Sponsor: Sanofi Drug substance(s): Hyoscine Butylbromide+ Ibuprofen	Study Identifiers: U1111-1243-6087, 2019-004138-41 Study code: LPS16145
Title of the study: A phase IV randomized, double-blind, 3-treatment, 3-period, 6-sequence cross-over clinical trial to assess the efficacy and safety of hyoscine butylbromide co-administered with ibuprofen compared to placebos in participants suffering from primary dysmenorrhea	
Study center: One study center (Germany)	
Study period: Date first participant enrolled: 28/Aug/2020 Date last participant completed: 20/Nov/2020 Study Status: Terminated, due to the Sponsor's strategic decision.	
Phase of development: Phase 4	
Objectives: Primary objective: • To assess the efficacy of hyoscine butylbromide (HBB) co-administered with ibuprofen, compared with placebos, for treating participants suffering from lower abdominal cramps in primary dysmenorrhea (PD), based on sum of pain intensity difference over 6 hours post dosing (SPID0-6) post dosing of the first study treatment intake on Day 1. Secondary Objectives: • To assess the safety of HBB co-administered with ibuprofen, for treating participants suffering from PD. • To evaluate the efficacy of HBB co-administered with ibuprofen, based on other efficacy variables post dosing of the first study treatment intake on Day 1.	

Methodology:

This was a Phase 4, double-blind, randomized, 3-treatment, 3-period, 6-sequence cross-over study in single study center.

- Tested treatment (T): HBB (Buscopan®) (20 mg) + ibuprofen (Brufen®) (400 mg)
- Control treatment (C): Placebo for HBB + placebo for ibuprofen
- Exploratory calibrator treatment (E): Ibuprofen (Brufen®) (400 mg) + placebo for HBB

Up to 102 participants with moderate to severe PD aged 18 years and up to 47 years (inclusive) were to be randomized to 6 different sequences (1:1:1:1:1:1; TCE, TEC, CTE, CET, ETC, ECT) to receive the above mentioned 3 treatments in the course of 3 Evaluation Periods for up to 3 times per day for a maximum of 3 days per Evaluation Period.

All randomized participants were to be treated in 3 consecutive menstrual pain eligible episodes (in case the participant's evaluation of pain was < 4 on 0-to-10 Numerical Rating Scale (NRS), before the first study drug intake on the first day of a menstrual period, an additional cycle was allowed either between Evaluation Periods 1 and 2 or between Evaluation Periods 2 and 3).

- First treatment intake on Day 1 of each Evaluation Period was mandatory, but could only be taken, in case of 0-to-10 NRS at baseline (just before intake) was ≥ 4.
- Subsequent treatment intakes: up to 2 additional treatments (i.e., 3 intakes/day), depending on the decision of the participant regarding the presence and intensity of pain ("as needed" approach [according to perception of participant]) for up to 3 days.
- As per labeling, an interval of at least 8 hours between 2 treatment intakes was to be respected/observed.

The maximum individual trial duration was to be 5 months (including the Screening window).

Number of participants:

Planned: 60 evaluable participants

Randomized: 39

Treated: 37

Evaluated: 39

Efficacy: Not applicable

Safety: 37

Diagnosis and criteria for inclusion:

• Female participants at least ≥ 18 and up to ≤ 47 years of age (inclusive), with PD, suffering from moderate to severe cramping pain in the last 4 months (abdominal pain intensity ≥ 4 on 0-to-10 NRS) prior to Screening.

• A body mass index (BMI) of ≥ 18.5 kg/m2 and ≤ 29.9 kg/m2.

Study products Investigational medicinal product: HBB (from Buscopan®) Formulation: Film-coated tablet Route of administration: Oral Dose regimen: One tablet each, up to 3 times per day for up to a maximum of 3 days per Evaluation Period. An interval of at least 8 hours between 2 intakes needed to be respected. Investigational medicinal product: Ibuprofen (from Brufen®) Formulation: Film-coated tablet Route of administration: Oral Dose regimen: One tablet each, up to 3 times per day for up to a maximum of 3 days per Evaluation Period. An interval of at least 8 hours between 2 intakes needed to be respected.
Duration of treatment: 3 days for each treatment period. Duration of observation: The duration for each single participant was up to 5 months.
Criteria for evaluation: The current report is an abbreviated report, and as such, only the demographic, participant disposition, exposure data and safety results are being presented in full. This study was terminated early due to the Sponsor's strategic decision. No participant completed 3 periods as planned and thus the predefined efficacy analysis cannot be evaluated. The following safety criteria were evaluated, and analyzed using descriptive statistics: Safety endpoints: • (Serious) adverse events/adverse events of special interest (AESIs) reported from the time of informed consent until the end-of trial • Treatment-emergent adverse events (TEAEs) reported from the time of first study drug intake until last intake plus 24 hours • Outcome of complete physical examination and vital signs
Statistical methods: All analyses were performed using SAS® release, version 9.4 or higher (SAS Institute Inc., Cary, NC, USA) or other validated statistical software. Continuous variables were summarized using descriptive statistics, including number of observations and mean, Standard Deviation, median, first quartile (Q1), third quartile (Q3), minimum, and maximum values. Categorical variables were summarized by frequency counts and percentage of participants. Safety Analyses The Safety Analysis Set was used to perform all safety analyses. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 23.1). Safety data were listed individually by participant and summarized descriptively by the actual treatment received.

Summary Results:

Study participants

• A total of 39 participants were randomized in the study. Of these, 37 (94.9%) participants received study treatment during Evaluation Period 1. Nine (23.1%) of 39 participants had entered the Evaluation Period 2 at the time of early termination of the trial.

• During the trial, 4 major protocol deviations were reported in 3 participants. All the 4 protocol deviations were related to questionnaire not completed by the participant within the protocol-specified time window at a given visit.

• The median age of the study population was 28.0 years (min, max: 21, 42 years). Majority of participants were White (92.3%) and none of the participants were of Hispanic or Latino origin.

• The median BMI for overall population was 22.70 kg/m2 (min, max: 18.8, 29.7 kg/m2).

Efficacy results

This report is being written as an abbreviated report as the study was terminated early and no participant completed 3 periods as planned. Therefore, the originally planned efficacy analyses were not performed.

Safety evaluation

• In the overall safety population of 37 participants, 3 TEAEs (nausea, cystitis, and headache) were reported in 2 (16.7%) participants, both in HBB from Buscopan® (20 mg) + Ibuprofen from Brufen® (400 mg) treatment group. The TEAEs of nausea and headache were reported as related to the study treatment, while the remaining TEAE of cystitis was reported to be not related to study treatment.

• The mean systolic blood pressure (BP) of the safety population was 107.8 mmHg [standard deviation (SD) ± 9.17] at screening and was 109.2 mmHg (SD ± 9.18) at follow-up. At screening, 3 participants were noted to have abnormal systolic BP which were all assessed to be clinically non-significant.

• The mean diastolic BP of the safety population was 69.4 mmHg (SD ± 5.66) at screening and was 71.5 mmHg (SD ± 6.98) at follow-up. None of the readings were reported to be abnormal.

• The mean heart rate of the safety population was 74.0 beats/min (SD ± 10.04) at screening and was 75.2 beats/min (SD ± 11.28) at follow-up. At screening, 3 participants had abnormal heart rate and 5 participants had abnormal heart rate at follow-up. None of these abnormal readings were noted to be clinically significant.

• The mean temperature of the safety population was 36.7°C (SD ± 0.391) at screening and was 36.76°C (SD ± 0.285) at follow up.

• The mean respiratory rate of the study population was 14.4 breaths/min (SD ± 1.88) at screening and was 15.6 breaths/min (SD ± 1.46) at follow-up.

• There were no relevant changes in physical examinations.

Issue date: 27-Jul-2021

Sponsor : SANOFI	
Product Code: SH41058I	Product INN: HYOSCINE BUTYLBROMIDE + IBUPROFEN
Study Code: LPS16145	EUDRACT Number: 2019-004138-41
Title of the study: A phase IV randomized, double-blind, 3-treatment, 3-period, 6-sequence cross-over clinical trial to assess the efficacy and safety of hyoscine butylbromide co-administered with ibuprofen compared to placebos in participants suffering from primary dysmenorrhea	

Study Status: A total of 39 participants were randomized in the study. 37 participants received study treatment during Evaluation Period 1. 9 of 39 participants had entered the Evaluation Period 2 at the time of early termination of the trial. No participant completed 3 periods as planned (See redacted Results Summary)

Reason of early termination: This study was terminated early due to the Sponsor's strategic decision.