Name of Sponsor/Company: Genkyotex SA	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Investigational Product: Setanaxib (INN)		
Name of Active Ingredient: Setanaxib (GKT137831)		

Title of Study: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial to Assess the Efficacy and Safety of Oral GKT137831 in Patients with Primary Biliary Cholangitis Receiving Ursodeoxycholic Acid and with Persistently Elevated Alkaline Phosphatase

Investigators: Refer to Attachment 1

Study center(s): Refer to Attachment 1

Publication (reference): N/A

Studied period (years): (date of first patient enrolled) (date of last patient completed): 06-Sep-2017 to 08-Apr-2019	**Phase of development:** II

Objectives:

Primary:

- To evaluate the efficacy of oral setanaxib in comparison with placebo, in subjects with PBC receiving UDCA and with persistently elevated Alkaline Phosphatase (ALP).

Secondary:

- To evaluate the safety of oral setanaxib in comparison with placebo, in subjects with PBC.
- To estimate the population pharmacokinetics (PK) of setanaxib and explore any potential Pharmacokinetics-Pharmacodynamics (PK-PD) relationships in this subject population.
- To explore any relationship between genetic parameters and therapeutic responses in a subset of subjects.

Methodology:

This was a double-blind, randomized, placebo-controlled, multi-center, parallel group phase 2 trial assessing a 24-week period of treatment with oral setanaxib administered in addition to standard of care medication (UDCA) in subjects with PBC.

Subjects were to be assessed for their eligibility during the 4-week screening period (V1), until the baseline/Day 1 visit (V2).

Eligible subjects were to be randomized to oral setanaxib (400 mg OD or 400 mg BID) or placebo, according to a 1:1:1 randomization ratio, stratified at study entry by disease severity defined as baseline serum GGT < 2.5 x

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Subjects were instructed to self-administer orally 400 mg OD or 400 mg BID of setanaxib or matching placebo for a total of 24 weeks.

Baseline assessments were to be performed at baseline/Day 1 (V2). The 24-week treatment period included assessments after 2 weeks of treatment (V3), after 6 weeks of treatment (V4), after 12 weeks of treatment (V5), after 18 weeks of treatment (V6) and after 24 weeks of treatment (End of Treatment/V7). Subjects were to be followed up for 28 days after the end of treatment (Week 28/V8), totaling 6 post-baseline visits. Subjects who discontinued treatment before Week 24 were to have an Early Termination visit (premature end of treatment).

Pharmacokinetic samples were to be taken at Week 2 (V3), Week 12 (V5) and Week 18 (V6).

Subjects had to be taking a stable dose of UDCA at enrollment and were to continue their UDCA treatment at a stable dose (no changes at all) during the treatment period.

A Safety Monitoring Board oversaw the conduct of the study to ensure the safety of participating subjects. An interim analysis (IA) was conducted when 80-90% of the planned number of subjects to be randomized in the study had completed their Week 6 visit (V4). These analyses did not impact the future conduct of the study, and the results are only briefly presented in this report.

Number of patients (planned and analyzed):

Planned: approximately 100

Analyzed: 111

Diagnosis and main criteria for inclusion:

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Approximately 100 subjects with primary biliary cholangitis receiving a stable dose of UDCA and with persistently elevated ALP, who met all the inclusion criteria and none of the exclusion criteria were to be included in this study.

Inclusion Criteria:

1. Male or female aged 18 to 80 years, inclusive.
2. Willing and able to give written informed consent and to comply with the requirements of the study.
3. 2

a) History of elevated ALP levels (>ULN) for at least 6 months;
b) Positive AMA titer or if AMA negative or in low titer (<1:80) PBC specific antibodies (anti-GP210 and/or anti-SP100 and/or antibodies against the major M2 components [PDC-E2, 2-oxo-glutaric acid dehydrogenase complex]);
c) Liver biopsy consistent with PBC (based on historic liver biopsy), including non-suppurative, destructive cholangitis affecting mainly the interlobular and septal bile ducts.

4.) -
5.) -
6. UDCA treatment for at least 6 months and stable dose for at least 3 months prior to Visit 1.
7. Subjects who were being treated for pruritus with colestyramine had to be on a stable dose of colestyramine for at least 8 weeks prior to baseline/Day 1 (Visit 2). Subjects had to be willing and able to take colestyramine at least 2 hours before or after study medication.
8. Female subjects of childbearing potential were expected to use a highly effective method of contraception to prevent pregnancy for 4 weeks before randomization and had to agree to continue strict contraception for 90 days after last administration of IMP. Male participants with female partners of childbearing potential had to be willing to use a condom and require their partner to use an additional form of adequate contraception as approved by the Investigator. This requirement began at the time of informed consent and ended 90 days after the last administration of IMP. Male study participants could also not donate sperm from baseline until 90 days after the last administration of IMP.

Exclusion Criteria:

1. A positive pregnancy test or breast-feeding for female subjects.
2. Any hepatic decompensation, defined as a past or current history of hepatic encephalopathy, gastrointestinal tract bleeding due to esophageal varices, or ascites.
3. INR > 1.2 unless subject was on anticoagulant therapy.
4. ALT > 3 x ULN.
5. Total bilirubin > 1 x ULN.
6. Planned or current plasmapheresis or other extra-corporeal treatments (e.g., MARS) for treatment-refractory pruritus.
7.)- .
8. Cirrhosis with complications, including history or presence of: spontaneous bacterial peritonitis, hepatocellular carcinoma.
9. Hepatorenal syndrome (type I or II) or Screening serum creatinine > ULN.
10. Competing etiology for liver disease (e.g., hepatitis C, active hepatitis B, NASH, ALD, autoimmune !
11. Subjects receiving prohibited medications within 3 months of Visit 1 according to the list (a, b and c) provided in the Study Protocol.
12. Treatment with any investigational agent within 4 weeks of Visit 1 or 5 half-lives of the IMP (whichever was longer).
13. A history of long QT syndrome.
14. Evidence of any of the following cardiac conduction abnormalities during the screening period: A QTc Fredericia interval > 450 milliseconds for males and > 470 milliseconds for females.

A second or third degree atrioventricular block not successfully treated with a pacemaker.

15. A history of severe cardiovascular disease defined as any of the following within the 12 weeks preceding initiation of study treatment:
    Acute myocardial infarction or unstable angina pectoris.
    A coronary revascularization procedure.
    Congestive heart failure New York Health Association (NYHA) Class III or IV.
    Stroke, including a transient ischemic attack.
16. History of cancer in the preceding 5 years, except adequately treated non-melanoma skin cancer, carcinoma in situ of the cervix, in situ prostate cancer, in situ breast ductal carcinoma, or superficial bladder cancer stage 0).
17. The occurrence of any acute infection requiring systemic antibiotic therapy within 2 weeks prior to Visit 1, or HIV infection.
18. A history of bone marrow disorder including aplastic anemia, or marked anemia defined as hemoglobin < 10.0 g/dL (or 6.2 mmol/L).
19. A known hypersensitivity to GKT137831 or to any of the excipients.
20. Any condition which, in the opinion of the Investigator, constituted a risk or contraindication for the participation of the subject in the study, or which could have interfered with the study objectives, conduct, or evaluation.

Product, dose and mode of administration, batch number(s):
Setanaxib (also known as GKT137831) 100 mg capsules for oral administration.
Matching placebo capsules for oral administration.
Kit numbers: Refer to Attachment 2

Duration of treatment:
24 weeks

Reference therapy, dose and mode of administration, batch number:
Not applicable.

Criteria for evaluation:
Efficacy:
Primary efficacy endpoint:
The percent change from baseline to Week 24 (Visit 7) in serum GGT.
Secondary efficacy endpoints:
Absolute and percent change in serum GGT from baseline to each assessment.
Absolute change in ELF score from baseline to Weeks 12 and 24.
Absolute and percent change in serum ALP from baseline to each assessment.
Absolute and percent change in serum levels of hsCRP, and fibrinogen, from baseline to each assessment.
Absolute and percent change in serum ALT, AST, conjugated and total bilirubin, from baseline to each assessment.
Absolute and percent change in the FIB-4 and APRI scores, from baseline to each assessment (FIB-4: age (years) x AST (IU/L)/(platelet count (10^9/L) x (ALT (IU/L)), APRI: AST (IU/L)/ upper normal limit AST)x100/platelet count (10^9/L).
Absolute and percent change in liver stiffness as assessed by transient elastography (FibroScan® or similar technology), from baseline to Week 24, in subjects with values at baseline and Week 24.
Absolute and percent change in serum levels of collagen fragments indicative of collagen formation and degradation, from baseline to Weeks 12 and 24.
Absolute and percent change in Quality of Life (QoL), Fatigue and Pruritus scores based on the PBC-40 and Pruritus Visual Analogue Score (VAS), from baseline to Weeks 12 and 24.
Tertiary efficacy endpoints:
Absolute and percent change in total bile acid levels from baseline to Week 12 and 24.
Proportion of subjects achieving a 15, 20, 30 and 40% reduction in serum ALP from baseline to each assessment.

Proportion of subjects who meet the definition of PBC responder criteria applying the Paris I, Toronto I, Toronto II, Toronto III, Toronto IV, Mayo II, and Barcelona disease prognostic risk criteria at Weeks 12 and 24.

Safety:

Subjects with AEs from starting IMP to 28 days after the last administration.

Clinical laboratory evaluations at Screening, baseline/Day 1 and Weeks 2, 6, 12, 18, 24 and 28.
Urinalysis at Screening and Weeks 12, 24 and 28.
Thyroid stimulating hormone (TSH) measured at baseline/Day 1 and Weeks 12 and 24.
Pulse rate, SBP and DBP at Screening, baseline/Day 1 and Weeks 2, 6, 12, 18, 24 and 28.
Body weight at baseline/Day 1 and at Week 24.
12-lead ECG during Screening and at Weeks 2, 12, and 24

Statistical methods:

Primary Efficacy Analysis

The mean of all assessments, including repeat assessments, prior to first dose was to be considered as the baseline value for the analysis.

Due to the small sample size the primary analysis was to be conducted using a stepwise approach. The percent change from baseline to Week 24 in serum GGT was to be analyzed using an Analysis of Covariance (ANCOVA) with treatment and disease severity as fixed effects, and baseline GGT as a continuous covariate. If the normality assumption for the analysis was not met then the percent change from baseline in GGT at Week 24 was to be analyzed non-parametrically through a stratified Wilcoxon Mann-Whitney (van Elteren) test. The normality assumption was to be assessed through the examination of diagnostic residual plots. Further details and assumption checking are detailed in the SAP.

The difference between each dose of setanaxib and placebo was to be calculated, along with 95% and 97.5% confidence intervals of the difference (to account for Hochberg adjustment).

The primary analysis was to be performed using the ITT population and a sensitivity analysis was to be done using the PP population. If the Wilcoxon Mann-Whitney test was used, a subgroup analysis for disease severity was also to be performed.

Secondary Efficacy Analysis

Serum ALP were to be summarized in the same way and analyzed using the same methodology as for serum GGT.

In addition, the proportion of subjects achieving a 15, 20, 30, and 40% reduction in serum ALP was to be tabulated.

Summary statistics were also to be presented for the percent change from baseline, change from baseline and absolute values for all continuous secondary efficacy endpoints. The change from baseline in liver function tests other than ALP may also have been analyzed in an exploratory manner using the same statistical methodology as for the serum GGT.

With regard to the PBC-40, analysis was by domain, with the scoring explained in the coded-PBC-40. Data were to be considered by domain rather than in terms of a cumulative PBC-40 score. If data were missing from a domain (typically missed or duplicated answers) the whole domain was to be discarded if <50% of items are completed. If >50% of responses were present then the median value for the completed items in the domain was to be ascribed to the missing item.

The number and percentage of subjects belonging to each group for categorical efficacy endpoints were to be presented by visit and treatment group. Such endpoints included but were not limited to, responders to the Paris I, Toronto I, Toronto II, Toronto III, Toronto IV, Mayo II, and Barcelona disease prognostic risk criteria for PBC.

All descriptive statistics were to be presented overall, by treatment severity and by any other appropriate subgroups as defined in the SAP provided sufficient subject numbers are available within each subgroup level, within each treatment group.

Pharmacokinetic/Pharmacodynamic Analysis:

Samples were to be analyzed to determine plasma drug concentrations and thus to aid investigation of any PK/PD relationship with PD and/or efficacy endpoints, and optionally for the relationships between plasma drug concentrations and pharmacogenomics data.

A population PK model describing the plasma concentrations of setanaxib and GKT138184 was to be developed using non-linear mixed-effects modelling. Relationships between drug concentrations/ exposure measures and selected PD and/or therapeutic efficacy endpoints in the same subject were to be graphically explored and formal PK/PD (exposure-response) analyses may have been performed. A separate Modeling and Simulation Analysis Plan (MSAP) for the PK/PD modeling describing the general approach to be taken was to be finalized prior to database lock. The actual execution of any PK/PD modeling would depend upon the data, and full details of this will be provided in a separate report.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

- The primary efficacy analysis of the percent change from baseline to Week 24 in serum GGT does not show a statistically significant difference versus placebo for the 400 mg OD dose (p-value=0.67) or for the 400 mg BID dose (p-value=0.31).
- For the 400 mg BID dose, the mean percent change from baseline in serum GGT is maintained at around -19% from Week 12 to Week 24.
- The secondary efficacy analysis of the percent change from baseline in serum GGT using a repeated measures ANCOVA across all post-baseline visits does not show a statistically significant overall difference between the treatment groups (i.e. no treatment is statistically different from another treatment) (p-value=0.12). The analysis shows a statistically significant decrease in percent change from baseline for

the 400 mg BID dose (-16.3%; p-value=0.002) but not for placebo (-4.7%; p-value=0.34) or the 400 mg OD dose (-3.1%; p-value=0.52).

- The secondary efficacy analysis of the percent change from baseline in serum ALP using a repeated measures ANCOVA across all post-baseline visits shows a statistically significant overall difference between the treatment groups (i.e. the treatments are not all the same) over all the post-baseline visits (p-value=0.002). The analysis shows a statistically significant decrease in percent change from baseline for the 400 mg BID dose (-12.7%; p-value<0.0001) and for the 400 mg OD dose (-6.2%; p-value=0.008).
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analysis of the percent change from baseline to any post-baseline visit in liver stiffness shows a difference in the least square means (LSQ) percent change of -26.12% between the 400 mg BID dose and placebo (p-value=0.039). While not reaching statistical significance after correction for multiple comparisons, this result supports the hypothesis of an anti-fibrotic mechanism.
- The analysis of the percent change from baseline to Week 24 in PBC-40 Questionnaire domains shows a statistically significant improvement for the 400 mg BID dose (versus placebo) in the fatigue, social and emotional domains (p-values equal to 0.027, 0.003, and 0.031 respectively).
- The analysis of the percent change from baseline to Week 24 in Pruritus score (using VAS) shows a statistically significant reduction for the 400 mg OD dose (p-value=0.004) versus placebo. For the 400 mg BID dose, the difference versus placebo is not statistically significant (p value=0.103).
- The post-hoc analyses of the percent change from baseline to Week 24 in serum GGT and ALP by baseline liver stiffness subgroup show that patients with elevated liver stiffness at baseline who received 400 mg BID dose achieved greater mean reductions in serum GGT and ALP at Week 24 (-32.4% and -24.3%, respectively) than those with normal or marginally elevated liver stiffness at baseline (-12.9% and -8.7%, respectively).

SAFETY RESULTS:

- Treatment-emergent adverse events were mainly mild to moderate in severity, generally balanced across treatment groups and were clustered in the gastrointestinal, neurology, infections, skin complaints and musculoskeletal categories.
- The incidences of adverse events were similar in the setanaxib treatment arms and in the placebo arm. No dose related pattern could be detected between the 2 two dose regimens of setanaxib.
- There were no deaths or drug-related serious adverse events, only 4% of subjects discontinued treatment due to adverse events and only 4% of subjects had brief treatment interruptions due to adverse events. Compliance with treatment was high overall at 99%.
- There was no evidence of hematological adverse effects in patient exposed to setanaxib compared to placebo and no patient experienced anemia or significant decreases in red blood cell counts.
- Clinically significant increases in liver function tests were noted in 3% of subjects (1 at the 400 mg OD dose and 2 at the 400 mg BID dose), although
attributed potentially to setanaxib with involvement of the underlying disease.
- Overall, no safety concerns were identified with setanaxib over 24-week treatment period; that would negatively impact the benefit-risk balance of setanaxib in the indications currently under development.

CONCLUSION:

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This trial was one of the largest Phase 2 PBC studies conducted to date. The primary efficacy endpoint was defined as the percent change in GGT at Week 24. Liver fibrosis was assessed noninvasively by measuring liver stiffness and circulating markers of fibrogenesis. Additional key secondary endpoints included additional markers of liver and bile duct injury, markers of inflammation. In addition, indicators of QoL, including pruritus and fatigue, were assessed. Markers of bile acid metabolism and immune activation were also investigated.

While the objective based on the primary efficacy endpoint was not met, the overall results indicate that setanaxib 400 mg BID dose reduces markers of cholestatic injury over the treatment period, including GGT and ALP. The analysis of the percent change from baseline to Week 6 in serum GGT and ALP shows a statistically significant difference for the 400 mg BID dose versus placebo. The analysis of the percent change from baseline in serum GGT across all post-baseline visits does not show a statistically significant overall difference between the treatment groups. However, the analysis of the percent change from baseline in serum ALP across all post-baseline visits shows a statistically significant overall difference between the treatment groups. These results show a marked and consistent dose response relationship indicating that 400 mg BID dose achieves superior therapeutic efficacy compared to 400 mg OD dose.

Setanaxib has shown marked anti-fibrotic activity in a broad range of animal models. Therefore, a key objective for this trial was to assess the effect of setanaxib on non-invasive measures of liver fibrosis. As anticipated, modest improvements were achieved in the full ITT population, in which about half of the subjects had minimal elevations in liver !
400 mg BID dose, a marked median reduction in liver stiffness (around 25%) was observed in subjects with 1 . !
(p=0.038) was achieved after just 24 weeks of treatment.

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post-baseline visit in liver stiffness shows a difference between the 400mg BID dose and placebo that is not statistically significant but supports the hypothesis of an anti-fibrotic mechanism.

Positive trends were observed for additional non-invasive measures of liver fibrosis (e.g. APRI, collagen fragments). However, these trends did not reach statistical significance. It may be that these markers are less sensitive to a therapeutic intervention than liver stiffness measurements. Alternatively, it is possible that the reduction in liver stiffness was due to a combination of factors including improvements in fibrosis, cholestasis, and inflammation.

Importantly, post-hoc analyses of the percent change from baseline to Week 24 in serum GGT and ALP by baseline liver stiffness subgroup show that subjects with elevated liver stiffness at baseline who received 400 mg BID dose achieved greater mean reductions in serum GGT and ALP at Week 24 than those with normal or marginally elevated liver stiffness at baseline. These results indicate that patients at high risk of progression achieve particularly important therapeutic benefits likely to delay disease progression.

Reduced quality of life is an important aspect of PBC, and a major unmet medical need. Setanaxib achieved consistent reductions of several QoL domains that are important to PBC patients. In particular, setanaxib at 400 mg BID dose achieved marked improvements in fatigue, the most common symptom in PBC. Chronic, intractable fatigue has an impact on the social and emotional QoL domains. It is therefore encouraging that setanaxib 400 mg BID dose achieved consistent improvements in these domains as well.

A review of adverse events, safety laboratory results, vital signs, physical examination findings, and ECG did not identify any safety concerns associated with setanaxib at 400 mg OD and 400 mg BID doses.

Date of the report: 07 February 2020