Clinical trial results:
A double-blind, randomized, vehicle-controlled clinical multi-center study to evaluate the efficacy and safety of N-Acetyl-GED-0507-34-LEVO gel, 2 and 5%, applied once daily for 12 weeks in patients with facial acne vulgaris

Summary

EudraCT number	2018-003307-19
Trial protocol	DE PL IT
Global end of trial date	13 May 2020

Results information

Result version number	v1 (current)
This version publication date	10 June 2022
First version publication date	10 June 2022
Summary attachment (see zip file)	GEDACNE - Summary final version_05.10.2020_signed (GEDACNE - Summary final version 05.10.2020 signed.pdf)

Trial information

Trial identification

Sponsor protocol code	NAC-GED-0507-ACN-01-18

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	PPM SERVICES SA
Sponsor organisation address	Viale Serfontana 10, Morbio Inferiore, Switzerland, 6834
Public contact	DR. SALVATORE BELLINVIA, PPM SERVICES SA, 0041 916969710, gedacne_globalpm@ppmservices.ch
Scientific contact	DR. SALVATORE BELLINVIA, PPM SERVICES SA, 0041 916969710, gedacne_globalpm@ppmservices.ch

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	05 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 May 2020
Global end of trial reached?	Yes
Global end of trial date	13 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the study is to evaluate the efficacy and the local and systemic safety of 2% and 5% N-Acetyl-GED-0507-34-Levo gel, in comparison to the corresponding vehicle gel, applied once daily (OD) for 12 weeks in patients with facial acne vulgaris

Protection of trial subjects:

The protocol version 1.2 of 28 January 2019 (Italy CA requirements added) was submitted both to the Italian and Polish Regulatory Agency and relative CECs and received a favourable opinion on 26 February 2019 (Italian CEC) and on 14 February 2019 (Polish CEC) and the authorization from Italian CA on 07 February 2019 and from Polish CA on 09May 2019. The protocol version 1.3 of 13 May 2019 (German CA requirements added) was submitted both to the German Regulatory Agency (BfArM) and relative CEC and received a favourable opinion on 27 June 2019 (German CA) and on 12 July 2019 (German CEC). This clinical trial was conducted in Italy, Poland and German under the supervision of the following national coordinators:
Prof. Mauro Picardo - Italy coordinator
Prof Christos C. Zouboulis – Germany coordinator
Prof. Adam Reich – Poland coordinator
The study protocol (no. NAC-GED-0507-ACN-01-18 Eudract Number: 2018-003307-19) was conducted in compliance with specific regulatory requirements of the involved countries' requirements This trial was conducted in compliance with the most recent version of the Declaration of Helsinki (Fortaleza, Brazil, October 2013), the most recent version of the Good Clinical Practice (GCP), and all applicable regulatory requirements (European Directive 2001/20/EC, 04 April 2001), and Italian Laws (D.lgs no. 211, 24 June 2003 and all applicable regulations).
The Study has been strongly affected by the COVID19 pandemic. All the COVID19 guidelines released by EMA and local Competent Authorities have been applied. On 22th March 2020 a contingency plan has been released by PPM Services and notified to all the involved CA and Ethics Committees accordingly to the local procedures.

Background therapy:

-

Evidence for comparator:

-

Actual start date of recruitment	29 March 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: 235
Country: Number of subjects enrolled	Germany: 46
Country: Number of subjects enrolled	Italy: 169

Worldwide total number of subjects	450
EEA total number of subjects	450

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)	263
Adults (18-64 years)	187
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Date of first enrolment: 29 March 2019 (first randomized patient)
Date of last completed: 13 May 2020 (last visit of the last patient)

Pre-assignment

Screening details:

A total of 450 patients have been recruited in the study:
• 150 Patients were randomized to NAC-GED 5%
• 150 Patients were randomized to NAC-GED 2%
• 150 Patients were randomized to vehicle

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	Investigator, Monitor, Data analyst, Subject, Carer, Assessor

Blinding implementation details:

The treatment group designation remained blinded to the sites until the final database was locked. Randomization was supported by the interactive web response system (IWRS) to ensure study medication assignment according to stratification.

Arms

Are arms mutually exclusive?	Yes
Arm title	IMP 5%

Arm description:

N-ACETYL-GED-0507-34-LEVO gel 5%

Arm type	Experimental
Investigational medicinal product name	N-Acetyl-GED-0507-34- Levo 5% gel
Investigational medicinal product code	N-Acetyl-GED-0507-34- Levo 5% gel
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

N-ACETYL-GED-0507-34-LEVO GEL 5% daily application for 12 weeks

Arm title	IMP 2%

Arm description:

N-ACETYL-GED-0507-34-LEVO GEL 2%

Arm type	Experimental
Investigational medicinal product name	N-Acetyl-GED-0507-34- Levo 2% gel
Investigational medicinal product code	N-Acetyl-GED-0507-34- Levo 2% gel
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

N-ACETYL-GED-0507-34-LEVO GEL 2% daily application for 12 weeks

Arm title	PLACEBO

Arm description:

PLACEBO

Arm type	Vehicle
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	IMP 5%	IMP 2%	PLACEBO
Started	150	150	150
Completed	137	134	129
Not completed	13	16	21
Consent withdrawn by subject	4	5	7
Adverse event, non-fatal	1	2	1
Other reasons	3	6	2
Lost to follow-up	1	2	8
Withdrawal by parents	-	-	2
Lack of efficacy	3	1	1
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
ITT	

Reporting group values	Overall trial	Total	
Number of subjects	450	450	
Age categorical			
In the ITT set, the mean age was 18.5 (±4.0) years (range 12-30), with subjects ≤18 years old representing 58.4%			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	263	263	
Adults (18-64 years)	187	187	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
In the ITT set, the mean age was 18.5 (±4.0) years (range 12-30), with subjects ≤18 years old representing 58.4%			
Units: years			
arithmetic mean	18.5		
standard deviation	± 4	-	
Gender categorical			
Male and female distribution			
Units: Subjects			
Female	277	277	
Male	173	173	
IGA			
Investigator's Global Assessment (IGA) at baseline between 3 (moderate) and 4 (severe)			
Units: Subjects			
IGA	450	450	
Inflammatory and non-inflammatory Lesion count			
Patients with ≥ 20 and ≤ 100 inflammatory lesions (papules and pustules) on the face and with ≥ 20 and ≤ 100 non-inflammatory lesions (open and closed comedones) on the face			
Units: Subjects			
Acne Lesion	450	450	

End points

End points reporting groups

Reporting group title	IMP 5%
Reporting group description: N-ACETYL-GED-0507-34-LEVO gel 5%	
Reporting group title	IMP 2%
Reporting group description: N-ACETYL-GED-0507-34-LEVO GEL 2%	
Reporting group title	PLACEBO
Reporting group description: PLACEBO	

Primary: Efficacy IGA score (Endpoint E2)

End point title	Efficacy IGA score (Endpoint E2)

End point description:

Proportion of patients with an IGA success defined as score of "clear" (score = 0) or "almost clear" (score = 1) and at least a 2-score point reduction in IGA at V6/Wk12. Both GED 2% and GED 5% demonstrated a high statistically significant superiority over vehicle, both in the ITT set and in the PP set.
For the IGA success rate (portion vs baseline of lesions classified "clear" or "almost clear") with GED 2% and GED 5% being better than vehicle in the ITT set with 9.3% (p=0.0749) and 21.3% (p=0.0001), respectively. GED 2% and GED 5% were better than vehicle in the PP set with 11.4% (p=0.0277) and 33.4% (p<0.0001), respectively.

End point type	Primary

End point timeframe:

week 12

End point values	IMP 5%	IMP 2%	PLACEBO	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	150	150	150	
Units: 0-100				
number (not applicable)				
IGA score	33.3	45.3	24.0	

Statistical analyses

Statistical analysis title	Primary endpoints

Statistical analysis description:

All statistical processing was performed using SAS®. Continuous variables were described by descriptive statistics (n, mean, standard deviation, Q1 and Q3, minimum, median and maximum). In the evaluation of both endpoints, the analysis was focused on the comparison between the active treatment and the control. The analysis of efficacy was conducted on the ITT and PP sets, with the ITT considered as the primary set for statistical analysis.

Comparison groups	IMP 5% v IMP 2% v PLACEBO

Number of subjects included in analysis	450
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05
Method	Regression, Logistic

Notes:

[1] - Frequency counts and percentages of subjects within each category were provided for categorical data. Summaries were provided for each treatment group. Hypothesis tests on the primary endpoints were conducted in the following hierarchical order: E1 and then E2 only if success on endpoint E1 was achieved. In the evaluation of both endpoints, the analysis was focused on the comparison between the active treatment and the control.

Primary: Efficacy Total lesion count (Endpoint E1)

End point title	Efficacy Total lesion count (Endpoint E1)

End point description:

Percent change from baseline in total lesion count (inflammatory plus non-inflammatory) at V6/Wk12. Regarding the percent change at final visit vs baseline of the total lesion count, both GED 2% and GED 5% demonstrated a high statistically significant superiority over vehicle, both in the ITT set and in the PP set.

End point type	Primary

End point timeframe:

W12

End point values	IMP 5%	IMP 2%	PLACEBO	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	150	150	150	
Units: -100-0				
number (not applicable)				
Total lesion Count	-44.7	-57.2	-33.8	

Statistical analyses

Statistical analysis title	Primary endpoints
Comparison groups	IMP 5% v IMP 2% v PLACEBO
Number of subjects included in analysis	450
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Regression, Logistic

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall

Adverse event reporting additional description:

Recording of treatment-emergent adverse events (TEAES) throughout the study; with special attention to local TEAEs in the treated facial area (local dermal safety*), and systemic (throughout the study)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	Overall

Reporting group description:

The most frequent TEAEs in the study were: nasopharyngitis (26), headache (9), followed by oropharyngeal pain (6) and upper respiratory tract infection (6). Also regarding topical signs and symptoms, the results are unchanged compared to the total adverse events discussed above (all the reported AEs were TEAEs).

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 450 (0.89%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 450 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Rehabilitation therapy			
subjects affected / exposed	1 / 450 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsillectomy			
subjects affected / exposed	1 / 450 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Urinary retention			
subjects affected / exposed	1 / 450 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastrointestinal infection			
subjects affected / exposed	1 / 450 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 450 (5.78%)		
Infections and infestations			
Nasopharyngitis	Additional description: The most frequent events reported are in the category "Infections and infestations", with a total of 59 events occurred. The most frequent event in this class was nasopharyngitis (26 AEs): 12 events in GED 5%, 4 in GED 2% and 10 in placebo.		
subjects affected / exposed	26 / 450 (5.78%)		
occurrences (all)	26		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 May 2020	The following Substantial Amendments were issued and competent EC/CAs notified: - Substantial Amendment 01 (SA01) – submitted in Italy and Poland, to reach a standardized and objective definition of measuring acne in line with the standard normal practice. This amendment introduces different wording for the definition of the severity grades to avoid numerical ranges of lesions in grading, there are no substantial differences from a clinical point of view. - Substantial Amendment 02 (SA02) - submitted in Germany, with the same aim of SA01. - Substantial Amendment 03 (SA03) - submitted in Germany, to include also minor patients (aged ≥ 14 to ≤ 30 years old instead of patients aged ≥ 18 to ≤ 30 years old). - Substantial Amendment 04 (SA04) - submitted in Germany, to add specific EC requirements. - Substantial Amendment 05 (SA05) - submitted in Germany, to include COVID-19 related procedures (BfArm requirement).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Treatment was limited to 12 weeks and therefore longer-term data on safety&tolerability are NA. Currently available data do not allow to validate the hypothesis that prolongation of therapy beyond 12W leads to a strengthening of therapeutic effect.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35553043