Sponsor

Novartis

Generic drug name

Camostat mesylate (QAU145A)

Trial indication(s)

Cystic fibrosis

Protocol number

CQAU145A2201

Protocol title

A two-part, randomized, double-blind, placebo-controlled, ascending single-dose, adaptive study to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of QAU145 administered via a nasal spray pump to patients with cystic fibrosis

Clinical trial phase

Phase IIA

Phase of Drug Development

Phase II

Study Start/End Dates

12 Jul 2007 to 12 Dec 2008

Study Design/Methodology

This study was a randomized, double-blind, placebo-controlled, alternating panel, ascending single-dose study conducted in two parts. The Part I of the study was comprised of 2 panels of patients (Panels A and B) which consisted of 3 patients in each panel. Panel A and B went through 3 treatment periods in an alternate fashion. In Treatment Periods 1 and 2, ascending single doses of 0.2 mg, 0.8 mg and 1.6 mg were administered. Of the 3 patients enrolled in Periods 1 and 2 respectively, 2 patients were randomized to receive QAU145 and 1 patient was randomized to receive placebo. In Treatment Period 3, patients received the 1.6 mg dose in a balanced crossover fashion with respect to Treatment Period 2. Different patients within each Panel were randomized to receive placebo in each treatment period. There was a gap of at least 7 days between dose administrations in subsequent dose levels. In addition, for individual patients in the same panel, doses of QAU145/Placebo were given at least 14 days apart (e.g., for a given patient, each Treatment Period 1, 2, and 3 was at least 14 days apart).

Centers

The study was conducted at single centre in the United States.

Objectives:

Primary objective(s)

The primary objective of this study was to preliminarily assess the pharmacodynamic response to single intranasal doses of QAU145 in patients with cystic fibrosis (CF) using nasal potential difference (NPD) measurements.

Secondary objective(s)

- To evaluate the safety and tolerability of single ascending doses of QAU145 administered via a nasal pump spray to patients with CF.
- To evaluate the pharmacokinetics (PK) (systemic exposure and urinary excretion during 6 hours) following single intranasal doses of QAU145 in patients with CF.

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

Dosing during Part I:

- In Panel A, patients received 0.2 mg of QAU145 or placebo (1 mg/mL x 1 actuation per nostril) in Treatment Period 1 and 1.6 mg of QAU145 or placebo (2 mg/mL x 4 actuations per nostril) in Treatment Periods 2 and 3 in a balanced crossover fashion.
- In Panel B, patients received 0.8 mg of QAU145 or placebo (2 mg/mL x 2 actuation per nostril) in Treatment Period 1 and 1.6 mg of QAU145 or placebo (2 mg/mL x 4 actuations per nostril) in Treatment Periods 2 and 3 in a balanced crossover fashion.

Dosing during Part II:

- Panel C patients were to receive doses between 0.5 and 20 µg QAU145 in each Treatment Period. Actual doses administered were 5 µg (0.025 mg/mL x 1 actuation per nostril), 10 µg (0.05 mg/mL x 1 actuation per nostril) and 20 µg (0.1 mg/mL x 1 actuation per nostril), or placebo. The dose was administered as 1 actuation per nostril in all treatment periods.

Statistical Methods

The primary variable was the change in maximal basal NPD from pre-dose to 2 hours post-dose in the target nostril (ΔNPD 2h). For Part I an analysis of covariance (ANCOVA) model was employed, including a fixed factor for treatment (placebo or dose of QAU145 received), a random factor for subject, and the pre-dose NPD value as a covariate. The primary contrast of interest was the difference between QAU145 at the maximum tolerated dose (1.6 mg) and placebo ($\Delta NPD_{2h,\ 1.6\ mg} - \Delta NPD_{2h,\ Placebo}$). After completion of Part I, an interim analysis was performed at which a Bayesian posterior distribution for this contrast was obtained using a non-informative prior. If this contrast was positive with a probability of at least 90%, i.e.

$$P[(\Delta NPD_{2h,QAU145} - \Delta NPD_{2h,Placebo}) > 0] > 90\%,$$

then positive proof of concept was to be declared.

Exploration of the dose-NPD response relationship in Part II was conducted using a Bayesian response-adaptive design.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Male and female (women must be post-menopausal or surgically sterile) patients with cystic fibrosis ages 18 to 50.

Exclusion criteria:

- Any presence of seasonal or non-seasonal allergies affecting the nose, nasal passages, throat or sinuses within 2 weeks prior to dosing.
- Any upper respiratory tract infection or signs or symptoms within 2 weeks prior to dosing.
- Any presence of nasal polyps or structural abnormalities, frequent history of nose bleeding, or any recent nasal surgery (within 12 weeks prior to dosing).

Participant Flow Table

Part	Total (N = 9)
Part I/ Panel A	
Started	4
Completed	3
Discontinued	1
Reason for discontinuation	
Subject withdrew consent	1
Part I/ Panel B	
Started	5
Completed	3
Discontinued	2
Reason for discontinuation	
Subject withdrew consent	1
Withdrawn from the study	1

Part II/Panel C	
Started	4[1]
Completed	4
Discontinued	0

[1] 2 patients were hospitalized during Part I of the study due to pulmonary exacerbation and not continued in Panel C.

Baseline Characteristics

		All subjects N = 9
Age (years)	Mean	30.3
	SD	9.43
	Median	31.0
	Range (min – max)	20 - 49
Gender – n (%)	Male	6 (66.7%)
	Female	3 (33.3%)
Race – n (%)	Caucasian	8 (88.9%)
	Black	1 (11.1%)
Weight (kg)	Mean	67.87
	SD	13.59
	Median	68.10
	Range (min – max)	49.8 – 91.4
Height (cm)	Mean	164.7
	SD	5.10
	Median	162.0
	Range (min – max)	160 - 172

Note: Weight and height were taken from Screening vital signs evaluations.

Summary of Efficacy

Primary Outcome Result(s)

Maximal basal NPD in target nostril for Parts I and II:

Part I

Treatment	Statistics	Pre-dose	2h Post-dose	Change
5 ug	n	4	4	4
	mean	-38.6	-46.75	-8.13
	SD	19.61	18.505	6.223
	minimum	-63	-65.5	-14.0
	median	-34.8	-47.50	-8.00
	maximum	-22	-26.5	-2.5
10 ug	n	3	3	3
	mean	-37.5	-34.50	3.00
	SD	9.96	14.257	8.047
	minimum	-49	-48.5	-3.5
	median	-32.0	-35.00	0.50
	maximum	-32	-20.0	12.0
20 ug	n	3	3	3
	mean	-50.8	-41.83	9.00
	SD	19.85	21.014	12.010
	minimum	-64	-64.5	-0.5
	median	-60.5	-38.00	5.00
	maximum	-28	-23.0	22.5
Placebo	n	2	2	2
	mean	-39.0	-54.75	-15.75
	SD	1.41	12.374	13.789
	minimum	-40	-63.5	-25.5
	median	-39.0	-54.75	-15.75
	maximum	-38	-46.0	-6.0

Part II

Treatment	Statistics	Pre-dose	2h Post-dose	Change
0.2 mg	n	2	2	2
	mean	-38.3	-14.75	23.50
	SD	8.13	3.182	4.950
	minimum	-44	-17.0	20.0
	median	-38.3	-14.75	23.50
	maximum	-33	-12.5	27.0
0.8 mg	n	2	2	2
	mean	-35.0	-22.75	12.25
	SD	22.63	10.960	11.667
	minimum	-51	-30.5	4.0
	median	-35.0	-22.75	12.25
	maximum	-19	-15.0	20.5
1.6 mg	n	7	7	7
	mean	-40.0	-27.79	12.21
	SD	17.09	11.895	12.335
	minimum	-64	-44.0	-6.0
	median	-38.0	-27.00	10.00
	maximum	-20	-9.5	31.0
Placebo	n	8	8	8
	mean	-46.1	-52.50	-6.44
	SD	21.94	13.328	13.181
	minimum	-78	-76.0	-28.0
	median	-45.3	-50.25	-3.00
	maximum	-23	-38.5	10.0

Analysis of maximal change from pre-dose dose in target nostril - basal NPD to 2 hours post-dose - Part 1

		Comparison to Placebo	
Treatment	LS Mean	Difference (80% CI)	p-Value
Placebo	-8.6		
QAU145 0.2 mg	26.4	35.0 (25.4, 44.6)	<.001
QAU145 0.8 mg	15.2	23.7 (14.4, 33.1)	0.004
QAU145 1.6 mg	13.1	21.7 (15.7, 27.8)	<.001

Secondary Outcome Result(s)

Arithmetic mean [CV%] plasma pharmacokinetic parameters of QAY243 after single intranasal administration of 0.8 mg and 1.6 mg QAU145

Parameter (Unit)	Intranasal QAU145 (N=1) Analyte QAY243	Intranasal QAU145 (N=7) Analyte QAY243
Dose (mg)	0.8	1.6
Tmax (h)	0.50	0.25 [0.07; 3.03] [a)]
Cmax (ng/mL)	0.90	2.39 [61.4]
Cmax/Dose ((ng/mL)/mg)	1.39	1.85 [61.4]
AUClast (h*ng/mL)	0.225	4.597 [59.2]
AUClast/Dose ((h*ng/mL)/mg)	0.281	2.873 [59.2]
Tlast (h)	0.50	3.00 [2.97; 3.25] [a)]

a) Median (min, max)

Arithmetic mean [CV%] urine pharmacokinetic parameters of QAY243 after single intranasal administration of 0.2 mg, 0.8 mg and 1.6 mg QAU145

Parameter (Unit)	Intranasal QAU145 (N=2) Analyte QAY243	Intranasal QAU145 (N=2) Analyte QAY243	Intranasal QAU145 (n=7) Analyte QAY243
Dose (mg)	0.2	0.8	1.6
Tmax (h)	1.50 [1.50; 1.50]	3.00 [1.50; 4.50]	1.50 [1.50; 1.50] [a)]
ERmax (ng/h)	800.4	1120	6356 [64.1]
% recovered (0-6h)	1.90	0.66	1.79 [65.7]
Ae (0-3h) (ng)	2401	2298	19070 [64.1]
Ae (3-6h) (ng)	655.8	1232	4052 [89.5]
Ae (0-6h) (ng)	3057	4231	23120 [65.7]

a) Median (min, max), ERmax - Maximum (peak) observed excretion rate of QAU145 and QAY243 in the urine, Ae0-t - Amount excreted into urine from time zero to t (h)

Summary of Safety

Safety Results

Adverse Events by System Organ Class

Number (%) of patients with adverse events by treatment group and preferred term for Parts I and II

	QAU145 5 µg N = 3 n (%)	QAU145 0.8 mg N = 2 n (%)	QAU145 1.6 mg N = 7 n (%)	Placebo N = 8 n (%)
Subjects with AE(s) [a]	2 (66.7)	1 (50.0)	6 (85.7)	5 (62.5)
Preferred term				
Appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
Condition aggravated	0 (0.0)	0 (0.0)	2 (28.6)	0 (0.0)
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
Depression	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
Electrocardiogram abnormal	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
Epistaxis	0 (0.0)	0 (0.0)	1 (14.3)	1 (12.5)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
Hemoptsis	0 (0.0)	0 (0.0)	1 (14.3)	1 (12.5)
Hematuria	0 (0.0)	0 (0.0)	1 (14.3)	1 (12.5)
Inflammation	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
Infusion site pain	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)
Infusion site swelling	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
Musculoskeletal chest pain	0(0.0)	0 (0.0)	1 (14.3)	0 (0.0)
Nasal congestion	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
Nasal mucosal disorder	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)
Oopharyngeal pain	1 (33.3)	0 (0.0)	0 (0.0)	1 (12.5)
Pain in extremity	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
Paranasal sinus hypersecretions	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
Rinorrhea	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)
Sensory disturbance	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)

[a] No AEs were reported for subjects treated with QAU145 10 µg, 20 µg, or 0.2 mg.
Note: Only AEs that occurred at or after the first study drug intake were included. An AE starting in one Treatment Period and continuing into the next Treatment Period was counted only in the onset Treatment Period.
N = number of subjects/periods studied and n = number of subjects/periods with at least one AE on the category.

Serious Adverse Events and Deaths

Three SAEs were reported during the study in Part I (2 patients in the 1.6 mg group and 1 in the placebo group). No patient died during the study or discontinued the study due to an AE.

Other Relevant Findings

None

Conclusion:

- Single intranasal doses of QAU145 induced a dose-dependent increase in maximal basal nasal potential difference change from pre-dose to 2 hours post dose in target nostril with an estimated maximal effect (E_{max}) over placebo of 24.8 mV (95% CI=17.0, 32.8) and ED50 of 18 µg (95% CI=5, 50).
- The administration of single intranasal doses of QAU145 ranging from 5 µg to 1.6 mg was generally safe and well tolerated.
- Mean plasma QAY243 concentrations were low (<3 ng/mL) but where measurable, Cmax increased with increasing dose. Mean maximum plasma concentrations were observed between 0.5 and 0.6 hours post-dose.
- The amount of QAY243 recovered over 6 hours (in ng) increased with increasing dose. The average urinary excretion of QAY243 over 6 hours was low and less than 2% of the nominal QAU145 dose.

Date of Clinical Trial Report

22 Nov 2010