Name of Sponsor Company	*Individual Study Table referring to the dossier*	*(for National Authority use only)*
PPM Services S.A.	PART: [……]	
Name of finished product NA	VOLUME: [……]	
Name of active ingredient N-Acetyl-GED-0507-34-Levo	PAGE: [……]	

Title of the study

AN OPEN LABEL CLINICAL STUDY TO EVALUATE THE LONG-TERM DERMAL SAFETY PROFILE OF 12-WEEKS TOPICAL ADMINISTRATION OF N-ACETYL-GED-0507-34-LEVO GEL 5% IN PATIENTS WITH FACIAL ACNE

Principal Investigators and study sites

The study took place entirely at one Italian site:

IRCCS ISTITUTO DERMATOLOGICO S. GALLICANO
(IFO - Istituti Fisioterapici Ospitalieri)
Clinical Study Early Phase (CSEP) unit
Via Elio Chianesi 53
00144 Roma

Principal Investigator: Dr. Bruno Capitanio

Publication (reference)	*Clinical phase*
Unpublished to date (2019)	Phase 1
Date of first enrolment	***Date of last completed***
09 October 2018 (first patient enrolled)	27 June 2019 (last visit of the last patient)

Objectives

Primary objective

Local and systemic safety and tolerability of N-Acetyl-GED-0507-34-Levo after 12 weeks repeated daily exposures to 5% gel in patients affected by facial acne vulgaris.

Plasma concentration of N-Acetyl-GED-0507-34-Levo after 12 weeks repeated daily exposures to the gel containing 5% of active principle.

Secondary objective

Preliminary evaluation of efficacy of N-Acetyl-GED-0507-34-Levo after 12 weeks repeated daily exposures to 5% gel in patients with facial acne vulgaris.

Study design

This is an open label phase 1 study to evaluate dermal and systemic safety/tolerability, cutaneous absorption and efficacy in patients with facial acne vulgaris. A total of 25 patients with mild, moderate or severe acne (in a rate 2:2:1) had to be recruited in the study, and treated with N-Acetyl-GED-0507-34-Levo 5% gel as single daily application for 12 consecutive weeks. A two-week follow up period was performed.

Name of Sponsor Company	*Individual Study Table referring to the dossier*	*(for National Authority use only)*
PPM Services S.A.	PART: [……]	
Name of finished product NA	VOLUME: [……]	
Name of active ingredient N-Acetyl-GED-0507-34-Levo	PAGE: [……]	

Patient population

A total of 25 patients have been recruited in the study:

- 10 Patients with facial acne vulgaris with IGA score = 2 (mild)
- 10 Patients with facial acne vulgaris with IGA score = 3 (moderate)
- 5 Patients with facial acne vulgaris with IGA score = 4 (severe)

Inclusion criteria

1. Informed consent and assent: Written informed consent, before any study-related procedure, personally signed and dated by the patient if the patient is ≥ 18 years old, or signed and dated by the parent(s) or the legal guardian if the patient is 12 - <18 years old. An additional informed assent form must be signed by the subject if 12 - <18 years old to confirm his willingness to participate in the study. If the subject becomes 18 years of age during the study, the subject must provide written informed consent at that time to continue study participation
2. Sex and Age: Male and female patients aged 18-30 years old inclusive; male patients aged 12 - <18 years old [12-20 years old (Juvenile Acne) and 21-30 (Acne Tarda)]
3. Race: White patients (i.e. people with European, Middle Eastern or North African ancestral origin)
4. Diagnosis: Patients with facial acne vulgaris with an investigator's global assessment score of 2-3-4 at screening and baseline visits
5. Inflammatory lesions: Patients with ≥20 and ≤ 100 inflammatory lesions (papules and pustules) on the face (including the nose) and ≤ 1 nodule
6. Non-inflammatory lesions: Patients with ≥20 and ≤ 100 non-inflammatory lesions (open and closed comedones) on the face (including the nose)
7. Full comprehension: Subject and parent/guardian for < 18 years old subjects' ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the investigator and to comply with the requirements of the entire study
8. Contraception and fertility (adult women, i.e. ≥ 18 years old; no female patients < 18 years old were enrolled): Adult women of childbearing potential who have been using and agree to use for all study duration at least one of the following reliable methods of contraception:
   - Hormonal oral, implantable, transdermal, or injectable contraceptives for at least 6 months before the screening visit
   - A non-hormonal intrauterine device [IUD] or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit
   - A male sexual partner who agrees to use a male condom with spermicide
   - A sterile sexual partner
9. Female participants of non-childbearing potential were admitted. For all female subjects, pregnancy test result must be negative at screening

Name of Sponsor Company	*Individual Study Table referring to the dossier*	*(for National Authority use only)*
PPM Services S.A.	PART: [……]	
Name of finished product NA	VOLUME: [……]	
Name of active ingredient N-Acetyl-GED-0507-34-Levo	PAGE: [……]	

Exclusion Criteria

1. Acne: spontaneously improving or rapidly deteriorating acne within at least 3 months before screening, known history of acne unresponsive to topical treatments, Acne Conglobata, Acne Fulminans, Acne Rosacea, Secondary Acne (Chloracne, drug-induced acne, etc), Nodule-Cystic Acne, Acne requiring Systemic Treatment.
2. Beard and facial hair: Patients who have a beard or intending to grow a beard during the study. Subject has facial hair that could interfere with the study assessments in the opinion of the investigator
3. Skin diseases: active skin diseases (e.g. urticaria, atopic dermatitis) or skin infections (bacterial, fungal, or viral) that might interfere with acne evaluation, with the exception of footpad trichophytosis (athlete's foot)
4. Allergy: Known or suspected hypersensitivity to any active or inactive ingredient in the study products. Subjects with a history of an allergic reaction or significant sensitivity to the formulations' ingredients
5. Topical therapies: 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 and retinoids.
6. Facial Procedures: 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. Chemical or laser peel, microderma abrasion, etc) within the past 4 weeks or during the study.
7. Phototherapy: 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 having the need or plan to be exposed to artificial tanning devices or excessive sunlight during the trial
8. Systemic therapies: 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 subject's acne (i.e. anabolics, lithium, EGRF inhibitors, iodides)
9. 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 within 6 months before study baseline
11. Diseases: Subject with underlying 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 immunocompromise the subject and/or place the subject at an unacceptable risk to receiving an immunomodulatory therapy. Any condition which in the investigator's opinion would make it unsafe for the subject to participate in the study
12. History of Alcohol and other substance abuse within one year before screening
13. Communication: Subject 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: Subject who may be unreliable for the study including subjects who are unable to return for the scheduled visits
15. Pregnancy (females only): Pregnant or breastfeeding women or planning pregnancy during the study.

Name of Sponsor Company	*Individual Study Table referring to the dossier*	*(for National Authority use only)*
PPM Services S.A.	PART: [……]	
Name of finished product NA	VOLUME: [……]	
Name of active ingredient N-Acetyl-GED-0507-34-Levo	PAGE: [……]	

Test product, dose and mode of administration, batch number

N-Acetyl-GED-0507-34-Levo gel

Dosage	5% (u.i.d.)
Acronym	NAC-GED-0507 5%
Duration of the therapy	84 days
Mode of administration	topical
Batch number	H011-485/01, H011-485/02

Statistical methods

The statistical analysis was performed by the Contract Research Organization (CRO) Hippocrates Research Srl, by using SAS® version 9.3 – SAS Institute Inc, Cary, NC, USA and carried out according to ICH guidelines ICH E9: "Statistical Principles for Clinical Trials" (CPMP/ICH/363/96 September 1998).

All patients who gave their informed consent were accounted for in this study. Summary statistics were presented as follows:

- Quantitative parameters were summarized using descriptive statistics: n, mean, SD, median, range (minimum, maximum).
- Qualitative parameters were summarized using frequency tables: n and percent of categorical class (%).

Descriptive statistics values were presented for efficacy data. Moreover, as exploratory intent, in the overall group of patients the IGA score and the counts of acne lesions, assessed at each visit as changes vs baseline, were analyzed by using Wilcoxon Signed-Ranks test.

All statistical tests were carried out at a significant level (α level) of 0.05, two tailed.

Other details regarding the final planned statistical analyses are documented in the Statistical Analysis Plan (SAP).

SUMMARY

Safety results (primary endpoint)

The IMP related TEAEs were mostly classified as application site disorders.

Overall, 2 of 25 subjects reported AEs judged related to study treatment. The most frequent AE was application site dryness (both patients). The other reported event was: application site erythema. Both of them were of mild intensity. No patients dropped-out for AEs.

- No Serious Adverse Events were reported. No subjects discontinued permanently IMP due to TEAEs. No SUSARs were reported.
- No clinically meaningful change in laboratory values (except two cases of increased CPK values, due to intense physical activity), vital sign measurements or physical findings occurred in any subject during the study.
- Overall, N-Acetyl-GED-0507-34-Levo 5% gel appeared to be safe and well tolerated in subjects with acne vulgaris when administered at daily doses for 84 days.
- No safety concerns that required to modify the study conduct and/or study drug administration arose from the study.

Name of Sponsor Company	*Individual Study Table referring to the dossier*	*(for National Authority use only)*
PPM Services S.A.	PART: [……]	
Name of finished product NA	VOLUME: [……]	
Name of active ingredient N-Acetyl-GED-0507-34-Levo	PAGE: [……]	

Plasma pharmacokinetics of N-Acetyl-GED-0507-34-Levo

Plasmatic dosage of N-Acetyl-GED-0507-34-Levo was performed on all the patients. The human plasma samples were collected pre-dose and at the end of treatment (Day 84).

On day 1 before the first dermal application, no detectable concentration of N-Acetyl-GED-0507-34-Levo was measured. Following 12-weeks dermal application of the compound, low levels of N-Acetyl-GED-0507-34-Levo were measured in plasma. The highest plasma concentration was measured for Pt. 011 (8.76 ng/mL) 13.6 hours post application. The average concentration in the 25 patients was 2.064 ng/mL.

For comparison, N-Acetyl-GED-0507-34-Levo plasma levels observed after 84 days of topical application in 48 patients treated with 1% and 2% gel (phase I trial GED-0507-ACN-01-14) were < LLOQ (5 ng/mL) both at end of treatment (Day 84) and at the end of follow-up period (Day 98) in all but one sample of 2% group (Pt 034 - Day 98), where negligible levels were detected (9.35 ng/mL).

Efficacy (secondary endpoints)

The IGA score and acne lesion count are commonly used as combined endpoints in clinical trials to evaluate the efficacy of experimental treatments.

Acne severity showed an improvement over time for the three groups, confirmed by both the parameters.

As early as three weeks of treatment until the end of study, NAC-GED-0507 5% application elicited a statistically significant change in IGA score, with reaching more than one point decrement at the end of the treatment and in the follow-up visit in the mild and moderate group and more than two point decrement in the severe group.

In particular, at the end of the treatment period, IGA score showed a mean decrease from baseline of -1.72 (baseline – Visit 5), while the mean absolute change between baseline and follow-up visit (baseline - V6) is of -1.60. In particular, the mild group reports a mean decrease of -1.40 and -1.10 respectively at EoT and at the Follow-up visit, the moderate group a mean decrease of -1.90 vs -1.70, and the severe group reports a mean value of decrease of -2.00 at V5 and -2.40 at V6.

As early as three weeks of treatment (V2) until the end of the study (V6), a statistically significant change in the overall acne lesion count was recorded, with a decrease at the end of treatment greater than 72 points (-87.6%) compared to baseline for all the groups ($p < 0.0001$).

In the whole study period (follow-up included), the lesion overall number showed a decrease over time in the mean value from 84.6 to 15.8 (absolute change: -68.8, percentage change: -83.8%).

In particular, the mild group reports a mean decrease of -56.5 (-92.3%) and -52.1 (-85.0%) respectively at EoT and at the Follow-up visit, the moderate group a mean decrease of -87.9 (-85.5%) vs -80.7 (-80.3%), and the severe group reports a mean value of decrease of -73.4 (-82.4%) at V5 and -78.4 (-88.0%) at V6.

Overlapping results were found by counting separately inflammatory and non-inflammatory lesions.

Conclusions and discussion

Safety. N-Acetyl-GED-0507-34-Levo appeared to be safe and well tolerated in subjects with acne vulgaris, independently from its severity, when administered at a 5% concentration for 84 days. No SUSARs were reported during the study; no SAE occurred. The IMP related TEAEs were mostly classified as application site disorders of mild intensity. Overall, 2 of 25 subjects with mild IGA reported a total of 3 AEs (two cases of application site dryness and one case of application site erythema) judged possible related to study treatment. No patients dropped-out for AEs or other reasons. No safety concerns that required to modify the study conduct and/or study drug administration arose from the study. Of the two patients reporting possibly related events, action was taken by one

Name of Sponsor Company PPM Services S.A.	***Individual Study Table referring to the dossier*** PART: [……] VOLUME: [……] PAGE: [……]	***(for National Authority use only)***
Name of finished product NA		
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patient, who interrupted the application for one day due to application site dryness and erythema; anyhow the IMP was taken again on the following day and no other events occurred up to the study end.

Plasma PK. Following 12-weeks dermal application of the compound, low levels of N-Acetyl-GED-0507-34-Levo were measured in plasma indicating a low systemic exposure. The highest plasma concentration was measured for Pt. 011 (8.76 ng/mL) 13.6 hours after last application. The median plasma concentration in the 25 patients was 1.81 ng/mL (mean 2.06 ng/mL, max 8.76 ng/mL, with levels below the limit of quantification in 8 out of 25 patients (32%). Anyway, by the present results it can be concluded that N-Acetyl-GED-0507-34-Levo following topical administration of NAC-GED-0507 5% gel formulation at a dose up to 2 g/day for 84 days to human patients, is not systemically bioavailable.

Efficacy. Even though the efficacy was a secondary endpoint in this Phase 1 study, results from IGA score and lesion count over time show consistently evidence of clinical effectiveness of N-Acetyl-GED-0507-34-Levo 5% gel in treatment of acne vulgaris for all the tested groups (mild, moderate and severe acne).

Limits of the study. Overall, the results of this study (safety, pharmacokinetics and efficacy) are consistent with those of studies conducted, in dermatological indications (psoriasis and acne), with other topical formulations (cream) or with other concentrations of the active ingredient (1% or 2%). However, in the interpretation of the results the main limits of this study must be considered: a) open study design; b) absence of control group; c) relatively small size of the three study groups; d) study duration limited to 12 weeks.

Final conclusions. In conclusion, according to the results of this study, N-Acetyl-GED-0507-34-Levo 5% gel appeared to be safe and well-tolerated, independently from severity of acne, negligible systemic absorption was obtained and evidence of clinical effectiveness in treatment of acne was observed.

Date of the report

11th June 2020