



## Clinical trial results:

**A placebo-controlled, proof-of-concept study to evaluate the safety and efficacy of Lanifibranor alone and in combination with the sodium-glucose transport protein 2 (SGLT2) inhibitor EmpaGliflozin in patiEnts with Non-alcoholic steatohepatitis (NASH) and type 2 Diabetes mellitus (T2DM)**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2021-005057-87 |
| Trial protocol           | FR BE NL       |
| Global end of trial date | 04 June 2024   |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 16 July 2026 |
| First version publication date | 16 July 2026 |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | 337HNAS21016 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | -              |
| ClinicalTrials.gov id (NCT number) | NCT05232071    |
| WHO universal trial number (UTN)   | -              |
| Other trial identifiers            | LEGEND: LEGEND |

Notes:

### Sponsors

|                              |                                                                                                                                                     |
|------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Inventiva SA                                                                                                                                        |
| Sponsor organisation address | 50 rue de Dijon, DAIX, France, 21121                                                                                                                |
| Public contact               | Martine ZIMMERMAN (Executive Vice President of Regulatory Affairs and Quality Assurance), Inventiva S.A.,<br>Martine.Zimmermann@inventivapharma.com |
| Scientific contact           | Thomas CAPOZZA (Senior VP Clinical Development), Inventiva S.A., Thomas.Capozza@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                       | 31 July 2024 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 08 May 2024  |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 04 June 2024 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

Primary objective

To assess the effect of lanifibranor alone compared to placebo and the effect of lanifibranor in combination with empagliflozin compared to placebo on HbA1c after a 24-week treatment duration.

Secondary objectives

To assess the effect of lanifibranor alone compared to placebo and lanifibranor in combination with empagliflozin compared to placebo after a 24-week treatment duration on:

- Liver tests
- Markers of glycemic control and insulin resistance
- Inflammatory markers
- Lipid parameters
- Body weight and body composition

and

To assess the safety and tolerability of lanifibranor alone and in combination with empagliflozin during the 24-week treatment period and the 4-week follow-up period.

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                          | 29 June 2022 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Netherlands: 2    |
| Country: Number of subjects enrolled | Belgium: 1        |
| Country: Number of subjects enrolled | United States: 35 |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Worldwide total number of subjects   | 39                |
| EEA total number of subjects         | 3                 |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|-------------------------------------------|----|
| 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)                      | 29 |
| From 65 to 84 years                       | 10 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment of patients started in June 2022 and last patient was recruited in November 2023. A total of 213 patients were screened for the study.

### Pre-assignment

Screening details:

Patients were invited to participate by their doctor based on their medical records. They had to fulfil all eligibility criteria. 41 patients were randomised. Main reason for non-randomization was screen failure. 2 of 41 patients were not treated and excluded from Full Analysis Set (FAS). Enrollment, disposition, analyses are based on FAS (n=39).

### 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                | Investigator, Subject, Monitor, Data analyst |

Blinding implementation details:

Group "lanifibranor 800mg" : blinded

Group "placebo" : blinded (lanifibranor 800mg matching placebo)

Group "lanifibranor 800mg + empagliflozin 10mg" : open-label

### Arms

|                              |           |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes       |
| <b>Arm title</b>             | LANI800mg |

Arm description:

Lanifibranor (800 mg/day): two film-coated tablets of 400 mg each, once-a-day (QD) with food. For oral use. QD for 24 weeks.

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | lanifibranor       |
| Investigational medicinal product code | IVA337             |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated 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

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | LANI800mg+EMPA10mg |
|------------------|--------------------|

Arm description:

Lanifibranor (800 mg/day): two film-coated tablets of 400 mg each.

Empagliflozin : one film-coated tablet of 10 mg (10mg/day)

Once-a-day (QD) with food.

For oral use. QD for 24 weeks.

|                                        |                            |
|----------------------------------------|----------------------------|
| Arm type                               | Experimental               |
| Investigational medicinal product name | lanifibranor+empagliglozin |
| Investigational medicinal product code |                            |
| Other name                             |                            |
| Pharmaceutical forms                   | Film-coated tablet         |
| Routes of administration               | Oral use                   |

Dosage and administration details:

Lanifibranor : white to off-white, bi-convex film-coated tablet of 400mg to be taken orally. Each tablet

contained 400 mg of the active ingredient in an immediate release formulation  
 Empagliflozin: 10 mg pale yellow, round, bi-convex and bevel-edged, film-coated tablets debossed with "S 10" on one side and the Boehringer Ingelheim company symbol on the other side

|                                                                                                     |                    |
|-----------------------------------------------------------------------------------------------------|--------------------|
| <b>Arm title</b>                                                                                    | Placebo            |
| Arm description:                                                                                    |                    |
| Two lanifibranor placebo-matching tablets once-a-day (QD) with food. For oral use. QD for 24 weeks. |                    |
| Arm type                                                                                            | Placebo            |
| Investigational medicinal product name                                                              | Placebo            |
| Investigational medicinal product code                                                              |                    |
| Other name                                                                                          |                    |
| Pharmaceutical forms                                                                                | Film-coated tablet |
| Routes of administration                                                                            | Oral use           |

Dosage and administration details:

2 lanifibranor matching-placebo tablets for oral use QD for 24 weeks

| <b>Number of subjects in period 1</b> | LANI800mg | LANI800mg+EMPA10mg | Placebo |
|---------------------------------------|-----------|--------------------|---------|
| Started                               | 12        | 13                 | 14      |
| Completed                             | 12        | 12                 | 9       |
| Not completed                         | 0         | 1                  | 5       |
| Adverse event, non-fatal              | -         | 1                  | -       |
| Non compliance with Study Drug        | -         | -                  | 1       |
| Lost to follow-up                     | -         | -                  | 2       |
| Withdrawal by subject                 | -         | -                  | 2       |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                  |                    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Reporting group title                                                                                                                                                                                                            | LANI800mg          |
| Reporting group description:<br>Lanifibranor (800 mg/day): two film-coated tablets of 400 mg each, once-a-day (QD) with food. For oral use. QD for 24 weeks.                                                                     |                    |
| Reporting group title                                                                                                                                                                                                            | LANI800mg+EMPA10mg |
| Reporting group description:<br>Lanifibranor (800 mg/day): two film-coated tablets of 400 mg each.<br>Empagliflozin : one film-coated tablet of 10 mg (10mg/day)<br>Once-a-day (QD) with food.<br>For oral use. QD for 24 weeks. |                    |
| Reporting group title                                                                                                                                                                                                            | Placebo            |
| Reporting group description:<br>Two lanifibranor placebo-matching tablets once-a-day (QD) with food. For oral use. QD for 24 weeks.                                                                                              |                    |

| Reporting group values                             | LANI800mg | LANI800mg+EMPA10mg | Placebo |
|----------------------------------------------------|-----------|--------------------|---------|
| Number of subjects                                 | 12        | 13                 | 14      |
| Age categorical<br>Units: Subjects                 |           |                    |         |
| In utero                                           | 0         | 0                  | 0       |
| Preterm newborn infants (gestational age < 37 wks) | 0         | 0                  | 0       |
| Newborns (0-27 days)                               | 0         | 0                  | 0       |
| Infants and toddlers (28 days-23 months)           | 0         | 0                  | 0       |
| Children (2-11 years)                              | 0         | 0                  | 0       |
| Adolescents (12-17 years)                          | 0         | 0                  | 0       |
| Adults (18-64 years)                               | 9         | 10                 | 10      |
| From 65-84 years                                   | 3         | 3                  | 4       |
| 85 years and over                                  | 0         | 0                  | 0       |
| Age continuous<br>Units: years                     |           |                    |         |
| arithmetic mean                                    | 55.1      | 54.2               | 54.7    |
| standard deviation                                 | ± 11.45   | ± 13.48            | ± 13.01 |
| Gender categorical<br>Units: Subjects              |           |                    |         |
| Female                                             | 6         | 8                  | 7       |
| Male                                               | 6         | 5                  | 7       |

| Reporting group values                             | Total |  |  |
|----------------------------------------------------|-------|--|--|
| Number of subjects                                 | 39    |  |  |
| Age categorical<br>Units: Subjects                 |       |  |  |
| In utero                                           | 0     |  |  |
| Preterm newborn infants (gestational age < 37 wks) | 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)      | 29 |  |  |
| From 65-84 years          | 10 |  |  |
| 85 years and over         | 0  |  |  |
| Age continuous            |    |  |  |
| Units: years              |    |  |  |
| arithmetic mean           |    |  |  |
| standard deviation        | -  |  |  |
| Gender categorical        |    |  |  |
| Units: Subjects           |    |  |  |
| Female                    | 21 |  |  |
| Male                      | 18 |  |  |

### Subject analysis sets

|                            |                         |
|----------------------------|-------------------------|
| Subject analysis set title | Full Analysis Set (FAS) |
| Subject analysis set type  | Full analysis           |

Subject analysis set description:

The FAS included all randomised patients who received at least 1 dose of the assigned study drug, regardless of whether they prematurely discontinued randomised treatment or experienced any other intercurrent event, and who met the targeted patient population of interest consistently with the primary estimand: Adults with non-cirrhotic NASH and T2DM defined by inclusion criteria No. 4 and 5 met, and exclusion criteria No. 2 and 15 not met. 'Received at least 1 dose of the assigned study drug' for the combination arm means that at least 1 dose of the 2 treatments empagliflozin and lanifibranor were to be received concomitantly, to be considered in the FAS. Patients were analysed according to their randomised treatment

|                            |                        |
|----------------------------|------------------------|
| Subject analysis set title | Per Protocol Set (PPS) |
| Subject analysis set type  | Per protocol           |

Subject analysis set description:

The PPS included all patients in the FAS who did not have any major protocol deviations (i.e. considered to have a significant effect on the primary endpoint) and who did not prematurely discontinue from treatment.

|                            |                           |
|----------------------------|---------------------------|
| Subject analysis set title | Safety Analysis Set (SAS) |
| Subject analysis set type  | Safety analysis           |

Subject analysis set description:

The SAS included all randomised patients who received at least 1 dose of study drug. Patients in the SAS were analysed and summarised based on the treatment they actually received. 'Received at least 1 dose of study drug' for the combination arm meant that at least 1 dose of lanifibranor, i.e. the IMP, was to be received.

| Reporting group values                             | Full Analysis Set (FAS) | Per Protocol Set (PPS) | Safety Analysis Set (SAS) |
|----------------------------------------------------|-------------------------|------------------------|---------------------------|
| Number of subjects                                 | 39                      | 29                     | 39                        |
| Age categorical                                    |                         |                        |                           |
| Units: Subjects                                    |                         |                        |                           |
| In utero                                           | 0                       | 0                      | 0                         |
| Preterm newborn infants (gestational age < 37 wks) | 0                       | 0                      | 0                         |
| Newborns (0-27 days)                               | 0                       | 0                      | 0                         |
| Infants and toddlers (28 days-23 months)           | 0                       | 0                      | 0                         |
| Children (2-11 years)                              | 0                       | 0                      | 0                         |
| Adolescents (12-17 years)                          | 0                       | 0                      | 0                         |
| Adults (18-64 years)                               | 29                      | 22                     | 29                        |
| From 65-84 years                                   | 10                      | 7                      | 10                        |

|                   |   |   |   |
|-------------------|---|---|---|
| 85 years and over | 0 | 0 | 0 |
|-------------------|---|---|---|

|                    |         |         |         |
|--------------------|---------|---------|---------|
| Age continuous     |         |         |         |
| Units: years       |         |         |         |
| arithmetic mean    | 54.6    | 55.6    | 54.6    |
| standard deviation | ± 12.38 | ± 12.26 | ± 12.38 |
| Gender categorical |         |         |         |
| Units: Subjects    |         |         |         |
| Female             | 21      | 16      | 21      |
| Male               | 18      | 13      | 18      |

## End points

### End points reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | LANI800mg |
|-----------------------|-----------|

Reporting group description:

Lanifibranor (800 mg/day): two film-coated tablets of 400 mg each, once-a-day (QD) with food. For oral use. QD for 24 weeks.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | LANI800mg+EMPA10mg |
|-----------------------|--------------------|

Reporting group description:

Lanifibranor (800 mg/day): two film-coated tablets of 400 mg each.

Empagliflozin : one film-coated tablet of 10 mg (10mg/day)

Once-a-day (QD) with food.

For oral use. QD for 24 weeks.

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

Reporting group description:

Two lanifibranor placebo-matching tablets once-a-day (QD) with food. For oral use. QD for 24 weeks.

|                            |                         |
|----------------------------|-------------------------|
| Subject analysis set title | Full Analysis Set (FAS) |
|----------------------------|-------------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

The FAS included all randomised patients who received at least 1 dose of the assigned study drug, regardless of whether they prematurely discontinued randomised treatment or experienced any other intercurrent event, and who met the targeted patient population of interest consistently with the primary estimand: Adults with non-cirrhotic NASH and T2DM defined by inclusion criteria No. 4 and 5 met, and exclusion criteria No. 2 and 15 not met. 'Received at least 1 dose of the assigned study drug' for the combination arm means that at least 1 dose of the 2 treatments empagliflozin and lanifibranor were to be received concomitantly, to be considered in the FAS. Patients were analysed according to their randomised treatment

|                            |                        |
|----------------------------|------------------------|
| Subject analysis set title | Per Protocol Set (PPS) |
|----------------------------|------------------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

The PPS included all patients in the FAS who did not have any major protocol deviations (i.e. considered to have a significant effect on the primary endpoint) and who did not prematurely discontinue from treatment.

|                            |                           |
|----------------------------|---------------------------|
| Subject analysis set title | Safety Analysis Set (SAS) |
|----------------------------|---------------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

The SAS included all randomised patients who received at least 1 dose of study drug. Patients in the SAS were analysed and summarised based on the treatment they actually received. 'Received at least 1 dose of study drug' for the combination arm meant that at least 1 dose of lanifibranor, i.e. the IMP, was to be received.

### Primary: Absolute change in HbA1c

|                 |                          |
|-----------------|--------------------------|
| End point title | Absolute change in HbA1c |
|-----------------|--------------------------|

End point description:

Absolute change in HbA1c from baseline (Week 0) to Week 24 (%)

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From baseline to Week 24

| End point values                             | LANI800mg              | LANI800mg+E<br>MPA10mg | Placebo              |  |
|----------------------------------------------|------------------------|------------------------|----------------------|--|
| Subject group type                           | Reporting group        | Reporting group        | Reporting group      |  |
| Number of subjects analysed                  | 11                     | 13                     | 13                   |  |
| Units: %                                     |                        |                        |                      |  |
| least squares mean (confidence interval 95%) | -1.11 (-1.60 to -0.62) | -1.54 (-2.02 to -1.06) | 0.16 (-0.32 to 0.63) |  |

## Statistical analyses

| Statistical analysis title | LANI800 vs PBO |
|----------------------------|----------------|
|----------------------------|----------------|

Statistical analysis description:

To assess the superiority of each active arm versus placebo on absolute change in HbA1c from baseline, a mixed model for repeated measures (MMRM) was used with treatment group, time, treatment×time interaction as fixed effects, baseline HbA1c value and sex as covariates and the patient effect as a random effect. The MMRM was used to handle missingness because outcomes are measured repeatedly over time. No explicit imputation was done for missing data.

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Comparison groups                       | LANI800mg v Placebo            |
| Number of subjects included in analysis | 24                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | < 0.001                        |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -1.27                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -1.95                          |
| upper limit                             | -0.58                          |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.33                           |

| Statistical analysis title | LANI800+EMPA10 vs PBO |
|----------------------------|-----------------------|
|----------------------------|-----------------------|

Statistical analysis description:

To assess the superiority of each active arm versus placebo on absolute change in HbA1c from baseline, a mixed model for repeated measures (MMRM) was used with treatment group, time, treatment×time interaction as fixed effects, baseline HbA1c value and sex as covariates and the patient effect as a random effect. The MMRM was used to handle missingness because outcomes are measured repeatedly over time. No explicit imputation was done for missing data.

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Comparison groups                       | LANI800mg+EMPA10mg v Placebo   |
| Number of subjects included in analysis | 26                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | < 0.001                        |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -1.7                           |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -2.38                      |
| upper limit          | -1.02                      |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.33                       |

### Secondary: Change in liver tests (ALT)

|                                                             |                             |
|-------------------------------------------------------------|-----------------------------|
| End point title                                             | Change in liver tests (ALT) |
| End point description:<br>ALT Absolute Change from Baseline |                             |
| End point type                                              | Secondary                   |
| End point timeframe:<br>From baseline to Week 24            |                             |

| End point values                             | LANI800mg                | LANI800mg+E<br>MPA10mg    | Placebo                |  |
|----------------------------------------------|--------------------------|---------------------------|------------------------|--|
| Subject group type                           | Reporting group          | Reporting group           | Reporting group        |  |
| Number of subjects analysed                  | 12                       | 13                        | 13                     |  |
| Units: U/L                                   |                          |                           |                        |  |
| least squares mean (confidence interval 95%) | -26.6 (-38.08 to -15.12) | -29.63 (-42.13 to -17.13) | -5.65 (-17.89 to 6.59) |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in liver tests (AST)

|                                                             |                             |
|-------------------------------------------------------------|-----------------------------|
| End point title                                             | Change in liver tests (AST) |
| End point description:<br>AST Absolute Change from Baseline |                             |
| End point type                                              | Secondary                   |
| End point timeframe:<br>From baseline to Week 24            |                             |

| End point values                             | LANI800mg                | LANI800mg+E<br>MPA10mg   | Placebo             |  |
|----------------------------------------------|--------------------------|--------------------------|---------------------|--|
| Subject group type                           | Reporting group          | Reporting group          | Reporting group     |  |
| Number of subjects analysed                  | 12                       | 13                       | 13                  |  |
| Units: U/L                                   |                          |                          |                     |  |
| least squares mean (confidence interval 95%) | -13.67 (-20.66 to -6.68) | -17.81 (-25.5 to -10.12) | 1.3 (-6.11 to 8.71) |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in insulin resistance and glycaemic control (HOMA-IR)

|                        |                                                              |
|------------------------|--------------------------------------------------------------|
| End point title        | Change in insulin resistance and glycaemic control (HOMA-IR) |
| End point description: | HOMA-IR Relative Change from Baseline                        |
| End point type         | Secondary                                                    |
| End point timeframe:   | From baseline to Week 24                                     |

| End point values                             | LANI800mg                | LANI800mg+E<br>MPA10mg   | Placebo                 |  |
|----------------------------------------------|--------------------------|--------------------------|-------------------------|--|
| Subject group type                           | Reporting group          | Reporting group          | Reporting group         |  |
| Number of subjects analysed                  | 11                       | 13                       | 13                      |  |
| Units: %                                     |                          |                          |                         |  |
| least squares mean (confidence interval 95%) | -50.79 (-95.69 to -5.89) | -45.23 (-89.86 to -0.61) | 35.01 (-10.29 to 80.32) |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in insulin resistance and glycaemic control (insulin)

|                        |                                                              |
|------------------------|--------------------------------------------------------------|
| End point title        | Change in insulin resistance and glycaemic control (insulin) |
| End point description: | Insuline - Relative Change from Baseline                     |
| End point type         | Secondary                                                    |
| End point timeframe:   | From baseline to Week 24                                     |

| End point values                             | LANI800mg               | LANI800mg+E<br>MPA10mg   | Placebo                 |  |
|----------------------------------------------|-------------------------|--------------------------|-------------------------|--|
| Subject group type                           | Reporting group         | Reporting group          | Reporting group         |  |
| Number of subjects analysed                  | 11                      | 13                       | 13                      |  |
| Units: %                                     |                         |                          |                         |  |
| least squares mean (confidence interval 95%) | -33.48 (-68.24 to 1.28) | -38.16 (-72.16 to -4.16) | 10.17 (-23.63 to 43.96) |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in insulin resistance and glycaemic control (adiponectin)

|                        |                                                                  |
|------------------------|------------------------------------------------------------------|
| End point title        | Change in insulin resistance and glycaemic control (adiponectin) |
| End point description: | Adiponectine Fold Change from Baseline                           |
| End point type         | Secondary                                                        |
| End point timeframe:   | From baseline to Week 24                                         |

| End point values                             | LANI800mg           | LANI800mg+E<br>MPA10mg | Placebo             |  |
|----------------------------------------------|---------------------|------------------------|---------------------|--|
| Subject group type                           | Reporting group     | Reporting group        | Reporting group     |  |
| Number of subjects analysed                  | 11                  | 13                     | 13                  |  |
| Units: fold change                           |                     |                        |                     |  |
| least squares mean (confidence interval 95%) | 2.87 (2.05 to 3.68) | 3.03 (2.18 to 3.89)    | 1.24 (0.39 to 2.09) |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in lipid parameters (HDL cholesterol)

|                        |                                                 |
|------------------------|-------------------------------------------------|
| End point title        | Change in lipid parameters (HDL cholesterol)    |
| End point description: | HDL cholesterol - Relative Change from Baseline |
| End point type         | Secondary                                       |
| End point timeframe:   | From baseline to Week 24                        |

| End point values                             | LANI800mg             | LANI800mg+E<br>MPA10mg | Placebo               |  |
|----------------------------------------------|-----------------------|------------------------|-----------------------|--|
| Subject group type                           | Reporting group       | Reporting group        | Reporting group       |  |
| Number of subjects analysed                  | 12                    | 13                     | 13                    |  |
| Units: %                                     |                       |                        |                       |  |
| least squares mean (confidence interval 95%) | 16.48 (5.24 to 27.72) | 15.30 (3.04 to 27.56)  | 2.55 (-9.76 to 14.86) |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in body weight and body composition (Body Weight)

|                                                                     |                                                          |
|---------------------------------------------------------------------|----------------------------------------------------------|
| End point title                                                     | Change in body weight and body composition (Body Weight) |
| End point description:<br>Body Weight Relative Change from Baseline |                                                          |
| End point type                                                      | Secondary                                                |
| End point timeframe:<br>from Baseline to Week 24                    |                                                          |

| End point values                             | LANI800mg          | LANI800mg+E<br>MPA10mg | Placebo               |  |
|----------------------------------------------|--------------------|------------------------|-----------------------|--|
| Subject group type                           | Reporting group    | Reporting group        | Reporting group       |  |
| Number of subjects analysed                  | 12                 | 13                     | 13                    |  |
| Units: %                                     |                    |                        |                       |  |
| least squares mean (confidence interval 95%) | 3.6 (2.00 to 5.19) | 0.25 (-1.50 to 2.01)   | -1.16 (-2.84 to 0.53) |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in body weight and body composition (VAT/SAT ratio)

|                                                                                                                                                                           |                                                            |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|
| End point title                                                                                                                                                           | Change in body weight and body composition (VAT/SAT ratio) |
| End point description:<br>Ratio VAT / SAT - Results for Relative Change from Baseline<br>VAT : MRI L3 visceral adipose tissue<br>SAT : MRI L3 subcutaneous adipose tissue |                                                            |
| End point type                                                                                                                                                            | Secondary                                                  |
| End point timeframe:<br>From baseline to Week 24                                                                                                                          |                                                            |

| <b>End point values</b>                      | LANI800mg             | LANI800mg+E<br>MPA10mg   | Placebo               |  |
|----------------------------------------------|-----------------------|--------------------------|-----------------------|--|
| Subject group type                           | Reporting group       | Reporting group          | Reporting group       |  |
| Number of subjects analysed                  | 9                     | 7                        | 7                     |  |
| Units: %                                     |                       |                          |                       |  |
| least squares mean (confidence interval 95%) | -4.6 (-14.44 to 5.25) | -17.45 (-28.67 to -6.23) | 2.01 (-9.12 to 13.14) |  |

### 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.

Adverse event reporting additional description:

TEAEs are events with start date & time on or after the date and time of 1st dose of study treatment and up to 30 days after date & time of last dose of study treatment, and events with start date and time prior to the date & time of first dose of study treatment whose severity worsens on or after the date and time of 1st dose of study treatment.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 26.0 |
|--------------------|------|

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | LANI800mg |
|-----------------------|-----------|

Reporting group description:

Lanifibranor 2 film-coated tablets for oral use of 400 mg (total dose 800 mg)

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | LANI800mg+EMPA10mg |
|-----------------------|--------------------|

Reporting group description:

Lanifibranor 2 film-coated tablets for oral use of 400 mg (total dose 800 mg) plus empagliflozin 1 tablet of 10 mg, QD for 24 weeks.

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

Reporting group description:

Lanifibranor matching placebo 2 tablets for oral use QD for 24 weeks

| Serious adverse events                            | LANI800mg                                                                                                                                                                                                                                                               | LANI800mg+EMPA10mg | Placebo        |
|---------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|----------------|
| Total subjects affected by serious adverse events |                                                                                                                                                                                                                                                                         |                    |                |
| subjects affected / exposed                       | 0 / 12 (0.00%)                                                                                                                                                                                                                                                          | 1 / 13 (7.69%)     | 0 / 14 (0.00%) |
| number of deaths (all causes)                     | 0                                                                                                                                                                                                                                                                       | 0                  | 0              |
| number of deaths resulting from adverse events    | 0                                                                                                                                                                                                                                                                       | 0                  | 0              |
| Renal and urinary disorders                       |                                                                                                                                                                                                                                                                         |                    |                |
| Haematuria                                        | Additional description: One patient experienced haematuria (described as hematuria). Started during the follow-up period, 26 days after final dose of study drug and was assessed as not treatment-related (neither lanifibranor nor empagliflozin) by the investigator |                    |                |
| subjects affected / exposed                       | 0 / 12 (0.00%)                                                                                                                                                                                                                                                          | 1 / 13 (7.69%)     | 0 / 14 (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 %

| <b>Non-serious adverse events</b>                           | LANI800mg        | LANI800mg+EMPA10mg | Placebo         |
|-------------------------------------------------------------|------------------|--------------------|-----------------|
| Total subjects affected by non-serious adverse events       |                  |                    |                 |
| subjects affected / exposed                                 | 10 / 12 (83.33%) | 9 / 13 (69.23%)    | 8 / 14 (57.14%) |
| <b>Vascular disorders</b>                                   |                  |                    |                 |
| Varicose vein                                               |                  |                    |                 |
| subjects affected / exposed                                 | 1 / 12 (8.33%)   | 1 / 13 (7.69%)     | 0 / 14 (0.00%)  |
| occurrences (all)                                           | 1                | 1                  | 0               |
| Hot flush                                                   |                  |                    |                 |
| subjects affected / exposed                                 | 0 / 12 (0.00%)   | 1 / 13 (7.69%)     | 0 / 14 (0.00%)  |
| occurrences (all)                                           | 0                | 1                  | 0               |
| <b>General disorders and administration site conditions</b> |                  |                    |                 |
| Fatigue                                                     |                  |                    |                 |
| subjects affected / exposed                                 | 0 / 12 (0.00%)   | 0 / 13 (0.00%)     | 1 / 14 (7.14%)  |
| occurrences (all)                                           | 0                | 0                  | 1               |
| Influenza like illness                                      |                  |                    |                 |
| subjects affected / exposed                                 | 1 / 12 (8.33%)   | 0 / 13 (0.00%)     | 0 / 14 (0.00%)  |
| occurrences (all)                                           | 1                | 0                  | 0               |
| Oedema peripheral                                           |                  |                    |                 |
| subjects affected / exposed                                 | 0 / 12 (0.00%)   | 1 / 13 (7.69%)     | 0 / 14 (0.00%)  |
| occurrences (all)                                           | 0                | 1                  | 0               |
| <b>Reproductive system and breast disorders</b>             |                  |                    |                 |
| Vaginal odour                                               |                  |                    |                 |
| subjects affected / exposed                                 | 1 / 12 (8.33%)   | 0 / 13 (0.00%)     | 0 / 14 (0.00%)  |
| occurrences (all)                                           | 1                | 0                  | 0               |
| <b>Respiratory, thoracic and mediastinal disorders</b>      |                  |                    |                 |
| Oropharyngeal pain                                          |                  |                    |                 |
| subjects affected / exposed                                 | 1 / 12 (8.33%)   | 0 / 13 (0.00%)     | 1 / 14 (7.14%)  |
| occurrences (all)                                           | 1                | 0                  | 1               |
| Cough                                                       |                  |                    |                 |
| subjects affected / exposed                                 | 0 / 12 (0.00%)   | 1 / 13 (7.69%)     | 0 / 14 (0.00%)  |
| occurrences (all)                                           | 0                | 1                  | 0               |
| Epistaxis                                                   |                  |                    |                 |
| subjects affected / exposed                                 | 0 / 12 (0.00%)   | 1 / 13 (7.69%)     | 0 / 14 (0.00%)  |
| occurrences (all)                                           | 0                | 1                  | 0               |
| Nasal congestion                                            |                  |                    |                 |

|                                                                                                                   |                     |                      |                     |
|-------------------------------------------------------------------------------------------------------------------|---------------------|----------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                                                                  | 0 / 12 (0.00%)<br>0 | 1 / 13 (7.69%)<br>1  | 0 / 14 (0.00%)<br>0 |
| Productive cough<br>subjects affected / exposed<br>occurrences (all)                                              | 0 / 12 (0.00%)<br>0 | 0 / 13 (0.00%)<br>0  | 1 / 14 (7.14%)<br>1 |
| Wheezing<br>subjects affected / exposed<br>occurrences (all)                                                      | 0 / 12 (0.00%)<br>0 | 1 / 13 (7.69%)<br>1  | 0 / 14 (0.00%)<br>0 |
| Psychiatric disorders<br>Depressed mood<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 12 (8.33%)<br>1 | 0 / 13 (0.00%)<br>0  | 0 / 14 (0.00%)<br>0 |
| Depression<br>subjects affected / exposed<br>occurrences (all)                                                    | 1 / 12 (8.33%)<br>1 | 0 / 13 (0.00%)<br>0  | 0 / 14 (0.00%)<br>0 |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                                                      | 1 / 12 (8.33%)<br>1 | 0 / 13 (0.00%)<br>0  | 0 / 14 (0.00%)<br>0 |
| Investigations<br>Blood glucose decreased<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 12 (0.00%)<br>0 | 1 / 13 (7.69%)<br>1  | 1 / 14 (7.14%)<br>1 |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 12 (0.00%)<br>0 | 0 / 13 (0.00%)<br>0  | 1 / 14 (7.14%)<br>1 |
| Injury, poisoning and procedural<br>complications<br>Overdose<br>subjects affected / exposed<br>occurrences (all) | 1 / 12 (8.33%)<br>1 | 2 / 13 (15.38%)<br>2 | 0 / 14 (0.00%)<br>0 |
| Congenital, familial and genetic<br>disorders<br>Phimosi<br>subjects affected / exposed<br>occurrences (all)      | 0 / 12 (0.00%)<br>0 | 0 / 13 (0.00%)<br>0  | 1 / 14 (7.14%)<br>1 |
| Cardiac disorders<br>Palpitations                                                                                 |                     |                      |                     |

|                                                  |                     |                     |                     |
|--------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0 | 1 / 13 (7.69%)<br>1 | 0 / 14 (0.00%)<br>0 |
| Nervous system disorders                         |                     |                     |                     |
| Headache                                         |                     |                     |                     |
| subjects affected / exposed                      | 2 / 12 (16.67%)     | 1 / 13 (7.69%)      | 0 / 14 (0.00%)      |
| occurrences (all)                                | 2                   | 1                   | 0                   |
| Neuropathy peripheral                            |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 13 (0.00%)      | 1 / 14 (7.14%)      |
| occurrences (all)                                | 0                   | 0                   | 1                   |
| Blood and lymphatic system disorders             |                     |                     |                     |
| Anaemia                                          |                     |                     |                     |
| subjects affected / exposed                      | 2 / 12 (16.67%)     | 0 / 13 (0.00%)      | 1 / 14 (7.14%)      |
| occurrences (all)                                | 2                   | 0                   | 1                   |
| Ear and labyrinth disorders                      |                     |                     |                     |
| Ear pruritus                                     |                     |                     |                     |
| subjects affected / exposed                      | 1 / 12 (8.33%)      | 0 / 13 (0.00%)      | 0 / 14 (0.00%)      |
| occurrences (all)                                | 1                   | 0                   | 0                   |
| Gastrointestinal disorders                       |                     |                     |                     |
| Nausea                                           |                     |                     |                     |
| subjects affected / exposed                      | 1 / 12 (8.33%)      | 2 / 13 (15.38%)     | 0 / 14 (0.00%)      |
| occurrences (all)                                | 1                   | 2                   | 0                   |
| Abdominal pain                                   |                     |                     |                     |
| subjects affected / exposed                      | 1 / 12 (8.33%)      | 0 / 13 (0.00%)      | 1 / 14 (7.14%)      |
| occurrences (all)                                | 1                   | 0                   | 1                   |
| Diarrhoea                                        |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 1 / 13 (7.69%)      | 1 / 14 (7.14%)      |
| occurrences (all)                                | 0                   | 1                   | 1                   |
| Toothache                                        |                     |                     |                     |
| subjects affected / exposed                      | 1 / 12 (8.33%)      | 1 / 13 (7.69%)      | 0 / 14 (0.00%)      |
| occurrences (all)                                | 1                   | 2                   | 0                   |
| Dyspepsia                                        |                     |                     |                     |
| subjects affected / exposed                      | 1 / 12 (8.33%)      | 0 / 13 (0.00%)      | 0 / 14 (0.00%)      |
| occurrences (all)                                | 1                   | 0                   | 0                   |
| Infrequent bowel movements                       |                     |                     |                     |
| subjects affected / exposed                      | 1 / 12 (8.33%)      | 0 / 13 (0.00%)      | 0 / 14 (0.00%)      |
| occurrences (all)                                | 1                   | 0                   | 0                   |
| Tongue discomfort                                |                     |                     |                     |

|                                                                         |                      |                     |                      |
|-------------------------------------------------------------------------|----------------------|---------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                        | 1 / 12 (8.33%)<br>1  | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)            | 0 / 12 (0.00%)<br>0  | 0 / 13 (0.00%)<br>0 | 1 / 14 (7.14%)<br>1  |
| Skin and subcutaneous tissue disorders                                  |                      |                     |                      |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)            | 2 / 12 (16.67%)<br>2 | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0  |
| Rash<br>subjects affected / exposed<br>occurrences (all)                | 0 / 12 (0.00%)<br>0  | 0 / 13 (0.00%)<br>0 | 2 / 14 (14.29%)<br>2 |
| Hidradenitis<br>subjects affected / exposed<br>occurrences (all)        | 0 / 12 (0.00%)<br>0  | 0 / 13 (0.00%)<br>0 | 1 / 14 (7.14%)<br>1  |
| Rosacea<br>subjects affected / exposed<br>occurrences (all)             | 1 / 12 (8.33%)<br>1  | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0  |
| Skin lesion<br>subjects affected / exposed<br>occurrences (all)         | 1 / 12 (8.33%)<br>1  | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0  |
| Renal and urinary disorders                                             |                      |                     |                      |
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)         | 1 / 12 (8.33%)<br>1  | 1 / 13 (7.69%)<br>1 | 1 / 14 (7.14%)<br>1  |
| Micturition urgency<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0  | 1 / 13 (7.69%)<br>1 | 0 / 14 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders                         |                      |                     |                      |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)          | 1 / 12 (8.33%)<br>1  | 1 / 13 (7.69%)<br>1 | 1 / 14 (7.14%)<br>1  |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)           | 1 / 12 (8.33%)<br>1  | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0  |
| Myalgia                                                                 |                      |                     |                      |

|                                                                       |                     |                     |                     |
|-----------------------------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                      | 0 / 12 (0.00%)<br>0 | 0 / 13 (0.00%)<br>0 | 1 / 14 (7.14%)<br>1 |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0 | 0 / 13 (0.00%)<br>0 | 1 / 14 (7.14%)<br>1 |
| Infections and infestations                                           |                     |                     |                     |
| COVID-19                                                              |                     |                     |                     |
| subjects affected / exposed<br>occurrences (all)                      | 1 / 12 (8.33%)<br>1 | 1 / 13 (7.69%)<br>1 | 0 / 14 (0.00%)<br>0 |
| Bronchitis                                                            |                     |                     |                     |
| subjects affected / exposed<br>occurrences (all)                      | 0 / 12 (0.00%)<br>0 | 0 / 13 (0.00%)<br>0 | 1 / 14 (7.14%)<br>1 |
| Gastroenteritis viral                                                 |                     |                     |                     |
| subjects affected / exposed<br>occurrences (all)                      | 0 / 12 (0.00%)<br>0 | 1 / 13 (7.69%)<br>1 | 0 / 14 (0.00%)<br>0 |
| Influenza                                                             |                     |                     |                     |
| subjects affected / exposed<br>occurrences (all)                      | 0 / 12 (0.00%)<br>0 | 0 / 13 (0.00%)<br>0 | 1 / 14 (7.14%)<br>1 |
| Oral herpes                                                           |                     |                     |                     |
| subjects affected / exposed<br>occurrences (all)                      | 0 / 12 (0.00%)<br>0 | 0 / 13 (0.00%)<br>0 | 1 / 14 (7.14%)<br>1 |
| Paronychia                                                            |                     |                     |                     |
| subjects affected / exposed<br>occurrences (all)                      | 0 / 12 (0.00%)<br>0 | 0 / 13 (0.00%)<br>0 | 1 / 14 (7.14%)<br>1 |
| Pneumonia                                                             |                     |                     |                     |
| subjects affected / exposed<br>occurrences (all)                      | 1 / 12 (8.33%)<br>1 | 0 / 13 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 |
| Tonsillitis                                                           |                     |                     |                     |
| subjects affected / exposed<br>occurrences (all)                      | 0 / 12 (0.00%)<br>0 | 1 / 13 (7.69%)<br>1 | 0 / 14 (0.00%)<br>0 |
| Tooth abscess                                                         |                     |                     |                     |
| subjects affected / exposed<br>occurrences (all)                      | 0 / 12 (0.00%)<br>0 | 1 / 13 (7.69%)<br>1 | 0 / 14 (0.00%)<br>0 |
| Tooth infection                                                       |                     |                     |                     |
| subjects affected / exposed<br>occurrences (all)                      | 0 / 12 (0.00%)<br>0 | 1 / 13 (7.69%)<br>1 | 0 / 14 (0.00%)<br>0 |

|                                                                                          |                     |                      |                     |
|------------------------------------------------------------------------------------------|---------------------|----------------------|---------------------|
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)    | 0 / 12 (0.00%)<br>0 | 1 / 13 (7.69%)<br>1  | 0 / 14 (0.00%)<br>0 |
| Metabolism and nutrition disorders                                                       |                     |                      |                     |
| Diabetes mellitus inadequate control<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0 | 2 / 13 (15.38%)<br>2 | 0 / 14 (0.00%)<br>0 |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 12 (0.00%)<br>0 | 0 / 13 (0.00%)<br>0  | 1 / 14 (7.14%)<br>1 |
| Increased appetite<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 12 (8.33%)<br>1 | 0 / 13 (0.00%)<br>0  | 0 / 14 (0.00%)<br>0 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|---------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 04 March 2022 | Protocol Version 2.0 dated 25-Jan-2022 (FDA May Proceed Letter): <ul style="list-style-type: none"><li>- Clarification regarding prohibited medication: treatment with substrates of CYP 2B6 and CYP2C8, CYP2C8 strong inducers and CYP2C8 strong inhibitors excluded</li><li>- In US and EU Renal Impairment guidances, the Food and Drug Administration and European Medicines Agency recommend expressing glomerular filtration rate (GFR) in mL/min because renal clearance of a drug is proportional to individual GFR and not to standard body surface area (BSA)-standardised GFR, therefore study parameters were modified: eGFR no-longer BSA normalised</li><li>- Clarification regarding SARS-CoV-2 infection</li><li>- Clarification of rational, background and study design</li><li>- Clarification regarding randomisation process</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 23 May 2022   | Protocol Version 3.0 dated 08-Apr-2022: <ul style="list-style-type: none"><li>- Clarification regarding stratifying factors in the randomisation process</li><li>- Addition of a randomisation procedure before baseline visit, allowing the treatment ordering and treatment shipment/delivery to the site</li><li>- Update of patient individual study duration, due to addition of randomisation procedure</li><li>- Update of exclusion criteria No. 1 &amp; No. 2 for further clarification</li><li>- Addition of the possibility to perform phone call visit if medically needed to ensure appropriate patient follow-up in case on-site visit is not possible</li><li>- Update of the AESI reporting period to be in line with lanifibranor AESI reporting guidelines</li><li>- To align with lanifibranor AE management guidelines across the clinical development programme, 1) the drug-Induced Liver Injury Monitoring and stopping rules were updated as were 2) the guideline for AEs requiring specific management related to anaemia, heart failure, aminotransferase elevation, bone fracture, peripheral oedema, cholelithiasis, hypoglycaemia, ovulation resumption and weight gain local guidelines/clinical practice</li><li>- Update of the known potential risks of empagliflozin in line with the empagliflozin labelling</li><li>- List of clinical laboratory parameters was updated (HIV-1 and HIV-2 antibodies and serum ketones measures) to document the history of HIV infection and to ensure appropriate monitoring for the risk of ketoacidosis due to the use of empagliflozin</li><li>- Justification for dose updated to clarify the choice of 800 mg dosage for lanifibranor</li><li>- Update of exclusion criteria N°36 with patient with history of pancreatitis excluded</li></ul> |

|                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 07 February 2023 | <p>Protocol Version 4.0 dated 12-Jan-2023 :</p> <ul style="list-style-type: none"> <li>- Additional details regarding exploratory endpoints related to cT1</li> <li>- Update of the inclusion criteria: <ul style="list-style-type: none"> <li>o No. 6, No. 19, and No. 38, for clarification</li> <li>o No. 7, to further define Gilberts Syndrome that is regarded as a benign trait</li> <li>o No. 9, to allow patients with 'Benign ethnic neutropenia' to be eligible based on the investigator's clinical judgement</li> <li>o No. 10, to allow recruitment of patients who have mild thrombocytopenia</li> <li>o No. 41</li> <li>o the list of prohibited medication was updated.</li> <li>o Correction of a typing error in Figure 1: Study design</li> <li>o Addition of one footnote related to screening period to the Schedule of Activities (Clarification in visit time window for screening period)</li> <li>o Addition of one footnote related to patient rescreening to the Schedule of Activities (allow the use of previous LMS result for patient re-screening)</li> <li>o Update of the allowable Medications for Standard Care or Precautions (clarification that patients who have clinically insignificant changes in the listed concomitant medications are eligible)</li> <li>o Addition of a reference added regarding the definition of NASH (Definition of NASH corresponding to the inclusion criterion 5 revised)</li> <li>o Update of the Adverse Event Reporting guidance (to precise the AESI reporting timelines applicable for the study)</li> <li>o Update of the guideline for Adverse Events requiring specific management related to Anemia (to clarify the guidance)</li> </ul> </li> </ul> |
| 13 December 2023 | <p>Protocol Version 5.0 dated 19-Oct-2023 :</p> <ul style="list-style-type: none"> <li>- An interim analysis was added to obtain preliminary information on observed effects sizes / variability allowing an early insight on the treatment effect on multiple mechanistic endpoints</li> <li>- Exclusion criterion N°48 was updated to refer to the full list of permitted and prohibited concomitant medications</li> <li>- Addition of the overall study termination to clarify that both investigator and Sponsor can terminate the study at any time, especially at time of interim analysis</li> <li>- The anti-SARS-CoV-2-IgM as serological test in case of aminotransferase elevation was deleted to align with the central lab testing availability</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 12 April 2024    | <p>Protocol Version 6.0 dated 22-Feb-2024:</p> <p>To mimic the recommendations issued by the Data Monitoring Committee for the Phase 3 study, NATiV3 (IND140010 EudraCT 2020-004986-38), in patients with NASH and liver fibrosis, following changes were implemented:</p> <ul style="list-style-type: none"> <li>- Update of the exclusion criterion No. 1</li> <li>- Addition of the exclusion criterion No. 50 related to autoimmunity and addition of corresponding laboratory parameters</li> <li>- Addition of liver tests and INR monitoring</li> <li>- Addition of the possibility to use local laboratories for the above tests</li> <li>- Update of the known potential risks</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------|--------------|--------------|
|------|--------------|--------------|

|               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |   |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|
| 15 March 2024 | <p>As planned per protocol, an interim analysis was conducted in March 2024 based on 32 patients randomised and treated, corresponding to half of the planned randomised patients. As per protocol, recruitment was to be paused at this time. Following the interim analysis results, recruitment was to be either re-initiated or stopped.</p> <p>Results of the interim analysis showed that the primary endpoint - i.e. demonstrating the superiority of lanifibranor alone and lanifibranor and empagliflozin versus placebo on the primary endpoint - was met based on the 32 patients analysed then. Since achieving the primary endpoint was one of the pre-defined study stopping criteria defined in the SAP and considering the overall interim study results (including secondary, exploratory, and safety outcomes), the Sponsor decided on the following:</p> <ul style="list-style-type: none"> <li>- not to re-initiate patient recruitment,</li> <li>- to continue monitoring the follow-up of the 7 patients that were still ongoing in the study at time of interim analysis,</li> <li>- to perform the final analysis based on 39 patients randomised and treated.</li> </ul> <p>The results posted are that from the final analysis based on 39 patients.</p> | - |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|

Notes:

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No multiplicity adjustments when testing for treatment effect on secondary endpoints. Numerical improvements with active vs placebo on some of these endpoints but the sample size was too small to achieve statistical significance.

Notes: