NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Fevipiprant

Trial Indication(s)

Asthma

Protocol Number

CQAW039A2108

Protocol Title

An open-label, single-dose, parallel-group study to assess the pharmacokinetics of Fevipiprant (QAW039) in patients with hepatic impairment compared to matched healthy subjects

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: May 2017 (Actual)
Primary Completion Date: April 2019 (Actual)
Study Completion Date: April 2019 (Actual)

Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

This was a phase I, open-label, parallel group study to assess the pharmacokinetics (PK) and safety of a single oral dose (450 mg) fevipiprant in patients with hepatic impairment and healthy subjects with demographically-matched normal hepatic function. The study was designed to determine if the pharmacokinetic profile of fevipiprant is different in patients with hepatic impairment compared to healthy matched subjects to an extent that would require an adjustment of the dosage. Data from this study contributes information on how to treat patients who have a therapeutic need for fevipiprant and have hepatic failure as comorbidity.

The study was comprised of a 14-day Screening period, including the Baseline visit, and a single-dose Treatment period of up to 14 days.

Patients were assigned to a hepatic impairment group based on hepatic function (according to the Child-Pugh classification) as determined at the Screening visit: mild hepatic impairment, moderate hepatic function, or severe hepatic impairment. Healthy subjects were matched by age, gender, smoking status and weight. A single healthy subject could be a match to a maximum of 3 different patients with hepatic impairment of 3 different severity groups.

Centers

United States(2)

Objectives:

Primary objective:

- To characterize the PK of fevipiprant after a single oral dose of fevipiprant in patients with hepatic impairment compared to healthy matched control subjects.

Secondary objectives:

- To assess the safety and tolerability of fevipiprant in patients with hepatic impairment and healthy matched controls.
- To assess the relationship between fevipiprant PK in plasma and Baseline hepatic function.
- To characterize the pharmacokinetics of the metabolite CCN362 following a single oral dose of fevipiprant in patients with hepatic impairment compared to healthy matched control subjects.

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

Fevipiprant film coated tablet was administered to the subjects at a single dose of 450 mg. Fevipiprant was administered to all subjects by the study center personnel via the oral route of administration with 240 mL of water in the morning on Day 1 of the 12-day Treatment period.

Statistical Methods

Log-transformed PK parameters (Cmax, AUClast and AUCinf) were analyzed separately using a linear mixed effects model with subject group as fixed effect and matched pair as random effect. Least square means for each subject group as well as contrasts between matched healthy and each hepatic impairment group with corresponding 90% confidence intervals (CIs) on the log-scale were calculated. Results were back transformed to provide ratio of geometric means (GMR) and 90% CIs. Separate models were fit for each comparison due to the fact that healthy subjects were matched to more than one hepatic patient from each impairment group.

A similar analysis as mentioned above as part of secondary endpoints was performed for PK parameters of CCN362.

Regression analysis for baseline hepatic function parameters (bilirubin, albumin) vs. plasma PK as well as regression analysis for relationship between Child-Pugh score and relevant PK parameters was performed. The plasma concentration data was listed by analyte, hepatic impairment group, matching healthy subject group, and sampling time point.

The assessment of safety was based mainly on the frequency of AEs and on the assessment of laboratory values that fell outside of pre-determined ranges.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
All subjects
- Male and female subjects aged 18 to 70 years of age inclusive.
- Weight of at least 50 kg and no more than 120 kg and with a body mass index in the range 18.0-36.0 kg/m2.

Patients with hepatic impairment
-Moderate hepatic impairment: Child-Pugh Class B (7-9 points).
-Severe hepatic impairment: Child-Pugh Class C (10-15 points).
-Mild hepatic impairment: Child-Pugh Class A (5-6 points).

Healthy subjects
- Each subject was required to match in age (±5 years), gender, smoking status, and weight (± 15%) to an individual patient.
- In good health as determined by past medical history, physical examination, electrocardiogram, laboratory tests and urinalysis at screening.

Exclusion Criteria:
All subjects
- History of hypersensitivity and/or idiosyncracies to fevipiprant or to drugs of similar classes (CRTh2 antagonists).
- Use of co-medications that could impact fevipiprant exposure such as broad range UGT inhibitors or strong inhibitors of OAT3, OATP1B3, and P-gp, including but not limited to probenecid, ritonavir, valproic acid, and rifampin.
- Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which might jeopardize the subject in case of participation in the study.
- History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there was evidence of local recurrence or metastases.
- Pregnant or nursing (lactating) women.
- Women of child-bearing potential.

Patients with hepatic impairment
- Hepatic impairment due to non-liver disease (e.g., right heart failure).
- Current symptoms or history of encephalopathy Grade III or IV within the past 6 months.
- Primary biliary liver cirrhosis and biliary obstruction.
- Emergency room visit or hospitalization due to liver disease within the preceding 3 months.
- Severe complications of liver disease within the preceding 3 months.

Healthy subjects
- Liver disease or liver injury as indicated by abnormal liver function tests.
- Any single parameter of ALT, AST, γ-GT, alkaline phosphatase or serum bilirubin could not exceed 1.5 x upper limit of normal (ULN).
- Any elevation above ULN of more than one parameter of ALT, AST, γ GT, alkaline phosphatase or serum bilirubin would exclude a subject from participation in the study.
- A positive Hepatitis B surface antigen or Hepatitis C test result.

Participant Flow Table

Overall Study

	Patients with Mild Hepatic Impairment (Cohort 1)	Patients with Moderate Hepatic Impairment (Cohort 2)	Patients with Severe Hepatic Impairment (Cohort 3)	Healthy Participants	Total
Arm/Group Description	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	
Started	8	8	8	18	42
PK Analysis Set	8	8	8	18	42
Safety Analysis Set	8	8	8	18	42
Completed	8	8	8	18	42
Not Completed	0	0	0	0	0

Baseline Characteristics

	Patients with Mild Hepatic Impairment (Cohort 1)	Patients with Moderate Hepatic Impairment (Cohort 2)	Patients with Severe Hepatic Impairment (Cohort 3)	Healthy Participants	Total
Arm/Group Description	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	

Number of Participants [units: participants]	8	8	8	18	42
Age Continuous (units: Years) Mean ± Standard Deviation					
	49.3±12.77	60.3±5.09	58.0±7.35	54.1±11.75	55.1±10.62
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)					
Female	3	4	2	9	18
Male	5	4	6	9	24
Race/Ethnicity, Customized (units: Participants) Count of Participants (Not Applicable)					
American Indian Or Alaska Native	0	0	0	2	2
Asian	0	0	1	0	1
Black Or African American	1	2	1	1	5
Other	1	0	0	1	2
White	6	6	6	14	32

Summary of Efficacy

There were no efficacy data in this trial. This section presents the pharmacokinetics data.

There was higher exposure (in terms of AUC and Cmax) to fevipiprant in the moderate and severe hepatic impairment groups relative to the respective healthy subject groups, and minimal impact in the mild impairment group.

Separate simple linear regression models were run to explore the possible trends between the log-transformed hepatic function parameters (albumin and bilirubin) and Child-Pugh score versus the log-transformed exposure PK parameters (Cmax, AUClast, AUCinf). Based on these analyses, PK parameters correlated significantly with hepatic function parameters and there was an increase in exposure with increasing severity of hepatic impairment.

The degree of hepatic impairment has no relevant impact on plasma PK of CCN362, the metabolite of fevipiprant.

Primary Outcome Result(s)

Pharmacokinetics: Area Under the Plasma Concentration-time Curve (AUC) From Time Zero to Time of the Last Quantifiable Concentration (AUClast) for Plasma Fevipiprant
(Time Frame: Pre-dose, 0.25, 0.5, 1, 2, 3, 6, 8, 12, 24, 48, 72, 96 and 120h)

	Patients with Mild Hepatic Impairment (Cohort 1)	Healthy Participants (Matched Control for Cohort 1)	Patients with Moderate Hepatic Impairment (Cohort 2)	Healthy Participants (Matched Control for Cohort 2)	Patients with Severe Hepatic Impairment (Cohort 3)	Healthy Participants (Matched Control for Cohort 3)
Arm/Group Description	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose
Number of Participants Analyzed [units: participants]	8	8	8	8	8	8
Pharmacokinetics: Area Under the Plasma Concentration-time Curve (AUC) From Time Zero to Time of the Last Quantifiable Concentration (AUClast) for Plasma Fevipiprant (units: Hours*nanograms						

per milliliter (h*ng/mL)) Mean ± Standard Deviation						
	9820 ± 2650	9280 ± 1570	19700 ± 8110	10600 ± 5290	24800 ± 8480	10300 ± 2630

Statistical Analysis

Groups	Patients with Mild Hepatic Impairment (Cohort 1), Healthy Participants (Matched Control for Cohort 1)	
Non-Inferiority/Equivalence Test	Other	Linear mixed effects model with subject group as fixed effect and matched pair as random effect.
Other Geometric Mean Ratio	1.04	
90 % Confidence Interval 2-Sided	0.846 to 1.27	

Statistical Analysis

Groups	Patients with Moderate Hepatic Impairment (Cohort 2), Healthy Participants (Matched Control for Cohort 2)	
Non-Inferiority/Equivalence Test	Other	Linear mixed effects model with subject group as fixed effect and matched pair as random effect.
Other Geometric Mean Ratio	1.87	

90 % Confidence Interval 2-Sided	1.23 to 2.84

Statistical Analysis

Groups	Patients with Severe Hepatic Impairment (Cohort 3), Healthy Participants (Matched Control for Cohort 3)	
Non-Inferiority/Equivalence Test	Other	Linear mixed effects model with subject group as fixed effect and matched pair as random effect.
Other Geometric Mean Ratio	2.35	
90 % Confidence Interval 2-Sided	2.00 to 2.76	

Pharmacokinetics: AUC From Time Zero Extrapolated to Infinity (AUCinf) for Plasma Fevipiprant

(Time Frame: Pre-dose, 0.25, 0.5, 1, 2, 3, 6, 8, 12, 24, 48, 72, 96 and 120h)

	Patients with Mild Hepatic Impairment (Cohort 1)	**Healthy Participants (Matched Control for Cohort 1)**	**Patients with Moderate Hepatic Impairment (Cohort 2)**	**Healthy Participants (Matched Control for Cohort 2)**	**Patients with Severe Hepatic Impairment (Cohort 3)**	**Healthy Participants (Matched Control for Cohort 3)**
Arm/Group Description	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose
Number of Participants Analyzed [units: participants]	8	8	8	8	8	8
Pharmacokinetics: AUC From Time Zero Extrapolated to Infinity (AUCinf) for Plasma						

Fevipiprant (units: Hours*nanograms per milliliter (h*ng/mL)) Mean ± Standard Deviation						
	10200 ± 2900	9480 ± 1390	20000 ± 8230	11000 ± 5990	24900 ± 8480	10400 ± 2630

Statistical Analysis

Groups	Patients with Mild Hepatic Impairment (Cohort 1), Healthy Participants (Matched Control for Cohort 1)	
Non-Inferiority/Equivalence Test	Other	Linear mixed effects model with subject group as fixed effect and matched pair as random effect.
Other Geometric Mean Ratio	1.04	
90 % Confidence Interval 2-Sided	0.853 to 1.28	

Statistical Analysis

Groups	Patients with Moderate Hepatic Impairment (Cohort 2), Healthy Participants (Matched Control for Cohort 2)	
Non-Inferiority/Equivalence Test	Other	Linear mixed effects model with subject group as fixed effect and matched pair as random effect.
Other Geometric Mean Ratio	1.86	

90 % Confidence Interval 2-Sided	1.20 to 2.86

Statistical Analysis

Groups	Patients with Severe Hepatic Impairment (Cohort 3), Healthy Participants (Matched Control for Cohort 3)	
Non-Inferiority/Equivalence Test	Other	Linear mixed effects model with subject group as fixed effect and matched pair as random effect.
Other Geometric Mean Ratio	2.31	
90 % Confidence Interval 2-Sided	1.93 to 2.76	

Pharmacokinetics: Maximum Observed Concentration (Cmax) for Plasma Fevipiprant

(Time Frame: Pre-dose, 0.25, 0.5, 1, 2, 3, 6, 8, 12, 24, 48, 72, 96 and 120h)

	Patients with Mild Hepatic Impairment (Cohort 1)	**Healthy Participants (Matched Control for Cohort 1)**	**Patients with Moderate Hepatic Impairment (Cohort 2)**	**Healthy Participants (Matched Control for Cohort 2)**	**Patients with Severe Hepatic Impairment (Cohort 3)**	**Healthy Participants (Matched Control for Cohort 3)**
Arm/Group Description	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose
Number of Participants Analyzed [units: participants]	8	8	8	8	8	8
Pharmacokinetics: Maximum Observed Concentration (Cmax) for Plasma Fevipiprant						

(units: Nanogram per milliliter (ng/mL)) Mean ± Standard Deviation						
	1860 ± 744	1810 ± 938	3760 ± 1580	2160 ± 1210	5040 ± 1820	2180 ± 709

Statistical Analysis

Groups	Patients with Mild Hepatic Impairment (Cohort 1), Healthy Participants (Matched Control for Cohort 1)	
Non-Inferiority/Equivalence Test	Other	Linear mixed effects model with subject group as fixed effect and matched pair as random effect.
Other Geometric Mean Ratio	1.07	
90 % Confidence Interval 2-Sided	0.714 to 1.60	

Statistical Analysis

Groups	Patients with Moderate Hepatic Impairment (Cohort 2), Healthy Participants (Matched Control for Cohort 2)	
Non-Inferiority/Equivalence Test	Other	Linear mixed effects model with subject group as fixed effect and matched pair as random effect.
Other Geometric Mean Ratio	1.82	

90 % Confidence Interval 2-Sided	1.12 to 2.95	

Statistical Analysis

Groups	Patients with Severe Hepatic Impairment (Cohort 3), Healthy Participants (Matched Control for Cohort 3)	
Non-Inferiority/Equivalence Test	Other	Linear mixed effects model with subject group as fixed effect and matched pair as random effect.
Other Geometric Mean Ratio	2.30	
90 % Confidence Interval 2-Sided	1.69 to 3.13	

Secondary Outcome Result(s)

Relationship Assessed by Coefficient of Correlation Between AUClast of Fevipiprant and Baseline Hepatic Function Parameters (Bilirubin and Albumin) and Child-Pugh Score

(Time Frame: Baseline, Pre-dose, 0.25, 0.5, 1, 2, 3, 6, 8, 12, 24, 48, 72, 96 and 120h)

	All Participants
Arm/Group Description	Participants received Fevipiprant 450 mg single dose
Number of Participants Analyzed [units: participants]	42

Relationship Assessed by Coefficient of Correlation Between AUClast of Fevipiprant and Baseline Hepatic Function Parameters (Bilirubin and Albumin) and Child-Pugh Score (units: R-squared)	
AUClast and Baseline Albumin Concentration	0.29
AUClast and Baseline Bilirubin Concentration	0.43
AUClast and Child-Pugh Score at Baseline	0.50

Relationship Assessed by Coefficient of Correlation Between AUCinf of Fevipiprant and Baseline Hepatic Function Parameters (Bilirubin and Albumin) and Child-Pugh Score

(Time Frame: Baseline, Pre-dose, 0.25, 0.5, 1, 2, 3, 6, 8, 12, 24, 48, 72, 96 and 120h)

	All Participants
Arm/Group Description	Participants received Fevipiprant 450 mg single dose
Number of Participants Analyzed [units: participants]	42
Relationship Assessed by Coefficient of Correlation Between AUCinf of Fevipiprant and Baseline Hepatic Function Parameters (Bilirubin and Albumin) and Child-Pugh Score (units: R-squared)	

AUCinf and Baseline Albumin Concentration	0.27
AUCinf and Baseline Bilirrubin Concentration	0.42
AUCinf and Child-Pugh Score at Baseline	0.48

Relationship Assessed by Coefficient of Correlation Between Cmax of Fevipiprant and Baseline Hepatic Function Parameters (Bilirubin and Albumin) and Child-Pugh Score

(Time Frame: Baseline, Pre-dose, 0.25, 0.5, 1, 2, 3, 6, 8, 12, 24, 48, 72, 96 and 120h)

	All Participants
Arm/Group Description	Participants received Fevipiprant 450 mg single dose
Number of Participants Analyzed [units: participants]	42
Relationship Assessed by Coefficient of Correlation Between Cmax of Fevipiprant and Baseline Hepatic Function Parameters (Bilirubin and Albumin) and Child-Pugh Score (units: R-squared)	
Cmax and Baseline Albumin Concentration	0.24
Cmax and Baseline Bilirrubin Concentration	0.46
Cmax and Child-Pugh Score at Baseline	0.54

Pharmacokinetics: AUClast of Metabolite CCN362 in Plasma

(Time Frame: Pre-dose, 0.25, 0.5, 1, 2, 3, 6, 8, 12, 24, 48, 72, 96 and 120h)

	Patients with Mild Hepatic Impairment (Cohort 1)	Healthy Participants (Matched Control for Cohort 1)	Patients with Moderate Hepatic Impairment (Cohort 2)	Healthy Participants (Matched Control for Cohort 2)	Patients with Severe Hepatic Impairment (Cohort 3)	Healthy Participants (Matched Control for Cohort 3)
Arm/Group Description	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose
Number of Participants Analyzed [units: participants]	8	8	8	8	8	8
Pharmacokinetics: AUClast of Metabolite CCN362 in Plasma (units: Hours*nanogram per mililiter (h*ng/mL)) Mean ± Standard Deviation						
	22200 ± 4090	18300 ± 5470	23500 ± 11000	20800 ± 4960	21200 ± 7440	21900 ± 4310

Statistical Analysis

Groups	Patients with Mild Hepatic Impairment (Cohort 1), Healthy Participants (Matched Control for Cohort 1)	
Non-Inferiority/Equivalence Test	Other	Linear mixed effects model with subject group as fixed effect and matched pair as random effect
Other Geometric Mean Ratio	1.25	

90 % Confidence Interval 2-Sided	0.980 to 1.61	

Statistical Analysis

Groups	Patients with Moderate Hepatic Impairment (Cohort 2), Healthy Participants (Matched Control for Cohort 2)	
Non-Inferiority/Equivalence Test	Other	Linear mixed effects model with subject group as fixed effect and matched pair as random effect
Other Geometric Mean Ratio	1.01	
90 % Confidence Interval 2-Sided	0.649 to 1.56	

Statistical Analysis

Groups	Patients with Severe Hepatic Impairment (Cohort 3), Healthy Participants (Matched Control for Cohort 3)	
Non-Inferiority/Equivalence Test	Other	Linear mixed effects model with subject group as fixed effect and matched pair as random effect
Other Geometric Mean Ratio	0.926	
90 % Confidence Interval 2-Sided	0.702 to 1.22	

Pharmacokinetics: AUCinf of Metabolite CCN362 in Plasma

(Time Frame: Pre-dose, 0.25, 0.5, 1, 2, 3, 6, 8, 12, 24, 48, 72, 96 and 120h)

	Patients with Mild Hepatic Impairment (Cohort 1)	Healthy Participants (Matched Control for Cohort 1)	Patients with Moderate Hepatic Impairment (Cohort 2)	Healthy Participants (Matched Control for Cohort 2)	Patients with Severe Hepatic Impairment (Cohort 3)	Healthy Participants (Matched Control for Cohort 3)
Arm/Group Description	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose
Number of Participants Analyzed [units: participants]	8	8	8	8	8	8
Pharmacokinetics: AUCinf of Metabolite CCN362 in Plasma (units: Hours*nanograms per mililiter (h*ng/mL)) Mean ± Standard Deviation						
	22700 ± 4650	18800 ± 5360	23700 ± 11000	21200 ± 5670	21200 ± 7430	22400 ± 4780

Statistical Analysis

Groups	Patients with Mild Hepatic Impairment (Cohort 1), Healthy Participants (Matched Control for Cohort 1)	
Non-Inferiority/Equivalence Test	Other	Linear mixed effects model with subject group as fixed effect and matched pair as random effect
Other Geometric Mean Ratio	1.24	

90 % Confidence Interval 2-Sided	0.991 to 1.55	

Statistical Analysis

Groups	Patients with Moderate Hepatic Impairment (Cohort 2), Healthy Participants (Matched Control for Cohort 2)	
Non-Inferiority/Equivalence Test	Other	Linear mixed effects model with subject group as fixed effect and matched pair as random effect
Other Geometric Mean Ratio	1.01	
90 % Confidence Interval 2-Sided	0.651 to 1.56	

Statistical Analysis

Groups	Patients with Severe Hepatic Impairment (Cohort 3), Healthy Participants (Matched Control for Cohort 3)	
Non-Inferiority/Equivalence Test	Other	Linear mixed effects model with subject group as fixed effect and matched pair as random effect.
Other Geometric Mean Ratio	0.908	
90 % Confidence Interval 2-Sided	0.691 to 1.19	

Pharmacokinetics: Cmax of Metabolite CCN362 in Plasma

(Time Frame: Pre-dose, 0.25, 0.5, 1, 2, 3, 6, 8, 12, 24, 48, 72, 96 and 120h)

	Patients with Mild Hepatic Impairment (Cohort 1)	Healthy Participants (Matched Control for Cohort 1)	Patients with Moderate Hepatic Impairment (Cohort 2)	Healthy Participants (Matched Control for Cohort 2)	Patients with Severe Hepatic Impairment (Cohort 3)	Healthy Participants (Matched Control for Cohort 3)
Arm/Group Description	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose
Number of Participants Analyzed [units: participants]	8	8	8	8	8	8
Pharmacokinetics: Cmax of Metabolite CCN362 in Plasma (units: Nanogram per mililiter (ng/mL)) Mean ± Standard Deviation						
	3550 ± 1000	2590 ± 1040	3720 ± 2020	3410 ± 1350	3610 ± 1350	3510 ± 900

Statistical Analysis

Groups	Patients with Mild Hepatic Impairment (Cohort 1), Healthy Participants (Matched Control for Cohort 1)	
Non-Inferiority/Equivalence Test	Other	Linear mixed effects model with subject group as fixed effect and matched pair as random effect.
Other Geometric Mean Ratio	1.42	

90 % Confidence Interval 2-Sided	1.03 to 1.96

Statistical Analysis

Groups	Patients with Moderate Hepatic Impairment (Cohort 2), Healthy Participants (Matched Control for Cohort 2)	
Non-Inferiority/Equivalence Test	Other	Linear mixed effects model with subject group as fixed effect and matched pair as random effect.
Other Geometric Mean Ratio	0.999	
90 % Confidence Interval 2-Sided	0.626 to 1.60	

Statistical Analysis

Groups	Patients with Severe Hepatic Impairment (Cohort 3), Healthy Participants (Matched Control for Cohort 3)	
Non-Inferiority/Equivalence Test	Other	Linear mixed effects model with subject group as fixed effect and matched pair as random effect
Other Geometric Mean Ratio	1.00	
90 % Confidence Interval 2-Sided	0.725 to 1.39	

Summary of Safety

A single oral dose of fevipiprant 450 mg was found to be safe and well tolerated both in healthy subjects as well as patients with mild, moderate, and severe hepatic impairment. There were no deaths, SAEs or AEs leading to discontinuation of study drug. All AEs were mild to moderate in severity. There were no AEs reported in the severe hepatic impairment group. No new safety signals were detected.

Safety Results

All-Cause Mortality

	Patients with Mild Hepatic Impairment (Cohort 1) N = 8	Patients with Moderate Hepatic Impairment (Cohort 2) N = 8	Patients with Severe Hepatic Impairment (Cohort 3) N = 8	Healthy Participants N = 18
Arm/Group Description	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Other Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first day of study treatment (Day 1) until until end of study treatment at Day 12.
Additional Description	Any sign or symptom that occurs at or after first drug intake
Source Vocabulary for Table Default	MedDRA version 21.1

Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	0%

	Patients with Mild Hepatic Impairment (Cohort 1) N = 8	**Patients with Moderate Hepatic Impairment (Cohort 2) N = 8**	**Patients with Severe Hepatic Impairment (Cohort 3) N = 8**	**Healthy Participants N = 18**
Arm/Group Description	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose	Fevipiprant 450 mg single dose
Total participants affected	1 (12.50%)	2 (25.00%)	0 (0.00%)	1 (5.56%)
Gastrointestinal disorders				
Diarrhoea	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections and infestations				
Oral Herpes	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)
Nervous system disorders				
Headache	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)
Hepatic Encephalopathy	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)

Other Relevant Findings

None

Conclusion:

After a single 450 mg dose, plasma exposure to fevipiprant increased with severity of hepatic impairment. This was more pronounced in the moderate and severe hepatic impairment groups, with a 87% and 135% increase, respectively, in AUClast relative to their respective matched healthy subject groups.

There were no new or unexpected safety findings in this study.

Date of Clinical Trial Report

26-Feb-2020