Name of Sponsor/Company: University Hospital of BORDEAUX	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product : Glivec	Volume:	
Name of Active Ingredient : Imatinib mesylate	Page:	

Title of Study :

"Phase II randomized double blind clinical trial of imatinib mesylate STI571 (Glivec®) versus placebo in patients with severe cutaneous scleroderma or systemic sclerosis with severe cutaneous involvement." ScleroGlivec

Investigators :

Study coordinator : Pr Alain TAÏEB

33 investigators (principal + co-investigators)

Names of principal investigators at the 13 investigating centers :

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Study centre(s) :

13 hospital services in France :

- Dermatology – CHU Hôpital Saint André – Bordeaux
- Dermatology – CHU Hôpital Haut-Lévêque – Bordeaux
- Rheumatology – CHU Pellegrin – Bordeaux
- Vascular and Internal Medicine – CHU Hôpital Saint André – Bordeaux
- Dermatology – CHU Hôpital Dupuytren – Limoges
- Dermatology – CHU Hôpital Larrey – Toulouse
- Vascular and Internal Medicine – CH Hôpital Robert Boulin – Libourne
- Internal A Medicine – CHRU Hôpital C. Huriez – Lilles
- Rheumatology – CHU Hôpital Hautepierre – Strasbourg
- Nephrology and Internal Medicine – CH de Valencienne
- Internal B Medicine – CHRU Hôpital Bretonneau – Tours
- Internal H Medecine – CHU Hôpital central de Nancy
- Internal Medecine – Hôpital Saint Louis APHP – Paris

Publication (reference)

Sorilla PREY, Khaled EZZEDINE, Adélaïde DOUSSAU, Anne-Sophie GRANDOULIER, Damien BARCAT, Emmanuel CHATELUS, Elisabeth DIOT, Cécile DURANT, Eric HACHULLA, Danièle IBBA-MULLER, Elise KOSTRZEWA, Thomas QUEMENEUR, Carle PAUL, Thierry SCHAEVERBEKE, Julien SENESCHAL, Anne SOLANILLA, Agnès SPARSA, Stéphane BOUCHET, Sébastien LEPREUX, François-Xavier MAHON, Geneviève CHENE, Alain TAÏEB. Imatinib mesylate in scleroderma associated-diffuse skin fibrosis : a Phase II multicenter randomized double-blinded controlled trial.

British Journal of Dermatology : PMID: **23039171**

Studied period : 3 years - date of first enrolment : 28 december 2007 - date of last completed : 17 december 2010	Phase of development : II

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Objectives :

- Main objective : Improvement in skin sclerosis by measuring the change in the modified Rodnan score from M0 vs. M6
- Secondary objectives :
  * Evaluation of treatment tolerance
  * Reduction in dermal thickness on skin biopsy
  * Change in patients' quality of life (modified HAQ scale for scleroderma and Dermatology Life quality Index)
  * Decrease in pulmonary fibrosis on pulmonary function tests (TLCO/VA ratio)

Methodology : Randomized, double-blind, multicenter, phase 2 clinical trial comparing imatinib mesylate 400mg/day to placebo for 6 months, followed by a 6-month treatment-free observation period.

Number of patients (planned and analysed) :

- Number of patients planned : 34
- Number of patients analysed : 28

Diagnosis and main criteria for inclusion : Systemic scleroderma with extensive skin involvement or extensive pure cutaneous scleroderma

Inclusion criteria

- Patient aged 18 or over,
- Pure severe cutaneous scleroderma (generalized, hemicorporeal or morphea affecting more than 20 % of skin surface) OR systemic scleroderma with a modified Rodnan score of more than 20 (maximum 51).
- Effective contraception during treatment and 3 months after cessation of treatment (men and women). For women of childbearing age, negative pregnancy test 7 days before first dose, for post-menopausal women: amenorrhea of at least 12 months.
- Free, informed and written consent signed by patient and investigator (no later than the day of pre-inclusion and prior to any examination required by the study)
- Subject affiliated or beneficiary of a social security scheme

Exclusion criteria

- Sabre-cut scleroderma
- Patient with pure skin scleroderma under concomitant treatment that may interfere with the course of the disease within 4 weeks prior to the first administration of the trial (systemic corticosteroids, methotrexate, cyclophosphamide, bosentan)
- Serious impairment of a vital organ or abnormal biological characteristics
- Patient with NYHA grade III/IV cardiac failure, myocardial infarction less than 6 months prior to pre-inclusion in the trial
- Patient with severe or poorly controlled associated disease (diabetes, chronic renal failure, chronic hepatitis, HIV infection), or cancer
- Patient who had surgery less than 2 weeks prior to pre-inclusion
- Pregnant or breastfeeding woman
- Contraindication to imatinib as specified in the Summary of Product Characteristics
- Patient for whom non-compliance may be anticipated, or unable to give informed consent, or placed under : under legal safeguard
- Patient who received other therapeutic agents in clinical trials within 28 days prior to the first dose of treatment

Test product, dose and mode of administration, batch number

Glivec® (Imatinib mesylate), 400 mg – per os – batches CLI5453/07-0248US then 09-3034CH

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Duration of treatment : 6 months

Reference therapy, dose and mode of administration, batch number
Placebo of Glivec® - per os – batches CLI5453/07-0248US then 09-3034CH

Criteria for evaluation :

Efficacy

- Primary outcome: proportion of change in modified Rodnan score between inclusion and 6 months
- Secondary outcomes : proportion of variation from inclusion of dermal thickness on skin biopsies at M6, quality of life scale (DLQI and modified HAQ for scleroderma) at M6, and pulmonary functional test DLCO/VA at M12

Safety : clinical adverses events, standard biology (haematology, biochemistry)

Other(s) : blood pharmacological assay of imatinib mesylate at M1 and M6

Statistical methods :
* Methods :
The proportions of variation are described by estimation of the median and inter-quartile interval (IQR), the groups are compared by Wilcoxon tests. The proportions are compared between groups by accurate Fisher tests.
* Populations for analysis:
- in intention to treat (ITT) all randomized patients are included in the analysis in the group in which they were randomized and all their data is used
- subpopulation excluding 2 patients recruited in placebo Arm and with a positiv Glivec dosage and reclassification of these patients based on the dosage result
- subpopulation of patients with biopsy location agreement between inclusion and M6.
* Analytical strategies:
- missing=failure : any missing value is replaced by a value of the highest ratio of all patients (corresponding to the least good result)
- Last Observation Carried Forward (LOCF) : a missing value at a given time is replaced by the last available value
- Analysis on censored data : the data of all randomized patients are censored at the definitive discontinuation of each patient's study

Summary – Conclusions

- Results of effectiveness evaluation, if applicable :
* There was no significant difference between groups in the change in modified Rodnan score from baseline to 6 months (imatinib: median proportion of change +10% (IQR, -26%; 32%) vs placebo: median proportion of change -16% (IQR, -39%; 0%), p=0.09).
* No significant difference in dermal thickness on skin biopsy, quality-of-life scales or pulmonary function parameter DLCO/VA

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	Placebo group Median (Q1-Q3) n = number of patients	**Imatinib group** Median (Q1-Q3) n = number of patients	p =
Modified rodnan score (M_0-M_6*)	-0.16 (-0.39-0.00) n=13	+0.10 (-0.26-0.32) n=15	0.0981
Dermal thickness (M_0-M_6)	-0.02 (-0.28-0.25) n=4	+0.20 (0.04-0.33) n=4	0.3460
HAQ modified for scleroderma (M_0-M_6)	-0.01 (-0.37-0.32) n=8	-0.05 (-0.32-0.50) n=10	1.0000
DLQI (M_0-M_6)	-0.59 (-1.00-0.90) n=7	-0.10 (-0.27-0.17) n=9	0.5004
DLCO/VA (%) (M_0-M_{12})	+0.06 (0.01-0.19) n=8	+0.00 (-0.10-0.07) n=9	0.1964

* Missing data are replaced using the missing=failure strategy.

- Results of safety evaluation, if applicable :
Tolerance did not differ between the 2 groups (53 adverse events in the imatinib arm and 39 in the placebo arm), and the proportion of patients with a grade 3 or 4 adverse event did not differ between the groups (imatinib 27%, vs. placebo 31%, p=1.0).

- Conclusion:
This randomized trial of imatinib versus placebo does not demonstrate the efficacy of imatinib mesylate 400 mg daily on skin sclerosis in patients with severe cutaneous scleroderma. Although the study size is smaller than initially planned, the lack of effect on all endpoints does not support the use of imatinib in this indication, especially as imatinib may be associated with potentially serious adverse events.

Date of report : 14/12/2011