Sponsor Novartis
Generic Drug Name Imatinib
Therapeutic Area of Trial Sarcoma (chordoma)
Approved Indication Chronic Myeloid Leukemia, GastroIntestinal Stromal Tumor (GIST) and DermatoFibroSarcoma Protuberans (DFSP)
Study Number CSTI571BIT15
Title Phase II study of Imatinib mesylate in chordoma
Phase of Development II
Study Start/End Dates 13-Oct-2004 to 05-May-2008
Study Design/Methodology Open label, single-arm, phase II clinical study of Imatinib mesylate (800 mg p.o./day) for 24 months in patients with advanced chordoma
Centres 13 centres: 12 in Italy and one in Switzerland

Objectives

Primary objective

- To assess the antitumor activity of Imatinib in advanced chordoma

Secondary objectives

- To explore how Imatinib can cooperate with other treatment modalities in the therapy of locally advanced chordomas.

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

Oral capsules of Imatinib 100 mg, 4 cps twice a day (8 cps = 800 mg daily)

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

None

Criteria for Evaluation

Primary variables

- Overall response rate (according to RECIST criteria)
- Patterns of tumor response

The tumor response was assessed every 3 months, with an imaging technique (CT scan or MRI).

Secondary variables

- Proportion of patients undergoing complete surgery
- Overall survival
- Progression-free-survival

Safety and tolerability

- Adverse events and serious adverse events
- Laboratory parameters including hematology, chemistry, vital signs, physical examinations, and documentation of all concomitant medications and/or therapies.
- Bone pain
- Use of analgesic medication

Statistical Methods

This was an open label clinical study. Due to the lack of validated criteria for assessing tumor responses that a) occur very slowly, often in the absence of measurable reductions in the size of the tumor lesion over long periods, and b) are best detected and monitored with radio metabolic approaches and/or by studying changes in signal intensity, contrast uptake/enhancement and tumor density at CT/MRI, it was not possible to design this study as a standard phase II trial, nor was it possible to apply in this study statistical rules with predetermined error rates for the acceptance/rejection of the new drug, based on predetermined target success/failure rates. Furthermore,

due to the long delay between the start of treatment and its clinical effects, it was not possible to strictly modulate patients enrolment based on the observed success rates.

Eligible patients were prospectively enrolled, treated and followed according to the study protocol, and the observed results, in terms of toxicity and activity, were continuously updated and monitored.

The **Safety Analyzable Population** includes all patients who received at least one dose of study medication.

The **Intention To Treat Population** (ITT) includes all enrolled patients who received at least one dose of study medication. Patients going off study due to AEs or toxicity prior to the key response evaluation were considered as treatment failures.

The **Efficacy Analyzable Population** (EAP) consists of all patients who:

- did not violate inclusion criteria

and

- completed the treatment study phase or withdrew from the study for progression or death or because of surgery;

or

- withdrew from the study for toxicity (AE related to study drug) and had at least one key response evaluation.

All the evaluation criteria were computed in the ITT and in the efficacy analyzable population.

Patients with very advanced disease (performance status 4, patients who have received radiotherapy greater or equal to 25% of the bone marrow before study entry or patients who had a major surgery within 2-4 weeks prior to study entry) were excluded from the efficacy analysis.

As the primary objective of the study was to assess the antitumoral activity of Imatinib, the primary analysis was run primarily on the efficacy analyzable population and confirmed on the ITT population; all secondary efficacy analyses were run on the ITT population only.

Replacement of patients who were not in the efficacy analyzable population was in general not foreseen. Patient replacement was allowed in individual cases after discussion between the Sponsor and the Investigators if a patient was felt not to provide sufficient information for the assessment of safety and efficacy of Imatinib.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

- Histological diagnosis of chordoma.
- Biomolecular or immunohistochemical evidence of Imatinib target (PDGFRβ activation and/or presence of PDGFB).
- Measurable or evaluable disease (even in progression).
- Evidence of progression if radiotherapy was the last previous treatment.
- Surgical resection of local disease unfeasible radically, or unaccepted by the patient, or amenable to become less demolitive, or easier, or likely more feasible, after cytoreduction, and/or

metastatic disease.

- Performance status 0, 1, 2, 3 or 4 (ECOG)
- Adequate end organ function, defined as follows: total bilirubin <1.5 x Upper Limit of Normal (ULN), SGOT and SGPT <2.5 x ULN, creatinine <1.5 x ULN.
- Adequate bone marrow function, defined as follows: Absolute Neutrophil Count (ANC) >1.5 x 109/L, platelets >100 x 109/L, Hb >9 g/dL.

Exclusion criteria:

- Previous treatment with any other investigational or not investigational agents within 28 days of first day of study drug dosing.
- Other primary malignancy with <5 years clinically assessed disease-free interval, except basal cell skin cancer, cervical carcinoma *in situ*, or other neoplasms judged to entail a low risk of relapse.
- Grade III/IV cardiac problems as defined by the New York Heart Association Criteria
- Severe and/or uncontrolled medical disease (i.e., uncontrolled diabetes, chronic renal disease, or active uncontrolled infection).
- Known brain metastasis.

Number of Subjects

	Imatinib mesylate
Planned N	50
Randomised n	56
Intent-to-treat population (ITT) n (%)	56 (100)
Completed n (%)	8 (14.3)
Withdrawn n (%)	48 (85.7)
Withdrawn due to adverse events n (%)	9 (18.8)
Withdrawn due to lack of efficacy n (%)	34 (70.8)
Withdrawn for other reasons n (%)	5 (10.4)

Demographic and Background Characteristics

	Imatinib mesylate
N (ITT)	56
Females : males	21:35
Mean age, years (SD)	58.9 (15.4)
Race White n (%)	56(100%)
Characteristics relevant to study population (eg, mean FEV1 % predicted [SD])	None

Primary Objective Result(s)

Patients with objective and clinical responses according to RECIST by investigator at study end (n=37) EA population

	Pts

	n (%)
Patients with objective response - n(%)	0 (0.0)
95% CI of objective response rate	0.0 – 0.0
Patients with clinical benefit - n(%)	12 (32.4)
95% CI of clinical benefit rate	17.3 – 47.5

Secondary efficacy parameters – Overall survival and progression free survival at 24 months (ITT population)

Overall survival (month)	
N	25
Probability rate (%)	72.3
25th percentile	nd
Median	34.9
75th percentile	15.8
Progression free survival according to RECIST (month)	
N	34
Probability rate (%)	23.7
25th percentile	3.1
Median	9.2
75th percentile	19.1

Safety Results

Adverse Events by System Organ Class

	N (%)
Patients studied	
Enrolled patients	56
Patients with drug-related AE	53 (94.6)
Drug-related AEs by primary system organ class	
Respiratory, thoracic and mediastinal disorders	2 (3.6)
General disorders and administration site conditions	36 (64.3)
Gastrointestinal disorders	32 (57.1)
Skin and subcutaneous tissue disorders	24 (42.9)
Nervous system disorders	7 (12.5)
Renal and urinary disorders	2 (3.6)
Vascular disorders	1 (1.8)
Infections and infestations	1 (1.8)
Psychiatric disorders	1 (1.8)
Reproductive system and breast disorders	1 (1.8)
Cardiac disorders	0
Ear and labyrinth disorders	0
Immune system disorders	0

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

	Imatinib mesylate
Nausea	21 (37.5)
Edema	20 (35.7)
Anemia	18 (32.1)
Vomiting	17 (30.4)
Asthenia	15 (26.8)
Edema peripheral	13 (23.2)
Abdominal pain upper	10 (17.9)
Diarrhea	10 (17.9)
Pyrexia	10 (17.9)
Leukopenia	9 (16.1)

Serious Adverse Events and Deaths

	Imatinib mesylate
No. (%) of subjects studied	56
No. (%) of subjects with AE(s)	55 (98.2)
Number (%) of subjects with serious or other significant events	**n (%)**
Death	6 (10.7)
SAE(s)	23 (41.1)
Discontinued due to SAE(s)	5 (8.9)

Other Relevant Findings

There was a time-dependent decrease of hemoglobin and hematocrit during the first 3 months with Imatinib. BUN increased time-dependently. LDH increased during the whole study duration, but the increase was independent on the study time.

Date of Clinical Trial Report

20 January 2011

Date Inclusion on Novartis Clinical Trial Results Database

29 June 2010

Date of Latest Update

28 March 2011