Sponsor Novartis
Generic Drug Name Imatinib mesylate
Therapeutic Area of Trial MPNST
Approved Indication - the adjuvant treatment of adult patients who are at significant risk of relapse following resection of c-Kit (CD117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment. - the treatment of adult patients with c-Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). - unresectable dermatofibrosarcoma protuberans (DFSP) and recurrent and/or metastatic DFSP if not eligible for surgery. - Philadelphia chromosome (bcr-abl) positive chronic myeloid leukemia, - Philadelphia chromosome positive acute lymphatic leukemia, - Recurrent Ph+ ALL - myelodysplastic/myeloproliferative diseases, - advanced hypereosinophilic syndrome and/or chronic eosinophilic leukemia with FIP1L1-PDGFRα rearrangement.
Study Number CSTI571BDE57
Title An open-label multicenter phase II study of imatinib mesylate (Glivec®) treatment of patients with malignant peripheral nerve sheath tumors
Phase of Development Phase II

Study Start/End Dates

FPFV: 20-April-2006

LPLV: 07-Jul-2008

Study Design/Methodology

This was an open-label, multicenter, exact single stage, phase-II study according to A'Hern (2001) conducted to investigate the response and safety in patients with MPNST treated with Imatinib for 36 weeks. Due to the assumption that patients with neurofibromatosis type 1 (NF1) or sporadic MPNST not associated with NF1 respond to treatment two patient subsamples will be included. Analysis will be performed for both subsamples separately. In each group up to 16 patients will be included. In total 32 patients will be included in the study. The study participants will receive therapy with Imatinib administered at a daily dosage of 400 mg p.o./day at the start of therapy. All patients will be monitored according to the same visit schedule with physical examination, blood chemistry and MRI. Treatment will be stopped in case of progressive disease. Nevertheless patients will be followed up for survival even after progression. Patients with a clinical benefit may be treated after end of study. For those patients response status will be evaluated regularly.

Centres

Germany (2)

Publication

N/A

Objectives

Primary: To assess response in patients with MPNST treated with Imatinib. Response is defined as at least stable disease according to RECIST criteria.

Secondary:

- To assess time to progression (TTP).
- To assess overall survival
- To assess of safety and tolerability.

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

Imatinib mesylate

The patients will be instructed to take a total daily dose of 400mg of the oral formulation of Glivec by mouth or a total daily dose of 800 mg (400 mg b.i.d.).

Duration of treatment: Duration of the study is 36 weeks. Treatment after 36 weeks is at the discretion of the investigator.

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

Criteria for Evaluation

Efficacy: The primary variable is the number of patients showing response defined as at least once at least stable disease (SD) within 36 weeks according to RECIST. The evaluation of the central radiologist will be used.

Safety: The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g., vital signs) will be considered as appropriate. All safety data will be listed.

Statistical Methods

Statistical and analytical plans

Safety population: Consists of all patients who received at least one dose of study drug.

Note: The statement that a patient had no adverse events (on the Adverse Event CRF) constitutes a safety assessment.

Intent-to-treat population: Consists of all patients of the safety population for whom at least one post baseline assessment according to RECIST is available. Patients without any post-baseline assessment of tumor will be included if they are defined as progressive disease based on

clinical evaluation. Confirmatory analysis of the primary efficacy variable will be performed for this population.

Demographic and other baseline data (including disease characteristics) will be summarized descriptively for the Safety and ITT populations.

Medical history will be coded using MedDRA and will be presented by system organ class and MedDRA preferred term. Separate tables will be provided for past medical condition and current medical condition.

Categorical data will be presented as absolute and relative frequencies. For continuous data, the number of values N, mean, standard deviation, median, minimum, and maximum will be presented.

Statistical hypothesis, model, and method of analysis

For this study, a response rate of lower than 5% is considered not to warrant further investigation of the drug, whereas a response rate of at least 25% is considered to warrant further investigation, i.e. the following hypothesis will be tested:

H_0: The true response rate is ≤ 5%.

vs.

H_1: The true response rate is ≥ 25%.

Based on the number of responders one of the following decisions will be made:

< 3 responder ⇨ reject H1 ⇨ Glivec® is not worth to be tested in a greater trial in this indication.

≥ 3 responder ⇨ reject H_0 ⇨ Glivec® is worth to be tested in a greater trial in this indication.

In addition the relative number of responder will be presented including the 95%-confidence interval.

Demographic and Background Characteristics

Demographic summary Safety population

Variable		Statistic	Total (N=10)
Age [yrs]		Mean	33
		Std	10.6
		Median	34
		Range	20-51
Sex	Male	n (%)	4 (40.0)
	Female	n (%)	6 (60.0)
Race	Caucasian	n (%)	10 (100.0)

Patient disposition

	Total
Number (%) of patients	
Screened	11
treated	10 (100.0)
discontinued	10 (100.0)
completed	0 0 (0.0)
Reason for discontinuation	
Unsatisfactory therapeutic effect	10 (100.0)

Overall exposure

Variable	Statistic	Total (N=405)
Duration of drug exposure [days]	Mean	110.5
	Std	73.6
	Median	84.0
	Range	41-239

Mean daily dose administered

Variable	Statistic	Total (N=10)
Mean daily dose [mg/day]	N	10
	NMiss	0
	Mean	480.3
	Std	101.5

Min	400.0
Median	427.2
Max	667.8
Sum	4803.0

Number of responders who showed at least once at least stable disease

	(N=10)		
	n	(%)	95 % CI [% - %]
Patients showing response at least once at least stable disease (response rate)	6	(60.0)	[29.6 - 90.4]

Response criteria by visit

Visit Report Number	Current objective status	Total (N=10) n (%)
3 week 6	Complete response	0 (0.0)
	Partial response	0 (0.0)
	Stable disease	6 (60.0)
	Progressive disease	3 (30.0)
	Not done	0 (0.0)
	Unknown	0 (0.0)
	Not applicable	0 (0.0)
5 week 12	Complete response	0 (0.0)
	Partial response	0 (0.0)
	Stable disease	4 (40.0)
	Progressive disease	0 (0.0)
	Not done	0 (0.0)
	Unknown	0 (0.0)
	Not applicable	0 (0.0)
7 week 18	Complete response	0 (0.0)
	Partial response	0 (0.0)
	Stable disease	1 (10.0)
	Progressive disease	2 (20.0)
	Not done	0 (0.0)
	Unknown	1 (10.0)
	Not applicable	0 (0.0)
9 week 24	Complete response	0 (0.0)
	Partial response	0 (0.0)
	Stable disease	1 (10.0)
	Progressive disease	1 (10.0)
	Not done	0 (0.0)
	Unknown	0 (0.0)

	Not applicable	0 (0.0)
13 end of study	Complete response	0 (0.0)
	Partial response	0 (0.0)
	Stable disease	0 (0.0)
	Progressive disease	7 (70.0)
	Not done	0 (0.0)
	Unknown	0 (0.0)
	Not applicable	0 (0.0)

Secondary Objective Result(s)

Secondary efficacy results

None were evaluated

Safety Results

Number (%) of patients with AEs overall and by system organ class

	No. of Patients with AEs	Total % of patients (n=10)	Total no. of AEs	% of all AEs
All System Organ Classes	8	(80.0)	50	(100.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	4	(40.0)	6	(12.0)
EAR AND LABYRINTH DISORDERS	1	(10.0)	1	(2.0)
EYE DISORDERS	2	(20.0)	2	(4.0)
GASTROINTESTINAL DISORDERS	2	(20.0)	5	(10.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	7	(70.0)	11	(22.0)
INFECTIONS AND INFESTATIONS	1	(10.0)	1	(2.0)
INVESTIGATIONS	4	(40.0)	14	(28.0)
METABOLISM AND NUTRITION DISORDERS	3	(30.0)	3	(6.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1	(10.0)	1	(2.0)
NERVOUS SYSTEM DISORDERS	1	(10.0)	1	(2.0)
PSYCHIATRIC DISORDERS	1	(10.0)	1	(2.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2	(20.0)	2	(4.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2	(20.0)	2	(4.0)

Number (%) of patients with most frequent AEs

Preferred term	n	% of patients (n=10)	% of all AEs
ANAEMIA	4	(40.0)	(8.0)
FATIGUE	3	(30.0)	(6.0)
OEDEMA PERIPHERAL	3	(30.0)	(6.0)
DECREASED APPETITE	3	(30.0)	(6.0)

Number (%) of patients who died, had other serious or clinically significant AEs or discontinued because of them

	Total	
	No. (%) of AEs	No. (%) of patients
Number of Patients		(n=10)
All AEs	50 (100.0)	8 (80.0)
with suspected drug relation	35 (70.0)	6 (60.0)
leading to dose adjustment or temp. interruption	2 (4.0)	2 (20.0)
leading to permanent discontinuation	0 (0.0)	0 (0.0)
requiring concomitant medication/non-drug therapy	11 (22.0)	6 (60.0)
Serious AEs	1 (2.0)	1 (10.0)
Deaths		0 (0.0)
SAEs with suspected drug relation	0 (0.0)	0 (0.0)
SAEs leading to permanent discontinuation	0 (0.0)	0 (0.0)

Other Relevant Findings

NA

Date of Clinical Trial Report

6-May-2010

Date Inclusion on Novartis Clinical Trial Results Database

10 September 2010

Date of Latest Update