Sponsor

Novartis

Generic Drug Name

Imatinib mesylate

Therapeutic Area of Trial

Allergic rhinitis

Approved Indication

Imatinib (Glivec®, Gleevec®, code number STI571) is registered in many countries for the treatment of patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase, blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha (IFN).

Imatinib is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

The originally approved oral dosage form of imatinib was a hard gelatin capsule (50 mg and 100 mg). Subsequently, the tablet dosage form (100 mg and 400 mg film-coated tablets) was approved by FDA on 18-Apr-2003, in Europe on 11-Nov-2003 and in Japan on 09-Mar-2005.

The worldwide approvals and orphan drug status granted for imatinib in USA, Europe and Japan are summarized for the various indications in the tables below.

Current worldwide approvals of imatinib

Indication	Country and Date of Approval
Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML) in blast crisis (BC), accelerated phase (AP) or chronic phase (CP) after interferon-α failure	USA: Accelerated:10-May-2001, Full: 08-Dec-2003 EU: 07-Nov-2001; Japan: 21-Nov-2001
Newly-diagnosed Ph+ CML in CP	Japan: 21-Nov-2001; EU: 19-Dec-2002; USA: 20-Dec-2002
Pediatric Ph+ CML	EU: 19-Dec-2002; USA: 20-May-2003
Metastatic and/or inoperable Kit+ gastrointestinal stromal tumors (GIST)	USA: 01-Feb-2002; EU: 24-May-2002; Japan: 17-Jul-2003

Orphan Drug Status

Indication	Country and Date of designation
CML	**USA: 31-Jan-2001; EU: 14-Feb-2001; Japan: 20-Dec-2000**
GIST	**USA: 01-Nov-2001; EU: 20-Nov-2001; Japan: 02-Oct-2002**
Acute lymphoblastic leukemia (ALL)	**USA: 11-Oct-2005; EU: 26-Aug-2005; Japan: 20-Dec-2000**
Dermatofibrosarcoma protuberans (DFSP)	**USA: 20-Dec-2005; EU: 26-Aug-2005**
Hypereosinophilic syndrome (HES)	**USA: 26-Aug-2005; EU: 28-Oct-2005**
Myelodysplastic/myeloproliferative diseases (MDS/MPD)	**USA: 05-Oct-2005; EU: 23-Dec-2005**
Systemic mastocytosis (SM)	**USA: 09-Sep-2005; EU: 26-Aug-2005**

Study Number

CSTI571E2204

Title

An exploratory study of the effects of Imatinib on allergic inflammation following out of allergy season repeated nasal allergen challenge in subjects with seasonal allergic rhinitis sensitive to Timothy grass pollen – an exploratory study of c-kit inhibition in allergic respiratory diseases

Phase of Development

Phase IIa

Study Start/End Dates

First patient first visit (screening): 14 Dec 06; First subject dosed: 7 Jan 07; Last patient last visit: 4 Apr 07

Study Design/Methodology

This was a randomized parallel-group, double-blind placebo-controlled (for imatinib) study with an open-label positive control group in Timothy grass-pollen sensitive subjects, performed out of season.

At the screening Visit (day -28 to day -7), subjects eligibility was determined, including a skin-prick test for Timothy grass and if positive, a nasal allergen challenge (NAC) using Timothy grass allergen extract. In the challenge a dose of 500 BU of Timothy grass pollen was sprayed onto the inside of each nostril. If sensitive, the subject develops acute hay fever symptoms which may include nasal congestion, itch, sneezing and rhinorrhea. Those individuals who demonstrate symptomatic worsening (Total Nasal Symptom Score (TNSS) ≥ 4) within one hour of nasal challenge were eligible for the study. Assessments associated with the nasal challenge included TNSS, nasal lavage to collect cells, and nasal filter paper adsorptions to collect mediators of inflammation from the nose.

At least seven days after the screening assessment eligible subjects returned to the unit on Day 1 and were randomized to one of the three treatment groups. Subjects randomized to receive fluticasone received their first dose of fluticasone after they had completed their 6 h time point on Day 1. This was followed by bid dosing, with the morning dose taken at least 30 minutes prior to any pre-challenge assessments. On day 4 subjects randomized to receive Imatinib or placebo received their single dose 3 hours prior to the NAC.

Subjects returned on Day 5 for the 24 hour assessments, but were not re-challenged. Subjects again returned to the clinic 5-9 days later to perform their study completion assessments.

Centres

One centre in the United Kingdom.

Publication

Objectives

Primary objective(s)

To assess the effects of Imatinib on allergic inflammation following repeated nasal allergen challenge (NAC) in subjects with seasonal allergic rhinitis sensitive to Timothy grass pollen – in particular to assess if Imatinib reduces mast cell degranulation (measured by β-tryptase and PGD2) in response to allergen challenge.

Secondary objective(s)

Additional markers of inflammation were measured following NAC:
• Enumeration of eosinophils in nasal lavage following nasal allergen challenge
• Total nasal symptom score (TNSS) following nasal allergen challenge
• Soluble mediators collected from adsorption onto nasal filter papers following nasal allergen challenge, with a focus on Th2-associated cytokines (to include IL-4, IL-5 and IL-13)

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

Single dose of Imatinib (labeled as STI571) 400 mg, administered as 4 x 100 mg hard gelatin capsules administered orally (Batch no. X368LA, product code 3752425.002)
Or
Single dose of matched placebo (Batch no. X366LA, product code 3760451.003)

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

Positive control: Intranasal fluticasone propionate, 100 μg per nostril, bid for four days

Criteria for Evaluation

Primary variables

β-tryptase and PGD2 levels collected from adsorption onto nasal filter papers following nasal allergen challenge

Secondary variables

Eosinophils count from nasal lavage following nasal allergen challenge
Total nasal symptom score (TNSS) following nasal allergen challenge
Soluble mediators (IL-4, IL-5 and IL-13) collected from adsorption onto nasal filter papers following nasal allergen challenge

Safety and tolerability

Physical examination (including nasal examination); vital signs, weight and body temperature; ECG; Hematology, Blood chemistry, Urinalysis; FEV1; Adverse events

Pharmacology

N/A.

Other

N/A.

Statistical Methods

This was an exploratory study and as such was not powered for any formal hypothesis testing. The endpoints of primary interest were β-tryptase levels and prostaglandin D2. Little was known about these data however, hence if during the trial the assay methods were unable to measure these data appropriately, or there was greater than expected variability, the study was to focus on eosinophils and total nasal symptoms scores (TNSS). No formal statistical hypothesis testing was planned in the protocol. Descriptive statistics and graphical tools were used to examine the relationship between treatment group and changes in the inflammatory markers over time.

Primary and secondary endpoints, β-tryptase and prostaglandin D2, TNSS, % eosinophils, IL-4, IL-5 and IL-13 were reported using descriptive statistics and plots. Summary statistics were tabulated for the raw data together with the changes on Day 4 from pre-NAC, adjusted for Day 1. The change pre-NAC on Day 4 was calculated, adjusting for Day 1 as follows: Change=(5 min post NAC on day 4 – pre NAC on day 4)-(5 min post NAC on day 1 – pre NAC on day 1). Boxplots of changes on Day 4 adjusted for Day 1, plots of medians and inter-quartile range, and individual patient profiles over time were produced.

A linear model was fitted to the Day 4 changes from pre-NAC values for each time point, with treatment group and Day 1 changes from pre-NAC fitted as fixed effects. These models were used to derive the 90% confidence intervals around the mean differences between the treatment groups for each time point. Where appropriate, the data were to be log transformed. Although for the analysis of this trial log-transformation was not considered necessary, an exploratory log-transformed analysis was performed to assist in the planning of future trials.

IL-13 plasma, IgE total, and IgE Timothy grass specific were summarized using descriptive statistics.

Study Population: Inclusion/Exclusion Criteria and Demographics

Key Inclusion Criteria:

1. Healthy male non-smoking subjects aged 18-55 years, with a history of seasonal allergic rhinitis consistent with Timothy grass pollen allergy. They must show:
   • a positive skin prick test to Timothy grass pollen (wheal difference Timothy grass pollen – negative control ≥ 3 mm) at or within the 12 months preceding the screening visit and
   • demonstrate symptomatic worsening (TNSS ≥4) within one hour after nasal allergen challenge

2. Be otherwise healthy with no health problems that may jeopardize the subjects participating in the study, absence of history of other significant allergies.

Key Exclusion Criteria:

1. Respiratory disease other than a history of mild stable asthma not requiring treatment and associated with normal lung function.

2. Presence of any structural nasal abnormalities or nasal polyps on examination, a history of frequent nose bleeding, recent nasal surgery (within 8 weeks prior to screening visit) or recent (four weeks) or ongoing upper or lower respiratory tract infection.

3. Use of any medication that would affect the response to the allergen challenge (e.g. corticosteroids, decongestants, anti-histamines, medications with anti-inflammatory effects) or any other nasally applied medication within 14 days prior to allergen challenge (30 days for systemic anti-inflammatory therapy including oral corticosteroids).

4. Use of any medication known to influence Imatinib bioavailability or clearance. Subjects receiving statins will not be eligible for participation or continuation in this study.

5. History or laboratory evidence of acute or chronic renal insufficiency or abnormal liver function. A past medical history of inherited heart disease, valve defect, cardiomyopathy, rheumatic fever, arrhythmias, cardiac interventions or clinically significant ECG abnormalities.

Number of Subjects

	Planned	Entered	Completed
Imatinib	12	13	12
Placebo	12	12	12
Fluticasone	6	6	6
Total	30	31	30

Demographic and Background Characteristics

	Novartis product	**Placebo**	**Flixonase**
N (ITT)	13	12	6
Males	13	12	6
Mean age, years (SD)	33.4 (8.92)	33.8 (7.8)	27.8 (5.12)
Mean weight, kg (SD)	76.19 (9.599)	88.42 (10.875)	78.50 (15.476)
Race White n (%) Black n (%) Asian n (%) Other n (%)	 10 (79.9%) 1 (7.7%) 2 (15.4%)	 8 (66.7%) 2 (16.7%) 2 (16.7%)	 4 (66.7%) 1 (16.7%) 1 (16.7%)

Primary Objective Result(s)

On average, PGD2 and tryptase were decreased after multiple allergen challenge in both the placebo and imatinib treatment groups. A single dose of imatinib prior to the last allergen challenge had no effect on either PGD2 or tryptase.

Secondary Objective Result(s)

Recruitment of eosinophils was, on average, increased by repeated daily challenge with allergen. A single dose of imatinib 3h prior to the last allergen challenge significantly reduced the recruitment of eosinophils. No effect of imatinib on TNSS was seen.

The increase in nasal cytokines 2-4h post allergen challenge was very variable. About 50% of patients in the fluticasone group responded with an increase in IL-5 and IL-13 after an allergen challenge at baseline. This was blocked by treatment with fluticasone. Only a few patients in the imatinib group showed a significant increase in IL-5 and IL-13 after an allergen challenge at baseline. Consequently, it is difficult to assess the effect of a single dose of imatinib prior to the last allergen challenge.

Safety Results

Adverse Events by Body system

Body system	Adverse event (preferred term)	Any treatment N=31 n (%)	Flixonase N=6 n (%)	Placebo N=12 n (%)	Imatinib N=13 n (%)
- any body system		10 (32.3)	3 (50.0)	2 (16.7)	5 (38.5)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	- Total	1 (3.2)			1 (7.7)
	LYMPHADENOPATHY	1 (3.2)			1 (7.7)
GASTROINTESTINAL DISORDERS	- Total	2 (6.5)		1 (8.3)	1 (7.7)
	ABDOMINAL PAIN	1 (3.2)		1 (8.3)	
	DYSPEPSIA	1 (3.2)			1 (7.7)
INVESTIGATIONS	- Total	3 (9.7)	1 (16.7)		2 (15.4)
	BLOOD CREATINE PHOSPHOKINASE INCREASED	1 (3.2)			1 (7.7)
	BLOOD LACTATE DEHYDROGENASE INCREASED	1 (3.2)			1 (7.7)
	ELECTROCARDIOGRAM QT PROLONGED	1 (3.2)	1 (16.7)		
NERVOUS SYSTEM DISORDERS	- Total	3 (9.7)		1 (8.3)	2 (15.4)
	DIZZINESS	1 (3.2)			1 (7.7)
	HEADACHE	2 (6.5)		1 (8.3)	1 (7.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	- Total	7 (22.6)	3 (50.0)	2 (16.7)	2 (15.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	COUGH	1 (3.2)			1 (7.7)
	DYSPNOEA	1 (3.2)	1 (16.7)		
	EPISTAXIS	1 (3.2)	1 (16.7)		
	NASAL CONGESTION	1 (3.2)		1 (8.3)	
	PHARYNGOLARYNGEAL PAIN	2 (6.5)	2 (33.3)		
	RHINORRHOEA	2 (6.5)		1 (8.3)	1 (7.7)
	SNEEZING	1 (3.2)		1 (8.3)	
	THROAT IRRITATION	1 (3.2)			1 (7.7)
	WHEEZING	1 (3.2)	1 (16.7)		

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

See above – pharyngolaryngeal pain was the only AE reported more than once in any treatment group.

Serious Adverse Events and Deaths

None

Other Relevant Findings

None

Date of Clinical Trial Report

2 April 08

Date Inclusion on Novartis Clinical Trial Results Database

July 2008

Date of Latest Update