Synopsis

Identifier: RM2007/00288/00 **Study Number:** FBX104114

Title: A Double-Blind, Randomized, Placebo-Controlled Multi-Center, Phase II Parallel Dose-Ranging Study to Assess the Antifibrotic Activity of GI262570 in Chronic Hepatitis C Subjects with Hepatic Fibrosis who Have Failed Prior Antiviral Therapy

Investigator(s): Multicenter

Study center(s): FBX104114 was a multicenter study conducted in North America, Europe, and the International region. There were 22 study sites in Europe (Czech Republic 4, Germany 9, Israel 5, Romania 1, and Russia 3) that enrolled 63 subjects. There were 9 study sites in the International region (Australia 3, New Zealand 1, Singapore 1, and Taiwan 4) that enrolled 25 subjects. There were 45 study sites in North America (Canada 6, Puerto Rico 1, and the United States 38) that enrolled 177 subjects.

Publication(s): None at the time of this report

Study Period: 14 Dec 2005 -03 Mar 2008

Phase of Development: II

Objectives:

- To describe the safety and efficacy of two doses of GI262570 treatment in chronic hepatitis C (HCV) subjects with Genotype 1 infection, who had failed prior anti-HCV therapy, in improving immunohistochemical markers of fibrogenesis (markers of hepatic stellate cell [HSC] activation) over the course of the study as compared with placebo-treated subjects.

- To describe changes in liver histology over 52 weeks of therapy with GI262570 or placebo.

- To explore potential relationships between serum markers of hepatic fibrosis, changes in histology and treatment with GI262570.

- To explore expression of serum proteins related to extracellular matrix deposition and breakdown, signalling pathways which may regulate HSC and those involved in hepatic inflammation.

- To characterise the effect of GI262570 on serum HCV RNA.

- To describe GI262570 serum pharmacokinetic (PK) parameters in HCV-infected adults.

- To explore relationships between serum PK parameters and pharmacodynamic (PD) measures (e.g., Ishak fibrosis score, alanine aminotransferase (ALT) and/or other biomarkers) collected throughout the study.

- To evaluate the molecular profile of whole blood samples and/or liver biopsy tissue (transcriptome analyses) to identify markers associated with hepatic fibrosis progression, severity or response to GI262570.

- To characterize the effect of GI262570 on insulin resistance and incident diabetes in subjects with HCV.

Methodology: This was a randomized, double-blind, placebo controlled study. Subjects were randomized to one of two doses of GI262570 (0.5 mg once daily or 1.0 mg once daily) or matching placebo for 52 weeks. Liver biopsies were assessed at screening and Week 52.

Number of subjects:

	Placebo N=88	GI262570 0.5 mg N=89	GI262570 1.0 mg N=88
Number of Subjects			
Planned, N	75	75	75
Randomized, N	88	89	88
Completed, n (%)	72 (82)	74 (83)	78 (89)
Number Withdrawn, n (%)	16 (18)	15 (17)	10 (11)
Withdrawn due to AE, n (%)	7 (8)	7 (8)	5 (6)
Lost to Follow-up, n (%)	0	1 (1)	0
Protocol Violation, n (%)	1 (1)	0	1 (1)
Subject Decision, n (%)	7 (8)	5 (6)	3 (3)
Other, n (%)	1 (1)	2 (2)	1 (1)

Diagnosis and main criteria for inclusion: Subjects between the ages of 40 and 70 years with a documented positive serology for HCV were eligible for entry. All subjects had to be serum HCV RNA positive and HCV viral genotype 1 with and Ishak fibrosis score of 2, 3, or 4. All subjects had to have failed to achieve a sustained virologic response (SVR) with previous interferon and ribavirin treatment for at least 12 weeks.

Treatment administration: All study medication was taken orally. Eligible subjects were randomly assigned in a 1:1:1 ratio to either placebo or one of two doses of GI262570. Study medication was taken once daily for 52 weeks.

The batch numbers for the study medication are presented in the table below.

Study Drug	Batch Number	
	US	EU and International
GI262570 (0.5 mg tablet)	041057644	041057644 071134929
GI262570 (1.0 mg tablet)	041057646	041057646 071134930
Matching Placebo	051094334	051094334 071134928

Criteria for evaluation:

The primary endpoints for this study included the change from baseline in liver biopsy immunohistochemical markers of hepatic stellate cell activation and collagen synthesis; change from baseline in fibrosis as quatified by morphometric image analysis; ranked histological assessment of the paired biopsies (Baseline vs Week 52); and assessment of safety and tolerability of GI262570 in comparison with placebo. Safety was measured by data collection on the nature and frequency of adverse events and laboratory abnormalities as well as changes over time in laboratory parameters and vital signs.

Secondary efficacy endpoints for this study included measuring fibrosis progression, regression or remaining unchanged by measuring a change in Ishak fibrosis score as well as measuring a change from Baseline in total Ishak score (necroinflammatory score and fibrosis score) at Week 52. Other secondary endpoints included change from Baseline in Metavir score, serum FibroSure™ score, serum ALT levels, measures of insulin resistance, and median serum ALT over time.

Pharmacokinetic measures included GI262570 serum PK parameters at Week 2 in a subset of subjects and GI262570 serum concentrations at Weeks 2, 16, 28, 40, and 52.

In addition, exploratory endpoints for this study included measuring the change from Baseline in potential serum markers of hepatic fibrosis, measuring the change from Baseline in transcriptomic analyses, and the change from Baseline in plasma proteomics.

Statistical methods:

Based on the alpha smooth muscle actin (α-SMA) endpoint, a sample size of approximately 50 subjects per arm would provide 90% power to detect a treatment difference (active minus placebo) of -0.65 units, assuming a two-sided test at the 0.05 alpha level and the standard deviation equal to 1.

The key efficacy measures of the study relied on interpretable liver biopsies. Hepatitis C treatment studies have consistently demonstrated that a significant proportion of subjects forgo liver biopsies subsequent to the pre-treatment biopsy. These studies report that approximately 25% of subjects will decline subsequent liver biopsies. We estimated in this study that 25%-30% of subjects would not have paired liver histology for review due to either declining to have a second biopsy or having a tissue sample that was not interpretable. Thus, in order to account for this attrition, the required sample size was 75 subjects per treatment arm.

The populations included in the analysis for this study were:

Modified Intent to Treat Population (mITT)

All subjects with chronic hepatitis C who have failed previous therapy that have been randomized, regardless of whether or not the study drug was actually taken or if the subject completed the planned duration of the study. Subjects were analyzed by randomization arm with no data exclusions. This was the primary population for all analyses of efficacy.

As Treated Population

All subjects for whom no clear evidence was available of failure to take study medication. Subjects were analyzed by treatment received. This was the primary population for the analyses of the safety data.

Evaluable Population

All subjects in the modified intent to treat population excluding all subjects with major protocol violations. Subjects were analyzed by treatment received. This was a secondary population for the analysis of key efficacy data. These results are only presented if the results are different to those from the modified intent to treat population.

PK Concentration Population

The PK Concentration Population includes all subjects who underwent plasma PK sampling during the study and for whom the samples were assayed. This population was used to list, summarize and plot the concentration data by treatment. Treatment was determined per assessment to account for the change in dose frequency (0.5 and 1.0 mg twice daily before amendment 4 or 0.5 mg and 1.0 mg once daily following amendment 4).

All treatment comparisons for efficacy were performed on the mITT population. The comparisons of interest were placebo vs. each dose of GI262570.

- Placebo vs. 0.5 mg (twice daily before amendment 4 and once daily after amendment 4)

- Placebo vs. 1.0 mg (twice daily before amendment 4 and once daily after amendment 4)

The overall treatment effect was tested first. Only if the overall treatment effect was determined significant would the pair-wise comparisons be considered interpretable.

Summary: For this study, 110 sites screened 862 subjects. Of these 265 were randomized, 227 subjects completed both biopsies, and 209 subjects had both a screening and a Week 52 or Withdrawal biopsy that could be assessed. The subjects in this study were predominantly white with a mean age of approximately 52. Across the treatment groups the subjects were well-matched with respect to demographic characteristics.

Efficacy

Primary Endpoints:

Change in αSMA after 52 weeks of Treatment**

Population mITT	Placebo N=88	GI262570 0.5 mg N=89	GI262570 1.0 mg N=88
Screening, n*	64	71	72
Mean (SD)	0.06 (0.047)	0.06 (0.041)	0.05 (0.036)
Median (Range)	0.05 (0.007, 0.215)	0.05 (0.006, 0.224)	0.04 (0.006, 0.155)
Week 52, n	65	72	72
Mean (SD)	0.08 (0.046)	0.08 (0.045)	0.08 (0.048)
Median (Range)	0.07 (0.009, 0.210)	0.07 (0.016, 0.231)	0.08 (0.012, 0.194)
Change from Screening at Week 52, n	64	71	72
Mean (SD)	0.02 (0.048)	0.03 (0.048)	0.03 (0.041)
Median (Range)	0.02 (-0.154, 0.156)	0.02 (-0.103, 0.218)	0.02 (-0.046-0.166)
p-value (reduced model)# = 0.576			

* only those subjects with a value at Week 52 or withdrawal are summarized at Screening

** expressed as proportion of area positive over the total area

p-value is based on the reduced regression model: $\alpha\text{-SMA}_{wk52}$ = treatment $\alpha\text{-SMA}_{screening}$ where screening value is a covariate in the model

At Week 52, the mean change from screening for αSMA was similar across the three treatment groups.

Change in Collagen after 52 Weeks of Treatment**

Population Mitt	Placebo N=88	GI262570 0.5 mg N=89	GI262570 1.0 mg N=88
Screening, n*	65	71	72
Mean (SD)	0.08 (0.059)	0.08 (0.073)	0.08 (0.075)
Median (Range)	0.07 (0.005, 0.259)	0.06 (0.012, 0.336)	0.06 (0.006, 0.393)
Week 52, n	66	72	72
Mean (SD)	0.10 (0.069)	0.11 (0.092)	0.11 (0.0735)
Median (Range)	0.09 (0.016, 0.316)	0.07 (0.010, 0.473)	0.09 (0.015, 0.316)
Change from Screening at Week 52, n	65	71	72
Mean (SD)	0.03 (0.058)	0.03 (0.056)	0.03 (0.061)
Median (Range)	0.01 (-0.102, 0.197)	0.02 (-0.126, 0.235)	0.01 (-0.105, 0.162)
p-value (reduced model)# = 0.994			

* only those subjects with a value at Week 52 or withdrawal are summarized at Screening
** expressed as proportion of area positive over the total area
# p-value is based on the reduced regression model: $collagen_{wk52}$ = treatment $collagen_{screening,}$ where screening value is a covariate in the model

There was no discernible difference in the rate of increase in collagen morphometry in any of the three treatment groups.

Ranked Assessment of Paired Biopsies at Week 52

Population mITT	Placebo N=88	GI262570 0.5 mg N=89	GI262570 1.0 mg N=88	p-value*
Number subjects with paired biopsies**, n(%)	65 (73.9)	72 (80.9)	72 (81.8)	
Ranked assessment (fibrosis)				0.6483
Better than screen, n (%)	13 (20.0)	17 (23.6)	11 (15.3)	
Same as screen, n(%)	35 (53.8)	38 (52.8)	35 (48.6)	
Worse than screen, n(%)	16 (24.6)	17 (23.6)	25 (34.7)	
Missing, n(%)	1 (1.5)	0	1 (1.4)	
Ranked assessment (necrosis)				0.1776
Better than screen, n(%)	11 (16.9)	20 (27.8)	27 (37.5)	
Same as screen, n(%)	23 (35.4)	24 (33.3)	23 (31.9)	
Worse than screen, n(%)	31 (47.7)	28 (38.9)	22 (30.6)	

* p-value is based on Cochran-Mantel-Haenszel Test
**The number of subjects with paired biopsies is based on the number with a ranked assessment

At Week 52, there were no differences across the three treatment groups in the proportion of subjects ranked better, the same or worse.

Secondary Endpoints:

There were no notable differences observed among the three treatment groups for any of the secondary endpoints.

Pharmacokinetic Endpoints:

For the once daily regimens, the increase in area under the curve 0-τ (AUC 0-τ) and maximum observed concentration (Cmax) was slightly less than dose proportional increase in dose from 0.5 to 1.0 mg. For the BID regimens, approximately dose proportional increases in AUC(0-τ) and Cmax were observed.

Elevated serum GI262570 exposures have been observed in approximately 45% of the HCV-infected subjects receiving active treatment in FBX104114 when compared to historical GI262570 exposures in healthy and type 2 diabetes mellitus (T2DM) subjects. Some of the subjects had exposures that were similar to those seen in subjects with hepatic impairment evaluated in a previous Phase I GI262570 hepatic impairment study. Serum GI262570 exposures for the remaining HCV-infected subjects in FBX104114 were generally within the range of observed values for historical data in healthy and type 2 diabetes mellitus (T2DM) subjects.

Pharmacogenetic Endpoints:

Functional, common variants in the genes encoding known metabolizing enzymes of GI262570 (CYP3A5, CYP2C19, CYP2C9, UGT1A3) did not exhibit effects on oral clearance that were substantial enough to merit inclusion in the population PK model.

The single genetic variant in *CYP2C19* that was evaluated (RS4244285) was significantly associated with oral clearance (P=0.008, uncorrected for multiple testing), however, the comparison groups were 111 subjects with the "normal" metabolizer phenotype and 1 subject with the abnormal (inactive) phenotype. While this result cannot be dismissed on statistical grounds alone, it may represent a false positive finding – particularly since, contrary to expectation, the oral clearance for the subject with the inactive metabolizer phenotype was *higher* than the mean of the other subjects.

A *post hoc* power analysis indicated that the final dataset was large enough to provide reasonable levels of statistical power for the detection of associations between the markers assessed and oral clearance. If genetic effects on oral clearance of moderate strength were present (1.36 fold difference between normal and abnormal metabolizers), then at least 80% power would have been attained for all of the variants, with the exception of the *CYP2C19* marker. With only one individual categorized as having the inactive phenotype, the effect of the *CYP2C19* marker would have had to be 6.9 to result in a statistical test with 80% power.

Safety

Most Frequent Adverse Events on Therapy

System Organ Class Preferred Term	Placebo N=88	GI262570 0.5 mg N=89	GI262570 1.0 mg N=88
Subjects with any AE, n(%)	75 (85)	68 (76)	71 (81)
Fatigue	14 (16)	15 (17)	10 (11)
Weight increased	13 (15)	17 (19)	16 (18)
Oedema peripheral	13 (15)	6 (7)	9 (10)
Headache	8 (9)	9 (10)	6 (7)
Nausea	7 (8)	3 (3)	6 (7)
Arthralgia	7 (8)	4 (4)	6 (7)
Abdominal pain upper	6 (7)	5 (6)	2 (2)
Dyspnoea	6 (7)	5 (6)	4 (5)
Upper respiratory tract infection	5 (6)	3 (3)	5 (6)
Urinary tract infection	5 (6)	2 (2)	1 (1)
Abdominal pain	5 (6)	4 (4)	4 (5)
Constipation	5 (6)	3 (3)	5 (6)
Back pain	5 (6)	5 (6)	5 (6)
Insomnia	5 (6)	5 (6)	6 (7)
Asthenia	4 (5)	2 (2)	3 (3)
Hypoaesthesia	4 (5)	2 (2)	3 (3)
Dyspnoea exertional	4 (5)	2 (2)	3 (3)
Depression	4 (5)	4 (4)	3 (3)
Rash	4 (5)	7 (8)	2 (2)
Nasopharyngitis	3 (3)	5 (6)	8 (9)
Sinusitis	3 (3)	1 (1)	4 (5)
Diarrhoea	3 (3)	10 (11)	4 (5)
Pain in extremity	3 (3)	0	4 (5)
Cough	3 (3)	4 (4)	4 (5)
Abdominal distension	2 (2)	5 (6)	3 (3)
Dizziness	2 (2)	5 (6)	10 (11)
Joint swelling	1 (1)	1 (1)	4 (5)
Musculoskeletal pain	1 (1)	1 (1)	4 (5)
Vomiting	0	2 (2)	4 (5)

Adverse Events Leading to Premature Discontinuation of Investigational Product and/or Study

If a subject was withdrawn from study drug, he would be automatically withdrawn from the study as dose reduction was not allowed. In the placebo group 11/88 (13%) subjects were withdrawn from study. In the 0.5 mg and 1.0 mg groups, 11/89 (12%) and 8/88 (9%) respectively were withdrawn from the study. There did not appear to be a similarity or a pattern across the three treatment groups in the adverse events that led to withdrawal. Two subjects in the placebo group, two in the 0.5 mg group and one subject in the 1.0 mg

group reported cardiac disorders. These were atrial fibrillation, sinus arrhythmia, and bradycardia in the placebo group, palpitations and myocardial ischemia in the 0.5 mg group, and congestive cardiac failure in the 1.0 mg group. Three subjects in the 0.5 mg group reported three different types of cancer (colon, pelvic, and prostate). Two subjects in the 1.0 mg group reported vascular disorders (hypertension and aortic stenosis).

Non-Fatal SAEs

The incidence of SAEs was similar across the three treatment groups. Seven of 88 (8%) subjects in the placebo group, 10/89 (11%) subjects in the 0.5 mg group, and 6/88 (7%) subjects in the 1.0 mg group reported an SAE. No SAE was reported more than once in any group.

There were no deaths or pregnancies reported during this study.

No notable trends were observed in laboratory values over the course of the study.

Conclusions:

Efficacy

- There was no difference observed between the placebo group and the two active treatment groups (0.5 mg and 1.0 mg GI262570) for the primary efficacy endpoints:
    - Change from Baseline in liver biopsy immunohistochemical markers of HSC activation and collagen synthesis
    - Change from Baseline in fibrosis quantified by morphometric image analysis
    - Ranked histological assessment of the paired biopsies (Screen vs Week 52)
- There were no notable differences observed among the three treatment groups for any of the secondary endpoints.

Safety

- The incidence of Adverse Events was similar across the three treatment groups with weight increased, fatigue, and peripheral oedema being reported most often.
- Dizziness was the only AE that appeared to have a dose relationship across the treatment groups.
- The incidence of Serious Adverse Events was similar across the three treatment groups with no SAE reported more than once within a treatment group.
- The incidence of Drug-related Adverse Events was similar across the three treatment groups.
- Adverse Events of special interest occurred with similar frequency in all three treatment groups with increased weight, peripheral oedema and dyspnoea being reported most often.
- There were no deaths in this study.
- No notable trends were observed in laboratory values over the course of the study.

Overall

- GI262570 did not improve immunohistochemical markers of fibrogenesis over the course of the study as compared with placebo-treated subjects in this population of Hepatitis C subjects with mild to moderate liver fibrosis.
- At the doses studied, GI262570 appeared to be generally well-tolerated in this population.

Date of Report: September 2008