute lymphoblastic leukaemia with mutated T315I.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

An opinion not recommending the removal of benzamide, 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl]) (EU/3/09/715) from the EC Register of Orphan Medicinal Products was adopted by consensus.

**5.1.2 (b)** Treatment of chronic myeloid leukaemia

The proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product. The prevalence of chronic myeloid leukaemia was estimated to remain below 5 in 10,000 at the time of the review of the designation criteria. The sponsor estimated the current prevalence at 0.6 in 10,000 people in the EU, based on a literature search and international cancer databases. The condition is life-threatening and chronically debilitating during blast crisis, due to invasion of the bloodstream by the leukemic cells and bone marrow failure. This results in increased susceptibility to infections and the possibility of fatal opportunistic infections, and in fever, anaemia, thrombocytopenia with easy bruising, malaise, and bone pain.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that benzamide, 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] is of significant benefit to those affected by the orphan condition still holds. The product resulted in favourable response rates in a phase II study in patients with chronic myeloid leukaemia who had not responded to previous treatment with the tyrosine kinase inhibitors dasatinib and/or nilotinib received in second or further line. The study included also a population of patients resistant to bosutinib. In addition the product is the only tyrosine kinase inhibitor up to date to show efficacy in patients whose chronic myeloid leukaemia harbours a specific mutation of the BCR ABL, the T315I mutation, linked to resistance to the currently authorized treatments, including bosutinib. The possibility of treating forms of chronic myeloid leukaemia resistant to the currently authorized tyrosine kinase inhibitors, and with theT315I mutation, is considered by the Committee to constitute a clinically relevant advantage for the patient population affected by chronic myeloid leukaemia.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

An opinion not recommending the removal of benzamide, 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl]) (EU/3/09/716) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinions was adopted for publication on the EMA website at the time of the marketing authorisation.

**5.1.3 Defitelio** (Defibrotide); Gentium S.p.A.

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

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

The Committee noted the CHMP negative opinion adopted at their March 2013 meeting.

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

**5.2.1 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) [Co-ordinators: V. Stoyanova / L. Fregonese]

## 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 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)

**5.3.3 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)

**5.3.4 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).

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

**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 (EU/3/02/092)

**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 GPLSCD01** (substance to be reviewed) (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)

**5.3.10 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)

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

**5.3.20 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)

**5.3.21 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** Wording of the COMP opinions

# 7. Any other business

**7.1** International Summer School “Clinical practice guidelines on rare diseases” to be held at the Italian National Institute of Health in Rome on 8-12 July 2013

- Meeting information

# Date of next COMP meeting: 14 - 15 May 2013

# List of participants

**Chair:**

Bruno Sepodes

**Vice-Chair:**

| | |
|---|---|
| Lesley Greene | Volunteer patient representative for Eurordis |

**COMP Members:**

| | |
|---|---|
| André Lhoir | België/Belgique/Belgien (present of 1st day only) |
| Irena Bradinova | България |
| Kateřina Kubáčková | Česká Republika |
| Dorthe Meyer | Danmark |
| Vacant | Deutschland |
| Vallo Tillmann | Eesti |
| Geraldine O'Dea | Éire/Ireland |
| Nikolaos Sypsas | Ελλάδα |
| Annie Lorence | France |
| 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 |
| 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:**

| | |
|---|---|
| Frauke Naumann-Winter | Germany |

**European Commission:**

| | |
|---|---|
| Agnès Mathieu | DG Health and Consumers |

**EMA:**

| | |
|---|---|
| Stiina Aarum | Scientific Administrator |
| Laura Fregonese | Scientific Administrator |
| Segundo Mariz | Scientific Administrator |
| Stylianos Tsigkos | Scientific Administrator |
| Federica Castellani | Scientific Administrator (for agenda point 5.1.1 and 5.1.2) |
| Agnieszka Wilk-Kachlicka | Assistant |
| Frederique Dubois | Assistant |

## Apologies

**Members:**

| | |
|---|---|
| Josep Torrent Farnell | España |
| Kerstin Westermark | Sverige |

**Observers:**

| | |
|---|---|
| Antonio Blazquez | Agencia Española de Medicamentos y Productos Sanitarios |
| Maria Mavris | Eurordis |
| Vesna Osrecki | Croatia |