SUMMARY STUDY REPORT

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

Investigational product	N-Acetyl-GED-0507-34-Levo 2% gel and 5%
Indication studied	Facial Acne Vulgaris
Name of the Sponsor	PPM Services S.A., Switzerland
Protocol identification	NAC-GED-0507-ACN-01-18
EudraCT Number	2018-003307-19
Phase of development	IIb
Study initiation date	29 March 2019 (first randomized patient)
Study completion date	13 May 2020 (last visit of the last patient)
Sponsor medical officer	Dr. Salvatore Bellinvia, M.D. Managing Director Viale Serfontana 10 6834 Morbio Inferiore, Switzerland
GCP compliance	This study, including the archiving of essential documents, was performed in compliance with Good Clinical Practice and specific regulatory requirements of the Ministry of Health of the involved countries.
Date of the report	05 October 2020
Company's Medical Officer Responsible	*Signature* 12/10/2020 *Date*

SYNOPSIS

PPM Services S.A., Switzerland	***Individual Study Table referring to the dossier***	***(for National Authority use only)***
Name of finished product Not assigned yet	PART: [……]	
Name of active ingredient N-Acetyl-GED-0507-34-Levo 2% gel and N-Acetyl-GED-0507-34-Levo 5% gel	VOLUME: [……] PAGE: [……]	

Title of the study

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

Principal Investigators/National coordinators:

Prof. Mauro Picardo - Italy coordinator
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Prof. Adam Reich – Poland coordinator

Publication (reference)	***Clinical phase***
Not applicable	IIb
Date of first enrolment	***Date of last completed***
29 March 2019 (first randomized patient)	13 May 2020 (last visit of the last patient)

Objectives

Primary objective

To demonstrate the efficacy of a 12 weeks treatment with 5% N-Acetyl-GED-0507-34-Levo gel, the following family of primary efficacy endpoints will be analysed:

1. Endpoint 1 (E1): the percent change from baseline in total lesion count (inflammatory plus non-inflammatory) at V6/Wk12.
2. Endpoint 2 (E2): 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.

The assessment of E1 and E2 will be performed according to the hierarchical order above (chosen according to each endpoint clinical relevance), i.e. success on endpoint E1 will permit analysis of E2.

Secondary objective

To demonstrate the efficacy of a 12 weeks treatment with 2% N-Acetyl-GED-0507-34-Levo gel in the family of primary efficacy endpoints defined above.

To demonstrate the efficacy of a 12 weeks treatment with both 2% and 5% N-Acetyl-GED-0507-34-Levo on the following parameters:

a. Absolute change from baseline in total lesion count at V6/Wk12.
b. Percent (%) change from baseline in inflammatory lesion count at V6/W12.
c. Percent (%) change from baseline in non-inflammatory lesion count at V6/W12.

d. Absolute change from baseline in inflammatory lesion count at V6/Wk12.
e. Absolute change from baseline in non-inflammatory lesion count at V6/Wk12.
f. Percent (%) change from baseline in total lesion count at each post-baseline visit.
g. Percent (%) change from baseline in inflammatory lesion count at the other post-baseline assessment times.
h. Percent (%) change from baseline in non-inflammatory lesion count at the other post-baseline assessment times.
i. 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 the other post-baseline assessment times.
j. Absolute change from baseline in total lesion count (inflammatory plus non-inflammatory) at the other post-baseline visits.
k. Absolute change from baseline in inflammatory and non-inflammatory lesion count separately at the other post-baseline assessments.

Study design

Three-arm (N-Acetyl-GED-0507-34-LEVO gel, 2% [IMP 1] and 5% [IMP 2], and vehicle [IMP 3-V]), multiple-center, randomized, parallel-group, vehicle-controlled, double-blind efficacy and safety study.

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.

Patient population

Male and female patients aged ⩾ 12 to ⩽ 30 years old inclusive, affected by facial acne vulgaris

Main inclusion criteria

1. Informed consent obtained;
2. *Sex and age*: Male and female patients aged ≥ 12 to ≤ 30 years old inclusive;
3. *Diagnosis*: Patients with facial acne vulgaris with an investigator's global assessment (IGA) score of 3‑4 at screening and baseline visits;
4. *Inflammatory lesions*: Patients with ≥ 20 and ≤ 100 inflammatory lesions (papules and pustules) on the face (excluding the nose) and ≤ 1 nodules;
5. *Non-inflammatory lesions*: Patients with ≥ 20 and ≤ 100 non-inflammatory lesions (open and closed comedones) on the face (excluding the nose);
6. *Full comprehension*: Patient and parent(s)/guardian for <18 years old patient's ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to cooperate with the investigator and to comply with the requirements of the entire study;
7. *Contraception and fertility*: Women of childbearing potential must be using an effective contraception method during the entire duration of the study. Stable treatment period is required for the following reliable methods of contraception:
   - Hormonal oral, implantable, transdermal, or injectable contraceptives must be stable for at least 6 months before the screening visit
   - A non-hormonal intrauterine device (IUD) must be started at least 2 months before the screening visit.

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Main Exclusion Criteria

1. *Acne*: Patients with spontaneously improving or rapidly deteriorating acne within at least 3 months before study baseline. Patients who have a known history of acne unresponsive to topical and/or oral treatments. In particular subjects with history of persistent acne (a continuation of the disease from adolescence into adulthood) and subjects with history of relapsing acne. Patients with generalized or localized acne forms other than acne vulgaris, e.g., acne conglobata, acne fulminans, acne rosacea, secondary acne (chloracne, drug-induced acne, etc), nodule-cystic acne, acne tarda or acne requiring systemic treatment.
2. *Beard and facial hair, tattoos*: Patients who have a beard or who intend to grow a beard and/or to perform a facial tattoo during the study. Patient has facial hair or facial tattoos that could interfere with the study assessments in the opinion of the investigator.
3. *Skin diseases*: Patients with other active skin diseases (e.g., urticaria, atopic dermatitis, sunburn, seborrheic dermatitis, perioral dermatitis, rosacea, skin malignancies) or active skin infections in the facial region (bacterial, fungal, or viral) or any other facial disease or condition that might interfere with the evaluation of acne or place the patient at unacceptable risk.
4. *Allergy*: Known or suspected hypersensitivity to any active or inactive ingredient in the study products. Patients with a history of an allergic reaction or significant sensitivity to the formulations' ingredients
5. *Topical therapies*: Patients using, had intention to use during the study, or discontinued less than 4 weeks before study baseline, prescribed or over-the-counter topical therapies for the treatment of acne including but not limited to: corticosteroids, antibiotics, azelaic acid, benzoyl peroxide salicylates, α-hydroxy/glycolic acid, any other topical cosmetic therapy for acne and retinoids on the face.
6. *Facial procedures*: Patients using, had intention to during the study, or discontinued less than 4 weeks before study baseline, facial application of products containing glycolic or other acids, masks, washes or soaps containing benzoyl peroxide or salicylic acid, non-mild cleansers or moisturizers containing retinol, salicylic or alpha- or beta-hydroxy acids, facial procedures such as chemical peel, laser treatment, photodynamic therapy, acne surgery, cryodestruction or chemodestruction, x-ray therapy, intralesional steroids, dermabrasion, or depilation (except eyebrow shaping).
7. *Phototherapy*: Patients using, had intention to use during the study, or discontinued less than 12 weeks before study baseline, phototherapy for the treatment of acne including but not limited to: UV-A, UV-B, heliotherapy. Patients who have the need or plan to be exposed to artificial tanning devices or excessive sunlight during the study.
8. *Systemic therapies*: Patients using, had intention to use during the study, or discontinued less than 12 weeks before study baseline, systemic therapies for the treatment of acne including but not limited to: antibiotics, isotretinoin. Other systemic therapy which, in the opinion of the investigator, could affect the patient's acne (i.e., anabolics, lithium, EGFR inhibitors, iodides, systemic corticosteroids or other immunosuppressants).
9. *Known systemic diseases that can lead to acneiform eruptions*:
    a. Increased androgen production. 1) Adrenal origin: e.g., Cushing's disease, 21-hydroxylase deficiency; 2) Ovarian origin: e.g., polycystic ovarian syndrome, ovarian hyperthecosis
    b. Cryptococcosis disseminated;
    c. Dimorphic fungal infections;
    d. Behçet's disease.
10. *Investigative studies*: Participation in the evaluation of any investigational product or device within 30 days before study baseline

11. *Diseases*: Patient with underlying uncontrolled or unstable conditions (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal) which in the opinion of the investigator could significantly compromise the patient's safety and/or place the patient at an unacceptable risk. Any condition which in the investigator's opinion would make it unsafe for the patient to participate in the study
12. *Alcohol and other substance abuse*: History of alcohol or other substance abuse within one year before screening
13. *Communication*: Patient and parent/guardian (if applicable) unable to communicate or cooperate with the investigator due to e.g., language problems, impaired cerebral function, bad mental conditions
14. *Reliability*: Patient who may be unreliable for the study including patients who are unable to return for the scheduled visits
15. *Pregnancy (females only)*: Pregnant or breastfeeding women or planning to become pregnant during the study.

Test product, dose and mode of administration, batch number

N-Acetyl-GED-0507-34-LEVO 2%, 5%, vehicle GEL (referred to as GED 2%, 5% and vehicle GEL):

	GED 2% GEL	**GED 5% GEL**	**Vehicle**
Dosage	2%	5%	0%
Duration of the therapy	12 weeks	12 weeks	12 weeks
Mode of administration	Topical	Topical	Topical
Lot number	201812005 201907010	201812005 201907010	201812005 201907010

Statistical methods

Sample size.

The sample size was dominated by the IGA success rate endpoint to reach a power of 90% at a level of 0.05. Assuming an active group IGA success rate of 38% and a vehicle group IGA success rate of 20% (odds ratio of 0,408), a Fisher's Exact conditional test for two proportions required a sample size in each group of 142 subjects (corresponding to a total sample size of 426). Considering an amount of around 5-6% of non-evaluable subjects, a total of 450 patients were estimated to be enrolled in the study. Withdrawals were not replaced.

Analysis sets.

Screened Analysis Set (SCR): this analysis set includes all patients who signed the informed consent and received a screening number, irrespective of the completion of all the screening procedures. Intent-To-Treat (ITT) Set: all randomized patients. Full Analysis Set (FAS): all randomized patients who received at least one dose of investigational product and have at least one valid post-baseline efficacy assessment for both primary endpoints. Per-Protocol Set (PPS): this set comprises all patients included in the FAS who completed the study without major protocol deviations. Safety Set (SS): all patients who received at least one dose of study medication.

Statistical methods.

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). Frequency counts and percentage 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. The analysis of efficacy was conducted on the FAS, ITT and PPS sets, with the ITT considered as the primary set for statistical analysis. Last observation carried forward (LOCF) imputation methodology was used to impute missing values for the lesions count and the IGA in the ITT and FAS.

SUMMARY

Study population

Disposition of patients and baseline characteristics

A total sample of 450 patients were randomized in the three treatment groups (150 per group), all of them received at least one study treatment and therefore all of them were included in the ITT set and in the safety set. The Per Protocol set included 401 patients as 49 of them were protocol violators: 21, 13 and 15 respectively for GED 5%, GED 2% and vehicle, without substantial differences regarding the reasons of the exclusion.

In the ITT set, the mean age was 18.5 (±4.0) years (range 12-28), with subjects ≤18 years old representing 58.4% and females 61.6%. No statistical difference was found in the composition of the PP population and in the three treatment groups at baseline.

Efficacy

Primary end-points

Regarding the percent change at final visit vs baseline of the total lesion count, as shown in the table below, both GED 2% and GED 5% demonstrated a high statistically significant superiority over vehicle, both in the ITT set and in the PP set.

As shown in the same table, the above pattern appears similar also in the IGA success rate (portion vs baseline of lesions classified “clear” or “almost clear”) with GED 2% and GED 5% respectively 9.3% (p=0.0749) and 21.3% (p=0.0001) better than vehicle in the ITT set and respectively 11.4% (p=0.0277) and 33.4% (p≤0.0001) better than vehicle in the PP set.

	Intention To Treat Set			Per Protocol Set		
Treatment (N of subjects)	GED 2% (N=150)	GED 5% (N=150)	Vehicle (N=150)	GED 2% (N=137)	GED 5% (N=129)	Vehicle (N=135)
Total lesion count (%) (ANOVA vs vehicle)	-44.7 % (p=0.0010)	-57.2 % (p<0.0001)	-33.8 %	-43.7 % (p=0.0006)	-61.6 % (p<0.0001)	-31.9 %
IGA success rate, n(%) (Logistic regr. vs vehicle)	33.3 % (p=0.0749)	45.3 % (p=0.0001)	24.0 %	29.2 % (p=0.0277)	51.2 % (p<0.0001)	17.8 %

Secondary end-points

Expressed as mean of absolute values at baseline (Bas), at week 12 for the end of treatment (Eot) and as mean of changes from baseline, (Δ) results of this secondary end-point were as follow:

	Intention To Treat Set			Per Protocol Set		
Treatment (N of subjects)	GED 2% (N=150)	GED 5% (N=150)	Vehicle (N=150)	GED 2% (N=137)	GED 5% (N=129)	Vehicle (N=135)
Total lesion count (ANOVA vs vehicle)	Bas: 80.5 Eot: 45.0 Δ: -35.5 (p=0.0006)	Bas: 80.3 Eot: 34.7 Δ: -45.5 (p<0.0001)	Bas: 81.2 Eot: 54.5 Δ: -26.7	Bas: 83.4 Eot: 47.0 Δ: -36.3 (p=0.0005)	Bas: 77.9 Eot: 29.0 Δ: -48.9 (p<0.0001)	Bas: 84.4 Eot: 57.6 Δ: -26.8

Other secondary end-points (summary of the major evidences)

The analysis carried out considering the **inflammatory status** of the lesions demonstrated the efficacy of GED in both non-inflammatory and inflammatory lesions. Regarding the non-inflammatory lesions in the ITT population, at visit 6 (EOT, week 12), the percent change from baseline was highly significant (ANCOVA p<0.0001) versus vehicle for GED 5% (-50.6% ±26.1 vs -29.7% ±25.5). Similar results were also observed in the PP population.

As far as inflammatory lesions are concerned, in the ITT population, at visit 6, the percent change from baseline for GED 5% versus vehicle was -64.1% ±26.4 vs -36.2% ±32.2 (ANCOVA p<0.0001). Similar results were observed also in the PP population.

A pattern similar to GED 5% was observed at week 12 for GED 2%, that demonstrated superiority versus vehicle, even if to a less extent compared to 5% and occasionally not statistically significant vs vehicle in the ITT population: non-inflammatory -36.2% ±43.1 vs 29.7 ±25.5 (ANCOVA p=1009) and inflammatory -51.5% ±37.3 vs -36.2% ±32.2 (ANCOVA p=0.0002). In the PP population percent changes vs vehicle were -35.1 vs -28.8 (ANCOVA p<0.1205) and -50.5% vs -32.9% (ANCOVA p<0.0001) for non-inflammatory and inflammatory, respectively.

Regarding the **age of the patients**, the statistical analysis was carried out differentiating two cohorts: patients with age ≤18 years and patients >18 years. As shown in the table below, in the cohort of patients above 18 years old, the percent change at final visit of the total lesion count vs baseline, appear to be well responsive to both GED 2% and GED 5%, with the latter formulation always significantly better than vehicle, despite statistically underpowered and also better than the 2% formulation.

Age: >18 years	Intention To Treat Set			Per Protocol Set		
Treatment (N of subjects)	GED 2% (N=65)	GED 5% (N=63)	Vehicle (N=59)	GED 2% (N=60)	GED 5% (N=49)	Vehicle (N=50)
Total lesion count (%) (ANOVA vs vehicle)	-50.6 % (p=0.0018)	-54.6 % (p<0.0001)	-34.6 %	-49.8 % (p=0.0010)	-60.6 % (p<0.0001)	-31.2 %
IGA success rate n(%) (Logistic regr. vs vehicle)	38.5 % (p=0.2582)	50.8% (p=0.0143)	28.8 %	35.0 % (p=0.0495)	63.3 % (p<0.0001)	18.0 %

Regarding the cohort of patients less than 18 years old, the percent change at week 12 vs baseline of the total lesion count, as shown in the table below, GED 5% appears to be always significantly better than vehicle, despite statistically underpowered. Also GED 2% appears better than vehicle, even if without reaching statistical significance.

Age: ≤18 years	Intention To Treat Set			Per Protocol Set		
Treatment (N of subjects)	GED 2% (N=85)	GED 5% (N=87)	Vehicle (N=91)	GED 2% (N=77)	GED 5% (N=80)	Vehicle (N=85)
Total lesion count (%) (ANOVA vs vehicle)	-40.1 % (p=0.1071)	-59.0 % (p<0.0001)	-33.4 %	-38.9 % (p=0.1257)	-62.2 % (p<0.0001)	-31.2 %
IGA success rate n(%) (Logistic regr. vs vehicle)	29.4 % (p=0.1931)	41.4 % (p=0.0036)	20.9 %	24.7 % (p=0.2744)	43.8 % (p<0.0004)	17.6 %

No difference was observed in the response to the treatment regarding the **gender**. In the ITT set, percent change from baseline to week 6 (EOT) of the total lesion count was -42.8% (p=0.0474 vs vehicle) in males and -45.6% (p=0.0086 vs vehicle) in females for GED 2%, whereas for GED 5% changes were: -57.6% (p<0.0001 vs vehicle) and -56.8 (p<0.0001 vs vehicle) in males and females respectively. Almost identical findings were observed in the PP set.

As far as **dose-effect** is concerned, the response to GED 5% was superior to GED 2%, and statistical significance reached for most of the end-points. Regarding the total lesion count, the change vs baseline was found dose dependent: 10.9% and 23.4% better than vehicle in the ITT, respectively for GED 2% and GED 5% (11.8% and 29.7% in the PP set). GED 5% was found statistically superior to GED 2% both in the ITT set (p=0.0002) and in the PP population (p<0.0001). Regarding IGA, GED 5% was superior to GED 2% both in the ITT set (45.3% vs 33.3%; p=0.0339) and in the PP set (51.2% vs 29.2%; p=0.0003).

Safety

As shown in the table below, the safety profile of the three treatment arms resulted very similar both for frequency and severity of events and, in general, events were mostly classified as application site disorders.

	GED 2%	GED 5%	Vehicle
Safety set (N.)	150	150	150
Total pts with at least one AE (N and %)	24 (16.0%)	28 (18.7%)	29 (19.3)%
Total number of AEs	37	45	45
1st most frequent AE: ***common cold***	4 (2.7%)	10 (6.7%)	9 (6.0%)
2nd most frequent AE: ***headache***	3 (2.0%)	4 (2.7%)	3 (2.0%)
3rd most frequent AE: ***sore throat***	3 (2.0%)	2 (1.3%)	0
Total pts with at least one SAE (N and %)	1 (0.7%)	0	3 (2.0%)
Total number of SAEs	1 (0.7%)	0	3 (2.0%)
AEs leading to premature treatment discontinuation	2 (1.3%)	1 (0.7%)	1 (0.7%)

Regarding topical signs and symptoms such as: non-lesional erythema, exfoliation, dryness, stinging, burning and itching no change was found during the course of the study and no difference in the three groups.

Discussion and conclusions

Safety. Overall, both GED 2% and GED 5% applied topically for 12 weeks appeared safe and well tolerated in subjects with acne vulgaris, with a safety profile not distinguishable from vehicle. No safety concerns that required modifying the study conduct and/or study drug administration arose from the study.

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Efficacy. Regarding the clinical efficacy for the treatment of acne vulgaris, both GED 2% and GED 5% resulted superior to vehicle after 12 weeks in all the experimental conditions and the following conclusions can be drawn:

- The treatment with GED 5% and GED 2% improves both total lesions count and IGA score.
- The two concentrations are effective on both non-inflammatory and inflammatory lesions.
- The age of the patients does not substantially affect the response to the treatment.
- The gender does not influence the response to the treatment.
- There is an evident dose-effect and in all cases GED 5% is better than GED 2%.

Study limitations. The duration of treatment was limited to 12 weeks and therefore longer term data on safety and tolerability are not available. As for efficacy, even if it is likely that the prolongation of therapy beyond 12 weeks leads to a strengthening of the therapeutic effect, the currently available data do not allow to validate this hypothesis.

Conclusions. GED 5% appear to be the best candidate for further clinical development as topical agent for the treatment of acne vulgaris, considering its safety profile, similar to GED 2% and vehicle, and its efficacy, always better than GED 2%,

Date of the report

05 October 2020