Sponsor

Novartis

Generic Drug Name

Omalizumab

Therapeutic Area of Trial

Mild to moderate asthma

Approved Indication

Indicated for the treatment of atopic asthma in adolescents and adults (12 years and above).

Study Number

CIGE025A2208

Title

Multi-center, open-label, multiple dose study in mild to moderate asthmatics (with IgE/body weight combinations above that in the SmPC dosing table) to determine safety, tolerability, pharmacokinetics, and pharmacodynamics of omalizumab.

Phase of Development

Phase IV

Study Start/End Dates

01-Jul-2007 to 07-Aug-2008

Study Design/Methodology

This was a multi-center, open-label multiple dose study in mild to moderate asthmatics (with IgE/body weight combinations above that in the SmPC dosing table) to determine safety, tolerability, pharmacokinetics, and pharmacodynamics of omalizumab. The patients were assigned to one of three treatment groups based on the extended SmPC dosing table. The three treatment groups were dosed in parallel and the patients received two single subcutaneous injections of 450 mg, 525 mg, or 600 mg omalizumab in a 14-day interval.

Centres

5 centres in 2 countries: Germany (4), South Africa (1)

Publication

None

Objectives

Primary

• To demonstrate safety and tolerability of omalizumab in mild and moderate asthmatics with baseline IgE/body-weight combinations above those defined in the extended dosing table.

Secondary

• To evaluate the pharmacokinetic/pharmacodynamic profile of multiple administration of omalizumab to mild/moderate allergic asthma patients with baseline IgE/body-weight combinations above those defined in the SmPC dosing table.

• To determine the pre-dose specific IgE levels in these patients.

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

Omalizumab (Xolair®); dose: 2 x 450 mg, 2 x 525 mg or 2 x 600 mg; subcutaneous injection; batch number: S0009.

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

None

Criteria for Evaluation

Efficacy:
Not applicable

Safety:
Vital signs, body measurements (height, weight, temperature), ECG recordings, safety laboratory, AEs, physical examination, previous and concomitant medication, anti-Xolair® antibodies, local tolerability, and lung function (spirometry).

Pharmacodynamics:
Serum free IgE: Cmin, and Tmin, max % decrease from screening, both after the first dose and the second dose of omalizumab; serum total IgE: Cmax, and Tmax, max % increase from screening, both after the first dose and the second dose of omalizumab; specific IgE at Baseline (Day 1, pre-dose) and extrapolated specific IgE at Day 4, Day 18, and Day 29.

Pharmacokinetics:
Omalizumab AUCinf, AUClast, Cmax, Tmax, T1/2, CL/F and Vz/F, and dosenormalized AUCinf, AUClast, and Cmax, referring to the serum concentration-time profile of the two omalizumab doses (i.e. doses were not separated for PK analysis).

Statistical Methods

All safety, tolerability, and pharmacodynamic variables were presented using descriptive statistics. Summary statistics were provided stratified by dose regimen. Standard summary statistics were provided for PK variables stratified by dose. For dose normalized AUCinf, AUClast, and Cmax, 95% confidence intervals for the geometric means were provided.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Diagnosis of allergic asthma = 1 year duration at screening and a history consistent with GINA (www.ginasthma.org) step 2 or 3 treatment (mild or moderate persistent asthma

severity);
- Eligible baseline serum IgE value and body weight combinations,
- Able to give signed informed consent (prior to admission to the study in accordance with GCP and local requirements);
- Male or female, 18 to 55 years old;
- For women of childbearing potential, a negative serum pregnancy test within 13 days and a negative urine pregnancy test within 24 hours of study drug administration, and all study drug administrations; women of childbearing potential had to either have been surgically sterilized or, in the opinion of the Investigator, be using an effective method of contraception.

Exclusion Criteria

- Documented medical history of anaphylaxis;
- Lung disease other than mild to moderate allergic asthma, e.g., COPD;
- Use of inhaled tobacco products within the last 12 months;
- History of smoking tobacco products of greater than or equal to “10 pack years”;
- History of significant medical illnesses other than mild/moderate allergic asthma, including diabetes mellitus, ischemic heart disease, cardiomyopathies, serious neurologic, gastroenterologic, or dermatologic disease, or chronic bronchitis;
- Use of oral corticosteroids 3 months prior to Day 1;
- Use of any monoclonal antibody in the 6 months before Day 1;
- Use of any investigational small molecule drug in the 3 months before Day 1;
- Respiratory tract infection in the 4 weeks before Day 1;
- History of asthma attack requiring a visit to an emergency room in the 6 weeks before or during screening;
- History of asthma attack requiring treatment with intubation and mechanical ventilation in the 12 months before Day 1;
- Evidence for ischemic heart disease or arrhythmia on screening electrocardiogram (patients not excluded for occasional premature atrial or ventricular contractions);
- Female subjects of child bearing potential who were pregnant, breast feeding, or who were either not surgically sterile or were sexually active and not using an acceptable form of contraception as either an hormonal contraceptive since at least two months or the doublebarrier method, i.e., cervical diaphragm with spermicide and condom for the male partner;
- Male subjects who were sexually active and had not been sterilized surgically had to use a condom during intercourse and ensure that the female partner used a reliable contraceptive method, or they had to refrain from sexual intercourse during the entire study;
- Vulnerable subjects (e.g., persons kept in detention);
- Inability to understand the protocol requirements, instructions and study-related restrictions, the nature, scope, and possible consequences of the study;
- Unlikely to comply with the protocol requirements, instructions and study-related restrictions; e.g., uncooperative attitude, inability to return for follow-up visits, and improbability of completing the study.
- Blood or plasma donation of more than 500 mL during the previous month before allocation and more than 50 mL in the two weeks before Day –1.

Number of Subjects

	Novartis product	**Comparator**
Planned N	32	N/A
Randomised n	32	N/A
Intent-to-treat population (ITT) n (%)	32 (100%)	N/A
Completed n (%)	31 (96.9%)	N/A
Withdrawn n (%)	1 (3.1%)	N/A

Withdrawn due to adverse events n (%)	N/A	N/A
Withdrawn due to lack of efficacy n (%)	N/A	N/A
Withdrawn for other reasons n (%)	1 (3.1%)	N/A

Demographic and Background Characteristics

	Novartis product	**Comparator**
N (ITT)	32	N/A
Females : males	12:20	N/A
Mean age, years (SD)	35.4	N/A
Mean weight, kg (SD)	83.0	N/A
Race White n (%) Black n (%) Asian n (%) Other n (%)	 29 (90.6%) 1 (3.1%) 1 (3.1%) 1 (3.1%)	N/A
Characteristics relevant to study population (eg, mean FEV1 % predicted [SD])		N/A

Primary Objective Result(s)

Objective: To demonstrate safety and tolerability of omalizumab in mild and moderate asthmatics with baseline IgE/body-weight combinations above those defined in the extended dosing table.

During this clinical study, no safety concerns were raised by the Investigator. All findings were consistent with the already known safety profile of omalizumab. There were no discontinuations due to AEs. There were no serious adverse events. Overall, 26 (81.3%) patients reported a total of 69 AEs. Of these, 10 AEs reported by a total of 6 (18.8%) patients across all dose groups were considered by the Investigators to be related to omalizumab. These drug-related AEs were most frequently nervous system disorders (specifically headaches) and gastrointestinal disorders, which were mainly of mild intensity and resolved at the end of the study. Safety laboratory measurements, vital signs, ECG recordings and spirometric results did not reveal any clinically relevant findings or trends in the study, which might be related to the treatment with omalizumab.

Secondary Objective Result(s):

Objective: To evaluate the pharmacokinetic/pharmacodynamic profile of multiple administration of omalizumab to mild/moderate allergic asthma patients with baseline IgE/body-weight combinations above those defined in the SmPC dosing table.

PK conclusions

Summary of PK parameter of omalizumab:

PK Parameter	[unit]	Omalizumab 2 x 450 mg (N=12)	Omalizumab 2 x 525 mg (N=8)	Omalizumab 2 x 600 mg (N=10)
AUClast	[day.µg/mL]	4347 (± 843)	6228 (± 1535)	5692 (± 1744)
AUClast/dose	[day.ng/mL/mg]	4830 (± 937)	5932 (± 1462)	4743 (± 1453)
AUCinf	[day.µg/mL]	4602 (± 944)	6666 (± 1570)	5946 (± 1910)
AUCinf/dose	[day.ng/mL/mg]	5113 (± 1049)	6349 (± 1495)	4955 (± 1591)
Cmax	[µg/mL]	121.9 (± 53.2)	161.2 (± 30.4)	148.1 (± 38)
Cmax/dose	[ng/mL/mg]	135.5 (± 59.1)	153.5 (± 28.9)	123.4 (± 31.7)
Tmax	[day]	20.0 (15.0 ; 24.1)	19.0 (15.0 ; 24.0)	17.0 (15.0 ; 21.0)
Vz/F	[mL]	5750 (± 904)	5176 (± 1538)	5372 (± 1314)
T1/2	[day]	19.9 (± 2.7)	21.6 (± 2.9)	17.6 (± 3.8)
CL/F	[mL/h]	8.49 (± 1.84)	6.90 (± 1.64)	9.18 (± 2.77)

Values are median (range) for Tmax, and arithmetic mean (± standard deviation) for all other parameters.
For AUClast, AUCinf and Cmax, concentrations herein are given in µg/mL in contrast to ng/mL given in the source tables.

• As observed after the administration of lower doses of Xolair, serum omalizumab concentrations slowly increased to reach maximum concentrations few days after administration, i.e. 3 to 6 days (median values) after the second dose in the present study. Thereafter omalizumab was eliminated with a terminal half life between 18 and 22 days (mean values).
• Systemic exposure to omalizumab, as characterized by AUCinf and Cmax, was in the same range after the administration of 2 x 450, 2 x 525 or 2 x 600 mg Xolair®.

PD conclusions

Summary of total IgE derived parameters after first (Day 1) and second omalizumab administration (Day 15), (Mean, SD):

	Day 1, post-dose			Day 15, post-dose		
Dose	**Cmax [ng/mL]**	**Tmax [days]***	**% increase from screening**	**Cmax [ng/mL]**	**Tmax [days]***	**% increase from screening**
2 x 450 mg, N=12	3559 (±899)	14 (10–14)	201 (±55.4)	4511 (±1378)	35 (17–70)	281 (±91.3)
2 x 525 mg, N=8	4060 (±896)	14 (10–14)	165 (±78.7)	5243 (±1621)	42 (24–70)	242 (±127)
2 x 600 mg, N=12	5157 (±1173)	14 (10–14)	120 (±47.0)	6058 (±1368)	35 (19–42)	159 (±60.3)

* Tmax given as median (min–max)
Tmax on Day 15 (second dose) refers to the onset relative to the first dose on Day 1

Summary of the free IgE derived parameters after first (Day 1) and second omalizumab administration (Day 15), (Mean, SD):

	Day 1			Day 15		
Dose	**Cmin [ng/mL]**	**Tmin [days]***	**% decrease from screening**	**Cmin [ng/mL]**	**Tmin [days]***	**% decrease from screening**
2 x 450 mg, N=12	11.85 (± 2.40)	2 (1–3)	99.0 (± 0.3)	12.09 (± 2.30)	19 (16–21)	99.0 (± 0.2)
2 x 525 mg, N=8	11.79 (± 2.73)	2.5 (1–3)	99.2 (± 0.2)	12.18 (± 2.65)	18 (16–21)	99.2 (± 0.3)
2 x 600 mg, N=12	16.56 (± 3.66)	3 (1–7)	99.3 (± 0.2)	16.26 (± 5.09)	19 (16–24)	99.3 (± 0.3)

* Tmin is given as median (min–max)
Tmin on Day 15 (second dose) refers to the onset relative to the first dose on Day 1

• Overall, mean total IgE and particularly the reduction of free IgE were consistent with levels previously demonstrated to be associated with clinical efficacy.
• Mean Cmin and median Tmin of free IgE were similar between the three dose levels.
• The maximum decrease of free IgE from screening was at least 99.0% for all three dose levels after the first and the second dosing. Mean free IgE concentrations remained below 25 ng/mL at least 2 weeks after the second administration.
• Mean Cmax of total IgE was reached between Study days 35 and 42 and the maximal relative increase of total IgE from screening was within the range of 1.2- to 2.8-fold across all three dose levels.
• Specific IgE was most likely reduced below the threshold of 0.35 IU/ml, that is typically the criterion for allergic sensitivity, in most (75-100%) instances.

Objective: To determine the pre-dose specific IgE levels in these patients.

Specific IgE levels against common perennial aeroallergens were quantified at on Day 1 (predose sample) prior to Xolair® administration in this population of atopic patients with elevated IgE. Of the antigens tested in this study, the % of patients with specific IgE levels of > 0.35 IU/ml (high values) ranged between 28.1 and 87.5%, depending on the allergen, consistent with allergic sensitization. One assumes that omalizumab exerts equivalent effects upon IgE regardless of specificity, so that one can infer the levels of free specific IgE from the proportion of free IgE on treatment relative to IgE at baseline. This extrapolation demonstrates that in most instances specific IgE can be reduced in most patients below the level of sensitivity. Thus, omalizumab should positively impact allergic phenomena despite higher baseline (Day 1) IgE levels.

Safety Results

Adverse Events overall and frequently affected system organ classes- n (%) of patients- Safety population

System organ class	Omalizumab 2 x 450 mg N=12 n (%)	Omalizumab 2 x 525 mg N=8 n (%)	Omalizumab 2 x 600 mg N=12 n (%)	All Patients N=32 n (%)
Patient with AE(s)	11 (91.7)	7 (87.5)	8 (66.7)	26 (81.3)
System organ class				
Infections and infestations	6 (50.0)	4 (50.0)	5 (41.7)	15 (46.9)
Nervous system disorders	5 (41.7)	4 (50.0)	3 (25.0)	12 (37.5)
Gastrointestinal disorders	2 (16.7)	1 (12.5)	1 (8.3)	4 (12.5)
Musculoskeletal and connective tissue disorders	2 (16.7)	1 (12.5)	1 (8.3)	4 (12.5)
Respiratory, thoracic and mediastinal disorders	1 (8.3)	1 (12.5)	2 (16.7)	4 (12.5)
Eye disorders	2 (16.7)	0 (0.0)	0 (0.0)	2 (6.3)
Reproductive system and breast disorders	1 (8.3)	0 (0.0)	1 (8.3)	2 (6.3)
Skin and subcutaneous tissue disorders	0 (0.0)	2 (25.0)	0 (0.0)	2 (6.3)

AE = Adverse event, N = total number of patients, n= number of patients

Most Frequently reported AEs Overall:

Organ system class	Omalizumab 2 x 450 mg N=12 n (%)	Omalizumab 2 x 525 mg N=8 n (%)	Omalizumab 2 x 600 mg N=12 n (%)	All Patients N=32 n (%)
Patient with AE(s)	11 (91.7)	7 (87.5)	8 (66.7)	26 (81.3)
Preferred term				
Headache	5 (41.7)	3 (37.5)	3 (25.0)	11 (34.4)
Nasopharyngitis	1 (8.3)	2 (25.0)	4 (33.3)	7 (21.9)
Bronchitis	2 (16.7)	0 (0.0)	1 (8.3)	3 (9.4)
Abdominal pain	1 (8.3)	0 (0.0)	1 (8.3)	2 (6.3)
Gastroenteritis	2 (16.7)	0 (0.0)	0 (0.0)	2 (6.3)
Back pain	1 (8.3)	1 (12.5)	0 (0.0)	2 (6.3)
Pain in extremity	1 (8.3)	0 (0.0)	1 (8.3)	2 (6.3)
Dysmenorrhoea	1 (8.3)	0 (0.0)	1 (8.3)	2 (6.3)
Pharyngolaryngeal pain	1 (8.3)	0 (0.0)	1 (8.3)	2 (6.3)

AE = Adverse event, N = total number of patients, n= number of patients

Serious Adverse Events and Deaths

	Novartis product	Comparator
No. (%) of subjects studied	32 (100%)	N/A
No. (%) of subjects with AE(s)	26 (81.3%)	N/A
Number (%) of subjects with serious or other significant events	n (%)	N/A
Death	0	N/A
SAE(s)	0	N/A
Discontinued due to SAE(s)	0	N/A

Other Relevant Findings

None

Date of Clinical Trial Report

19 May 2009

Date Inclusion on Novartis Clinical Trial Results Database

11 August 2009

Date of Latest Update

N/A