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Novartis Clinical Trial Results

Sponsor

Novartis

Generic Drug Name

Imatinib

Trial Indication(s)

Systemic sclerosis

Protocol Number

CSTI571E2205

Protocol 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

Clinical Trial Phase

Phase IIA

Phase of Drug Development

Phase IIA

Study Start/End Dates

2 Jan 2008 to 13 Jan 2010

Reason for Termination

Not applicable.

Study Design/Methodology

This was a multicenter, open-label, efficacy and safety study of STI571 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. STI571 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.

Centers

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

Objectives:

Primary objective(s)

- Change From Baseline in Modified Rodnan Skin Score (MRSS) at Each Time Point of Analysis
- Number of Participants With Adverse Events (AE's) and Serious Adverse Events (SAE's)

Secondary objective

- Number of Participants With Non-response, Partial Response, Complete Response, and Remission Assessed by MRSS Values

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

Oral tablets of imatinib 100 mg.

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: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Male and female participants who are equal to or older than 18 years of age and who have early diffuse cutaneous systemic sclerosis (Disease duration < 18 months from the first non-Raynaud's symptom)
- Participants with a modified Rodnans Skin Score (MRSS) of at least 20 in the absence of trunk involvement or a MRSS of at least 16 in patients with trunk involvement
- Female patients of childbearing potential practicing two acceptable forms of contraception

Exclusion Criteria:

- SSc patients with a MRSS greater than 35
- Concurrent connective tissue diseases other than systemic sclerosis
- Significant pre-existing heart, liver, lungs, digestive system, blood and other diseases, cancer
- Conditions that might mimic the potential side effects of STI571 (blood conditions, liver damage, chronic diarrhea, edema)
- Concurrent medical therapies (or during last 6 weeks before first dosing) that may potentially influence outcome of the study
- Allergic to the study medication
- Pregnancy
- Breast feeding

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Participant Flow Table

Patient disposition

	All subjects N=27 n (%)
Patients	
Completed	13 (48%)
Discontinued	14 (52%)
Main cause of discontinuation	
Adverse event(s)	7 (26%)
Subject with drew consent	3 (11%)
Other	4 (15%)

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Baseline Characteristics

Summary of Demographic Information

	Statistic	All subjects N=27
Age (years)	Mean (Range)	45.7 (20 – 64)
Height (cm)	Mean (Range)	165.1 (132 – 182)
Weight (kG)	Mean (Range)	67.1 (47.4 – 104.1)
Gender - Female	n (%)	21 (78%)
Gender – Male	n (%)	6 (22%)
Predominant Race – Black	n (%)	1 (4%)
Predominant Race - Caucasian	n (%)	24 (89%)
Predominant Race – Native American	n (%)	1 (4%)
Predominant Race - Other	n (%)	1 (4%)
Body Mass Index (kg/m^2)	Mean (Range)	24.59 (18.29 – 39.67)

Primary Outcome Result(s)

Change From Baseline in Modified Rodnan Skin Score (MRSS) at Each Time Point of Analysis

Arm/Group Title		STI571
Arm/Group Description:		Participants received ST1571 100 mg tablets, orally, once daily. 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 well tolerated.
Overall Number of Participants Analyzed		27
Mean (Standard Deviation) Unit of Measure: units on a scale		
Baseline	Number Analyzed	27 participants
		25.7 (5.83)
Week 2	Number Analyzed	27 participants
		6.58 (18.416)
Week 4	Number Analyzed	27 participants
		5.97 (17.382)
Week 6	Number Analyzed	27 participants
		8.34 (24.645)
Week 8	Number Analyzed	24 participants
		8.48 (27.096)
Week 12	Number Analyzed	18 participants
		3.34 (27.525)
Week 16	Number Analyzed	18 participants
		12.70 (28.399)
Week 20	Number Analyzed	18 participants
		12.41 (28.149)
Week 24	Number Analyzed	16 participants
		9.90 (23.675)
Week 28	Number Analyzed	14 participants
		-3.17 (19.891)

Week 32	Number Analyzed	14 participants
		-5.67 (18.013)
Week 36	Number Analyzed	12 participants
		-12.61 (27.383)
Week 40	Number Analyzed	12 participants
		-5.23 (27.506)
Week 44	Number Analyzed	13 participants
		-13.57 (26.763)
Week 48/ EOS	Number Analyzed	13 participants
		-20.89 (24.946)

Secondary Outcome Result(s)

Number of Participants With Adverse Events (AE's) and Serious Adverse Events (SAE's)

Arm/Group Title	STI571
Arm/Group Description:	Participants received ST1571 100 mg tablets, orally, once daily. 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 well tolerated.
Overall Number of Participants Analyzed	27
Measure Type: Count of Participants Unit of Measure: Participants	
Participants Experiencing AE's	27 100.0%
Participants Experiencing SAE's	5 18.5%

Number of Participants With Non-response, Partial Response, Complete Response, and Remission Assessed by MRSS Values

Arm/Group Title		STI571
▼ Arm/Group Description:		Participants received STI571 100 mg tablets, once daily. 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 Week24, if well tolerated.
Overall Number of Participants Analyzed		27
Measure Type: Count of Participants Unit of Measure: Participants		
Week 2	Number Analyzed	27 participants
	Non-response	27 100.0%
	Partial Response	0 0.0%
	Complete Response	0 0.0%
	Remission	0 0.0%
Week 4	Number Analyzed	27 participants
	Non-response	25 92.6%
	Partial Response	2 7.4%
	Complete Response	0 0.0%
	Remission	0 0.0%
Week 6	Number Analyzed	27 participants

	Non-response	24 88.9%
	Partial Response	2 7.4%
	Complete Response	1 3.7%
	Remission	0 0.0%
Week 8	Number Analyzed	24 participants
	Non-response	22 91.7%
	Partial Response	2 8.3%
	Complete Response	0 0.0%
	Remission	0 0.0%
Week 12	Number Analyzed	18 participants
	Non-response	15 83.3%
	Partial Response	3 16.7%
	Complete Response	0 0.0%
	Remission	0 0.0%
Week 16	Number Analyzed	18 participants
	Non-response	16 88.9%
	Partial Response	2

		11.1%
	Complete Response	0 0.0%
	Remission	0 0.0%
Week 20	Number Analyzed	18 participants
	Non-response	16 88.9%
	Partial Response	2 11.1%
	Complete Response	0 0.0%
	Remission	0 0.0%
Week 24	Number Analyzed	16 participants
	Non-response	15 93.8%
	Partial Response	1 6.3%
	Complete Response	0 0.0%
	Remission	0 0.0%
Week 28	Number Analyzed	14 participants
	Non-response	13 92.9%
	Partial Response	1 7.1%
	Complete Response	0 0.0%

	Remission	0 0.0%
Week 32	Number Analyzed	14 participants
	Non-response	13 92.9%
	Partial Response	1 7.1%
	Complete Response	0 0.0%
	Remission	0 0.0%
Week 36	Number Analyzed	12 participants
	Non-response	9 75.0%
	Partial Response	3 25.0%
	Complete Response	0 0.0%
	Remission	0 0.0%
Week 40	Number Analyzed	12 participants
	Non-response	9 75.0%
	Partial Response	3 25.0%
	Complete Response	0 0.0%
	Remission	0 0.0%
Week 44	Number Analyzed	13 participants

	Non-response	8 61.5%
	Partial Response	5 38.5%
	Complete Response	0 0.0%
	Remission	0 0.0%
Week 48/EOS	Number Analyzed	13 participants
	Non-response	5 38.5%
	Partial Response	8 61.5%
	Complete Response	0 0.0%
	Remission	0 0.0%

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Safety Results

Adverse events overall and affected system organ classes – n (%) of subjects (all patients)

	All subjects N=27 n (%)
Patients with AEs	27 (100%)
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 & administration site conditions	21 (78%)
Infections & infestations	13 (48%)
Injury, poisoning and procedural complications	4 (15%)
Investigations	14 (52%)
Metabolism and nutrition disorders	6 (22%)
Musculoskeletal & connective tissue disorders	14 (52%)
Nervous system disorders	5 (19%)
Psychiatric disorders	5 (19%)
Reproductive system & breast disorders	1 (4%)
Respiratory, thoracic & mediastinal disorders	8 (30%)
Skin & subcutaneous tissue disorders	19 (70%)
Vascular disorders	5 (19%)

AEs arranged alphabetically.

Adverse events overall and specific events – n(%) of subjects (all patients)

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	All subjects N=27 n (%)
Patients with at least one AE	27 (100%))
Preferred term	
Blood and Lymphatic system disorders	
Anaemia	6 (22%)
Gastrointestinal disorders	
Abdominal discomfort	3 (11%)
Abdominal distension	4 (15%)
Abdominal pain upper	3 (11%)
Constipation	3 (11%)
Diarrhea	7 (26%)
Dyspepsia	4 (15%)
Flatulence	3 (11%)
Nausea	15 (56%)
Vomiting	6 (22%)
General disorders and administration site condition	
Face Oedema	6 (22%)
Fatigue	5 (19%)
Oedema peripheral	16 (59%)
Infections and infestations	
Lower respiratory tract infection	3 (11%)
Nasopharyngitis	3 (11%)
Urinary tract infection	4 (15%)
Investigations	
Blood creatine phosphokinase increased	3 (11%)
C-reactive protein increased	3 (11%)
Gamma-glutamyltransferase increased	3 (11%)
Red blood cell sedimentation rate increased	4 (15%)
White blood cell count decreased	3 (11%)
Metabolism and nutrition disorders	
Decreased appetite	3 (11%)
Musculoskeletal and connective tissue disorders	
Arthralgia	7 (26%)
Myalgia	3 (11%)
Pain in extremity	3 (11%)
Nervous system disorders	
Headache	5 (19%)
Skin and subcutaneous tissue disorders	
Periorbital oedema	5 (19%)

	All subjects N=27 n (%)
Patients with at least one AE	27 (100%))
Preferred term	
Pruritus	9 (33%)
Skin tightness	3 (11%)
Skin ulcer	5 (19%)
Raynaud's phenomenon	4(15%)

AEs are presented alphabetically by body system and preferred term

Only AEs with incidence ≥10% are listed

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%)

Conclusion:

STI571 showed no significant clinical benefit in diffuse systemic sclerosis (SSc). There was a trend towards an improvement in Modified Rodnan Skin Score (MRSS) (-20.9%) and global physician/patient health assessment after 48 weeks (24 weeks after the end of treatment).

All patients had one or more AEs reported in the study. The AE profile was as expected for STI571 and this patient population.

Date of Clinical Trial Report

12-Jan-2011