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CLINICAL STUDY REPORT: FULL VERSION FOR REGULATORY SUBMISSION

A randomised, double-blind, placebo-controlled, multicentre proof-of-concept trial of IVA337 in the treatment of diffuse cutaneous systemic sclerosis

Test product: *Lanifibranor*

Sponsor's responsible medical officer name
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Protocol number: EudraCT no: 2015-001617-27
Clinicaltrials.gov /kofam.ch
Internal reference: IVA_01_337_HSSC_15_001

Study initiation date*:* 29-Oct-2015 (First patient first visit)
Study completion date: 12-Oct-2018 (Last patient last visit)

Study Phase: II, proof-of-concept

This study was performed in compliance with the current version of the declaration of Helsinki and with the ICH note for guidance on GCP (CPMP/ICH/135/95), including the archiving of essential documents.

Version 1.0 (25-Sep-2019)
(Earlier reports from the same study by version and date)

2 SYNOPSIS

Name of sponsor/Company: Inventiva SA
Name of investigational product: 200 mg capsules of IVA337 (lanifibranor)
Name of active ingredient: Lanifibranor: 4-(1-[1,3-benzothiazol-6-ylsulfonyl]-5-chloro-1H-indol-2-yl)butanoic acid
Title of the study: A randomised, double-blind, placebo-controlled, multicentre proof-of-concept trial of IVA337 in the treatment of diffuse cutaneous systemic sclerosis.
Principal/coordinating investigators: Pr. Yannick Allanore and Pr. Christopher Denton.
Study centres: The study was conducted in 10 countries. A total of 63 centres were opened out of which 47 centres screened for patients. Forty-six (46) centres randomised at least one patient leading to a total of 145 patients assigned to one of the study treatments: 4 centres in Bulgaria (12 patients), 5 centres in France (15 patients), 9 centres in Germany (19 patients), 6 centres in Italy (15 patients), 8 centres in Poland (57 patients), 2 centres in Slovenia (4 patients), 5 centres in Spain (8 patients), 2 centres in Switzerland (4 patients), 2 centres in The Netherlands (2 patients) and 3 centres in The United Kingdom (9 patients).
Publication (reference): Not applicable
Study period: The study was conducted from 29-Oct-2015 (date of patient first visit) to 12-Oct-2018 (date of last patient last visit), which corresponds to a study duration of 35.4 months.
Phase of development: II, proof-of-concept
Background and rationale for the study Systemic sclerosis (SSc), or scleroderma, is a connective tissue disease of autoimmune origin. It is a life-threatening orphan disease with severe physical and psychosocial consequences. There is currently no cure for this debilitating disease. Two subsets of SSc were identified: the diffuse cutaneous (dcSSc) one with early and severe organ damages and the limited cutaneous subset with later organ complications. DcSSc represents 40% of the ~12000 SSc patients of European Scleroderma Trials and Research Group (EUSTAR) cohort. Currently, the optimal treatment of SSc is a challenge because the pathogenesis of this disease is unclear and it is an uncommon and clinically heterogeneous disease affecting multiple organ systems. Despite the availability of a range of drugs to treat specific symptoms such as non-steroidal anti-inflammatory drugs for arthritis, corticosteroids for overt myositis, methotrexate for arthritis or skin thickening, mycophenolate mofetil for early skin and lung disease, and various other immunosuppressants, these treatments are considered as background therapy and are not an effective cure for SSc. Hence, there is a high unmet medical need for the treatment of SSc. Lanifibranor (IVA337) was shown to be active in both preventive as well as curative mode in a pre-clinical skin fibrosis model induced by bleomycin. This provides evidence for an anti-fibrotic effect potentially offering a new therapeutic approach for SSc.

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Objectives

Primary objective

The primary objective of this study was to evaluate in patients suffering from dcSSc the effect of 800 mg and 1200 mg lanifibranor daily on the skin compared to placebo. The modified Rodnan Skin Score (MRSS) was used to determine the changes in skin.

Secondary efficacy objectives *were to evaluate changes in regard to:*

- Skin (MRSS)
- Overall progression of the disease
- Pulmonary function (percentage predicted Forced Vital Capacity [%pFVC] and % predicted Diffusing Capacity of the Lung for Carbon Monoxide [%pcDLCO] corrected for haemoglobin)
- Patient reported outcomes (Scleroderma Health Assessment Questionnaire [SHAQ], UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument 2.0 [UCLA SCTC GIT], Patient Reported Outcomes Measurement Information System [PROMIS] 29, Short Form [36] Health Survey [SF-36])
- Digital ulcer (DU) net burden and proportion of patients who did not develop new ulcers
- Cochin hand function scale
- Physician and patient global assessments of disease activity (Visual Analogue Scale [VAS])
- Combined Response Index for Systemic Sclerosis (CRISS)
- Need for escape therapy
- Severe organ involvement (SOI)

Secondary safety objectives *were to evaluate:*

- Adverse events (AEs) and results of the laboratory tests

Exploratory objectives *were:*

- To explore changes of the Raynaud phenomenon
- To explore changes in activity biomarkers
- To evaluate population pharmacokinetics (PK)
- To evaluate changes at a follow-up visit 4 weeks after completion of the treatment
- To evaluate changes of SSc activity index

Methodology

This study was a randomised, double-blind, placebo-controlled, multicentre phase II proof-of-concept trial designed to evaluate the efficacy and safety of 800 mg and 1200 mg lanifibranor daily compared to placebo in patients suffering from dcSSc.

It was initially planned to enrol 132 patients with dcSSc (44 in each treatment group). The participating investigators were mainly members of EUSTAR network and were based in Europe.

There were 3 parallel treatment groups: placebo (PLA), lanifibranor 400 mg twice daily (LAN800) and 600 mg twice daily (LAN1200). All patients took 6 capsules per day (3 capsules twice daily with food; identical capsules of 200 mg lanifibranor or placebo) according the following scheme:

- Patients who were to receive placebo: 3 capsules of placebo twice daily
- Patients who were to receive 800 mg lanifibranor: 2 capsules of lanifibranor 200 mg and one capsule of placebo, twice daily
- Patients who were to receive 1200 mg lanifibranor: 3 capsules of lanifibranor 200 mg twice daily

Both, patients and investigators were blinded. The packaging and the capsules were all identical. The treatments were randomly assigned. The randomisation was stratified for background therapy (azathioprine, leflunomide, mycophenolate mofetil, methotrexate, no background therapy) to ensure even distribution of background therapies among treatment groups.

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Number of patients (planned and analysed)

Planned: 132 (44 in each group)

Actually included: A total of 161 patients were screened and 145 patients were randomised 1:1:1 to one of the 3 treatment arms (**Intent-To-Treat**, **ITT population**). All randomised patients who took at least one dose of treatment (N=145) were grouped under **mITT population (modified ITT)**. All patients from the ITT/mITT population (N=145) were evaluable for safety (**safety population, SAF**). The 3 populations were therefore identical. All patients from the mITT population who did not have a major protocol deviation (N=104) were grouped under the per protocol population (**PP population**).

Main criteria for inclusion and exclusion

Inclusion Criteria

- Informed consent documented by signature
- Systemic sclerosis according to American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) 2013 classification criteria
- Diffuse cutaneous SSc subset according to LeRoy's criteria
- Diagnosis within the past 3 years as defined by the first non-Raynaud's symptom
- MRSS between 10 and 25
- Age between 18 and 75, male or female

Patients on stable treatment (for >3 months) with prednisone ≤10 mg, methotrexate ≤20 mg/week, azathioprine ≤150 mg/day, mycophenolate mofetil ≤2 g/day, or leflunomide ≤20 mg/day could be included in the study; the therapy was to be maintained as background therapy.

Exclusion criteria

- Cyclophosphamide during the past 3 months
- Requirement of intravenous (IV) prostanoids for pulmonary hypertension in the last 3 months
- Renal insufficiency defined by a creatinine clearance of less than 30 mL/min (Chronic Kidney Disease - Epidemiology Collaboration or Modification of diet in renal disease formula) and/or past/current renal crisis
- Hepatic impairment, i.e. primary biliary cirrhosis and unexplained persistent liver function abnormality,
- Gallbladder disease (Cholelithiasis was not an exclusion criterion)
- Diabetic ketoacidosis
- Severe cardiac (Left Ventricular Ejection Fraction <45%) and/or pulmonary disease (FVC <50% or pulmonary hypertension proven by right heart catheterisation)
- History of heart failure, symptomatic coronary artery disease, significant ventricular tachyarrhythmia, stent placement, coronary artery bypass surgery, and/or myocardial infarction
- Recipient of solid organ transplant
- Gastrointestinal involvement preventing oral administration of study drug
- Chronic infections, positive serology for infection with hepatitis B or C
- Pregnancy, lactation.
- Woman of childbearing potential unwilling to use a medically acceptable form of birth control until at least 2 weeks after the last dose
- History of malignancy within the last 5 years, except for resected basal or squamous cell carcinoma of the skin, treated cervical dysplasia, or treated in situ cervical cancer
- A recent history of alcohol or drug abuse, non-compliance with other medical therapies
- Participation in a clinical study involving another investigational drug or device within the past 4 weeks or during the study
- Laboratory parameters at the pre-treatment visit showing any of the following abnormal results: transaminases >2x the upper limit of normal (ULN) and/or bilirubin >2x ULN; neutrophil count <1,500/mm^3; platelet count <100,000/mm^3; haemoglobin <9 g/dL
- Known hypersensitivity or allergy to class of drugs or the investigational product
- Any condition or treatment, which in the opinion of the investigator, placed the subject at unacceptable risk as a patient in the trial

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- Co-therapy with biologics. Wash-out period: any anti-TNF agent in the last 3 months: adalimumab, certolizumab, etanercept, golimumab, infliximab; abatacept and tocilizumab in the last 3 months; rituximab in the last 6 months
- Any other significant heart disease or any clinically significant electrocardiogram (ECG) abnormality reported by central ECG reading

Test product: lanifibranor

Dose: 800 mg or 1200 mg daily for 48 weeks

Mode of administration, batch number(s): Oral administration. All patients were supposed to take twice daily 3 capsules (either lanifibranor or placebo). To maintain double blind conditions, treatments were administered in capsules of 200 mg lanifibranor or indistinguishable placebo. The batch numbers of the bulk capsules were W027045, W027092, W027857, W028156, 160771 for the active treatment and W026834, W027860, 69003 for the placebo. Patients kits were all constituted with these bulk capsule batches.

Reference product: The control intervention was based on placebo, presented in matching packaging.

Duration of the treatment: 48 weeks

Endpoints

Primary endpoint

Absolute change of the MRSS from baseline to 48 weeks.

Secondary efficacy endpoints

- MRSS responder and progressor response rates at 48 weeks.

  Two definitions of MRSS responders were used, both corresponding to a reduction:
  - Initial definition: ≥5 points and ≥25 % of MRSS compared to baseline
  - Additional definition: ≥4 points and ≥20% MRSS compared to baseline

  Two definitions of MRSS progressors were used, both corresponding to an increase:
  - Initial definition: ≥5 points and ≥25% of MRSS compared to baseline
  - Additional definition: ≥4 and ≥20% of MRSS compared to baseline.
- Overall progression of the disease: defined as presence of escape therapy and presence of SOI (see definition below)
- Absolute change from baseline in pulmonary function tests (%pFVC) and diffusing capacity for carbon monoxide haemoglobin corrected (%pcDLCO)
- Absolute change from baseline in patient reported outcomes (SHAQ, UCLA SCTC GIT, PROMIS-29, SF-36)
- Change in DU net burden over time and proportion of patients who did not develop new ulcers
- Absolute change from baseline in Cochin Hand Function Scale
- Absolute change from baseline in physician and patient global assessments of disease activity (VAS)
- Absolute change from baseline in the Combined Response Index for Systemic Sclerosis (CRISS), consisting of 5 variables: MRSS, %pFVC, physician and patient global assessments, and HAQ-DI score (from SHAQ patient reported outcome).
- Need for escape therapy (% patients)
- SOI (% patients) defined by: new renal crisis, OR new or worsened clinically symptomatic and significant heart disease, considered secondary to dcSSc, OR relative decline in %pFVC by ≥10% or relative decline in %pFVC predicted between 5 to <10% with associated relative decline in %pcDLCO by ≥15%, provided that the decline in FVC results in FVC <75% of predicted, OR new worsening of gastrointestinal disease requiring hospitalisation or new requirement for parenteral nutrition, OR critical ischaemia of the extremities promoting necrosis and/or gangrene, OR new development of pulmonary hypertension associated with pulmonary fibrosis – defined by a mean pulmonary arterial pressure of 25 mmHg or more at right heart catheterisation.

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Safety endpoints

- Frequency and type of AEs
- Laboratory tests: mean change from baseline and frequency of values outside the normal range

Exploratory endpoints

- Raynaud phenomenon (Raynaud's condition score)
- Mean changes in activity biomarkers
- Population PK parameters
- SSc activity index

Statistical methods

Analysis populations

Intent-To-Treat (ITT) population: all randomised patients

Safety (SAF) population: all patients who took at least one dose of treatment (used for safety analyses and treatment compliance)

modified ITT (mITT) population: the mITT population was the same as the SAF (used for demographics and disease characteristics and efficacy analyses)

Per-Protocol (PP) population: all patients from the mITT population with no "major" protocol deviations identified during the Blind Data Review Meetings (used for demographics, disease characteristics and efficacy analyses)

Descriptive analyses

Descriptive statistics were performed for each treatment group (PLA, LAN800, and LAN1200) and overall (for baseline characteristics only).

Continuous variables were summarised in terms of number of non-missing observations (N), number of missing observations (Nmiss), mean (Mean), standard deviation (SD), minimum (MIN), quartile 1 (Q1), median (Median), quartile 3 (Q3) and maximum (MAX).The 95% two-sided Confidence Interval (CI) was calculated when appropriate using the Wald method.

Categorical variables were presented using the number of non-missing observations (N), number of missing observations (Nmiss) and percentages (%). Missing data was not included in the denominator for the calculation of percentages. The 95% two-sided CI was calculated when appropriate using the exact (Clopper-Pearson) method.

For statistical tests, the type I error risk was set at 5% (2-sided) without adjustments for multiplicity testing, unless specified otherwise. When specified, the ascending Hochberg procedure was used to adjust for multiplicity testing.

Comparison of treatment groups for quantitative variables was performed using Wilcoxon-Mann-Whitney test, an Analysis of Covariance or Mixed Model for Repeated Measures (MMRM) as specified.

Comparisons of treatment groups for qualitative variables were carried out using Cochran–Mantel–Haenszel test, stratified on the use of background therapy (yes/no).

Analysis of the primary endpoint

This primary endpoint (absolute change in MRSS from baseline) was analysed at Week 48 using a Mixed-effect Model for Repeated Measures (MMRM) that incorporated the time, treatment, use of a background therapy (yes/no) and the interaction (treatment * time) as fixed effects and a time repeated effect within each patient. With this MMRM model, different treatment effects were evaluated:

- Evaluation of treatment effect (dose-response relationship)
- Evaluation of treatment effect (Each dose *versus* placebo)
- Evaluation of dose effect (800 mg *versus* 1200 mg)

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The **primary analysis of the primary endpoint** was carried out on the mITT population and consisted of implementing the MMRM model at Week 48 using the primary missing data imputation method (i.e. 'linear interpolation + placebo slope'), assessing whether there was a dose-response relationship between the placebo-adjusted mean difference in change from baseline in MRSS and the 2 doses of lanifibranor at Week 48. Several sensitivity analyses of the primary endpoint were performed on the different study populations (ITT, mITT, PP) using various imputation methods (including among others, LOCF under treatment, observed cases under treatment, and multiple imputation). Finally, additional analyses of the primary endpoint (descriptive statistics only) were performed in the mITT and PP populations in the following subgroups of interest: by anticentromere antibody [ACA] results at baseline, by MRSS at baseline, by combination of ACA and MRSS at baseline, by presence of interstitial lung disease [ILD] at baseline, by disease duration at baseline, and by background therapy.

Secondary analyses of the primary efficacy endpoint were carried out on the mITT population, using the same methodology, and consisted of comparing each lanifibranor dose with placebo or with each other.

Summary of results and overall conclusions

Patient disposition

A total of 161 patients were screened for the study of whom 16 (9.9%) were not included because inclusion criteria were not met (10 patients, 62.5%), exclusion criteria were met (2 patients, 12.5%), consent was withdrawn (2 patients, 12.5%), forbidden concomitant medications were taken (one patient, 6.3%), and both inclusion and exclusion criteria were not met (one patient, 6.3%).

Accordingly, 145 patients were randomised 1:1:1 into the 3 treatment arms: 49 patients in the LAN800 arm, 48 patients in the LAN1200 arm and 48 patients in the PLA arm. One of these 145 randomised patients did not present dcSSc at inclusion according to Leroy's criteria and hence was wrongly included in the study. The 48-week expected treatment period was completed by 106 patients (73.1%) distributed as follows: 34 patients (69.4%, N=49) in the LAN800 arm, 32 patients (66.7%, N=48) in the LAN1200 arm and 40 patients (83.3%, N=48) in the PLA arm. In line with these results, the mean (SD) treatment duration was slightly higher in the PLA arm (44.1 [8.7] months) compared to the active treatment arms (39.7 [14.8] and 37.7 [16.3] months in the LAN800 and LAN1200 arms, respectively).

A total of 39 patients (26.9%) prematurely discontinued the study treatment and the majority of treatment discontinuations were due to AEs (29/39 patients [74.4%]). There were more patients who discontinued due to AEs in the active treatment arms (12/15 patients [80.0%] and 13/16 patients [81.3%] in the LAN800 and LAN1200 arms, respectively) than in the PLA arm (4/8 patients [50.0%]). It should be noted that there was one discontinuation due to a fatal *septic shock* that was not related to the study treatment. The remaining 10 patients who prematurely discontinued the study treatment were distributed as follows: 6 patients (15.4%) discontinued the treatment based on their own decision, one patient based on physician's decision (in the PLA arm), one patient due to protocol deviation (in the LAN1200 arm), and 2 patients (one each in LAN800 and LAN1200 arms) for other reasons.

Out of the 145 randomised patients, 41 (28.3%) had at least one major protocol deviation, including 14 patients (28.6%, N=49) in the LAN800 arm, 18 patients (37.5%, N=48) in the LAN1200 arm and 9 patients (18.8%, N=48) in the PLA arm. All treatment arms combined, the most common major protocol deviations were non-availability of MRSS at Week 48 +/- 30 days in 22 patients (15.2%, N=145) and, when MRSS was available at Week 48, low compliance to treatment (≤80%) at the time of MRSS assessment in 19 patients (13.1%, N=145). Of note, these 19 patients prematurely discontinued the study treatment (i.e. treatment duration <48 weeks).

Demographic and disease characteristics

Demographics

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In the mITT population (N=145), the majority of patients were female (120 patients, 82.8%). There were more female patients in the LAN800 and LAN1200 arms (45 [91.8%] and 40 [83.3%], respectively) compared to the PLA arm (35 [72.9%]). Consistent with the inclusion criteria, all patients were aged between 18 and 75 years. The mean (SD) age of patients was 48.1 (11.3) years overall and was similar in the 3 arms (from 46.4 [11.4] years in the LAN800 arm to 49.0 [11.5;11.1] years in the LAN1200 and PLA arms). The mean (SD) age at dcSSc diagnosis was 46.7 (11.4) years, with 85.5% (124/145) of patients aged ≤60 years. Patients were evenly distributed in all 3 arms according to their body mass index (BMI). The mean (SD) BMI was 24.8 (4.6) kg/m² overall.

Disease characteristics: Systemic sclerosis

In the mITT population, all patients met the SSc (2013 ACR/EULAR) classification criteria and had definite SSc. As previously mentioned, one patient did not present dcSSc according to LeRoy's criteria and hence was not eligible. The mean (SD) SSc activity index at baseline was 2.4 (1.7) and 27.7% (23/145) of SSc patients had an active disease (as defined by a SSc activity index >3). No notable differences in SSc activity index were observed between treatment arms.

In the mITT population, the duration of the disease at inclusion ranged from 0 to 37 months, with a mean (SD) of 17.1 (11.3) months. Half of patients (73/145, 50.3%) had a disease duration ≤15 months (cut-off for early onset dcSSc). Results across treatment arms were similar to those in the overall mITT population.

In the mITT population, the MRSS score at baseline ranged from 10 to 25, in line with inclusion criteria. The mean (SD) MRSS score was 17.7 (3.8) and the majority of patients (104/145, 71.7%) had an MRSS score within the [16-25] range. No notable differences were observed between treatment arms.

Other disease characteristics at baseline (%pFVC and %pcDLCO, DU count, disease activity assessed by the physician and the patient using a VAS, HAQ-DI score) were also similar across treatment arms.

Compliance to treatment

The mean overall compliance corresponds to the ratio between the actual number of capsules taken and the theoretical number of capsules received from baseline up to the time of MRSS assessment at Week 48. The mean (SD) overall compliance was comparable across the 3 arms, although slightly lower in the LAN1200 arm (80.9% [32.6] compared to 92.1% [19.2] and 93.1% [16.5] for the LAN800 and PLA arms, respectively). However, the mean overall persistence, which corresponds to the ratio between the actual number of capsules taken and the theoretical number of capsules received from initiation to discontinuation of therapy, was identical in all 3 arms (97.4%).

Efficacy Results

Primary efficacy endpoint

Primary, sensitivity and subgroup analyses of the primary efficacy endpoint:

The primary endpoint was defined as the mean absolute change in MRSS score from baseline to Week 48.

The MMRM-adjusted mean change from baseline in MRSS at Week 48 was -3.75 (Standard Error [SE]: 0.64) for the LAN800 arm, -4.39 (SE: 0.65) for the LAN1200 arm and -5.03 (SE: 0.65) for the PLA arm. Based on the primary analysis, the adjusted mean difference (SE) for LAN800 *versus* PLA was 1.28 (0.91) and LAN1200 *versus* PLA was 0.63 (0.91). The treatment effect of lanifibranor *versus* placebo at Week 48 through dose-response relationship was not statistically significant (p=0.3614), showing no lanifibranor dose-response relationship for the change from baseline in MRSS. Therefore, the primary endpoint was not met.

Several sensitivity analyses of the primary endpoint were performed on the different study populations (ITT, mITT, PP) using various imputation methods (including among others, LOCF under treatment, observed cases under treatment, and multiple imputation). Sensitivity analyses confirmed the results from the primary efficacy analysis, with no significant dose-response relationship in any sensitivity analysis performed. Additional analyses of the primary endpoint were performed on the mITT and PP populations in different subgroups of interest (by ACA results at baseline, by MRSS at baseline, by combination of ACA and MRSS at baseline, by presence of ILD at baseline, by disease duration at baseline, and by background therapy). There were no major differences in the MRSS mean change from baseline to Week 48 between the 3 treatment arms for any of the subgroups of interest.

In the coming results, as the primary objective regarding the dose-response relationship was not met, all p-values are provided as exploratory results.

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Secondary analyses of the primary efficacy endpoint:

Secondary analyses of the primary endpoint showed no statistically significant differences between the placebo and either dose of lanifibranor (p=0.1582 and p=0.9605 for comparisons with LAN800 and LAN1200, respectively) or between the low and high doses of lanifibranor (p=0.4743).

Secondary efficacy endpoints

MRSS responders/progressors:

Patients were considered as MRSS responders when their MRSS score decreased by at least 5 points and by 25% compared to baseline (initial definition). The proportion of responders at Week 48 was higher in the PLA arm (26 patients, 54.2%) compared to the LAN800 and LAN1200 arms (14 patients [28.6%] and 17 patients [35.4%], respectively). When the definition was adjusted to a decrease of at least 4 points and of 20% compared to baseline, the proportion of responders also appeared to be higher in the PLA arm compared to the active treatment arms.

Patients were considered as MRSS progressors when their MRSS score increased of at least 5 points and of 25% compared to baseline (initial definition) or increased of at least 4 points and of 20% compared to baseline (additional definition). Only few patients met these criteria at Week 48: 2 patients in the LAN1200 arm with the initial definition and 2 additional patients (one in the LAN800 arm and one in the PLA arm) when the additional definition was considered.

%pFVC and %pcDLCO:

The mean %pFVC was close to 100% at baseline in all three 3 arms and remained stable over the 48-week treatment period, with mean changes from baseline in %pFVC close to 0% at each evaluated time point (range: -0.8% to 0.8%). There were no statistically significant dose-response relationship and no statistically significant differences between treatment arms (p>0.05) in the %pFVC change from baseline at Week 48.

The mean %pcDLCO remained stable from baseline to Week 48 in the LAN800 arm and PLA arm (around 77-78% in the LAN800 arm and around 71% in the PLA arm) while it decreased in the LAN1200 arm (from 71% to 67%). Consequently, the 1200 mg dose of lanifibranor, but not the 800 mg dose, induced a statistically significant reduction in %pcDLCO compared to placebo (p=0.0366 and p=0.6542, respectively). High dose of lanifibranor also resulted in a statistically significant reduction in %pcDLCO compared to the low dose (p=0.0120). However, no statistically significant lanifibranor dose-response relationship was shown for the change from baseline in the %pcDLCO (p=0.0835).

Digital Ulcers:

At baseline, the percentage of patients reporting DUs ranged 12-17% across the 3 arms. This proportion decreased over the study treatment period to 3-7% at Week 48. Only few patients (≤2 patients in each treatment arm) experienced an increase in the number of DUs at Week 48 (described as number of DUs at a certain time point greater than the number at baseline). The effect of LAN800 and LAN1200 *versus* placebo at Week 48 on DU count was not statistically significant (p=0.9220 and 0.4185, respectively).

CRISS:

The CRISS predictive probability was available for most of the patients (>75%) at both Weeks 24 and 48. Mean values were comparable across all 3 arms and no marked differences were observed between Week 24 (ranged from 0.29-0.32) and Week 48 (ranged from 0.41-0.43). There were no statistically significant dose-response relationship and no statistically significant differences between treatment arms (p>0.05) in the CRISS predictive probability change from baseline at Week 48.

HAQ-DI:

At baseline, the mean HAQ-DI score derived from SHAQ questionnaire ranged from 0.6-0.8 across the 3 arms. The mean HAQ-DI score remained relatively the same over time (the mean [SD] absolute change from baseline to Week 48 was -0.10 [0.34] for the LAN800 arm, -0.08 [0.37] for the LAN1200 arm and -0.05 [0.34] for the PLA arm). There were no statistically significant dose-response relationship and no statistically significant differences between treatment arms (p>0.05) in the HAQ-DI score change from baseline at Week 48.

VAS physician and patient global assessment of disease activity:

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At baseline, the mean physician score was slightly lower in the PLA arm compared to the active treatment arms (38.9 *versus* 48.5 for the LAN800 arm and 45.1 for the LAN1200 arm). At Week 48, the mean score decreased in the 3 treatment arms and reached a value of about 32−33 (mean absolute change was -15.4 in the LAN800 arm, -12.9 in the LAN1200 arm and -7.1 in the PLA arm). Consequently, a trend toward an improved perception of the disease activity was observed in the active treatment arms compared to placebo. However, no statistically significant dose-response relationship, nor any statistically significant effect of lanifibranor doses compared to placebo or compared between each other were evidenced (p>0.05).

The patient global assessment of disease activity followed the same pattern: the mean baseline score was slightly lower in the PLA arm compared to the active treatment arms (36.2 *versus* 43.3 for the LAN800 arm and 42.3 for the LAN1200 arm). The mean score decreased in the 2 active treatment arms while it remained fairly stable in the PLA arm (mean absolute change was -10.2 in the LAN800 arm, -11.8 in the LAN1200 arm and -2.7 in the PLA arm). This suggests a trend toward a better improvement with lanifibranor compared to placebo. The effect of the high lanifibranor dose (1200 mg/day) compared to placebo was close to the significant threshold (p=0.0787).

Overall progression of the disease, need for escape therapy and treatment discontinuation:

After 48 weeks of treatment, overall progression of the disease was reported for a total of 12 patients (3 in the LAN800 arm, 5 in the LAN1200 arm and 4 in the PLA arm). Therefore, no difference between arms was observed in the occurrence of overall disease progression (p>0.05). Similarly, only few patients needed escape therapy during the treatment period: one each in the LAN1200 and PLA arms. Finally, about one third of patient in each active treatment arm and 1/6 in the PLA arm discontinued permanently the study treatment, mainly following occurrence of AEs.

Safety Results

All patients from the ITT population (N=145) were evaluable for safety (safety population, SAF). Safety results focus on the description of treatment emergent adverse events (TEAEs), defined as AEs that occurred on or after the first dose of treatment up to 30 days post-last dose.

Overall TEAEs reported throughout the study period

Of the 145 patients included in the SAF population, 128 (88.3%) experienced at least one TEAE, with similar incidence rates among treatment arms (44 patients [89.8%], 41 patients [85.4%], and 43 patients [89.6%] in the LAN800, LAN1200 and PLA arms, respectively). The most common TEAEs (i.e. reported by >20% of the patients in any treatment arm) were *weight increased*, *oedema peripheral* and *nasopharyngitis*. These events occurred more frequently in lanifibranor-treated patients than in those receiving the placebo: 1) *weight increased*: all patients except one were in the active treatment arms (10 patients [20.4%], 19 patients [39.6%], and one patient [2.1%] in the LAN800, LAN1200, and PLA arms, respectively); 2) *oedema peripheral:* all patients were in the active treatment arms (16 patients [32.7%] and 13 patients [27.1%] in the LAN800 and the LAN1200 arms, respectively); 3) *nasopharyngitis*: 13 patients (26.5%) in the LAN800 arm and 8 patients (16.7%) in the LAN1200 arm *versus* 4 patients (8.3%) in the PLA arm.

Treatment-related TEAEs reported throughout the study period

In the SAF population, the number (%) of patients who experienced at least one TEAE related to the study treatment was almost thrice higher in the active treatment arms (32 patients [65.3%] and 31 patients [64.6%] in the LAN800 and LAN1200 arms, respectively) than in the PLA arm (11 patients [22.9%]). *Weight increased* was the most commonly encountered TEAE related to the study treatment (8 patients [16.3%] and 16 patients [33.3%] in the LAN800 and LAN1200 arms, respectively *versu*s one patient [2.1%] in the PLA arm), followed by *oedema peripheral* (10 patients [20.4%] and 12 patients [25.0%] in the LAN800 and LAN1200 arms, respectively).

Severe TEAEs

In the SAF population, 14 patients (9.7%) experienced at least one severe TEAE: 8 patients (16.3%) in the LAN800 arm and 3 patients each (6.3%) in the LAN1200 and PLA arms. The most common severe TEAE was *systemic scleroderma**, presented by 3 patients (6.1%) in the LAN800 arm and one patient each in the LAN1200 and PLA arms. None of these events were considered as related to the study treatment.

Severe TEAEs related to the study treatment were all reported in lanifibranor-treated patients: 3 patients (6.1%) in the LAN800 arm (*gastric disorder*, *weight increased*, and *dermatitis*) and one patient (2.1%) in the LAN1200 arm (*oedema peripheral*). There were no severe study-treatment-related TESAEs reported during the study.

Name of sponsor/Company: Inventiva SA

Name of investigational product: 200 mg capsules of IVA337 (lanifibranor)

Name of active ingredient: Lanifibranor: 4-(1-[1,3-benzothiazol-6-ylsulfonyl]-5-chloro-1H-indol-2-yl)butanoic acid

Serious TEAEs

In the SAF population, 16 patients (11.0%) experienced during the whole study period a total 18 TESAEs. Apart from one event, all TESAEs were reported in lanifibranor-treated patients: 8 patients (16.3%; 10 events) in the LAN800 arm, 7 patients (14.6%; 7 events) in the LAN1200 arm, and one patient (2.1%; one event) in the PLA arm.

One TESAE – moderate *oedema peripheral* − was classified as a SUSAR and was reported in a patient from the LAN1200 arm. Apart from this SUSAR, no other TESAE were considered as related to the study treatment.

The most common TESAE was *systemic scleroderma** (2 patients [4.1%] in the LAN800 arm and one patient [2.1%] in the LAN1200 arm), followed by *scleroderma associated digital ulcer* (one patient [~2.0%] each in the LAN800 and PLA arms).

There was one fatal TESAE in the LAN800 arm, assessed as not related to the study treatment, wherein the patient died of *septic shock*.

TEAEs leading to permanent treatment discontinuation

In the SAF population, 29 patients (20%) experienced at least one TEAE leading to permanent treatment discontinuation. The incidence of these events was higher in the active treatment arms (12 patients [24.5%] and 13 patients [27.1%] for the LAN800 and LAN1200 arms, respectively) compared to the PLA arm (4 patients [8.3%]). TEAEs leading to permanent treatment discontinuation related to the study treatment were all reported in lanifibranor-treated patients (5 patients [10.2%] and 7 patients [14.6%] for the LAN800 and LAN1200 arms, respectively). *Oedema peripheral* was the most common study-treatment-related TEAEs that led to permanent treatment discontinuation and was presented by one patient (2.0%) in the LAN800 arm and 2 patients (4.2%) in the LAN1200 arm.

TEAEs reported as SOI:

A total of 7 events were adjudicated as SOI by the Independent Central Adjudication Committee and were reported by 3 patients (6.1%) in the LAN800 arm, and 2 patients (4.2%) each in the LAN1200 and PLA arms. These TEAE reported as SOI consisted of 4 cases of ILD and 3 cases of digital ulcers.

Of the 4 cases of ILD, 3 were of moderate intensity and one was of mild intensity. The latter case was deemed study-treatment-related and occurred in a patient treated with the high dose of lanifibranor (1200 mg/day).

All 3 cases of digital ulcers were TESAEs (moderate or severe in intensity), and none was considered as study-treatment-related.

Fluid retention TEAEs

The fluid retention TEAEs included face oedema, generalised oedema, oedema peripheral, periorbital oedema, peripheral swelling, swelling face, swelling of the eyelid, joint swelling and weight increased.

In the SAF population, fluid retention TEAEs were mainly observed in lanifibranor-treated patients, with around half of patients reporting such events in each active treatment arm (25 patients [51.0%] in the LAN800 arm and 26 patients [54.2%] in the LAN1200 arm), compared to 4 patients (8.3%) in the PLA arm. For 19 patients (38.8%) in the LAN800 arm and 22 patients (42.3%) in the LAN1200 arm, at least one fluid retention TEAE was considered as related to the study treatment, compared to one patient (2.1%) in the PLA arm. The most common fluid retention TEAEs related to the study treatment (i.e. reported by >10% of the patients in any treatment arm) were *weight increased* (8 patients [16.3%], 16 patients [33.3%], and one patient [2.1%] in the LAN800, LAN1200, and PLA arms, respectively), *oedema peripheral* (10 patients [20.4%] and 12 patients [25.0%] in the LAN800 and LAN1200 arms, respectively), and *peripheral swelling* (5 [10.2%] and 2 [4.2%] in the LAN800 and LAN1200 arms, respectively).

**All TEAEs coded as systemic scleroderma were associated with an exacerbation/worsening of patient's SSc or an increase in MRSS.*

Clinical laboratory evaluation, vital signs, and clinical examinations

No substantial changes between treatment arms were observed over time in any of the assessed laboratory parameters, vital signs, and body systems.

Other Results

Name of sponsor/Company: Inventiva SA
Name of investigational product: 200 mg capsules of IVA337 (lanifibranor)
Name of active ingredient: Lanifibranor: 4-(1-[1,3-benzothiazol-6-ylsulfonyl]-5-chloro-1H-indol-2-yl)butanoic acid
During this study, patients were treated with 2 different doses of lanifibranor (800 mg and 1200 mg daily doses). PK parameters showed a dose-proportional increase in lanifibranor exposure, with mean C_{max} values of 3.3 µg.h/mL and 5.0 µg.h/mL and mean daily AUC values of 56 µg.h/mL and 86 µg.h/mL for the low and high doses of lanifibranor, respectively. ***Conclusions*** This study conducted in patients with early dcSSc failed to show, after 48 weeks of treatment, any statistical efficacy benefit of the 2 tested doses of lanifibranor (IVA337; 800 mg/day and 1200 mg/day) *versus* placebo on the MRSS. Similarly, there was no statistically significant effect of lanifibranor on the pulmonary function tests and other secondary efficacy endpoints. It is noteworthy to point out that there was a trend towards an improved perception of the disease activity with lanifibranor, based on the VAS physician and patient global assessments. Lanifibranor (IVA337) in these patients with early dcSSc was observed to be associated with an acceptable safety profile and no major safety concerns were identified when lanifibranor was administered concomitantly with immunosuppressive background therapy and/or corticoids. Circulating adiponectin levels indicated strong PPARγ target engagement in lanifibranor-treated SSc patients, possibly due to twice daily dosing. This may explain the high rate of oedema/weight gain in lanifibranor groups. Overall, lanifibranor was well-tolerated and reported AEs were consistent with its known safety profile.
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