Clinical summary

Title of the study

A DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED CLINICAL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF N-ACETYL-GED-0507-34-LEVO GEL, 1 AND 2%, APPLIED ONCE DAILY FOR 12 WEEKS IN PATIENTS WITH MILD TO MODERATE FACIAL ACNE VULGARIS

Country Coordinating Investigators

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Date of first enrolment	***Date of last completed***
13 July 2016 (first patient randomized)	10 January 2017 (last visit of the last patient)

Objectives

Primary objective. The primary objective of the study was to evaluate the efficacy of 1% and 2% N-Acetyl-GED-0507-34-Levo gel, in comparison to the matching placebo gel, on the basis of the percentage of change from baseline in inflammatory lesions at week 12.

Secondary objectives. Evaluation the efficacy of 1% and 2% N-Acetyl-GED-0507-34-Levo gel, in comparison to the matching placebo gel, on: (a) absolute change from baseline in inflammatory lesions at week 12; (b) change from baseline (absolute and percentage) in inflammatory lesions at the other post-baseline assessment times; (c) change from baseline (absolute and percentage) in non-inflammatory lesions and total lesions (inflammatory plus non-inflammatory) at week 12 (d) proportion of subjects with an Investigator's Global Assessment (IGA) score of "clear" (score=0) or "almost clear" (score=1) at week 12.

Evaluation of safety, tolerability and local tolerability of the test treatments as compared to the matching placebo gel.

Study design

This was a double-blind, randomised, parallel-group, placebo (vehicle)-controlled, efficacy and safety study. The enrolled patients were randomly allocated (1:1:1) to N-Acetyl-GED-0507-34-Levo 1% gel (T1), 2% gel (T2) or placebo (P) treatment group.

Each patient applied the gel (T1, T2 or P) once a day, for 12 weeks. The first dose was applied at the clinical centre (Visit 2, day 1) by the investigator or study nurse. The other doses were applied by the subjects at home following the instructions received at the clinical centre by the investigator/study nurse on the correct method of product application.

At each application, the gel was applied to the entire involved facial surface (inflammatory and non-inflammatory lesions). The amount of gel received in a day by each subject was approximately 2 mg/cm^2, with a total daily amount of gel of approximately 600 mg, assuming a treated surface of 300 cm^2, corresponding to a daily dose of 6 mg or 12mg of N-Acetyl-GED-0507-34-Levo 1% and 2%, respectively, or placebo (vehicle).

Patient population

The study was designed to recruit a total of 144 male subjects 14 - < 18 years old and male and female subjects

18-30 years old inclusive with mild to moderate facial acne vulgaris were allocated.

Main 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 14 - <18 years old. An additional informed assent form was signed by the subject if 14 - <18 years old confirming his willingness to participate in the study. If the subject became 18 years of age during the study, the subject provided written informed consent at that time to continue study participation.
2. Sex and Age: Male and female patients aged 18-30 years old inclusive; only male patients aged 14 - <18 years old [14-20 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 mild to moderate facial acne vulgaris with an investigator's global assessment score of 2-3 at screening and baseline visits.
5. Inflammatory lesions: Patients with ≤ 50 inflammatory lesions (papules, pustules, nodules) on the face (except the nose, that must have ≤ 10 inflammatory lesions) and ≤ 1 nodule.
6. Non-inflammatory lesions: Patients with ≤ 50 non-inflammatory lesions (open and closed comedones) on the face (except the nose, that must had ≤ 10 non-inflammatory lesions).
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 will be enrolled): Adult women of childbearing potential had to use at least one of the following reliable methods of contraception: a. Hormonal oral, implantable, transdermal, or injectable contraceptives for at least 3 months before the screening visit; b. 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; c. A male sexual partner who agreed to use a male condom with spermicide; d. A sterile sexual partner.

If National regulations required, only highly reliable contraception methods (i.e. hormonal, intrauterine device, sterilization) were allowed at study entry. In that case, one-barrier methods were allowed.

In Countries where no such regulation was in place, contraception with one-barrier methods was also allowed. Female participants of non-childbearing potential were admitted. For all female subjects, pregnancy test result were requested be negative at screening.

Main Exclusion Criteria

1. Acne: Patients with spontaneously improving or rapidly deteriorating acne within at least 3 months before screening. Patients who had a known history of acne unresponsive to topical treatments. Patients with generalized or localized severe acne.
2. Beard and facial hair: Patients who had a beard or who intended to grow a beard during the study. Subject with facial hair that potentially interfering with the study assessments in the opinion of the investigator.
3. Skin diseases: Subjects with other active skin diseases (e.g. urticaria, atopic dermatitis) or skin infections (bacterial, fungal, or viral) that might interfere with the evaluation of acne, with the exception of footpad trichophytosis (athlete's foot) or common warts.
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: Patients who used 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. Phototherapy: Patients who used 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 had the need or plan to be exposed to artificial tanning devices or excessive sunlight during the trial.
7. Systemic therapies: Patients who used 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, were able to affect the subject's acne (Women on hormonal acne therapy were allowed to be enrolled if they were on the hormonal therapy for at least 3 months before the screening visit and were anticipated to continue the hormonal therapy during the entire study).
8. Investigative studies: Participation in the evaluation of any investigational product or device within 30 days before study baseline.
9. Diseases: Subject with underlying conditions (incl., but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal) which, in the investigator's opinion, was able to 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 was able to make it unsafe for the subject to participate in the study. Patients with Polycystic ovary syndrome.
10. Alcohol and other substance abuse: History of alcohol or other substance abuse within one year before screening.
11. 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.
12. Reliability: Subject who was potentially unreliable for the study including subjects who were unable to return for the scheduled visits.
13. Pregnancy (females only): Pregnant or breastfeeding women or planning to become pregnant during the study.

Test product, dose and mode of administration

TEST (T1, T2): T1: N-Acetyl-GED-0507-34-Levo 1% gel (1 mg/100 mg), PPM Services S.A., Switzerland

T2: N-Acetyl-GED-0507-34-Levo 2% gel (2 mg/100 mg), PPM Services S.A., Switzerland

PLACEBO (P): P: N-Acetyl-GED-0507-34-Levo matching placebo, PPM Services S.A., Switzerland

Statistical methods

All patients who gave their informed consent were accounted for in this study. Different analysis sets are planned for the analyses: (a)All Randomized Set comprising all patients randomized into the trial; (b) Full Analysis Set (FAS) comprising all randomized subjects who have received at least one dose of investigational product; (c) Intention To Treat set (ITT) comprising all randomized patients, drop-out included; , whereas patients having completed 12 weeks' study period and presenting overdosing (>400 gr GEL) or underdosing (<50 gr GEL) have been excluded; (d) .Modified Intention To Treat set (mITT) comprising all subjects in the ITT set, with exclusion of subjects with reported concomitant therapies (topical or systemic) acting on acne process (i.e. antibiotics, NSAIDs, ecc.) and/or affected by endocrinopathies.

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

An Ancova model, with baseline value as covariate and treatment as fixed factor will be applied to test the null hypothesis H0: "The mean score on the changes (absolute and percent) from baseline are identical among treatment groups" (both for inflammatory, non inflammatory, and total lesion counts).

SUMMARY OF THE RESULTS

A total of 147 patients were randomized and included in the FAS analysis (GED-0507-34-Levo 1% n=50; 2% n=50; placebo n=47). The 120 patients included in the ITT set were on average 21.3 years old (st.dev. 3.6), 48 of

them were males and 72 females.

At baseline, in the ITT set, the mean total number of inflammatory lesions (papules, pustules and nodules) was: 20.3, 21.3 and 20.0 in GED-0507-34-Levo 1%, 2% and placebo groups, respectively, whereas in mITT set it was: 20.0, 21.1 and 19.5 respectively.

At the same time point the mean IGA score was the same in the three study groups (2.5) in all the groups , either in the ITT and in the mITT sets.

Efficacy

Primary end-point

After 12 weekd of treatment the percent changes from baseline were -45.2 for GED-0507-34-Levo 1% group, -57.2 for 2% and -28.7 for placebo (ITT set). Results from pairwise two-sided multiple comparison analysis were statistically significant for GED-0507-34-Levo 2% vs placebo (p=0.0003) and GED-0507-34-Levo 1% vs placebo (p= 0.0329) but not for GED-0507-34-Levo 2% vs GED-0507-34-Levo 1% (p=0.1085). A similar pattern was also observed in the mITT set.

Secondary end-points

After 12 weeks of treatment the mean absolute changes from baseline of inflammatory lesions were -9.6 for GED-0507-34-Levo 1% group, -12.1 for 2% and -5.5 for placebo (ITT set). As observed for percent changes, results from pairwise two-sided multiple comparison analysis were statistically significant for GED-0507-34-Levo 2% vs placebo (p=0.0002) and GED-0507-34-Levo 1% vs placebo (p= 0.0142) but not for GED-0507-34-Levo 2% vs GED-0507-34-Levo 1% (p=0.1725). A similar pattern was also observed in, for this end-point, the mITT set.

Regarding the changes of non inflammatory lesions, the absolute difference between GED-0507-34-Levo 2% vs placebo that was statistically significant both in ITT set (-11,9; p=0.0182) and mITT set (-11.8; p=0.0185).

As time course of total inflammatory lesions count is concerned, GED-0507-34-Levo 2% induced, after 3 weeks (visit 3) a remarkable reduction, compared to placebo, of the absolute count both in the ITT set (-6.8 vs -2.7; p=0.0111) and in the mITT set (-6.8 vs -2.1; p=0.0044). The reduction of the same parameter in patients receiving GED-0507-34-Levo 1% was better than placebo but not statistically significant in ITT set (-4.7 vs -2.7; p=0.1945) and nearly significant in the mITT set (-5.0 vs 2.1; 0.0650). However, after 6 weeks (visit 4) the changes of the absolute count of total inflammatory lesions was statistically significant compared to placebo in both in groups and in both datasets.

After 12 weeks of treatment the mean IGA score was 1.8 (vs 2.5 at baseline) in both 1% and 2% groups and 2.0 (vs 2.5 at baseline) in the placebo group in the ITT set and 1.8, 1.8 and 2.1 respectively in the mITT set (vs 2.5 in all groups at baseline). At the same time point, in the ITT set, the portion of patients with IGA classified as “clear” or “almost clear” was 31.0% and 33.3% in GED-0507-34-Levo 1% and 2% respectively and 16.7% in the placebo group, without statistically significant differences between groups. A similar pattern was observed in the mITT set.

Safety

Deaths and Serious Adverse Event (SAEs)

No patient died during the study. Two SAEs were reported: (1) pneumothorax spontaneous, not related to study drug and resolved without dose change, in a 19 y.o. male patient taking GED-0507-34-Levo 2% and (2) increase of laboratory values, not related to study drug,, of AST, ALT and CPK in a 17 y.o. male patient taking placebo. Nome of the SAEs led to premature discontinuation of the study treatment.

Treatment Emergent Adverse Events (TEAEs)

No substantial differences were observed in the number and in the description of TEAEs. In total, in the group receiving GED-0507-34-Levo 1% 69 TEAEs were reported in 30 (60%) patients, 46 in 22 (44%) patients receiving GED-0507-34-Levo 2% and 47 in 22 (47%) patients receiving placebo. Nome of the TEAEs led to premature discontinuation of the study treatment.

The most frequent class of TEAEs was classified as application site disorders interesting 11 patients (22%) in low dose group, 7 (14%) in high dose group and 9 (19%) in the placebo group. This class of TEAEs was mainly

represented by dryness or exfoliation and erythema.

Regarding other classes AEs the most frequent TEAEs were headache or migraine reported in 11 (22%), 5 (10%) and 6 (13%) in GED-0507-34-Levo 1%, 2% and placebo respectively. Less frequently reported TEAEs were intercurrent infections, mainly seasonal (upper respiratory infections, influenza, bronchitis) without differences between groups

Adverse Events (AEs)

The total number of AEs was similar in the high dose group taking GED-0507-34-Levo 2% (47 in 22 patients equal to 44%) and in placebo group (48 in 22 patients equal to 47%). In the low dose group taking GED-0507-34-Levo 1% a total of 70 AEs involved 30 patients (60%).

The pattern of AEs was very similar in the three study groups being application site disorders (dryness or exfoliation and erythema) and headache or migraine the most frequent ones. They were followed by seasonal infections such as upper respiratory infections, influenza, rhinitis bronchitis or pharyngitis.

With exception of AEs classified as application site disorders, no relationship with study drug was reported in all the groups for any other AE. With very few exception all the AEs were reported as mild. Those reported as moderate (4 in the low dose group, 2 in the high dose group and 1 in the placebo group) were usually classified as application site disorders.

Other safety parameters

No clinically meaningful change in laboratory values, vital sign measurements, physical findings, or other observations related to safety occurred in any subject during the study.

Discussion and conclusions

Efficacy

This study demonstrated that 1% and 2% N-Acetyl-GED-0507-34-Levo gel are both superior to placebo (vehicle gel) in reducing the total number of inflammatory lesions in patients with mild to moderate facial acne vulgaris.

In particular, after 12 weeks of treatment, the clinical efficacy of N-Acetyl-GED-0507-34-Levo 1% and 2% gel, expressed as both percentage or absolute change versus baseline, is proved to be statistically superior to placebo in reducing the number of inflammatory lesions.

Moreover, a clear dose effect relationship emerged from the comparison of the effect size of the low and high dose formulations, even if not statistically significant.

The effect of both formulations on the inflammatory lesions, is fast as, after 3 weeks the reduction of the absolute number of the lesions versus baseline was statistically significant with 2% gel and almost significant with 1% gel ($p=0.0650$ in the mITT set). After 6 weeks the changes of the absolute count of total inflammatory lesions was statistically significant compared to placebo in both in groups and in both datasets.

Regarding the changes of non inflammatory lesions, in general a decrease in the number versus baseline was observed compared to placebo even if usually not statistically significant.

The IGA score mirrored the overall picture of efficacy just described: after 12 weeks of treatment, the mean IGA score and the portion of patients with IGA classified as “clear” or “almost clear” were better than placebo even if without statistically significant differences, due to a sample size not powered for this end.point.

Safety

No patient died during the study. Two SAEs were reported and both not related to study drug or led to premature discontinuation of the study treatment. No substantial differences were observed between groups in the number and in the description of TEAEs. No premature discontinuation of the study treatment was related to TEAEs. The pattern of AEs was very similar in the three study groups being application site disorders (dryness or exfoliation and erythema) and headache or migraine the most frequent ones. With exception of AEs classified as application site disorders, no relationship with study drug was reported in all the groups for any other AE.

Summarizing, the incidence of AEs was not dose-dependent and the pattern of the AEs suggested that they were related to the acne itself rather than to the study treatment.

Conclusions

Overall, GED-0507-34-Levo 1% and 2% appeared to be effective, safe and well tolerated in subjects with acne vulgaris when administered at both 1% and 2% doses for 12 weeks. The clinical effectiveness is clearly superior to placebo (vehicle gel) also at le lower concentration of 1%, is dose dependent and is evident even after 3 weeks of treatment. No safety concerns that required modifying the study conduct and/or studying drug administration arose from the study.

Date of the report

20th October 2017