



Clinical trial results:

A randomized, double-blind, placebo-controlled, multicenter, dose-range, proof-of-concept, 24-week treatment study of IVA337 in adult subjects with nonalcoholic steatohepatitis (NASH)

Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2016-001979-70 |
| Trial protocol | BE GB CZ AT PT ES NL PL FR BG SI IT |
| Global end of trial date | 16 March 2020 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 01 April 2021 |
| First version publication date | 01 April 2021 |

Trial information

Trial identification

| | |
|-----------------------|------------------------|
| Sponsor protocol code | IVA_01_337_HNAS_16_002 |
|-----------------------|------------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03008070 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Inventiva S.A. |
| Sponsor organisation address | 50 rue de Dijon, Daix, France, 21121 |
| Public contact | Mathilde Merot, Regulatory Affairs Manager, INVENTIVA S.A., +33 380447616, native.public@inventivapharma.com |
| Scientific contact | Michael Cooreman, Chief Medical Officer, INVENTIVA S.A., +33 380447616, native.scientists@inventivapharma.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 16 March 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 16 March 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 16 March 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The study main objective was to assess the safety and the efficacy (based on the activity part of the Steatosis Activity Fibrosis [SAF-A] histological score [inflammation and ballooning]) of a 24-week treatment with 2 doses of lanifibranor (800 mg/day and 1200 mg/day) in NASH adult patients.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 03 January 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Poland: 6 |
| Country: Number of subjects enrolled | Slovenia: 1 |
| Country: Number of subjects enrolled | Spain: 12 |
| Country: Number of subjects enrolled | United Kingdom: 7 |
| Country: Number of subjects enrolled | Austria: 1 |
| Country: Number of subjects enrolled | Belgium: 32 |
| Country: Number of subjects enrolled | Bulgaria: 55 |
| Country: Number of subjects enrolled | Czech Republic: 8 |
| Country: Number of subjects enrolled | France: 39 |
| Country: Number of subjects enrolled | Germany: 13 |
| Country: Number of subjects enrolled | United States: 36 |
| Country: Number of subjects enrolled | Australia: 13 |
| Country: Number of subjects enrolled | Canada: 8 |
| Country: Number of subjects enrolled | Mauritius: 7 |
| Country: Number of subjects enrolled | Switzerland: 4 |
| Country: Number of subjects enrolled | Italy: 5 |
| Worldwide total number of subjects | 247 |
| EEA total number of subjects | 179 |

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 199 |
| From 65 to 84 years | 48 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Recruitment of patients started in January 2017, and last patient was recruited on March 2019. A total of 868 patients were screened for the study.

Pre-assignment

Screening details:

Patients were invited to participate into the study by their referent doctor according to the patient's medical records. Patients had to fulfil all the inclusion and none of the exclusion criteria to be eligible. A total of 247 patients were randomised. Main reason for non randomization was inclusion/exclusion criteria not met (470 - 76%).

Period 1

| | |
|------------------------------|--|
| Period 1 title | Core Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst |

Arms

| | |
|------------------------------|--------|
| Are arms mutually exclusive? | Yes |
| Arm title | LAN800 |

Arm description:

Patients who received lanifibranor 800mg daily: 2 tablets of lanifibranor and 1 tablet of placebo.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Lanifibranor |
| Investigational medicinal product code | IVA337 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

White to off-white, bi-convex tablet of 400mg to be taken orally. Each tablet contained 400 mg of the active ingredient in an immediate release formulation.

| | |
|------------------|---------|
| Arm title | LAN1200 |
|------------------|---------|

Arm description:

Patients who received lanifibranor 1200mg daily: 3 tablets of lanifibranor

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Lanifibranor |
| Investigational medicinal product code | IVA337 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

White to off-white, bi-convex tablet of 400mg to be taken orally. Each tablet contained 400 mg of the active ingredient in an immediate release formulation.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Patients who received placebo: 3 tablets of placebo daily

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|-------------------------------|
| Investigational medicinal product name | Placebo to match lanifibranor |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Film-coated tablets containing a mixture of lactose monohydrate, microcrystalline cellulose, sodium starch and magnesium stearate served as placebo. 3 tablets to be taken orally.

| Number of subjects in period 1 | LAN800 | LAN1200 | Placebo |
|---|--------|---------|---------|
| Started | 83 | 83 | 81 |
| Completed | 77 | 77 | 74 |
| Not completed | 6 | 6 | 7 |
| Consent withdrawn by subject | - | 2 | 1 |
| Adverse event, non-fatal | 3 | 3 | 3 |
| Non compliance | - | - | 1 |
| Non-compliance | 1 | - | - |
| Withdrawal by patient + Adverse event non fatal | 1 | - | - |
| Lost to follow-up | 1 | 1 | - |
| Use of prohibited drug | - | - | 2 |

Baseline characteristics

Reporting groups

| | |
|--|---------|
| Reporting group title | LAN800 |
| Reporting group description: | |
| Patients who received lanifibranor 800mg daily: 2 tablets of lanifibranor and 1 tablet of placebo. | |
| Reporting group title | LAN1200 |
| Reporting group description: | |
| Patients who received lanifibranor 1200mg daily: 3 tablets of lanifibranor | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Patients who received placebo: 3 tablets of placebo daily | |

| Reporting group values | LAN800 | LAN1200 | Placebo |
|------------------------|--------|---------|---------|
| Number of subjects | 83 | 83 | 81 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 69 | 67 | 63 |
| From 65-84 years | 14 | 16 | 18 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 55.0 | 52.2 | 53.4 |
| standard deviation | ± 10.4 | ± 13.8 | ± 13.1 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 54 | 49 | 41 |
| Male | 29 | 34 | 40 |

| Reporting group values | Total | | |
|------------------------|-------|--|--|
| Number of subjects | 247 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 199 | | |
| From 65-84 years | 48 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | - | | |
| standard deviation | | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 144 | | |
| Male | 103 | | |

End points

End points reporting groups

| | |
|--|---------|
| Reporting group title | LAN800 |
| Reporting group description: | |
| Patients who received lanifibranor 800mg daily: 2 tablets of lanifibranor and 1 tablet of placebo. | |
| Reporting group title | LAN1200 |
| Reporting group description: | |
| Patients who received lanifibranor 1200mg daily: 3 tablets of lanifibranor | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Patients who received placebo: 3 tablets of placebo daily | |

Primary: SAF Activity score (SAF-A) decrease of at least 2 points with no worsening of the CRN Fibrosis score (CRN-F)

| | |
|--|--|
| End point title | SAF Activity score (SAF-A) decrease of at least 2 points with no worsening of the CRN Fibrosis score (CRN-F) |
| End point description: | |
| SAF-A is the activity part of the Steatosis Activity Fibrosis [SAF] histological score, calculated as the sum of lobular inflammation score and ballooning score. No worsening of fibrosis means that the CRN fibrosis score (CRN-F) remains stable or decreases. | |
| End point type | Primary |
| End point timeframe: | |
| From baseline to Week 24. | |

| End point values | LAN800 | LAN1200 | Placebo | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 83 | 83 | 81 | |
| Units: number of patients | | | | |
| Yes | 34 | 41 | 22 | |
| No | 49 | 42 | 59 | |

Statistical analyses

| | |
|--|---------------------------------|
| Statistical analysis title | Comparison of LAN800 vs Placebo |
| Statistical analysis description: | |
| The primary endpoint was a binary outcome (Yes/No). Responders rates were compared between the placebo and lanifibranor 800 mg at the end of the treatment period (week 24) using a Cochran Mantel Haenzel test stratified on diabetic status at baseline (that was the stratified factors in the randomisation). The CMH risk ratio is used to estimate the effect size. Patients with missing data are considered as non-responders. | |
| Comparison groups | Placebo v LAN800 |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 164 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.061 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.98 |
| upper limit | 2.12 |

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | Comparison of LAN1200 vs Placebo |
|-----------------------------------|----------------------------------|

Statistical analysis description:

The primary endpoint was a binary outcome (Yes/No). Responders rates were compared between the placebo and lanifibranor 1200 mg at the end of the treatment period (week 24) using a Cochran Mantel Haenzel test stratified on diabetic status at baseline (that was the stratified factors in the randomisation).

The CMH risk ratio is used to estimate the effect size.

Patients with missing data are considered as non-responders.

| | |
|---|-------------------------|
| Comparison groups | LAN1200 v Placebo |
| Number of subjects included in analysis | 164 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.004 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.24 |
| upper limit | 2.4 |

Secondary: NASH improvement

| | |
|-----------------|------------------|
| End point title | NASH improvement |
|-----------------|------------------|

End point description:

NASH improvement is defined as a decrease of at least 2 points in NAS score (sum of CRN Steatosis, Inflammation and Ballooning scores) without worsening of CRN Fibrosis score.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to Week 24.

| End point values | LAN800 | LAN1200 | Placebo | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 83 | 83 | 81 | |
| Units: number | | | | |
| Yes | 43 | 53 | 26 | |
| No | 40 | 30 | 55 | |

Statistical analyses

No statistical analyses for this end point

Secondary: NASH resolution and no worsening of fibrosis

| | |
|------------------------|--|
| End point title | NASH resolution and no worsening of fibrosis |
| End point description: | Resolution of NASH is defined as a CRN Inflammation score equal to 0 or 1, and a CRN Ballooning score equal to 0. No worsening of fibrosis means that the CRN fibrosis score remains stable or decreases. |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 83 | 83 | 81 | |
| Units: number | | | | |
| Yes | 27 | 37 | 15 | |
| No | 56 | 46 | 66 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Improvement of fibrosis by at least 1 stage and no worsening of NASH

| | |
|------------------------|---|
| End point title | Improvement of fibrosis by at least 1 stage and no worsening of NASH |
| End point description: | Improvement of fibrosis is defined as a decrease of at least one stage in CRN Fibrosis score. No worsening of NASH is defined as no increase of CRN Steatosis score, no increase of CRN Inflammation score and no increase of CRN Ballooning score. |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 83 | 83 | 81 | |
| Units: number | | | | |
| Yes | 23 | 35 | 19 | |
| No | 60 | 48 | 62 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Activity (SAF-A) improvement

| | |
|---|------------------------------|
| End point title | Activity (SAF-A) improvement |
| End point description: | |
| SAF-A is the activity part of the Steatosis Activity Fibrosis [SAF] histological score, calculated as the sum of lobular inflammation score and ballooning score. Improvement of SAF-A is defined as a decrease of at least 1 point | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline to Week 24. | |

| End point values | LAN800 | LAN1200 | Placebo | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 83 | 83 | 81 | |
| Units: number | | | | |
| Yes | 54 | 62 | 40 | |
| No | 29 | 21 | 41 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Steatosis (CRN-S) improvement

| | |
|--|-------------------------------|
| End point title | Steatosis (CRN-S) improvement |
| End point description: | |
| Improvement of CRN Steatosis score (CRN-S) is defined as a decrease of at least 1 point. | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline to Week 24. | |

| End point values | LAN800 | LAN1200 | Placebo | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 83 | 83 | 81 | |
| Units: number | | | | |
| Yes | 46 | 54 | 21 | |
| No | 37 | 29 | 60 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Lobular inflammation (CRN-I) improvement

| | |
|------------------------|---|
| End point title | Lobular inflammation (CRN-I) improvement |
| End point description: | Improvement of CRN Lobular inflammation score (CRN-I) is defined as a decrease of at least 1 point. |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 83 | 83 | 81 | |
| Units: number | | | | |
| Yes | 34 | 43 | 30 | |
| No | 49 | 40 | 51 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Hepatocyte ballooning (CRN-B) improvement

| | |
|------------------------|---|
| End point title | Hepatocyte ballooning (CRN-B) improvement |
| End point description: | Improvement of CRN Ballooning (CRN-B) is defined as a decrease of at least 1 point. |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 83 | 83 | 81 | |
| Units: number | | | | |
| Yes | 54 | 60 | 37 | |
| No | 29 | 23 | 44 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Fibrosis (CRN-F) improvement

| | |
|------------------------|---|
| End point title | Fibrosis (CRN-F) improvement |
| End point description: | Improvement of CRN Fibrosis score (CRN-F) is defined as a decrease of at least 1 point. |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 83 | 83 | 81 | |
| Units: number | | | | |
| Yes | 28 | 36 | 22 | |
| No | 55 | 47 | 59 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Modified ISHAK Fibrosis (ISHAK-F) improvement

| | |
|------------------------|--|
| End point title | Modified ISHAK Fibrosis (ISHAK-F) improvement |
| End point description: | Improvement of Modified ISHAK Fibrosis (ISHAK-F) is defined as a decrease of at least 1 point. |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 83 | 83 | 81 | |
| Units: number | | | | |
| Yes | 32 | 41 | 25 | |
| No | 51 | 42 | 56 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in ALT

| | |
|------------------------|---|
| End point title | Absolute change in ALT |
| End point description: | Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|----------------------------------|----------------------|----------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 72 | 74 | 72 | |
| Units: U/L | | | | |
| arithmetic mean (standard error) | -26.08 (\pm 3.85) | -24.54 (\pm 3.82) | -1.4 (\pm 3.88) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in AST

| | |
|------------------------|---|
| End point title | Absolute change in AST |
| End point description: | Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|----------------------------------|---------------------|----------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 72 | 74 | 72 | |
| Units: U/L | | | | |
| arithmetic mean (standard error) | -15.11 (\pm 3.2) | -12.04 (\pm 3.17) | -0.08 (\pm 3.22) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in GGT

| | |
|---|------------------------|
| End point title | Absolute change in GGT |
| End point description: Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. | |
| End point type | Secondary |
| End point timeframe: From baseline to Week 24. | |

| End point values | LAN800 | LAN1200 | Placebo | |
|----------------------------------|----------------------|----------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 72 | 74 | 72 | |
| Units: U/L | | | | |
| arithmetic mean (standard error) | -43.38 (\pm 5.61) | -27.87 (\pm 5.57) | 4.41 (\pm 5.65) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Fibrinogen

| | |
|---|-------------------------------|
| End point title | Absolute change in Fibrinogen |
| End point description: Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. | |
| End point type | Secondary |
| End point timeframe: From baseline to Week 24. | |

| End point values | LAN800 | LAN1200 | Placebo | |
|----------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 69 | 73 | 73 | |
| Units: g/L | | | | |
| arithmetic mean (standard error) | -0.17 (± 0.08) | -0.1 (± 0.07) | 0.02 (± 0.07) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Hs-CRP

| | |
|------------------------|---|
| End point title | Absolute change in Hs-CRP |
| End point description: | Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|----------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 72 | 74 | 72 | |
| Units: mg/L | | | | |
| arithmetic mean (standard error) | -2.05 (± 0.47) | -1.37 (± 0.46) | 0.11 (± 0.47) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Alpha2 macroglobulin

| | |
|------------------------|---|
| End point title | Absolute change in Alpha2 macroglobulin |
| End point description: | Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|----------------------------------|--------------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 68 | 72 | 71 | |
| Units: gram(s)/litre | | | | |
| arithmetic mean (standard error) | 0.15 (\pm 0.40) | 0.13 (\pm 0.38) | 0.05 (\pm 0.35) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Haptoglobin

| | |
|------------------------|---|
| End point title | Absolute change in Haptoglobin |
| End point description: | Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|--------------------------------------|-----------------------|-----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 72 | 74 | 72 | |
| Units: g/L | | | | |
| arithmetic mean (standard deviation) | -0.053 (\pm 0.256) | -0.099 (\pm 0.378) | 0.074 (\pm 0.291) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change of Fasting Plasma Glucose

| | |
|------------------------|--|
| End point title | Absolute change of Fasting Plasma Glucose |
| End point description: | Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. Only fasting values were considered. |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|----------------------------------|---------------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 71 | 73 | 72 | |
| Units: mmol/L | | | | |
| arithmetic mean (standard error) | -0.78 (\pm 0.12) | -0.6 (\pm 0.12) | 0.24 (\pm 0.12) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Insulin

| | |
|------------------------|--|
| End point title | Absolute change in Insulin |
| End point description: | Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. Only fasting values were considered. |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|----------------------------------|------------------------|------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 68 | 65 | 66 | |
| Units: pmol/L | | | | |
| arithmetic mean (standard error) | -118.66 (\pm 11.66) | -114.91 (\pm 11.75) | -35.7 (\pm 11.6) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in HOMA index

| | |
|------------------------|--|
| End point title | Absolute change in HOMA index |
| End point description: | Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. Only fasting values were considered. |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|----------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 64 | 63 | 65 | |
| Units: NA | | | | |
| arithmetic mean (standard error) | -5.79 (± 0.58) | -5.46 (± 0.58) | -1.47 (± 0.57) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in HbA1c

| | |
|------------------------|---|
| End point title | Absolute change in HbA1c |
| End point description: | Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|----------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 72 | 74 | 72 | |
| Units: percentage | | | | |
| arithmetic mean (standard error) | -0.38 (± 0.05) | -0.41 (± 0.05) | 0.07 (± 0.05) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Total Cholesterol

| | |
|------------------------|--|
| End point title | Absolute change in Total Cholesterol |
| End point description: | Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. Only fasting values were considered. |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|----------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 72 | 74 | 73 | |
| Units: mmol/L | | | | |
| arithmetic mean (standard error) | -0.02 (± 0.08) | -0.07 (± 0.07) | 0.01 (± 0.08) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change of HDL-Cholesterol

| | |
|------------------------|--|
| End point title | Absolute change of HDL-Cholesterol |
| End point description: | Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. Only fasting values were considered. |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|----------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 71 | 74 | 73 | |
| Units: mmol/L | | | | |
| arithmetic mean (standard error) | 0.16 (± 0.02) | 0.11 (± 0.02) | 0.01 (± 0.02) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change of LDL-Cholesterol

| | |
|------------------------|--|
| End point title | Absolute change of LDL-Cholesterol |
| End point description: | Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. Only fasting values were considered. |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|----------------------------------|--------------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 71 | 73 | 69 | |
| Units: mmol/L | | | | |
| arithmetic mean (standard error) | 0.03 (\pm 0.07) | 0.03 (\pm 0.07) | 0.01 (\pm 0.07) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Triglycerides

| | |
|------------------------|--|
| End point title | Absolute change in Triglycerides |
| End point description: | Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. Only fasting values were considered. |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|----------------------------------|---------------------|---------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 71 | 74 | 72 | |
| Units: mmol/L | | | | |
| arithmetic mean (standard error) | -0.49 (\pm 0.09) | -0.44 (\pm 0.09) | 0.06 (\pm 0.09) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Apo A1

| | |
|------------------------|---------------------------|
| End point title | Absolute change in Apo A1 |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|----------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 72 | 73 | 72 | |
| Units: mg/dL | | | | |
| arithmetic mean (standard error) | -0.29 (± 2.19) | -4.39 (± 2.16) | 0.03 (± 2.18) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Adiponectin

| | |
|------------------------|--|
| End point title | Absolute change in Adiponectin |
| End point description: | Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. Only fasting values were considered. |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|----------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 66 | 73 | 72 | |
| Units: microgram(s)/millilitre | | | | |
| arithmetic mean (standard error) | 11.95 (± 1.51) | 17.12 (± 1.44) | -0.35 (± 1.44) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Resolution of NASH and improvement of fibrosis by at least 1 stage

| | |
|------------------------|--|
| End point title | Resolution of NASH and improvement of fibrosis by at least 1 stage |
| End point description: | Resolution of NASH is defined as a CRN Inflammation score equal to 0 or 1, and a CRN Ballooning score equal to 0. Improvement of fibrosis is defined as a decrease of at least one stage in CRN Fibrosis score. |
| End point type | Secondary |
| End point timeframe: | From baseline to Week 24. |

| End point values | LAN800 | LAN1200 | Placebo | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 83 | 83 | 81 | |
| Units: number | | | | |
| Yes | 17 | 26 | 6 | |
| No | 66 | 57 | 75 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On or after the first dose of treatment up to 30 days post last dose.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------|
| Reporting group title | LAN800 |
|-----------------------|--------|

Reporting group description:

Patients who received lanifibranor 800mg daily: 2 tablets of lanifibranor and 1 tablet of placebo.

| | |
|-----------------------|---------|
| Reporting group title | LAN1200 |
|-----------------------|---------|

Reporting group description:

Patients who received lanifibranor 1200mg daily: 3 tablets of lanifibranor

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Patients who received placebo: 3 tablets of placebo daily

| Serious adverse events | LAN800 | LAN1200 | Placebo |
|--|----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 83 (3.61%) | 7 / 83 (8.43%) | 3 / 81 (3.70%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Post procedural haematoma | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 83 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 83 (1.20%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 83 (1.20%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wrist fracture | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 83 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 83 (1.20%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 83 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Foot operation | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 83 (1.20%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 83 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Pneumobilia | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 83 (1.20%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 83 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Undifferentiated connective tissue disease | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 83 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 83 (1.20%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 83 (1.20%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | LAN800 | LAN1200 | Placebo |
|--|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 25 / 83 (30.12%) | 23 / 83 (27.71%) | 19 / 81 (23.46%) |
| Investigations | | | |
| Weight increased | | | |
| subjects affected / exposed | 8 / 83 (9.64%) | 7 / 83 (8.43%) | 0 / 81 (0.00%) |
| occurrences (all) | 8 | 7 | 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 5 / 83 (6.02%) | 2 / 83 (2.41%) | 0 / 81 (0.00%) |
| occurrences (all) | 5 | 2 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 4 / 83 (4.82%) | 7 / 83 (8.43%) | 4 / 81 (4.94%) |
| occurrences (all) | 6 | 7 | 5 |
| Dizziness | | | |
| subjects affected / exposed | 2 / 83 (2.41%) | 6 / 83 (7.23%) | 3 / 81 (3.70%) |
| occurrences (all) | 3 | 6 | 3 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |

| | | | |
|---|---------------------|------------------------|---------------------|
| subjects affected / exposed occurrences (all) | 2 / 83 (2.41%) 2 | 10 / 83 (12.05%) 10 | 6 / 81 (7.41%) 6 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 5 / 83 (6.02%) 5 | 7 / 83 (8.43%) 7 | 2 / 81 (2.47%) 2 |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 8 / 83 (9.64%) 8 | 10 / 83 (12.05%) 11 | 1 / 81 (1.23%) 2 |
| Nausea subjects affected / exposed occurrences (all) | 8 / 83 (9.64%) 8 | 7 / 83 (8.43%) 7 | 3 / 81 (3.70%) 3 |
| Constipation subjects affected / exposed occurrences (all) | 3 / 83 (3.61%) 3 | 5 / 83 (6.02%) 5 | 6 / 81 (7.41%) 6 |
| Infections and infestations | | | |
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 3 / 83 (3.61%) 4 | 3 / 83 (3.61%) 5 | 5 / 81 (6.17%) 5 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 10 March 2017 | <ul style="list-style-type: none">• Inclusion/exclusion criteria were updated:<ul style="list-style-type: none">o The contraceptive method was to be followed for at least one menstruation cycle after the end of the study.o Patients with type 2 diabetes on insulin, patients with any clinically significant ECG abnormality reported by central ECG reading, patients with CPK >5xULN and patients with osteopenia or any other well documented bone disease with the exception of patients treated with vitamin D and/or calcium based supplements for preventive reasons, were to be excluded from the study. Also, details of the excipients were added to the criterion excluding patients with hypersensitivity to IMP excipients.• Prohibited and allowed medications update: i) specification of the prohibited anticoagulants medications (warfarin, dabigatran, rivaroxaban and apixaban); ii) addition of some medications allowed during the study (antiplatelet agents, aspirin, ticlopidine, clopidogrel, prasugrel and ticagrelor). |
| 03 August 2017 | <ul style="list-style-type: none">• The initial study enrolment period of 6 months was extended to 16 months. Consequently, the expected study completion date was extended to Q1 2019,• Regarding laboratory assays, beta human chorionic gonadotropin (βHCG) was added at screening as biological parameter to collect to assess pregnancy, INR was added to specify the measure used to express the prothrombin time and the laboratory category for plasma iron, transferrin and ferritin was updated to chemistry to be consistent with the Clinical Data Interchange Standards Consortium (CDISC).• Number of kits to be dispensed at each visit was clarified as well as the process for accountability.• Upon request of DSMB members, the frequency of the DSMB meeting was updated: the formal analysis meeting to review data was to be held every 50 patients for the entire duration of the study. |
| 02 November 2017 | <ul style="list-style-type: none">• A liver biopsy was added as screening tests procedures when a liver biopsy was not performed within 6 months from screening. For these patients, the screening phase was organised in 3 successive and detailed steps to avoid unnecessary biopsy and the screening period was extended to 8 weeks.• Two (2) exclusion criteria were added for patients undergoing an MRI/LMS in the selected centres: patients suffering from claustrophobia to a degree to not tolerate MRI scanning procedure and patients with metallic implant of any sort preventing MRI examination were to be excluded from the study.• A FibroScan® was to be performed at screening and at the end of the treatment period, if available, to evaluate TE and CAP. FibroScan® at screening was mandatory only if a liver biopsy within the 6 months prior screening was not available.• In selected centres (Bulgaria), a LMS was set for patient's liver examination at screening, to propose to undergo a liver biopsy only for the patients who would have had a higher probability of fulfilling the histological inclusion criteria. |

| | |
|--------------|--|
| 09 July 2019 | <ul style="list-style-type: none"> • Minor modifications of anti-diabetic treatments or dosages were allowed if done in a context of stable type 2 diabetes (HbA1c <8.5% in the previous 6 months). • Exclusion criteria were clarified: <ul style="list-style-type: none"> o Patients with a history of sustained excess alcohol ingestion in the year before the pre-study treatment biopsy were to be excluded. o Details on dosages of drugs known to produce hepatic steatosis were given as exclusion criteria. Similarly, the route of administration (oral) was specified for corticosteroids as prohibited concomitant medication. • The percent of patients with at least one-point improvement of fibrosis score on a 4-point scale (SAF) without worsening of NASH, defined as no increase for ballooning, or inflammation, or steatosis, using the SAF scoring system, from baseline to end of treatment (Week 24) was added as secondary endpoint. • The following exploratory endpoints were added: TE and CAP changes from baseline to the end of treatment and if deemed necessary, the change in the semi-quantitative score of ballooning and stellate cell activation from baseline to end of treatment. • P3NP was added as central laboratory test for efficacy assessment to be performed before and at the end of the treatment period. |
|--------------|--|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported