Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Imatinib mesylate

Therapeutic Area of Trial

Glioblastoma Multiforme (GBM)

Approved Indication

Chronic myeloid leukemia (Ph+, AP, BC), Gastrointestinal stromal tumors (GIST), Dermatofibrosarcoma protuberans, Idiopathic Pulmonary Fibrosis, Juvenile myelomonocytic leukemia, Myelodysplastic syndrome, Myeloproliferative disorder, Medullary thyroid cancer, Philadelphia-positive Acute Lymphoblastic Leukemia, aggressive systemic mastocytosis and Hypereosinophilic syndrome

Study Numbers

CSTI571H2201 & H2202

Title

A phase II, open label, multicenter, single-arm study, evaluating the efficacy of Glivec® plus hydroxyurea (HU) in patients with progressive glioblastoma multiforme (GBM) not receiving (H2201) and receiving (H2202) enzyme inducing anticonvulsant drugs (EIACDs)

Phase of Development

Phase II

Study Start / End Dates

Study STI571H2201:13 Feb 2006 to 24 Jul 2008

Study STI571H2202: 20 Feb 2006 to 19 Aug 2008

Study Design/Methodology

These were open-label, multicenter, single arm trials. The trials were identical in design with the key exception that H2201 did not allow concurrent use of EIACDs, whereas H2202 required concurrent use of EIACDs. The original study design prescribed that patients remain on the studies for two years unless they withdrew consent or developed unacceptable toxicity or tumor progression. After the start of the study, an interim analysis was introduced into the design via Amendment 1 (28 Jul 2006), with the decision to combine the datasets for the two trials into one

analysis for both the interim and final analyses. The interim data cut-off occurred 4 months after the 101st patient had been enrolled to allow 16 weeks of treatment assessment. The interim analysis was used to make specific decisions about the development program of imatinib within GBM. The results of the interim analysis clearly demonstrated a lack of efficacy according to the Simon-type design decision rules (1 confirmed responder). Recruitment was therefore stopped. Amendment 2 (19 Dec 2007) formalized the decision to bring forward the main analysis to July 2008. At the time of recruitment stop, 131 patients had entered Study H2201 and 100 patients had entered Study H2202.

Centres

Study STI571H2201: Belgium (2 centers), Canada (1 center), Denmark (2 centers), France (2 centers), Germany (5 centers), Netherlands (2 centers), Spain (2 centers), Sweden (2 centers), Switzerland (1 center), United States (2 centers)

Study STI571H2202: Australia (1 center), Belgium (2 centers), Canada (2 centers), Denmark (2 centers), France (2 centers), Germany (4 centers), Netherlands (2 centers), Sweden (2 centers), United States (2 centers)

Objectives

Primary objective(s)

- To assess the clinical efficacy of combination therapy of imatinib plus HU based on objective overall response rate (ORR), calculated as the rate of best overall response of complete response (CR) plus partial response (PR)?

Secondary objective(s)

To determine

- the duration of ORR
- Clinical benefit (CB) determined by the proportion of the patient with ORR plus stable disease (SD) for > 6 months
- PFS at 6 and 12 months and median PFS
- Survival rate at 6, 12 and 24 months along with safety and tolerability
- To compare the PK profiles of imatinib with that of imatinib plus HU and to evaluate the PK profiles of HU plus imatinib

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

Study CSTI571H2201: continuous oral dosing of 600 mg once daily imatinib and 500 mg twice daily HU with a glass of water

Study CSTI571H2202: continuous oral dosing of 500 mg twice daily imatinib with 500 mg twice daily HU with a glass of water

Criteria for Evaluation

Primary variables

The primary variable was the ORR which represents the sum of CR and PR as the best overall responses. The best overall response was calculated according to the modified MacDonald criteria for patients with GBM. The patients were evaluated for objective responses by gadolinium enhanced MRI conducted at Visit 1, during the study and at the end of the study. All scans were measured at the local sites and validated by the central independent review team throughout the trial.

Secondary variables

No formal inferential procedure was carried out on secondary endpoints.

Safety and tolerability

Safety assessments consisted of monitoring and recording all adverse events (AE) and serious adverse events (SAE), the regular monitoring of hematology and blood chemistry, regular assessments of vital signs and the performance of physical examinations. Additional safety assessments included neurological examination, ECOG performance status, and Electrocardiogram (ECG). An evaluation of the metabolic activity, extent and change of GBM tumors via PET scan imaging

Pharmacology

Pharmacokinetic assessments were planned in a subset of 15 patients in each study at selected sites. Blood samples for the measurement of the plasma profiles of imatinib, its metabolite and HU were collected

Other

Conduct of correlative science studies to gain a mechanistic understanding of clinical and molecular responses to treatment with imatinib and HU.

Conduct PET imagery investigations in a planned subset of 15 patients in each study at selected sites. Images were independently reviewed to further understand the movement of study drug around the brain.

Statistical Methods

The primary endpoint was overall response rate (ORR) during combination therapy with imatinib plus HU. ORR represents the sum of complete response (CR) and partial response (PR) as the best overall responses. The best overall response was calculated according to the modified MacDonald criteria for patients with GBM. The primary endpoint was analyzed for ITT (intention to treat), PP (per protocol), and DE (disease evaluable) populations. In accordance with the Simon-type design, the combination therapy (imatinib plus HU) was to be declared as having insufficient activity if the number of patients with an objective response was 15 or less among the 220 patients included and treated in studies H2201 and H2202 together, or 4 or less among the 100 patients included and treated in both studies at the time of the interim analysis. If the number of

responders was higher, the hypothesis of a true response rate of 5% or less was to be rejected. No formal inferential procedure was carried out for secondary endpoints.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

The population consisted of male and female patients. 110 patients were intended to be recruited to each study, but final recruitment numbers were 131 in H2201 and 100 in H2202. Patients had the following diagnosis: Adults with histologically confirmed diagnosis of GBM following failure of the frontline therapy, including surgery, radiotherapy and TMZ treatment.

- Males and females = 18 years old
- Histologically-confirmed diagnosis of progressive primary GBM based on original diagnosis. Patients with prior low-grade glioma were eligible if histological re-assessment demonstrated transformation to GBM
- No more than one prior episode of progressive disease following previously received surgery and/or radiation and only one prior chemotherapy exposure of either temozolomide or nitrosourea including the application of Glidel wafers
- Presence of measurable disease on gadolinium-enhanced magnetic resonance imaging (MRI)
- Patients taking steroids: must have been on stable dose for = 7 days
- Eastern Cooperative Oncology Group (ECOG) performance score ≤ 2
- Hemoglobin = 10 g/dL (**or** hematocrit > 29%), absolute neutrophil count (ANC) > 1500 cells/L, platelets > 100,000 cells/L
- Serum creatinine < 1.5 mg/dL, blood urea nitrogen (BUN) < 25 mg/dL, serum aspartate aminotransferase (AST) and bilirubin < 1.5 x upper limit of normal (ULN)
- Sexually-active male and female patients were required to use double-barrier contraception (oral contraceptive plus barrier contraceptive) or must have undergone clinically documented total hysterectomy, ovariectomy, or tubal ligation
- Female patients of child bearing potential must have had a negative pregnancy test within 48 hours prior to Visit 1 (start of study drug)
- Life expectancy = 8 weeks
- Signed informed consent by the patient prior to patient entry and any study procedure

Exclusion Criteria

Patients were excluded if they meet following criteria

- Receipt of imatinib or HU prior to study entry or receipt of any investigational agent within the last 6 months
- Patients who had received a second course of chemotherapy or radiotherapy, unless given as a single localized application of radio surgery
- In study STI571H2201 only, receipt of EIACDs (e.g. carbamazepine, phenobarbital, phenytoin, phosphenytoin, oxcarbamazepine, primadone). Previous EIACD should have been interrupted 4 weeks prior to study start

- Grade = 2 peripheral edema or pulmonary or pericardial effusions or ascites of any grade
- Presence of any uncontrolled systemic infection
- Patients who were not a minimum of 12 weeks from completion of conventional external beam radiotherapy unless:
- There was new radiographical enhancement outside the field of radiation, or
- There was new pathological confirmation of recurrent tumor, or
- Progressive radiographical enhancement noted on post-radiotherapy/TMZ continue to worsen after an additional course of TMZ
- Evidence of intra-tumor hemorrhage on pretreatment diagnostic imaging, except for stable post-operative grade 1 hemorrhage, patients with an excessive risk of an intracranial hemorrhagic event and patients with history of central nervous system (excluding post-operative grade 1) or intraocular bleed
- Patients who had undergone major surgery within 2 weeks prior to study entry or who had not recovered from prior major surgery, patients who had received chemotherapy within 4 weeks prior to study start, or who have not recovered from toxic effects of such therapy
- Impairment of gastrointestinal function or gastrointestinal disease that could significantly alter the absorption of imatinib
- Patients taking warfarin sodium
- Known history of human immunodeficiency virus (HIV) seropositivity; testing for HIV was not required at study entry
- For the purposes of MRI, patients with a pacemaker; ferromagnetic metal implants other than those approved as safe for use in MR scanners (e.g. some types of aneurysm clips, shrapnel), patients suffering from uncontrollable claustrophobia, or those physically unable to fit into the machine (e.g. obesity)
- Patients considered by the investigator as unlikely to be compliant with the study, take the study medications, travel for the necessary assessment visits, or have other medical conditions likely to interfere with the study assessments.
- Patients with another primary malignancy treated within the prior 3 years except excised squamous cell carcinomas of the skin and carcinoma in situ lesions of other organs which had been treated for cure.
- Patients not able to provide reliable informed consent and who did not have a legal representative for healthcare decisions on their behalf

Number of Subjects

Patient disposition (ITT population)

	Study H2201 (N=131) n (%)	Study H2202 (N=100) n (%)	All patients (N=231) n (%)
Patients			
Discontinued study treatment	131 (100.0)	100 (100.0)	231 (100.0)
Main cause of discontinuation of study treatment			
Disease progression	95 (72.5)	73 (73.0)	168 (72.7)
Death	11 (8.4)	10 (10.0)	21 (9.1)
Adverse Event(s)	12 (9.2)	6 (6.0)	18 (7.8)
Subject withdrew consent	5 (3.8)	6 (6.0)	11 (4.8)
Treatment duration completed as per protocol	4 (3.1)	3 (3.0)	7 (3.0)
Administrative problems	2 (1.5)	1 (1.0)	3 (1.3)
Protocol violation	2 (1.5)	0	2 (0.9)
Lost to follow-up	0	1 (1.0)	1 (0.4)

Demographic and Background Characteristics

Demographic summary (ITT population)

Variable	Statistic / Category	Study H2201 (N=131)	Study H2202 (N=100)	All patients (N=231)
Age (years)	Mean	53.7	52.8	53.3
	SD	11.9	11.4	11.7
	Median	55.0	55.0	55.0
	Range	18 - 80	21 - 75	18 - 80
Age group - n (%)	18 - 34 years	10 (7.6)	6 (6.0)	16 (6.9)
	35 - 49 years	31 (23.7)	32 (32.0)	63 (27.3)
	50 - 64 years	71 (54.2)	47 (47.0)	118 (51.1)
	>= 65 years	19 (14.5)	15 (15.0)	34 (14.7)
Sex - n (%)	Male	79 (60.3)	65 (65.0)	144 (62.3)
	Female	52 (39.7)	35 (35.0)	87 (37.7)
Race - n (%)	Caucasian	126 (96.2)	96 (96.0)	222 (96.1)
	Black	2 (1.5)	2 (2.0)	4 (1.7)
	Asian	1 (0.8)	1 (1.0)	2 (0.9)
	Native American	1 (0.8)	1 (1.0)	2 (0.9)
	Other	1 (0.8)	0	1 (0.4)

Primary Objective Result(s)

Best overall response, objective response, and clinical benefit (ITT population)

	Study H2201 (N=131)	Study H2202 (N=100)	All patients (N=231)
Best overall response - n (%)			
Complete response (CR)	0	1 (1.0)	1 (0.4)
Partial response (PR)	5 (3.8)	2 (2.0)	7 (3.0)
Stable disease (SD)	26 (19.8)	19 (19.0)	45 (19.5)
Lasting for more than 6 months	8 (6.1)	3 (3.0)	11 (4.8)
Progressive disease (PD)	79 (60.3)	63 (63.0)	142 (61.5)
Early death [a]	14 (10.7)	6 (6.0)	20 (8.7)
Due to study indication	11 (8.4)	4 (4.0)	15 (6.5)
Due to other cause	3 (2.3)	2 (2.0)	5 (2.2)
Not assessable (NA)	7 (5.3)	9 (9.0)	16 (6.9)
Objective response (CR + PR) - n (%)	5 (3.8)	3 (3.0)	8 (3.5)
95% confidence interval	1.3 -8.7	0.6 -8.5	1.5 -6.7
Clinical benefit [b] - n (%)	13 (9.9)	6 (6.0)	19 (8.2)
95% confidence interval	5.4 - 16.4	2.2 - 12.6	5.0 - 12.5
CR + PR + SD - n (%)	31 (23.7)	22 (22.0)	53 (22.9)
95% confidence interval	16.7 - 31.9	14.3 - 31.4	17.7 - 28.9
CR + PR, both without confirmation - n (%)	9 (6.9)	4 (4.0)	13 (5.6)
95% confidence interval	3.2 - 12.6	1.1 -9.9	3.0 -9.4

a. Patients who died during the first 8 weeks after start of treatment without assessment of tumor response

b. Clinical benefit was defined as objective response or as SD lasting for > 6 months from start of treatment

Secondary Objective Result(s)

Progression-free survival (ITT population)

	Study H2201 (N=131)	Study H2202 (N=100)	All patients (N=231)
Number of patients with events / censorings	127 / 4	94 / 6	221 / 10
Progression-free survival time [wks], Percentiles			
25%	4.0	4.0	4.0
50% median (95% CI)	6.1 (4.1-7.9)	4.6 (4.1-7.9)	5.6 (4.3-7.7)
75%	12.0	11.9	11.9
Progression-free survival rates, % (95% CI)			
at 6 months	11.2 (5.7-16.6)	9.9 (3.8-15.9)	10.6 (6.5-14.7)
at 12 months	6.9 (2.4-11.3)	3.3 (0.0-6.9)	5.3 (2.3-8.3)

CI = confidence interval

Patients alive and without progression were considered as censored at time of last available tumor assessment.

Progression-free survival time percentiles and rates were calculated by the Kaplan-Meier method.

Classification of PFS event confirmation (derived from programmed overall response from CIR data and reports of death) (ITT population)

	Study H2201 (N=131) n (%)	Study H2202 (N=100) n (%)	All patients (N=231) n (%)
Number of patients with events (PD or death)	127 (100.0)	94 (100.0)	221 (100.0)
Progressive disease (PD) confirmed by			
MRI assessment	61 (48.0)	53 (56.4)	114 (51.6)
Neurological examination but not by MRI	17 (13.4)	9 (9.6)	26 (11.8)
Increased steroid use only	23 (18.1)	18 (19.1)	41 (18.6)
Death without previous PD determination	26 (20.5)	14 (14.9)	40 (18.1)

CIR = Central Independent Review, MRI = magnetic resonance imaging

Overall survival (ITT population)

	Study H2201 (N=131)	Study H2202 (N=100)	All patients (N=231)
Number of patients with events / censorings	109 / 22	74 / 26	183 / 48
Overall survival time [wks], Percentiles			
25%	12.3	12.4	12.3
50% median (95% CI)	25.3 (19.9-33.0)	27.1 (19.9-39.1)	26.0 (21.3-31.3)
75%	64.3	57.7	62.3
Overall survival rates, % (95% CI)			
at 6 months	49.2 (40.7-57.8)	50.9 (40.9-61.0)	50.0 (43.4-56.5)

at 12 months	28.5 (20.7-36.2)	31.3 (21.9-40.7)	29.7 (23.7-35.7)
at 24 months	10.7 (3.3-18.1)	20.3 (11.8-28.9)	13.9 (8.0-19.7)

CI = confidence interval

Patients alive were considered as censored at time of last survival follow-up. Overall survival time percentiles and rates were calculated by the Kaplan-Meier method.

Safety Results

Patients taking imatinib on these trials have experienced no unexpected adverse reactions.

The safety and tolerability of imatinib plus HU was consistent with the safety record reported in the literature from investigator–initiated trials evaluating imatinib plus HU in this patient population.

Adverse Events by System Organ Class

Number of patients with adverse events, overall and by system organ class (Safety population)

	Study H2201 (N=131)	Study H2202 (N=99)	All patients (N=230)
	n (%)	n (%)	n (%)
Patients with AEs	129 (98.5)	98 (99.0)	227 (98.7)
System organ class			
General disorders and administration site conditions	94 (71.8)	69 (69.7)	163 (70.9)
Nervous system disorders	89 (67.9)	74 (74.7)	163 (70.9)
Gastrointestinal disorders	88 (67.2)	58 (58.6)	146 (63.5)
Infections and infestations	54 (41.2)	32 (32.3)	86 (37.4)
Skin and subcutaneous tissue disorders	43 (32.8)	33 (33.3)	76 (33.0)
Blood and lymphatic system disorders	45 (34.4)	30 (30.3)	75 (32.6)
Psychiatric disorders	49 (37.4)	25 (25.3)	74 (32.2)
Eye disorders	37 (28.2)	24 (24.2)	61 (26.5)
Musculoskeletal and connective tissue disorders	39 (29.8)	19 (19.2)	58 (25.2)
Metabolism and nutrition disorders	32 (24.4)	19 (19.2)	51 (22.2)
Respiratory, thoracic and mediastinal disorders	25 (19.1)	22 (22.2)	47 (20.4)
Investigations	18 (13.7)	16 (16.2)	34 (14.8)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	16 (12.2)	12 (12.1)	28 (12.2)
Vascular disorders	12 (9.2)	15 (15.2)	27 (11.7)
Injury, poisoning and procedural complications	19 (14.5)	5 (5.1)	24 (10.4)
Reproductive system and breast disorders	11 (8.4)	10 (10.1)	21 (9.1)
Renal and urinary disorders	8 (6.1)	9 (9.1)	17 (7.4)
Cardiac disorders	9 (6.9)	4 (4.0)	13 (5.7)
Endocrine disorders	5 (3.8)	8 (8.1)	13 (5.7)
Ear and labyrinth disorders	3 (2.3)	5 (5.1)	8 (3.5)
Hepatobiliary disorders	1 (0.8)	1 (1.0)	2 (0.9)
Immune system disorders	1 (0.8)	1 (1.0)	2 (0.9)
Congenital, familial and genetic disorders	0	1 (1.0)	1 (0.4)

All AEs starting after first dose but not later than 28 days after last dose were analyzed.

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

Number of patients with adverse events, overall and by most frequent events (> 10% in any column) (Safety population)

	Study H2201 (N=131) n (%)	Study H2202 (N=99) n (%)	All patients (N=230) n (%)
Patients with AEs	129 (98.5)	98 (99.0)	227 (98.7)
Preferred term			
Nausea	50 (38.2)	39 (39.4)	89 (38.7)
Fatigue	41 (31.3)	37 (37.4)	78 (33.9)
Vomiting	41 (31.3)	26 (26.3)	67 (29.1)
Headache	35 (26.7)	23 (23.2)	58 (25.2)
Edema peripheral	31 (23.7)	24 (24.2)	55 (23.9)
Diarrhea	27 (20.6)	16 (16.2)	43 (18.7)
Thrombocytopenia	23 (17.6)	11 (11.1)	34 (14.8)
Anaemia	21 (16.0)	11 (11.1)	32 (13.9)
Constipation	22 (16.8)	10 (10.1)	32 (13.9)
Asthenia	17 (13.0)	13 (13.1)	30 (13.0)

All AEs starting after first dose but not later than 28 days after last dose were analyzed.

Serious Adverse Events and Deaths

Summary of serious or clinically significant adverse events or discontinuations due to adverse events (Safety population)

	Study H2201 (N=131) n (%)	**Study H2202 (N=99) n (%)**	**All patients (N=230) n (%)**
All AEs			
Total	129 (98.5)	98 (99.0)	227 (98.7)
Suspected to be drug-related	104 (79.4)	78 (78.8)	182 (79.1)
Leading to dose adjustment or interruption	45 (34.4)	39 (39.4)	84 (36.5)
Leading to permanent discontinuation	36 (27.5)	26 (26.3)	62 (27.0)
NCI CTC Grade 3 or 4	97 (74.0)	72 (72.7)	169 (73.5)
Leading to hospitalization/prolonged hospitalization	55 (42.0)	44 (44.4)	99 (43.0)
Serious AEs			
Total	62 (47.3)	53 (53.5)	115 (50.0)
Suspected to be drug-related	15 (11.5)	8 (8.1)	23 (10.0)
Leading to dose adjustment or interruption	17 (13.0)	13 (13.1)	30 (13.0)
Leading to permanent discontinuation	21 (16.0)	19 (19.2)	40 (17.4)
NCI CTC Grade 3 or 4	55 (42.0)	46 (46.5)	101 (43.9)
Leading to hospitalization/prolonged hospitalization	55 (42.0)	44 (44.4)	99 (43.0)

All AEs starting after first dose but not later than 28 days after last dose were analyzed.

Other Relevant Findings

A PET scan imaging sub-study was performed to evaluate the metabolic activity, extent and change of GBM tumors induced by treatment with imatinib and HU. In total, images from 19 patients only were received for evaluation. The sub-study concluded that the data did not provide evidence for efficacy of imatinib plus HU in the majority of patients with pretreated progressive GBM. Thus, the PET sub-study confirmed the conclusions drawn in the main study.

The PK results of this study demonstrated that in patients with GBM, the plasma exposure of imatinib in patients receiving EIACDS were lowered than that for patients not receiving EIACDs. Hydroxyurea (HU) administration with imatinib did not significantly affect the plasma exposure of imatinib alone. The co-administration of HU with imatinib had no effect on the systemic exposure of HU either in patients receiving or not receiving EIACDs

Date of Clinical Trial Report

23 Apr 2009

Date Inclusion on Novartis Clinical Trial Results Database

19 Aug 2009

Date of Latest Update

08 Jul 2009