CLINICAL STUDY REPORT SYNOPSIS OF D.A.N.T.E STUDY

Protocol No: MOLT-2009-01

EudraCT No: 2010-019598-13

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Clinical Study Report Synopsis
Protocol No: MOLT-2009-01
EudraCT No: 2010-019598-13

Name of Company: Molteni Therapeutics S.r.1	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
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Title of Study:

A Randomised, Double-Blind, Dose-Response, Placebo-Controlled, Multicenter, Phase IIA Clinical Study to Evaluate the Efficacy and Safety of Topical Application of G.68.γ/EtOH in Patients with Type 1 or Type 2 Diabetes with Infected Foot Ulcers.

(D.A.N.T.E [**D**iabetic ulcer **A**ntimicrobial **N**ew **T**opical treatment **E**valuation] Study)

Coordinating Investigator:

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Study Centre(s)/Site(s):

This study was conducted in five centres across Italy.

Note: A total of 6 sites were initiated. Site 2 was initiated, but was closed due to some difficulties in the patients' recruitment. Hence, Site 6 was initiated, and the study was conducted across five centres.

Publication (Reference):

Not Applicable

Phase of Development:

Phase IIA

Studied Period (years): approximately 13 months

Date of First Enrolment*:* 21 Oct 2010

Date of Last Completed: 23 Nov 2011

Objectives:

Primary:

The primary objective of this study was:

- To evaluate the efficacy of a single, topical dose of G.68.γ/EtOH (0.10%, 0.30%, 0.50% w/w) compared to placebo immediately after photoactivation with red light in patients with type 1 or type 2 diabetes with infected grade 2 foot ulcers, as measured by reduction in ulcer bacterial load

Secondary:

The secondary objectives of this study were:

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- To evaluate at Day 3, Day 8 and Day 15, the maintenance of efficacy, and the safety and tolerability of a single, topical dose of G.68.γ/EtOH (0.10%, 0.30%, 0.50% w/w) after photoactivation with red light compared to placebo, in patients with type 1 or type 2 diabetes with infected grade 2 foot ulcers

Methodology:

Patients were screened for eligibility at the Screening Visit (Visit 0), which could be the same day as Day 1 (Visit 1, treatment visit), or up to 2 days before Visit 1. Patients with type 1 or type 2 diabetes with infected grade 2 foot ulcers were randomised in a 1:1:1:1 ratio to receive G.68.γ/EtOH 0.10% w/w, G.68.γ/EtOH 0.30% w/w, G.68.γ/EtOH 0.50% w/w, or placebo. The total study duration, including Screening, for each patient was approximately 15 days (from 13 to 19 days).

The primary efficacy endpoint was the reduction in the ulcer bacterial load between pre-treatment (Baseline) and post-illumination on Day 1 (Visit 1). Secondary efficacy and safety endpoints were then assessed at post-treatment visits on Day 3 (Visit 2), Day 8 (Visit 3), and Day 15 (Visit 4). The secondary pharmacokinetic (PK) end-point was assessed at Day 1 (Visit 1) and Day 3 (Visit 2).

Prior to dosing, each ulcer underwent a mild sharp debridement in the peripheral area and a washing with physiological solution in the whole area, followed by collection of a bacteria sample with a Copan® flocked nylon swab to evaluate the pre-dose total bacterial load (aerobic and anaerobic bacteria), the pre-dose load of pathogenic bacteria only (aerobic and anaerobic) and the pre-dose bacterial load of single pathogens. A standard antibiogram was performed on the two most represented aerobic pathogenic bacteria detected on the pre-dose sample. Washing was performed using a 10 mL syringe (without the needle), with 5 mL of physiological solution maintaining a distance of 5 cm from the wound. After washing, the peripheral area of the wound was softly plugged with gauze.

After the swab collection, all patients received a single dose (25 μL/cm^2) of topical G.68.γ/EtOH (0.10% or 0.30% or 0.50% w/w) or placebo gel.

After the application of study drug or placebo, every wound was covered with a Tegaderm™ patch. To maintain the double blind until illumination, a non-transparent bandage were fixed on the Tegaderm™ patch.

One hour after the application of study drug or placebo, the Tegaderm™ patch was removed and each ulcer was illuminated with red light (689 ± 5 nm) for approximately 8 min 20 s, providing a total energy exposure of 60 J/cm2. Drug application and drug illumination was performed by an unblinded Investigator.

After photoactivation, the unblinded Investigator washed each ulcer (whole area) with a physiological solution and then performed the post illumination swab collection to re-evaluate the bacterial load. If necessary, additional washings were done to remove any traces of the study drug or placebo after the swab procedure.

After the post-illumination swab procedure, each ulcer was covered with a fixed vaseline gauze.

Starting from baseline (Visit 1), after the post-illumination swab collection, all patients received

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the first package of a standard oral antibiotic treatment with Augmentin® (amoxicillin trihydrate/clavulanic potassium – 1 g three times a day) and was instructed to take the first dose on the same day soon before lunch or soon before dinner depending on the time of the Visit.
This antibiotic treatment was administered for 7 days starting from Visit 1.
Patients returned to the hospital at Day 3 (Visit 2), Day 8 (Visit 3) and Day 15 (Visit 4). No other study drug or placebo treatments were performed but at each visit a new swab sample was collected to evaluate bacterial load. At each visit, the ulcer was evaluated by the blinded Investigator.
The ulcer assessment consisted of the grade of infection according the PEDIS system and the area/depth measured by VISITRAK™.
A visual analogue scale (VAS) was used to evaluate ulcer pain due to the infected ulcer, at all visits. Pain medication use was also collected at all visits.
At Visit 3, according to the antibiogram results, the Investigator established the most appropriate antibiotic treatment as per local standards of care or decided to interrupt the background therapy.

If the patient felt additional ulcer pain, or other signs or symptoms of inflammation, he/she could contact the Investigator to schedule extra visits between the planned visits. The Investigator could also schedule optional extra visits as appropriate. During these visits the Investigator managed the ulcer and changed the fixed vaseline gauze.

Duration of Treatment:

The total study duration, including Screening, for each patient was approximately 15 days (from 13 to 19 days). There was no wash-out period.

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Number of Patients:

Planned:

A total of 60 in- patients and/or out-patients were planned to be enrolled in four treatment arms (15 patients per arm).

Analysed:

A total of 62 patients were enrolled and randomised in four treatment arms:

14 patients in G.68.γ/EtOH 0.10% w/w,
16 patients in G.68.γ/EtOH 0.30% w/w,
17 patients in G.68.γ/EtOH 0.50% w/w, and
15 patients in the placebo arm.

Safety population: 62 patients analysed:
14 patients in G.68.γ/EtOH 0.10% w/w,
16 patients in G.68.γ/EtOH 0.30% w/w,
17 patients in G.68.γ/EtOH 0.50% w/w, and
15 patients in the placebo arm.

Full Analysis Set (FAS) population: 55 patients analysed:
11 patients in G.68.γ/EtOH 0.10% w/w,
15 patients in G.68.γ/EtOH 0.30% w/w,
16 patients in G.68.γ/EtOH 0.50% w/w, and
13 patients in the placebo arm.

Per-Protocol (PP) population: 54 patients analysed:
11 patients in G.68.γ/EtOH 0.10% w/w,
15 patients in G.68.γ/EtOH 0.30% w/w,
15 patients in G.68.γ/EtOH 0.50% w/w, and
13 patients in the placebo arm.

Diagnosis and Main Criteria for Inclusion:

Patients with type 1 or type 2 diabetes with infected grade 2 foot ulcers were randomised in a 1:1:1:1 ratio to receive either of the four treatment arms. Male or females aged 18 years and above, with a confirmed diagnosis of type 1 or 2 diabetes; a diabetic foot wound grade I or II and staging B or D (TEXAS classification); presence of infected foot ulcer of grade 2 (PEDIS classification) and presence of ulcer with an area from 2 to 15 cm^2 and with a maximum diameter/length ≤4.6 cm measured by the VISITRAK™ system. Patients were to have no concurrent illness indicating a life expectancy of less than 3 months. Females of childbearing potential were to have a negative urine pregnancy test prior to commencing the study. Non-childbearing potential and childbearing potential female patients who agreed to use an

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acceptable method of contraception for 60 days after the Treatment Visit (i.e., 60 days from the first and only application of the study drug) providing they were not pregnant or lactating. Male patients who agreed to use adequate methods of contraception for 30 days from the time of the Treatment Visit (i.e. 30 days from the first and only application of the study drug) were included in the study.

Investigational Product: G.68.γ/EtOH drug product is a sterile gel

Dose: G.68.γ/EtOH (0.10% w/w, 0.30% w/w, 0.50% w/w)

Mode of Administration: Topical administration

Manufactured Batch Number(s): G.68.γ/EtOH 0.10% = 0912006, G.68.γ/EtOH 0.30% = 0912023, and G.68.γ/EtOH 0.50% = 0912032 and 1106008

Reference Therapy: Placebo drug product is a sterile gel

Dose: 0% G.68.γ/EtOH (excipients only)

Mode of Administration: Topical administration

Batch Number(s): 0911019

Criteria for Evaluation:

Efficacy:

Primary Efficacy endpoint:

- Reduction in the ulcer total bacterial load between pre-treatment (Baseline Day 1) and post-illumination on Day 1 (Visit 1) as measured by an ulcer sample drawn with a flocked nylon swab

Secondary Efficacy endpoints:

- Reduction in ulcer total bacterial load measured by swab collection between pre-treatment (Baseline Day 1) and Day 3 (Visit 2), Day 8 (Visit 3), and Day 15 (Visit 4)
- Maintenance of the reduction in ulcer total bacterial load measured by swab collection at Day 3 (Visit 2), Day 8 (Visit 3), and Day 15 (Visit 4) compared with the ulcer total bacterial load measured at Day 1 post-illumination
- Clinical improvement of the foot ulcer from Day 1 (Visit 1) through Day 15 (Visit 4), as measured by reduction in the ulcer grade of infection assessed by the PEDIS system and by reduction of ulcer dimensions and depth assessed by the VISITRAK™ system
- Reduction in ulcer pain between pre-treatment (Baseline Day 1) and Day 3 (Visit 2), Day 8 (Visit 3), and Day 15 (Visit 4), assessed by Visual Analogue Scale (VAS)
- Eradication in total and pathogen bacterial load (reduction to 0 or < Limit of Detection) measured by swab collection between pre-treatment (Baseline Day 1) and immediately after illumination on Day 1 (Visit 1)
- Reduction in pathogen bacterial load between pre-treatment (Baseline, Day 1) and post-illumination on Day 1 (Visit 1) measured on an ulcer sample drawn with a flocked

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nylon swab

The other end-points of this study were the following:

Pharmacokinetics:

- Evaluation of plasma levels of RLP068 and possible photoproduct at Day 1 (Visit 1) and Day 3 (Visit 2)

Safety:

- The relationship between adverse events (AE) and topical application of G.68.γ/EtOH (0.10%, 0.30% or 0.50% w/w) from Day 1 (Visit 1) through Day 15 (Visit 4)

Statistical Methods:

Appropriate summary statistics were presented by treatment groups and time point of assessment for all recorded parameters.

The primary efficacy endpoint, the reduction in ulcer bacterial load between pre-treatment (Baseline) and post-illumination on Day 1, was evaluated comparing the three active treatment groups and the placebo group by using non-parametric tests: the Kruskal-Wallis' test was used to assess the comparability of the four treatment groups and a Mann-Whitney's test (2 independent samples) were used to compare the efficacy of the three treatments versus placebo, differences were considered significant with a $p \leq 0.05$. A multiple comparison approach was used to assess the differences between the three treatment groups and the placebo. All the patients who had a pre-treatment value of colony forming units (CFU)/mL=0 (or < Limit of Detection) were not considered for the evaluation of the primary endpoint. A value < Limit of Detection in a post-treatment assessment was considered as CFU/mL=0.

All other endpoints, such as secondary efficacy and safety endpoints, were analysed descriptively. For missing post-baseline values of any of the secondary outcome parameters, a LOCF procedure as for the primary parameter was used. Patients with a missing Baseline value were excluded from the analysis of the corresponding parameter. Regarding the secondary endpoints which evaluated the reduction in bacterial load (total or pathogens) or eradication (total or pathogens), all the patients who had a pre-treatment value of CFU/mL=0 (or < Limit of Detection) were not considered for the evaluation of the endpoint. A value < Limit of Detection in a post-treatment assessment was considered as CFU/mL=0.

The following analysis populations were defined for the study analyses:

Safety analysis set:

The Safety analysis set consisted of all randomised patients who received a single dose of study medication. For those patients, all available safety data was used in the safety analyses.

Full analysis set (FAS):

The FAS consisted of all randomised patients who received a single dose of study medication and who had at least the Baseline assessment for the primary efficacy parameter, i.e. with a non-missing Baseline bacterial load assessment. Also patients with a bacterial load assessment at

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Baseline which showed no total bacterial load present at Baseline, i.e., with bacterial load =0 CFU/mL or < Limit of Detection (defined in 1000 CFU/mL), were excluded from FAS.

Per-Protocol (PP) analysis set:

The PP analysis set consisted of all patients from the FAS without any major protocol violations and who had at least one post-baseline assessment for the respective efficacy parameter.

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SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Primary Endpoint:

Reduction in ulcer total bacterial load immediately after illumination: The primary efficacy endpoint of the study was the reduction in ulcer total bacterial load (Log_{10}CFU/mL) between pre-treatment on Day 1 (Visit 1) and immediately after illumination on Day 1 (Visit 1).

In the FAS population, there was a highly statistically significant overall treatment effect in reduction of ulcer total bacterial load (from pre-treatment to post-illumination) compared to placebo, with a p-value of $p<0.001$. The overall mean (SD) change of ulcer total bacterial load (from pre-treatment to post-illumination) was predominantly observed to be more effective in G.68.γ/EtOH 0.50% and G.68.γ/EtOH 0.30% groups as compared to G.68.γ/EtOH 0.10% and placebo groups. The comparison of each G.68.γ/EtOH treatment group to placebo also showed a highly significant difference for the G.68.γ/EtOH 0.30% and 0.50% groups (p-value of $p<0.001$) but no statistical significant difference to placebo for the G.68.γ/EtOH 0.10% group ($p=0.107$). This suggests a treatment effect on ulcer total bacterial load at post-illumination on Day 1 (Visit 1).

The results observed in the PP analysis set were consistent with FAS results.

The following secondary efficacy endpoints were assessed for this study in the FAS population:

Secondary Enpoints:

Reduction in ulcer total bacterial load during the study: The mean (SD) change from Baseline values of reduction in ulcer total bacterial load on Visit 2 (Day 3), Visit 3 (Day 8) and Visit 4 (Day 15) were not pronounced enough to be interpreted as a treatment effect; the change from Baseline in placebo group was in a similar range as in all G.68.γ/EtOH treatment groups. The comparison of each G.68.γ/EtOH treatment group to placebo did not show any statistical significant difference to placebo for ulcer total bacterial load suggesting no treatment effect on these visits (that is there was no reduction in the ulcer total bacterial load on Days 3, 8 and 15).

Maintenance of the reduction in ulcer total bacterial load: Also for maintenance of the reduction in ulcer total bacterial load, there was no statistically significant treatment effect, neither overall effect ($p=0.281$), nor with respect to any of the comparisons of each G.68.γ/EtOH treatment group to placebo; only a statistically significant overall time effect for changes from baseline ($p=0.042$) was seen. This effect over time was in line with the strong treatment effect had immediately after illumination on Day 1 (Visit 1), but no treatment effect was shown at Visits 2, 3 and 4. The ulcer total bacterial load diminished immediately after treatment (post-illumination) at Visit 1 more significantly in the treatment groups than in placebo group, but increased again over time. No difference for ulcer total bacterial load between placebo group and treatment groups was maintained, neither overall nor for any particular treatment group.

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Clinical improvement of the wound (PEDIS and VISITRAK™ system): At Visit 1 (Day 1), all patients in each treatment group had grade II ulcer (according to PEDIS). At Visit 2 (Day 3), at least 3 patients in each treatment group had an improved ulcer infection from grade II to grade I. At Visit 3 (Day 8), additional patient in each treatment group (except for G.68.γ/EtOH 0.50% group) reported an improved ulcer infection from grade II to grade I. G.68.γ/EtOH 0.30% group reported the maximum number of patients with grade I ulcer (7/15 patients [46.7%]). At Visit 4, the maximum percentage of patients with an improved ulcer infection grade (grade II to grade I) were reported in G.68.γ/EtOH 0.30% group (66.7%) followed by G.68.γ/EtOH 0.50% group (50%), G.68.γ/EtOH 0.10% group (36.4%) and placebo group (30.8%).

For reduction in ulcer grade, at Visit 3, G.68.γ/EtOH 0.30% group reported the maximum number of patients with grade I ulcer (7/15 patients [46.7%]). Similarly, at Visit 4, maximum number of patients with grade I was reported from G.68.γ/EtOH 0.30% group (10/15 patients [66.7%]) followed by G.68.γ/EtOH 0.50% group (8/16 patients [50.0%]).

The mean (SD) change from Baseline values of area, maximal diameter and depth of ulcer (measured with VISITRAK™) on Visit 2 (Day 3), Visit 3 (Day 8) and Visit 4 (Day 15) were not pronounced enough to be interpreted as a treatment effect. The change from Baseline in placebo group was in a similar range as in all G.68.γ/EtOH treatment groups.

Also for ulcer grade (PEDIS) and wound dimensions (area, maximal diameter and depth of diameter measured with VISITRAK™) the differences to placebo of change from Baseline were not statistically significant for any of the three G.68.γ/EtOH treatment groups at any timepoint. Nor could a maintained statistically significant reduction of ulcer grade (PEDIS) and wound dimensions (area, maximal diameter and depth of diameter measured with VISITRAK™) over all treatments or a maintained reduction for any active treatment group as compared to placebo be detected.

Reduction in ulcer pain: The mean (SD) change from Baseline values of reduction in ulcer pain on Visit 2 (Day 3), Visit 3 (Day 8) and Visit 4 (Day 15) were not pronounced enough to be interpreted as a treatment effect. The change from Baseline in placebo group was in a similar range as in all G.68.γ/EtOH treatment groups. The comparison of each G.68.γ/EtOH treatment group to placebo did not show any statistical significant difference to placebo for reduction of ulcer pain at any timepoint. For overall treatments there was no maintained reduction statistically significant, nor any active treatment group showed as compared to placebo a maintained reduction.

Eradication of ulcer total and pathogen ulcer bacterial load: On Visit 1 (Day 1, post-illumination), an overall success rate of 40% (22/55 patients) and 39.6% (19/48 patients) was achieved in eradication of ulcer total bacterial load and pathogen ulcer bacterial load, respectively. At Visit 1 (Day 1, post-illumination) the eradication of ulcer total bacterial load difference from placebo was statistically significant in G.68.γ/EtOH 0.50% group only (p=0.024), depicting a treatment effect in eradication of ulcer total bacterial load at Day 1 post-illumination.

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At all visits the observed eradication rate of total and pathogen bacterial load was found higher in the G.68.γ/EtOH 0.50% group and G.68.γ/EtOH 0.30% group compared to G.68.γ/EtOH 0.10% and placebo groups, but there wasn't a statistically significant effect (except for the G.68.γ/EtOH 0.50% group at Visit 1, Day 1 post-illumination for eradication of ulcer total bacterial load).

Reduction in pathogen bacterial load: A highly statistically significant overall treatment effect in reduction of pathogen bacterial load (from pre-treatment to post-illumination) compared to placebo was observed (p=0.008). At the same timepoint (immediately after illumination on Visit 1, Day 1 post-illumination) the comparison of each G.68.γ/EtOH treatment group to placebo also showed a significant difference for the G.68.γ/EtOH 0.30% (p-value=0.028), but no statistical significant difference for the G.68.γ/EtOH 0.10% and G.68.γ/EtOH 0.50% groups. The reduction in ulcer pathogen bacterial load (Log_{10} CFU/mL) on Visit 2 (Day 3), Visit 3 (Day 8) and Visit 4 (Day 15) were not pronounced enough to be interpreted as a treatment effect. The change from Baseline in placebo group was in a similar range as in all G.68.γ/EtOH treatment groups.

PHARMACOKINETIC RESULTS:

Evaluation of plasma levels of RLP068 and its possible photoproduct at Day 1 (Visit 1) and Day 3 (Visit 2): The PK plasma levels of RLP068 (LLOQ<0.500 ng/mL) and of its photoproduct (LLOQ<0.20 ng/mL) on Visit 1 (Day 1) 1 h after study drug application, Visit 1 (Day 1) 2 h after study drug application and Visit 2 (Day 3) 48 h after study drug application were below LLOQ.

SAFETY RESULTS:

A total of 47 AEs were reported in an overall 21/62 patients (33.9%). Out of these, 14 AEs each were reported in 6 patients each in G.68.γ/EtOH 0.10%, 0.30% and 0.50% groups. In the placebo group, 3/15 patients reported 5 AEs.

Related AEs were reported in one patient each of the G.68.γ/EtOH group.

Only 2 patients were withdrawn from the study due to an AE: Patient 0135 (G.68.γ/EtOH 0.10% group) due to an AE of pulmonary oedema and Patient 0607 (placebo group) due to an AE of renal failure.

Overall, the majority of AEs reported were mild in intensity (30/47 AEs) followed by moderate (15 AEs) and severe (2 AEs).

The majority of reported AEs were assessed as not related to the study drug. Two AEs were assessed as unlikely to be related to the study drug in Patient 0604 (G.68.γ/EtOH 0.10% group, moderate renal failure) and Patient 0605 (G.68.γ/EtOH 0.30% group, mild vomiting). Patient 0606 (G.68.γ/EtOH 0.50% group) reported an AE of application site pain (mild), which was assessed to be possibly related to the study drug. No action was taken for this AE and the study drug was applied.

There were 2 SAEs reported in Patient 0135 (G.68.γ/EtOH 0.10% group): pulmonary oedema and

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ischaemic stroke (SAE of ischemic stroke resulted in death). These 2 SAEs were assessed as not related to the study drug.

The clinically significant laboratory values of haematology, biochemistry and urinalysis; which were captured as AEs were assessed as not related to the study drug.

There were few AEs related to vital signs and ECG. Two patients reported respectively 1 AE of hypertension (G.68.γ/EtOH 0.10% group) and hypertensive crisis (placebo group), 1 patient (G.68.γ/EtOH 0.30% group) reported 1 AE of mild pulse abnormal.

Three AEs of carotid bruit each in G.68.γ/EtOH 0.10%, 0.30% and 0.50% groups were reported, 1 AE of arrhythmia in G.68.γ/EtOH 0.30% group and 2 AEs of tachycardia respectively in G.68.γ/EtOH 0.30% and 0.50% groups.

Two AEs of left ventricular hypertrophy each in G.68.γ/EtOH 0.10% and 0.30% groups and 1 AE of moderate ventricular extrasystoles in G.68.γ/EtOH 0.50% group were reported.

CONCLUSION:

- The primary objective of the study (reduction in ulcer total bacterial load between pre-treatment and post-illumination on Day1) was met. Infact it was observed a highly statistically significant overall treatment effect in comparison to placebo ($p<0.001$) in reduction of ulcer total bacterial load immediately after the photoactivation.
- The single, topical dose of G.68.γ/EtOH 0.30%:
  - ✓ *Reduction of total bacterial load post-illumination on Day 1:*

    The single dose of G.68.γ/EtOH 0.30% showed a strong treatment effect (highly statistically significant, $p<0.001$) compared to placebo in the reduction of the total bacterial load from baseline to immediately after illumination. Moreover, G.68.γ/EtOH 0.30% showed the capacity to reduce the total bacterial load of about 3 Log (-2.94 Log_{10}CFU/mL) at the same timepoint.

  - ✓ *Reduction of pathogen bacterial load post-illumination on Day 1:*

    The comparison of G.68.γ/EtOH 0.30% treatment group to placebo showed a significant difference from pre-treatment (Baseline, Day 1) to post-illumination on Day 1 in ulcer pathogen bacterial load, with a p-value of 0.028.

  - ✓ *Eradication of total bacterial load post-illumination on Day 1:*

    Even if the data is not statistically significant, in almost half of patients treated with G.68.γ/EtOH 0.30% (7/15 patients) it was observed the eradication immediately after the illumination on Day 1. The eradication rate observed in G.68.γ/EtOH 0.30% group was 46.7% (7/15 patients). The eradication rate, observed in placebo group was only 15.4% (2/13 patients) while the eradication rate, observed in G.68.γ/EtOH 0.10%

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group was 36.4% (4/11 patients).

✓ *Clinical improvement as PEDIS:*

Almost half of patients treated with G.68.γ/EtOH 0.30% at Visit 3 (Day 8) was found to have a clinical diagnosis of "non-infected" ulcer according to PEDIS. Infact at Visit 3, in the group G.68.γ/EtOH 0.30%, the patients with grade I ulcer was 7 on 15 patients [46.7%].

At Visit 4 (Day 15), more than half of patients in G.68.γ/EtOH 0.30% group had a clinical diagnosis of "non-infected" ulcer according to PEDIS. Infact 10 on 15 patients [66.7%] treated with G.68.γ/EtOH 0.30% had an ulcer infection of grade I.

- The single, topical dose of G.68.γ/EtOH 0.50%:

✓ *Reduction of total bacterial load post-illumination on Day 1:*

The single dose of G.68.γ/EtOH 0.50% showed a strong treatment effect (highly statistically significant, $p<0.001$) compared to placebo in the reduction of the total bacterial load from baseline to immediately after illumination. Moreover, G.68.γ/EtOH 0.50% showed the capacity to reduce the total bacterial load of about 3 Log (-2.998 Log_{10}CFU/mL) at the same timepoint.

✓ *Reduction of pathogen bacterial load post-illumination at Visit 1:*

The comparison of G.68.γ/EtOH 0.50% treatment group to placebo showed no statistical significant difference pre-treatment (Baseline, Day 1) to post-illumination on Day 1.

✓ *Eradication of total bacterial load post-illumination at Visit 1:*

The eradication rate in the G.68.γ/EtOH 0.50% group was 56.3% (9/16 patients). This was statistically significant with a p-value of 0.024, depicting a treatment effect in eradication of ulcer total bacterial load at Day 1, post-illumination.

✓ *Clinical improvement as PEDIS:*

At Visit 4 (Day 15), half of patients in G.68.γ/EtOH 0.50% group had a clinical diagnosis of "non-infected" ulcer according to PEDIS. Infact 8 on 16 patients [50.0%] treated with G.68.γ/EtOH 0.50% had an ulcer infection of grade I.

- The strong treatment effect on bacterial load in post-illumination evaluation on Day 1 was not maintained over time as well as for individual time points in any particular treatment group.
- None of the treatment groups showed an effect in maintaining the reduction in ulcer total/pathogen bacterial load over time (at Visits 2, 3 and 4).
- The PK plasma levels of RLP068 and of its photoproduct on Visit 1 (Day 1) 1 h after

Name of Company: Molteni Therapeutics S.r.1	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Not Applicable	Volume:	
Name of Active Ingredient: G.68.γ/EtOH	Page:	

study drug application (before red light illumination), Visit 1 (Day 1) 2 h after study drug application and Visit 2 (Day 3) 48 h after study drug application were below LLOQ.

- A total of 47 adverse events were reported involving 21 patients [33.9% of total enrolled patients (62)] and the majority of them were mild and not related to any the G.68γ/EtOH group. Three adverse events were evaluated as related to G.68.γ/EtOH (= adverse reactions). None of these adverse reactions were classified as serious.

  The adverse reactions were:

  - Moderate renal failure, related to G.68.γ/EtOH 0.10%;

  - Mild vomiting, related to G.68.γ/EtOH 0.30%;

  - Mild pain at the site of application, related to G.68.γ/EtOH 0.50%.

- There were no notable changes in clinical laboratory parameters, vital signs or ECGs for any patient.

In conclusion:

- The activity of RLP068 gel is confirmed for the first time in patients with infected diabetic foot ulcers. So the proof of concept has been demonstrated;
- The G.68.γ/EtOH 0.30% gel, as well as G.68.γ/EtOH 0.50% gel, showed a highly significant effect in reducing bacterial load at the level of infected diabetic foot ulcers compared to placebo. No statistical significant difference to placebo was observed for the G.68.γ/EtOH 0.10%;
- The treatment with the 3 different (0.10%, 0.30% and 0.50%) concentrations of RLP068 was well tolerated;
- Considering the data about the efficacy, tolerability and safety of RLP068, the concentration 0.30% is assumed to be the best concentration for further development for clinical use.

Date of the report: 24 July 2012