1 Title Page

A double-blind, randomized, cross-over, multi-center efficacy and safety study of ibuprofen plus hyoscine butylbromide for pain management due to primary dysmenorrhea

CLINICAL STUDY REPORT

(**Version 1.0**)

Author: PPD	**Date**: 09-Apr-2024
Project number: CRO22001 (CRO)	**Clinical trial phase**: Phase III
Sponsor: RONTIS HELLAS S.A. Medical and Pharmaceuticals Products 38 Sorou St. GR15125, Maroussi, Greece Phone: PPD Fax: PPD	**Sponsor's Project Manager**: PPD RONTIS HELLAS S.A. Medical and Pharmaceuticals Products 38 Sorou St. GR15125, Maroussi, Greece Phone: PPD Fax: PPD
Trial period: from 13-JAN-2023 to 28-JUN-2023	**Early termination**: Yes: ☒ (after first stage) No: ☐
End of clinical trial: 28-JUN-2023	
Coordinating Investigator: Dr. Anna Chorbova, DCC Ascendent, 47 Bacho Kiro Str., Sofia 1202	
Indication: Management of pain due to primary dysmenorrhea	
Name of test drug/investigational product:	ibuprofen plus hyoscine butylbromide
Earlier reports from the same trial: none	**Archiving**: Source data at principal investigator as specified in the ICH Topic E 6(R2) guideline (chapter 8)
Medical Officer responsible for the medical content of this report	
Name:	PPD
Affiliation:	CCDRD AG, Lindenallee 70, 15366 Hoppegarten, Germany. Phone: PPD

This trial was conducted in compliance with Good Clinical Practice (GCP) and Good Laboratory Practice (GLP)

The report was produced on a word-processing system and bears no signatures. The signatures of all persons responsible are filed separately in chapter 16.1.5

2 Synopsis

NAME OF COMPANY **RONTIS HELLAS S.A.** **NAME OF FINISHED PRODUCT:** **ibuprofen plus hyoscine butylbromide** **NAME OF ACTIVE INGREDIENT(S):** **ibuprofen and hyoscine butylbromide**	**INDIVIDUAL TRIAL TABLE REFERRING TO CLINICAL DOCUMENTATION OF THE DOSSIER:** **Volume:** **Page:**	*(FOR NATIONAL AUTHORITY USE ONLY)*
Title of the trial: A double-blind, randomized, cross-over, multi-center efficacy and safety study of ibuprofen plus hyoscine butylbromide for pain management due to primary dysmenorrhea		
Coordinating Investigator: Dr. Anna Chorbova, DCC Ascendent, 47 Bacho Kiro Str., Sofia 1202, Bulgaria		
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Publication (reference):		The results are not yet published
Studied period: 13-JAN-2023 to 28-JUN-2023 First Subject First Visit: 13-JAN-2023 First Subject First Dose: 17-JAN-2023 Last Subject Last Visit: 28-JUN-2023		**Phase of development:** Phase III

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Objectives:
The main objectives of the present trial was to assess the efficacy of a combination of ibuprofen plus hyoscine butylbromide (Test IMP: ibuprofen plus hyoscine butylbromide) as compared to ibuprofen (Reference 1: Brufen 400 mg) alone and hyoscine butylbromide (Reference 2: Buscopan 10 mg) alone for the management of pain due to primary dysmenorrhea.

Methodology:
Double-blind, randomized, verum-controlled, multi-center, cross-over trial in three study periods.

Subjects (planned and analyzed):	planned for screening (stage 1):	approximately 80
	planned for randomization (stage 1):	54
	screened (*trial population*):	57
	screening failures:	2
	randomized:	55
	trial withdrawals (prior to IMP administration):	1 (Rnd. no. 0068, by patient's request)
	number of randomized and treated subjects *(full analysis set [FAS]):*	54
	trial withdrawals (after IMP administration):	1 (Rnd. no. 0049, randomized by mistake)
	completed:	53
	per protocol [PP] set:	48

Diagnosis and main criteria for inclusion:	[1] Female patients ≥18 and ≤40 years of age [2] Patients with a history of primary dysmenorrhoea [3] Patients with moderate to severe pain in at least 5 of the last 6 menstrual cycles [4] Patients willing and able (e.g., mental and physical condition) to participate in all aspects of the study as evidenced by providing signed written informed consent

TEST product dose and mode of administration, batch number:	name:	ibuprofen plus hyoscine butylbromide
	manufacturer:	RONTIS HELLAS S.A.
	active ingredient:	ibuprofen and hyoscine butylbromide
	dosage form:	Film coated tablet
	final dosage form:	hard capsule
	over-encapsulating:	RONTIS HELLAS S.A.
	unit dose (strength):	400 mg ibuprofen and 20 mg hyoscine butylbromide
	mode/ route:	oral administration
	regimen:	one hard capsule three times per day (=1200 mg ibuprofen and 60 mg hyoscine butylbromide)
	batch no. (final dosage form): retest date (final dosage form):	BL221003 (TC2206042) / CL2210005 06.2023

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	batch no. (film-coated tablet): retest date (film-coated tablet):	TC2206042 06.2023
	blind batch no.: blind retest date:	BL221001-3 06.2023
REFERENCE 1 product dose and mode of administration, batch number:	name	Brufen 400 mg
	marketing authorization holder:	Mylan EPD bvba/sprl Terhulpsesteenweg, 6A 1560 Hoeilaart, Belgium
	active ingredient:	ibuprofen
	dosage form:	Film coated tablet
	final dosage form:	hard capsule
	over-encapsulating:	RONTIS HELLAS S.A.
	unit dose (strength):	400 mg ibuprofen
	mode/ route:	oral administration
	regimen:	one hard capsule three times per day (=1200 mg ibuprofen)
	batch no. (final dosage form): expiry date (final dosage form):	BL221001 (28238PC / CL2210006) 03.2024
	batch no. (film-coated tablet): expiry date (film-coated tablet):	28238PC 03.2024
	blind batch no.: blind retest date:	BL221001-3 06.2023
REFERENCE 2 product dose and mode of administration, batch number:	name	Buscopan 10 mg
	marketing authorization holder:	Sanofi Belgium Leonardo da Vincilaan 19 1831 Diegem, Belgium
	active ingredient:	hyoscine butylbromide
	dosage form:	Coated tablet
	final dosage form:	hard capsule (containing 2 coated tablets)
	over-encapsulating:	RONTIS HELLAS S.A.
	unit dose (strength):	10 mg hyoscine butylbromide
	mode/ route:	oral administration
	regimen:	one hard capsule three times per day (= 60 mg hyoscine butylbromide)
	batch no. (final dosage form): expiry date (final dosage form):	BL221002 (201658 / CL2210007) 10/2023

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	batch no. (coated tablet): expiry date (coated tablet): blind batch no.: blind retest date:	201658 10/2023 BL221001-3 06.2023

Duration of treatment:

The duration of treatment in each of the 3 study periods was 1 day: the first day of onset of symptoms of dysmenorrhea.

Eligible patients received the study medication and were instructed to administer the study drugs (3 doses with an interval of 6-8 hours between doses) on the first day of onset of symptoms of dysmenorrhea associated with their menstrual bleeding. The administration sequence of the test, reference 1 and reference 2 products in the 3 study periods was randomly assigned.
In case the menstrual bleeding was not accompanied by dysmenorrhea, the corresponding menstrual cycle was skipped and the study medication was administered during the next cycle. The maximum number of cycles which could be skipped due to lack of dysmenorrhea was 2.

Criteria for evaluation:

Efficacy parameters

- Assessments of pain intensity in a patient's diary on an 11-point numeric rating scale (with 0 defined as the absence of pain and 10 defined as the worst possible pain) at pre-defined points in time: before intake as well as 10, 20, 30, 40, 50, 60 minutes and 1.5, 2, 3, 4, 5, and 6 hours after each of the first 2 doses of study medication.
- Patient's global rating of pain relief for the whole day of treatment in each cycle in a patient's diary on a 5-point scale (0=none, 1=a little, 2=some, 3=a lot, 4=complete relief)

Safety parameters

- Rating of tolerability of study drug by the patient
- Treatment-emergent adverse events
- Results of clinical examination

Primary endpoint:

- Area under the curve from 0 to 4 hours after each of the first two doses (AUC0-4h) for the pain intensity differences (pre-dose - post dose)

Secondary endpoints:

- Area under the curve from 0 to 2 hours after each of the first two doses for the pain intensity differences (pre-dose - post dose)
- Area under the curve from 0 to 6 hours after each of the first two doses for the pain intensity differences (pre-dose - post dose)
- Partial areas under the curve: 0 to 1 hour, 1 to 2 hours, and 2 to 6 hours after each of the first two doses for the pain intensity differences (pre-dose - post dose)
- Pain intensity differences (pre-dose - post dose) at each of the pre-defined points in time: 10, 20, 30, 40, 50, 60 minutes and 1.5, 2, 3, 4, 5, and 6 hours after each of the first two doses of study medication
- Percentage of patients who reach at least 30% reduction in pain intensity after each of the first two doses

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- Percentage of patients who reach at least 50% reduction in pain intensity after each of the first two doses
- Time to at least 30% reduction in pain intensity after each of the first two doses
- Time to at least 50% reduction in pain intensity after each of the first two doses
- Number of patients using rescue medication within the first 2 hours post dose
- Number of patients using rescue medication within the entire duration of treatment
- Patient's global ratings of pain relief

Safety endpoints:

- Evaluation of tolerability
- Evaluation of treatment-emergent adverse events (safety evaluation)
- Evaluation of results of clinical examination (vital signs, ECG, physical examination, gynecological examination, laboratory examination of blood and pregnancy test in urine)

Statistical methods:

Analysis Populations

Full-Analysis Set (FAS): all randomised patients who received at least one dose of the study medication. This was the primary dataset for comparison of the primary endpoint.

The last observation (rating of pain) within the respective study period was carried forward for calculating the primary endpoint in patients who prematurely terminated any of the study periods.

Patients who needed rescue analgesic medication must not terminate the trial but proceeded with treatment and ratings of pain while receiving concomitant rescue medication in order to allow for an additional sensitivity analysis that targeted the treatment policy effect where the pain AUC was derived from all measurements irrespective of the intake of rescue medication.

If patients missed whole study period(s) (e.g., drop-outs) the missed periods were not taken into account for statistical comparisons.

Per-Protocol Set (PPS): all FAS patients without major protocol deviation that could affect the efficacy evaluation. This was defined in a blinded data review meeting before unblinding the trial.

Efficacy
The primary dataset for the evaluation of efficacy was the FAS.

The trial was planned according to a group sequential design in two stages with one unblinded interim analysis after the first stage.

A Bonferroni adjustment of alpha was used as the most conservative approach of keeping the overall alpha within the acceptance range (total two-sided alpha for both stages of up to 0.05). The two-sided alpha value at each of both stages was be 0.025.

The primary endpoint (Area under the curve from 0 to 4 hours after each of the first two doses (AUC0-4h) for the pain intensity differences (pre-dose - post dose)) was analysed by analysis of covariance (ANCOVA) using PROC MIXED in SAS with a covariate for baseline pain intensity (for the relevant period), fixed-effect terms for treatment, sequence, and period and with patient within sequence as a random effect.

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Two separate comparisons were done, each with an alpha of 0.025:

1. Test vs. Reference 1
2. Test vs. Reference 2

Each of both comparisons was performed with an alpha of 0.025.

An overall positive study result could only be concluded if both comparisons provided statistically significant results. Due to this reason no further alpha adjustment for multiple testing was practiced.

Safety
The FAS was also used for the analysis of the safety data.

All safety data obtained in this trial were tabulated descriptively with descriptive group statistics (mean, standard deviation, minimum, maximum, number of valid cases) where appropriate.

RESULTS

The trial was conducted according to a group sequential design in two stages with an interim analysis after the first stage. The results of the first stage analysis is described in this report. Based on these result the study was not continued in a second stage.

A total of 55 subjects were randomized and 53 subjects completed the trial according to the protocol.
One subject (Rnd. No. 0049) did not fulfill inclusion criterion no.1 but was randomized by mistake and took study medication in the first cycle. This patient was exluded thereafter. One subject (Rnd. No. 0068) was randomized but did not start the first cycle by own request and was considered drop-out.

Primary endpoint
The results of the primary endpoint area under the curve from 0 to 4 hours after each of the first two doses (AUC0-4h) for the pain intensity differences (pre-dose - post dose) are as follows:

TT 1 AUC(0-4h), ANCOVA, Full Analysis Set

Comparison	Difference of Mean Changes	Standard error of difference	97.5%-confidence interval	p-value
T vs. R1	0.28	0.6354	[-1.15, 1.71]	0.6588
T vs. R2	0.47	0.8025	[-1.34, 2.28]	0.5571

The comparison of the test product with the 2 reference products does not show a statistically significant difference between the products (p-values > 0.025).

Secondary endpoints
- Area under the curve from 0 to 2 hours after each of the first two doses for the pain intensity differences (pre-dose - post dose):

TT 2 AUC(0-2h), ANCOVA, Full Analysis Set

Comparison	Difference of Mean Changes	Standard error of difference	97.5%-confidence interval	p-value
T vs. R1	0.59	1.2072	[-2.13, 3.31]	0.6272
T vs. R2	0.90	1.1897	[-1.78, 3.58]	0.4506

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- Area under the curve from 0 to 6 hours after each of the first two doses for the pain intensity differences (pre-dose - post dose):

TT 3 AUC(0-6h), ANCOVA, Full Analysis Set

Comparison	Difference of Mean Changes	Standard error of difference	97.5%-confidence interval	p-value
T vs. R1	-0.05	0.3250	[-0.78, 0.68]	0.8802
T vs. R2	0.21	0.4083	[-0.71, 1.13]	0.6132

The results for both secondary endpoints do not show statistically significant differences in the pain intensity pre-post dose between the products (p-values > 0.025).

The results regarding the comparisons of the following secondary endpoints

- Partial areas under the curve: 0 to 1 hour, 1 to 2 hours, and 2 to 6 hours after each of the first two doses for the pain intensity differences (pre-dose - post dose)
- Pain intensity differences (pre-dose - post dose) at each of the pre-defined points in time: 10, 20, 30, 40, 50, 60 minutes and 1.5, 2, 3, 4, 5, and 6 hours after each of the first two doses of study medication
- Percentage of patients who reach at least 30% reduction in pain intensity after each of the first two doses
- Percentage of patients who reach at least 50% reduction in pain intensity after each of the first two doses
- Time to at least 30% reduction in pain intensity after each of the first two doses
- Time to at least 50% reduction in pain intensity after each of the first two doses

do also not show considerable differences between the combination test product and the 2 single reference drugs.

- Number of patients using rescue medication within the first 2 hours post dose

Four patients used rescue medication 9 times within the first 2 hours post dose as follows: 1 patient after all three doses of R2 (cycle 1), and after the third dose of Test (cycle 3); 1 patient after the first dose of R2 (cycle 1); 1 patient after the second dose of Test (cycle 1), after the second dose of R1 (cycle 2) and after the first dose of R2 (cycle 3); and 1 patient after the second dose of R1 (cycle 1).

- Number of patients using rescue medication within the entire duration of treatment

One patient took rescue medication 3.5 hours post dose (third dose of Test in cycle 1).

One patient took rescue medication 1 hour prior to the second dose of R2 in cycle 3.

In total, 5 patients used rescue medication during the entire duration of treatment.

- Patient’s global ratings of pain relief

The majority of patients reported a “complete relief” after intake of the Test (40.74 %), the Reference 1 (44.23 %) and the Reference 2 (39.62 %) followed by “a lot relief” after intake of the Test (37.04 %), the Reference 1 (34.62 %) and the Reference 2 (32.08 %) (data pooled over the 3 cycles). Looking into the separate cycles with the Test product, there was a “complete relief” after intake in 11.11 % of patients (cycle 1), 57.89 % (cycle 2) and 52.94 % (cycle 3).

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SAFETY RESULTS

Adverse events (AEs)

The Test IMP and the two Reference IMPs were equally well tolerated. Serious adverse events (SAEs) were not registered in the course of the trial.

A total of 2 non-serious adverse events (AEs) were registered in 1 subject in the course of the trial: Conjunctivitis and Nasopharyngitis (MedDRA PT). Both events were assessed by the investigator as not related to the study medication intake and recovered completely.

No clinically relevant laboratory changes or trends were observed during the present trial. The laboratory and clinical screening revealed no indications for adverse events or poor tolerability.

The study drugs were equally well tolerated based on patient's ratings.

CONCLUSIONS

The statistical results obtained for the primary and secondary endpoints after the first stage of the trial do not show a statistically significant difference between the combination test product and the two single reference products.
With the present trial it could be demonstrated that the overall pain relief by the patients has practically no differences between the treatment groups.
Furthermore, the fixed dose combination test product was well tolerated by the patients and did not show differences with regards to safety compared to the two single reference products.

Date of Clinical Study Report (Version 1.0): 09-Apr-2024