Sponsor
Novartis

Generic Drug Name
QAX576

Therapeutic Area of Trial
Idiopathic pulmonary fibrosis

Approved Indication
Investigational

Protocol Number
CQAX576A2203

Title
A randomized, double-blind, placebo-controlled, multiple-dose, exploratory proof of concept study to assess the safety, tolerability, efficacy, pharmacodynamics and pharmacokinetics of QAX576 in patients with rapidly progressive idiopathic pulmonary fibrosis

Study Phase
Phase II

Study Start/End Dates
First patient first visit: 04-Feb-2011
Last patient last visit: 26-Apr-2013
Early termination date: 22-Feb-2013. The study was terminated after the interim analysis showed the probability of futility was 100%.

Study Design/Methodology
This was an exploratory double-blind, randomized, placebo-controlled study in patients with idiopathic pulmonary fibrosis (IPF). [Amendment 4 eliminated the selection of patients with "rapidly progressive" IPF and allowed "all" patients with IPF to enroll in the trial]. A total of 40 patients were randomized in a 3:1 ratio (active to placebo) to receive either QAX576 10 mg/kg or matching placebo.
The study consisted of a screening period lasting a maximum of 28 days, a baseline visit (Day -1) and a treatment period consisting of thirteen 4-weekly visits followed by end of study evaluations approximately four weeks following the last drug administration. Patients who met the inclusion/exclusion criteria at screening progressed to baseline evaluations.

Each patient was expected to spend up to 56 weeks in the study - 4 weeks screening period, 48 weeks of dosing (dose every 4 weeks), and 4 weeks for follow up after the final administration of study drug. The study drug was administered as an intravenous infusion (over 2 hours) every 4 weeks (± 7 day window).

Centers

9 centers in 2 countries: United States (6), United Kingdom (3)

Publication

Objectives

Primary objectives

- To evaluate the safety and tolerability of multiple intravenous dosing of QAX576 in patients with idiopathic pulmonary fibrosis (IPF).
- To evaluate the effect of multiple intravenous dosing of QAX576 on lung function assessed by forced vital capacity (FVC) at 1 year as compared to baseline.

Secondary objectives

- To evaluate the effect of multiple intravenous dosing of QAX576 on additional measures of clinical efficacy, including:
    - All-cause mortality, time to clinical worsening defined as 10% fall in FVC or 15% fall in DLco, lung transplant or lung disease (IPF)-related death.
    - Incidence of exacerbation of IPF.
    - Lung volume (TLC, RV, FRV) and diffusing capacity of the lung for carbon monoxide (DLco).
    - 6 minute walk distance, pulse oximetry and heart rate recovery.
    - Progression of fibrosis in the lungs as measured by Quantitative High Resolution Computerized Tomography (HRCT).
    - Patient reported symptoms.
- To evaluate the pharmacokinetics of QAX576 in this patient population.

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

QAX576 for intravenous (i.v.) infusion was supplied as lyophilized powder in a sterile vial of 150 mg. The lyophilized powder was reconstituted with 1 mL sterile water for injection to final drug concentrations of 150 mg/mL. The concentrate for solution for infusion contained 150 mg QAX576 in a solution of histidine (pH 6.0 ± 0.5), sucrose, glycine and Polysorbate 80. Final dosage (10 mg/kg) was calculated using subject's weight at the screening visit. The calculated volume of concentrate for solution for infusion was withdrawn and injected into an infusion bag containing 5% glucose solution. Infusion was done over a 2 hour period.

Reference therapy - Placebo for i.v. infusion was provided as a lyophilized powder in a sterile vial. The lyophilized powder was dissolved in sterile water to produce 1 mL of placebo for injection. The solution for infusion contained histidine (pH 6.0 ± 0.5), sucrose, glycine and Polysorbate 80. The calculated volume of concentrate for solution for infusion was withdrawn and injected into an infusion bag containing 5% glucose solution. Infusion was over a 2 hour period.
QAX576 10 mg/kg or Placebo was administered 13 times. Each dose was separated by 4 weeks.

Statistical Methods

No formal statistical hypothesis was tested in this exploratory proof of concept study.
Primary analysis assessed treatment benefit in terms of the primary efficacy endpoint. The primary efficacy endpoint was change from baseline in absolute FVC measurement (post bronchodilator) at 52 weeks extrapolated from FVC at each clinical visit post-baseline. Change in FVC for QAX576 arm was expressed in terms of relative % change from baseline and is identified with ΔFVC_{QAX576}. The relative change in absolute FVC measurements was evaluated using a mixed effect model as well as with a Bayesian model-based paradigm where the probability of fulfilling a specified efficacy level was quantified. This Bayesian model was used in the decision-making at the time of the IA to determine evidence of futility and/or efficacy, as well as at the end of the trial.
The mixed-effect regression model for the primary parameter included treatment as a fixed effect and subject as a random effect; time was a continuous covariate. The model included random factors for subject, slope and intercept, and additionally included a quadratic term ($time^2$) if non-linearity was apparent. Bayesian analysis evaluated futility and efficacy:

- Futility criteria: probability $P(\Delta FVC_{QAX576} \leq -5\%) > 50\%$
- Efficacy (hypothesis testing) criteria: probability $P(\Delta FVC_{QAX576} > 0\%) > 50\%$

An Interim Analysis (IA) was conducted to assess futility and efficacy after approximately half of the patients completed 26 weeks on treatment, in order to review assumptions and inform internal decision-making based on the assessment of the rates of change in Forced Vital Capacity (FVC) for both active and placebo-treated subjects. The treatment remained blinded to the investigator, site staff and the Novartis clinical trial team. Trial statistician and programmer were unblinded and conducted the analysis.
The posterior probabilities, given the observed data that above events occur at interim and at final analysis were assessed using non-informative priors for the primary endpoint. Only subjects within the PD population contributed to the primary efficacy analysis. For the statistical analysis, Week 52 values were estimated by extrapolation from the available values. For the primary Bayesian analysis, the FVC relative change from baseline at 52 weeks was estimated using only the non-missing values and such estimates imputed into the Bayesian model.

Data from other pulmonary function tests, DLco, 6-minute walk test, and Borg scores/SGRQ were listed and summarized, and changes assessed using mixed effects repeated measures models where appropriate. The mixed-effect regression model for these secondary parameters included treatment and time of measurement (categorized according to visits) as fixed effects and a treatment*time interaction and subject fitted as a random effect. Contrasts for treatment group differences over placebo at the different time points were provided together with 95% confidence intervals. Differences were tested for statistical significance at the two-sided 5% alpha level. An unstructured covariance structure was fitted where possible.
Time to clinical worsening (as defined by at least a 10% decline from baseline in FVC post bronchodilator or at least a 15% decline in absolute DLco post bronchodilator measurements or lung transplant or IPF-related death), was estimated via Kaplan-Meier curves and a p-value was calculated to investigate the treatment effect (on each of these variables separately and clinical worsening as a 'whole' i.e. the event which is observed first is the event). No multiplicity adjustment was taken into account for testing on these secondary endpoints due to the exploratory nature of the trial. Graphical representations were used to describe the time progression of these measures. These variables were considered as censored from the time of their last visit if they did not experience an event. If clinical worsening was experienced, the time to this event was calculated from the date of visit at which the worsening occurred. For the assessment of overall clinical worsening, if several of the variables worsen, the date used was the earliest date of worsening.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Diagnosis of Idiopathic Pulmonary Fibrosis (IPF), based on an appropriate clinical definition of IPF as detailed in the ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management Diagnosis must be confirmed by a diagnostic HRCT or surgical lung biopsy.
- A 6-minute walk test (6MWT) distance ≥50 meters at screening (use of supplemental oxygen allowed).

Exclusion criteria

- Smokers (use of tobacco products in the previous 3 months). Urine cotinine levels will be measured during screening for all subjects. Smokers will be defined as any subject who reports tobacco use or has a urine cotinine levels in the range defined as 'smokers' per the local lab.
- Lung residual volume > 120% predicted at Screening.

Participant Flow

	QAX576 N=30 n (%)	Placebo N=10 n (%)	Total N=40 n (%)
Subjects			
Completed	6 (20.0%)	0 (0.0%)	6 (15.0%)
Discontinued	24 (80.0%)	10 (100.0%)	34 (85.0%)
Main cause of discontinuation			
Adverse Event(s)	1 (3.3%)	1 (10.0%)	2 (5.0%)
Unsatisfactory therapeutic effect	16 (53.3%)	7 (70.0%)	23 (57.5%)
Subject withdrew consent	6 (20.0%)	1 (10.0%)	7 (17.5%)
Death*	1 (3.3%)	1 (10.0%)	2 (5.0%)

Early discontinuations due to study termination are presented as Unsatisfactory therapeutic effect
* Two additional subjects discontinued the trial and subsequently died but are not included in this table
(QAX576: one subject withdrew consent and one subject following study termination notification

Baseline Characteristics

Demographic summary by treatment group		QAX576 N=30	Placebo N=10	Total N=40
Age (years)	Mean (SD)	68.2 (7.02)	66.6 (7.11)	67.8 (6.98)
	Median	70.5	67.0	69.5
	Range	51, 78	58, 78	51, 78
Sex – n(%)	Male	20 (66.7%)	8 (80.0%)	28 (70.0%)
	Female	10 (33.3%)	2 (20.0%)	12 (30.0%)
Race – n(%)	Caucasian	29 (96.7%)	10 (100.0%)	39 (97.5%)
	Black	1 (3.3%)		1 (2.5%)
Ethnicity – n(%)	Hispanic/Latino	1 (3.3%)	1 (10.0%)	2 (5.0%)
	Mixed ethnicity	4 (13.3%)		4 (10.0%)
	Other	25 (83.3%)	9 (90.0%)	34 (85.0%)
Weight (kg)	Mean (SD)	88.4 (14.26)	90.9 (12.81)	89.1 (13.79)
	Median	89.6	90.5	89.6
	Range	54.8, 120.2	72.6, 108.0	54.8, 120.2
Height (cm)	Mean (SD)	169.4 (9.69)	172.8 (6.76)	170.2 (9.09)
	Median	170.2	175.2	172.8
	Range	151.0, 188.0	160.0, 179.6	151.0, 188.0
BMI (kg/m2)	Mean (SD)	30.75 (3.767)	30.45 (3.992)	30.67 (3.775)
	Median	30.09	31.10	30.27
	Range	22.4, 37.6	23.0, 35.1	22.4, 37.6

Outcome Measures
Summary of Efficacy

Primary Outcome Result(s)
Assessment of lung function assessed by force vital capacity (FVC) at one year compared to baseline

	QAX576 10 mg/kg n=27 (LS means (SE))	Placebo n=10 (LS means (SE))	(95% CL)
% Change from baseline to 52 weeks in FVC *Pre-bronchodilator*	-13.83 (3.156)	-13.42 (5.458)	(-13.03, 12.21) p-value (2-sided) = 0.948
	QAX576 10 mg/kg n=27 (LS means SE)	Placebo n=8 (LS means SE)	
% Change from baseline to 52 weeks in FVC *Post-bronchodilator*	-15.95 (3.174)	-11.27 (6.198)	(-18.72, 9.35) p-value (2-sided) = 0.502

Bayesian analysis of FVC percentage change from baseline at week 52
PD analysis set

Pre-Bronchodilator

Treatment effect /contrast	N	Posterior Mean	SD	Q5	Q95
QAX576	27	-14.00	1.69	-16.78	-11.19
Placebo	10	-12.94	3.28	-18.28	-7.42
QAX576 vs Placebo		-1.05	3.55	-6.96	4.73
P(QAX576 % change <= -5% | data):		100.0%			
P(QAX576 % change > 0% | data):		0.0%			

Bayesian analysis of FVC percentage change from baseline at week 52
PD analysis set

Post-Bronchodilator

Treatment effect /contrast	N	Posterior Mean	SD	Q5	Q95
QAX576	27	-15.93	1.59	-18.52	-13.26
Placebo	8	-9.28	3.49	-14.87	-3.28
QAX576 vs Placebo		-6.64	3.73	-12.86	-0.52
P(QAX576 % change <= -5% | data):		100.0%			
P(QAX576 % change > 0% | data):		0.0%			

Secondary Outcome Result(s)

Time to clinical worsening of 10% decline from baseline in FVC by treatment

Treatment	N	Statistic	Time to clinical worsening (weeks)	Log-Rank p-value #
QAX576	30	Mean (S.E.)	28.77 (2.73)	
		Median (95% CI)	39.84 (19.28, NC)	
Placebo	10	Mean (S.E.)	13.95 (1.71)	0.661
		Median (95% CI)	NC	

Percent change from baseline in Lung volume measurements

Treatment: QAX576

Visit		Actual total lung capacity (%)	Actual thoracic gas volume (%)	Actual residual volume (%)	Actual inspiratory capacity (%)	Expiratory reserve volume (%)	Breath hold time (%)
WK13	n	25	25	25	25	25	26
	mean	-5.30	-5.07	-5.98	-5.55	6.84	-0.88
	SD	6.566	8.990	22.393	11.738	26.726	4.592
	minimum	-19.9	-21.0	-43.9	-31.3	-32.9	-9.3
	median	-5.05	-4.85	-11.52	-4.58	7.55	-1.34
	maximum	6.1	15.4	60.9	29.3	83.3	11.5
WK25	n	22	22	22	22	22	22
	mean	-4.22	-0.80	4.39	-9.17	65.31	-0.65
	SD	12.764	13.931	40.462	18.842	220.333	3.117
	minimum	-35.2	-33.0	-43.1	-60.7	-36.1	-4.3
	median	-3.85	-0.97	-2.36	-2.34	0.83	-1.56
	maximum	34.2	24.9	168.8	25.3	981.8	7.0
WK37	n	13	13	13	13	12	14
	mean	-4.80	-5.53	-1.60	-2.26	-9.96	-2.70
	SD	10.095	10.901	16.939	19.810	33.510	6.290
	minimum	-28.4	-19.2	-23.6	-38.6	-52.0	-12.0
	median	-5.83	-7.67	-3.38	-3.08	-20.58	-2.86
	maximum	10.5	17.3	36.8	36.0	54.5	12.1

Treatment: Placebo

Visit		Actual total lung capacity (%)	Actual thoracic gas volume (%)	Actual residual volume (%)	Actual inspiratory capacity (%)	Expiratory reserve volume (%)	Breath hold time (%)
WK13	n	9	9	9	9	9	8
	mean	-0.23	-4.14	20.93	0.17	0.92	1.73
	SD	9.900	8.637	93.035	9.919	27.395	3.865
	minimum	-12.1	-14.3	-32.3	-15.9	-44.2	-4.8
	median	-0.69	-5.18	-3.47	0.00	-1.51	1.34
	maximum	22.4	12.3	266.7	13.3	40.9	8.1
WK25	n	5	5	5	5	5	5
	mean	0.26	3.39	49.55	-6.40	19.00	1.73
	SD	16.666	11.074	138.586	15.504	54.808	2.946
	minimum	-15.3	-12.8	-26.6	-31.1	-34.9	-2.4
	median	-1.29	6.55	-4.86	-4.63	4.71	1.33
	maximum	27.8	16.3	296.7	11.5	110.3	5.1
WK37	n	2	2	2	2	2	2
	mean	-2.81	9.07	5.04	-8.79	6.82	-0.49
	SD	3.733	4.594	10.550	4.580	26.616	11.423
	minimum	-5.4	5.8	-2.4	-12.0	-12.0	-8.6
	median	-2.81	9.07	5.04	-8.79	6.82	-0.49
	maximum	-0.2	12.3	12.5	-5.6	25.6	7.6

Six minute distance walked absolute change from baseline

Visit	Treatment effect /contrast	N	LSmean (SE)	Difference (SE)	95% CI	p-value (2-sided)
WK13	QAX576	27	-2.41 (8.855)			
	Placebo	9	-6.97 (15.338)			
	QAX576 - Placebo			4.55 (17.710)	(-31.44,40.54)	0.799

Visit	Treatment effect /contrast	N	LSmean (SE)	Difference (SE)	95% CI	p-value (2-sided)
WK37	QAX576	15	-31.01 (15.761)			
	Placebo	2	-71.78 (40.193)			
	QAX576 - Placebo			40.77 (43.173)	(-48.82,130.35)	0.355

Visit	Treatment effect /contrast	N	LSmean (SE)	Difference (SE)	95% CI	p-value (2-sided)
WK37	QAX576	15	-31.01 (15.761)			
	Placebo	2	-71.78 (40.193)			
	QAX576 - Placebo			40.77 (43.173)	(-48.82,130.35)	0.355

Visit	Treatment effect /contrast	N	LSmean (SE)	Difference (SE)	95% CI	p-value (2-sided)
WK49	QAX576	6	-40.94 (31.581)			

Summary of Safety

Safety Results

Adverse Events by System Organ Class

	QAX576 N=30 n (%)	Placebo N=10 n (%)	Total N=40 n (%)
Subjects with AE(s)	26 (86.7)	10 (100.0)	36 (90.0)
System organ class			
Infections and infestations	18 (60.0)	7 (70.0)	25 (62.5)
Respiratory, thoracic and mediastinal disorders	12 (40.0)	7 (70.0)	19 (47.5)
Musculoskeletal and connective tissue disorders	9 (30.0)	2 (20.0)	11 (27.5)
Injury, poisoning and procedural complications	7 (23.3)	3 (30.0)	10 (25.0)
Investigations	6 (20.0)	3 (30.0)	9 (22.5)
General disorders and administration site conditions	5 (16.7)	2 (20.0)	7 (17.5)
Skin and subcutaneous tissue disorders	6 (20.0)	1 (10.0)	7 (17.5)
Gastrointestinal disorders	4 (13.3)	2 (20.0)	6 (15.0)
Nervous system disorders	5 (16.7)	0 (0.0)	5 (12.5)
Psychiatric disorders	3 (10.0)	1 (10.0)	4 (10.0)
Cardiac disorders	2 (6.7)	1 (10.0)	3 (7.5)
Eye disorders	2 (6.7)	0 (0.0)	2 (5.0)
Metabolism and nutrition disorders	2 (6.7)	0 (0.0)	2 (5.0)
Renal and urinary disorders	2 (6.7)	0 (0.0)	2 (5.0)
Ear and labyrinth disorders	1 (3.3)	0 (0.0)	1 (2.5)
Immune system disorders	1 (3.3)	0 (0.0)	1 (2.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (3.3)	0 (0.0)	1 (2.5)
Vascular disorders	1 (3.3)	0 (0.0)	1 (2.5)

Most Frequently Reported AEs Overall by Preferred Term n (%)

	QAX576 N=30 n (%)	Placebo N=10 n (%)	Total N=40 n (%)
Subjects with AE(s)	26 (86.7)	10 (100.0)	36 (90.0)
Preferred term			
Nasopharyngitis	5 (16.7)	4 (40.0)	9 (22.5)
Dyspnoea	7 (23.3)	1 (10.0)	8 (20.0)
Upper respiratory tract infection	6 (20.0)	2 (20.0)	8 (20.0)
Cough	4 (13.3)	2 (20.0)	6 (15.0)
Lower respiratory tract infection	4 (13.3)	2 (20.0)	6 (15.0)
Sinusitis	4 (13.3)	0 (0.0)	4 (10.0)
Headache	3 (10.0)	0 (0.0)	3 (7.5)
Muscle spasms	1 (3.3)	2 (20.0)	3 (7.5)
Rash	2 (6.7)	1 (10.0)	3 (7.5)
Arthralgia	2 (6.7)	0 (0.0)	2 (5.0)

Note: There were numerous AEs ≤2% frequency; only first 10 AEs were selected for this Table.

Serious Adverse Events and Deaths

	QAX576 n (%)	Placebo n (%)
No. (%) of subjects studied	30 (75.0)	10 (25.0)
No. (%) of subjects with AE(s)	26 (86.7)	10 (100.0)
Number (%) of subjects with serious or other significant events		
Death*	2 (6.7)	2 (20.0)
SAE(s)	3 (10.0)	4 (40.0)
Discontinued due to SAE(s)	1 (3.3)	2 (20.0)

* Two subjects died while on study treatment (QAX576 subject with reason unknown and one Placebo subject due to exacerbation of IPF). Two subjects discontinued the trial and subsequently died (QAX576 subject withdrew consent and later died due to acute respiratory failure of unknown etiology. A Placebo subject withdrew following the study termination and died due to decreased O_2 saturation, advanced pulmonary fibrosis and respiratory failure).

Other Relevant Findings

None

Date of Clinical Trial Report

27 February 2014

Date Inclusion on Novartis Clinical Trial Results Database

21 April, 2014

Date of Latest Update