Sponsor

Novartis

Generic Drug Name

QAX576

Therapeutic Area of Trial

Idiopathic Pulmonary Fibrosis (IPF)

Study Number

CQAX576A2202

Title

A open-label, multi-center study with a single intravenous dose of QAX576 to determine IL-13 production in patients with Idiopathic Pulmonary Fibrosis

Phase of Development

Phase II

Study Start/End Dates

25 Sep 07 to 4 Jun 09

Reason for Termination

The study was terminated early after 31 patients were enrolled and randomized to receive QAX576 due to slow enrollment rate.

Study Design/Methodology

This was an open label study of IL-13 production in patients with idiopathic interstitial pulmonary fibrosis (IPF) using a single intravenous dose of 0.3 mg/kg QAX576. The single dose of QAX576 was administrated to help assess the amount of bound IL-13 (1L-13+QAX576 antibody complex).

This study consisted of a 28 day screening period (Day -29 to -5), a baseline period (Day -4 to Day -1), a single intravenous infusion of 0.3 mg/kg QAX576 on Day 1 and a 4 week follow-up period thereafter. An end-of-study visit (EOS) was conducted 4 weeks after the dose administration.

The single-dose of study drug was administrated as an intravenous infusion over 2 hours. Subjects were domiciled in the Clinical Research Unit (CRU) for 6 hours after the infusion. Blood samples were obtained on Day 1 and every week thereafter for 4 weeks, for measurement of IL-13 production.

Centres

US (6 centers)

Objectives

Primary objective(s)

- To investigate the hypothesis that there is a subset of IPF patients with increased IL-13 production
- To investigate the hypothesis that QAX576 will neutralize IL-13 in patients with IPF

Secondary objective(s)

- To evaluate the changes in biomarkers in blood over time in patients with IPF including (but are not limited to), TGFβ1, IGF-1, PDGF-A/B, CCL-18, pro-collagen (Type I and III), fibronectin and CTGF

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

QAX576 powder for solution (for IV infusion) was provided in glass vials containing 100 mg QAX576 as a lyophilized cake. This was reconstituted and given as a single intravenous dose of 0.3 mg/kg QAX576.

Statistical Methods

Total and, if applicable, free IL-13 concentrations summarized by time point and plots of mean (±std) and median values over time will be provided. For plasma concentrations of total IL-13, the maximum concentration, the time of the maximum concentration, and maximum percent in-crease from baseline will be determined for each patient. Likewise, if free IL-13 can be measured in plasma, the minimum concentration of free IL-13, the time of the minimum concentration and the maximum decrease from baseline will be obtained for each patient and summarized by de- scriptive statistics.

IL-13 production rates will be estimated from a PK/PD model. A typical value for fibrosis pa-tients and if the data support it, individual predictions for each patient in the QAX576 group will be obtained.

If individual predictions can be obtained, summary statistics will be provided including n, mean, standard deviation, coefficient of variation, minimum, median, maximum, 10%, 25%, 75%, and 90% percentile. A mixture model will be fitted to the IL-13 production rates to explore the possi-bility that there is a subgroup of patients that has higher IL-13 values compared to the rest of the IPF patients. For this analysis, it will be assumed that the log IL-13 production rates are a mixture of two normal distributions with shifted means. The correlation of baseline plasma IL-13 with IL-13 production rates will be assessed. IL-13 production rates of IPF patients will be compared to historical data collected in 32 healthy volunteers (study QAX576A2101). The change from baseline in biomarkers (e.g, TGFβ1, IGF-1, PDGF-A/B, CCL-18,

pro-collagen (Type I and III), fibronectin and CTGF) will be summarized descriptively and graphically by visit.

Sample size

N=50 patients were planned be included in this study.
The objective of this exploratory study was to learn about the distribution if IL-13 production rates in IPF patients and to investigate the hypothesis that there is a subset of patients with IPF with increased IL-13 production. The distribution of IL-13 production rates in IPF patients is un-known, it may follow a standard curve but shifted, be skewed, or have a bimodal distribution. A mixture model will be fitted to the IL-13 production rates to explore the possibility that there is a subgroup of patients that has higher IL-13 values compared to the rest of the IPF patients. For this analysis, it will be assumed that the log IL-13 production rates are a mixture of two normal distributions with shifted means. Simulations indicate that if for 10 out of 50 patients the log IL-13 values are shifted by 2 standard deviations, then the fraction of the subpopulation (here
10/50=20%) and the shift in means can be estimated with reasonable precision. In a simulation study (500 simulation runs, std=1, shift of 2) , the median estimate (standard error) for the differ-ence in means was 2.16 (±0.45) and median estimates for the size of the subpopulation were 23% (±9.8%). This was considered adequate for the purpose of this study.
Note that if the CV of the IL-13 productions rates is 50%, the standard deviation of log IL-13 is 0.47 and a difference of two standard deviations on the log scale corresponds to a change by factor of exp(2*0.47)=2.56 on the original scale. Likewise, if the CV of the IL-13 productions rates is 100%, the standard deviation of log IL-13 is 0.83 and a difference of two standard deviations on the log scale corre-sponds to a change by factor exp(2*0.83)=5.36 on the original scale.
If no subgroup can be detected in the population of IPF patients, the distribution of the IL-13 production rates will be estimated with some focus on the higher end of the distribution (e.g. up-per 90% percentile). With n=50 patients and if the CV of the IL-13 productions rates is 50%, the standard deviation of log IL-13 is 0.47 and a 90% confidence interval for the upper 90% percen-tile on the log scale will have a distance from the estimate to the lower limit of 0.13, and a dis-tance from the estimate to the upper limit of 0.17. Likewise, if the CV of the IL-13 productions rates is 100%, the standard deviation of log IL-13 is 0.83 and a 90% confidence interval for the upper 90% percentile will have a distance from the estimate to the lower limit of 0.23, and a dis-tance from the estimate to the upper limit of 0.30. This was considered adequate for the purpose of this study.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Men and women between the ages of 40 and 80 years with a confirmed diagnosis of idiopathic pulmonary fibrosis
- Both men and women must be on non-childbearing potential. Additional information regarding this requirement is available at screening.
- Capability to meet certain lung function tests at screening
- Non-smokers
- No participation in another clinical study within 4 weeks of study start.

Exclusion criteria

- Certain medical conditions may exclude candidates from participation.
- Blood loss or donation of 400 mL or more within 2 months of study start Significant illness (other than respiratory) within 2 weeks of study start
- Past medical personal or close family history ~~o~~f clinically significant ECG abnormalities
- Connective tissue disorders
- Active infection or history of systemic parasitic infection
- Known hypersensitivity to the drug.
- History of immunocompromise, including a positive HIV test result.
- History of drug or alcohol abuse within 12 months of study start
- Any condition that may compromise patient safety

Number of Subjects

	QAX576
Patients	
Completed	31 (100%)
Discontinued	0
Main cause of discontinuation	
Death	0
Adverse events(s)	0
Lack of efficacy	0
Protocol violation(s)	0
Administrative reasons	0
Lost to follow-up	0
Other	0

Demographic and Background Characteristics

Parameters		QAX576 N=31
Age (years)	Mean (SD)	66.4 (6.38)
	Median	66.0
	Range	57, 79
Gender - n(%)	Female	9 (29.0%)
	Male	22 (71.0%)
Race - n(%)	Caucasian	31 (100.0%)
Ethnicity - n(%)	Mixed Ethnicity	1 (3.2%)
	Other	30 (96.8%)
Weight (kg)	Mean (SD)	87.48 (11.571)
	Median	89.70
	Range	59.4, 106.0
Height (cm)	Mean (SD)	171.8 (8.42)
	Median	173.0
	Range	150, 185

Primary Outcome Result(s)

Free and total IL-13

Determination of free and total IL-13 in plasma is not presented in this report due to issue identified with validation of the IL-13 assay.

Secondary Outcome Result(s)
To evaluate the changes in biomarkers in blood over time in patients with IPF

The planned biomarker analysis was not performed.

Summary of Safety

Serious Adverse Events

Three SAEs of pneumonia, hemoptysis, and atrial fibrillation were reported in one patient. A SAE of adenocarcinoma was reported in another patient.

Incidence of AEs by preferred term (all patients)

	QAX576 N=31 n (%)
Patients with AE(s)	13 (41.9)
Preferred term	
Atrial fibrillation	1 (3.2)
Back pain	1 (3.2)
Benign prostatic hyperplasia	1 (3.2)
Bradycardia	1 (3.2)
Constipation	1 (3.2)
Cough	1 (3.2)
Decreased appetite	1 (3.2)
Dermatitis contact	1 (3.2)
Dyspnea	1 (3.2)
Feces hard	1 (3.2)
Fatigue	2 (6.5)
Hemoptysis	1 (3.2)
Headache	1 (3.2)
Herpes zoster	1 (3.2)
Malaise	1 (3.2)
Muscle fatigue	1 (3.2)
Nausea	1 (3.2)
Pneumonia	1 (3.2)
Presyncope	1 (3.2)
Syncope	1 (3.2)
Toothache	1 (3.2)
Urinary tract infection	1 (3.2)
Vomiting	1 (3.2)

Other Relevant Findings

Summary statistics for total QAX576 pharmacokinetic parameters after a single 2-hour intravenous infusion of QAX576 at 0.3 mg/kg

	Cmax (µg/mL)	Tmax (hr)	AUCinf (µg*day/mL)	CL (mL/day/kg)	Vss (mL/kg)	T1/2 (day)
n	28	28	15	15	15	26
Mean	**7.2**	**3.4**	**77.2**	**4.0**	**49.7**	**13.3**
SD	1.3	1.9	12.9	0.6	13.3	4.8
CV%	18.1	54.5	16.7	15.6	26.9	36.1

Date of Clinical Trial Report

09-May-2011