Sponsor

Novartis

Generic Drug Name

Tropifexor (LJN452)

Trial Indication(s)

Non-alcoholic steatohepatitis

Protocol Number

CLJN452A2109

Protocol Title

A Phase 1, open-label, single-dose, multi-center, parallel group study to evaluate the pharmacokinetics of tropifexor (LJN452) in subjects with mild, moderate or severe hepatic impairment compared to healthy control subjects

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase II

Study Start/End Dates

24-Sep-2018 to 25-Sep-2019

Study Design/Methodology

This was a Phase 1, multi-center study with parallel groups. The study employed a single-dose, open-label design in subjects with mild, moderate, or severe hepatic impairment along with matched healthy control subjects with normal hepatic function. Subjects with normal hepatic function were matched with subjects with hepatic impairment for gender, age (± 10 years), body weight (± 10%), and smoking status, since these covariates could contribute to the pharmacokinetics (PK) variability of tropifexor. The matching criteria helped to reduce between-group differences due to these contributing covariates.

The study was comprised of an up to 21-day screening period (Days -21 to -2), a baseline evaluation (Day -1) prior to treatment on Day 1, and a follow-up period of 7 days for PK sample collection (pre-dose, 1 h, 2 h, 4 h, 8 h, 10 h, 12 h, 24 h, 48 h, 72 h, 96 h, 120 h, 144 h and 168 h post-dose). A safety follow-up phone call was done 30 days after administration of the study drug.

A total of 42 subjects were enrolled (8 each of mild [Child-Pugh A], moderate [Child-Pugh B], severe hepatic impairment [Child-Pugh C]), and 18 healthy control subjects). Each subject received a single oral dose of 200 µg of tropifexor on Day 1.

PK parameters were determined using the actual recorded sampling times and non-compartmental methods with Phoenix WinNonlin version 8.0. Tropifexor PK parameters were calculated based on tropifexor plasma concentrations determined by a validated liquid chromatography and tandem mass spectrometry (LC-MS/MS) method. All drug concentrations below the lower limit of quantification (LLOQ) (0.02 ng/mL for tropifexor) were reported as zero and treated as zero for the calculation of PK parameters.

For plasma protein binding, a single predose plasma sample was collected and was spiked with radiolabeled tropifexor. After separation with equilibrium dialysis, the samples were analyzed using a liquid scintillation counting method.

Centers

3 centers in 1 country (United States).

Objectives:

The primary purpose of this study was to evaluate the effect of hepatic impairment on the systemic exposure of tropifexor and to evaluate the safety of tropifexor in subjects with hepatic impairment. The results of this study will support treatment and dosing decisions for patients with varying degrees of hepatic impairment.

Primary objective(s)

To assess the pharmacokinetic (PK) properties of tropifexor after a single oral dose of 200 µg in subjects with mild, moderate, or severe hepatic impairment as compared to healthy subjects with normal hepatic function as classified by a Child-Pugh score by assessing PK parameters, including the observed maximum concentration (Cmax), the time to reach maximum concentration (Tmax), the area under the concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration (AUClast), and the AUC from time zero to infinity (AUCinf), along with the terminal elimination half-life (T1/2), apparent total clearance of the drug from plasma (CL/F), and the apparent volume of distribution during terminal phase (Vz/F).

Secondary objective(s)

- Objective 1: To assess the safety and tolerability of tropifexor after a single oral dose of 200 µg of tropifexor in subjects with mild, moderate, or severe hepatic impairment as compared to healthy subjects with normal hepatic function, by evaluating all safety endpoints up until and including 30 days post dose.
- Objective 2: To assess the relationship between baseline hepatic function parameters and tropifexor PK parameters by comparing the hepatic function parameters, Child-Pugh scores, total bilirubin, prothrombin time, albumin and aspartate aminotransferase (AST), and the PK parameters, Cmax, AUClast, AUCinf, and CL/F.
- Objective 3: To assess the plasma protein binding free fraction of tropifexor (fu) in subjects with hepatic impairment as compared to healthy subjects. If the protein bindings are different between hepatically impaired subjects and their healthy counterparts, to calculate the unbound PK parameters i.e., unbound Cmax (Cmax,u), unbound AUClast (AUClast,u), unbound AUCinf (AUCinf,u), and unbound CL/F (CL/F,u) and to assess the relationship with baseline hepatic function parameters listed in Objective 2.

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

A single oral dose of 200 µg (2 capsules of 100 µg, each) of tropifexor was administered to each subject on Day 1.

Statistical Methods

Log-transformed PK parameters (Cmax, AUClast, AUCinf, Cmax,u; AUClast,u; and AUCinf,u) were analyzed using separate linear mixed effects models with group as fixed effect (2 group levels) and matched pair (approximately 6 to 8 pairs) as random effect to compare each hepatic impairment group with its matching control group. Least squares means for each hepatically impaired group and its matching control

group, as well as the difference between each hepatically impaired group and its matching control group, along with the corresponding 90% confidence interval (CI) on the log-scale were calculated for each PK parameter in each of the 3 analyses. Back transformed ratios and 90% CIs were provided. For Tmax and Tmax,u; median, and difference of medians for each hepatically impaired group (mild, moderate, or severe) and the matched control group were provided.

The relationship between PK parameters (Cmax, AUClast, AUCinf, CL/F, Cmax,u; AUClast,u; AUCinf,u; and CL/F,u) and hepatic function tests (Child-Pugh score, total bilirubin, prothrombin time, albumin, and AST) were explored using ordinary least squares regression of the PK parameters (dependent variable; log-scale for all parameters, except CL/F; because CL/F = dose/AUCinf and log-transformed CL/F analysis is the same as AUCinf) on the Child-Pugh score and liver function tests (predictors).

Safety data were summarized, and no formal statistical analysis was performed.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria

All subjects

- Written informed consent obtained before performing any assessments.
- Male and female subjects 18 to 70 years of age.
- Subjects had to weigh at least 50 kg to participate in the study, and had to have a body mass index (BMI) within the range of 18 to 38 kg/m2.
- Subjects had to be able to communicate well with the Investigator, to understand and comply with the requirements of the study.
- Subjects had to be willing to remain in the clinical research unit as required by the protocol.

Group 1 (Healthy Subjects)

- Each subject had to match in age (± 10 years), gender, weight (± 10%), and smoking status to an individual subject in Group 2, 3, and 4.
- Subjects had to be in good health as determined by past medical history, physical examination, electrocardiogram (ECG), laboratory tests, and urinalysis screening.

- At Screening and Baseline, vital signs (systolic and diastolic blood pressure, and pulse rate) were assessed in the supine position after the subjects had rested for at least 5 minutes. Supine vital signs had to be within the following ranges:
  - Oral body temperature, 35.0 to 37.5°C
  - Systolic blood pressure, 89 to 139 mmHg
  - Diastolic blood pressure, 50 to 89 mmHg
  - Pulse rate, 40 to 90 bpm

Group 2, 3, and 4 (Subjects with mild, moderate, or severe hepatic impairment)

- Vital signs after 5 minutes of rest in the supine position had to be within the following ranges:
  - Oral body temperature, 35.0 to 37.5°C
  - Systolic blood pressure, 89 to 160 mmHg
  - Diastolic blood pressure, 50 to 100 mmHg
  - Pulse rate, 50 to 100 bpm
- A Child-Pugh score clinically determined and calculated as per the Child-Pugh classification in line with the hepatic impairment of each Group, i.e., Group 2, 3, and 4 (subjects with mild, moderate, or severe hepatic impairment).
- Hepatic impairment as defined by the Child-Pugh classification for severity of liver disease:
  - Group 2; mild; Child-Pugh score 5-6; Class A.
  - Group 3; moderate; Child-Pugh score 7-9; Class B.
  - Group 4; severe; Child-Pugh score 10-15; Class C.
- Stable Child-Pugh status and no worsening of more than 1 point in Child-Pugh score within 28 days prior to dosing.

- Subjects with impaired hepatic function with other stable medical disorders such as controlled diabetes, hyperlipidemia, hypothyroidism, etc., may be eligible as long as they are considered appropriate for enrollment as determined by the Investigator by past medical history, physical examination, vital signs, ECG, and laboratory tests at Screening.

Key Exclusion Criteria

All subjects

- Use of other study drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days, whichever is longer; or longer if required by local regulations.
- History of hypersensitivity to any of the study treatments or excipients, or to drugs of similar chemical classes.
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during the study and for 2 weeks after stopping of the study drug. Women are considered postmenopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate, history of vasomotor symptoms), or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks prior to taking the study drug. In the case of oophorectomy alone, only when the reproductive status of the woman was confirmed by follow-up hormone level assessment will she be considered not of child-bearing potential.
- Known history of, or current clinically significant arrhythmias.
- History of immunodeficiency disease, or a positive HIV test result.
- History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in-situ cervical cancer), treated or untreated, within the past 3 years, regardless of whether there is evidence of local recurrence or metastases.
- Taking medication prohibited by the protocol. Hepatically impaired subjects had to be excluded if there have been changes in dose regimen of medically-required medication within the last 2 weeks prior to Screening, or if there has been a significant change or addition to their

routine medication (prescribed) within 1 month of dosing on Day 1. Minor changes to medications that require frequent dose adjustment, such as insulin or analgesia, can be made up to 2 weeks prior to Day 1 as agreed between the Investigator and Novartis.

- Donation or loss of 450 mL or more of blood within 8 weeks prior to taking the study drug, or longer if required by local regulation.
- History of drug abuse or unhealthy alcohol use within 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during Screening and/or Baseline. Note: Subjects who do not agree to comply with abstinence from alcohol use from Screening to the End of Study had to be excluded. Unhealthy alcohol use is defined as 5 or more drinks on the same occasion on each of 10 or more days in the past 30 days.
- Sexually active males unwilling to use a condom during intercourse while taking the study drug and for 2 weeks afterwards. A condom is required for all sexually active male participants to prevent them from fathering a child and to prevent delivery of the study drug via seminal fluid to their partner. In addition, male participants should not donate sperm for the time period specified above.
- Recent (within the last 3 years) or recurrent history of autonomic dysfunction (e.g. recurrent episodes of fainting, palpitations, etc.).
- Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drug (apart from cholecystectomy), or may jeopardize the subject in case of participation in the study. The Investigator had to make this determination in consideration of the subject's medical history and/or clinical laboratory evidence of the following:
  - Inflammatory bowel disease, peptic ulcers, gastrointestinal including rectal bleeding within 3 months prior to screening.
  - Major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection.
  - Pancreatic injury or pancreatitis.

Group 1 (Healthy subjects)

- Significant illness which has not resolved within 2 weeks prior to dosing.
- Liver disease or liver injury as indicated by abnormal liver function tests. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltransferase (GGT), alkaline phosphatase (ALP), and serum bilirubin had to be tested.
- Any single parameter of ALT, AST, GGT, ALP, or serum bilirubin had not to exceed the upper limit of normal (ULN). If necessary, laboratory testing may be repeated on 1 occasion, as soon as possible, prior to study drug administration to rule out any laboratory error.

- Subjects known to have Gilbert's syndrome.
- Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV). A positive HBV surface antigen test, or if standard local practice, a positive HBV core antigen test, excluded a subject. Subjects with a positive HCV antibody test had to have HCV ribonucleic acid (RNA) levels measured. Subjects with positive (detectable) HCV RNA were excluded.
- Hemoglobin levels below 12.0 g/dL at Screening and Baseline.
- Evidence of urinary obstruction or difficulty in voiding at Screening.
- History or presence of impaired renal function as indicated by clinically significant abnormal creatinine or blood urea nitrogen (BUN) and/or urea values, or abnormal urinary constituents (e.g. albuminuria).
- Symptomatic genital or urinary tract infection in the 4 weeks prior to dosing or the presence of active urinary tract infection at Screening.
- Total white blood cell count which falls outside the range of 3.5 to 10.7 × 109/L, or platelets < 100 × 109/L at Screening.
- A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at Screening and/or pretreatment:
  - PR > 200 msec.
  - QRS complex > 120 msec.
  - QTcF > 450 msec (males).
  - QTcF > 460 (females).
- Use of any prescription drugs, herbal supplements, including Silybum marianum and Valeriana officinalis, within 4 weeks prior to dosing, and/or over the counter medication or dietary supplements (vitamins included) within 2 weeks prior to dosing.

Groups 2 and 3 (Subjects with mild or moderate hepatic impairment)

- Hepatically impaired subjects with abnormal laboratory values for the following parameters:
  - Hemoglobin < 9 g/dL
  - Platelet count < 30 × 109/L

  - White blood cell count < 2.5 × 109/L
  - Absolute neutrophil count < 1.5 × 109/L
  - Lymphocytes < 0.8 × 109/L
  - Total bilirubin > 8 mg/dL
  - Serum amylase > 2 × ULN
  - International standardized ratio (INR) > 2.3
  - Corrected serum calcium < 8.6 or > 10.2 mg/dL
- Severe complications of liver disease within the preceding 3 months.
- Emergency room visit or hospitalization due to liver disease within the preceding 3 months.
- Subject who had received liver transplant at any time in the past and was on immunosuppressant therapy.
- Subjects requiring paracentesis more than every 30 days for the management of ascites were excluded. Subjects who were receiving diuretics to manage ascites could be enrolled and were assigned the Child-Pugh score for the degree of ascites while on diuretic treatment. The diuretic dose had to have been stable for 28 days prior to dosing.
- Transjugular intrahepatic portosystemic shunt and/or had undergone portacaval shunting.
- Acute HBV or HBC infection.
- Clinically significant abnormal findings in physical examination, ECG, or laboratory evaluations, not consistent with known clinical disease. Subjects having myocardial infarction ≥ 5 years ago were eligible to participate.
- Use of any prescription or non-prescription medication, dietary supplements, or vitamins that have the potential to interact with tropifexor during the study from dosing until the End of Study visit (Day 8) had been conducted. Hepatically impaired subjects had to be excluded if there have been changes in dose regimen of medically-required medication within 2 weeks prior to Screening or if there had been a significant change or addition to their routine medication (prescribed) within 1 month prior to drug administration. Minor changes to medication that require frequent dose adjustments, such as insulin or analgesia, can be made up to 2 weeks prior to drug administration, as agreed between the Investigator and Novartis.

- A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at Screening and/or pretreatment:
  - PR > 225 msec.
  - QRS complex > 120 msec.
  - QTcF > 470 msec (males).
  - QTcF > 460 (females).
- Presence of moderate to severe impaired renal function as indicated by any or all of the following criteria:
  - Creatinine clearance < 45 mL/min as calculated using the Cockroft-Gault formula or eGFR < 45 mL/min/1.73 m2 based on MDRD calculation.
  - Serum creatinine > 1.5 × ULN.
- Encephalopathy Grade 3 or worse within 28 days of planned dosing.
- Primary biliary cholangitis or biliary obstruction.
- History of gastrointestinal bleeding within the past 3 months prior to Screening.

Group 4 (Subjects with severe hepatic impairment)

- Hepatically impaired subjects with abnormal laboratory values for the following parameters:
  - Hemoglobin < 8.5 g/dL.
  - Platelet count < 30 × 109/L.
  - White blood cell count < 2.5 × 109/L.
  - Total bilirubin > 8 mg/dL.
  - Serum amylase > 2 × ULN.
  - International standardized ratio (INR) > 2.3.

- Severe complications of liver disease within the preceding 3 months.
- Emergency room visit or hospitalization due to liver disease within the preceding 1 month.
- Subject who had received liver transplant at any time in the past and was on immunosuppressant therapy.
- Subjects requiring paracentesis more than every 30 days for the management of ascites were excluded. Subjects who were receiving diuretics to manage ascites could be enrolled and were assigned the Child-Pugh score for the degree of ascites while on diuretic treatment. The diuretic dose had to have been stable for 28 days prior to dosing.
- Transjugular intrahepatic portosystemic shunt and/or have undergone portacaval shunting.
- Acute HBV or HCV infection.
- Clinically significant abnormal findings in physical examination, ECG, or laboratory evaluations, not consistent with known clinical disease. Subjects having myocardial infarction ≥ 5 years ago were eligible to participate.
- Use of any prescription or non-prescription medication, dietary supplements, or vitamins that have the potential to interact with tropifexor during the study from dosing until the End of Study visit (Day 8) had been conducted. Hepatically impaired subjects were excluded if there had been changes in the dose or schedule of medically-required medication within 2 weeks prior to Screening or if there had been a change or addition to their routine medication (prescribed) within 1 month prior to drug administration, except for changes to medication that require frequent dose adjustments, such as insulin or analgesia, which could be made within 2 weeks prior to drug administration, as agreed between the Investigator and Novartis.
- A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at Screening and/or pretreatment:
  - PR > 225 msec.
  - QRS complex > 120.
  - QTcF > 480 msec (males).
  - QTcF > 480 (females).
- Presence of moderate to severe impaired renal function as indicated by any or all of the following criteria:

- Creatinine clearance < 45 mL/min as calculated using the Cockroft-Gault formula or eGFR < 45 mL/min/1.73 m2 based on MDRD calculation.
- Serum creatinine > 1.5 × ULN.

- Encephalopathy Grade 3 or worse within 28 days of planned dosing.
- Primary biliary cholangitis or biliary obstruction.
- History of gastrointestinal bleeding within the past 3 months prior to Screening.

Participant Flow Table

Study phase subject disposition – n (percent) of subjects (Safety analysis set)

	Normal N = 18 n (%)	Mild N = 8 n (%)	Moderate N = 8 n (%)	Severe N = 8 n (%)	Total N = 42 n (%)
Subjects					
Completed the study	17 (94.4)	8 (100.0)	8 (100.0)	8 (100.0)	41 (97.6)
Discontinued	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Primary reason for discontinuation					
Subject/guardian decision	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)

N = Number of subjects in the safety analysis set.
Percentages were based upon the number of subjects in the safety analysis set.

Baseline Characteristics

Subject demographics by hepatic function groups and matching normal group (Safety analysis set)

		Normal All N = 18 n (%)	Normal (Paired with Mild) N = 6 n (%)	Mild N = 8 n (%)	Normal (Paired with Moderate) N = 9 n (%)	Moderate N = 8 n (%)	Normal (Paired with Severe) N = 5 n (%)	Severe N = 8 n (%)	Total N = 42 [a] n (%)
Age (years)	Mean (SD)	48.8 (10.83)	50.3 (9.91)	52.8 (12.01)	47.2 (11.53)	49.8 (13.30)	52.6 (10.62)	56.0 (8.02)	51.1 (11.06)
	Median	51.5	52.5	59.0	51.0	55.0	53.0	56.0	52.5
	Range	30 - 65	36 - 61	32 - 63	30 - 64	26 - 62	37 - 65	46 - 68	26 - 68
Sex - n(%)	Male	13 (72.2)	5 (83.3)	7 (87.5)	6 (66.7)	5 (62.5)	4 (80.0)	7 (87.5)	32 (76.2)
	Female	5 (27.8)	1 (16.7)	1 (12.5)	3 (33.3)	3 (37.5)	1 (20.0)	1 (12.5)	10 (23.8)
Childbearing status - n(%)	Able to Bear Children	0	0	1 (100.0)	0	0	0	0	1 (10.0)
	Post Menopausal	3 (60.0)	0	0	2 (66.7)	3 (100.0)	1 (100.0)	1 (100.0)	7 (70.0)
	Sterile - of Child Bearing Age	2 (40.0)	1 (100.0)	0	1 (33.3)	0	0	0	2 (20.0)

		Normal All N = 18 n (%)	Normal (Paired with Mild) N = 6 n (%)	Mild N = 8 n (%)	Normal (Paired with Moderate) N = 9 n (%)	Moderate N = 8 n (%)	Normal (Paired with Severe) N = 5 n (%)	Severe N = 8 n (%)	Total N = 42 [a] n (%)
Race - n(%)	White	13 (72.2)	4 (66.7)	6 (75.0)	7 (77.8)	6 (75.0)	3 (60.0)	6 (75.0)	31 (73.8)
	Black or African American	5 (27.8)	2 (33.3)	1 (12.5)	2 (22.2)	2 (25.0)	2 (40.0)	2 (25.0)	10 (23.8)
	Asian	0	0	1 (12.5)	0	0	0	0	1 (2.4)
Ethnicity - n(%)	Hispanic or Latino	5 (27.8)	2 (33.3)	1 (12.5)	3 (33.3)	0	0	1 (12.5)	7 (16.7)
	Mixed Ethnicity	1 (5.6)	1 (16.7)	0	0	0	0	0	1 (2.4)
	Not Reported	6 (33.3)	3 (50.0)	4 (50.0)	3 (33.3)	4 (50.0)	2 (40.0)	1 (12.5)	15 (35.7)
	Unknown	0	0	0	0	1 (12.5)	0	0	1 (2.4)
	Other	6 (33.3)	0	3 (37.5)	3 (33.3)	3 (37.5)	3 (60.0)	6 (75.0)	18 (42.9)
Smoking status - n(%)	Never	8 (44.4)	4 (66.7)	2 (25.0)	2 (22.2)	2 (25.0)	2 (40.0)	1 (12.5)	13 (31.0)
	Current	8 (44.4)	2 (33.3)	4 (50.0)	5 (55.6)	4 (50.0)	3 (60.0)	5 (62.5)	21 (50.0)
	Former	2 (11.1)	0	2 (25.0)	2 (22.2)	2 (25.0)	0	2 (25.0)	8 (19.0)
Weight (kg)	Mean (SD)	88.44 (20.332)	86.48 (13.817)	88.44 (14.796)	94.62 (24.376)	96.15 (26.594)	81.56 (15.048)	81.46 (9.235)	88.58 (19.110)
	Median	86.80	85.75	86.70	101.60	97.75	84.70	80.10	86.80
	Range	51.3 – 122.7	70.6 – 102.8	68.4 – 107.3	51.3 – 122.7	55.3 – 130.6	62.0 – 101.7	65.7 – 94.2	51.3 – 130.6
Height (cm)	Mean (SD)	173.85 (11.627)	176.72 (10.233)	168.26 (8.308)	174.18 (12.673)	172.83 (12.585)	174.60 (14.135)	172.64 (7.854)	172.36 (10.475)
	Median	177.65	178.40	170.00	178.00	173.35	179.60	171.00	173.15
	Range	151.2 - 192.0	165.0 - 192.0	155.4 - 178.0	151.2 - 187.0	158.1 - 195.3	156.2 - 192.0	162.0 - 184.6	151.2 - 195.3

		Normal All N = 18 n (%)	Normal (Paired with Mild) N = 6 n (%)	Mild N = 8 n (%)	Normal (Paired with Moderate) N = 9 n (%)	Moderate N = 8 n (%)	Normal (Paired with Severe) N = 5 n (%)	Severe N = 8 n (%)	Total N = 42 [a] n (%)
Body Mass Index (kg/m^2)	Mean (SD)	29.071 (5.2143)	27.570 (2.6014)	31.115 (3.7864)	30.907 (6.2892)	31.834 (6.5306)	26.708 (3.5453)	27.404 (3.2807)	29.669 (5.0320)
	Median	27.075	26.525	30.610	33.800	34.225	26.260	27.730	29.870
	Range	21.39 - 38.01	25.78 - 32.74	26.07 - 36.70	21.39 - 38.01	20.81 - 37.93	22.28 - 32.00	22.63 - 31.84	20.81 - 38.01

[a] The total includes normal, mild, moderate, and severe groups only. Subjects paired with each respective group (N) are not counted under the total. Each healthy subject (Group 1) was matched to one or more corresponding, hepatically impaired subjects.

BMI = body mass index; N = number of subjects screened; n = number of subjects in each category; SD = standard deviation.
Percentages (except for Child bearing status) were based upon the number of subjects in the safety analysis set.
Percentages for Child bearing status were based upon the number of female subjects in the safety analysis set.
Weight (kg), height (cm), and BMI (kg/m^2) were taken from screening vital signs evaluations.

Primary Outcome Result(s)

Summary statistics for plasma PK parameters of tropifexor (total) by hepatic function groups and matching normal group (Pharmacokinetic analysis set)

Hepatic function group	Statistics	Cmax (ng/mL)	Tmax (h)	AUClast (ng*h/mL)	AUCinf (ng*h/mL)	T1/2 (h)	CL/F (L/h)	Vz/F (L)
Normal (paired with mild) (N = 6)	n	6	6	6	6	6	6	6
	Mean (SD)	4.03 (2.29)		76.7 (24.9)	77.4 (24.9)	14.5 (4.46)	2.85 (1.01)	63.9 (39.5)
	CV% mean	56.8		32.4	32.1	30.9	35.3	61.8
	Geo-mean	3.42		73.1	73.8	13.9	2.71	54.4
	CV% Geo-mean	74.6		35.9	35.6	30.7	35.6	68.7
	Median	3.88	4.00	81.7	82.4	14.1	2.50	51.1
	[Min; Max]	[1.31; 6.70]	[4.00; 8.00]	[46.8; 101]	[47.4; 101]	[9.67; 21.9]	[1.98; 4.22]	[27.6; 123]
Mild (N = 8)	n	8	8	8	8	8	8	8
	Mean (SD)	3.46 (1.40)		83.1 (32.1)	84.5 (32.9)	19.4 (12.6)	2.81 (1.43)	68.8 (29.1)
	CV% mean	40.7		38.6	39.0	64.9	51.0	42.2
	Geo-mean	3.15		76.9	78.2	17.2	2.56	63.6
	CV% Geo-mean	52.7		46.4	46.5	49.5	46.5	44.5
	Median	3.76	4.00	83.8	84.2	14.4	2.38	58.8
	[Min; Max]	[1.23; 5.17]	[2.00; 8.00]	[33.0; 129]	[33.6; 130]	[11.2; 49.7]	[1.54; 5.96]	[36.8; 113]

Hepatic function group	Statistics	Cmax (ng/mL)	Tmax (h)	AUClast (ng*h/mL)	AUCinf (ng*h/mL)	T1/2 (h)	CL/F (L/h)	Vz/F (L)
Normal (paired with moderate) (N = 9)	n	9	9	8	8	8	8	8
	Mean (SD)	3.76 (0.912)		86.6 (34.0)	88.4 (36.2)	19.3 (15.2)	2.54 (0.799)	58.3 (17.8)
	CV% mean	24.3		39.2	40.9	79.1	31.4	30.6
	Geo-mean	3.66		81.6	82.9	16.2	2.41	56.5
	CV% Geo-mean	24.1		36.7	37.8	59.6	37.8	25.3
	Median	3.60	4.00	67.0	67.7	13.3	2.95	52.2
	[Min; Max]	[2.74; 5.27]	[2.00; 8.07]	[58.1; 152]	[58.9; 160]	[10.4; 56.0]	[1.25; 3.40]	[46.4; 101]
Moderate (N = 8)	n	8	8	8	8	8	8	8
	Mean (SD)	4.33 (2.29)		116 (61.2)	117 (61.7)	20.6 (9.69)	2.07 (0.910)	59.7 (37.0)
	CV% mean	52.9		53.0	52.6	47.1	43.9	61.9
	Geo-mean	3.81		104	106	18.7	1.89	51.0
	CV% Geo-mean	59.5		50.3	50.0	49.6	50.0	64.1
	Median	4.14	6.00	104	108	17.9	1.88	39.5
	[Min; Max]	[1.90; 7.88]	[4.00; 10.00]	[52.9; 249]	[53.5; 252]	[9.39; 37.7]	[0.794; 3.74]	[27.3; 115]

Hepatic function group	Statistics	Cmax (ng/mL)	Tmax (h)	AUClast (ng*h/mL)	AUCinf (ng*h/mL)	T1/2 (h)	CL/F (L/h)	Vz/F (L)
Normal (paired with severe) (N = 5)	n	5	5	5	5	5	5	5
	Mean (SD)	4.98 (1.97)		83.5 (15.9)	84.2 (15.8)	12.5 (5.48)	2.44 (0.458)	46.2 (28.0)
	CV% mean	39.6		19.1	18.8	43.8	18.8	60.7
	Geo-mean	4.61		82.3	83.1	11.6	2.41	40.4
	CV% Geo-mean	48.0		19.4	19.1	43.9	19.1	61.0
	Median	5.99	4.00	81.9	82.7	10.5	2.42	30.3
	[Min; Max]	[2.51; 6.70]	[4.00; 8.00]	[67.0; 101]	[67.8; 101]	[6.96; 21.1]	[1.98; 2.95]	[24.3; 89.8]
Severe (N = 8)	n	8	8	8	8	8	8	8
	Mean (SD)	3.35 (1.93)		92.7 (46.6)	93.4 (46.7)	19.8 (6.13)	2.64 (1.21)	72.6 (33.4)
	CV% mean	57.6		50.3	50.0	31.0	45.7	46.0
	Geo-mean	2.94		83.0	83.8	19.0	2.39	65.5
	CV% Geo-mean	56.8		53.1	52.8	29.8	52.8	53.7
	Median	2.51	8.00	66.6	67.3	18.0	2.97	69.4
	[Min; Max]	[1.68; 7.14]	[4.00; 10.00]	[41.9; 159]	[42.4; 160]	[13.1; 30.2]	[1.25; 4.72]	[28.5; 129]

CV% = coefficient of variation; CV% geo-mean = sqrt (exp [variance for log-transformed data]-1) × 10; CV% mean = coefficient of variation (%) (SD/mean × 100); Geo = geometric; h = hour; N = number of subjects screened; max = maximum; min = minimum; n = number of subjects in each category; PK = pharmacokinetic; SD = standard deviation.

Statistical analysis of pharmacokinetic parameters of tropifexor (total) (Pharmacokinetic analysis set)

Pharmacokinetic parameter (unit)	Hepatic function group	n	Least square geo-mean (90% CI)	Comparison (impaired/normal)	Group comparison		
					Geo-mean ration	90% CI	
						Lower	Upper
Cmax (ng*h/mL)	Normal	6	3.42 (2.24, 5.21)	Mild versus normal	0.90	0.52	1.55
	Mild	8	3.07 (2.05, 4.58)				
	Normal	9	3.66 (2.87, 4.67)	Moderate versus normal	1.03	0.74	1.44
	Moderate	8	3.78 (2.91, 4.89)				
	Normal	5	4.61 (3.08, 6.91)	Severe versus normal	0.64	0.38	1.07
	Severe	8	2.94 (2.14, 4.05)				
AUClast (ng*h/mL)	Normal	6	73.1 (54.2, 98.6)	Mild versus normal	1.04	0.71	1.53
	Mild	8	75.9 (57.1, 101)				
	Normal	8	81.6 (62.3, 107)	Moderate versus normal	1.28	1.02	1.59
	Moderate	8	104 (79.5, 136)				
	Normal	5	82.3 (59.0, 115)	Severe versus normal	1.01	0.66	1.54
	Severe	8	83.0 (63.8, 108)				
AUCinf (ng*h/mL)	Normal	6	73.8 (54.8, 99.5)	Mild versus normal	1.05	0.71	1.54
	Mild	8	77.2 (58.0, 103)				
	Normal	8	82.9 (63.1, 109)	Moderate versus normal	1.28	1.03	1.58
	Moderate	8	106 (80.5, 139)				
	Normal	5	83.1 (59.7, 116)	Severe versus normal	1.01	0.66	1.54
	Severe	8	83.8 (64.5, 109)				

CI = confidence interval; Geo = geometric; N = number of subjects screened; n = number of subjects in each category; PK = pharmacokinetic.
A separate linear mixed effects model, with group as a fixed effect and matched pair as random effect, was fitted to compare each hepatic impairment group with its matching control group for each log-transformed PK parameter. Results were back transformed to obtain least square geo-mean, geo-mean ratio, and 90% CI on the original scale.

Secondary Outcome Result(s)

Statistical assessment of relationship between PK parameters and hepatic function tests at baseline (Pharmacokinetic analysis set)

			Slope				Intercept				
PK parameter (unit)	Hepatic Function Parameter	n	Estimate	SE	90% CI	P Value	Esti-mate	SE	90% CI	P Value	Coeffi-cient of Determ-ination
Cmax (ng/mL)	Child-Pugh Score	24	-0.0234	0.0462	(-0.103,0.0560)	0.6182	1.37	0.376	(0.724,2.01)	0.0014	0.0115
	Total Bilirubin	42	0.00150	0.00358	(-0.00453,0.00752)	0.6777	1.20	0.0965	(1.04,1.36)	<.0001	0.0044
	Prothrombin Time	42	-0.0145	0.0276	(-0.0610,0.0320)	0.6022	1.42	0.376	(0.786,2.05)	0.0005	0.0069
	Albumin	42	0.0138	0.0101	(-0.00310,0.0308)	0.1766	0.673	0.407	(-0.0120,1.36)	0.1059	0.0452
	AST	42	-0.000829	0.00326	(-0.00632,0.00466)	0.8005	1.25	0.132	(1.03,1.47)	<.0001	0.0016

AST = aspartate aminotransferase; SE = standard error; CI = confidence interval.
Results are based on an ordinary least square regression of log PK parameters on the Child-Pugh score and liver function tests.
Analysis for Child-Pugh score excludes Normal hepatic group, since no such score is defined.

			Slope				Intercept				
PK parameter (unit)	Hepatic Function Parameter	n	Estimate	SE	90% CI	P Value	Esti-mate	SE	90% CI	P Value	Coeffi-cient of Determ-ination
AUClast (ng*h/mL)	Child-Pugh Score	24	0.00810	0.0424	(-0.0648,0.0810)	0.8505	4.41	0.345	(3.81,5.00)	<.0001	0.0017
	Total Bilirubin	41	0.00375	0.00307	(-0.00142,0.00892)	0.2290	4.35	0.0837	(4.21,4.49)	<.0001	0.0369
	Prothrombin Time	41	0.00695	0.0240	(-0.0336,0.0475)	0.7741	4.32	0.327	(3.77,4.88)	<.0001	0.0021
	Albumin	41	0.00387	0.00894	(-0.0112,0.0189)	0.6674	4.26	0.362	(3.65,4.87)	<.0001	0.0048
	AST	41	0.00213	0.00283	(-0.00263,0.00690)	0.4554	4.34	0.116	(4.15,4.54)	<.0001	0.0144

AST = aspartate aminotransferase; SE = standard error; CI = confidence interval.
Results are based on an ordinary least square regression of log PK parameters on the Child-Pugh score and liver function tests.
Analysis for Child-Pugh score excludes Normal hepatic group, since no such score is defined.

			Slope				Intercept				
PK parameter (unit)	Hepatic Function Parameter	n	Estimate	SE	90% CI	P Value	Esti-mate	SE	90% CI	P Value	Coeffi-cient of Determ-ination
AUCinf (ng*h/mL)	Child-Pugh Score	24	0.00702	0.0423	(-0.0657,0.0797)	0.8699	4.43	0.344	(3.84,5.02)	<.0001	0.0012
	Total Bilirubin	41	0.00362	0.00308	(-0.00156,0.00881)	0.2461	4.37	0.0839	(4.22,4.51)	<.0001	0.0343
	Prothrombin Time	41	0.00609	0.0241	(-0.0345,0.0467)	0.8018	4.35	0.328	(3.80,4.90)	<.0001	0.0016
	Albumin	41	0.00399	0.00895	(-0.0111,0.0191)	0.6582	4.27	0.363	(3.66,4.88)	<.0001	0.0051
	AST	41	0.00205	0.00283	(-0.00272,0.00683)	0.4732	4.36	0.116	(4.17,4.56)	<.0001	0.0133

AST = aspartate aminotransferase; SE = standard error; CI = confidence interval.
Results are based on an ordinary least square regression of log PK parameters on the Child-Pugh score and liver function tests.
Analysis for Child-Pugh score excludes Normal hepatic group, since no such score is defined.

PK parameter (unit)	Hepatic Function Parameter	n	Slope				Intercept				Coefficient of Determination
			Estimate	SE	90% CI	P Value	Estimate	SE	90% CI	P Value	
CL/F (L/h)	Child-Pugh Score	24	-0.0256	0.108	(-0.211,0.159)	0.8140	2.71	0.875	(1.20,4.21)	0.0053	0.0026
	Total Bilirubin	41	-0.00819	0.00775	(-0.0213,0.00487)	0.2973	2.73	0.211	(2.37,3.08)	<.0001	0.0278
	Prothrombin Time	41	-0.0121	0.0605	(-0.114,0.0899)	0.8428	2.74	0.823	(1.36,4.13)	0.0019	0.0010
	Albumin	41	-0.0160	0.0224	(-0.0537,0.0217)	0.4799	3.22	0.908	(1.69,4.75)	0.0010	0.0129
	AST	41	-0.00432	0.00713	(-0.0163,0.00770)	0.5484	2.73	0.291	(2.24,3.22)	<.0001	0.0093

AST = aspartate aminotransferase; SE = standard error; CI = confidence interval.
Results are based on an ordinary least square regression of log PK parameters on the Child-Pugh score and liver function tests.
Analysis for Child-Pugh score excludes Normal hepatic group, since no such score is defined.

Summary statistics for plasma PK parameters of tropifexor (unbound) by hepatic function groups and matching normal group (Pharmacokinetic analysis set)

Hepatic function group	Statistics	Cmax,u (ng/mL)	AUClast,u (ng*h/mL)	AUCinf,u (ng*h/mL)	CL/F,u (L/h)	fu
Normal (paired with mild) (N = 6)	n	6	6	6	6	6
	Mean (SD)	0.00554 (0.00383)	0.103 (0.0452)	0.104 (0.0454)	2250 (956)	0.00132 (0.00028)
	CV% mean	69.3	44.0	43.7	42.5	21.4
	Geo-mean	0.00444	0.0950	0.0960	2080	0.00130
	CV% Geo-mean	87.8	45.6	45.4	45.4	20.6
	Median	0.00459	0.0971	0.0980	2040	0.00128
	[Min; Max]	[0.00147; 0.0118]	[0.0524; 0.180]	[0.0530; 0.181]	[1100; 3770]	[0.00102; 0.00182]
Mild (N = 8)	n	8	8	8	8	8
	Mean (SD)	0.00482 (0.00202)	0.116 (0.0470)	0.118 (0.0482)	2060 (1170)	0.00139 (0.00008)
	CV% mean	41.9	40.5	40.9	56.7	5.8
	Geo-mean	0.00436	0.107	0.108	1850	0.00138
	CV% Geo-mean	55.8	49.9	50.0	50.0	5.9
	Median	0.00516	0.114	0.115	1750	0.00140
	[Min; Max]	[0.00155; 0.00744]	[0.0416; 0.186]	[0.0423; 0.187]	[1070; 4730]	[0.00126; 0.00151]

Hepatic function group	Statistics	Cmax,u (ng/mL)	AUClast,u (ng*h/mL)	AUCinf,u (ng*h/mL)	CL/F,u (L/h)	fu
Normal (paired with moderate) (N = 9)	n	9	8	8	8	9
	Mean (SD)	0.00527 (0.00155)	0.117 (0.0460)	0.119 (0.0495)	1880 (587)	0.00142 (0.00033)
	CV% mean	29.5	39.3	41.4	31.3	23.2
	Geo-mean	0.00508	0.110	0.112	1780	0.00138
	CV% Geo-mean	29.4	35.9	37.3	37.3	22.0
	Median	0.00511	0.104	0.105	1920	0.00128
	[Min; Max]	[0.00328; 0.00809]	[0.0787; 0.215]	[0.0792; 0.227]	[882; 2520]	[0.00108; 0.00210]
Moderate (N = 8)	n	8	8	8	8	8
	Mean (SD)	0.00751 (0.00378)	0.218 (0.144)	0.223 (0.152)	1290 (743)	0.00199 (0.00140)
	CV% mean	50.3	66.1	68.2	57.6	70.5
	Geo-mean	0.00663	0.181	0.184	1090	0.00174
	CV% Geo-mean	59.6	71.7	73.1	73.1	50.9
	Median	0.00632	0.195	0.197	1020	0.00151
	[Min; Max]	[0.00295; 0.0130]	[0.0874; 0.489]	[0.0887; 0.518]	[386; 2250]	[0.00116; 0.00541]

Hepatic function group	Statistics	Cmax,u (ng/mL)	AUClast,u (ng*h/mL)	AUCinf,u (ng*h/mL)	CL/F,u (L/h)	fu
Normal (paired with severe) (N = 5)	n	5	5	5	5	5
	Mean (SD)	0.00748 (0.00323)	0.126 (0.0319)	0.127 (0.0319)	1640 (336)	0.00151 (0.00021)
	CV% mean	43.2	25.3	25.1	20.4	14.2
	Geo-mean	0.00689	0.123	0.124	1610	0.00149
	CV% Geo-mean	49.0	23.3	23.1	23.1	14.3
	Median	0.00817	0.120	0.122	1650	0.00149
	[Min; Max]	[0.00384; 0.0118]	[0.102; 0.180]	[0.104; 0.181]	[1100; 1930]	[0.00122; 0.00182]
Severe (N = 8)	n	8	8	8	8	8
	Mean (SD)	0.00794 (0.00419)	0.222 (0.115)	0.224 (0.116)	1110 (529)	0.00244 (0.00055)
	CV% mean	52.8	52.1	51.9	47.5	22.6
	Geo-mean	0.00700	0.198	0.200	1000	0.00238
	CV% Geo-mean	58.5	54.4	54.1	54.1	22.7
	Median	0.00658	0.183	0.185	1090	0.00234
	[Min; Max]	[0.00304; 0.0141]	[0.0988; 0.438]	[0.100; 0.441]	[453; 2000]	[0.00181; 0.00329]

CV% = coefficient of variation; CV% geo-mean = sqrt (exp [variance for log-transformed data]-1) × 10, CV% mean = coefficient of variation (%) (SD/mean × 100); Geo = geometric; N = number of subjects screened; n = number of subjects in each category; PK = pharmacokinetic; SD = standard deviation.

Statistical analysis of pharmacokinetic parameters of tropifexor (unbound) (Pharmacokinetic analysis set)

					Group comparison		
						90% CI	
Pharmacokinetic parameter (unit)	Hepatic function group	n	Least square geo-mean (90% CI)	Comparison (impaired/normal)	Geo-mean ration	Lower	Upper
Cmax,u (ng*h/mL)	Normal	6	0.00444 (0.00280, 0.00705)	Mild versus normal	0.95	0.52	1.75
	Mild	8	0.00424 (0.00274, 0.00656)				
	Normal	9	0.00508 (0.00394, 0.00654)	Moderate versus normal	1.30	0.96	1.76
	Moderate	8	0.00658 (0.00504, 0.00860)				
	Normal	5	0.00689 (0.00456, 0.0104)	Severe versus normal	1.02	0.60	1.72
	Severe	8	0.00700 (0.00505, 0.00971)				
AUClast,u (ng*h/mL)	Normal	6	0.0950 (0.0680, 0.133)	Mild versus normal	1.11	0.70	1.74
	Mild	8	0.105 (0.0765, 0.144)				
	Normal	8	0.110 (0.0791, 0.154)	Moderate versus normal	1.64	1.26	2.15
	Moderate	8	0.181 (0.130, 0.253)				
	Normal	5	0.123 (0.0870, 0.173)	Severe versus normal	1.61	1.04	2.50
	Severe	8	0.198 (0.151, 0.260)				
AUCinf,u (ng*h/mL)	Normal	6	0.0960 (0.0687, 0.134)	Mild versus normal	1.11	0.71	1.75
	Mild	8	0.107 (0.0777, 0.147)				
	Normal	8	0.112 (0.0798, 0.158)	Moderate versus normal	1.64	1.25	2.16
	Moderate	8	0.184 (0.131, 0.259)				
	Normal	5	0.124 (0.0881, 0.175)	Severe versus normal	1.61	1.04	2.49
	Severe	8	0.200 (0.152, 0.262)				

CI = confidence interval; Geo = geometric; N = number of subjects screened; n = number of subjects in each category; PK = pharmacokinetic.
A separate linear mixed effects model, with group as a fixed effect and matched pair as random effect, was fitted to compare each hepatic impairment group with its matching control group for each log-transformed PK parameter. Results were back transformed to obtain least square geo-mean, geo-mean ratio, and 90% CI on the original scale.

Statistical assessment of relationship between PK parameters (unbound) and hepatic function tests at baseline (Pharmacokinetic analysis set)

			Slope				Intercept				
PK parameter (unit)	Hepatic Function Parameter	n	Estimate	SE	90% CI	P Value	Estimate	SE	90% CI	P Value	Coefficient of Determination
Cmax,u (ng/mL)	Child-Pugh Score	24	0.0818	0.0473	(0.000542, 0.163)	0.0979	-5.78	0.385	(-6.44, -5.11)	<.0001	0.1196
	Total Bilirubin	42	0.00928	0.00372	(0.00302, 0.0155)	0.0168	-5.37	0.100	(-5.54, -5.21)	<.0001	0.1347
	Prothrombin Time	42	0.0386	0.0303	(-0.0124, 0.0895)	0.2097	-5.73	0.412	(-6.42, -5.04)	<.0001	0.0391
	Albumin	42	-0.0163	0.0112	(-0.0351, 0.00255)	0.1533	-4.57	0.452	(-5.33, -3.80)	<.0001	0.0503
	AST	42	0.00500	0.00355	(-0.000972, 0.0110)	0.1663	-5.38	0.144	(-5.62, -5.14)	<.0001	0.0473

AST = aspartate aminotransferase; SE = standard error; CI = confidence interval.
Results are based on an ordinary least square regression of log PK parameters on the Child-Pugh score and liver function tests.
Analysis for Child-Pugh score excludes Normal hepatic group, since no such score is defined.

PK parameter (unit)	Hepatic Function Parameter	n	Slope				Intercept				Coefficient of Determination
			Estimate	SE	90% CI	P Value	Estimate	SE	90% CI	P Value	
AUClast,u (ng*h/mL)	Child-Pugh Score	24	0.113	0.0478	(0.0312, 0.195)	0.0270	-2.74	0.388	(-3.41, -2.07)	<.0001	0.2034
	Total Bilirubin	41	0.0116	0.00363	(0.00549, 0.0177)	0.0028	-2.23	0.0990	(-2.39, -2.06)	<.0001	0.2076
	Prothrombin Time	41	0.0600	0.0299	(0.00963, 0.110)	0.0517	-2.82	0.407	(-3.51, -2.14)	<.0001	0.0936
	Albumin	41	-0.0263	0.0109	(-0.0447, -0.00791)	0.0207	-0.975	0.442	(-1.72, -0.230)	0.0335	0.1297
	AST	41	0.00805	0.00348	(0.00218, 0.0139)	0.0263	-2.30	0.142	(-2.54, -2.06)	<.0001	0.1204

AST = aspartate aminotransferase; SE = standard error; CI = confidence interval.
Results are based on an ordinary least square regression of log PK parameters on the Child-Pugh score and liver function tests.
Analysis for Child-Pugh score excludes Normal hepatic group, since no such score is defined.

PK parameter (unit)	Hepatic Function Parameter	n	Slope				Intercept				Coefficient of Determination
			Estimate	SE	90% CI	P Value	Estimate	SE	90% CI	P Value	
AUCinf,u (ng*h/mL)	Child-Pugh Score	24	0.112	0.0481	(0.0296, 0.195)	0.0293	-2.72	0.391	(-3.39, -2.05)	<.0001	0.1982
	Total Bilirubin	41	0.0115	0.00366	(0.00530, 0.0176)	0.0033	-2.21	0.0999	(-2.38, -2.04)	<.0001	0.2010
	Prothrombin Time	41	0.0591	0.0301	(0.00842, 0.110)	0.0566	-2.80	0.410	(-3.49, -2.11)	<.0001	0.0900
	Albumin	41	-0.0262	0.0110	(-0.0446, -0.00767)	0.0221	-0.966	0.445	(-1.72, -0.216)	0.0361	0.1272
	AST	41	0.00797	0.00351	(0.00206, 0.0139)	0.0287	-2.28	0.143	(-2.52, -2.04)	<.0001	0.1168

AST = aspartate aminotransferase; SE = standard error; CI = confidence interval.
Results are based on an ordinary least square regression of log PK parameters on the Child-Pugh score and liver function tests.
Analysis for Child-Pugh score excludes Normal hepatic group, since no such score is defined.

PK parameter (unit)	Hepatic Function Parameter	n	Slope				Intercept				Coefficient of Determination
			Estimate	SE	90% CI	P Value	Estimate	SE	90% CI	P Value	
CL/F,u (L/h)	Child-Pugh Score	24	-165	75.3	(-294, -35.9)	0.0391	2770	612	(1720, 3820)	0.0002	0.1795
	Total Bilirubin	41	-13.9	6.13	(-24.3, -3.61)	0.0286	1940	167	(1660, 2230)	<.0001	0.1171
	Prothrombin Time	41	-54.8	49.5	(-138, 28.6)	0.2749	2430	673	(1300, 3560)	0.0009	0.0305
	Albumin	41	33.4	17.9	(3.27, 63.6)	0.0694	366	726	(-858, 1590)	0.6174	0.0821
	AST	41	-12.0	5.63	(-21.4, -2.49)	0.0397	2110	230	(1720, 2490)	<.0001	0.1040

AST = aspartate aminotransferase; SE = standard error; CI = confidence interval.
Results are based on an ordinary least square regression of log PK parameters on the Child-Pugh score and liver function tests.
Analysis for Child-Pugh score excludes Normal hepatic group, since no such score is defined.

Safety Results

Incidence of treatment-emergent adverse events by system organ class – n (percent) of subjects (Safety analysis set)

Primary system organ class	Normal N = 18 n (%)	Mild N = 8 n (%)	Moderate N = 8 n (%)	Severe N = 8 n (%)	Total N = 42 n (%)
Number of subjects with at least one TEAE	2 (11.1)	0 (0.0)	1 (12.5)	2 (25.0)	5 (11.9)
Injury, poisoning and procedural complications	1 (5.6)	0 (0.0)	0 (0.0)	1 (12.5)	2 (4.8)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (2.4)
General disorders and administration site conditions	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Nervous system disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (2.4)

N = number of subjects in the safety analysis set; n = number of subjects with at least one TEAE in the category; TEAE = treatment-emergent adverse event.
A subject with multiple TEAEs was counted only once in the “at least one TEAE” row.
A subject with multiple TEAEs within a primary system organ class was counted only once for that system organ class and hepatic function group.
Arranged in descending order of frequency, as reported in the 'Total' column and alphabetically by system organ class.

Incidence of treatment-emergent adverse events by preferred term – n (percent) of subjects (Safety analysis set)

Preferred term	Normal N = 18 n (%)	Mild N = 8 n (%)	Moderate N = 8 n (%)	Severe N = 8 n (%)	Total N = 42 n (%)
Number of subjects with at least one TEAE	2 (11.1)	0 (0.0)	1 (12.5)	2 (25.0)	5 (11.9)
Ascites	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (2.4)
Constipation	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (2.4)
Hepatic encephalopathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (2.4)
Infusion site extravasation	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Multiple fractures	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (2.4)
Vascular procedure complication	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)

N = number of subjects in the safety analysis set; n = number of subjects with at least one TEAE in the category; TEAE = treatment-emergent adverse event.
A subject with multiple TEAEs was counted only once in the “at least one TEAE” row.
A subject with multiple TEAEs with the same preferred term was counted only once for that preferred term and group.
Preferred terms were sorted in descending frequency, as reported in the 'Total' column.

Serious Adverse Events and Deaths

There were 2 SAEs (multiple fractures [the subject fell off a roof] and hepatic encephalopathy) reported in this study for subjects in Group 4 (severe).

No deaths were reported in this study.

Conclusion:

- A single oral dose of 200 µg tropifexor was well-tolerated in subjects with normal hepatic function as well as by subjects with mild, moderate, and severe hepatic impairment enrolled in this study.
- There was no relevant increase in exposure to total tropifexor in subjects with mild, moderate and severe hepatic impairment. However, exposure to unbound tropifexor was increased in subjects with moderate and severe hepatic impairment compared with their healthy controls.
- The safety and efficacy profile for doses planned in future studies will determine if dose adjustments in patients with moderate and/or severe hepatic impairment will be warranted based on the observed increase in tropifexor unbound AUC.

Date of Clinical Study Report

09-Jun-2020