FRM-7043019 version 2.0

Sponsor
Novartis

Generic Drug Name
QAW039/Fevipiprant

Trial Indication(s)
Renal impairment

Protocol Number
CQAW039A2107

Protocol Title
An open-label, single-dose, parallel group study to assess the pharmacokinetics of fevipiprant (QAW039) in patients with End-stage Renal Disease on hemodialysis and optionally in patients with severe to moderate and mild renal impairment compared to matched healthy volunteers including a cross-over assessment in End-stage Renal Disease patients on the effect of dialysis on fevipiprant pharmacokinetics

Clinical Trial Phase
Phase I

Phase of Drug Development
Phase III

Study Start/End Dates
05Jul2017 to 07Aug2018

Reason for Termination (If applicable)

N/A

Study Design/Methodology

This was an open-label, parallel-group study to assess the pharmacokinetics of fevipiprant (QAW039) in patients with ESRD (Group 1) and their matched healthy volunteers (Group 2a). Patients with severe/moderate (Group 3), and mild (Group 4) renal impairment and their matched healthy controls (Group 2b) were also enrolled. In addition to the parallel groups, the study had a cross-over element, where enrolled patients with ESRD (Group 1) underwent hemodialysis to asses impact of dialysis on pharmacokinetics of fevipiprant. In the first period (Period 1), fevipiprant was administered after dialysis completion. Subsequently in Period 2, fevipiprant was administered 1 hour before dialysis start.

Centers

2 centers in 2 countries: United States of America (1), Germany (1)

Objectives:

Primary objective:

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

Secondary objectives:

- To assess the relationship between estimated Glomerular Filtration Rate (eGFR) as well as creatinine clearance and plasma PK parameters for fevipiprant
- To assess the safety and tolerability of fevipiprant in patients with renal impairment
- To assess the effect of dialysis on fevipiprant PK in patients with ESRD
- To assess the urinary excretion of fevipiprant in patients with renal impairment compared to healthy controls

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

All subjects were assigned to receive fevipiprant 450 mg; patients with ESRD received 2 single doses of fevipiprant 450 mg in 2 consecutive periods separated by a wash-out period of at least 7 days. All other patients and healthy subjects received 1 single dose of fevipiprant 450 mg.

Statistical Methods

Pharmacokinetic parameters Cmax, AUC0–68h (maximum 68 h PK collection was possible between two dialyses in ESRD patients) and AUCinf for fevipiprant were the primary variables for the assessment of PK of fevipiprant in patients with renal impairment compared to healthy matched controls. Individual log-transformed PK parameters (Cmax, AUC0–68h and AUCinf) of fevipiprant were analyzed separately using a linear mixed effects model with group as fixed effect and matched pair as random effect. Least square means for each group as well as contrasts between matched healthy and each renal impaired group with corresponding 90% confidence intervals on the logscale were calculated. Results were back transformed to provide ratio of geometric means and 90% confidence interval. Period 1 ESRD patients' data (dosing after dialysis) were used for comparison with matched healthy subjects.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Male or female subjects between 18 and 75 years of age, inclusive
- Healthy subjects must satisfy the criteria for normal renal function as evidenced by normal Glomerular Filtration Rate (GFR): eGFR ≥ 90 mL/min/1.73m2; each healthy subject must match in age (+/- 10years), gender, smoking status, and weight (+/- 15%), a patient from the renail impaired patient groups:
- A body mass index (BMI) within the range of 18 - 36 kg/m2
- ESRD patients on hemodialysis: eGFR of < 15 mL/min/1.73 m2
- Patients with severe renal impairment: eGFR of< 30 mL/min/1.73m2 (without need of hemodialysis);
- Patients with moderate renal impairment: 30 mL/min/1.73m2 ≤ eGFR < 60 mL/min/1.73m2;
- Patients with mild impairment: 60 mL/min/1.73m2 ≤ eGFR < 90 mL/min/1.73m2

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Exclusion Criteria:

- Pregnant or nursing (lactating) women
- History or evidence of any inherited bilirubin disease or disorder
- subjects participating in another study
- malignancies in the past
- Hemoglobin levels below 10 g/dL at screening
- HIV positiv
- Heavy smokers (≥20 cigarettes per day)
- Liver disease, as indicated by ALT, γ-GT, AST and alkaline phosphatase which should not exceed twice the upper limit of normal and should be stable (e.g. increased liver values known from previous patient records). Serum bilirubin > 27 µmol/L (1.6 mg/dL)
- Clinically significant ECG changes and/or arrhythmias
- Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV)

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Participant Flow Table

Subject disposition (Safety analysis set)

Disposition/Reason	ESRD patients N=8 n (%)	Matched healthy subjects N=8 n (%)	Severe/ Moderate renal impairment N=8 n (%)	Matched healthy subjects N=8 n (%)	Mild renal impairment N=8 n (%)	Matched healthy subjects N=8 n (%)	Pooled healthy subjects N21* n (%)	Total subjects N=45 n (%)
Epoch: Screening								
Completed	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	21 (100)	45 (100)
Epoch: Treatment Period 1								
Completed	8 (100)	7(87.5)	8 (100)	8 (100)	8 (100)	8 (100)	20(95.2)	44(97.8)
Discontinued	0	1(12.5)#	0	0	0	0	1 (4.8)#	1 (2.2)
Primary reason for discontinuing								
Subject/guardian decision	0	1(12.5)	0	0	0	0	1 (4.8)	1 (2.2)
Epoch: Treatment Period 2†	**N=8**	**N=0**	**N=0**	**N=0**	**N=0**	**N=0**	**N=0**	**N=8**
Completed	8 (100 %)	0	0	0	0	0	0	8 (100)

M = Number of subjects who entered the Epoch

* Healthy subjects can be a match to more than 1 patient with renal impairment

the discontinued subject in column "Matched healthy subject" and "Pooled healthy subjects" is the same subject

†All 8 patients with ESRD entered treatment Period 2 and completed the cross-over treatment period of the study

Baseline Characteristics

Summary of subject demographics (safety analysis set)

Characteristic		ESRD patients N=8	Matched healthy subjects to ESRD N=8	Severe/ moderate renal impairment N=8	Matched healthy subjects to Severe/moderate N=8	Mild renal impairment N=8	Matched healthy subjects to Mild N=8	Pooled healthy subjects N=21	Total subjects N=45
Age (years)									
	Mean (SD)	54.1 (9.14)	54.4 (9.50)	63.0 (11.34)	62.9 (10.83)	68.6 (6.46)	63.9 (6.62)	59.5 (9.89)	60.8 (10.28)
	Median	54.0	56.0	69.0	63.0	70.5	64.5	58.0	60.0
	Range	38–68	40–71	39–71	44–74	54–74	53–73	40–74	38–74
Sex – n (%)									
	Male	5 (62.5)	5 (62.5)	6 (75)	6 (75)	4 (50)	4 (50)	13 (61.9)	28 (62.2)
	Female	3 (37.5)	3 (37.5)	2 (25)	2 (25)	4 (50)	4 (50)	8 (38.1)	17 (37.8)
Race – n (%)									
	Other	0	0	0	0	1 (12.5)	0	0	1 (2.2)
	Black	3 (37.5)	3 (37.5)	1 (12.5)	1 (12.5)	0	1 (12.5)	4 (19)	8 (17.8)
	Caucasian	5 (62.5)	5 (62.5)	7 (87.5)	7 (87.5)	7 (87.5)	7 (87.5)	17 (81)	36 (80)

Characteristic		ESRD patients N=8	Matched healthy subjects to ESRD N=8	Severe/ moderate renal impairment N=8	Matched healthy subjects to Severe/moderate N=8	Mild renal impairment N=8	Matched healthy subjects to Mild N=8	Pooled healthy subjects N=21	Total subjects N=45
Ethnicity – n (%)									
	Hispanic or Latino	0	0	0	0	2 (25)	0	0	2 (4.4)
	Not Hispanic or Latino	8 (100)	8 (100)	7 (87.5)	8 (100)	6 (75)	8 (100)	21 (100)	42 (93.3)
	Not reported	0	0	1 (12.5)	0	0	0	0	1 (2.2)
Weight (kg)									
	Mean (SD)	79.7 (14.15)	83.5 (15.06)	81.6 (13.32)	82.6 (12.13)	71.4 (14.86)	73.6 (15.85)	79.7 (14.38)	78.6 (14.18)
	Median	81.5	85.6	83.1	84.9	75.5	78.5	83.4	81.0
	Range	50.5–96.1	58.0–102.9	63.8–98.9	59.6–94.0	53.0–88.2	52.0–93.4	52.0–102.9	50.5–102.9
Height (cm)									
	Mean (SD)	173 (13.5)	174 (8.8)	168 (7.1)	173 (12.7)	166 (12.1)	163 (9.9)	171 (11.4)	170 (11.2)
	Median	171	173	168	174	167	167	172	169
	Range	155–196	162–185	154–178	153–189	143–180	146–176	146–189	143–196

Summary of Efficacy

Primary Outcome Result(s)

Summary statistics of plasma PK parameters for fevipiprant (PK analysis set)

PK parameter (unit)	ESRD patients† N=8	Matched healthy subjects to ESRD N=8	Severe/ moderate renal impairment*** N=8	Matched healthy subjects to Severe/moderate N=8	Mild renal impairment N=8	Matched healthy subjects to Mild N=8	Pooled healthy subjects N=21
Cmax (ng/mL)	2820 ± 1610 (56.8)	2090 ± 991 (47.4)	2580 ± 1030 (40.0)	2280 ± 1330 (58.6)	3820 ± 3580 (93.8)	4750 ± 3180 (66.9)	3010 ± 2430 (80.9)
AUC0-68 (h*ng/mL)	17600 ± 8360 (47.4)	8870 ± 2930 (33.1)	18100 ± 8160 (45.1)	9380 ± 3460 (36.9)	17300 ± 9720 (56.1)	15200 ± 7060 (46.4)	11100 ± 5710 (51.4)
AUCinf (h*ng/mL)	20000 ± 12100 (60.7)*	9530 ± 3280 (34.4)	17000 ± 7280 (42.8)*	10200 ± 3740 (36.5)*	15900 ± 8280 (52.2)*	15800 ± 7400 (46.9)	11900 ± 5970 (50.2)**
Tmax# (h)	2.00 (0.500–6.00)	2.00 (0.500–2.00)	1.00 (0.500–8.00)	2.00 (2.00–3.00)	2.00 (1.00–3.00)	2.00 (2.00–3.00)	2.00 (0.500–3.00)
fu	0.126 ± 0.0172 (13.6)	0.111 ± 0.00703 (6.4)	0.105 ± 0.0155 (14.8)	0.113 ± 0.0121 (10.7)	0.0988 ± 0.00697 (7.1)	0.113 ± 0.0132 (11.6)	0.113 ± 0.0110 (9.8)
T1/2 (h)	24.6 ± 15.9 (64.6)	21.6 ± 11.9 (55.3)	18.7 ± 9.76 (52.2)*	12.6 ± 2.24 (17.9)*	31.0 ± 27.1 (87.3)	16.3 ± 5.75 (35.3)	17.5 ± 8.91 (50.9)**
Vz/F (L)	786 ± 338 (43.0)*	1650 ± 1160 (70.3)	751 ± 265 (35.3)*	851 ± 197 (23.1)*	1080 ± 603 (55.7)*	767 ± 357 (46.6)	1150 ± 854 (74.5)**
Cl/F (L/h)	31.0 ± 18.3 (59.1)*	51.9 ± 16.0 (30.8)	31.4 ± 14.6 (46.4)*	49.0 ± 16.3 (33.3)*	36.1 ± 19.4 (53.9)*	34.5 ± 16.6 (48.2)	45.2 ± 17.3 (38.4)**

Values are presented as Mean ± SD (CV%) [n]; CV% = Coefficient of variation (%) = SD/mean*100

†Period 1 ESRD patients' data (dosing after dialysis) were used for comparison with matched healthy subjects

#For Tmax, values are Median (Min–Max) [n]

Geometric mean ratio and 90% confidence intervals for fevipiprant PK parameters for patients with ESRD and renal impairment versus matched healthy subjects (PK analysis set)

					Group Comparison		
Parameter	**Group**	**n***	**Adjusted Geo-mean**	**Comparison**	**Geo-mean ratio**	**(SE)**	**(90% CI)**
Cmax (ng/mL)	Matching healthy subjects for ESRD	8	1854.03				
	ESRD patients with dialysis (Period 1)	8	2490.84	versus Healthy matches	1.34	1.31	(0.84, 2.15)
	Matching healthy subjects for severe/moderate renal impairment	8	1960.12				
	Patients with severe / moderate renal impairment	8	2383.75	versus Healthy matches	1.22	1.30	(0.77, 1.93)
	Matching healthy subjects for mild renal impairment	8	3815.83				
	Patients with mild renal impairment	8	2954.15	versus Healthy matches	0.77	1.30	(0.47, 1.27)

					Group Comparison		
Parameter	**Group**	**n***	**Adjusted Geo-mean**	**Comparison**	**Geo-mean ratio**	**(SE)**	**(90% CI)**
AUC0–68 (h*ng/mL)	Matching healthy subjects for ESRD	8	8466.09				
	ESRD patients with dialysis (Period 1)	8	15858.05	versus Healthy matches	1.87	1.23	(1.27, 2.75)
	Matching healthy subjects for severe/moderate renal impairment	8	8863.20				
	Patients with severe / moderate renal impairment	8	16433.28	versus Healthy matches	1.85	1.20	(1.32, 2.60)
	Matching healthy subjects for mild renal impairment	8	13876.60				
	Patients with mild renal impairment	8	15001.24	versus Healthy matches	1.08	1.18	(0.78, 1.49)
AUCinf (h*ng/mL)	Matching healthy subjects for ESRD	8	9075.67				
	ESRD patients with dialysis (Period 1)	7	16844.88	versus Healthy matches	1.86	1.25	(1.21, 2.84)
	Matching healthy subjects for severe/moderate renal impairment	7	9762.34				

					Group Comparison		
Parameter	Group	n*	Adjusted Geo-mean	Comparison	Geo-mean ratio	(SE)	(90% CI)
	Patients with severe / moderate renal impairment	7	15856.59	versus Healthy matches	1.62	1.23	(1.09, 2.43)
	Matching healthy subjects for mild renal impairment	8	14354.83				
	Patients with mild renal impairment	7	14799.04	versus Healthy matches	1.03	1.22	(0.70, 1.52)

n*=number of subjects with non-missing values

Secondary Outcome Result(s)

Summary statistics of fevipiprant plasma PK parameter values in patients with ESRD in Period 1 and Period 2

	ESRD patients	
PK parameter (unit) #	Not on dialysis (Period 1) N=8	With dialysis (Period 2) N=8
Cmax (ng/mL)	2820 ± 1610 (56.8)	1710 ± 686 (40.0)
AUC1–5 (h*ng/mL)	5710 ± 2050 (35.9)	4060 ± 1750 (43.0)
AUC0–68 (h*ng/mL)	17600 ± 8360 (47.4)	12500 ± 6750 (53.8)
AUCinf (h*ng/mL)	20000 ± 12100 (60.7)*	15000 ± 8600 (57.4)
Tmax (h)	2.00 (0.500–6.00)	2.00 (1.00–3.00)
T1/2 (h)	24.6 ± 15.9 (64.6)	32.1 ± 16.3 (50.9)
Vz/F (L)	786 ± 338 (43.0)*	1610 ± 851 (52.8)
Cl/F (L/h)	31.0 ± 18.3 (59.1)*	44.0 ± 36.4 (82.7)

Values are presented as mean ± SD (CV%) [n]; CV% = Coefficient of variation (%) = SD/mean*100

For Tmax, statistics are median (min–max) [n]

*n=7

N=number of subjects studied; n=number of subjects with non-missing values

Period 1: Fevipiprant dosing after dialysis; Period 2: Fevipiprant dosing before dialysis

Geometric mean ratio and 90% confidence intervals for fevipiprant PK parameters for patients with ESRD in Period 1 versus Period 2 (PK analysis set)

				Group Comparison		
Parameter	ESRD patients	n*	Adjusted Geo-mean	Comparison	Geo-mean ratio	(SE)	(90% CI)
Cmax (ng/mL)	Not on dialysis (Period 1)	8	2490.84				
	With dialysis (Period 2)	8	1590.52	versus Not on dialysis (Period 1)	1.57	1.18	(1.14, 2.15)
AUC0–68 (h*ng/mL)	Not on dialysis (Period 1)	8	15858.05				
	With dialysis (Period 2)	8	10859.05	versus Not on dialysis (Period 1)	1.46	1.07	(1.29, 1.66)
AUCinf (h*ng/mL)	Not on dialysis (Period 1)	7	17318.08				
	With dialysis (Period 2)	8	12682.41	versus Not on dialysis (Period 1)	1.37	1.08	(1.18, 1.58)
AUC1–5 (h*ng/mL)	Not on dialysis (Period 1)	8	5417.52				
	With dialysis (Period 2)	8	3672.56	versus Not on dialysis (Period 1)	1.48	1.13	(1.17, 1.85)

n* = number of subjects with non-missing values;

Period 1: Fevipiprant dosing after dialysis; Period 2: Fevipiprant dosing before dialysis

Summary statistics of Urine PK parameter values

PK parameter (unit)	Severe/Moderate Renal impairment N=8	Mild renal impairment N=8	Pooled healthy subjects N=21
Renal clearance (CLr) (L/h)	1.72 ± 0.825 (48.1) [8]	3.31 ± 1.83 (55.2) [8]	7.95 ± 2.84 (35.7) [20]
Amount (Ae0–24h) (mg)	25.4 ± 17.2 (67.6) [8]	36.9 ± 13.9 (37.7) [8]	67.1 ± 23.0 (34.3) [20]
Fraction of dose excreted unchanged in urine (%)	5.65 ± 3.82 (67.6) [8]	8.20 ± 3.09 (37.7) [8]	14.9 ± 5.11 (34.3) [20]

Values are presented as mean ± SD (CV%) [n]

CV% = coefficient of variation (%)=sd/mean*100

Summary of Safety

Safety Results

Incidence of AEs by primary system organ class - n (percent) of subjects (Safety analysis set)

	ESRD (Period 1) N=8 n (%)	ESRD (Period 2) N=8 n (%)	Severe/ Moderate Renal Impairment N=8 n (%)	Mild Renal Impairment N=8 n (%)	Pooled Healthy Subjects N=21 n (%)	Total N=45 n (%)
Number of subjects with at least one AE	0	0	1 (12.5)	2 (25.0)	4 (19.0)	7 (15.6)
Primary system organ class						
Nervous system disorders	0	0	0	1 (12.5)	2 (9.5)	3 (6.7)
Gastrointestinal disorders	0	0	0	0	2 (9.5)	2 (4.4)
General disorders and administration site conditions	0	0	0	1 (12.5)	0	1 (2.2)
Musculoskeletal and connective tissue disorders	0	0	1 (12.5)	0	0	1 (2.2)
Skin and subcutaneous tissue disorders	0	0	0	1 (12.5)	0	1 (2.2)

A subject with multiple AEs was counted only once in the "at least one AE" row
A subject with multiple AEs within a primary system organ class was counted only once for that system organ class and group
Primary system organ classes were sorted in descending frequency, as reported in the Total column

Incidence of AEs by preferred term - n (percent) of subjects (Safety analysis set)

	ESRD (Period 1) N=8 n (%)	ESRD (Period 2) N=8 n (%)	Severe/ Moderate Renal Impairment N=8 n (%)	Mild Renal Impairment N=8 n (%)	Pooled Healthy Subjects N=21 n (%)	Total N=45 n (%)
Number of subjects with at least one AE	0	0	1 (12.5)	2 (25.0)	4 (19.0)	7 (15.6)
Preferred term						
Headache	0	0	0	1 (12.5)	2 (9.5)	3 (6.7)
Back pain	0	0	1 (12.5)	0	0	1 (2.2)
Constipation	0	0	0	0	1 (4.8)	1 (2.2)
Dry skin	0	0	0	1 (12.5)	0	1 (2.2)
Thirst	0	0	0	1 (12.5)	0	1 (2.2)
Toothache	0	0	0	0	1 (4.8)	1 (2.2)

A subject with multiple AEs was counted only once in the "at least one AE" row
A subject with multiple AEs with the same preferred term was counted only once for that preferred term & group
Preferred terms are sorted in descending frequency, as reported in the Total column

Other Relevant Findings

N/A

Conclusion:

The results of the study showed an increase in AUC0–68h of fevipiprant by 1.87-, 1.85- and 1.08-fold in patients with ESRD, severe/moderate and mild renal impairment relative to their matched healthy subjects, respectively. Considering variability, total Cmax values were comparable with geo-mean ratios of 1.34 and 1.22, and 0.77 respectively for patients with ESRD (dosed after dialysis), severe/moderate, and mild impairment in comparison to matched healthy subjects. In ESRD patients when undergoing dialysis (1h to 5h after dosing), systemic exposure to fevipiprant decreased by approximately 1.5 fold as compared to when fevipiprant was dosed after dialysis. There was no impact of renal impairment on plasma protein binding of fevipiprant. Therefore, the PK profile of unbound fevipiprant was overall similar to bound fevipiprant in plasma. The AUC0–68h,u of fevipiprant were 2.13, 1.71 and 0.95-fold in patients with ESRD, severe/moderate and mild renal impairment relative to their matched healthy subjects. The modest correlation of the degree of renal impairment (as assessed by eGFR or the creatinine clearance) with AUC0–68h values confirms the relevance of non-renal elimination pathways for fevipiprant. The correlation was comparable for the BSA normalized measure of renal function (eGFR) and the estimates of absolute eGFR.

Renal clearance of fevipiprant and the fraction of dose excreted unchanged in urine decreased in patients with mild and severe/moderate renal impairment as compared to healthy subjects. Due to lack of urine production, impact could not be assessed in ESRD subjects. While the impact on renal clearance was pronounced even in mild renal impairment, no relevant changes in systemic exposure were observed in this population. Again, the contribution of non-renal elimination pathways of fevipiprant explains why only high degrees of renal impairment have an impact on systemic PK.

Overall severe/moderate and end stage renal impairment as well as dialysis can impact systemic exposure of fevipiprant, but the impact is small (≤ 2 fold). The single oral dose of 450 mg fevipiprant was safe and well tolerated in patients with ERSD, varying degree of renal impairment and matched healthy subjects.

Date of Clinical Trial Report

12 Feb 2019