Efficacy of GKT831 in patients with primary biliary cholangitis and inadequate response to ursodeoxycholic acid:

Interim efficacy results of a phase 2 clinical trial


1University of Thessaly, Greece; 2University of Milano-Bicocca, Italy; 3UZ Leuven, Belgium; 4Ghent University Hospital, Belgium; 5Tel Aviv Sourasky Medical Center/Sheba Medical Center, Israel; 6King’s College Hospital NHS Foundation Trust, United Kingdom; 7University of Rochester Medical Center, United States; 8University of British Columbia, Canada; 9University of California Davis, United States; 10Hospital Universitario Virgen de la Victoria, Spain; 11Sheba Medical Center, Israel; 12Medical School, Johannes Gutenberg University Mainz, Germany; 13Hospital Erasmus, Belgium; 14Baylor College of Medicine Medical Center, Houston, United States; 15University of Montreal, Canada; 16University of Erlangen-Nuremberg, Germany; 17University of California Davis, United States; 18Rabin Medical Center, Haifa, Israel; 19IRCSS Ospedale Civile Universitario, Pavia, Italy; 20Queen Elizabeth Medical Center, United Kingdom; 21University Hospitals Cleveland Medical Center, United States; 22Goethe University Frankfurt, Germany; 23Abertawe Bro Morgannwg University, United Kingdom; 24Schiff Center for Liver Diseases, United States; 25Tayside Medical Science Centre (TASC), United Kingdom; 26Hospital Ramón Y Cajal, Spain; 27John Radcliffe Hospital, United Kingdom; 28Hull Royal Infirmary, United Kingdom; 29Icahn School of Medicine at Mount Sinai, United States; 30University of Erlangen-Nuremberg, Germany; 31Laiko General Hospital of Athens, Greece; 32Dayton Gastroenterology-Sylvania, United States; 33Yale School of Medicine, United States; 34North Shore University Hospital, Israel; 35University of Padua, Italy; 36Southern Therapy and Advanced Research, United States; 37Mayo Clinic Hospital, United States; 38Gloucestershire Hospitals NHS Trust, United Kingdom; 39Methodist University Hospital, United States; 40Marche Polytechnic University Faculty of Medicine, Italy; 41University of Pittsburgh Medical Center, United States; 42University Clinic Heidelberg, Germany; 43Plymouth Hospitals NHS Trust, United Kingdom; 44NYU Hepatology Associates, United States; 45University of Calgary, Canada; 46Rambam Healthcare Campus, Israel; 47General Hospital of Athens Hippocrates, Greece; 48Genkyotex, Plan-les-Ouates, Switzerland
Unmet needs in primary biliary cholangitis (PBC)

• **Definition** - Chronic, cholestatic liver disease characterized by non-suppurative granulomatous cholangitis; duct destruction and ductopenia, and portal fibrosis that progresses slowly to biliary cirrhosis.

• **Etiology** – Complex disorder, caused by a complex of largely unknown genetic and environmental factors. Putative autoimmune pathogenesis.

• **Therapy** - Ursodeoxycholic acid (UDCA) is the first-line drug effective in the majority (60-70% of responders). Obeticholic acid (OCA) is the licensed second-line therapy.
Current PBC therapies target cholestasis by modulating bile acid metabolism (UDCA, OCA)

However inflammation & fibrosis contribute to cholestasis, bile duct & liver injury

NADPH oxidases NOX1 & NOX4 produce ROS and modulate signaling through oxidation of signaling proteins

NOX1/4 drive multiple inflammatory & fibrogenic pathways (TGFβ, PDGF, TLR4, ASK1, NF-κB, CCL2,…)

NOX1 also activates pathways thought to mediate itching, such as TRPV1

GKT831 shows marked activity in animal models (bile duct ligation, MDR2 KO, STAM, diet-induced NASH, CCL4)
GKT831 in PBC: Study design and Key eligibility criteria

Study design (objectives)
- 24-week treatment period - 4-week follow up
- **Primary efficacy endpoint** for interim and final analysis: *Percent change in serum GGT from baseline*
- Key secondary endpoint is **ALP reduction**
- **Safety and tolerability**
- Interim analysis at week 6 and final analysis at week 24

Key eligibility criteria (population)
- Male or female PBC patient aged 18-80 years
- **Serum ALP ≥1.5XULN** and **serum GGT ≥1.5XULN** (stratification according to baseline GGT (> or < 2.5XULN))
- On UDCA for ≥ 6 months & stable dose for ≥ 3 months
- Exclusion of history of **cirrhosis with complications** or **current MELD score ≥ 15**
- **ALT > 3XULN** or total bilirubin > **1XULN**
- Hepatorenal syndrome or **serum creatinine > ULN**
- Prohibited medications: **fibrates and obeticholic acid (12-week wash out)**
GSN000300 – A large 24-week Phase 2 trial in patients with primary biliary cholangitis

**Baseline**
- Placebo
- GKT831 400mg once a day
- GKT831 400mg twice a day

**Interim analysis**
- GGT, ALP, bilirubin
- ALT, AST
- hsCRP
- FIB-4, APRI

**Main analysis**
- GGT, ALP, bilirubin
- ALT, AST, CK-18
- hsCRP, IL-6
- Fibroscan, ProC3, ELF, FIB-4, APRI
- PBC-40, pruritus VAS
- IL-4, IL-12, IL-17A, IgM, IFN-γ
- FGF-19, C4, total bile acids

**Inadequate biochemical response to UDCA**
- ALP ≥1.5XULN
- GGT ≥1.5XULN

**111 randomized (initial target 102)**

**Follow up**

**Cholestasis**

**Liver injury**

**Inflammation**

**Fibrosis**

**Quality of life**

**Immune activation**

**Bile acid metabolism**
**Interim analysis at Week 6: Baseline patient characteristics**

As per protocol, the predefined interim analysis was conducted when > 90 patients (92) reached Week 6

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>GKT831 400mg OD(^1)</th>
<th>GKT831 400mg BID(^2)</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>31</td>
<td>31</td>
<td>30</td>
<td>92</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>56 (10)</td>
<td>56 (10)</td>
<td>55 (9)</td>
<td>56 (9)</td>
</tr>
<tr>
<td><strong>Females (%)</strong></td>
<td>97</td>
<td>84</td>
<td>93</td>
<td>91</td>
</tr>
<tr>
<td><strong>ALP (U/L)</strong></td>
<td>304 (151)</td>
<td>282 (89)</td>
<td>350 (177)</td>
<td>312 (145)</td>
</tr>
<tr>
<td><strong>GGT (U/L)</strong></td>
<td>224 (212)</td>
<td>215 (154)</td>
<td>237 (193)</td>
<td>225 (187)</td>
</tr>
<tr>
<td><strong>ALT (U/L)</strong></td>
<td>44 (18)</td>
<td>44 (22)</td>
<td>55 (34)</td>
<td>47 (26)</td>
</tr>
<tr>
<td><strong>AST (U/L)</strong></td>
<td>44 (19)</td>
<td>43 (20)</td>
<td>50 (33)</td>
<td>46 (24)</td>
</tr>
<tr>
<td><strong>Total bilirubin (µmol/L)</strong></td>
<td>11 (5)</td>
<td>11 (5)</td>
<td>10 (4)</td>
<td>11 (4)</td>
</tr>
<tr>
<td><strong>hsCRP (mg/L)</strong></td>
<td>5.0 (4.9)</td>
<td>5.8 (5.7)</td>
<td>4.7 (5.1)</td>
<td>5.2 (5.2)</td>
</tr>
</tbody>
</table>

Values expressed as mean (SD). Baseline: Day 1. Normal ranges: GGT up to 45 and 65 U/L (F/M), ALP up to 125 U/L

Population includes very active, difficult to treat PBC patients

\(^1\) Once daily; \(^2\) Twice daily
Primary efficacy endpoint: GKT831 achieves statistically significant reductions in GGT at Week 6

Primary endpoint: percent change in GGT

Absolute change in GGT over time
Greater GGT reductions in patients with higher baseline GGT (≥2.5XULN, \(n=68\))

GGT ≥2.5XULN was the pre-specified stratification cut-off

GKT831 also benefits patients with more active disease
GKT831 also achieves statistically significant reductions in ALP at week 6

Key secondary endpoint: percent change in ALP

Absolute change in ALP levels

### Table: Proportion of patients with ≥15% reduction in ALP at Week 6

<table>
<thead>
<tr>
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<th>GKT831 400mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients with ≥15% reduction in ALP at Week 6</td>
<td>16.1%</td>
<td>25.8%</td>
<td>53.3%</td>
</tr>
</tbody>
</table>
GKT831 achieves dose dependent reductions in liver transaminases at week 6

**Serum AST levels**

![Graph showing mean AST levels for Placebo and GKT831 at baseline and week 6.](image)

**Serum ALT levels**

![Graph showing mean ALT levels for Placebo and GKT831 at baseline and week 6.](image)

**Percent change from Baseline to Week 6**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Week 6</strong></td>
<td></td>
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</tbody>
</table>

**Mean values**

- Placebo: Mean AST (U/L)
- GKT831 400mg OD: Mean AST (U/L)
- GKT831 400mg BID: Mean AST (U/L)

- Placebo: Mean ALT (U/L)
- GKT831 400mg OD: Mean ALT (U/L)
- GKT831 400mg BID: Mean ALT (U/L)
No detectable changes in total or conjugated bilirubin from baseline to week 6

**Total bilirubin**

- Placebo: n=31
- GKT831 400mg OD: n=31
- GKT831 400mg BID: n=30

**Conjugated bilirubin**

- Placebo: n=31
- GKT831 400mg OD: n=31
- GKT831 400mg BID: n=30
Reduction in inflammatory marker hsCRP consistent with anti-inflammatory mechanism

**Mean hsCRP**

- Baseline
- Week 6

**Percent change in hsCRP**

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>GKT831 400mg OD</th>
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</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>31</td>
<td>31</td>
<td>30</td>
</tr>
</tbody>
</table>

Mean ± SEM

Median values

$p=NS$
Dose dependent reductions in FIB-4 and APRI, consistent with anti-fibrotic mechanism

<table>
<thead>
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</thead>
<tbody>
<tr>
<td>Median % change in FIB-4 score from Baseline to Week 6</td>
<td>n=31</td>
<td>n=31</td>
<td>n=30</td>
</tr>
<tr>
<td>Median values</td>
<td>-5</td>
<td>0</td>
<td>-15</td>
</tr>
</tbody>
</table>

\( p<0.05 \)

<table>
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<th>GKT831 BID</th>
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</thead>
<tbody>
<tr>
<td>Median % change in APRI score from Baseline to Week 6</td>
<td>n=31</td>
<td>n=31</td>
<td>n=30</td>
</tr>
<tr>
<td>Median values</td>
<td>-5</td>
<td>0</td>
<td>-15</td>
</tr>
</tbody>
</table>

\( p=NS \)

At weeks 12 & 24, assessments of liver fibrosis include Pro-C3 and the ELF score. Transient elastography (Fibroscan®) performed at week 24.
Clinical safety profile

- **Positive recommendation at each of the 3 Safety Monitoring board meetings**
  - 3 pre-planned data review meetings by Independent Safety Monitoring Board
  - Positive recommendation to continue trial as per protocol after each of the 3 review meetings
  - Last SMB review meeting held when 87 patients had completed week 6 and 41 had completed week 24

- **Favorable clinical safety profile over the full 24-week treatment period**
  - High treatment completion rate (>96% of patients have completed the full 24-week treatment)
  - 4 patients discontinued treatment prematurely; 2 for administrative reasons and 2 for safety reasons:
    - One patient with dizziness, abdominal bloating, dyspnea, and palpitations after a single dose
    - One patient with elevations in transaminases (similar elevations a few months prior to study start, decision made to interrupt treatment)
  - 2 SAEs, both unrelated to study drug
    - One case of grade 1 urinary tract infection (subject hospitalized to initiate IV antibiotics)
    - Once case of multiple bone fractures due to a traffic accident
  - No treatment interruption or discontinuations due to pruritus or fatigue
Key Findings and Conclusions

- In patients with inadequate response to UDCA, GKT831 induces time and dose dependent reduction in GGT and ALP after only 6 weeks of treatment
- GKT831 is the first non-anticholestatic compound to significantly improve markers of cholestasis, inflammation and fibrosis in PBC
- GKT831 appears to be well tolerated with no signals related to pruritus or fatigue
- Final results at after 24 weeks of treatment will provide information about GKT831 effects on liver fibrosis and quality of life
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