NOVARTIS

**Clinical Trial Results Website**

## Sponsor

Novartis Pharmaceuticals

## Generic Drug Name

Not applicable

## Trial Indication(s)

Non-alcoholic Fatty Liver Disease
Non-alcoholic Steatohepatitis

## Protocol Number

CADPT02A12001

## Protocol Title

NASH EXploratory Single and COmbination Treatment (NEXSCOT): An open label, multicenter, platform study to evaluate the safety, tolerability, pharmacokinetics and efficacy of various single and combination treatments in patients with non-alcoholic fatty liver disease (NAFLD) who manifest a non-alcoholic steatohepatitis (NASH)-like biomarker phenotype

## Clinical Trial Phase

Phase 2

## Phase of Drug Development

Phase 2

## Study Start/End Dates

Study Start Date: June 04, 2020 (Actual)
Primary Completion Date: January 06, 2022 (Actual)
Study Completion Date: January 06, 2022 (Actual)

## Reason for Termination (If applicable)

Sponsor Decision

## Study Design/Methodology

This was a Phase II, non-confirmatory, multicenter, open label, platform study in NAFLD participants with a NASH-like biomarker phenotype to examine the effects of single and combination therapies over 12 weeks of treatment

## Centers

10 centers in 3 countries: United States(8), Germany(1), Argentina(1)

## Objectives:

Primary Objective: To determine the safety and tolerability of single or combination therapy during 12 weeks of treatment

Secondary objectives:

- To determine the effect of single or combination therapy on circulating markers of ongoing
- liver fibrosis
- To determine the effect of single or combination therapy on intrahepatic lipid content
- To determine the effect of single or combination therapy on cardio-metabolic risk parameters
- To determine the effect of single or combination therapy on circulating markers of liver and/or systemic inflammation
- To evaluate the pharmacokinetics (PK) of each individual agent when administered as a single or combination therapy

## Test Product (s), Dose(s), and Mode(s) of Administration

LYS006 20 mg was administered orally twice per day (b.i.d) for 12 weeks. LYS006 20 mg was administered orally twice per day (b.i.d) in addition to LJN452 200ug administered orally once daily for 12 weeks

## Statistical Methods

Formal statistical analyses were not performed on the safety and tolerability data.
A mixed-effects model for repeated measures (MMRM) analysis was conducted for log-transformed ratio to baseline in ELF Test and ALT. The model included effects for treatment, visit, treatment by visit interaction, stratification factor (race and BMI stratum at baseline), log-transformed baseline, and log-transformed baseline by visit interaction. An unstructured variance-covariance matrix was used to account for correlation among multiple measurements from the same participant and variance heterogeneity. If the unstructured covariance caused model convergence issues, then other simpler covariance structures were considered. Least squares mean, the associated 2-sided 80% confidence interval and the p-value were obtained for each treatment at each visit and back transformed to the original scale.

## Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Phenotypic diagnosis of NASH based on the presence of all of the following:
  - ALT ≥ 43 IU/L (males) or ≥ 28 IU/L (females)
  - BMI ≥ 27 kg/m2 (race other than Asian) or ≥ 23 kg/m2 (Asian race)
  - History of type 2 diabetes mellitus with HbA1c ≤ 9%
  - ELF test score ≥ 8.5 and ≤ 10.5
  - Liver fat ≥ 8%
- Patients must weigh between 40 kg (88 lbs.) and 150 kg (330 lbs.)

Exclusion Criteria:

- Use of other investigational drugs within 5 half-lives of randomization or within 3 months, whichever is longer
- Use of obeticholic acid (OCA) or pharmacologically-active weight loss drugs within 1 month of randomization
- Use of strong CYP3A4/5 inhibitors or strong CYP3A4 inducers within 5 half-lives or 7 days of randomization, whichever is longer
- History or presence of other concomitant liver diseases
- History or current diagnosis of ECG abnormalities

- Patients with contraindications to MRI imaging
- Current or history of significant alcohol consumption
- Clinical evidence of hepatic decompensation or severe liver impairment
- Women of child bearing potential (unless on highly effective methods of contraception)
- Presence of liver cirrhosis
- Use of OAT3 inhibitors within 5 half-lives or 7 days of randomization, whichever is longer

## Participant Flow Table

### Overall Study

| | LYS006 | LYS006 + LJN452 | Total |
|---|---|---|---|
| **Arm/Group Description** | LYS006 20 mg was administered orally twice per day (b.i.d) for 12 weeks | LYS006 20 mg was administered orally twice per day (b.i.d) in addition to LJN452 200ug administered orally once daily for 12 weeks | |
| **Started** | 20 | 21 | 41 |
| **PD analysis set** | 20 | 17 | 37 |
| **Completed** | 16 | 15 | 31 |
| **Not Completed** | 4 | 6 | 10 |
| Adverse Event | 0 | 3 | 3 |
| Study Terminated by Sponsor | 4 | 2 | 6 |
| Withdrawal by Subject | 0 | 1 | 1 |

## Baseline Characteristics

| | LYS006 | LYS006 + LJN452 | Total |
|---|---|---|---|

| Arm/Group Description | LYS006 20 mg was administered orally twice per day (b.i.d) for 12 weeks | LYS006 20 mg was administered orally twice per day (b.i.d) in addition to LJN452 200ug administered orally once daily for 12 weeks | |
|---|---|---|---|
| **Number of Participants [units: participants]** | 20 | 21 | 41 |
| **Age Continuous**<br>(units: Year)<br>Analysis Population Type: Participants<br>Mean ± Standard Deviation | | | |
| | 52.0±9.23 | 54.9±8.36 | 53.5±8.81 |
| **Sex: Female, Male**<br>(units: Participants)<br>Analysis Population Type: Participants<br>Count of Participants (Not Applicable) | | | |
| Female | 11 | 11 | 22 |
| Male | 9 | 10 | 19 |
| **Race (NIH/OMB)**<br>(units: Participants)<br>Analysis Population Type: Participants<br>Count of Participants (Not Applicable) | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 1 | 1 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | 1 |
| Black or African American | 1 | 1 | 2 |
| White | 19 | 17 | 36 |
| More than one race | 0 | 1 | 1 |
| Unknown or Not Reported | 0 | 0 | 0 |

## Primary Outcome Result(s)

### 1.1 Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

Description: Number of participants with AEs and SAEs including significant changes from baseline in vital signs, electrocardiograms and laboratory parameters qualifying and reported as AEs. The number of participants in each category is reported in the table.

Time Frame: From the start of treatment to 28 days after end of treatment, assessed up to maximum duration of 113 Days

| | LYS006 | LYS006 + LJN452 |
|---|---|---|
| **Arm/Group Description** | LYS006 20 mg was administered orally twice per day (b.i.d) for 12 weeks | LYS006 20 mg was administered orally twice per day (b.i.d) in addition to LJN452 200ug administered orally once daily for 12 weeks |
| **Number of Participants Analyzed [units: participants]** | 20 | 21 |
| **Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)** (units: Participants) | **Count of Participants (Not Applicable)** | **Count of Participants (Not Applicable)** |
| AEs | 14 (70%) | 17 (80.95%) |
| Treatment-related AEs | 2 (10%) | 15 (71.43%) |
| SAEs | 0 (%) | 0 (%) |
| AEs leading to discontinuation of study treatment | 0 (%) | 3 (14.29%) |

## Secondary Outcome Result(s)

### 1.2 Change From Baseline in Non-invasive Markers of Hepatic Fibrosis: Enhanced Liver Fibrosis Test (ELF) Score

Description: The markers of fibrosis assessed in this test comprised hyaluronic acid (HA), tissue inhibitor of metalloproteinase (TIMP1) and procollagen III N-terminal peptide (PIIINP); these are components of the extracellular matrix and basement sinusoidal membrane of the liver and are elevated during fibrogenesis as a result of activation of the hepatic stellate cell. The ELF test is a composite score: < 7.7: no to mild fibrosis; ≥ 7.7 - < 9.8: Moderate fibrosis; ≥ 9.8 - < 11.3: Severe fibrosis; ≥ 11.3: Cirrhosis. Baseline is defined as the last non-missing measurement taken at the Screening and Baseline visits (prior to the first dose of study drug administered at the Day 1). A negative change from Baseline indicates decreased fibrosis.

Time Frame: Baseline and Days 57, 85 and EOS (Day 113)

| | **LYS006** | **LYS006 + LJN452** |
|---|---|---|
| **Arm/Group Description** | LYS006 20 mg was administered orally twice per day (b.i.d) for 12 weeks | LYS006 20 mg was administered orally twice per day (b.i.d) in addition to LJN452 200ug administered orally once daily for 12 weeks |
| **Number of Participants Analyzed [units: participants]** | 20 | 17 |
| **Change From Baseline in Non-invasive Markers of Hepatic Fibrosis: Enhanced Liver Fibrosis Test (ELF) Score** (units: Scores on a scale) | **Mean ± Standard Deviation** | **Mean ± Standard Deviation** |
| Day 57 | -0.25 ± 0.564 | 0.29 ± 0.286 |
| Day 85 | -0.12 ± 0.780 | 0.18 ± 0.687 |
| EOS | 0.01 ± 0.713 | 0.09 ± 0.461 |

### 1.3 Change from Baseline in Cholesterol: fasting lipid profile endpoint

Description: Fasting lipid profile (total cholesterol) was examined as a cardiometabolic risk parameter. Total cholesterol was measured on blood samples under fasted conditions and analyzed at a central laboratory. Baseline is defined as the last non-missing measurement taken at the Screening and Baseline visits (prior to the first dose of study drug administered at the Day 1). A negative change from Baseline indicates cardiovascular risk.

Time Frame Baseline and Days 15, 29, 43, 57, 85 and EOS (Day 113)

| | LYS006 | LYS006 + LJN452 |
|---|---|---|
| **Arm/Group Description** | LYS006 20 mg was administered orally twice per day (b.i.d) for 12 weeks | LYS006 20 mg was administered orally twice per day (b.i.d) in addition to LJN452 200ug administered orally once daily for 12 weeks |
| **Number of Participants Analyzed [units: participants]** | 20 | 17 |
| **Change from Baseline in Cholesterol: fasting lipid profile endpoint** (units: mmol / L) | **Mean ± Standard Deviation** | **Mean ± Standard Deviation** |
| Day 15 | -0.025 ± 0.5814 | 0.086 ± 0.8825 |
| Day 29 | -0.058 ± 0.6058 | 0.431 ± 1.0688 |
| Day 43 | -0.109 ± 0.6758 | 0.474 ± 1.0364 |
| Day 57 | -0.246 ± 0.6341 | 0.463 ± 1.3026 |
| Day 85 | 0.001 ± 0.8558 | 0.754 ± 0.9915 |
| EOS | -0.283 ± 1.1182 | 0.249 ± 0.5175 |

## 1.4 Change from Baseline in percent liver fat at day 85

Description Percent (%) Liver fat was measured by Magnetic Resonance Imaging Proton Density Liver Fat Fraction (MRIPDFF). Participants underwent magnetic resonance imaging twice during the course of the study (baseline and end of treatment) to quantitate liver fat. Baseline is defined as the last non-missing measurement taken at the Screening and Baseline visits (prior to the first dose of study drug administered at the Day 1). A negative change from Baseline indicates a reduction in a component of NAFLD.

Time Frame Baseline and Day 85

| | LYS006 | LYS006 + LJN452 |
|---|---|---|
| **Arm/Group Description** | LYS006 20 mg was administered orally twice per day (b.i.d) for 12 weeks | LYS006 20 mg was administered orally twice per day (b.i.d) in addition to |

| | | LJN452 200ug administered orally once daily for 12 weeks |
|---|---|---|
| **Number of Participants Analyzed [units: participants]** | 14 | 11 |
| **Change from Baseline in percent liver fat at day 85** (units: Percentage of Liver Fat) | **Mean ± Standard Deviation** | **Mean ± Standard Deviation** |
| Day 85 | -3.74 ± 3.470 | -7.52 ± 5.846 |

## 1.5 Change From Baseline in Total Body Weight

Description: Body weight (to the nearest 0.1 kilogram [kg] was measured on a calibrated scale. The measurement was performed with the study participant in underwear and without shoes; or while wearing minimal indoor clothing. Baseline is defined as the last non-missing measurement taken at the Screening and Baseline visits (prior to the first dose of study drug administered at the Day 1). A negative change from Baseline indicates improvement in obesity.

Time Frame: Baseline and Days 15, 29, 43, 57, 85 and EOS (Day 113)

| | **LYS006** | **LYS006 + LJN452** |
|---|---|---|
| **Arm/Group Description** | LYS006 20 mg was administered orally twice per day (b.i.d) for 12 weeks | LYS006 20 mg was administered orally twice per day (b.i.d) in addition to LJN452 200ug administered orally once daily for 12 weeks |
| **Number of Participants Analyzed [units: participants]** | 20 | 17 |
| **Change From Baseline in Total Body Weight** (units: kg) | **Mean ± Standard Deviation** | **Mean ± Standard Deviation** |
| Day 15 | -0.21 ± 1.412 | -1.09 ± 2.030 |
| Day 29 | -0.27 ± 1.513 | -1.17 ± 2.455 |
| Day 43 | -0.24 ± 1.664 | -1.94 ± 2.780 |
| Day 57 | -0.48 ± 1.548 | -2.97 ± 3.144 |
| Day 85 | -0.54 ± 2.334 | -3.33 ± 2.892 |
| EOS | 0.17 ± 2.753 | -2.56 ± 2.789 |

## 1.6 Change from Baseline in Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) at Day 85

Description: HOMA-IR is a test that uses a simultaneous fasting blood glucose test and fasting insulin test to accurately estimate the degree of insulin resistance (IR) and β-cell function (the cells of the pancreas that produce insulin). HOMA-IR scores are classified as follows: Insulin sensitive is considered less than 1.0, Healthy is considered 0.5-1.4, Above 1.8 is early insulin resistance and Above 2.7 is considered significant insulin resistance HOMA-IR= [Fasting glucose (mmol/L) x (fasting insulin (pmol/L)/6)] / 22.5 Baseline is defined as the last non-missing measurement taken at the Screening and Baseline visits (prior to the first dose of study drug administered at the Day 1). A negative change from Baseline indicates improvement in insulin sensitivity.

Time Frame: Baseline and Day 85

| | LYS006 | LYS006 + LJN452 |
|---|---|---|
| **Arm/Group Description** | LYS006 20 mg was administered orally twice per day (b.i.d) for 12 weeks | LYS006 20 mg was administered orally twice per day (b.i.d) in addition to LJN452 200ug administered orally once daily for 12 weeks |
| **Number of Participants Analyzed [units: participants]** | 14 | 9 |
| **Change from Baseline in Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) at Day 85** (units: HOMA-IR score) | **Mean ± Standard Deviation** | **Mean ± Standard Deviation** |
| | -3.74 ± 9.865 | 1.67 ± 7.741 |

## 1.7 Change from baseline in Fasting Glucose

Description: Fasting Glucose was examined as a cardiometabolic risk parameter. Total fasting glucose was measured on blood samples under fasted conditions and analyzed at a central laboratory. Baseline is defined as the last non-missing measurement taken at the Screening and Baseline visits (prior to the first dose of study drug administered at the Day 1). A negative change from Baseline indicates improvement in glycemic control.

Time Frame: Baseline and Days 15, 29, 43, 57, 85 and EOS (Day 113)

| | LYS006 | LYS006 + LJN452 |
|---|---|---|
| **Arm/Group Description** | LYS006 20 mg was administered orally twice per day (b.i.d) for 12 weeks | LYS006 20 mg was administered orally twice per day (b.i.d) in addition to LJN452 200ug administered orally once daily for 12 weeks |
| **Number of Participants Analyzed [units: participants]** | 20 | 17 |
| **Change from baseline in Fasting Glucose** (units: mmol / L) | **Mean ± Standard Deviation** | **Mean ± Standard Deviation** |
| Day 15 | 0.26 ± 2.609 | 0.26 ± 2.402 |
| Day 29 | -0.04 ± 3.541 | 0.61 ± 2.362 |
| Day 43 | -0.53 ± 3.655 | 1.05 ± 2.449 |
| Day 57 | -0.82 ± 3.176 | 0.84 ± 1.960 |
| Day 85 | -1.74 ± 3.810 | 0.41 ± 2.023 |
| EOS | -1.01 ± 3.627 | -0.40 ± 1.563 |

## 1.8 Change from Baseline in Fasting Insulin at Day 85

Description: Fasting insulin was examined as a cardiometabolic risk parameter. Total fasting insulin was measured on blood samples under fasted conditions and analyzed at a central laboratory. Baseline is defined as the last non-missing measurement taken at the Screening and Baseline visits (prior to the first dose of study drug administered at the Day 1). A negative change from Baseline indicates improvement in insulin sensitivity.

Time Frame: Baseline and Day 85

| | LYS006 | LYS006 + LJN452 |
|---|---|---|
| **Arm/Group Description** | LYS006 20 mg was administered orally twice per day (b.i.d) for 12 weeks | LYS006 20 mg was administered orally twice per day (b.i.d) in addition to LJN452 200ug administered orally once daily for 12 weeks |
| **Number of Participants Analyzed [units: participants]** | 14 | 9 |

| Change from Baseline in Fasting Insulin at Day 85<br>(units: pmol / L) | Mean<br>± Standard Deviation | Mean<br>± Standard Deviation |
|---|---|---|
| | -28.36 ± 139.23 | 14.23 ± 63.875 |

## 1.9 Change from baseline in Hemoglobin A1c (HbA1c)

Description: HbA1c was examined as a cardiometabolic risk parameter. HbA1c was measured on blood samples under fasted conditions and analyzed at a central laboratory. Baseline is defined as the last non-missing measurement taken at the Screening and Baseline visits (prior to the first dose of study drug administered at the Day 1). A negative change from Baseline indicates improvement in glycemic control.

Time Frame: Baseline and Days 15, 29, 43, 57, 85 and EOS (Day 113)

| | LYS006 | LYS006 + LJN452 |
|---|---|---|
| **Arm/Group Description** | LYS006 20 mg was administered orally twice per day (b.i.d) for 12 weeks | LYS006 20 mg was administered orally twice per day (b.i.d) in addition to LJN452 200ug administered orally once daily for 12 weeks |
| **Number of Participants Analyzed [units: participants]** | 20 | 17 |
| **Change from baseline in Hemoglobin A1c (HbA1c)**<br>(units: Percentage) | **Mean**<br>**± Standard Deviation** | **Mean**<br>**± Standard Deviation** |
| Day 15 | 0.10 ± 0.194 | 0.08 ± 0.338 |
| Day 29 | 0.03 ± 0.431 | 0.21 ± 0.487 |
| Day 43 | -0.02 ± 0.544 | 0.31 ± 0.884 |
| Day 57 | -0.11 ± 0.730 | 0.36 ± 0.680 |
| Day 85 | -0.48 ± 0.834 | -0.03 ± 0.863 |
| EOS | -0.59 ± 0.961 | 0.34 ± 0.359 |

## 1.10 Change from Baseline in Alanine aminotransferase (ALT)

Description: Alanine aminotransferase (ALT) is an enzyme found primarily in the liver. ALT is increased with liver damage. In this study, the blood levels of ALT was used to detect liver inflammation. Baseline is defined as the mean of the last 2 non-missing measurements taken at the Screening and Baseline visits (prior to the first dose of study drug administered at the Day 1). A negative change from Baseline indicates a reduction in liver inflammation.

Time Frame: Baseline and days 15, 29, 43, 57, 85 and EOS (Day 113)

| | LYS006 | LYS006 + LJN452 |
|---|---|---|
| **Arm/Group Description** | LYS006 20 mg was administered orally twice per day (b.i.d) for 12 weeks | LYS006 20 mg was administered orally twice per day (b.i.d) in addition to LJN452 200ug administered orally once daily for 12 weeks |
| **Number of Participants Analyzed [units: participants]** | 20 | 17 |
| **Change from Baseline in Alanine aminotransferase (ALT)** (units: U / L) | **Mean ± Standard Deviation** | **Mean ± Standard Deviation** |
| Day 15 | 0.97 ± 18.255 | -19.75 ± 25.617 |
| Day 29 | -6.92 ± 22.166 | -9.63 ± 13.774 |
| Day 43 | -11.13 ± 21.624 | -8.68 ± 14.573 |
| Day 57 | -12.09 ± 25.401 | -17.04 ± 12.841 |
| Day 85 | -7.21 ± 34.702 | -11.14 ± 26.318 |
| EOS | -14.50 ± 29.619 | -8.05 ± 14.570 |

## 1.11 Change from baseline in High-sensitivity C-reactive Protein (hsCRP)

Description: High-sensitivity C-reactive protein is a blood test marker for inflammation in the body. HsCRP was measured from a blood sample and analyzed at a central laboratory. Baseline is defined as the last non-missing measurement taken at the Screening and Baseline visits (prior to the first dose of study drug administered at the Day 1). A negative change from Baseline indicates a reduction in liver inflammation.

Time Frame: Baseline and Days 57, 85 and EOS (Day 113)

| | LYS006 | LYS006 + LJN452 |
|---|---|---|
| **Arm/Group Description** | LYS006 20 mg was administered orally twice per day (b.i.d) for 12 weeks | LYS006 20 mg was administered orally twice per day (b.i.d) in addition to LJN452 200ug administered orally once daily for 12 weeks |
| **Number of Participants Analyzed [units: participants]** | 20 | 17 |
| **Change from baseline in High-sensitivity C-reactive Protein (hsCRP)** (units: mg / L) | **Mean ± Standard Deviation** | **Mean ± Standard Deviation** |
| Day 57 | -0.32 ± 2.192 | -7.78 ± 27.500 |
| Day 85 | -0.62 ± 2.180 | 0.24 ± 1.692 |
| EOS | 0.19 ± 3.432 | 0.05 ± 1.015 |

## 1.12 LYS006 plasma concentration

Description LYS006 plasma concentrations were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. No methods for imputation of missing data were used.

Time Frame pre-dose at Days 1, 29, 57 and 85 and post-dose (1, 2, 3 and 4 hours) at Days 29 and 57

| | LYS006 | LYS006 + LJN452 |
|---|---|---|
| **Arm/Group Description** | LYS006 20 mg was administered orally twice per day (b.i.d) for 12 weeks | LYS006 20 mg was administered orally twice per day (b.i.d) in addition to LJN452 200ug administered orally once daily for 12 weeks |
| **Number of Participants Analyzed [units: participants]** | 20 | 21 |
| **LYS006 plasma concentration** (units: ng / mL) | **Mean ± Standard Deviation** | **Mean ± Standard Deviation** |
| Day 1 (0 h) | 0.162 ± 0.648 | 0.00 ± 0.00 |
| Day 29 (0 h) | 78.9 ± 74.0 | 53.5 ± 74.9 |

| | | |
|---|---|---|
| Day 29 (1 h) | 174 ± 89.6 | 169 ± 105 |
| Day 29 (2 h) | 224 ± 113 | 189 ± 105 |
| Day 29 (3 h) | 188 ± 89.8 | 145 ± 54.9 |
| Day 29 (4 h) | 149 ± 73.6 | 110 ± 31.8 |
| Day 57 (0 h) | 58.0 ± 57.2 | 24.0 ± 21.4 |
| Day 57 (1 h) | 200 ± 118 | 123 ± 123 |
| Day 57 (2 h) | 222 ± 80.3 | 198 ± 88.7 |
| Day 57 (3 h) | 188 ± 74.3 | 156 ± 59.2 |
| Day 57 (4 h) | 140 ± 83.3 | 126 ± 54.1 |
| Day 85 (0 h) | 15.2 ± 17.6 | 10.2 ± 18.7 |

## 1.13 Maximum observed plasma concentration (Cmax) of LYS006

Description: LYS006 plasma concentrations were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. Cmax of LYS006 was determined with Phoenix WinNonlin (Version 8.0 or higher). No methods for imputation of missing data were used.

Time Frame: pre-dose and post-dose (1, 2, 3 and 4 hours) at Days 29 and 57

| | **LYS006** | **LYS006 + LJN452** |
|---|---|---|
| **Arm/Group Description** | LYS006 20 mg was administered orally twice per day (b.i.d) for 12 weeks | LYS006 20 mg was administered orally twice per day (b.i.d) in addition to LJN452 200ug administered orally once daily for 12 weeks |
| **Number of Participants Analyzed [units: participants]** | 20 | 21 |
| **Maximum observed plasma concentration (Cmax) of LYS006** (units: ng / mL) | **Mean ± Standard Deviation** | **Mean ± Standard Deviation** |
| Day 29 | 264 ± 87.7 | 215 ± 98.8 |
| Day 57 | 271 ± 71.1 | 228 ± 88.1 |

## Safety Results

### All-Cause Mortality

| | LYS006<br>N = 20 | LYS006 + LJN452<br>N = 21 | Total<br>N = 41 |
|---|---|---|---|
| **Arm/Group Description** | LYS006 20 mg was administered orally twice per day (b.i.d) for 12 weeks | LYS006 20 mg was administered orally twice per day (b.i.d) in addition to LJN452 200ug administered orally once daily for 12 weeks | Total |
| **Total Number Affected** | 0 | 0 | 0 |
| **Total Number At Risk** | 20 | 21 | 41 |

### Serious Adverse Events by System Organ Class

No data identified.

### Other Adverse Events by System Organ Class

| | LYS006<br>N = 20 | LYS006 + LJN452<br>N = 21 | Total<br>N = 41 |
|---|---|---|---|
| **Arm/Group Description** | LYS006 20 mg was administered orally twice per day (b.i.d) for 12 weeks | LYS006 20 mg was administered orally twice per day (b.i.d) in addition to | Total |

| | | LJN452 200ug administered orally once daily for 12 weeks | |
|---|---|---|---|
| **Total # Affected by any Other Adverse Event** | 9 | 15 | 24 |
| **Total # at Risk by any Other Adverse Event** | 20 | 21 | 41 |
| **Gastrointestinal disorders** | | | |
| Abdominal pain upper | 1 (5.00%) | 2 (9.52%) | 3 (7.32%) |
| Diarrhoea | 3 (15.00%) | 0 (0.00%) | 3 (7.32%) |
| Nausea | 3 (15.00%) | 2 (9.52%) | 5 (12.20%) |
| **Investigations** | | | |
| Alanine aminotransferase increased | 0 (0.00%) | 2 (9.52%) | 2 (4.88%) |
| Aspartate aminotransferase increased | 0 (0.00%) | 2 (9.52%) | 2 (4.88%) |
| Blood alkaline phosphatase increased | 0 (0.00%) | 3 (14.29%) | 3 (7.32%) |
| **Metabolism and nutrition disorders** | | | |
| Hyperglycaemia | 1 (5.00%) | 3 (14.29%) | 4 (9.76%) |
| **Nervous system disorders** | | | |
| Dizziness | 2 (10.00%) | 0 (0.00%) | 2 (4.88%) |
| Headache | 4 (20.00%) | 4 (19.05%) | 8 (19.51%) |
| **Psychiatric disorders** | | | |
| Insomnia | 0 (0.00%) | 2 (9.52%) | 2 (4.88%) |
| **Skin and subcutaneous tissue disorders** | | | |
| Pruritus | 0 (0.00%) | 13 (61.90%) | 13 (31.71%) |
| Rash | 0 (0.00%) | 2 (9.52%) | 2 (4.88%) |

## Other Relevant Findings

Not applicable

## Conclusion:

LYS006 20 mg b.i.d. monotherapy and LYS006 20 mg b.i.d. + tropifexor 200 ug QD combination were safe and well tolerated. While reduction of ALT and liver fat was greater in the combination arm compared to the LYS006 monotherapy arm, efficacy thresholds for reduction in biomarkers of fibrosis, inflammation and hepatic fat reduction were not achieved for either treatment arm.

## Date of Clinical Study Report

02-Sep-2022