Clinical trial results:
Randomized, double-blind, cross-over efficacy and safety study based on the pharmacodynamic model of topical use of the new combination gel containing diphenhydramine hydrochloride 20 mg/g and lidocaine hydrochloride 10 mg/g versus placebo in the treatment of local skin inflammatory and allergic lesions induced by the provocative test with histamine in healthy subjects.

Summary

EudraCT number	2018-004502-26
Trial protocol	PL
Global end of trial date	26 August 2019

Results information

Result version number	v1 (current)
This version publication date	16 May 2021
First version publication date	16 May 2021

Trial information

Trial identification

Sponsor protocol code	DL/HL/09/18

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Przedsiębiorstwo Produkcji Farmaceutycznej (P.P.F.) HASCO-LEK S.A.
Sponsor organisation address	Żmigrodzka 242E , Wrocław, Poland, 51-131
Public contact	Clinical Trial Information Desk, Przedsiębiorstwo Produkcji Farmaceutycznej (P.P.F.) HASCO-LEK S.A., 48 71327 18 61 261, a.puchala@hasco-lek.pl
Scientific contact	Clinical Trial Information Desk, Przedsiębiorstwo Produkcji Farmaceutycznej (P.P.F.) HASCO-LEK S.A., 48 71327 18 61 261, a.puchala@hasco-lek.pl

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 August 2019
Global end of trial reached?	Yes
Global end of trial date	26 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate efficacy and safety of the new combination topical gel containing diphenhydramine hydrochloride 20 mg/g and lidocaine hydrochloride 10 mg/g versus placebo in the treatment of local skin inflammatory and allergic lesions induced in the provocative test with histamine (skin prick test)

Protection of trial subjects:

Observation per subject from enrolment to the study (screening examination) until the end-of study evaluation. Medical surveillance at site. Safety procedures: physical examination, vital signs, laboratory tests, safety monitoring (AEs).

Background therapy:

Not applicable

Evidence for comparator: -

Actual start date of recruitment	09 August 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 44
Worldwide total number of subjects	44
EEA total number of subjects	44

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	44
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The screening procedures applied. Volunteers who signed informed consent form (ICF), met all inclusion criteria and none of the exclusion criteria were enrolled into the study.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The double-blind design was used for the study. The aim of this was to decrease the risk of systematic error. Especially, this ensured more results reliability at the point of asking subjects about symptoms intensity as well as during taking measurements by the Investigator. Blinding could have been only broken in emergency situations for reasons of subjects safety. IPs were packed and labelled in a way that prevented unblinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence TP - Test product then Placebo

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Diphenhydramine hydrochloride and lidocaine hydrochloride, 20 mg/g and 10 mg/g, gel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Dose: 0.16 mL of a product - single application
Mode of administration: Topical administration

Investigational medicinal product name	Placebo, gel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Dose: 0.16 mL of a product - single application
Mode of administration: Topical administration

Arm title	Sequence PT - Placebo than Test product

Arm description: -

Arm type	Experimental

Investigational medicinal product name	Placebo, gel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Dose: 0.16 mL of a product - single application
Mode of administration: Topical administration

Investigational medicinal product name	Diphenhydramine hydrochloride and lidocaine hydrochloride, 20 mg/g and 10 mg/g, gel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Dose: 0.16 mL of a product - single application
Mode of administration: Topical administration

Number of subjects in period 1	Sequence TP - Test product then Placebo	Sequence PT - Placebo than Test product
Started	22	22
wash-out	21	22
Completed	21	22
Not completed	1	0
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	44	44	
Age categorical Units: Subjects			
Adults (18-64 years)	44	44	
Gender categorical Units: Subjects			
Female	24	24	
Male	20	20	

Subject analysis sets	
Subject analysis set title	Test product
Subject analysis set type	Sub-group analysis
Subject analysis set description: Diphenhydramine hydrochloride and lidocaine hydrochloride, 20 mg/g and 10 mg/g, gel	
Subject analysis set title	Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Placebo, gel	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: all subjects exposed to the study products were the part of the safety analysis	

Reporting group values	Test product	Placebo	Safety population
Number of subjects	43	44	44
Age categorical Units: Subjects			
Adults (18-64 years)	43	44	44
Gender categorical Units: Subjects			
Female	23	24	24
Male	20	20	20

End points

End points reporting groups

Reporting group title	Sequence TP - Test product then Placebo
Reporting group description: -	
Reporting group title	Sequence PT - Placebo than Test product
Reporting group description: -	
Subject analysis set title	Test product
Subject analysis set type	Sub-group analysis
Subject analysis set description: Diphenhydramine hydrochloride and lidocaine hydrochloride, 20 mg/g and 10 mg/g, gel	
Subject analysis set title	Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Placebo, gel	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: all subjects exposed to the study products were the part of the safety analysis	

Primary: Difference in itching AUC

End point title	Difference in itching AUC
End point description:	
End point type	Primary
End point timeframe: Evaluation of itch using VAS scale was performed after histamine administration (time "0") and at: 2, 4, 6, 8, 10, 15, 20, 30, 60 and 90 minutes after test product/placebo administration	

End point values	Test product	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	39		
Units: minute				
arithmetic mean (standard deviation)	185.7 (± 289.3)	301.5 (± 504.4)		

Statistical analyses

Statistical analysis title	Comparison of itching AUC between products
Statistical analysis description: Wilcoxon test for paired data	
Comparison groups	Test product v Placebo

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison of logarithmically transformed itching
Statistical analysis description: t-test for paired data	
Comparison groups	Test product v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024
Method	t-test, 2-sided

Secondary: Change in diameter of the wheal

End point title	Change in diameter of the wheal
End point description:	

End point type	Secondary
End point timeframe: Evaluation of the diameter of the wheal and the erythema was performed after histamine administration (time "0") and at: 2, 4, 6, 8, 10, 15, 20, 30, 60 and 90 minutes after test product/placebo administration	

End point values	Test product	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	39		
Units: mm				
arithmetic mean (standard deviation)				
0min	1.7 (± 1.1)	1.8 (± 1.1)		
2min	2.1 (± 0.9)	1.9 (± 0.9)		
4min	2.9 (± 0.9)	3.0 (± 0.9)		
6min	3.8 (± 0.7)	4.0 (± 0.8)		
8min	4.2 (± 0.8)	4.4 (± 0.9)		
10min	4.6 (± 0.9)	4.9 (± 1.1)		
15min	4.6 (± 1.1)	5.2 (± 1.4)		
20min	4.8 (± 1.1)	5.1 (± 1.4)		
30min	4.5 (± 1.6)	4.8 (± 1.5)		
60min	2.6 (± 2.1)	3.3 (± 2.0)		
90min	1.6 (± 1.7)	2.3 (± 2.2)		

Statistical analyses

Statistical analysis title	Change in diameter of the wheal
Statistical analysis description: Linear mixed effect model	
Comparison groups	Test product v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [1]
Method	Mixed models analysis

Notes:
[1] - NA

Secondary: Peak itching intensity

End point title	Peak itching intensity
End point description:	
End point type	Secondary
End point timeframe: Evaluation of itch using VAS scale was performed after histamine administration (time "0") and at: 2, 4, 6, 8, 10, 15, 20, 30, 60 and 90 minutes after test product/placebo administration.	

End point values	Test product	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	39		
Units: number				
arithmetic mean (standard deviation)	22.8 (± 16.6)	24.9 (± 17.0)		

Statistical analyses

Statistical analysis title	Comparison of peak itching intensity
Statistical analysis description: Wilcoxon signed rank test	
Comparison groups	Test product v Placebo

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.311
Method	Wilcoxon (Mann-Whitney)

Secondary: Rate of decrease in itching

End point title	Rate of decrease in itching

End point description:

End point type	Secondary

End point timeframe:

Evaluation of itch using VAS scale was performed after histamine administration (time "0") and at: 2, 4, 6, 8, 10, 15, 20, 30, 60 and 90 minutes after test product/placebo administration.

End point values	Test product	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	39		
Units: number				
arithmetic mean (standard deviation)				
0min	20.8 (± 16.1)	21.0 (± 17.1)		
2min	14.9 (± 15.5)	18.4 (± 17.4)		
4min	11.5 (± 13.9)	15.0 (± 15.6)		
6min	7.4 (± 11.3)	11.7 (± 15.3)		
8min	5.7 (± 11.1)	8.4 (± 13.1)		
10min	4.2 (± 8.9)	6.2 (± 11.8)		
15min	3.1 (± 8.0)	4.8 (± 11.3)		
20min	2.1 (± 6.7)	4.2 (± 10.4)		
30min	1.2 (± 3.0)	3.1 (± 8.3)		
60min	0.4 (± 1.2)	0.9 (± 2.5)		
90min	0.2 (± 0.4)	0.4 (± 1.5)		

Statistical analyses

Statistical analysis title	Rate of decrease in itching intensity

Statistical analysis description:

Linear mixed effect model

Comparison groups	Placebo v Test product

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Secondary: Change in area of the wheal

End point title	Change in area of the wheal

End point description:

End point type	Secondary

End point timeframe:

Evaluation of the diameter of the wheal and the erythema was performed after histamine administration (time "0") and at: 2, 4, 6, 8, 10, 15, 20, 30, 60 and 90 minutes after test product/placebo administration.

End point values	Test product	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	39		
Units: mm2				
arithmetic mean (standard deviation)				
0min	2.68 (± 2.33)	3.22 (± 3.00)		
2min	3.71 (± 2.38)	3.40 (± 2.24)		
4min	6.79 (± 3.42)	7.49 (± 3.46)		
6min	11.30 (± 3.92)	11.62 (± 3.72)		
8min	13.09 (± 4.51)	14.88 (± 5.06)		
10min	15.91 (± 5.54)	17.44 (± 6.89)		
15min	15.89 (± 6.69)	20.28 (± 10.07)		
20min	17.58 (± 7.61)	20.44 (± 11.63)		
30min	17.02 (± 10.15)	19.11 (± 11.05)		
60min	7.93 (± 7.86)	10.67 (± 9.45)		
90min	4.13 (± 5.62)	7.27 (± 8.86)		

Statistical analyses

Statistical analysis title	Change in area of the wheal

Statistical analysis description:

Linear mixed effect model

Comparison groups	Test product v Placebo

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Secondary: Change in diameter of the erythema

End point title	Change in diameter of the erythema

End point description:

End point type	Secondary

End point timeframe:

Evaluation of the diameter of the wheal and the erythema was performed after histamine administration (time "0") and at: 2, 4, 6, 8, 10, 15, 20, 30, 60 and 90 minutes after test product/placebo administration.

End point values	Test product	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	39		
Units: mm				
arithmetic mean (standard deviation)				
0min	2.1 (± 1.3)	2.6 (± 2.0)		
2min	2.6 (± 1.0)	2.5 (± 1.3)		
4min	5.1 (± 5.0)	4.4 (± 3.5)		
6min	6.1 (± 4.8)	6.6 (± 5.3)		
8min	6.8 (± 4.1)	7.7 (± 6.1)		
10min	6.9 (± 3.6)	8.4 (± 6.5)		
15min	6.7 (± 3.6)	9.7 (± 7.7)		
20min	6.8 (± 3.7)	9.5 (± 7.3)		
30min	6.1 (± 3.5)	8.4 (± 6.7)		
60min	2.6 (± 2.1)	4.2 (± 4.6)		
90min	1.6 (± 1.7)	2.3 (± 2.2)		

Statistical analyses

Statistical analysis title	Change in diameter of the erythema

Statistical analysis description:

Linear mixed effect model

Comparison groups	Test product v Placebo

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Secondary: Change in area of the erythema

End point title	Change in area of the erythema

End point description:

End point type	Secondary

End point timeframe:

Evaluation of the diameter of the wheal and the erythema was performed after histamine administration (time "0") and at: 2, 4, 6, 8, 10, 15, 20, 30, 60 and 90 minutes after test product/placebo administration.

End point values	Test product	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	39		
Units: mm2				
arithmetic mean (standard deviation)				
0min	4.01 (± 4.14)	7.83 (± 13.64)		
2min	5.46 (± 3.58)	5.80 (± 5.07)		
4min	36.33 (± 89.24)	21.69 (± 58.86)		
6min	41.34 (± 89.62)	49.42 (± 105.58)		
8min	44.30 (± 72.79)	63.96 (± 120.36)		
10min	41.89 (± 65.54)	69.26 (± 149.16)		
15min	41.75 (± 66.89)	102.67 (± 197.67)		
20min	42.89 (± 69.09)	90.52 (± 149.26)		
30min	36.55 (± 60.21)	73.20 (± 129.09)		
60min	8.26 (± 8.43)	25.60 (± 65.97)		
90min	4.23 (± 5.86)	7.79 (± 9.31)		

Statistical analyses

Statistical analysis title	Change in area of the erythema

Statistical analysis description:

Linear mixed effect model

Comparison groups	Test product v Placebo

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Secondary: Occurance of AEs

End point title	Occurance of AEs

End point description:

End point type	Secondary

End point timeframe:

all subjects exposed to study product were included into the safety population

End point values	Test product	Placebo	Safety population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	43	44	44	
Units: number	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All subjects exposed to the study products were a part of the safety analysis. All Adverse Events (AE) reported during the study should be included in this analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Safety population
Reporting group description: -	
Reporting group title	Test product
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Safety population	Test product	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	0 / 44 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	Safety population	Test product	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	0 / 44 (0.00%)

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: During the study there were no adverse events (AEs) reported in the study subjects

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported