Thalidomide for nose bleeding in persons affected by hereditary hemorrhagic telangiectasia

WHO WE ARE

PlumeStars, Italian innovative start-up company, laid its foundation from Biopharmanet-TEC, the Interdipartimental Center of the University of Parma, in September 2013. Plumestars leverages on its strong technological know-how to design and develop dry powders for inhalation and orphan medicines designation. Plumestars holds a patented technology claiming the molecular deposition of fatty acids on drug microparticles applicable to several drugs.

The founders of PlumeStars, Paolo Colombo (CEO), Anna Giulia Balducci, Francesca Buttini and Ruggero Bettini, are four scientists that share the same passion for science and technology. In the Advisory Board, Fabio Borella, is the mentor of PlumeStars.

WHAT WE DO

Hereditary haemorrhagic telangiectasia (HHT) is a rare genetic disease characterized by vascular malformations with a prevalence of about 1-2 in 10,000 individuals. HHT is caused by mutations in genes encoding proteins mostly expressed in vascular endothelial cells. These proteins are involved in transforming the growth factor-beta superfamily signalling pathway. Clinical manifestations include arteriovenous malformations (AVM), which can be classified as small telangiectasia (regions of capillary dilation) and large AVMs, where arterioles and venules are directly connected with no capillaries in between. In particular, arteriovenous malformations appear in the nose, oral mucosa and gastrointestinal tract, whereas large AVMs mainly occur in the lung, brain and liver. Recurrent epistaxis is the most common manifestation of nasal HHT and begins by the age of 10-20 years in many patients, increasing in severity with ageing. Epistaxis may be so severe as to require blood transfusions and oral iron supplementation.

Clinical studies in HHT patients with severe recurrent epistaxis, refractory to mini-invasive surgical procedures, have been conducted using capsule of thalidomide. Low-dose of oral thalidomide (50 mg) was safe and effective for the therapy of epistaxis in HHT patients who did not benefit from other modalities of treatment. A rapid clinical improvement of the intensity and frequency of the epistaxis was obtained. Unfortunately, the result obtained using oral thalidomide was not durable. When the drug oral administration was suspended due to the appearance of thalidomide adverse effects, the epistaxis episodes come back to the previous frequency and gravity.

A maintenance therapy was considered a good solution in case of a local treatment since the disease site is easy accessible and the blood level of drug could result quite low. Hence, novel nasal powder formulations of thalidomide have been studied to enable thalidomide administration in the nose. The formulation can provide HHT patients after oral thalidomide with a complementary or substitutive anti-epistaxis therapy. The goal was to sustain the effect obtained with the oral treatment avoiding the side effects and at the same time, improving the convenience and compliance of the patients.

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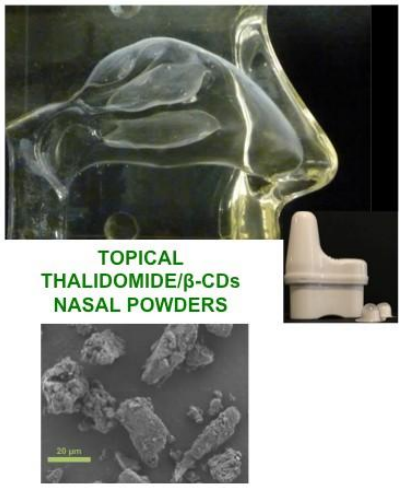

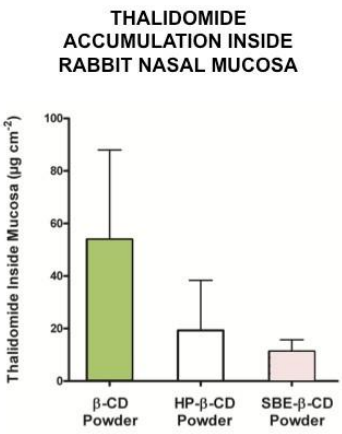

DESCRIPTION OF THE PRODUCT

The product is a powder of thalidomide compounded with β-cyclodextrin or hydroxypropyl-β-cyclodextrin or sulphobutylether- β-cyclodextrin as carriers, to be used orally and intranasally.

The nasal powder formulations were combined with different devices to measure the powder plume emission and deposition in a model cast of human nose. The formulation of thalidomide nasal powder gave rise to stable products with suitable technological properties for nasal insufflation. The improved dissolution rate, compared to that of the raw material, made the thalidomide promptly available in an aqueous environment.

Surprisingly, the trans-mucosal transport of thalidomide was very low. On the contrary, a significant accumulation of the drug in the mucosa was found. This *in vitro* result suggested a low likelihood of significant systemic absorption of thalidomide. The topical action on bleeding would benefit from the poor absorption and from the fact that about 2-3% of the thalidomide applied on the mucosa *in vitro* was found within the tissue, particularly with the β-cyclodextrin nasal powder. Furthermore, the residence time in nasal cavity was prolonged by the mucoadhesive action provided by this nasal powder.

MAIN ADVANTAGES

Clinical study demonstrated that low-dose thalidomide was safe and effective for the therapy of epistaxis in HHT patients. However, following two months of oral administration, important adverse effects have been registered obliging the discontinuation of the therapy. The local administration into the nose of the drug is a way to maintain the positive result obtained, eliminating adverse effects. The nasal powders will enable thalidomide maintenance therapy as a complement of systemic oral administration. This result contributes to a safer re-positioning of a very active drug. The insignificant *in vitro* trans-mucosal transport of thalidomide from the nasal powder suggests a low likelihood of systemic absorption.

TECHNOLOGY KEY WORDS

Nasal powders, Tablets, Local and systemic delivery, Thalidomide, Cyclodextrin, Hereditary hemorrhagic telangiectasia.

CURRENT STAGE OF DEVELOPMENT

Preclinical studies for the nasal administration to be done. Clinical studies in human on the oral formulation have been already published. Nasal *in vitro* data and in human oral administration allowed to obtain the orphan drug designation from EMA and FDA.

TECHNICAL AND SCIENTIFIC PUBLICATIONS

Invernizzi R, Quaglia F, Klersy C, Pagella F, Ornati F, Chu F, Matti E, Spinozzi G, Plumitallo S, Grignani P, Olivieri C, Bastia R, Bellistri F, Danesino C, Benazzo M, Balduini CL. Efficacy and safety of thalidomide for the treatment of severe recurrent epistaxis in hereditary haemorrhagic telangiectasia: results of a non-randomised, single-centre, phase 2 study. Lancet Haematol 2015; 2:e465-473.

G. Colombo, F. Bortolotti, V. Chiapponi, F. Buttini, F. Sonvico, R. Invernizzi, F. Quaglia, C. Danesino, F. Pagella, P. Russo, R. Bettini, P. Colombo, A. Rossi. Nasal powders of thalidomide for local treatment of nose bleeding in persons affected by hereditary hemorrhagic telangiectasia. Int. J. Pharm. 514, 229-237 (2016).

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