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Generic Drug Name

QAX576

Therapeutic Area of Trial

Gastro-intestinal

Approved Indication

Investigational

Protocol Number

CQAX576A2205

Title

A double blinded, randomized, placebo-controlled trial of intravenous QAX576 in the treatment of eosinophilic esophagitis

Study Phase

Phase II

Study Start/End Dates

First patient first visit: 29-Dec-2009

Last patient last visit: 26-Jan-2012

Study Design/Methodology

This study was a randomized, double-blind, placebo-controlled, multiple-dose, multi-center study to assess the efficacy, safety/tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of QAX576 in subjects with eosinophilic esophagitis (EoE). It consisted of a 21 day screening period, an initial treatment period, followed by an observation period to ascertain the duration of response. The study enrolled subjects aged 18-50 years old, and eligible subjects were administered QAX576 or Placebo in a ratio 2:1. 21 subjects (14 active and 7 placebo) were to be enrolled in order to have 18 subjects complete the study. Subjects were randomized to receive 3 intravenous infusions of QAX576 or placebo (on Day 1, Day 29 and Day 57), and were observed for not less than 24 weeks after the last dose, with follow-up every 4 weeks and an endoscopy with esophageal biopsy at baseline/screening, 4 weeks after the last dose (Week 13, Day 85) and at the end of study (i.e. either at treatment failure or at Week 34). The study measured the effects on the counts of esophageal

eosinophils, symptoms and various serum and tissue biomarkers at Day 85 compared to baseline.

An open label extension with QAX576 at 6 mg/kg administered every 4 weeks, (total 3 doses), was offered to responders (defined as those who showed at least a 75% decrease in the peak eosinophil count per high power field (hpf) at Week 13) who then relapsed (defined as worsening of eosinophilic esophagitis symptoms after a clinical improvement confirmed at Week 13 and based on the judgment of the subject and the investigator) during the observation period.

Centers

4 centers in the United States.

Publications

None

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

QAX576 for intravenous (i.v.) injection was supplied as lyophilized powder in a sterile vial of 100 mg (Batch Y180 1206 and Batch Y062 0507). The lyophilized powder was reconstituted with 1 mL sterile water for injection to final drug concentrations of 100 mg/mL. Final dosage was calculated using subject's weight (6 mg/kg).

Reference therapy - Placebo (Batch U017 0606 and Batch Y006 0110) for i.v. injection 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.

QAX576 6 mg/kg or Placebo was administered three times as an infusion over 2 hours. Each dose was separated by 4 weeks.

Statistical Methods

No formal statistical hypothesis was tested in this exploratory proof of concept study.

The number of responders i.e. subjects with a reduction of 75% or more in the peak eosinophils per hpf (distal and proximal esophagus combined) from baseline to week 13 (Day 85), was the main efficacy variable. The proportion of responders and the two-sided 90% confidence intervals were calculated for the QAX576 group using the Agresti-Coull type confidence intervals for binomial proportions. The same analysis was performed separately for the number of subjects with a reduction of 75% or more in peak eosinophils per hpf, separately for the proximal esophagus and distal esophagus from baseline to week 13. The same three analyses was performed for the number of subjects with a reduction of 75% or more in mean eosinophils per hpf from baseline to week 13 (distal and proximal esophagus combined, and separately for distal esophagus and proximal esophagus).

No alpha adjustments were performed.

Clinical symptoms were measured by the Mayo Dysphagia Questionnaire (MDQ). For the purpose of the study database, the symptoms were captured as 36 separate questions and were summarized descriptively. The changes in clinical symptoms from baseline compared to Day 85 were "scored" using a sub-set of 10 questions from the MDQ. The treatment difference was assessed using the Wilcoxon rank sum test.

Descriptive statistics of pharmacokinetic parameters included mean, standard deviation (SD), and coefficient of variation (CV) and range.

Safety data were listed by treatment group and subject and summary statistics were provided by treatment group.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

1. Male and female subjects with symptomatic eosinophilic esophagitis aged 18 to 50 years of age.
2. Female subjects were required to be:
   Surgically sterilized at least 6 months prior to study participation (documentation of sterilization to be provided);

OR

   Post menopausal (no regular bleeding for at least 2 year) postmenopausal status must be confirmed by a plasma FSH level of >40 IU/L at screening or baseline.
   Note: A pregnancy test was to be done on all female subjects regardless of reported reproductive status at specified time points throughout the study.
3. Histological findings on esophageal biopsy to include peak eosinophil density ≥24 per high power field (400x) in the proximal or distal esophagus validated by a central laboratory pathologist (Quintiles Laboratory).
4. Elimination diet must either:
   → Not be indicated following allergy evaluation including skin-prick testing with multiple food antigens. The type of allergy testing will be determined at the discretion of clinical staff allergists.
   → Have been refused to be followed by subject.
   → Have undergone a minimum of 3 months of elimination diet as indicated by skin prick testing without detectable resolution by repeat endoscopy with biopsies demonstrating persistent EoE or subject refusal to follow elimination diet.
5. Subjects treated with a proton-pump inhibitor (PPI) must have been on treatment for at least two months prior to enrollment. The PPI must be used prior to endoscopy to rule out the possibility of GERD in the proximal or distal esophagus.
6. Failure of histological improvement. Failure of histological improvement is defined as eosinophil density ≥24 per high power field (400x) after 2 months treatment of proton pump inhibitor or documented by prior endoscopy.

OR

   Lack of complete disappearance of symptoms.

7. Subject had to be able to communicate well with the investigator, to understand and comply with the requirements of the study. Understand and sign the written informed consent.

Exclusion criteria

1. Subject has received systemic corticosteroid therapy, by any route of administration, within 3 months before dosing or has received topical corticosteroids (swallowed aerosolized fluticasone or budesonide) within 2 months prior to dosing.
2. Co-morbid eosinophilic disorders (other than atopic dermatitis not requiring chronic steroid therapy).

3. History of exposure to human therapeutic antibody, immunoglobulin, or other plasma product within 6 months of dosing (e.g. Xolair®).
4. History of clinical schistosomiasis, or stool examination positive for ova or parasites or travel within the preceding 6 months to an area with endemic schistosomiasis, including but not limited to Southeast and Southwest Asia, South America and Africa. Travel to these areas was not to be planned for at least 6 months after the last dose.
5. Subjects who have not had a trial of PPI or prior allergy testing/elimination diet and who did not fulfill entry criteria after PPI or elimination diet therapy has been initiated.
6. Participation in any clinical intervention with any drug administration within four (4) weeks prior to initial dosing or longer if required by local regulations, and for any other limitation of participation based on local regulations.
7. Donation or loss of 400 mL or more of blood within eight (8) weeks prior to initial dosing, or longer if required by local regulation.
8. A past medical history of clinically significant ECG abnormalities. An abnormal ECG is defined as PR >220 msec, QRS complex >120 msec, QTcB> >430 msec, or any significant morphological changes, other than non-specific T-wave changes.
9. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study. The Investigator was to make this determination in consideration of the subject's medical history and/or clinical or laboratory evidence of any of the following: major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection.
10. History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result.
11. Positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result.

12. History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during the screening.
13. Subjects that took acetaminophen (paracetamol) chronically, i.e. more than 1 g/day for more than 3 out of 7 days, or more than 2 g/ day for more than 1 day out of 7 days.

Participant Flow

Subject disposition – n (%) of subjects	QAX576 6mg/kg N=17 n (%)	Placebo N=8 n (%)	Total N=25 n (%)
Subjects			
Completed	13 (76.5)	5 (62.5)	18 (72.0)
Discontinued	4 (23.5)	3 (37.5)	7 (28.0)
Main cause of discontinuation			
Adverse Event(s)	1 (5.9)		1 (4.0)
Abnormal laboratory value(s)	1 (5.9)		1 (4.0)
Unsatisfactory therapeutic effect		2 (25.0)	2 (8.0)
Lost to follow-up	2 (11.8)	1 (12.5)	3 (12.0)

Two subjects continued to the extension phase of the study.

Baseline Characteristics

Demographic summary by treatment groups	QAX576 6 mg/kg n=17	Placebo n=8	Total n=25
Age (years)			
Mean (SD)	30.7 (9.58)	29.5 (11.22)	30.3 (9.92)
Median	31.0	27.5	30.0
Range	18 – 45	18 – 48	18 – 48
Gender - n(%)			
Male	16 (94.1%)	8 (100%)	24 (96%)
Female	1 (5.9%)	0 (0%)	1 (4%)
Race - n(%)			
Caucasian	16 (94%)	8 (100%)	24 (96%)
Black	1 (6%)	0 (0%)	1 (4%)
Ethnicity - n(%)			
Other	17 (100%)	8 (100%)	25 (100%)
Weight (Kg)			
Mean (SD)	85.44 (20.730)	81.60 (19.813)	84.21 (20.108)
Median	82.10	84.0	82.10
Range	57.7 - 138.3	52.9 - 105.5	52.9 - 138.3
Height (cm)			
Mean (SD)	178.2 (6.73)	175.9 (8.06)	177.4 (7.10)
Median	177.0	176.0	176.0
Range	171 - 192	163 - 191	163 - 192
BMI (kg/m2)			
Mean (SD)	26.789 (5.6310)	26.203 (5.3193)	26.601 (5.4286)
Median	26.128	27.229	26.196

Demographic summary by treatment groups	QAX576 6 mg/kg n=17	Placebo n=8	Total n=25
Range	18.42 - 38.03	18.09 - 34.06	18.09 - 38.03

Outcome Measures

Primary Outcome Result(s)

Number and % responders in terms of peak eosinophils per hpf

Reduction of 75% or more		QAX576(n=15) 13 weeks	Placebo(n=8) 13 weeks
Proximal and distal esophagus combined	Responder	6 (40.00%)	1 (12.50%)
	90% CI	[22.27, 60.79]	[1.16, 42.79]

Secondary Outcome Result(s)

Number and % responders in terms of peak eosinophils per hpf

Reduction of 75% or more		QAX576(n=15) 13 weeks	Placebo(n=8) 13 weeks
Proximal esophagus	Responder	5 (33.33%)	1 (12.50%)
	90% CI	[17.13, 54.63]	[1.16, 42.79]
Distal esophagus	Responder	7 (50.00%)	1 (12.50%)
	90% CI	[29.88, 70.12]	[1.16, 42.79]

Number of responders in distal esophagus for QAX576 [7 (50%)] is out of 14 subjects

Number and % responders in terms of mean eosinophils per hpf

Reduction of 75% or more		QAX576(n=15) 13 weeks	Placebo(n=8) 13 weeks
Proximal and distal esophagus combined	Responder	8 (53.33%)	2 (25.00%)
	90% CI	[33.31, 72.34]	[8.00, 54.63]
Proximal esophagus	Responder	5 (33.33%)	2 (25.00%)
	90% CI	[17.13, 54.63]	[8.00, 54.63]
Distal esophagus	Responder	8 (57.14%)	2 (25.00%)
	90% CI	[36.01, 75.96]	[8.00, 54.63]

Change from baseline to week 13 in peak and mean eosinophil counts in proximal and distal esophageal biopsies combined

	QAX576 (N=15)		Placebo (N=8)		
	Baseline	**Day 85 (wk 13)**	**Baseline**	**Day 85 (wk 13)**	**P-value***
Peak eosinophils per hpf					
Mean (SD)	89.80 (45.95)	42.60 (52.45)	91.25 (26.40)	72.63 (40.62)	
Range	48; 200	0; 212	38; 130	4; 136	
Mean (SD) % change from baseline		-46.75% (56.34)		-9.29% (61.19)	0.137
Mean eosinophils per hpf					
Mean (SD)	35.69 (25.45)	13.59 (19.24)	39.11 (22.93)	34.28 (23.03)	
Range	10.1; 98.3	0; 75.7	13.4; 81.9	1.8; 70	
Mean (SD) % change from baseline		-60.04% (42.96)		23.34% (92.13)	0.004

*P-values for percent change from baseline were analyzed using an analysis of covariance (ANCOVA) with treatment as the classification variable and baseline value as a covariate.
P-values for difference between QAX576 and Placebo absolute change from baseline: Peak p=0.186 and Mean=0.038

Analysis of the change in Mayo Dysphagia Questionnaire **(***MDQ) score*[1, 2]

Treatment	n	Mean	Median	Min, Max	P-value
QAX576 6mg/kg	15	1.7	1.0	-5, 7	0.301
Placebo	7	-0.1	0.0	-7, 5	

[1] Pharmacodynamic analysis set; [2]Wilcoxon rank sum test.
The changes in clinical symptoms from baseline to subsequent study visits were scored using a sub-set of 10 questions from the MDQ. Responses to some questions (e.g. yes/no) allowed for a change of +/-1 whereas others responses (e.g. mild/moderate/severe) allowed for a change of up to +/-2. An improvement in symptoms was thus scored +1 or +2 and a worsening -1 or -2, and a no change in symptoms was scored 0. On this scoring system a positive value for the sum change would indicate an improvement in symptoms.

Safety and tolerability of QAX576 in subjects with EoE

See Safety Result Section

Duration of clinical benefit

Two subjects went on to the open-label extension phase of the study and received three further doses of QAX576 (6mg/kg) every 4 weeks. One had no eosinophils in the esophageal biopsies on Day 85 of the study; biopsy by the end of the study on Day 456 also showed no eosinophils. In the other subject both the peak and the mean eosinophil counts had a decrease of more than 80% by Day 85 and maintained this level of improvement to the end of the study on Day 449. Both patients continued to have difficulty in swallowing although the severity the symptoms had improved.

PK/PD relationships, genomics and biomarkers

Summary statistics for QAX576 pharmacokinetic parameters following repeat administration

Parameters		**Values** [f]
Tmax (day) [a]	Median	56.09 [e]
	Min - Max	56.10 - 56.10
Cmax (µg/mL) [b]	Mean (SD)	192 (58.9)
	Min - Max	90.8 - 311
	CV% [c]	30.7
Cmax/Dose (µg*kg/mL/mg)	Mean (SD)	32.1 (9.81)
	Min - Max	15.1 - 51.8
	CV%	30.7
AUCtau (µg*day/mL) [b]	Mean (SD)	3400 (910)
	Min - Max	1760 - 5010
	CV% [c]	26.7
Cav,ss (µg/mL) [b]	Mean (SD)	122 (32.5)
	Min - Max	62.8 - 179
	CV% [c]	26.7
CLss (mL/day/kg) [b]	Mean (SD)	1.9 (0.59)
	Min - Max	1.2 - 3.4
	CV% [c]	30.8
Fluctuation (%) [d]	Mean (SD)	120 (15)
	Min - Max	100 - 150
	CV% [c]	12.5
Accumulation index [d]	Mean (SD)	2.2 (0.7)
	Min - Max	1.5 - 3.6
	CV% [c]	31.6

[a] Rounded to 2 decimal places; [b] rounded to 3 significant digits; [c] rounded to 1 decimal place ; [d] rounded to 2 significant digits; [e] third dose was given on study Day 57, and time 0 (used for computation) is study Day 1; f for all parameters n=15, with exception of the accumulation index for which n=12.

PK/PD relationships were not evaluated as almost all subjects had very similar AUCtau,ss values resulting in no 'dynamic range' for a useful evaluation of the PK/PD relationships.

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Safety Results

Adverse Events by System Organ Class

	QAX576 6mg/kg N=17 n (%)	Placebo N=8 n (%)
Subjects with AE(s)	10 (58.8)	5 (62.5)
System organ class		
Respiratory, thoracic and mediastinal disorders	7 (41.2)	2 (25.0)
Gastrointestinal disorders	5 (29.4)	3 (37.5)
Injury, poisoning and procedural complications	4 (23.5)	3 (37.5)
General disorders and administration site conditions	4 (23.5)	2 (25.0)
Infections and infestations	4 (23.5)	2 (25.0)
Nervous system disorders	4 (23.5)	2 (25.0)
Skin and subcutaneous tissue disorders	4 (23.5)	1 (12.5)
Musculoskeletal and connective tissue disorders	2 (11.8)	2 (25.0)
Investigations	2 (11.8)	1 (12.5)
Ear and labyrinth disorders	0 (0.0)	1 (12.5)
Eye disorders	0 (0.0)	1 (12.5)
Immune system disorders	1 (5.9)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (5.9)	0 (0.0)
Psychiatric disorders	1 (5.9)	0 (0.0)
Vascular disorders	1 (5.9)	0 (0.0)

Arranged in descending order of frequency

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

	QAX576 6mg/kg N=17 n (%)	Placebo N=8 n (%)
Subjects with AE(s)	10 (58.8)	5 (62.5)
Preferred term		
Cough	4 (23.5)	1 (12.5)
Nasal congestion	3 (17.6)	2 (25.0)
Oropharyngeal pain	3 (17.6)	2 (25.0)
Gastrooesophageal reflux disease	4 (23.5)	0 (0.0)
Headache	3 (17.6)	1 (12.5)
Nausea	3 (17.6)	1 (12.5)
Chills	2 (11.8)	1 (12.5)
Contusion	2 (11.8)	1 (12.5)
Vomiting	2 (11.8)	1 (12.5)
Arthralgia	1 (5.9)	1 (12.5)

Serious Adverse Events and Deaths

	QAX576 6mg/kg n (%)	Placebo n (%)
No. (%) of subjects studied	17 (68.0)	8 (32.0)
No. (%) of subjects with AE(s)	10 (58.8)	5 (62.5)
Number (%) of subjects with serious or other significant events	n (%)	n (%)
Death	0 (0.0	0 (0.0)
SAE(s)	1 (5.9)	1 (12.5)
Discontinued due to SAE(s)	1 (5.9)	0 (0.0)

Other Relevant Findings

Date of Clinical Trial Report

17-Dec-2012 (content final); 23-Jan-2013 (published report eSigned)

Date Inclusion on Novartis Clinical Trial Results Database

3-June-2013

Date of Latest Update