genkyotex
the nox company

Phase 2 trial of GKT831 in patients with primary biliary cholangitis

Interim analysis results

Euronext: GKTX

November 5 2018

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Key findings from the interim efficacy analysis

- The data establish GKT831 as an attractive therapeutic option in a broad PBC population and support its development in multiple fibrotic diseases including NASH and IPF
- Rapid, significant and dose dependent improvements in markers of liver and bile duct injury, a very strong result for an anti-inflammatory and anti-fibrotic drug not targeting cholestasis
- Greater GGT reductions in patients with higher baseline GGT; suggests benefit in patients with advanced disease, the patient population with the highest medical need and limited therapeutic options
- Progressive reductions from baseline to week 2 and to week 6 suggest that further improvements with continued treatment could be achieved
- Good safety and no signal related to itching (pruritus)

Discovery platform delivers broad pipeline in diseases with high medical need

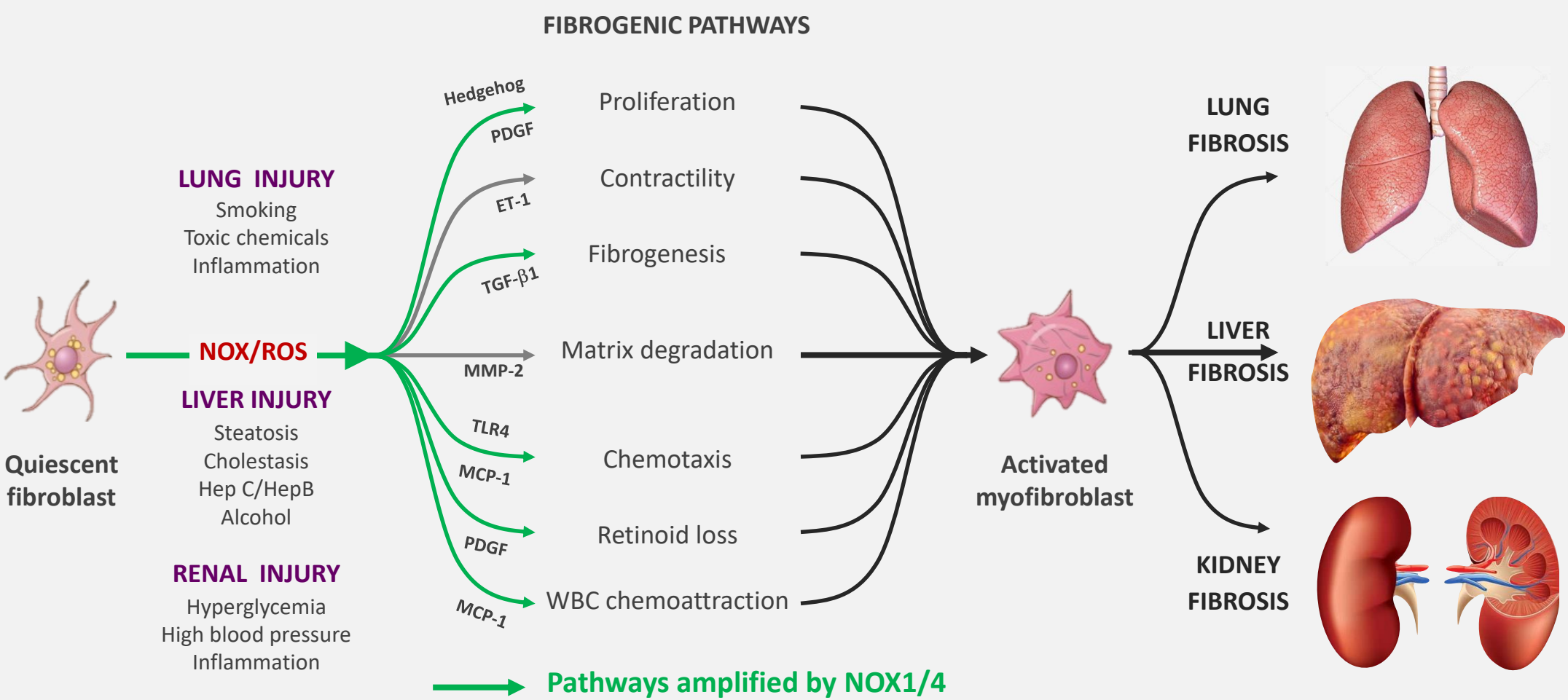
Positive PBC interim efficacy data released on November 5 2018 - Full data in Spring 2019

Program	Preclinical	Phase 1	Phase 2	Phase 3
GKT831 - Liver Fibrosis (NOX1/4 inhibitor)	**Primary Biliary Cholangitis (PBC)** (Positive interim efficacy data released November 5 2018)			
GKT831 - Kidney Fibrosis (NOX1/4 inhibitor)	**Diabetic Kidney Disease (DKD) in T1D** (IIT[1] funded by JDRF[2] - Trial launched 2017)			
GKT831 - Lung Fibrosis (NOX1/4 inhibitor)	**Idiopathic Pulmonary Fibrosis (IPF)** (IIT funded by US NIH[3] - Trial launch H1 2019)			
GKT771 (NOX1 inhibitor)	**Preclinical**			
Novel NOX inhibitor	**Discovery**			
Vaxiclase	**Pertussis vaccine** (Licensed to SIIPL)			

[1] *Investigator initiated trial*
[2] *Juvenile Diabetes Research Foundation*
[3] *National Institutes of Health*

NOX 1 & 4 are major drivers of fibrogenesis in multiple organs

NOXs act upstream of targets such as TGF-β, MCP-1 and ASK1



GKT831 downregulates the activation of multiple clinically validated fibrogenic pathways*

Sources:
Brenner DA, Hepatology 2012, Brenner DA, PLoS One, 2015, Torok N, Free Radic Biol Med, 2012. Torok N, Gastroenterology, 2015; Thannickal V, Science Trans Med, 2014; Gray SP, Circulation, 2013

International liver fibrosis trial in primary biliary cholangitis

GKT831

Trial	Patients	Design

Phase 2	• 111 PBC patients
	  • Confirmed PBC
	  • UDCA non responder
	  • Baseline ALP & GGT ≥1.5ULN
	  • Normal bilirubin
		• Randomized, double blind, placebo controlled, parallel group
		• 24-week treatment with interim analysis on week 6 data
		• UDCA plus placebo or one of 2 doses of GKT831 (400 mg once-daily (OD) and 400 mg twice daily (BID)) – randomization ratio 1:1:1

Primary endpoint

- A marker of liver injury (Change in serum Gamma Glutamyl Transferase - GGT)

Secondary endpoint

- Markers of liver fibrosis (ELF score, collagen fragments, transient elastography)
- Markers of cholestasis (ALP, bilirubin)
- Markers of liver injury (AST, ALT, CK-18)
- Markers of inflammation (hsCRP, fibrinogen, IL-6)
- Quality of life and itching (PBC40 questionnaire and VAS score)

Interim analysis conducted when 92 patients completed their week 6 visit

Sources:

[1]ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CK-18: cytokeratin-18; hsCRP: high sensitivity C-reactive protein; IL-6: interleukin-6)

Patient enrollment exceeded target - interim efficacy analysis completed

GKT831

- Global network of investigational centers
  - 62 centers in Canada, USA, Belgium, Italy, Germany, Greece, Spain, United Kingdom, & Israel
- Enrollment target of 102 patients exceeded with 111 patients randomized
  - Patient enrollment completed on September 25, 2018
  - Patients are all UDCA non-responders, a refractory and difficult to treat population
- Interim efficacy analysis conducted as per protocol when 92 patients completed week 6
  - Primary interim efficacy endpoint:
    - Change in GGT, a marker of liver and bile duct injury, at week 6 compared to baseline
  - Secondary interim efficacy endpoints:
    - Marker of bile duct injury: ALP
    - Markers of liver injury: ALT, AST, GGT, total and conjugated bilirubin
    - Marker of inflammation: hsCRP
- Final results at week 24 will include additional endpoints assessing quality of life (fatigue & pruritus), fibrosis and cholestasis
- Positive recommendation at each of the 3 Safety Monitoring board meetings
  - No patient drop outs due to pruritus

Phase 2 trial of GKT831 in PBC: Baseline patient characteristics

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

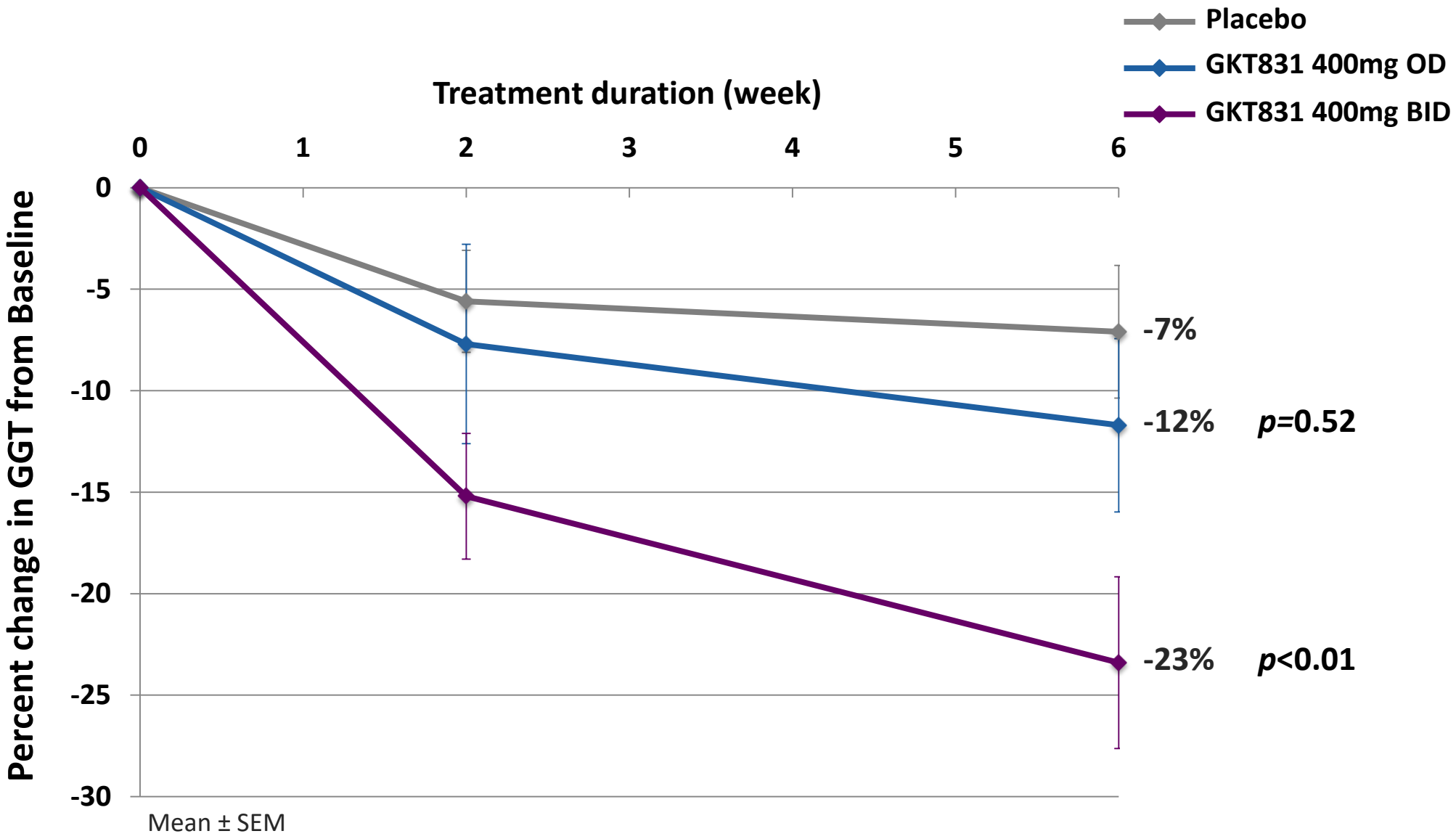
Values expressed as mean (SD). Baseline: Day 1

[1] Once daily; [2] Twice daily

Baseline characteristics in line with the targeted population of active PBC patients

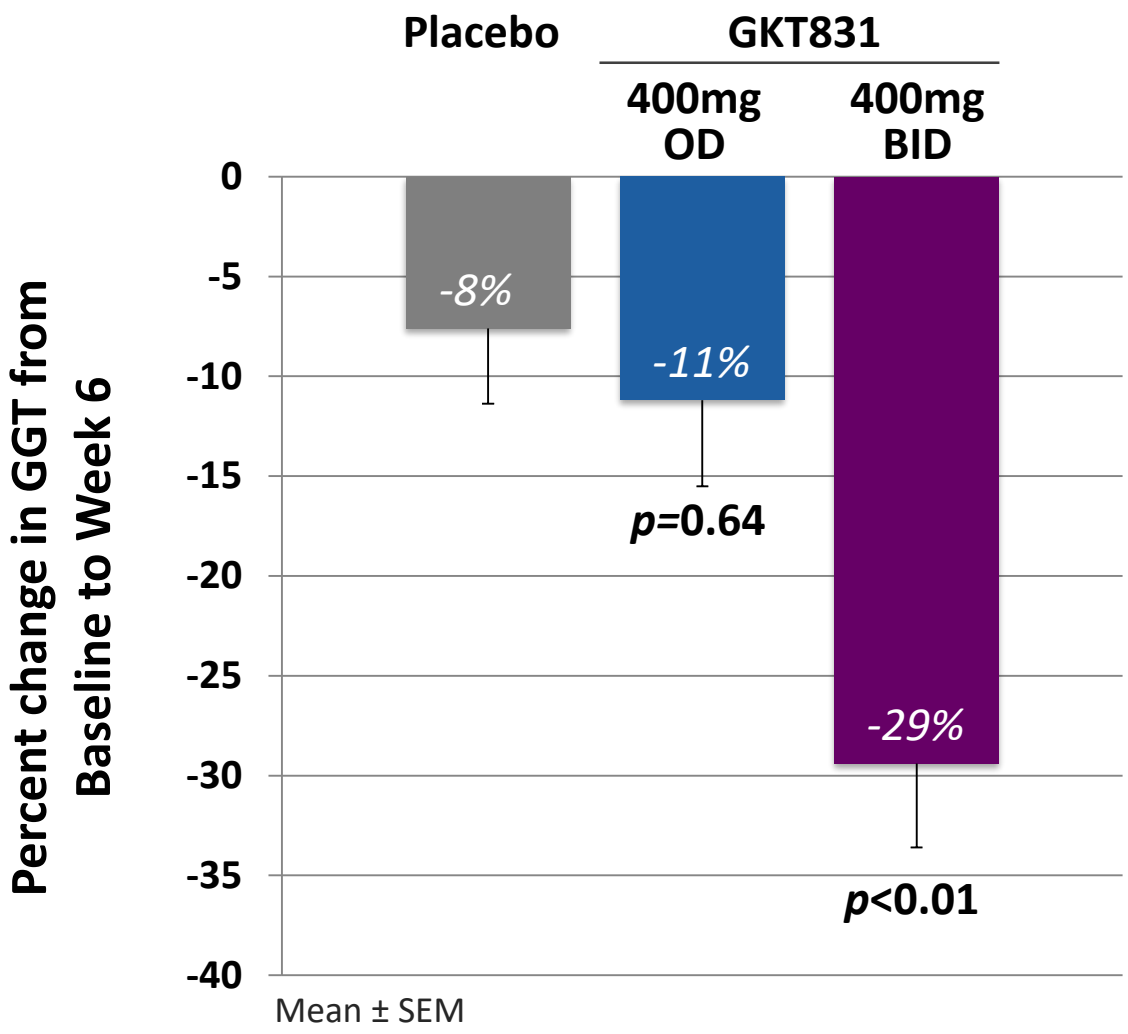
Dose dependent and statistically significant reductions in GGT

GKT831



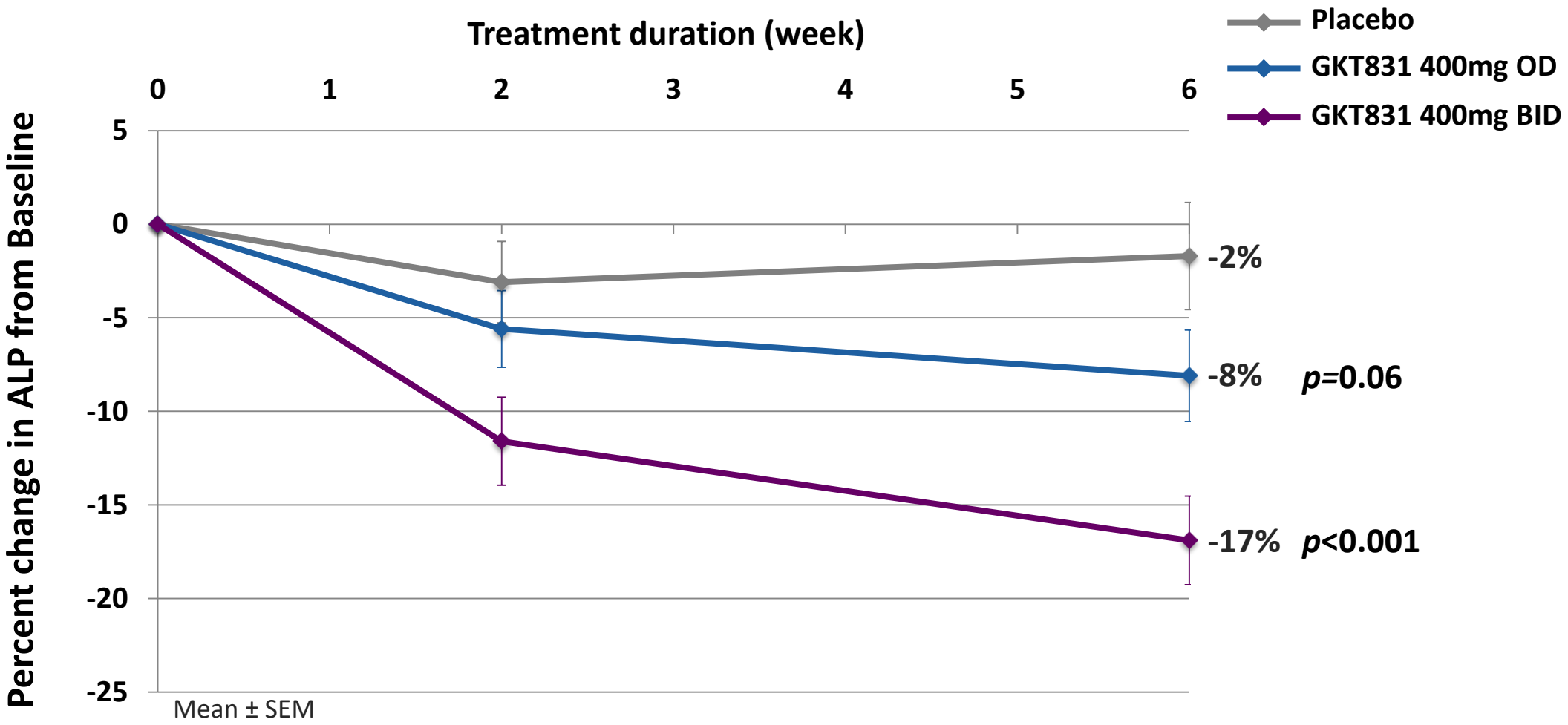
The progressive reductions from baseline to week 2 and to week 6 suggest that further improvements can be achieved with continued treatment

Greater GGT reductions in patients with higher baseline GGT (≥2.5XULN)



These results suggest that GKT831 may also benefit patients with more advanced disease

GKT831 also achieves statistically significant reductions in ALP

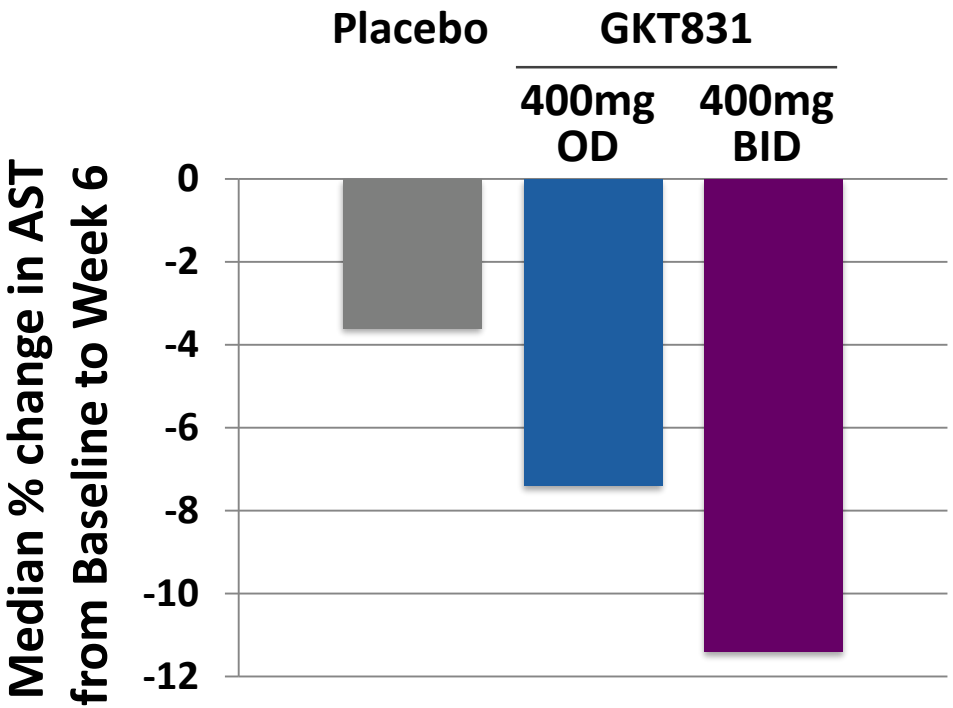


	Placebo	GKT831 400mg OD	GKT831 400mg BID
Proportion of patients with ≥15% reduction in ALP at Week 6	16.1%	25.8%	53.3%

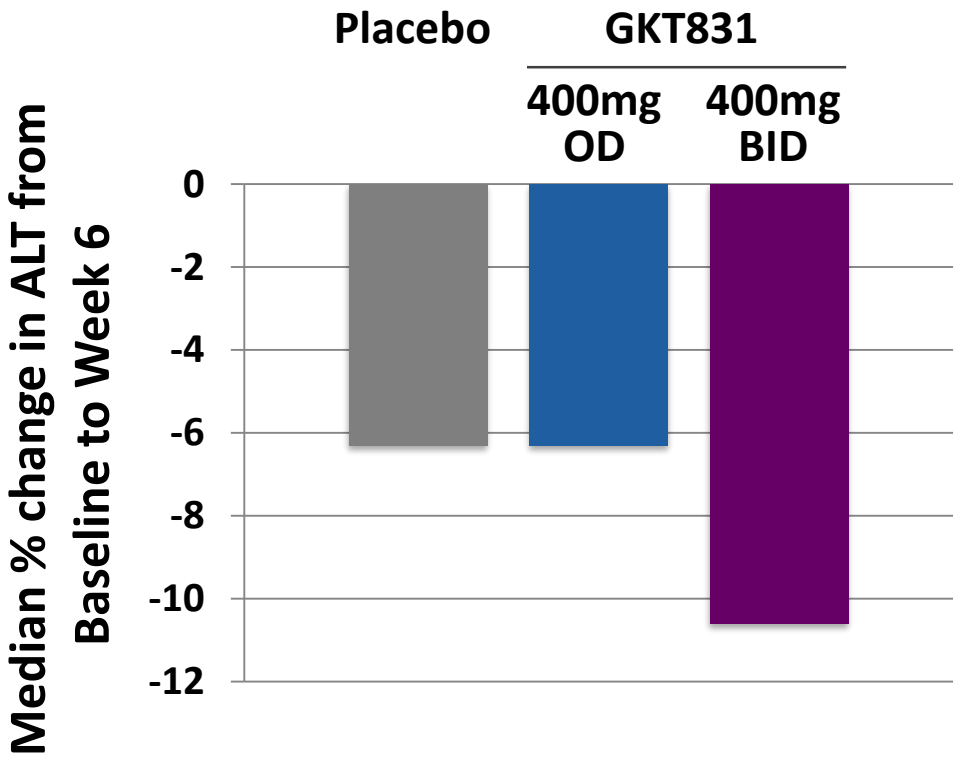
Dose dependent reductions in liver transaminases at week 6

GKT831

Change in AST

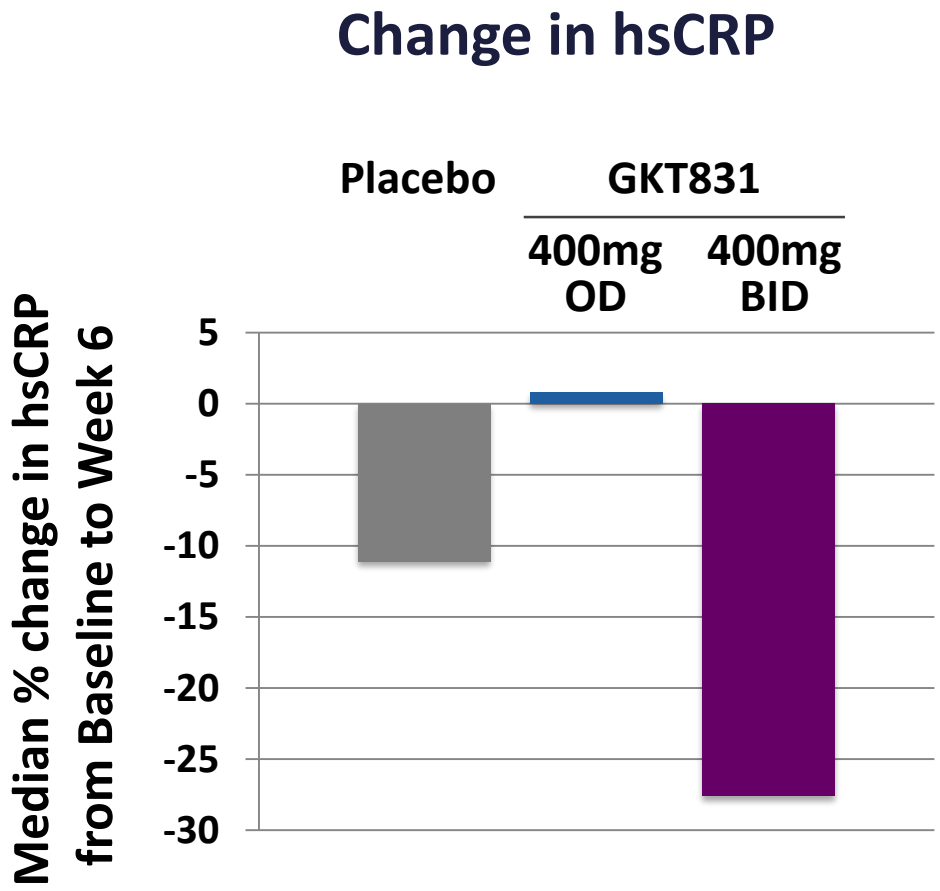


Change in ALT



Although enrolled patients had relatively low levels of liver transaminases, dose dependent reductions were observed

Changes in inflammatory marker hsCRP at week 6



Although enrolled patients had relatively low levels of high sensitivity C-reactive protein, dose dependent reductions were observed

The good safety profile of GKT831 appears to be confirmed in PBC patients

GKT831

- **Positive recommendation at each of the 3 Safety Monitoring board meetings**
  - **Third SMB meeting held October 25 2018 to review data from 110 patients:**
    - **87 completing week 6**
    - **69 completing week 12**
    - **41 completing week 24**
  - **SMB recommendation to continue trial as per protocol**
  - **One SAE to date: grade 1 urinary tract infection. Criterion for seriousness was hospitalization to initiate IV antibiotics. SAE deemed unrelated to study drug by investigator**
  - **One patient drop out due to adverse events: dizziness, abdominal swelling, palpitations, and dyspnea after first dose**
  - **No drop out and no treatment interruption due to pruritus**
  - **This good safety profile is in line with findings in healthy subjects and diabetic patients**
  - **Substantial safety database with over 240 subjects exposed to GKT831 to date**

Conclusions

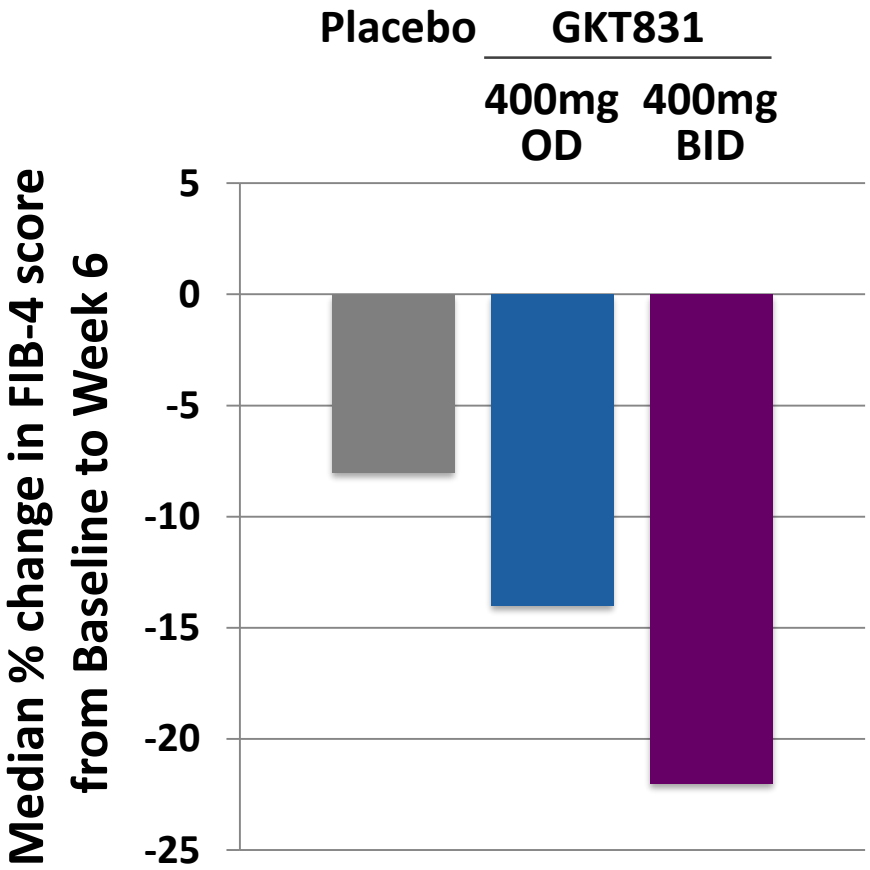
- These results allow us to accelerate & expand our clinical programs with GKT831
  - Prepare Phase 3 PBC program
  - Further investigate options in NASH and PSC
  - Consider acceleration and/or expansion of investigator initiated trials in DKD and IPF
- Continue research work on novel NOX inhibitors

Appendices

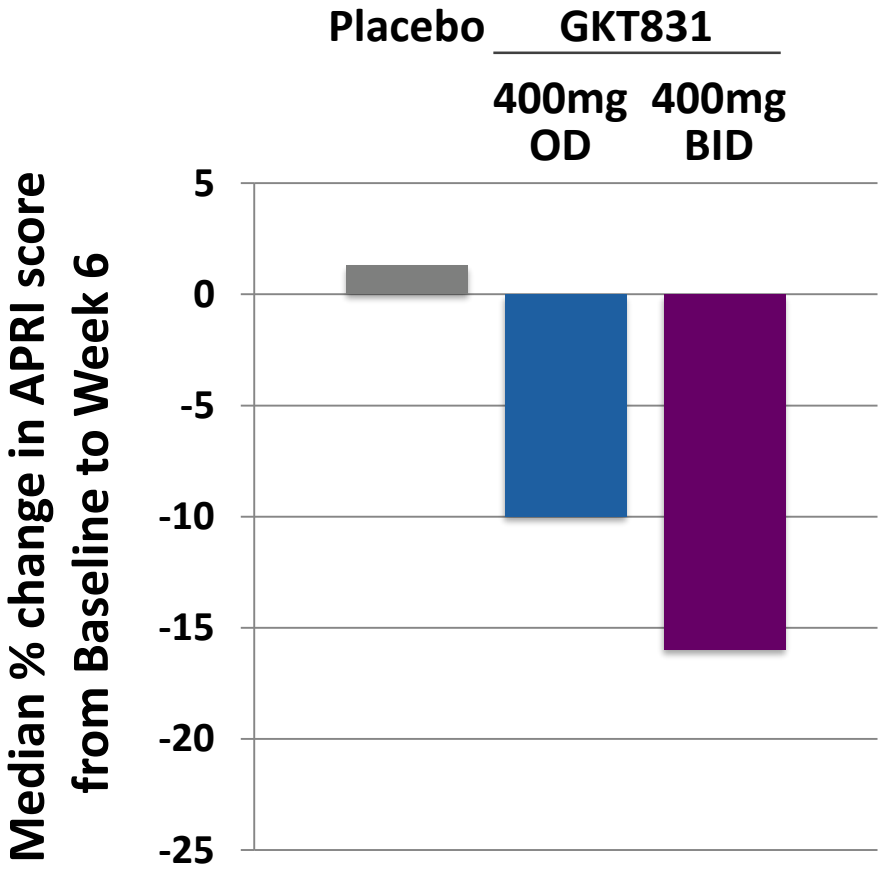
Dose dependent reductions in FIB-4 and APRI

GKT831

FIB-4 score



APRI score



At weeks 12 and 24, assessments of liver fibrosis will include collagen fragments (e.g. Pro-C3), the Enhanced Liver Fibrosis (ELF) score. Transient elastography (i.e. Fibroscan®) will be done at week 24

Pharmacokinetics analysis indicates good exposure and a dose effect

- Drug levels were measured at weeks 2 (n=44), 12 (n=29), and 18 (n=17)
- The main findings are:
  - All patients allocated to GKT831 had detectable drug levels indicating good compliance
  - As expected, patients receiving GKT831 400mg BID had higher plasma levels compared to patients receiving 400mg OD
  - As anticipated in PBC patients with cholestasis and reduced biliary elimination, drug levels were higher than in healthy subjects or diabetic patients