Sponsor

Novartis

Generic Drug Name

Imatinib

Therapeutic Area of Trial

Systemic sclerosis

Approved Indication

Indicated for the treatment of Philadelphia chromosome positive (Ph+) chronic myoloid leukemia in chronic phase, blast crisis, accelerated phase, and chronic phase after failure of interferon-α. It is also approved for patients with repapsed or refractory Ph+ acute lymphoblastic leukemia, hypereosinophilic syndrome / chronic eosinophilic leukemia, myelodysplastic / myeloproliferative diseases, and aggressive systemic mastocytosis.

For solid tumors, imatinib is indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors, for the adjuvant treatment of adult patients following resection of Kit (CD117)-positive gastrointestinal stromal tumors and dermatofibrosarcoma protuberans.

Study Number

CSTI571E2205

Title

A multi-centre, open-label, Proof of Concept (PoC) study to evaluate the efficacy and tolerability of STI571 for the treatment of fibrosis in patients with systemic sclerosis

Phase of Development

IIA

Study Start/End Dates

02 Jan 2008 to 13 Jan 2010

Study Design/Methodology

Multicenter, open label, efficacy and safety study of imatinib in patients with systemic scleroderma. The study consisted of a treatment period of 24 weeks and a follow-up period of 24 weeks with no study drug. Imatinib was initiated at an oral dose of 200 mg/day for 4 weeks then titrated up to 400 mg/day for 2 weeks followed by 600 mg/day until Week 24, if safety and tolerability permitted.

Centres

7 centers in 5 countries: USA (3), UK (1). Germany (1), Switzerland (1), Italy (1).

Publication

N/A

Objectives

Primary objective(s)

- To assess the efficacy of oral STI571 in skin fibrosis in systemic sclerosis (SSc) patients as measured by an improvement in the modified Rodnan Skin Score (MRSS)
- To assess the safety and tolerability of oral STI571 in SSc patients

Secondary objective(s)

- To assess improvement in lung function as measured by CO diffusion capacity (DLCO) and Forced Vital Capacity (FVC).
- To assess biomarkers reflecting the direct effects of STI571 on its biological targets.
- To determine the PK trough levels of STI571 and its major active metabolite CGP74588 during dose escalation and the maintenance phase of the study

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

Oral tablets of imatinib 100 mg once each morning.

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

N/A

Criteria for Evaluation

Primary variable

The modified Rodnan skin score (MRSS) determined at Screen, Baseline (Day -1), Weeks 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48/Study Completion.

- The percentage change from baseline constitutes the primary endpoint. It was analyzed after 6, 12 and all patients completed 12 weeks of treatment and a final analysis was performed after all patients completed 24 weeks of treatment.

Secondary variables

- Skin scales: Screen, Baseline (Day -1), Weeks 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48/Study Completion
- Oral aperture, active hand extension: Baseline (Day -1), Weeks 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48/Study Completion
- Health Assessment Questionnaire (HAQ): Baseline (Day -1), Weeks 4, 8, 12, 16, 20, 24 and 48/Study Completion
- Erythrocyte sedimentation rate (ESR): Baseline (Day -1), Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48/Study Completion
- C-Reactive Protein (CRP): Baseline (Day -1), Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48/Study Completion
- Antinuclear antibody (ANA): Screening. If the result is positive, assess at Weeks 12, 24, 36 and 48/Study Completion
- DNA topoisomerase I antibody (anti-Topo): Screening. If positive, assess at Weeks 2, 4, 6, 8, 12, 16, 20, 24, 36 and 48/Study Completion
- Lung function tests as measured by CO Diffusion Capacity (DLCO) and Forced Vital Capacity (FVC): Screening, Weeks 12, 24, 36 (if available) and 48/Study Completion
- High Resolution Computer Tomography (HRCT): Screening (if available) or Baseline (Day -1), Week 48/Study Completion
- Patient and physician global assessment as recorded on a 100mm visual analog scale (VAS): Baseline (Day -1), Weeks 12, 24 and 48/Study Completion

Safety and tolerability

Frequency of adverse events, incidence of clinically notable laboratory abnormalities, particularly involving vital signs, echocardiography, and ECG data.

Pharmacology

The trough plasma concentrations of STI571 and CGP74588 at steady state measured at Baseline, prior to the morning dose on the last day (or within 3 days before the last day) of Weeks 2 (200 mg daily dose), 4 (200 mg daily dose), 6 (400 mg daily dose), and 8 (600 mg daily dose) as well

as on the last day (or within 3 days before the last day) of Weeks 12 and 24.

Other

Exploratory biomarker samples were collected and analyzed in an exploratory manner.

Statistical Methods

Data from all centers were pooled to ensure that adequate subject numbers are available. Data were summarized with appropriate descriptive statistics (sample size, mean, standard deviation, minimum, median, and maximum for continuous variables; frequencies and percentage for discrete variables) and graphically. Statistical analysis was performed for the set of patients that received at least one dose of study drug with at least one post-baseline assessment.

The primary endpoint was the change from baseline in MRSS was calculated for each patient during the treatment period as % change from baseline at week t = (MRSS(t)-MRSS(baseline))/MRSS(baseline).

The chances that the mean % change from baseline in MRSS under STI571 is ≤ -25% were assessed by a Bayesian analysis. It assumed normal distribution of the % change in MRSS and a skeptical prior distribution for the mean % change from baseline with mean 0 and weight of 2 patients.

As an additional analysis, the following MRSS categories were calculated for time points 12, 24 and 48 weeks:

- Non-response: a reduction in MRSS <25%
- Partial response: a reduction in MRSS between 25-<50%
- Complete response: a reduction in MRSS between 50-<80%
- Remission: a reduction in MRSS ≥80%

Adverse events were summarized by the number and percentage of subjects who had any adverse event (AE), who had an AE in each body system, and who had each individual AE.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

1. Male and female patients equal to or older than 18 years of age and fulfilling the American College of Rheumatology criteria for systemic sclerosis (SSc).
2. Diffuse cutaneous SSc (dcSSc) according to the LeRoy criteria with disease duration less than 18 months from the appearance of the first non-Raynaud´s symptom judged by a physician to be part of SSc.
3. Patients with a MRSS of at least 20 (maximum score 51) in the absence of trunk involvement or a MRSS of at least 16 in patients with trunk involvement.
4. Female patients of childbearing potential must be using two acceptable methods of contracep-

tion, (e.g., intra-uterine device plus condom, spermicidal gel plus condom, diaphragm plus condom, etc.), from the time of screening and for the duration of the study, through study completion.

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Female patients who report surgical sterilization must have had the procedure at least six (6) months prior to initial dosing. Surgical sterilization procedures should be supported with clinical documentation made available to the sponsor and noted in the Relevant Medical History / Current Medical Conditions section of the CRF.

All female patients must have negative pregnancy test results at screening and at baseline.

5. Male patients must be using a two acceptable methods of contraception , (e.g., spermicidal gel plus condom) for the entire duration of the study, up to the Study Completion visit, and refrain from fathering a child in the three (3) months following the last study drug administration.

   Periodic abstinence and withdrawal are not acceptable methods of contraception.
6. 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. SSc patients with a MRSS greater than 35.
2. Concurrent connective tissue diseases other than SSc including SSc-like illnesses related to environmental, ingested or injected agents, and also including overlap syndromes and mixed connective tissue disease.
3. Significant pre-existing internal organ damage:
   - kidneys:
     - MDRD calculated creatinine clearance < 40 mL/min
     - renal crisis (acute onset of renal failure, moderate to marked hypertension, and normal urine sediment with mild proteinuria) in the 2 months prior to treatment
   - lungs:
     - FVC < 50% predicted
     - CO diffusion capacity < 40% predicted
   - heart:
     - left ventricular ejection fraction < 40%
     - ECG conduction abnormalities deemed by the Investigator to be clinically significant (including atrio-ventricular blocks, atrial or ventricular arrhythmias, sinus pauses > 3 seconds)
   - gut:
     - pseudo-obstruction
     - mal-absorption requiring parental nutrition.
4. Existing myositis: serum creatine phosphokinase > 3 fold of the upper-limit

5. Conditions that might mimic potential side effects of STI571:
   - hematological conditions: - thrombocytopenia < 100 x 10^9/L
   - neutropenia < 1.5 x 10^9/L
   - moderate hepatic insufficiency with transaminase levels >3 fold the upper limit of normal, or bilirubin > 2 fold the upper limit of normal
   - chronic diarrhea for more than 4 weeks
   - peripheral edemas
6. Active or opportunistic infection
7. Concurrent interventional medical therapy that might potentially influence the outcome of the disease. Treatment with other potentially disease modifying agents during the last 6 weeks, including prednisone or corticosteroid equivalent in doses higher than 15 mg/d or changes in the prednisone doses during the last 1 month before first dosing.
8. Grapefruit juice should not be drunk whilst patients participate in the study. Special attention should be given to the co-prescription of CYP3A4 inhibitors (e.g. Amiodarone, Diltiazem, Verapamil, macrolide antibiotics, Itraconazole and Ketoconazole), and to some of the drugs metabolized by CYP450 isoenzymes (Phenytoin, Carbamazepin, Rifampicin, Phenobarbital, Saint-John's Wort, Cyclosporine, Warfarin or Paracetamol).
9. Other conditions that might be associated with an increased risk to the patient or interfere with successful conduction of the trial:
   - underlying chronic debilitating diseases such as cancer,
   - pregnancy, breast feeding or lack of safe contraception (IUD, diaphragm, bilateral tubal ligation, hysterectomy) in women of childbearing potential.
10. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of drugs or which may jeopardize the patient in case of participation in the study. The Investigator should be guided by evidence of any of the following:
    - history of inflammatory bowel syndrome, gastritis, ulcers, gastrointestinal or rectal bleeding;
    - history of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection;
    - history or clinical evidence of pancreatic injury or pancreatitis.
11. Participation in any treatment studies within 3 months prior to dosing or longer if required by local regulations, and for any other limitation of participation based on local regulations.
12. Donation or loss of 400 ml or more of blood within 8 weeks prior to first dosing, or longer if required by local regulation.
13. History of acute or chronic bronchospastic disease (at the discretion of Investigators)
14. History of clinically significant drug allergy or history of atopic allergy (asthma, urticaria, eczematous dermatitis). A known hypersensitivity to the study drug or drugs similar to the study drug.
15. History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result.
16. A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result.

17. History of drug abuse within the 12 months prior to dosing or evidence of such abuse as indicated by the laboratory assays conducted during the screening evaluations at the discretion of the Investigator.
18. Chronic thromboembolic pulmonary hypertension.
19. Severe systemic arterial hypertension (>180 mm Hg [systolic] or >110 mm Hg [diastolic])
20. Congenital or acquired valvular or myocardial disease.
21. A past medical history of clinically significant ECG abnormalities.
22. History of autonomic dysfunction (e.g. history of fainting, orthostatic hypotension, sinus arrhythmia).
23. History of myocardial ischemia or infarction.
24. History of heart failure.
25. Disseminated intravascular coagulation (DIC).
26. Sickle cell anemia or other anemia associated with hemoglobin < 10 mg/dL.
27. Evidence of major bleeding or intracranial hemorrhage in the last two years.
28. Hemochromatosis.
29. Ischemic stroke in the last two years.
30. History of other significant illness within four weeks prior dosing.

Number of Subjects

Planned N	27	
Treated n	27	
Analyzed n (%)	27 (100%)	
Completed n (%)	13 (48%)	
Withdrawn n (%)	14 (52%)	
Withdrawn due to adverse events n (%)	7 (26)	
Subject withdrew consent	3 (11%)	
Withdrawn for other reasons n (%)	4 (15%)	

Demographic and Background Characteristics

N (ITT)	27 (100%)	
Females : males	21 : 6	
Mean age, years (Range)	45.7 (20 – 64)	
Mean weight, kg (Range)	67.1 (47.4 – 104.1)	
Race Caucasian n (%) Black n (%) Native American n (%) Other n (%)	 24 (89%) 1 (4%) 1 (4%) 1 (4%)	

Primary Objective Result(s)

	MRSS total score	% change from baseline MRSS
Baseline (n=27)		
Mean ± SD	25.7 ± 5.83	not applicable
Week 12 (n=18)		
Mean ± SD	26.7 ± 8.26	3.3 ± 27.53
Week 24 (n=16)		
Mean ± SD	28.4 ± 7.01	9.9 ± 23.68
Week 48/EOS* (n=13)		
Mean ± SD	19.8 ± 5.65	-20.9 ± 24.95

* Only subjects completing the study are included at EOS (planned week 48) timepoint.

The posterior probability for the mean % change from baseline ≤ -25% either at week 12 or at 24 was less than 1%.

Secondary Objective Result(s)

	Lung function tests	
	FVC (% of predicted)	DLCO (% of predicted)
Screening		
Mean ± SD	93.0 ± 19.56	76.9 ± 16.22
Week 12		
Mean ± SD	92.2 ± 22.59	70.8 ± 13.55
Week 24		
Mean ± SD	93.3 ± 21.14	71.9 ± 15.17
Week 48 (EOS)*		
Mean ± SD	97.5 ± 27.40	72.9 ± 15.42

* Only subjects completing the study are included at EOS (planned week 48) timepoint.

Pharmacokinetics data and biomarker data are being analyzed and will be reported separately.

Safety Results

Adverse Events by System Organ Class

	All subjects N=27 n (%)
Patients with AEs	27 (100%)
AEs by primary system organ class	
Blood and lymphatic system disorders	9 (33%)
Cardiac disorders	1 (4%)
Ear and labyrinth disorders	4 (15%)
Eye disorders	3 (11%)
Gastrointestinal disorders	23 (85%)
General disorders and administration site condition	21 (78%)
Infections and infestations	13 (48%)
Injury, poisoning and procedural complications	4 (15%)
Investigations	14 (52%)
Metabolism and nutrition disorders	6 (22%)
Musculoskeletal and connective tissue disorders	14 (52%)
Nervous system disorders	5 (19%)
Psychiatric disorders	5 (19%)
Reproductive system and breast disorders	1 (4%)
Respiratory, thoracic and mediastinal disorders	8 (30%)
Skin and subcutaneous tissue disorders	19 (70%)
Vascular disorders	5 (19%)

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

	All subjects N=27 n (%)
Oedema peripheral	16 (59%)
Nausea	15 (56%)
Pruritus	9 (33%)
Constipation	7 (26%)
Diarrhea	7 (26%)
Arthralgia	7 (26%)
Anaemia	6 (22%)
Vomiting	6 (22%)
Face oedema	6 (22%)
Fatigue	5 (19%)

Serious Adverse Events and Deaths

No. (%) of subjects studied 27

Number (%) of subjects with serious or other significant events	n (%)
Death	1 (4%)
SAE(s)	5 (19%)
Discontinued due to SAE(s)	3 (11%)

Other Relevant Findings

N/A

Date of Clinical Trial Report

TBD.

Date Inclusion on Novartis Clinical Trial Results Database

13th January 2011

Date of Latest Update

6-Jan-2011