mini-SAWP activity

CHMP Protocol Assistance

Briefing Document

Invented Name:	Antonicaftor
Active substance:	ExPRESS2017
Pharmaco-therapeutic group:	CF transmembrane conductance regulator (CFTR) corrector
Intended indication(s):	ExPRESS2017 is indicated for the treatment of CF in patients
Company:	Gaudipharm Ltd (Europe) Ltd.
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Cystic fibrosis

Cystic fibrosis is a hereditary (genetic) disease that affects the production of secretions (such as mucous) from the glands in the body. It affects the lungs and the digestive system (gut) in particular. Cystic fibrosis is caused by abnormalities in a gene called 'cystic-fibrosis transmembrane conductance regulator' (CFTR). The CFTR gene is responsible for the production of CFTR, a protein that regulates the production of mucus and digestive juices by acting as a chloride-ion channel to allow proper movement of salt and water in and out of certain cells in the lungs and other tissues. In patients with cystic fibrosis, there is an overproduction of mucous in the lungs and a reduced production of digestive juices from the pancreas (an organ near the stomach). This leads to long-term infection and inflammation of the lungs and problems with the digestion and absorption of food resulting in poor growth.

Cystic fibrosis is a long-lasting and life-threatening disease.

Mechanism of action of Antonicaftor

Antonicaftor is thought to restore the ability of CFTR channels to transport chloride ions into and out of cells. This is intended to help maintain the proper level of salt and water on airway surfaces, reducing the formation and accumulation of mucus in the lung, and thus improving the symptoms of the disease.

Questions and Companies position

Non-clinical

Question 1:

Does the SAWP agree that data from the current and ongoing nonclinical safety studies would support the initiation of the proposed clinical study and that the proposed nonclinical development plan will support an MAA for antonicaftor?

Nonclinical Toxicology Summary and Exposure Margins for Antonicaftor

The safety profile of antonicaftor has been well characterised in animal and in vitro studies. Antonicaftor has been shown to have no safety pharmacology (cardiovascular, central nervous system, gastrointestinal, and respiratory models), or genotoxicity (reverse mutation and chromosomal aberration assays in vitro and mouse micronucleus assay in vivo. In addition, the major human metabolite of antonicaftor has been shown to have no genotoxicity (reverse mutation and chromosomal aberration assays in vitro) or teratogenic potential (Segment II study in rats).

Antonicaftor was well tolerated in acute toxicity studies at oral doses up to 2000 mg/kg (the highest doses tested). Repeat-dose toxicity studies up to 3 months duration were conducted with antonicaftor in mice, rats, and dogs. There were no adverse findings in mice at dosages up to 1000 mg/kg/day or in rats at dosages up to 2000 mg/kg/day for 3 months duration, but some mortality was observed in dogs at 1000 mg/kg/day in the 3-month study due to deteriorating body condition, severely decreased food consumption, lower absolute body weight and body weight gains (up to 23% more than controls), and/or associated clinical signs (high incidence/occurrence of abnormal stools and vomiting).

Clinical

Question 2

Does the SAWP agree with the population selected for the study?

Population:

The study will enrol subjects 2 years of age and older diagnosed with cystic fibrosis (CF)

Question 3

Does the SAWP agree with the primary endpoint selected for evaluation in the study?

- absolute change from baseline in percent predicted FEV1 through Week 24

Question 4

Does the SAWP agree with the key secondary endpoints selected for evaluation in the study?

Endpoints:

The key secondary endpoints will include the following:

- absolute change from baseline in body mass index (BMI) at Week 24
- number of pulmonary exacerbations through Week 24
- measures of patient-reported health with the cystic fibrosis questionnaire—revised (CFQ-R)

Statistics

Question 5

Does the SAWP agree with the proposed statistical analysis for the study?

Company's position:

The primary analysis for the primary efficacy endpoint will be based on a mixed effect model repeated measure (MMRM) model. The model will include the relative change from baseline in percent predicted FEV1 as the dependent variable, treatment and visit as fixed effects, subject as a random effect, with adjustment for sex, age group at baseline, and percent predicted FEV1 severity at baseline.

The main effect of treatment obtained from the model will be interpreted as the average treatment effect across all post-baseline visits. This is a weighted average of the treatment effect across all post-baseline visits under the no-treatment-by-visit interaction model. The estimated mean treatment effect, a 95% confidence interval, and a 2-sided P value will be provided.

Significant benefit

Questions 5

Does the SAWP agree that this development programme and survey will support significant benefit at marketing authorisation?

Company's position:

The company plans conduct a phase II open label study with Antonicaftor and compare FEV1 change from baseline.

As there are several products authorised for treatment of cystic fibrosis, we would like to question patients for their preferences using a survey.