SCIENTIFIC DISCUSSION

1. Introduction

The scope of this Type II variation is to extend the currently approved Glivec indications including the following new orphan indication: *"Treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP)"*.The proposed dose is 800 mg/day.

Dermatofibrosarcoma protuberans is a rare monoclonal cutaneous soft tissue sarcoma. It is a slowly evolutive lesion that leads to local malignancy. The estimated prevalence of DFSP in the European Union member states is 0.93 per 10,000. Clinically, DFSP initially presents as an asymptomatic, indolent, indurated plaque. The sarcoma increases in size slowly and over a period of years protuberant nodules develop within the plaque. Once nodules develop, growth can become more rapid, and up to 25% of patients may complain of ulceration, bleeding, or pain at the lesion site. It is highly invasive, can be locally aggressive and has significant risk of recurrence, though it rarely metastasizes. The most common site of origin is the skin of the trunk (50% to 60%), followed by the proximal extremities (20% to 30%), and the head and neck (10% to 15%). The lesion tends to grow slowly over several years so that treatment is frequently delayed, and all too often, inadequate.

This infiltrative tumour is characterized by translocations activating PDGF genes, observed in 90% of the cases. The translocation t(17:22)(q22:q13) which often manifests itself as a supernumerary ring chromosome r(17:22). The translocation results in the fusion of 2 genes, the collagen type 1 alpha 1(COL1A1) and platelet-derived growth factor B-chain (PDGFβ) gene. This aberrant gene produces the COL1A1/PDGFβ fusion protein that is eventually processed to mature PDGFβ protein, indistinguishable from wild-type PDGFβ. There is a characteristic amplification of sequences from chromosomes 17q and 22q, demarcated by the COL1A1 and PDGFβ genes, respectively, and is associated with elevated expression of the amplified genes. The mechanism underlying DFSP oncogenesis appears to be an excessive autocrine stimulation of wild-type PDGFRβ in cells that normally produce collagen.

Both a "classic" form (most prevalent) and a "high-grade" variant fibrosarcomatous form (FSDFSP) have been described. Among the patients with classic DFSP, the recurrence rate is approximately 19% at 5 years, compared with 72% among the patients with FS-DFSP. Thus, a more intensive treatment approach should be considered for the latter.

Because DFSP tends to spread to multiple microscopic projections away from the visible lesions, wide local surgical excision is the main therapy. However, the local recurrence rate is high (20% to 60%). The post-surgical recurrence rate is approximately 50% with standard surgery and 13 to 20% after wide excision. Mohs micrographic surgery using successive fixed-tissue sections to guide surgical removal is relatively tissue sparing, but is labor intensive. Results may also depend from the surgical policy followed at each institution. Recent data from a large series from a single institution indicated that a more aggressive surgical policy with reconstructive surgery could reduce the recurrence rate to a crude cumulative incidence at 5 year of 2% in patients with primary tumour and 5% in patients with recurrent tumour. A non-statistical difference in the 5-year crude cumulative incidence of recurrence (2.3% and 8.0% respectively) and distant metastasis (1.4% and 3.6% respectively) was observed between patients with and without disease-free margins. Although more effective at establishing local control of DFSP, wide excision frequently leads to significantly reduced quality of life due to dysfunctional impairment and cosmetic defects.

Adjuvant radiotherapy may be of value in patients who have or who are likely to have close or positive margins, but there is limited experience with this therapy and it is of limited value in macroscopic disease. Chemotherapy is not extensively used in DFSP, recurrences are largely local and metastases are rare. Surgical resection with wide local excision margins is therefore the accepted treatment for DFSP. Maximizing local tumour control often entails excision of considerable tissue volumes that can include underlying striated muscle and bone. Wide surgical margins may not be possible in head and neck tumours or may contribute to substantial morbidity or considerable functional and cosmetic deficits.

Metastasis of DFSP is rare, occurring in approximately 1% to 4% of cases, but is a definite risk and it can contribute to mortality associated with uncontrolled disease.

2. Clinical aspects

Imatinib inhibits the activity of the platelet-derived growth factor receptors α and β (PDGFRα and PDGFRβ). The over-expression of PDGFBB protein, makes DFSP a candidate for Imatinib treatment.

As mentioned, DFSP is characterized by the translocation t(17:22)(q22:q13) which results in the fusion of COL1A1 and PDGFβ genes. This translocation was indeed identified in 10 out of the 18 the patients described in this submission.

In the submitted documentation, the clinical data that support the claimed indication and posologic regimen are limited to the experience in 18 patients:

- A phase II open label [Study B2225] in patients with life threatening diseases, including DFSP, known to be associated with one or more imatinib-sensitive tyrosine kinases (**N=12**)
- Five publications (**N=6**) (Maki, et al 2002, Rubin, et al 2002, Labropoulos et al 2005, Mizutani et al 2004, Price, et al 2005).

Clinical pharmacology.

Detailed Clinical Pharmacology was already studied in previous applications of this product.

Pharmacokinetic studies in DFSP patients

B2225 PK study.

In sparse pharmacokinetic blood samples were collected after the first dose on day 1 and at steady state on day 29. The sampling times depended on the convenience of the patient, one being taken between 1 hour and 3 hours and one between 6 hours and 9 hours after the morning dose, and another one before dose on the following day. Full PK profile samples were taken from selected patients where it was deemed necessary, e.g.
- when concomitant medication was known or suspected to interact with imatinib
- patients with liver impairment (e.g. metastases)
- patients with metabolic, absorption, excretion disorders

Basic PK characteristics of Imatinib and its major metabolite CGP74588 were measured and described. On day 1, the full-profile had the time schedule: 0 hr (pre-dose), 1 hr, 2 hrs, 3 hrs, 8 hrs, 24 hrs (no study drug), 48 hrs (no study drug), and 72 hrs (prior to resuming study drug).
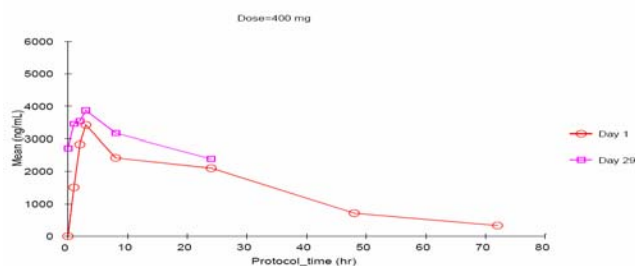On day 29 the full-profile had the time schedule: 0 hr (pre-dose), 1 hr, 2 hrs, 3 hrs, 8 hrs, and 24 hrs (prior to resuming study drug).

Plasma concentrations of imatinib and its major metabolite CGP74588 were determined by a high performance liquid chromatography MS/MS method (LC/MS/MS).

The sparse PK concentrations after single and multiple doses were tabulated with descriptive statistics for each dose level. Where full PK profiles were available, the basic PK parameters of Imatinib and its metabolite (tmax, Cmax, AUCτ and AUC) were determined.

PK data are available at different dose levels from 200 mg to 800 mg per day following the first dose on day 1 and at steady state on day 29 either by intensive PK sampling or sparse PK sampling . The majority of the PK data are from the 400 mg qd dose. Figure and table below summarise the PK profile of imatinib in patients with DFSP. The metabolite CGP74588 showed a greater accumulation, 2-3 fold, and longer half-life, 36 hours, than the parent compound. At steady state, the imatinib to metabolite exposure ratio is approximately 5-fold. These results are comparable with those observed in patients

with GIST, suggesting a similar PK between solid tumour patients and GIST patients, although the results should be interpreted with caution due to the amount of missing data.

Dose (mg/day)	Parameter (units)	Day 1	Day 29
200	N	3	3
	$AUC_{(0-24)}$ (ng.h/mL)	25927(4058)	38016(8394)
	$AUC_{(0-\infty)}$ (ng.h/mL)	34780(1672)	NA
	C_{max} (ng/mL)	2500(266)	2387(729)
	t_{max} (h)	2[1-2.1]	1.9[1-3]
	$t_{1/2}$ (h)	14.0(6.3)	NA
300	N	1	2
	$AUC_{(0-24)}$ (ng.h/mL)	47353	33603-159136
	$AUC_{(0-\infty)}$ (ng.h/mL)	64798	NA
	C_{max} (ng/mL)	3490	1880-9230
	t_{max} (h)	3	3-3.3
	$t_{1/2}$ (h)	14.3	NA
400	N	21	11
	$AUC_{(0-24)}$ (ng.h/mL)	56011(30174)	75223(22356)
	$AUC_{(0-\infty)}$ (ng.h/mL)	102295(65194)	NA
	C_{max} (ng/mL)	3447(1523)	4207(1342)
	t_{max} (h)	3[2-72]	3[1-22.9]
	$t_{1/2}$ (h)	16.4(3.5)	NA
800	N	2	2
	$AUC_{(0-24)}$ (ng.h/mL)	33155-71032	12038-55480
	$AUC_{(0-\infty)}$ (ng.h/mL)	57716-156143	NA
	C_{max} (ng/mL)	2800-3630	1190-3660
	t_{max} (h)	3	2-3
	$t_{1/2}$ (h)	12.6-24-7	NA

Data presented are mean (SD), median [range] value presented for tmax
NA: Not applicable

Pharmacodynamics

Mechanism of Action

As already mentioned, Dermatofibrosarcoma protuberans is characterized by the translocation t(17:22)(q22:q13) which results in the fusion of the collagen type 1 alpha 1 (COL1A1) and the platelet-derived growth factor B-chain (PDGFβ) genes. This aberrant gene produces the COL1A1/PDGFβ fusion protein that is processed to mature PDGFBB protein, indistinguishable from wild-type PDGFBB, with an excessive autocrine stimulation of wild-type PDGFRβ in cells that normally produce collagen. Imatinib inhibits the activity of the platelet-derived growth factor receptors α and β (PDGFRα and PDGFRβ). The over-expression of PDGFBB protein, makes DFSP a candidate for Imatinib treatment.

Preclinical research has shown that imatinib selectively inhibits the Abl and PDGF receptor tyrosine kinases in vitro and blocks cellular proliferation and tumour growth of Bcr-Abl- or v- Abl-expressing cells, leading to its evaluation for use in Ph+ CML. When tested for its effects on PDGF-mediated cellular events, imatinib was shown to inhibit PDGFα- and PDGFβ- stimulated signaling and proliferation. Moreover, showed that imatinib disrupted the PDGFR autocrine loops and inhibited the proliferation of human glioblastoma cell lines *in vitro* and *in vivo*.
Additional preclinical evidence for the potential use of imatinib in DFSP has been provided from studies using COL1A1-PDGFβ transformed mouse fibroblasts as well as primary cultures derived from human DFSP tumours. In NIH 3T3 fibroblasts carrying the DFSP-associated COL1A1-PDGFβ rearrangement the growth rate was reduced and the transformed phenotype reverted in the presence of imatinib.

Furthermore, using cultures derived from human DFSP and giant cell fibroblastoma, showed that imatinib inhibits autocrine PDGFRβ signaling and reduces tumour growth *in vitro* and in mice; the growth inhibitory effect was predominantly mediated by induction of apoptosis.

The dependency of fibroblasts transformed by transfection of DFSP-derived fusion genes from PDGF receptor signaling has been demonstrated in vitro (Greco, et al 1998, Shimizu, et al 1999, Greco, et al 20001). The growth rate of a morphologically-transformed cell line carrying the DFSP-associated COL1A1/PDGFβ rearrangement was reduced and the associated transformed phenotype changed to a flattened one in presence of imatinib (Greco, et al 2001). This effect could be reversed on removal of the inhibitor. The growth rate of tumours induced by this cell line in nude mice was reduced by imatinib administration (Shimizu, et al 1999). Also, Sjoblom, et al (2001) identified activated PDGFRβ in vitro in 3 different primary cell cultures from DFSP and giant cell fibroblastoma tumours. In comparison with normal fibroblasts, these cell lines showed increased sensitivity to imatinib, such that phosphorylation (activation) of PDGFRβ was inhibited. Furthermore, in vitro experimentation with tumour cells grown in the presence of 1 μmol/L of imatinib showed inhibition of proliferation. The growth-inhibitory effects of imatinib were then replicated in tumours induced in mice from one of the DFSP primary cultures, leading to the conclusion that imatinib inhibited DFSP cell growth in vitro and in vivo primarily through induction of apoptosis (Sjoblom, et al 2201).

Clinical efficacy

This application is supported by phase II open label [**Study B2225**] in patients with life threatening diseases, including DFSP, known to be associated with one or more imatinib-sensitive tyrosine kinases and **five publications**. The total number of DFSP patients enclosed in this application is **18** (**12** from study B2225 and **6** from the publications).

Study B2225

Study No.	Study objective, population	Enrolled patients	Treatment duration	Dosage	Efficacy endpoint
B2225	efficacy/safety in target population	185	indefinite	Up to 1000 mg/day	Primary in solid tumour indications: anti-tumour activity
					Primary in hematologic malignancies: blood counts normalization and/or relevant bone marrow or radiological assessments

Ref.	Protocol No. & Study Dates Investigator & Country Publication Reference	Study Design & Purpose Population Studied Evaluations	Total No.& Race (w,b,a,o) Age Range (mean) Group No. & Sex	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status Type of Report General Results
Location in M5:	protocol: CSTI571B2225 (M.5, 5.3.5.2, p.1) invest.: Demetri et al. start: 05-Feb-2001 end: 19-Dec-2006 publ.: Apperley J, et al. (2002) N Engl J Med.; 347(7):481–7 McArthur GA, et al. (2005) J Clin Oncol; 23(4):866–73	design, goal & population: Phase II, open-label exploratory study to examine the effect(s) of Imatinib treatment on life threatening rare diseases with known associations to one or more Imatinib - sensitive tyrosine kinases, and to identify the contribution of specific PTKs of that specific disease. evaluations: PET and/or MRI imaging, correlative sciences- tissue biopsies, pharmacokinetic assessments, performance status safety: AEs, SAEs, hematology, blood chemistry including evaluation of liver function, renal function.	total: 191 patients age: 15 years or older groups: male and female multinational patients	form: 400 mg tablets po duration: 24 months doses: 400 mg/day with dose escalation option to 400, 600, 800, and 1000 mg/day if no significant improvement in disease occurred after the first four weeks on therapy. PK assessments: Day 1 – 0 hr (pre-dose), 1 hr, 2 hr, 3 hr, 8 hr, 24 hrs (no study drug), 48 hrs (no study drug), and 72 hrs (prior to resuming study drug) Day 29 – 0hr (pre-dose, 1hr, 2hr, 3hr, 8hr, 24 hrs (prior to resuming study drug)	status: no longer recruiting patients report: Preliminary results are reported in an interim Clinical Study Report (of 186 patients with a database cut- off date of 31-Dec-2004). general results: A total of 185 patients suffering from 40 different malignancies were recruited into the study. STI571/Glivec can be successfully employed in the treatment of patients suffering from the following malignancies: • DFSP • HES • MDS/MPD • SM STI571/Glivec was generally well tolerated and the pattern of AEs reported was similar to that seen in the treatment of CML or GIST.

Published studies

Published studies	Objective, population	Patients	Treatment duration	Dosage	Efficacy endpoint	
Maki RG, et al (2002)	Efficacy/safety in DFSP patients	2	4-8 weeks	400 mg/day	Tumour volume	mass
Rubin BP, et al (2002)	Efficacy/safety in DFSP patients	1	4 months	400 mg bid	Tumour volume	mass
Mizutani K, et al (2004)	Efficacy/safety in FS-DFSP patients	1	3 months	400 mg/day	Tumour volume	mass
Price VE, et al (2005)	Efficacy/safety in a pediatric DFSP patient	1	23 weeks	400 mg/m^2/day	Tumour volume	mass
Labropoulos SV, et al (2005)	Efficacy/safety in DFSP patients	1	3 months	400 mg/day	Tumour volume	mass
Mc Arthur GA, et al (2005)*	Efficacy/safety in DFSP patients	10	Up to 24 months	400 mg bid /day	Tumour volume	mass

* part of [Study B2225]

The largest published series of DFSP patients treated with imatinib is from McArthur, et al (2005) and refers to patients treated in the context of (Study B2225).
.

Main study (B2225)

Title of study: Open Label, Pilot Phase II Study of STI571 (Imatinib) in Patients with Life Threatening Diseases Known to be Associated with one or more STI571-Sensitive Tyrosine Kinases.

Primary objective: To assess the efficacy of imatinib in patients with life threatening diseases known to be associated with one or more of the known imatinib-sensitive tyrosine kinases, following failure of standard therapeutic options.
Secondary objective: To assess the safety and tolerability of imatinib in these populations.
To evaluate the pharmacokinetic (PK) profile of imatinib in selected patients.
To assess, where feasible, the functional significance of relevant signal-transduction components in target tissues by:
- Measurement of indices of cellular proliferation
- Evaluation of expression and activation status of the relevant protein tyrosine kinases (PTK) or associated signaling molecules
- Correlation of changes in the above findings with clinical outcomes.

Inclusion criteria

Five to ten patients per condition, or disease were initially accepted for treatment. It was planned that lack of clinical efficacy coupled with lack of demonstration of any surrogate pharmacodynamic effect (target PTK inhibition in the first 5 patients) excluded future patients with the same conditioner disease from the study. Patients included in the study were male or female who were ≥ 15 years of age. Had a malignant and/or a life threatening disease documented by conventional criteria to be refractory to standard, approved therapy, or for which no conventional beneficial therapies existed. Experimental documentation had been confirmed to support the possible functional significance of one or more of the relevant imatinib-sensitive PTKs, a performance status 0, 1, or 2 (ECOG), adequate end organ function or in the case of patients with life-threatening diseases were eligible for the study despite deviation from the above criteria, when approved by Novartis.

Female patients of child-bearing potential must have had a negative pregnancy test and agreed to a method of birth control. Life expectancy of more than 3 months in the absence of any intervention was required. Patients must have had a fresh tissue biopsy prior to treatment with imatinib and an additional biopsy was required while undergoing treatment in the absence of serious safety concerns.

Exclusion criteria

Patients with a condition which was investigated or planned for investigation in other imatinib clinical protocols, e.g. SCLC, GIST, prostate cancer or glioma or patients treated with any other investigational agents within 28 days of first day of study drug dosing were not included in the study. Patients with another primary malignancy or patients who had received chemotherapy within 4 weeks (6 weeks for nitrosourea, mitomycin-C or any antibody therapy) prior to study entry were excluded.

Patient distribution by malignancy type and diagnosis. (Study B2225)

Malignancy type	Diagnosis	n (%)
Solid Tumours	Adenoid cystic carcinoma	12 (6.5)
	Aggressive fibromatosis	20 (10.8)
	Chondrosarcoma	7 (3.8)
	Chordoma	4 (2.2)
	Dermatofibrosarcoma protuberans	**12 (6.5)**
	Leiomyosarcoma	11 (5.9)
	Liposarcoma	11 (5.9)
	Mesothelioma	6 (3.2)
	Synovial sarcoma	16 (8.6)
	Other	41 (22.2)
Hematological malignancies	Hypereosinophilic syndrome	14 (7.6)
	Mastocytosis	5 (2.7)
	Myelofibrosis	8 (4.3)
	Myeloproliferative disorder	7 (3.8)
	Other	11 (5.9)

Dose selection

The planned starting dose differed between the two groups of malignancies, with the 45 patients with hematological malignancies initially receiving imatinib at 400 mg p.o. daily with a provision for a dose increase up to 800 mg p.o. daily if progression or absence of significant improvement in the disease was observed after at least 4 weeks of therapy.

The other 140 patients with solid tumours initially received imatinib at 800 mg p.o. daily with a provision for a dose increase up to 1000 mg p.o. daily if progression or absence of significant improvement in the disease was observed after at least 8 weeks in solid tumour of therapy.

Dose intensity in DFSP patients

DFSP (N=12)
Mean ± SD   741.2 ± 122.98
Median   799.7
Min — Max   400 - 800

Duration of Exposure (months)	DFSP patients N = 12 n (%)
0 - <5	4 (33.3)
5 - <10	4 (33.3)
10 - <15	1 (8.3)
15 - <20	0
20 - <25	3 (25.0)
25+	0
Mean ±SD	9.2 ±8.31
Median	6.2
Min − Max	0.1 − 24.3

Efficacy results

The efficacy of imatinib was evaluated on the basis of the frequency of the tumour response.
Overall best response was tabulated based on modified SWOG criteria taking into account the investigator's assessment of a patient's tumour response at each assessment.

Wherever possible, the status of tumour lesions in patients with solid tumours was assessed by means of CT or MRI. For patients with DFSP, the skin lesions were evaluated for surface area, depth, thickness and consistency of the lesions. The defined secondary endpoint was the ECOG status.

Tissue samples were to be collected when possible and analyzed for the possible functional significance of one or more of the relevant imatinib-sensitive PTKs. Ideally pre- and post treatment samples were to be obtained. Whenever feasible, functional significance of relevant cell-signaling components in target tissues were to be described at the beginning of the study, including measure of indices of cellular proliferation, evaluation of expression and activation, (e.g. phosphorylation) status of the relevant PTKs or associated effector molecules and any changes in these findings were to be correlated with clinical outcomes. However, the tissue sample collection of pre- and during- treatment specimens and their analysis proved to be very challenging due to the following factors: (i) the rarity of the diseases investigated, hence only few samples were obtained hampering the possibility of running correlative analysis; (ii) samples containing necrosis or connective tissue rather than malignant cells; (3) lack of paired samples in many cases.
All statistical procedures are descriptive in nature.

Best responses to Imatinib in DFSP patients in B2225 study

Country/Center/Subject	Site of Disease	Cytogenetics[1]	Best Response	Duration of Response (days)
BEL/101/082 *	Perineum	t(17:12)	PR	112
BEL/101/155 *	Right shoulder	t(17:12)	PR	83
BEL/101/179	Skin (scalp)	t(17:12)	PR [3]	56
BEL/101/182	Left side	t(17:12)	PR [3]	35
USA/501/068 *	Left arm	t(17:12)	PR	36
USA/501/108	Vulvar region	t(17:12)	UNK [3]	-
USA/501/115	Right leg, spinal cord, bone	NA	UNK	-
USA/501/154	Right lower back, bone, lung, pleura	Complex [$]	PR	160
USA/501/158	Skin (scalp)	t(17:12)	CR	365
USA/501/183	Left supra-clavicular fossa	NA	PR	115
USA/504/044 *	Left check, face, skin	t(17:12)	PR	434
AUS/901/113 [2]	Forearm, lung and bone	Complex [§]	UNK	-

PR=partial response; CR=complete response; SD=stable disease; UNK=unknown
* Patients were made disease-free by surgery; [$] Complex cytogenetics, no t(17:22) translocation; [§] complex cytogenetics, including t(17:22); [1] as described in McArthur, et al (2005) [2] described as SD in the patient profile; [3] defined as CR in McArthur, et al (2005)

Best response	n	%
Complete response (CR)	1	8.3
Partial response (PR)	8	66.7
Unknown	3	25.0

Out of the 12 DFSP patients enrolled, one experienced a complete response (CR) and 8 others had a partial response (PR) as their best response. Two patients subsequently progressed, one with PR (patient 501/154) and one with subsequent complete surgical resection (patient 504/044). Patient 501/154 experienced a massive disease progression after an initial response to the study drug. A third responding patient 101/182 attained PR but was prematurely withdrawn on day 184 of the study because of a CTC grade 3 elevation of AST and ALT.

Tumour response data are not available for three patients. In three patients with locally advanced disease, therapy was withdrawn when the tumour had regressed to such an extent that a successful surgical resection was possible, making the patients disease-free, while in a fourth patient (504/044) surgery was performed successfully as soon as progression was detected.

Of note, three more patients were reported as being in CR in Mc Arthur, el al (2005) after longer follow-up.

Onset date of response, time to progression and duration of response in patients with dermatofibrosarcoma protuberans

Country/Center/ Subject	first CR	Onset date/day of first PR	first SD	first PD	Best response	Time to progression	Duration of response
BEL/101/082		22AUG2002/ 58	23JUL2002/ 28		PR	169+	112
BEL/101/155		12MAR2003/ 66	03FEB2003/ 29		PR	148+	83
BEL/101/179		29OCT2003/ 113	06AUG2003/ 29		PR	168+	56
BEL/101/182		26FEB2004/ 86	30DEC2003/ 28		PR	120+	35
USA/501/068		15MAR2002/ 24			PR	59+	36
USA/501/108					UNK	1+	
USA/501/115					UNK	1+	
USA/501/154		19MAR2003/ 76	29JAN2003/ 27	25AUG2003 / 235	PR	235	160
USA/501/158	09APR2003/ 83				CR	447+	365
USA/501/183		19APR2004/ 26			PR	140+	115
USA/504/044		16JUL2002/ 294	23OCT2001/ 28	22SEP2003/ 727	PR	727	434
AUS/901/113			12SEP2002/ 22		UNK	51	

DFSP Patient disposition

Disposition/Reason	(N=12) n	(%)
Completed	1	(8.3)
Discontinued	8	(66.7)
Unsatisfactory therapeutic effect	2	(16.7)
Adverse events	2	(16.7)
Condition no longer required study drug	4	(33.3)
Ongoing at cut-off date	3	(25.0)

The median duration of therapy was 6.2 months with a minimum duration of 4 days and a maximum duration of 595 days. In 4 patients, the therapy was prematurely withdrawn because of remission of the disease.

Ten patients with DFSP were enrolled and treated with 400 mg of imitibib twice daily. Of the 10 patients, 8 had locally advanced disease and 2 had metastasic disease. Four of the patients with locally advanced disease had a complete response and 4 had a partial response and were disease- free after surgical resection. One patient with metastasic disease had a partial response to imatinib, with a clear demonstration of response after 3 months of therapy, but experienced disease progression after 7 months of therapy. The patient who did not respond had widespread metastatic disease and was found to have a complex genotype with no obvious t(12:22) translocation.

Secondary endpoints

The evolution of the ECOG status for patients with DFSP is summarized below

ECOG at baseline	N	End of study status						
		0	1	2	3	4	Missing	Total
0	9	8	1	0	0	0	0	9
1	0	0	0	0	0	0	0	0
2	2	1	0	0	1	0	0	2
3	1	0	0	0	0	1	0	1
Total	12	9	1	0	1	1	0	12

The DFSP population had an ECOG performance status at baseline similar to that of the overall population. The ECOG performance status worsened in three patients, one of them deteriorating from ECOG 3 to 4, and improved in one patient from ECOG 2 to 0.

Efficacy in Published literature

All **publications** refer to case reports, with 6 patients in total. The doses were 400mg/day in three of the publications, 400 mg b.i.d. for two of them and 400 mg/m²/day in the other one.

Publication	Study Design	Number of patients	Dose
Maki, et al (2002)	Case Report	2	400 mg/day
Rubin, et al (2002)	Case Report	1	400 mg b.i.d.
Mizutani, et al (2004)	Case Report	1	400 mg/day
Price, et al (2005)	Case Report	1*	400 mg/m^2/day
Labropoulos, et al (2005)	Case Report	1	400 mg/day
Mc Arthur, et al (2005)	Clinical study	10**	400 mg b.i.d.

- Pediatric case; ** part of Study B2225

Results

No. of patients	Sex	Age	Disease Site	Cytogenetics	Daily Dose	Therapy* Duration	Response
Maki, et al (2002)							
2	M	19	Scalp, lung, pleura	Complex ^{A}	400 mg	4 weeks	1 Transient
	M	29	Shoulder, mediastinal, lung	NA		6 months+	1 Partial
Rubin, et al (2002)							
1	M	25	Tight, paravertebral	Complex §	400 mg bid	4 months	Complete
Mizutani, et al (2004)							
1	M	49	Lung	NA	400 mg	3 months	Complete
Price, et al (2005)							
1**	F	1.5	Lower limb	Der(22)t(17:22)	400 mg/m^2	23 weeks	Partial $^\#$
Labropoulos, et al (2005)							
1	F	48	Back. lung	NA	400 mg	20 months	Complete

Duration of therapy as reported in the published literature; therapy for responders may have continued beyond. ** Pediatric case. # Rendered disease free after surgery. § Cytogenetic: 49 XY, del(3)(p13), add(5)(p14), +ins(7,?)(p?13,?)+8,+16,add(22,q13.3). A Cytogenetic: 92-98<4n+>XXYY, der(2)del(2)(q31)t(2:3)(q31:p21),-4 X2,-5 X2, del(5)(q13:q25) X2,-10,-15,+16,+21 X2, -22 X2,+1-5mars.

No secondary end-point was specified in the published case reports, although cytogenetic response could be also considered as a secondary endpoint.

The following tables provide a descriptive global view of the results and also a 95%CI (using an exact method) for the collapsed data (not pooled, i.e. not adjusted by study):

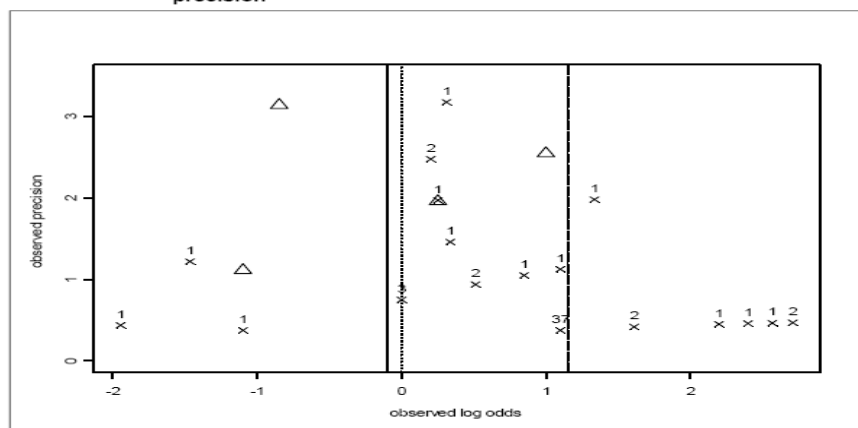**Observed response rates and exact 95%-confidence interval per indication and global**

	DFSP	HES	MPD	SM	Global
	Observed (L,U)	Observed (L,U)	Observed (L,U)	Observed (L,U)	Observed (L,U)
Published literature	83.3% (35.9%,99.6%)	83.5% (74.6%,90.3%)	58.3% (36.6%,77.9%)	64.3% (44.1%,81.4%)	76.1% (68.6%,82.6%)
STI571B2225	75.0% (42.8%,94.5%)	28.6% (8.4%,58.1%)	57.1% (18.4%,90.1%)	20.0% (0.5%,71.6%)	47.4% (31.0%,64.2%)

Meta-analyses of published data

Bias of publication

As a previous step to the formal meta-analysis a funnel plot is presented below:

Figure 3-1 Funnel plot of observed log-odds of response against observed precision

Numbers indicate how many trials each data point represents; dotted line plotted at the level of a 50% response rate; dashed line indicating the overall observed log-odds of response obtained by for the published data (1.15), solid line indicating the overall STI571B2225 observed log-odds of response (-0.10).

The main conclusion from this plot is that a publication bias cannot be discharged due to the asymmetry of the plot.

The results observed in the STI571B2225 trial, although slightly lower, could be considered consistent with the results of the pooled published data.

Clinical safety

Safety data were obtained from study B2225 up to the cut-off date of 31-Dec-2004.
Some others safety data have been extracted from the published case reports (Maki, et al 2002, Rubin, el al 2002, Mirzutani, el al 2004, Price et al 2005, Labropoulos, et al 2005).
Additional sources of data consisted of:
- A worldwide literature search, to capture any investigator reports on safety aspects not included in the study reports (date of search: 14- Oct-2005).
- A review of safety reports from ongoing trials submitted to the Novartis Clinical safety and Epidemiology department (cut-off date: 10 May 2005), and
- A review of post- marketing surveillance data from the 99 countries in which Glivec is registered for marketing (cut-off date:10 May 2005).

Study B2225 Safety data.
Patient exposure

Patients with hematological malignancies tended to stay on treatment longer, while patients with solid tumour dropped out from the study rather quickly, with 72.9% of them leaving the study after 5 months or less vs. 48.9% for patients with hematological malignancies. The median exposure clearly reflects this phenomenon, with a median exposure of 2.6 months for patients with solid tumours (max 42.7 months), 5.1 months for patients with haematological malignancies (max 26.7 months). Patients with DFSP were the ones with longer exposure in the solid tumour group, with a mean exposure of 9.2 months, and a median of 6.2 months.

Long-term exposure

Data concerning long-term exposure to imatinib is available from the regular safety updates submitted to the authorities, the patient treated for longest in this study was patient 101/012, a 63 year old male

suffering from adenoid cystic carcinoma in whom therapy was withdrawn after 811 days because of an unsatisfactory therapeutic effect.

Adverse events

Information about all AEs, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, was collected and recorded on the AE CRF and followed as appropriate. An AE was defined as any undesirable sign, symptom or medical condition occurring after starting study treatment, even if not considered to be treatment-related.

Overall, the most frequently affected SOCs in all patients in both malignancy types were the gastrointestinal system, the general disorders or disorders of the skin, the musculoskeletal, respiratory and nervous systems. Patients with hematological malignancies had a higher frequency of skin disorders (68.9% vs.57.1%), blood disorders (48.9% vs. 24.3%) and cardiac disorders (11.1% vs. 6.4%) than patients with solid tumours and a lower frequency of general disorders (62.2% vs. 80.7%), of metabolic and nutrition disorders (24.4% vs. 42.1%) and of eye disorders (13.3% vs. 26.4%).

Next table presents the most common adverse events in patients with DFSP by system organ class. Of note, all patients experienced at least one adverse event, the most common being gastroinstestinal, cutaneous and general disorders.

Primary system organ class	DFSP patients N = 12 n (%)
Any primary system organ class	12 (100)
Gastrointestinal disorders	10 (83.3)
Skin and subcutaneous tissue disorders	8 (66.7)
General disorders and administration site conditions	7 (58.3)
Eye disorders	6 (50.0)
Musculoskeletal and connective tissue disorders	6 (50.0)
Nervous system disorders	4 (33.3)
Respiratory, thoracic and mediastinal disorders	4 (33.3)
Blood and lymphatic system disorders	3 (25.0)
Investigations	3 (25.0)
Infections and infestations	3 (25.0)
Metabolism and nutrition disorders	3 (25.0)
Cardiac disorders	2 (16.7)

Most frequently adverse events in the DFSP population

Preferred term	DFSP patients N = 12 n (%)
Nausea	5 (41.7)
Diarrhea	3 (25.0)
Vomiting	3 (25.0)
Periorbital edema	4 (33.3)
Face edema	2 (16.7)
Rash	3 (25.0)
Fatigue	5 (41.7)
Edema peripheral	4 (33.3)
Pyrexia	2 (16.7)
Eye edema	4 (33.3)
Lacrimation increased	3 (25.0)
Dyspnea exertional	2 (16.7)
Anaemia	3 (25.0)
Rhinitis	2 (16.7)
Anorexia	2 (16.7)

One patient was withdrawn from treatment because of transaminitis, considered drug- related. No SAE affecting hepatobiliary system was reported. Treatment was also withdrawn because of a gastrointestinal event, drug related nausea and/or vomiting in a patient with recurrent progressive DFSP. No patient experienced SAEs involving nervous system and no patient was withdrawn from treatment because of nervous system AEs. The worst haematological events were CTC grade 3 in severity, except one case of CTC grade 4 neutropenia.

The results reveal that imatinib was generally well tolerated and the pattern of AEs observed was similar, in terms of the nature, frequency and severity of the events reported, to those observed in the treatment of patients suffering from CML or GIST.

Overall discussion and Benefit-risk assessment.

DFSP is an uncommon, low-grade sarcoma of fibroblast origin with an estimated incidence rate below of 1 case per million persons per year. It rarely metastasises. First line treatment of DSFP is surgical. Since DFSP has irregular shapes and frequent finger-like extensions, incomplete removal and subsequent recurrence are common. The surgical approach to DFSP must be meticulously planned. Size and location of tumour will dictate the most appropriate surgical procedure.

In some cases, tumour is unresectable or other patients suffered from recurrent and/or metastatic DFSP who are not eligible for surgery. In these cases, other treatment alternatives should be explored.

At present, no single agent has a recognised role as chemotherapeutic option for DFSP.
The MAH provide limited data on the antitumour effect of imatinib in patients with DFSP, due to the extreme rarity of this disease. Nevertheless, the biological plausability is undisputable. Trial B2225 found 8 responses (1CR) out of 12 patients, and finally 3 of the 7 PR were afterwards published as complete responses. Moreover, 6 additional patients from published case-reports are also provided.

Additional studies are ongoing, trying to enrol patients at the moment, so there are no results yet.
In addition to the dossier filed, information on five ongoing and two planned investigator-initiated trials for sarcomas including DFSP patients was provided. The accrual of these trials has been slow due to the rarity of the disease and no conclusions can be drawn from these studies at this time. These investigator-initiated trials for sarcomas including DFSP patients are exploratory and uncontrolled. Final results from these investigator-initiated trials will be provided when completed. It should be noted however, that some of these studies have been open for enrollment for years, but have not yet approached their accrual goals. Only study *CSTI571BFR16* has obtained results at date. The response rate observed is 50 % (15 patients enrolled) in contrast to the overall response rate of 83% in the population of patients with DFSP in Study B2225. However, the used dose is 600mg instead of 800mg, and only during a 2 months period time.

With regard to the safety of imatinib, the results from the clinical trials and those observed in the treatment of patients suffering from CML or GIST, reveal that in these group of patients, imatinib was generally well tolerated. Taking into account that no toxicity problems were found with a dose of 800 mg/daily, and due to the rarity of the disease, which makes it difficult to collect dose-response data, and considering that a better response is achieved with 800 mg dose, rather than 600 mg or 400 mg, the proposed dose acceptable.

Mohs Micrographic surgery and surgical resection with local excision margins are still the primary option for DFSP patients. Glivec could play an important role for the treatment of adult patients with unresectable DFSP and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

It is true that due to the rarity of the disease, submitted data seems limited, so it is important that the ongoing clinical trials provide more data to complete the information about the true effect of Glivec.

The MAH should commit to provide yearly updated information on ongoing CTs of Glivec in DFSP. The final results of these studies should be provided when available. Due to the rarity of the disease and the independent sponsorship of these trials, the request of a clear-cut deadline for the submission of the final results seems unrealistic.

Follow-up measures undertaken by the Marketing Authorisation Holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below and to submit any variation application which would be necessary in the light of compliance with these commitments (see Letter of Undertaking attached to this report):

Area[1]	Description	Due date[2]
Clinical	To provide <u>yearly</u> updated information on ongoing CTs of Glivec in DFSP. The final results of these studies should be provided when available. Novartis is aware of five ongoing and two planned investigator-initiated trials for sarcomas including DFSP patients. Novartis is providing drug and further support for the conduct of these studies. The accrual of these trials has been slow due to the rarity of the disease and no conclusions can be drawn from these studies at this time. These investigator-initiated trials for sarcomas including DFSP patients are exploratory and uncontrolled. Novartis does not have primary access to the data on these ongoing studies. Novartis will provide the EMEA with any public disclosure of the results of these trials and update the EMEA on the accrual progress on these trials.	31/07/2007

1. Areas: Quality, Non-clinical, Clinical, Pharmacovigilance
2. Due date for the follow-up measure or for the first interim report if a precise date cannot be committed to.