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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

FIA586

Trial Indication(s)

Hepatic impairment

Protocol Number

CFIA586A02101

Protocol Title

A Phase I, single-dose, open-label, parallel-group study to assess the pharmacokinetics, safety, and tolerability of FIA586 in participants with mild and moderate hepatic impairment compared to matched healthy participants

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase 1

Study Start/End Dates

Study Start Date: December 10, 2021 (Actual)
Primary Completion Date: June 28, 2022 (Actual)
Study Completion Date: June 28, 2022 (Actual)

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Study Design/Methodology

This was a Phase 1, single-dose, open-label, parallel-group study in participants with mild and moderate hepatic impairment (HI) and matched healthy participants with normal hepatic function.

Approximately 24 to 40 participants were to be enrolled, with 8 to 10 participants in each of the mild (Child Pugh A) and moderate (Child-Pugh B) HI (Groups 2 and 3, respectively) and 8 to 20 healthy matched control participants (Group 1). Healthy control participants were matched by gender, age (±10 years), weight (±15%), and smoking status (smoker or nonsmoker). Each participant in the matched healthy control group may have been matched to 1 or more evaluable participants with HI, but could not be matched to more than 1 participant from the same HI group. A total of 29 participants were enrolled and completed the study (8 participants with mild HI, 8 participants with moderate HI, and 13 healthy matched control participants).

Centers

2 centers in 1 country: United States

Publication

Not applicable.

Objectives:

Primary

- To characterize the pharmacokinetic (PK) properties of FIA586 after a single dose of 350 mg in participants with mild and moderate hepatic impairment (HI) based on the Child Pugh classification as compared to matched healthy participants with normal hepatic function.

Secondary

- To assess safety and tolerability after a single dose of FIA586 in participants with mild and moderate HI as compared to matched healthy participants with normal hepatic function.

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

Each participant received a single oral dose of 350 mg FIA586, administered as 3 x 100 mg capsules and 2 x 25 mg capsules.

Statistical Methods

Analysis of Variance (ANOVA)

The natural log (ln)-transformed PK parameters (Cmax, AUClast, and AUCinf) for FIA586 were analyzed using ANOVA models with group as fixed effects. Least-squares means- (LSMs) for each group as well as the difference between mild and moderate HI groups (test) and their respective matched healthy participants (reference) along with the corresponding 90% confidence interval (CI) on the log scale were calculated for each PK parameter. Back--transformed ratios and 90% CIs were provided.

Non-parametric Analysis of Tmax

Non-parametric analysis of Tmax was performed. The non-parametric Mann-Whitney U-test was performed and the p-value was presented for the comparison of Tmax between each HI group (mild or moderate) and the respective matched healthy control group. Median and range (minimum to maximum) and difference of medians for each HI group and the respective matched healthy control group were provided. Note that Tmax was not ln-transformed for these analyses.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

All Participants had to be:
• Male and non-childbearing potential female participants 18 to 70 years of age (inclusive) at Screening.
• Weighted at least 50.0 kg with a body mass index (BMI) within the range of 18.0 to – 38.0 kg/m2 at Screening.
• A non-smoker or agreed to smoke no more than 5 cigarettes (or equivalent) per day, and maintain the same smoking status from Screening until the Study Completion (Day -28 to Day 6).

Healthy participants (Group 1)
• Had to be in good health as determined by past medical history, physical examination, vital signs, ECG, and laboratory tests at Screening.
• Each participant matched in age (±10 years), gender, weight (±15%), and smoking status (smoker or non-smoker) to an individual participant in at least one HI group but not to more than 1 participant in the same HI group.

Participants with mild and moderate HI (Groups 2 and 3)
• Had to satisfy the criteria for HI as evidenced by a Child-Pugh class of A or B at Screening:
-Class A; Mild; Child-Pugh score 5-6
-Class B; Moderate; Child-Pugh score 7-9

Exclusion Criteria:

All participants:
• Used other investigational drugs within the last 30 days or 5 half-lives prior to dosing of study treatment, whichever is longer.
• Known history of, or current clinically significant arrhythmias. Had clinically significant ECG abnormality or history of long-QT syndrome.
• Myocardial infarction < 5 years prior to Screening.
• Recent (within the last 3 years of Screening) or recurrent history of autonomic dysfunction (e.g. recurrent episodes of fainting or palpitations).
• History of immunodeficiency diseases or had a positive HIV test result at Screening.
• 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 of Screening, regardless of whether there was evidence of local recurrence or metastases.
• Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs (apart from cholecystectomy), or which may jeopardize the participants in case of participation in the study. The investigator made this determination in consideration of the participant's medical history and/or clinical or laboratory evidence of any 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.

Healthy participants (Group 1):
• Any single parameter of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), or alkaline phosphatase (ALP) exceeding 1.2 × upper limit of normal (ULN) or ≥ 1.5 × ULN total bilirubin (TBL) OR any elevation above ULN of more than one parameter of ALT, AST, GGT, ALP, or serum bilirubin at screening.

• Known to have Gilbert's syndrome.
• Hemoglobin levels below 12.0 g/dL for males and 11.0 g/dL for females at Screening or Baseline.
• 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 at Screening.
• Total white blood cell (WBC) count which falls outside the range of 3.5 to 10.7 × 109/L, or platelets < 100 × 109/L at Screening or Baseline.
• Evidence of urinary obstruction or difficulty in voiding at Screening.
• Symptomatic genital or urinary tract infection in the 4 weeks prior to dosing of study treatment or the presence of active urinary tract infection at Screening.

Participants with mild and moderate HI (Groups 2 and 3):
• Had abnormal laboratory values for any of the following parameters at Screening or Baseline:
-Hemoglobin < 9 g/dL.
-Platelet count < 30 × 109/L.
-WBC count < 2.5 × 109/L.
-Absolute neutrophil count < 1.5 × 109/L.
-Lymphocytes < 0.8 × 109/L.
-TBL > 8 mg/dL.
-Serum amylase > 2 × ULN.
-International normalized ratio (INR) > 2.3
-Corrected serum calcium < 8.6 or > 10.2 mg/dL.
• Had hepatic impairment due to non-liver disease.
• Had presence of any non-controlled and clinically significant disease that could affect the study outcome or that would place the participant at undue risk.
• Had treatment with any vasodilator, autonomic alpha blocker or β2 agonist within 2 weeks prior to dosing of study treatment.
• Had primary biliary cholangitis or biliary obstruction.
• Participants requiring paracentesis more than every 30 days for the management of ascites were excluded. Participants 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 must have been stable for 28 days prior to dosing of study treatment.
• Had transjugular intrahepatic portosystemic shunt and/or had undergone portacaval shunting.
• Had encephalopathy Grade 3 or worse within 28 days prior to dosing of study treatment.
• Presence of moderate to severe impaired renal function as indicated by estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73 m2 based on the modification of diet in renal disease calculation at Screening.

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Participant Flow Table

Overall Study

	FIA586 oral 350mg in Healthy participants	FIA586 oral 350mg with mild hepatic impairment	FIA586 oral 350mg with moderate hepatic impairment	Total
Arm/Group Description	Healthy participants with normal hepatic function received a single oral dose of FIA586 (350mg)	Participants with mild hepatic impairment received a single oral dose of FIA586 (350mg)	Participants with moderate hepatic impairment received a single oral dose of FIA586 (350mg)	
Started	13	8	8	29
Completed	13	8	8	29
Not Completed	0	0	0	0

Baseline Characteristics

	FIA586 oral 350mg in Healthy participants	FIA586 oral 350mg with mild hepatic impairment	FIA586 oral 350mg with moderate hepatic impairment	Total
Arm/Group Description	Healthy participants with normal hepatic function received a single oral dose of FIA586 (350mg)	Participants with mild hepatic impairment received a single oral dose of FIA586 (350mg)	Participants with moderate hepatic impairment received a single oral dose of FIA586 (350mg)	
Number of Participants [units: participants]	13	8	8	29
Baseline Analysis Population Description				
Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
Female	7	3	5	15

Male	6	5	3	14
Race/Ethnicity, Customized (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
Asian	0	1	0	1
Black or African American	1	1	0	2
White	12	6	8	26
Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation				
	62.3±5.09	61.0±5.29	63.6±5.40	62.3±5.13

Primary Outcome Result(s)

Maximum observed plasma concentrations (Cmax) of FIA586

Description	Pharmacokinetic (PK) parameters were calculated using non-compartmental methods based on FIA586 concentrations in plasma determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. Cmax is the maximum (peak) observed plasma concentration of FIA586 after dose administration.
Time Frame	pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, 92 and 120 hours
Analysis Population Description	The PK set includes all participants who provided an evaluable PK profile. Each healthy participant was matched in age (±10 years), gender, weight (±15%), and smoking status (smoker or nonsmoker) to an individual participant in at least 1 hepatic impairment (HI) group but not to more than 1 participant in the same HI group.

	FIA586 oral 350mg in Healthy Matched Control (Mild HI)	FIA586 oral 350mg with mild hepatic impairment	FIA586 oral 350mg in Healthy Matched Control (Moderate HI)	FIA586 oral 350mg with moderate hepatic impairment

Arm/Group Description	Healthy matched control participants (Mild hepatic impairment) with normal hepatic function received a single oral dose of FIA586 (350mg)	Participants with mild hepatic impairment received a single oral dose of FIA586 (350mg)	Healthy matched control participants (Moderate hepatic impairment) with normal hepatic function received a single oral dose of FIA586 (350mg)	Participants with moderate hepatic impairment received a single oral dose of FIA586 (350mg)
Number of Participants Analyzed [units: participants]	8	8	8	7
Maximum observed plasma concentrations (Cmax) of FIA586 (units: ng/mL)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
	19100 (33.8%)	15600 (28.4%)	16400 (20.0%)	16200 (65.3%)

Statistical Analysis

Groups	FIA586 oral 350mg in Healthy Matched Control (Mild HI), FIA586 oral 350mg with mild hepatic impairment	
Type of Statistical Test	Other	
Method	ANOVA	
Other Geometric mean ratio	0.81	Geometric Mean Ratio = Test/Reference. Mild HI (Test) vs Healthy Matched Control (Mild HI) (Reference)
90 % Confidence Interval 2-Sided	0.622 to 1.064	

Statistical Analysis

Groups	FIA586 oral 350mg in Healthy Matched Control (Moderate HI), FIA586 oral 350mg with moderate hepatic impairment

Type of Statistical Test	Other	
Method	ANOVA	
Other Geometric mean ratio	0.99	Geometric Mean Ratio = Test/Reference. Moderate HI (Test) vs Healthy Matched Control (Moderate HI) (Reference)
90 % Confidence Interval 2-Sided	0.666 to 1.465	

Area under plasma concentration-time curve from time zero to the last measurable concentration sampling time (AUClast) of FIA586

Description	Pharmacokinetic (PK) parameters were calculated using non-compartmental methods based on FIA586 concentrations in plasma determined by validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. AUClast is the area under the plasma concentration-time curve from time zero to the time of last quantifiable concentration (tlast) of FIA586
Time Frame	pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, 92 and 120 hours
Analysis Population Description	The PK set includes all participants who provided an evaluable PK profile. Each healthy participant was matched in age (±10 years), gender, weight (±15%), and smoking status (smoker or nonsmoker) to an individual participant in at least 1 hepatic impairment (HI) group but not to more than 1 participant in the same HI group.

	FIA586 oral 350mg in Healthy Matched Control (Mild HI)	**FIA586 oral 350mg with mild hepatic impairment**	**FIA586 oral 350mg in Healthy Matched Control (Moderate HI)**	**FIA586 oral 350mg with moderate hepatic impairment**
Arm/Group Description	Healthy matched control participants (Mild hepatic impairment) with normal hepatic function received a single oral dose of FIA586 (350mg)	Participants with mild hepatic impairment received a single oral dose of FIA586 (350mg)	Healthy matched control participants (Moderate hepatic impairment) with normal hepatic function received a single oral dose of FIA586 (350mg)	Participants with moderate hepatic impairment received a single oral dose of FIA586 (350mg)
Number of Participants Analyzed [units: participants]	8	8	8	7

Area under plasma concentration-time curve from time zero to the last measurable concentration sampling time (AUClast) of FIA586 (units: ng*h/mL)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
	49400 (37.8%)	49400 (23.1%)	46600 (36.9%)	54000 (47.6%)

Statistical Analysis

Groups	FIA586 oral 350mg in Healthy Matched Control (Mild HI), FIA586 oral 350mg with mild hepatic impairment	
Type of Statistical Test	Other	
Method	ANOVA	
Other Geometric mean ratio	1.00	Geometric Mean Ratio = Test/Reference. Mild HI (Test) vs Healthy Matched Control (Mild HI) (Reference)
90 % Confidence Interval 2-Sided	0.764 to 1.307	

Statistical Analysis

Groups	FIA586 oral 350mg in Healthy Matched Control (Moderate HI), FIA586 oral 350mg with moderate hepatic impairment	
Type of Statistical Test	Other	
Method	ANOVA	
Other Geometric mean ratio	1.16	Geometric Mean Ratio = Test/Reference. Moderate HI (Test) vs Healthy Matched Control (Moderate HI) (Reference)

90 % Confidence Interval 2-Sided	0.800 to 1.677

Area under the plasma concentration-time curve from time zero extrapolated to infinity (AUC[0-inf]) of FIA586

Description	Pharmacokinetic (PK) parameters were calculated using non-compartmental methods based on FIA586 concentrations in plasma determined by validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. The AUC from time zero to infinity (mass x time x volume-1)
Time Frame	pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, 92 and 120 hours
Analysis Population Description	The PK set includes all participants who provided an evaluable PK profile. Each healthy participant was matched in age (±10 years), gender, weight (±15%), and smoking status (smoker or nonsmoker) to an individual participant in at least 1 hepatic impairment (HI) group but not to more than 1 participant in the same HI group.

	FIA586 oral 350mg in Healthy Matched Control (Mild HI)	**FIA586 oral 350mg with mild hepatic impairment**	**FIA586 oral 350mg in Healthy Matched Control (Moderate HI)**	**FIA586 oral 350mg with moderate hepatic impairment**
Arm/Group Description	Healthy matched control participants (Mild hepatic impairment) with normal hepatic function received a single oral dose of FIA586 (350mg)	Participants with mild hepatic impairment received a single oral dose of FIA586 (350mg)	Healthy matched control participants (Moderate hepatic impairment) with normal hepatic function received a single oral dose of FIA586 (350mg)	Participants with moderate hepatic impairment received a single oral dose of FIA586 (350mg)
Number of Participants Analyzed [units: participants]	8	8	8	7
Area under the plasma concentration-time curve from time zero extrapolated to infinity (AUC[0-inf]) of FIA586 (units: ng*h/mL)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
	49900 (37.8%)	49800 (23.0%)	47100 (36.8%)	54500 (47.4%)

Statistical Analysis

Groups	FIA586 oral 350mg in Healthy Matched Control (Mild HI), FIA586 oral 350mg with mild hepatic impairment	
Type of Statistical Test	Other	
Method	ANOVA	
Other Geometric mean ratio	1.00	Geometric Mean Ratio = Test/Reference. Mild HI (Test) vs Healthy Matched Control (Mild HI) (Reference)
90 % Confidence Interval 2-Sided	0.764 to 1.306	

Statistical Analysis

Groups	FIA586 oral 350mg in Healthy Matched Control (Moderate HI), FIA586 oral 350mg with moderate hepatic impairment	
Type of Statistical Test	Other	
Method	ANOVA	
Other Geometric mean ratio	1.16	Geometric Mean Ratio = Test/Reference. Moderate HI (Test) vs Healthy Matched Control (Moderate HI) (Reference)
90 % Confidence Interval 2-Sided	0.800 to 1.672	

Area under the plasma concentration-time curve from time zero to 48 hours (AUC0-48h) of FIA586

Description: Pharmacokinetic (PK) parameters were calculated using non-compartmental methods based on FIA586 concentrations in plasma determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. The AUC from time zero to the 48-hour postdose sampling time (mass x time x volume-1).

Time Frame	pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours
Analysis Population Description	The PK set includes all participants who provided an evaluable PK profile. Each healthy participant was matched in age (±10 years), gender, weight (±15%), and smoking status (smoker or nonsmoker) to an individual participant in at least 1 hepatic impairment (HI) group but not to more than 1 participant in the same HI group.

	FIA586 oral 350mg in Healthy Matched Control (Mild HI)	**FIA586 oral 350mg with mild hepatic impairment**	**FIA586 oral 350mg in Healthy Matched Control (Moderate HI)**	**FIA586 oral 350mg with moderate hepatic impairment**
Arm/Group Description	Healthy matched control participants (Mild hepatic impairment) with normal hepatic function received a single oral dose of FIA586 (350mg)	Participants with mild hepatic impairment received a single oral dose of FIA586 (350mg)	Healthy matched control participants (Moderate hepatic impairment) with normal hepatic function received a single oral dose of FIA586 (350mg)	Participants with moderate hepatic impairment received a single oral dose of FIA586 (350mg)
Number of Participants Analyzed [units: participants]	8	8	8	7
Area under the plasma concentration-time curve from time zero to 48 hours (AUC0-48h) of FIA586 (units: ng*h/mL)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
	49200 (37.1%)	49400 (22.7%)	46600 (36.2%)	53800 (46.7%)

Time to reach maximum plasma concentration (Tmax) of FIA586

Description	Pharmacokinetic (PK) parameters were calculated using non-compartmental methods based on FIA586 concentrations in plasma determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. Tmax is the time to reach maximum (peak) drug concentration after single-dose administration (time).
Time Frame	pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, 92 and 120 hours. Actual sampling times were taken into consideration for the calculation of PK parameters.
Analysis Population Description	The PK set includes all participants who provided an evaluable PK profile. Each healthy participant was matched in age (±10 years), gender, weight (±15%), and smoking status (smoker or nonsmoker) to an individual participant in at least 1 hepatic impairment (HI) group but not to more than 1 participant in the same HI group.

	FIA586 oral 350mg in Healthy Matched Control (Mild HI)	FIA586 oral 350mg with mild hepatic impairment	FIA586 oral 350mg in Healthy Matched Control (Moderate HI)	FIA586 oral 350mg with moderate hepatic impairment
Arm/Group Description	Healthy matched control participants (Mild hepatic impairment) with normal hepatic function received a single oral dose of FIA586 (350mg)	Participants with mild hepatic impairment received a single oral dose of FIA586 (350mg)	Healthy matched control participants (Moderate hepatic impairment) with normal hepatic function received a single oral dose of FIA586 (350mg)	Participants with moderate hepatic impairment received a single oral dose of FIA586 (350mg)
Number of Participants Analyzed [units: participants]	8	8	8	7
Time to reach maximum plasma concentration (Tmax) of FIA586 (units: hours)	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**
	0.50 (0.50 to 1.50)	1.00 (0.50 to 2.00)	0.75 (0.50 to 4.00)	0.50 (0.50 to 4.00)

Terminal elimination half-life (T1/2) of FIA586

Description	Pharmacokinetic (PK) parameters were calculated using non-compartmental methods based on FIA586 concentrations in plasma determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. T1/2 is the elimination half-life associated with the terminal slope.
Time Frame	pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, 92 and 120 hours
Analysis Population Description	The PK set includes all participants who provided an evaluable PK profile. Each healthy participant was matched in age (±10 years), gender, weight (±15%), and smoking status (smoker or nonsmoker) to an individual participant in at least 1 hepatic impairment (HI) group but not to more than 1 participant in the same HI group.

	FIA586 oral 350mg in Healthy Matched Control (Mild HI)	FIA586 oral 350mg with mild hepatic impairment	FIA586 oral 350mg in Healthy Matched Control (Moderate HI)	FIA586 oral 350mg with moderate hepatic impairment
Arm/Group Description	Healthy matched control participants (Mild hepatic impairment) with normal hepatic function received	Participants with mild hepatic impairment received a single oral dose of FIA586 (350mg)	Healthy matched control participants (Moderate hepatic impairment) with normal hepatic function	Participants with moderate hepatic impairment received a

	a single oral dose of FIA586 (350mg)		received a single oral dose of FIA586 (350mg)	single oral dose of FIA586 (350mg)
Number of Participants Analyzed [units: participants]	8	8	8	7
Terminal elimination half-life (T1/2) of FIA586 (units: hours)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	12.2 ± 6.91	7.31 ± 2.17	8.18 ± 2.54	9.17 ± 1.68

Apparent plasma clearance (CL/F) of FIA586

Description	Pharmacokinetic (PK) parameters were calculated using non-compartmental methods based on FIA586 concentrations in plasma determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. CL/F is the apparent total body clearance of drug from plasma following extravascular administration.
Time Frame	pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, 92 and 120 hours
Analysis Population Description	The PK set includes all participants who provided an evaluable PK profile. Each healthy participant was matched in age (±10 years), gender, weight (±15%), and smoking status (smoker or nonsmoker) to an individual participant in at least 1 hepatic impairment (HI) group but not to more than 1 participant in the same HI group.

	FIA586 oral 350mg in Healthy Matched Control (Mild HI)	**FIA586 oral 350mg with mild hepatic impairment**	**FIA586 oral 350mg in Healthy Matched Control (Moderate HI)**	**FIA586 oral 350mg with moderate hepatic impairment**
Arm/Group Description	Healthy matched control participants (Mild hepatic impairment) with normal hepatic function received a single oral dose of FIA586 (350mg)	Participants with mild hepatic impairment received a single oral dose of FIA586 (350mg)	Healthy matched control participants (Moderate hepatic impairment) with normal hepatic function received a single oral dose of FIA586 (350mg)	Participants with moderate hepatic impairment received a single oral dose of FIA586 (350mg)
Number of Participants Analyzed [units: participants]	8	8	8	7
Apparent plasma clearance (CL/F) of FIA586 (units: L/h)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**

	7.42 ± 2.54	7.19 ± 1.61	7.84 ± 2.68	6.94 ± 2.70

Apparent volume of distribution during terminal elimination phase (Vz/F) of FIA586

Description	Pharmacokinetic (PK) parameters were calculated using non-compartmental methods based on FIA586 concentrations in plasma determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. Vz/F is the apparent volume of distribution during terminal elimination phase following extravascular administration.
Time Frame	pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, 92 and 120 hours
Analysis Population Description	The PK set includes all participants who provided an evaluable PK profile. Each healthy participant was matched in age (±10 years), gender, weight (±15%), and smoking status (smoker or nonsmoker) to an individual participant in at least 1 hepatic impairment (HI) group but not to more than 1 participant in the same HI group.

	FIA586 oral 350mg in Healthy Matched Control (Mild HI)	**FIA586 oral 350mg with mild hepatic impairment**	**FIA586 oral 350mg in Healthy Matched Control (Moderate HI)**	**FIA586 oral 350mg with moderate hepatic impairment**
Arm/Group Description	Healthy matched control participants (Mild hepatic impairment) with normal hepatic function received a single oral dose of FIA586 (350mg)	Participants with mild hepatic impairment received a single oral dose of FIA586 (350mg)	Healthy matched control participants (Moderate hepatic impairment) with normal hepatic function received a single oral dose of FIA586 (350mg)	Participants with moderate hepatic impairment received a single oral dose of FIA586 (350mg)
Number of Participants Analyzed [units: participants]	8	8	8	7
Apparent volume of distribution during terminal elimination phase (Vz/F) of FIA586 (units: Liters)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	115 ± 36.5	72.6 ± 14.9	89.9 ± 36.6	87.8 ± 28.6

Safety Results

Time Frame	Treatment emergent adverse events were reported from the day of study drug administration (Day 1) up to 30 days post dose.
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	FIA586 oral 350mg in Healthy participants N = 13	FIA586 oral 350mg with mild hepatic impairment N = 8	FIA586 oral 350mg with moderate hepatic impairment N = 7
Arm/Group Description	Healthy participants with normal hepatic function received a single oral dose of FIA586 (350mg)	Participants with mild hepatic impairment received a single oral dose of FIA586 (350mg)	Participants with moderate hepatic impairment received a single oral dose of FIA586 (350mg)
Total Number Affected	0	0	0
Total Number At Risk	13	8	7

Serious Adverse Events

None

Other (Not Including Serious) Adverse Events

None

Conclusion:

- FIA586 plasma Cmax was slightly lower in participants with mild HI compared to healthy matched control participants, while AUClast and AUCinf were comparable between both groups.
- FIA586 plasma Cmax was comparable between participants with moderate HI and healthy matched control participants, while AUClast and AUCinf were slightly higher in the moderate HI group.
- Single doses of FIA586, administered to participants with mild or moderate HI and to healthy matched participants, were well tolerated in this study.

Date of Clinical Trial Report

26-May-2023