CLINICAL STUDY REPORT

Name of the Sponsor: Laboratoires SMB S.A.	**Protocol Number:** ASPER-III-19-1
Name of Investigational Product: Itraconazole Dry Powder for Inhalation (ITZ DPI)	**EudraCT Number:** 2019-002408-42
Title of the Study: A Phase 3, Double-Blind, Multicentric, Randomised, Placebo-Controlled Study to Assess the Efficacy, Safety and Tolerability of Itraconazole Dry Powder for Inhalation for the Prevention of Invasive Mould Disease in Patients with Acute Leukaemia and Neutropaenia.	
Development Phase of the Study: Phase 3	
Study Initiation Date (date of First patient screened): 02 April 2020 **Date of Notification of the Anticipated End of the Trial:** 27 May 2022 **Study Completion Date (Date Last Patient Completed Last Observation):** 28 June 2022	
Number of Patients (total and for each treatment group): It was planned to enrol approximately 462 patients (308 patients in the ITZ DPI group and 154 patients in the Placebo DPI group). A total of 315 patients were assigned to one of both group (ITZ DPI or Placebo DPI).	
Test Product(s), Dose(s) and Mode(s) of administration: The patients were randomly (ratio 2:1) assigned to study treatment (three capsules of ITZ DPI were inhaled BID) or placebo treatment (three capsules of placebo DPI were inhaled BID).	
Sites: This study was conducted in 75 sites in 10 countries: Belgium (4), Spain (10), Italy (6), Poland (5), Greece (13), Romania (3), Bulgaria (5), Serbia (3), Russia (14) and Ukraine (12).	
Study Objectives: The objectives of the study were to compare the efficacy, safety, and tolerability of Itraconazole DPI versus Placebo DPI for the prevention of IMD in patients with acute leukaemia undergoing remission-induction chemotherapy.	

Overall Study Design:

This was a Phase 3, double-blind, multicentric, randomised, placebo-controlled study in patients with acute leukaemia undergoing remission-induction chemotherapy.

Patients were screened for enrolment into the study from Day -14 to Day -1. Eligible patients were randomised in a 2:1 ratio to receive ITZ DPI or PBO DPI.

Patients received the first dose of study drug as soon as possible within 5 days of the start of remission-induction chemotherapy. In ALL patients, as soon as possible within 5 days of the start of remission-induction chemotherapy meant as soon as possible within 5 days of the start of high-dose steroid therapy. Patients used the Axahaler® inhaler device to administer study drug twice daily (BID, morning and evening). Concomitantly, patients received fluconazole once a day (QD) by oral (preferred formulation) or IV administration (used only when the oral intake for a particular patient was not possible) for the prevention of invasive candidiasis. Patients continued to receive study drug until one of the following events occurs (whichever comes first):

- Recovery from neutropaenia (an absolute neutrophil count >500 cell/mm^3 or 0.5 x 10^9 cell/L)
- Occurrence of an IMD
- Study drug treatment for up to 12 weeks
- A mould-active antifungal treatment was necessary to treat a fungal disease
- A study-drug-related AE that according to Investigators required study drug discontinuation

Recovery from neutropaenia after induction chemotherapy was a cause for study drug discontinuation unless the patient was qualified for an immediate re-induction chemotherapy. Safety assessments, efficacy evaluations, PK blood draws in a subgroup of patients, and exploratory endpoint evaluations occurred throughout the study.

Management of a suspected IMD was done according to defined algorithms from randomisation through End of Study (EOS). EOS was defined as 30 days after end of treatment (EOT). Blood samples were drawn twice weekly and tested for galactomannan. Chest computed tomography (CT) scan, sputum collection, bronchoalveolar lavage (BAL), and polymerase chain reaction (PCR) on blood and BAL samples were performed when needed to confirm IMD in the lungs.

Criteria for Evaluation:

<u>Primary efficacy endpoint</u>

- Proportion of patients with proven or probable IMD at EOT. Diagnoses of proven or probable IMD were evaluated according to the 2019 EORTC/MSGERC (Donnelly JP *et al*, 2019) criteria, as assessed by the Independent Data Review Board (IDRB) that was blinded to treatment assignment.

<u>Secondary efficacy endpoints:</u>

- Treatment success at EOT (success defined as patients who completed treatment without developing a proven, probable, or possible IMD, without requiring systemic mould-active antifungal treatment, without discontinuation from the study due to an adverse event [AE], and who were alive).
- The proportion of patients:
    - with proven, probable, or possible IMD at EOT and EOS
    - who had neutropaenia ≥10 days and with proven, probable, or possible IMD at EOT and EOS
    - with radiographic pulmonary infiltrates according to the central image reader at EOT and EOS
    - with bronchopulmonary aspergillosis at EOT and EOS
    - with fungal sinusitis at EOT and EOS
    - with proven or probable or possible IA at EOT and at EOS
    - with candidemia/candidiasis at EOT and EOS
    - requiring systemic mould-active antifungal treatment at EOT and EOS to treat a breakthrough fungal disease
    - alive at EOT and EOS
    - who died at EOT and EOS due to IMD or IA
    - in complete remission of their underlying malignancy at EOT and EOS
- The proportion of pathogenic moulds causing proven and probable IMDs at EOT and EOS
- Time to:
    - diagnosis of proven, probable, or possible IMD
    - diagnosis of IA
    - the onset of systemic mould-active antifungal treatment for a breakthrough fungal disease
    - death of any cause

Safety Endpoints and Analyses:

The safety endpoints were:

- AEs
- Pulmonary function parameters (FEV1, FEV1% predicted, FVC, and PEF)
- 12-lead electrocardiogram (ECG)
- Echocardiogram
- Vital signs (blood pressure, pulse rate, respiratory rate, and temperature)
- Clinical laboratory tests (haematology, biochemistry, and coagulation)

Bronchospasm that was Grade 2 or higher according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) was considered an adverse event of special interest (AESI) if the AE was not present at baseline and was a treatment-emergent adverse event (TEAE).

PK Endpoints and Analyses:

The PK endpoints were:

- ITZ and hydroxyl-itraconazole (OH-ITZ) concentrations in plasma in a subgroup of patients including adolescents
- Fluconazole concentrations in plasma in a subgroup of patients including adolescents

Exploratory Endpoint and Analysis:

The exploratory endpoint was:

- The proportion of proven, possible, or probable IMD at EOT, as confirmed by the IDRB, in patients located in rooms with and without high-efficiency particulate air (HEPA) filtration.

Sample Size Determination:

Patients were allocated to the ITZ DPI and PBO DPI groups in 2:1 ratio. Assuming a proportion of 12% of patients with proven or probable IMDs in the PBO DPI group, and an expected relative decrease of 63% in the proportion of proven or probable IMDs in the ITZ DPI group, a sample size of 438 patients allowed the detection of the difference between the ITZ DPI and PBO DPI groups with 80% power at a 2-sided alpha level of 0.05 using a Chi-square test.

Further assuming a drop-out rate of 5% from the mITT Population and accounting for the 2:1 randomisation ratio, a total of 462 patients had to be enrolled.

The rationale for the treatment effect was that a relative decrease of risk of IMD of 63% in the ITZ DPI group compared to the PBO DPI group was expected based on the available published literature.

Unblinded re-assessment of the sample size was performed after 50% of patients have completed the study. The assumptions about the overall drop-out rate from the mITT population and proportion of patients with proven or probable IMD in the PBO DPI group only were evaluated and compared versus expected. The protocol-planned sample size re-estimation was performed, using the parameters above and keeping all other assumptions of the initial sample size calculation unchanged. The recalculated total sample size was 1353 patients. The higher number of patients to include in the study in addition to the changes in the external environment (COVID-19 and geopolitical situation in Ukraine and Russia) made the study continuation unfeasible. The study was therefore prematurely stopped.

Results of the study:

Due to the premature stop of the study, no statistical analyses were performed. Key safety data extracted from the clinical database are presented below.

Summary of Results

A total of 315 patients have been included in this study (211 in the itraconazole group and 104 in the placebo group), of which 210 completed the treatment period (146 patients in the itraconazole group and 64 in the placebo group).

During the treatment period, there have been 105 dropouts from the study. Dropouts were associated with adverse events (n= 40, 21 in itraconazole group and 19 in placebo group), death (n=18, 12 vs 6), withdrawal of consent (n= 19, 14 vs 5), investigator/sponsor decision (n=16, 11 vs 5) and other reason (n=11, 7 vs 4).

Patients were male (51.1%) or female (48.9%) and the mean age was 48.0 ± 16.4 years. The mean height was 169.9 ± 9.3 cm and the mean weight was 77.9 ± 18.0 kg.

Three hundred fifteen patients took at least one study treatment (211 in the itraconazole group and 104 in the placebo group).

The percentage of patients with one or more treatment emergent adverse events was similar among the 2 treatment groups (itraconazole - 94.8%; placebo – 95.2%). Among them, 7.3% reported a drug-related TEAE (itraconazole - 7.6 %; placebo - 6.7%).

The SOC with the most TEAEs was Blood and Lymphatic system disorders followed by Gastrointestinal disorders and Infections and infestations.

Serious AEs were reported in 107 patients and all of them were not related to the study treatment (itraconazole – 65 (30.8%); placebo – 42 (40.4%)).

The SOC with the most SAEs was Infections and Infestations ((itraconazole – 32 (15.2%); placebo – 26 (25.0%)). Covid-19 pneumonia was reported with a similar frequency in both groups (5.2% vs 8.7%).

Two episodes of Grade 2 Bronchospasm (Adverse event of special interest) were reported in one patient (itraconazole group). The events were reported at the end of treatment visit (Day 28) and at the end of study visit (Day 60). They were both considered by the investigator as not related to the study treatment but related to the spirometry manoeuvre.

Ninety-five patients discontinued prematurely from study drug due to treatment emergent adverse events (itraconazole – 62 (29.4%); placebo – 33 (31.7%)). Percentage of discontinuation in both groups was similar.

No clinically effects of the study treatment were noted on vital signs (blood pressure, pulse rate, respiratory rate, temperature), ECG and spirometry parameters (percent predicted FEV1%, forced expiratory volume in 1 second).