19 January 2017
EMA/COMP/742800/2016 **CONFIDENTIAL**
Committee for Orphan Medicinal Products

EMA/COMP summary report

On an application for orphan medicinal product designation

Thalidomide

Treatment of hereditary haemorrhagic telangiectasia

EMA/OD/268/16

Sponsor: PlumeStars s.r.l.

This report represents a critical review of the application for orphan medicinal product designation. It assesses whether the sponsor has established that the criteria for designation provisioned in Article 3 of Regulation (EC) No 141/2000 are met.
For the full details of the data evaluated by the COMP, please refer to the sponsor's application included in the supporting documents below.

Supporting documents

- Sponsor's application

Section A-E.doc

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1. Product and administrative information

Product	
Active substance:	Thalidomide
International Non-proprietary Name (INN), (accompanied by its salt or hydrate form if relevant):	Thalidomide
Proposed invented name of the medicinal product (tradename):	-
Orphan indication:	Treatment of hereditary haemorrhagic telangiectasia
Pharmaceutical form:	Tablets and nasal powder
Route of administration:	Oral (tablet) and nasal (powder insufflation)
Sponsor:	PlumeStars s.r.l. Strada Inzani 1 43125 Parma Italy
Procedural history	
COMP Co-ordinator:	I. Barisic
EMA Co-ordinator:	L. Fregonese
Expert:	No experts were appointed by the COMP for this application
A pre-submission meeting was held on	13 October 2016
The sponsor submitted the application on	25 October 2016
The procedure started on	21 November 2016
Circulation of draft summary report to COMP on	3 January 2017
The application was discussed by the COMP on	18 January 2017

- During the meeting on 17-19 January 2017 the COMP, in the light of the overall data submitted and the discussion within the Committee, issued a positive opinion by consensus on orphan medicinal product designation for thalidomide for treatment of hereditary haemorrhagic telangiectasia on 19 January 2017.

Regulatory considerations

- The COMP recommends that protocol assistance is sought from the Agency prior to submission of the application for marketing authorisation.
- Due to the potential interest of developing the product in a paediatric indication in the proposed condition and in related conditions where the medicinal product could be used, the sponsor is advised to (i) consider the requirements of Regulation (EC) No 1901/2006 with regards to the development and application for marketing authorisation of the medicinal product, and (ii) consider the possibility to apply for orphan designation for those conditions affecting children and where a paediatric development can be requested.
- It should be highlighted that further to Article 5(12)(b) of Regulation (EC) No 141/2000 and Article B 2.1 of Communication from the Commission on Regulation (EC) No 141/2000, when a sponsor submits an application for marketing authorisation for a designated orphan medicinal product, it is

the responsibility of the sponsor to submit a report on the criteria that led to the designation of the product as an orphan medicinal product and updated information on the current fulfilment of these criteria.

2. Criteria for orphan designation

Article 3 (1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Hereditary haemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber syndrome, is an autosomal-dominantly inherited vascular malformation syndrome characterized by telangiectasia and large arteriovenous malformations.

HHT is caused in about 85% of cases by mutations in either the gene for endoglin (ENG) or activin A receptor type II-like 1 (ACVRL1), which are involved in transforming growth factor-beta (TGF-β) signalling pathway that regulates cell proliferation, differentiation, apoptosis, and migration. ENG and ACVRL1 are expressed predominantly in endothelial cells as receptors for TGF-β/BMP. In most cases HHT results from insufficiency of these transmembrane glycoproteins for normal function. Although pathogenesis of HHT is still poorly defined, it has been suggested that ENG and ACVRL1 mutations cause decreased TGF-β activation (Fernandez-L et al, 2005) and increased vascular endothelial growth factor (VEGF) production (Sadick et al, 2008) that, in turn, result in excessive proliferation and migration of endothelial cells, with reduced vessel maturation and thinning of the vascular wall.

The clinical manifestations of HHT derive from arteriovenous malformations (AVMs), which range from small telangiectasias in the nasal, oral and gastrointestinal mucosa to large AVMs in the lung, brain and liver. Recurrent and severe epistaxis caused by the rupture of nasal telangiectasias is the most common presentation of HHT. Less frequently, rupture of telangiectasias in the digestive tract causes gastrointestinal bleeding. Haemorrhages usually worsen with age and lead to severe anaemia requiring intravenous iron and blood transfusions. Also large AVMs can cause severe morbidity because of rupture or right-to-left blood shunting. A number of patients develop a pulmonary artery hypertension (PAH)-syndrome, suggesting that ACVRL1 mutations are also likely to be involved in PAH.

HHT is diagnosed by the presence of "Curaçao" clinical criteria: (a) spontaneous and recurrent epistaxis; (b) telangiectasias at characteristic sites, as lips, oral cavity, nose, fingertips and gastrointestinal mucosa; (c) AVMs at characteristic sites, as liver, lungs and central nervous system, and (d) family history. Diagnosis is “definite” if at least three criteria are present (Shovlin et al, 2000).

Hereditary Haemorrhagic Telangiectasia is a distinct medical entity.

Intention to diagnose, prevent or treat

Thalidomide [(RS)-2-(2,6-dioxopiperidin-3-yl)-1H-isoindole-1,3(2H)-dione; C13H10N2O4; THAL] is a neutral racemic compound derived from glutamic acid. It consists of equimolar mixture of (+)-(R)- and (–)-(S)-enantiomers. The sponsor aims at developing both an oral formulation and a formulation (powder) for intranasal administration. As thalidomide is practically insoluble in water and undergoes

rapid and spontaneous hydrolysis in aqueous environment, it is formulated as dry powder for insufflation to maintain the drug physico-chemical and microbiological stability.

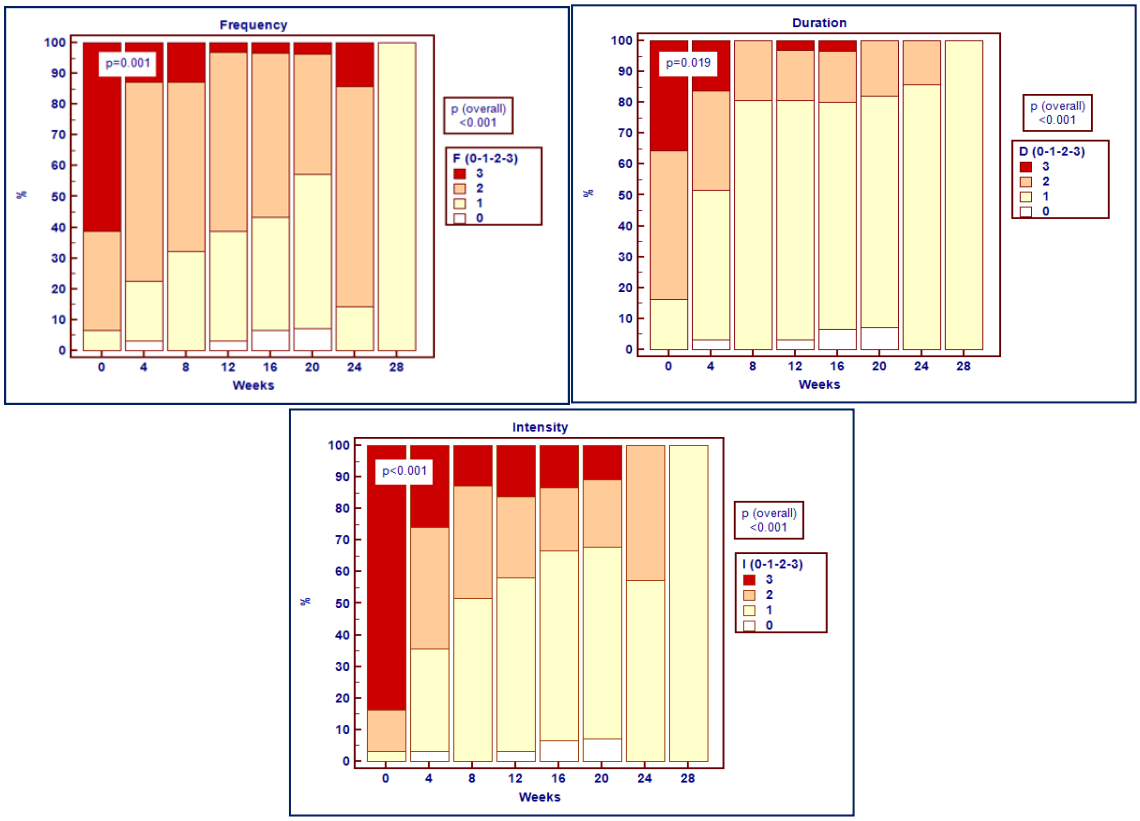
Thalidomide was introduced in late 1950s to prevent insomnia and morning sickness during pregnancy, but it was withdrawn from the market in 1961 because of teratogenicity. Subsequently, THAL was disclosed to have immunomodulatory, anti-inflammatory and anti-angiogenic activity by inhibiting the phagocytic ability of inflammatory cells and the production of cytokines, such as tumour necrosis factor-alpha (TNF-α) (Moreira et al, 1993; D'Amato et al, 1994). This stimulated clinical trials in immune and inflammatory disorders, as well as in various malignancies.

The scientific rationale of using thalidomide in HHT is based on some of the described pharmacological activities including suppression of TNF-α and of other pro-inflammatory cytokines. Moreover, thalidomide inhibits production of VEGF and basic fibroblast growth factor, thus antagonizing angiogenesis and modifying the bone marrow microenvironment. Recent data showed that thalidomide modulates the activation of mural cells in HHT, enhancing their proliferation and ability to envelop blood vessels, i.e., making blood vessels firmer and less prone to breaking (Lebrin et al, 2010). Bleeding inhibition has been observed in HHT patients who received thalidomide as an antiangiogenic cancer therapy (Kurstin et al, 2002), and significant clinical improvements have been described in patients with intestinal angiodysplasias treated with thalidomide. In isolated case reports, patients with severe recurrent intestinal bleeding, refractory to standard treatment achieved prolonged complete remission with thalidomide at a dose of 100 to 300 mg/day for few months. Cessation of bleeding was associated with a reduction in serum VEGF levels.

The sponsor supported the medical plausibility with clinical data. Building on five human studies that reported favourable effect for the treatment of nose bleeding in 17 of 20 patients with HHT receiving oral doses of THAL from 50 to 200 mg/daily (Lebrin et al, 2010; Franchini et al, 2013), the sponsor performed a phase II, prospective, non-randomized, single-centre study (ClinicalTrials.gov NCT01485224) to assess the effects of THAL oral therapy on the severity of epistaxis in subjects with HHT refractory to standard therapies (Invernizzi et al, 2015). THAL was administered at a starting dose of 50 mg/day orally as immediate release dosage form. In the event of no response, dosage was increased by 50 mg/day every four weeks until response to a maximum dose of 200 mg/day. After response achievement, patients were treated for 8 to 16 additional weeks. Monthly follow-up was based on the epistaxis severity score and transfusion need.

Thirty-one patients, 20 men and 11 women, mean age 62.6 (SD 11.1) years, were enrolled. They had previously been treated with many surgical procedures; in all cases there was also skin involvement, in 25 cases involvement of the gastro-intestinal tract, lung or liver. Various types of mutations were observed in either ACVRL1 gene (23 cases) or ENG gene (3 cases). Median follow-up was 15.9 months, 25th-75th 10.1-22.3. Treatment induced cessation of bleeding in three cases (9.7%) and a significant decrease in all epistaxis parameters in 28 cases (90.3%) (Figure 1)

Figure 1. Change in epistaxis parameters (frequency, intensity and duration) with time



Twenty-five patients (80.7%) obtained remission with 50 mg/day of thalidomide, five (16.1%) with 100 mg/day and one (3.2%) with 150 mg/day. Treatment significantly increased haemoglobin levels ($p<0.001$), and abolished or greatly decreased the transfusion need ($p<0.001$). At a median follow-up after the end of therapy of 14.1 months, 8 (27%) patients maintained a response, whereas 21 (70%) patients relapsed with a median relapse free-survival of 7 months.

The sponsor discusses that since the observed anti-epistaxis effect obtained with oral thalidomide is reversible and nose bleeding recurs after discontinuation of the oral treatment, systemic administration may have to be resumed at the risk of causing adverse effects, such as reversible neuropathy, constipation and sedation. However since the nasal mucosa is in many cases the most importantly affected site in HHT, the sponsor suggests that the topical administration of thalidomide inside the nasal cavity for a maintenance treatment prolonging the effect obtained with the oral systemic administration, is a logical therapeutic hypothesis. Preclinical *in vitro* studies of nasal mucosa absorption conducted with application of the nasal powder on excised rabbit mucosa demonstrated that thalidomide accumulated into the nasal mucosa, with a minimal transport through the tissue.

The medical plausibility of the proposed product appears justified.

Chronically debilitating and/or life-threatening nature

The most common symptoms of the disease are spontaneous and frequent nosebleeds, and red spots on the skin, particularly on the face and hands and in the mouth. Recurrent and severe epistaxis, due to the presence of telangiectasias in nasal mucosa, being the most common presentation of HHT, frequently leads to severe anaemia requiring intravenous iron and blood transfusions. Severe and frequent epistaxis have a great impact on quality of life in HHT patients and it represents the most important impediment in daily activities. Bleeding can also occur in the stomach, gut, brain, liver and lungs, and stroke and liver problems are life-threatening complications of the condition.

Number of people affected or at risk

The sponsor estimated the prevalence of the condition based on literature sources and a critical review of the retrieved sources. The sponsor discussed the limitations to estimating incidence and prevalence of HHT, including the wide clinical heterogeneity both among patients and within families and the penetrance complete only after age 40, which makes the diagnosis difficult in many cases. As a result, different incidences of the disease have been reported in different countries, and that a founder effect is present in many countries. The sponsor concludes with an estimated prevalence of not more than 2/10,000, which is acceptable.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There are no medicinal products authorized for the treatment of the condition in the EU, and the current treatment is aimed to symptom control.

Trans-catheter embolotherapy with occluder devices is a well-established and effective treatment for large AVMs in the lung and brain of HHT patients, local treatment is difficult for largely disseminated telangiectasias and no medical therapy for preventing their rupture has been approved (Faughnan et al, 2011). Various treatment options allow controlling nose bleedings, but these interventions often lose efficacy over time and patients eventually require risky or debilitating treatments, as embolization of the nasal vasculature or nose closure. Surgical treatment of epistaxis in HHT should be approached in a stepwise manner, escalating as need to treat the patient while at the same time minimizing risk of septal perforation. There are many different surgical approaches available, such as laser and bipolar cautery, argon plasma coagulation and coblation (Syed et al 2015; Chin et al, 2016). However, surgical options are largely palliative with variable and temporary results. Systemic administration of antifibrinolytic agents has been empirically used since a long time. Tranexamic acid inhibits fibrinolysis in the vessel walls of telangiectasias and stabilizes the clot. However, two recent prospective clinical trials concluded that their efficacy was small and did not result in increases of haemoglobin levels (Gaillard et al, 2014; Geisthoff et al, 2014). Contrasting results have been obtained with hormone therapy.

Significant benefit

Not applicable.

3. COMP list of issues

Not applicable.

4. Grounds for the opinion on orphan medicinal product designation

The sponsor PlumeStars s.r.l. submitted on 25 October 2016 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing thalidomide for treatment of hereditary haemorrhagic telangiectasia (hereinafter referred to as “the condition”. The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing thalidomide was considered justified based on preliminary clinical data showing reduction of frequency, intensity and duration of nasal epistaxis and improvement of haemoglobin levels in patients affected by the condition;
- the condition is life-threatening and chronically debilitating due to arteriovenous malformations in different organs, leading to recurrent bleeding from the nasal mucosa with development of severe anaemia, and to potentially fatal bleeding in the stomach, gut, brain, liver and lungs;
- the condition was estimated to be affecting not more than 2 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

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

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing thalidomide as an orphan medicinal product for the orphan indication: treatment of hereditary haemorrhagic telangiectasia.