Sponsor

Novartis

Generic Drug Name

NVA237

Therapeutic Area of Trial

Renal impairment

Approved Indication

Investigational

Protocol Number

CNVA237A2105

Title

An open label, non-randomized, parallel-group study to characterize and compare the pharmacokinetics, safety, and tolerability of a single dose of NVA237 in subjects with mild, moderate, severe and end-stage renal impairment with that in matched healthy control subjects

Phase of Development

Phase I

Study Start/End Dates

25-Jun-10 to 08-Nov-10

Study Design/Methodology

This was a single-dose, open-label, non-randomized, parallel-group study in subjects with mild, moderate, severe or end-stage renal impairment and healthy volunteers. Each renally impaired subject was appropriately matched to a healthy volunteer. The study consisted of a 28-day screening period, a baseline period, one treatment period followed by an end of study evaluation (for all groups except for the end-stage subjects requiring dialysis (ESRD), for whom a second treatment period was envisioned).

All subjects received a single dose of 100 µg NVA237. The ESRD subjects were to receive another dose of 100 µg NVA237 in the second treatment period just after the start of 4-hour dialysis.

Centres

Russia (2 centers)

Publication

None

Outcome measures

Primary outcome measures(s)

- Area under the plasma concentration-time curve from time 0 to the last quantifiable concentration (AUC_{last}) of NVA237
- Maximum plasma concentration (C_{max}) of NVA237
- Renal clearance (CL_R) of NVA237
- Time to C_{max} (T_{max}) of NVA237
- AUC extrapolated to infinity (AUC_{inf}) of NVA237
- Terminal elimination half-life, determined from plasma concentrations and urinary excretion rates ($T_{1/2}$) of NVA237
- f Apparent systemic clearance (CL/F) of NVA237
- Amount excreted into the urine from time 0 to 96 h post-dose (Ae0-96h) of NVA237

Secondary outcome measures(s)

- change in effect of dialysis in End-stage subjects requiring dialysis (ESRD) using PK parameter C_{max}
- change in effect of dialysis in End-stage subjects requiring dialysis using PK parameter AUC_{last}
- safety and tolerability of a single inhalation dose of 100µg NVA237 in subjects with mild, moderate, severe, and end-stage renal impairment

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

The investigational drug was NVA237 50µg dry powder capsules for inhalation

Statistical Methods

The primary PK parameters were compared between each renally impaired group (mild, moderate, severe and ESRD respectively) vs. the matched control group, using an analysis of covariance model for the (natural) log-transformed PK values, with body weight at baseline, age and gender as covariates. The matched control group was (for each of the renally impaired Groups 2 to 5) a subset of the healthy volunteers group of the same size as the renally impaired group to which it was matched. Least square means for each group as well as contrasts between control and each renally impaired group with corresponding 90% confidence intervals on the log-scale were calculated via the model. Back-transformed ratios and 90% confidence interval were provided. A sensitivity analysis was also performed where each renally impaired group was compared jointly to the full group of 18 healthy volunteers, while still maintaining the pair

information

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Male and female subjects age 18 to 70 years of age inclusive.
- Female subjects of childbearing potential must be using two acceptable methods of contraception, (e.g., intra-uterine device plus condom, spermicidal gel plus condom, diaphragm plus condom, etc.), from the time of screening and for the duration of the study, through study completion.
- Subjects must weigh at least 50 kg to participate in the study, and must have a body mass index (BMI) within the range of 17 to 35 kg/m2.
- Able to communicate well with the investigator, to understand and comply with the requirements of the study. Understand and sign the written informed consent
- For renal insufficient subjects only - Subjects must have stable renal disease without evidence of renal progressive disease (for the purpose of this study stable renal disease will be defined as no significant change for 12 weeks).
- For health subjects only - A serum creatinine within the normal range and an eGFR >80 mL/min/1.73 $m^{2.}$
- For health subjects only - Matched to at least one renal impaired subjects undergoing study by age (±5 years), sex and weight (±10% BMI).

Exclusion criteria

- Smokers (use of tobacco products in the previous 3 months). Smokers were defined as any subject who reports tobacco use and/or who has a urine cotinine ≥ 500 ng/mL. If non-smoking subject were too difficult to recruit, smokers were allowed to participate in the study provided they commit to smoke no more than 10 cigarettes/day during the days of PK-assessment
- For healthy subjects, use of any prescription drugs, herbal and fitness/bodybuilding/athletic performance-enhancing supplements, within four (4) weeks prior to initial dosing, and/or over-the-counter (OTC) medication, dietary supplements (vitamins included) within two (2) weeks prior to initial dosing
- Recent (within the last three [3] years) and/or recurrent history of autonomic dysfunction (e.g., recurrent episodes of fainting (unless related to water withdrawal during dialysis), palpitations, etc).
- Recent (within the last three [3] years) and/or recurrent history of acute or chronic bronchospastic disease (including asthma and chronic obstructive pulmonary disease, treated or not treated).
- History of multiple and recurring allergies or allergy to the investigational compound/compound class being used in this study.
- Total WBC count which falls outside the range of 3000–12,000/µL, or platelets <100,000/µl at screening.
- History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result.

Other protocol-defined inclusion/exclusion criteria may apply.

Participant Flow

Patient disposition (Safety analysis set)

	Healthy volunteers (Group 1)	Renally impaired groups			
		Mild (Group 2)	Moderate (Group 3)	Severe (Group 4)	ESRD (Group 5)
	N=18	N=8	N=8	N=8	N=6
	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects					
Completed	18 (100)	8 (100)	8 (100)	8 (100)	5 (83)
Discontinued	0	0	0	0	1 (17)
Main cause of discontinuation					
Subject withdrew consent	0	0	0	0	1 (17)

Baseline Characteristics

Demographic summary by group (Safety analysis set)

Demographic variable		Renally impaired subjects				Healthy volunteers (Group 1)
		Mild (Group 2)	Moderate (Group 3)	Severe (Group 4)	ESRD (Group 5)	
		N=8	N=8	N=8	N=6	N=18
Age (years)	Mean	58	59	59	48	54
	SD	6.6	8.2	6.0	11.8	11.0
	Range	52-69	48-69	51-69	34-66	29-69
Sex – n (%)	Male	4 (50%)	3 (38%)	4 (50%)	6(100%)	12 (67%)
	Female	4 (50%)	5 (63%)	4 (50%)	0	6 (33%)
Race – n (%)	Caucasian	8 (100%)	8 (100%)	8 (100%)	6 (100%)	18 (100%)
Weight (kg)	Mean	82.6	85.7	89.0	80.5	81.6
	SD	12.22	9.80	7.04	17.34	10.79
	Range	67.0-99.7	66.1-100.5	80.1-104.1	58.0-104.5	68.3-108.9
Height (cm)	Mean	169	165	166	175	170
	SD	6.9	6.5	9.5	3.3	12.0
	Range	156-177	155-176	157-181	170-180	148-192
BMI (kg/m^2)	Mean	28.9	31.7	32.3	26.2	28.5
	SD	4.92	4.55	2.52	5.21	4.02
	Range	22.1-34.9	21.3-34.8	27.7-34.8	18.7-33.7	20.5-34.6

Outcome measures

Primary Outcome Result(s)

1. Key plasma PK parameters

Summary of key plasma PK parameters (PK analysis set, Period 1)

PK parameter		Renally impaired subjects				Healthy volunteers (Group 1)
		Mild (Group 2)	Moderate (Group 3)	Severe (Group 4)	ESRD* (Group 5)	
		N=8	N=8	N=8	N=6	N=18
Cmax	Mean	336	277	334	303	356
(pg/mL)	SD	158	123	106	174	164
	CV%	47.1	44.4	31.9	57.4	46.1
AUClast	Mean	1180	847	2080	1940	821
(hr*pg/mL)	SD	428	276	1410	1560	288
	CV%	36.2	32.7	67.5	80.7	35.1
AUCinf	N[1]	7	4	7	6	12
(hr*pg/mL)	Mean	1630	1320	2730	3740	1020
	SD	485	320	1730	4970	400
	CV%	29.9	24.4	63.4	133	39.2
Tmax (hr)	Median	0.083	0.083	0.083	0.125	0.083
	Range	0.083-0.083	0.083-0.25	0.083-0.25	0.083-0.25	0.083-0.167
T1/2 (hr)	N[1]	7	4	7	6	12
	Mean	50.9	39.9	46.0	61.7	32.5
	SD	19.4	27.6	7.01	38.0	23.4
	CV%	38.1	69.1	15.2	61.6	72.1
CL/F (L/hr)	N[1]	7	4	7	6	12
	Mean	66.8	79.7	49.5	50.9	114
	SD	21.6	20.3	26.5	23.1	46.2
	CV%	32.3	25.4	53.6	45.4	40.6

All values rounded to 3 significant digits; * data for Period 1 only.
[1] Reduced values of N provided for parameters that could not be estimated for all subjects

2. Key urine PK parameters

Summary of key urine PK parameters (PK analysis set)

PK parameter		Renally impaired subjects			Healthy volunteers (Group 1)
		Mild (Group 2)	Moderate (Group 3)	Severe (Group 4)	
		N=8	N=8	N=8	N=18
Ae0-96h	Mean	16.3	9.89	8.43	20.0

(µg) or (% dose)[1]	SD	4.39	3.71	4.28	6.38
	CV%	27.0	37.5	50.8	31.9
T1/2 (hr)	N[2]	7	7	8	17
	Mean	45.9	46.1	47.5	35.1
	SD	12.2	13.7	14.0	11.5
	CV%	26.6	29.7	29.6	32.6
CLr	Mean	14.2	10.4	4.88	23.0
(L/hr)	SD	4.52	2.70	2.63	7.50
	CV%	31.8	25.9	53.9	32.6

All values rounded to 3 significant digits; ESRD patients were not included as they did not produce urine. [1] Ae0-96h values in µg and % dose are the same as the dose is 100 µg.

[2] Reduced values of N provided for parameters that could not be estimated for all subjects/group

Secondary Outcome Result(s)

Change in effect of dialysis in End-stage subjects requiring dialysis (ESRD)

Summary of statistical analysis of PK parameters for ESRD subjects with and without dialysis (Group 5 of PK analysis set)

Parameter	Period	LS Mean (90% CI)	Ratio Period 2 vs Period 1 (90% CI)
Cmax (pg/mL)	1	5.52 (5.44, 5.60)	
	2	4.92 (4.50, 5.34)	0.55 (0.35, 0.87)
AUClast	1	7.28 (7.05, 7.52)	
(hr*pg/mL)	2	7.00 (6.85, 7.14)	0.75 (0.54, 1.05)

Safety Results

No adverse events, serious adverse events or deaths were reported by or for the subjects in this study.

Other Relevant Findings

None.

Date of Clinical Trial Report 30-Jun-2011
Date Inclusion on Novartis Clinical Trial Results Database 14March2012
Date of Latest Update 14March2012