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Sponsor

Novartis

Generic Drug Name

Imatinib mesylate

Trial Indication(s)

GIST (gastro intestinal stroma tumors)

Protocol Number

CSTI571JDE74

Protocol Title

An open-label, multicenter, expanded access study of imatinib mesylate in adult patients with GIST in adjuvant setting after R0-resection

Clinical Trial Phase

Phase IIIb

Phase of Drug Development

Phase IIIb

Study Start/End Dates

16-Oct-2008 to 16 Apr 2012

Reason for Termination

Not applicable.

Study Design/Methodology

This was a multicenter, open-label, single-arm, phase IIIb trial evaluating imatinib mesylate in adult patients with GIST in adjuvant setting. The purpose of the study – 'expanded access program' – was to make this drug available to a larger number of patients who were without satisfactory treatment alternatives.

At Visit 1 patients were assessed for eligibility for study participation. After fulfilling all criteria to enter the study, eligible patients started study treatment with imatinib mesylate 400mg/d. The study sites were provided with study drug until the product was commercially available for the appropriate indication.

The original protocol dated 24-June-2008, was amended on 08-Dec-2008 in the following countries: Germany, Belgium, Czech Republic, Hungary, and Slovakia to implement additional laboratory evaluations on a monthly basis to control hematology and liver enzymes, to clarify the condition for excluding women with child bearing potential and to add further specifications for study procedures. In addition, positive immunostaining for KIT was not required anymore for inclusion and a new CT/MRI scan was added to subjects who have undergone surgery for more than 4 weeks before the screening to confirm that no recurrence of disease had occurred. Additional local amendments were implemented in Italy on 29-Aug-2008, in Spain on 18-Oct-2008 and in Hungary on 25-Jan-2011 mainly to align the protocol with local regulatory requirements.

Centers

89 centers in 8 countries: Germany and Spain (25 centers each), France (15), Italy (11), Belgium (5), Czech Republic and Hungary (3 centers each), Slovakia (2).

Objectives:

Primary objective(s)

Primary Objective*:* The primary objective of this study was to evaluate the safety and tolerability of imatinib mesylate as measured by rate and severity of adverse events. The trial was intended to provide patients with gastrointestinal stromal tumors (GIST) in an adjuvant setting with expanded access to imatinib mesylate until market availability of the drug in this stage of the disease.

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

	Imatinib mesylate	Imatinib mesylate
Dosage form	tablets	Capsules
Strength	400 mg	100mg
Dosage information	400 mg/d	400 mg/d
Mode of administration	oral	Oral

Statistical Methods

As the expanded access program was focused on safety and tolerability, there was no minimum treatment duration defined for the inclusion into the analysis. The only requirements were that patients received at least one dose of imatinib mesylate and had at least one post-baseline safety assessment. All analyses were done based on the Safety population.

Data were summarized with respect to demographic and baseline characteristics (including disease characteristics), safety observations and measurements and efficacy observations and measurements (optional).

Frequency distributions (absolute numbers and percentages based on the specific total numbers of the respective analysis population) were provided for categorical variables. Descriptive statistics of mean, standard deviation, minimum, median and maximum were presented for continuous variables. Time-to-event data including rates of affected patients were assessed by Kaplan-Meier statistics. Pharmacokinetics: Results of the pharmacokinetics analysis were reported separately. Sample size: As per the study protocol, it was planned to enroll approximately 750 patients from 10 countries into this trial. The sample size was based neither on statistical considerations nor statistical calculations. With a sample size of 750 patients, the probability of detecting adverse events occurring with incidence rates of 0.001 to 0.1 was considered adequate.

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Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

Male or female patients aged ≥ 18 years with histologically confirmed diagnosis of GIST on a tumor sample taken within 12 weeks of the study entry were included in this study. Further key inclusion criteria were complete gross resection of the tumor, risk of relapse documented as “intermediate and high” according to NIH criteria, WHO Performance Status 0, 1 or 2, normal organ, electrolyte, and marrow function, ability to understand and willingness to sign a written informed consent. Male and female patients who were sexually active had to use double-barrier contraception, oral contraceptive plus barrier contraceptive, or had to have undergone clinically documented total hysterectomy and/or ovariectomy, or tubal ligation.

Exclusion criteria

Key exclusion criteria were prior participation in an adjuvant GIST trial, prior treatment with imatinib, treatment with any cytotoxic and/or investigational cytotoxic drug ≤ 4 weeks (6 weeks for nitrosurea or mitomycin C) prior to Visit 1, known history of hypersensitivity against imatinib, severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol, use of therapeutic coumarin derivatives, major surgery ≤ 2 weeks prior to Visit 1 or who had not recovered from side effects of such surgery, history of noncompliance to medical regimens, unwillingness or inability to comply with the protocol, female patients who were pregnant or breast feeding or patients of reproductive potential not employing an effective method of birth control

Participant Flow Table

	Total
Number (%) of patients	
Screened	316
Treated	300
Discontinued	40
Completed	260

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Baseline Characteristics

	Safety set N = 300
Gender - n (%)	
Male	163 (54.33%)
Female	137 (45.67%)
Race - n (%)	
Caucasian	289 (96.33%)
Black	0 (0.00%)
Asian/Oriental	4 (1.33%)
Other	7 (2.33%)
Age (years)	
Mean (± SD)	59.4 ± 12.1
Median (Range)	60 (19 – 89)

Primary Outcome Result(s)

Refer to Safety Result section for primary outcome result.

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Safety Results

Number (%) of patients with most frequent AEs (5% or more overall)

	Grade					
	All		<2		>2	
AE preferred term	n	(%)	n	%	n	%
Total number (%) of patients	300	100.0				
Number (%) of patients with AE(s)	272	90.7	227	76	45	15
Nausea	102	34.0	101	34	1	0.3
Diarrhoea	99	33.0	96	32	3	1
Periorbital oedema	64	21.3	64	21	0	0
Muscle spasms	48	16.0	48	16	0	0
Oedema peripheral	45	15.0	45	15	0	0
Asthenia	44	14.7	43	14	1	0.3
Eyelid oedema	42	14.0	42	14	0	0
Fatigue	36	12.0	36	12	0	0
Abdominal pain	30	10.0	27	9	3	1
Rash	30	10.0	26	9	4	1
Anaemia	28	9.3	27	9	1	0.3
Vomiting	27	9.0	27	9	0	0
Decreased appetite	22	7.3	22	7	0	0
Dyspepsia	22	7.3	22	7	0	0
Oedema	19	6.3	19	6	0	0
Leukopenia	18	6.0	16	5	2	0.7
Neutropenia	18	6.0	14	5	4	1
Lacrimation increased	18	6.0	18	6	0	0
Constipation	17	5.7	17	6	0	0
Abdominal pain upper	15	5.0	14	5	1	0.3
Nasopharyngitis	15	5.0	15	5	0	0
Alopecia	15	5.0	15	5	0	0

Sorted by decreasing incidence.

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

	N=300	
Total number (%) of patients	300	100.0
Number (%) of patients with AE(s)	272	90.7
Deaths	0	0.0
SAE(s)	25	8.3
SAE(s) with suspected relationship to study drug	9	3.0
SAE(s) leading to permanent discontinuation	3	1.0
AE(s) with suspected relationship to study drug	246	82.0
AE(s) leading to dose adjustments or temporary interruption	57	19.0
AE(s) leading to permanent discontinuation	19	6.3
AE(s) requiring concomitant medication	150	50.0

Other Relevant Findings

Overall exposure (days) – Safety population

	Including off days	**Excluding off days**
Exposure (days)		
Mean (± SD)	208.6±123.8	205.7±123.5
Median	181.0	179.0
Range	9 - 420	9 – 420

Conclusion:

The aim of the trial was to grant access to imatinib to patients with GIST in an adjuvant setting until commercially available for the indication, in each respectively country.

The trial confirmed the safety of imatinib mesylate when used to treat patients with GIST in adjuvant setting at 400 mg daily. The occurrence of AEs, the type and the severity showed that imatinib mesylate treatment is generally well tolerated and that risk to develop severe AEs is low. AEs occurred in the patients enrolled in the trial were in line with the known safety profile of imatinib supporting the use of imatinib mesylate as adjuvant treatment for this stage of the disease.

The mean overall exposure was 208.6±123.8 days (including off days) as most of the patients (260 out of 300 treated) completed the study (i.e., moved to the commercial drug) data were censored. 294 patients completed the study without disease recurrence.

Date of Clinical Trial Report

07-June-2013