genkyotex
the nox company

Phase 2 trial of GKT831 in patients with primary biliary cholangitis

Top line final results

Euronext: GKTX

May 2 2019

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Discovery platform delivers broad pipeline in diseases with high medical need
GKT831 Phase 2 PBC data support development in multiple fibrotic diseases

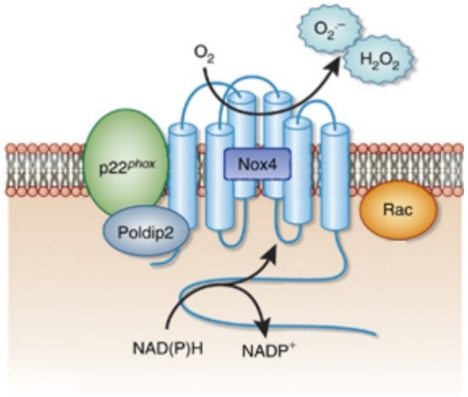
Program	Preclinical	Phase 1	Phase 2	Phase 3
GKT831 - Liver Fibrosis (NOX1/4 inhibitor)	**Primary Biliary Cholangitis (PBC) Top-line results published in May 2019**			
GKT831 - Kidney Fibrosis (NOX1/4 inhibitor)	**Diabetic Kidney Disease (DKD) in T1D** (IIT[1] funded by JDRF[2] - Trial launched in H2 2017)			
GKT831 - Lung Fibrosis (NOX1/4 inhibitor)	**Idiopathic Pulmonary Fibrosis (IPF)** (IIT funded by US NIH[3] - Trial launch H1 2019)			
NOX1 inhibitors	**Preclinical**			
Novel NOX inhibitors	**Discovery**			
Vaxiclase	**Pertussis vaccine** (Licensed to SIIPL)			

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

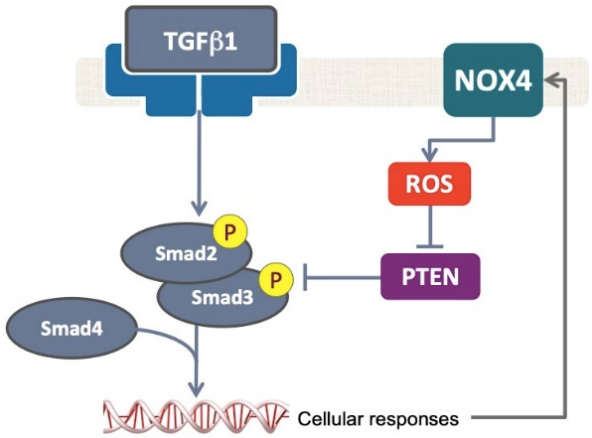
Rationale for NOX1/4 inhibition with GKT831 in inflammatory and fibrotic disorders

- Available PBC therapies target cholestasis by modulating bile acid metabolism (UDCA, fibrates, 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)

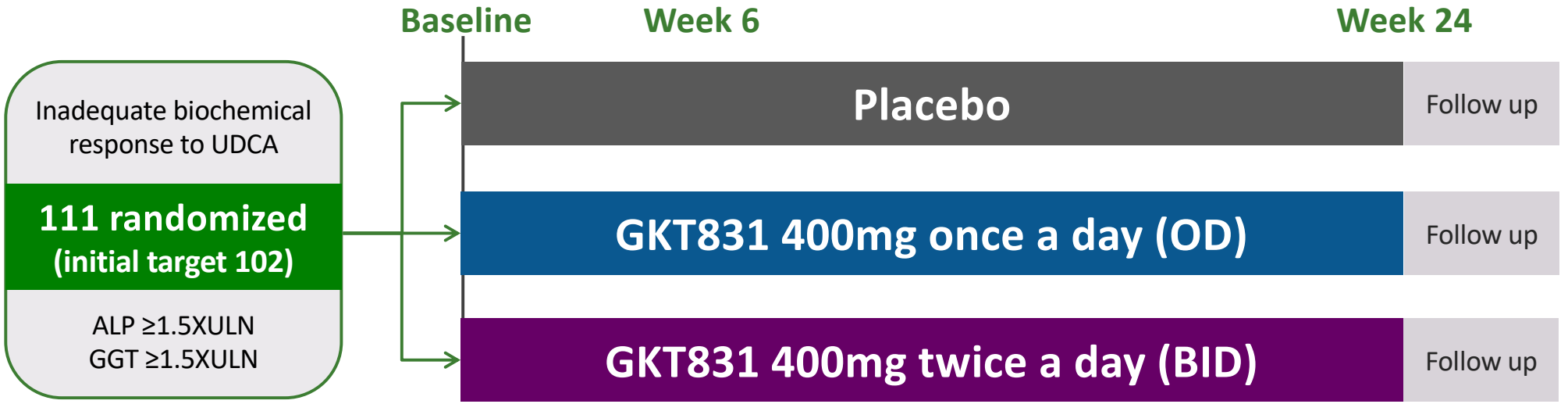
NOX structure



TGFβ signaling



GKT831 in PBC: Study design



- Primary efficacy endpoint: change in GGT at week 24
- Key secondary endpoints: changes in ALP, liver stiffness (Fibroscan®) & QoL
- Statistical significance for all endpoints at week 24 was set at p<0.023, according to the Hochberg adjustment method for multiple analyses
- **Key eligibility criteria**
  - ALP ≥1.5XULN & GGT ≥1.5XULN (stratification according to baseline GGT (> or < 2.5XULN))
  - On UDCA for ≥ 6 months & stable dose for ≥ 3 months – stable UDCA dose continued throughout 24-week treatment period
  - Exclusion of history of cirrhosis with complications or current MELD score ≥ 15
  - ALT > 3XULN or total bilirubin > 1XULN
  - Prohibited medications: fibrates and obeticholic acid (12-week wash out)

Phase 2 trial of GKT831 in PBC: Baseline patient characteristics

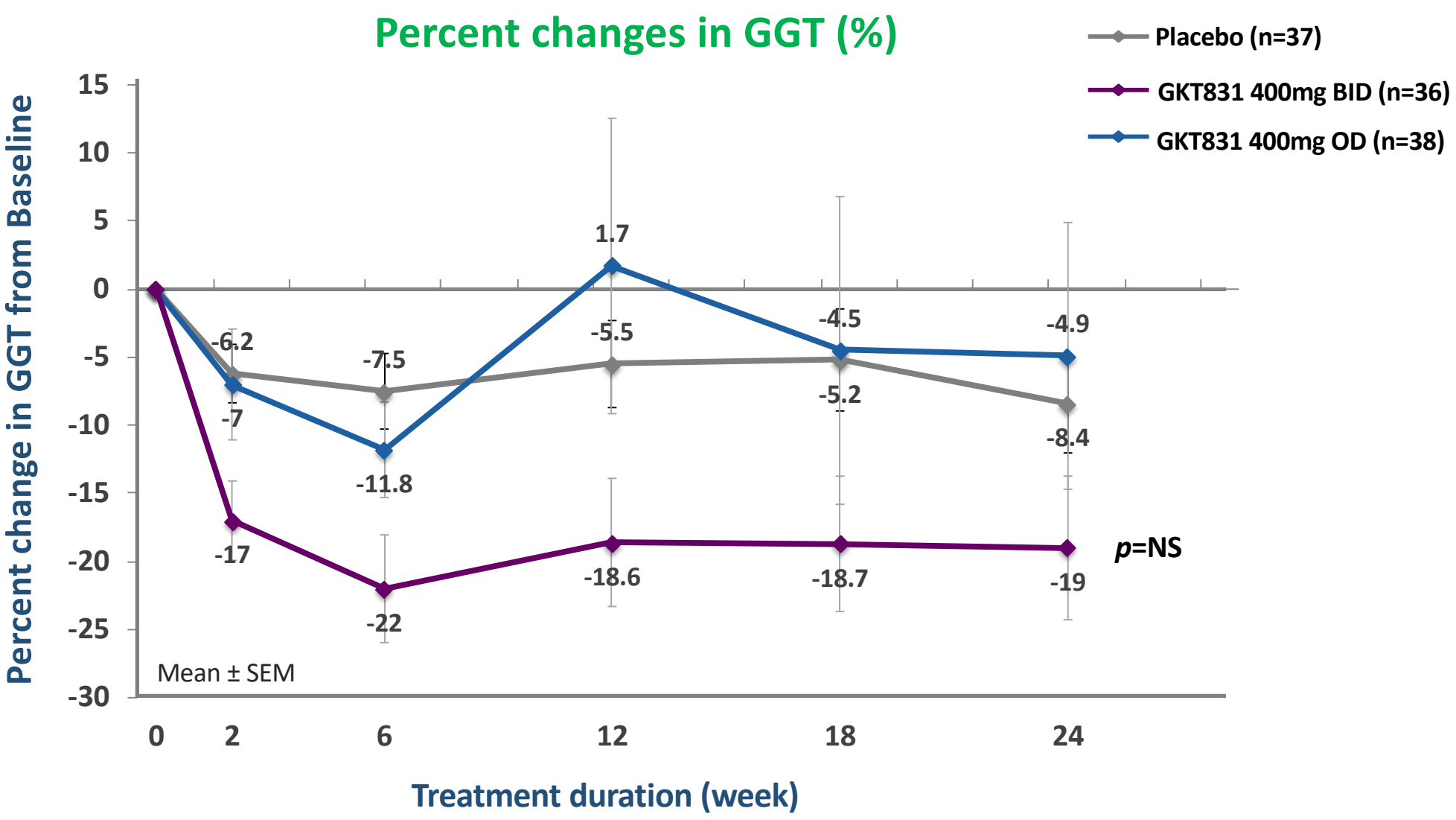
GKT831

Baseline patient characteristics	Placebo	GKT831 400mg OD	GKT831 400mg BID	ALL
N	37	38	36	111
Age (years)	56 (9)	57 (9)	56 (9)	56 (9)
Females (%)	95	79	94	89
Body weight (kg)	73 (15)	73 (13)	70 (16)	72 (15)
UDCA dose (mg/kg)	13.0 (4.1)	15.9 (5.6)	16.4 (10.4)	15.1 (7.3)
Liver stiffness measurement (kPa)	10.7 (7.0)	12.5 (13.7)	8.3 (3.7)	10.7 (9.5)
GGT (IU/L)	227 (200)	242 (167)	242 (181)	237 (182)
ALP (IU/L)	300 (141)	302 (121)	346 (164)	315 (143)
ALT (IU/L)	43 (16)	45 (22)	56 (35)	48 (26)
AST (IU/L)	43 (17)	44 (21)	50 (31)	46 (24)
Total bilirubin (umol/L)	10.7 (4.3)	11.1 (4.6)	10.4 (4.6)	10.7 (4.5)
hsCRP (mg/L)	4.8 (4.6)	5.8 (5.2)	5.1 (5.1)	5.3 (4.9)
Values expressed as mean (±SD)				[1] Once daily; [2] Twice daily

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

GGT reduction stabilizes at around 20% over the treatment period

GKT831

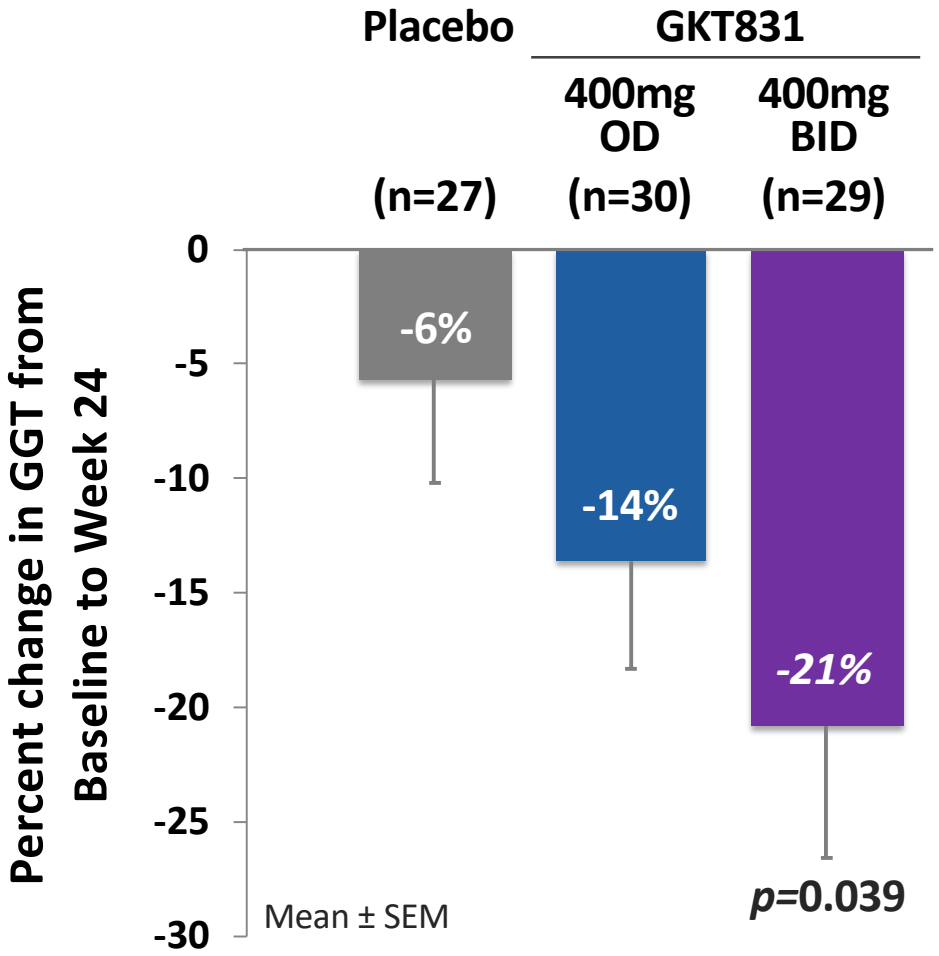


GGT maintained effect over treatment period but lost at week 24 statistical significance observed at interim analysis

Robust GGT reductions in patients with high baseline GGT (≥2.5XULN, n=86)

GKT831

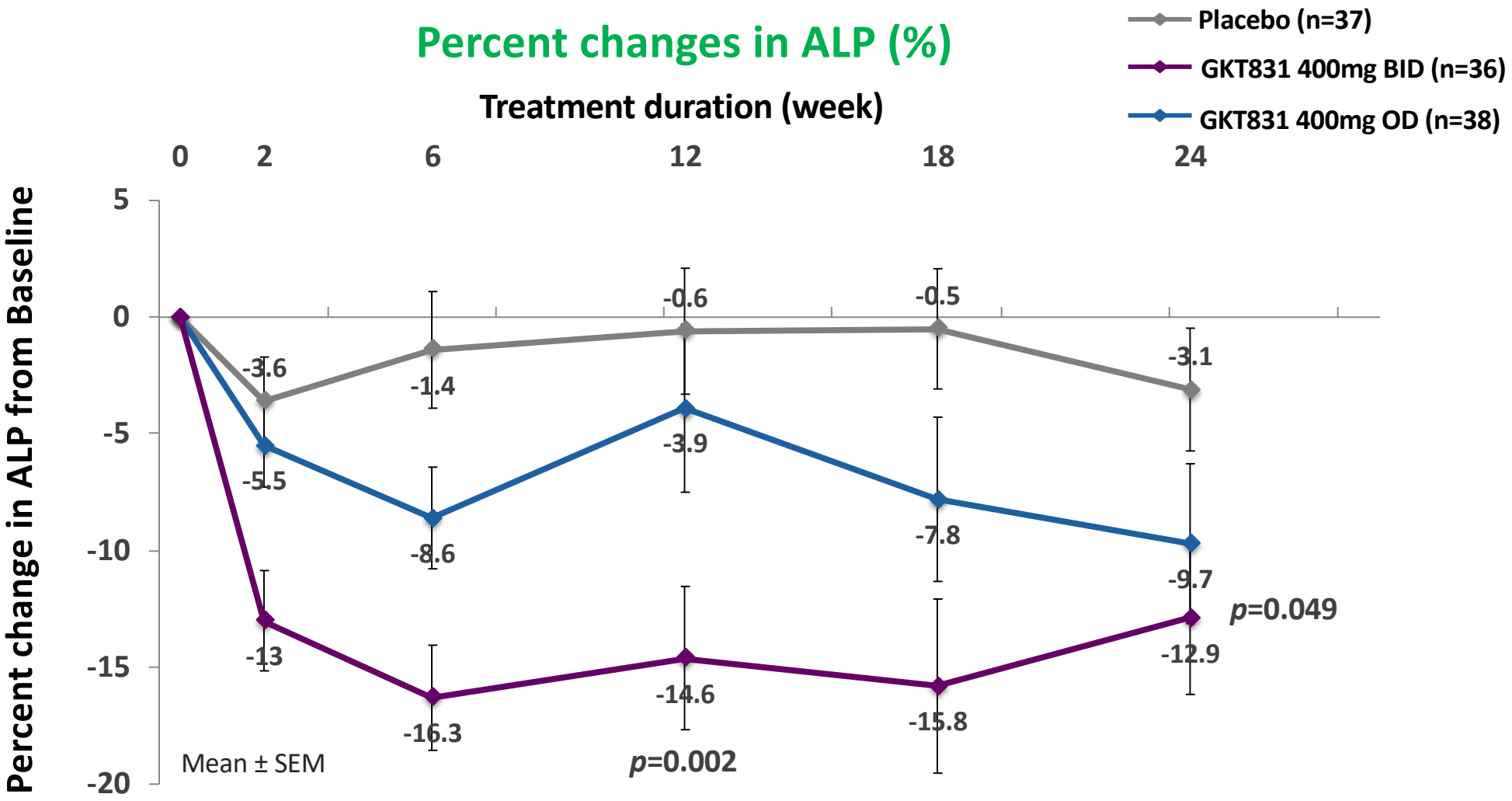
Percent changes in GGT (%)



These results suggest that GKT831 offers superior benefit to patients with more active disease (higher baseline GGT)

Overall treatment effect achieved statistical significance on ALP (p=0.002)

GKT831



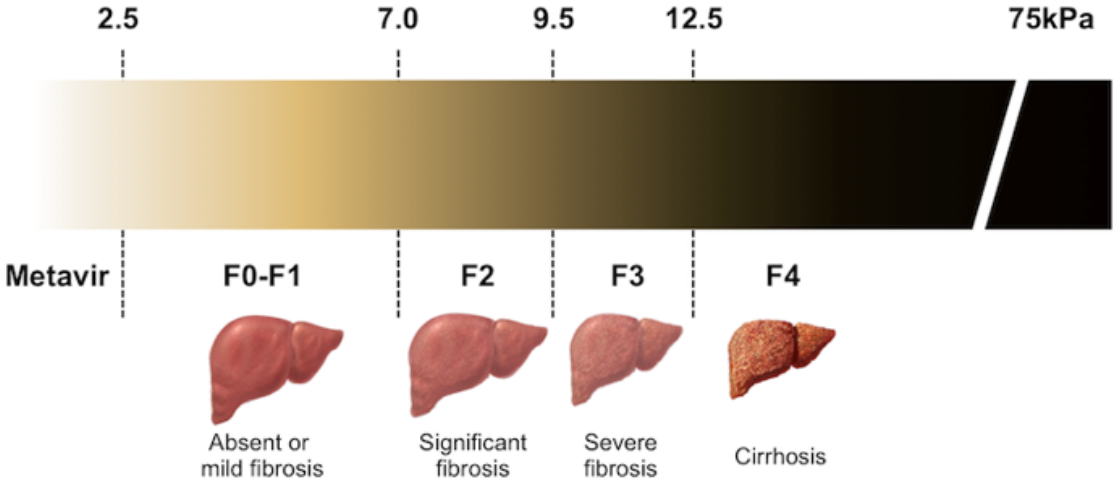
	Placebo	GKT831 400mg OD	GKT831 400mg BID
Response rate for composite endpoint*	5%	18%	25%

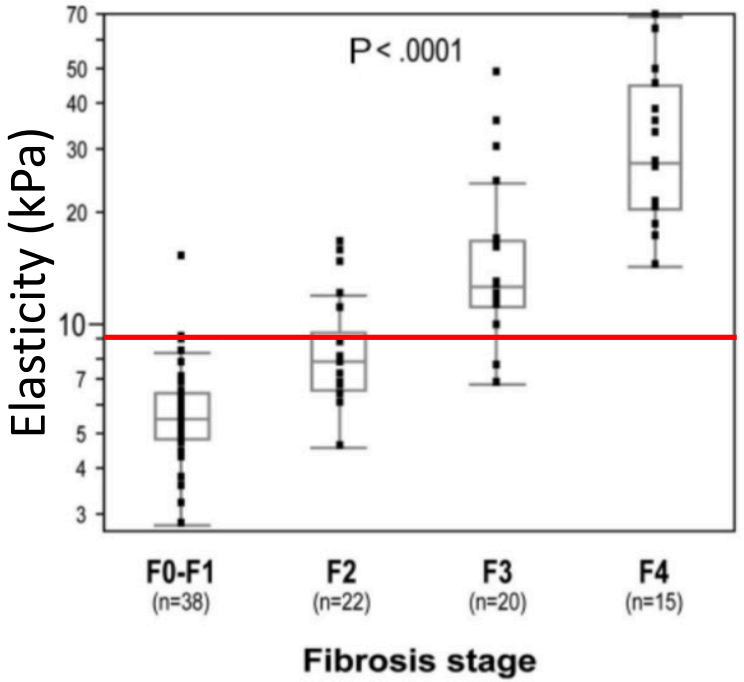
[1] ALP<1.67XULN, ALP reduction≥15%, TB <ULN

Non-invasive assessment of GKT831 effect on fibrosis with Fibroscan®
In PBC, liver stiffness > 9.6 kPa corresponds to advanced liver fibrosis of ≥F3

GKT831

Liver stiffness is an indicator of liver inflammation (edema), cholestasis and fibrosis





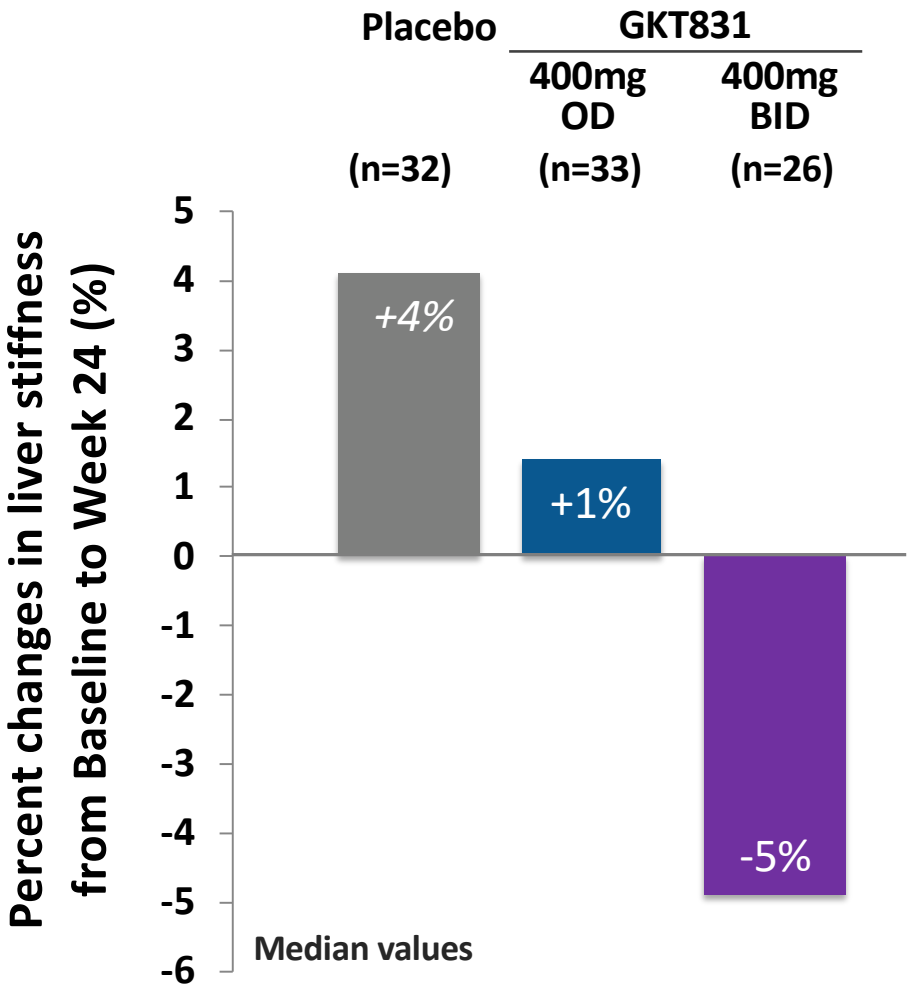
- In multiple liver diseases including PBC, NASH and PSC, liver stiffness correlates with the histologic liver fibrosis stage (F0 to F4)[1]
- In PSC, elevated liver stiffness is associated with adverse disease outcomes, including liver transplant, hepatic complication and death[1]
- Our predefined value of 9.6 kPa was pre-defined in our statistical plan and has been validated and used in previous trials[1]

[1]Corpechot C et al. Baseline Values and Changes in Liver Stiffness Measured by Transient Elastography Are Associated With Severity of Fibrosis and Outcomes of Patients With Primary Sclerosing Cholangitis. Gastroenterology 2014;146:970–979. Corpechot C et al. Assessment of Biliary Fibrosis by Transient Elastography in Patients With PBC and PSC. Hepatology 2006;43:1118-1124. Park CC et al. Magnetic Resonance Elastography vs Transient Elastography in Detection of Fibrosis and Noninvasive Measurement of Steatosis in Patients with Biopsy-proven Nonalcoholic Fatty Liver Disease. Gastroenterology 2017; 152(3): 598–607.

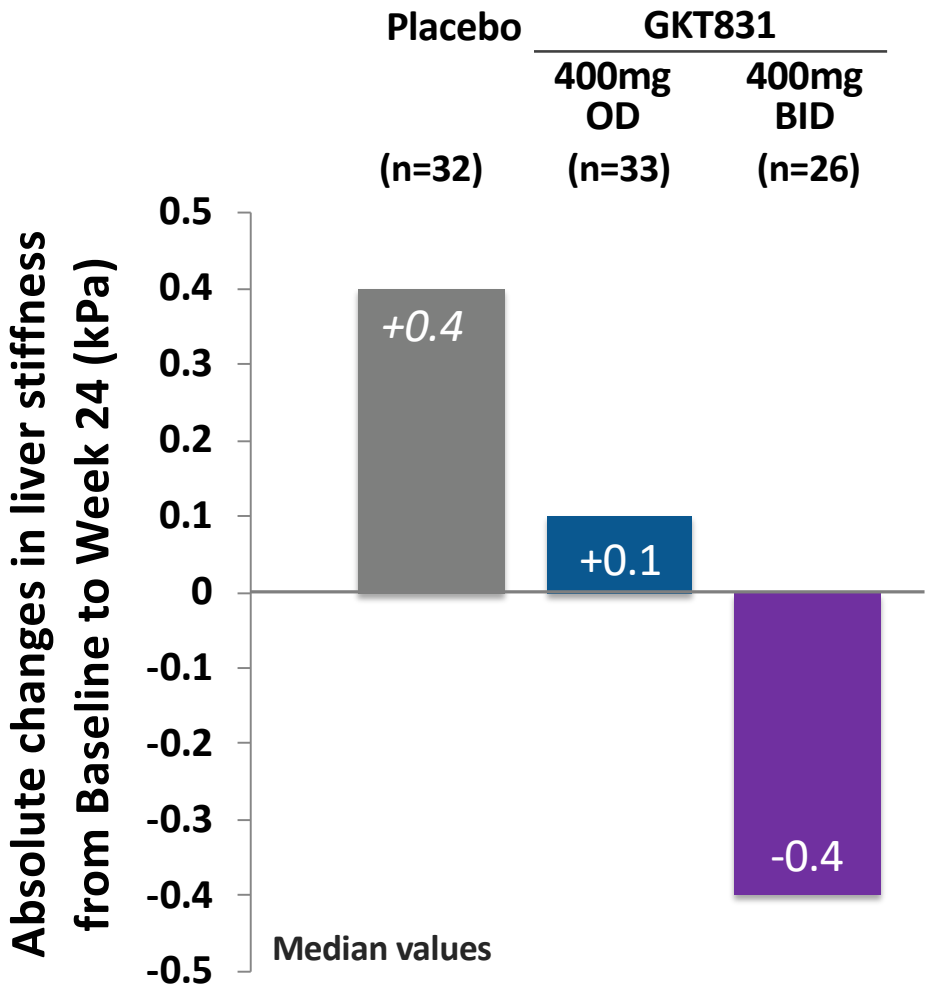
GKT831 achieved a positive trend in reduction liver stiffness in full population

GKT831

Percent changes in liver stiffness (%)



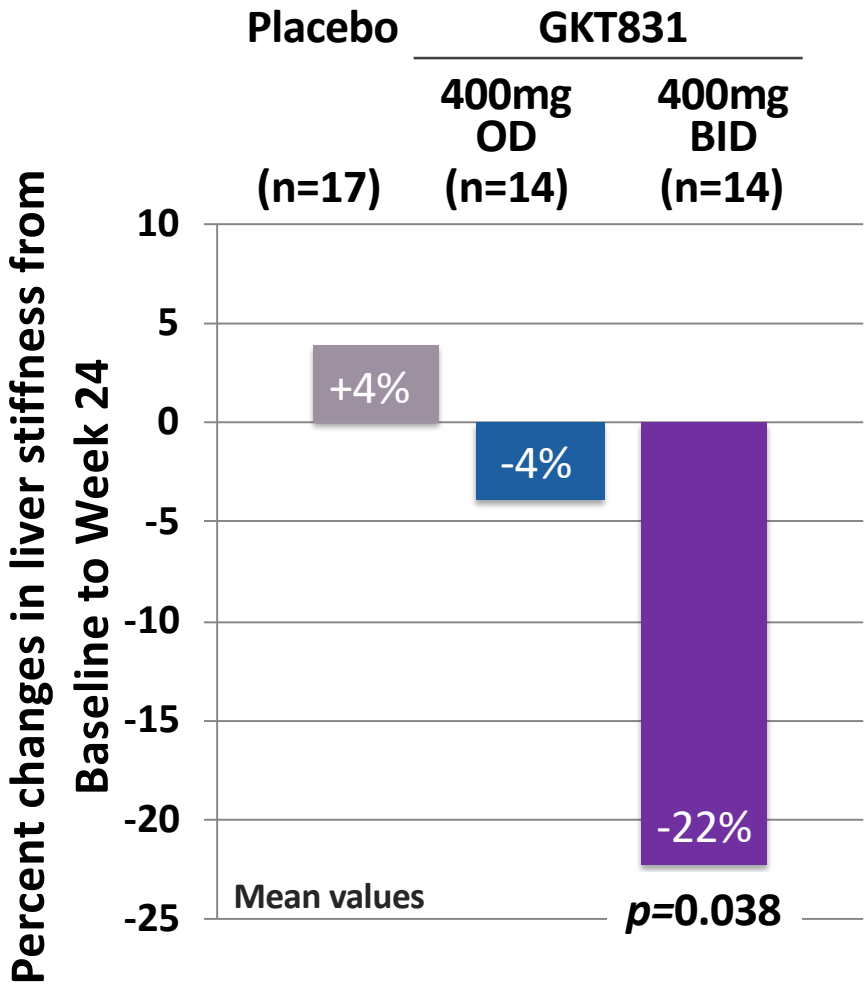
Absolute changes in liver stiffness (kPa)



Trend seems to be dose dependent, baseline values are 10.7 for placebo, 12.5 for 400mg OD and 8.3 kPa for 400mg BID

GKT831 achieved a clinically meaningful 22% reduction on liver stiffness in patients with estimated fibrosis of F3 or greater

GKT831



GKT831 achieved a clinically meaningful reduction of liver stiffness in just 24 weeks of treatment

Quality of Life trended positively in key parameters such as fatigue, emotional and social domains

GKT831

Percent changes in QoL domain scores	Placebo	GKT831 400mg OD	GKT831 400mg BID
Symptoms	1.1	1.1	-3.7
Itch (Pruritus)	-6.8	-11.4	-9.5
Emotional	8.7	4.9	-16.9
Fatigue	2.4	0.3	-9.9
Social	9.3	8.1	-7.7
Cognitive	5.2	16	-1.9

Percent changes in pruritus VAS	Placebo	GKT831 400mg OD	GKT831 400mg BID
Pruritus VAS	27.3	-36.9	-0.3

Values expressed as means

[1] Once daily; [2] Twice daily

GKT831 400mg BID improved quality of life across multiple domains important to PBC patients

Conclusions: results support advancing GKT831 into late stage clinical trials

GKT831

- The top-line data highlight the potential of GKT831 as an anti-fibrotic therapy in the liver and other organs
  - 22% reduction in liver stiffness in PBC patients with liver fibrosis, compared to a 4% increase for placebo, supports anti-fibrotic mechanism
  - Statistically significant reduction in alkaline phosphatase (ALP) for overall treatment effect
  - Further analyses are ongoing and the full results will be submitted for presentation at an upcoming international liver conference
- Company planning to advance GKT831 into late stage clinical trials in PBC and other fibrotic liver diseases, like NASH and PSC
- JDRF funded Phase 2 diabetic kidney disease (DKD) trial ongoing
- NIH funded Phase 2 idiopathic pulmonary fibrosis (IPF) trial to be launched in the next months

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Top line results

GKT831 Phase 2 trial in primary biliary cholangitis

Q&A

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