Results of ITCH, A Multi-center Randomized Double-blind Placebo-controlled Trial of Maralixibat, an Intestinal Bile Salt Transport Inhibitor, for Pruritus in Alagille Syndrome

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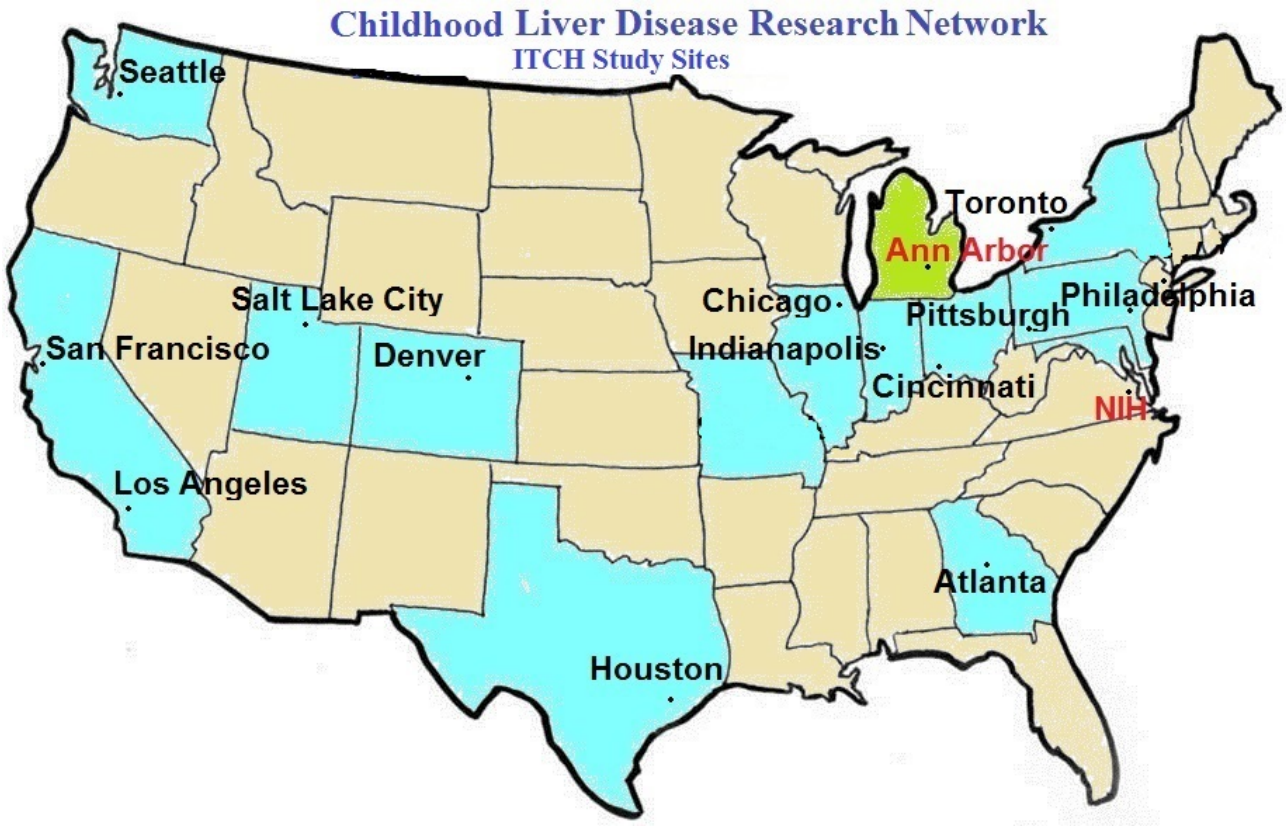
Supported by

NIH National Institute of Diabetes and Digestive and Kidney Diseases

ChiLDReN Childhood Liver Disease Research Network

Sites

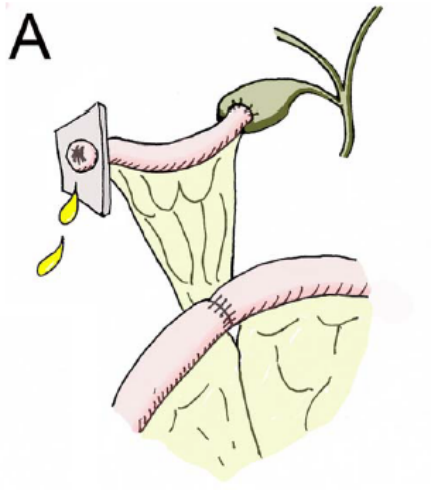

Childhood Liver Disease Research Network
ITCH Study Sites
Seattle
Toronto
Ann Arbor
Salt Lake City
Chicago
Philadelphia
Pittsburgh
San Francisco
Denver
Indianapolis
Cincinnati
NIH
Los Angeles
Atlanta
Houston

Grant Support

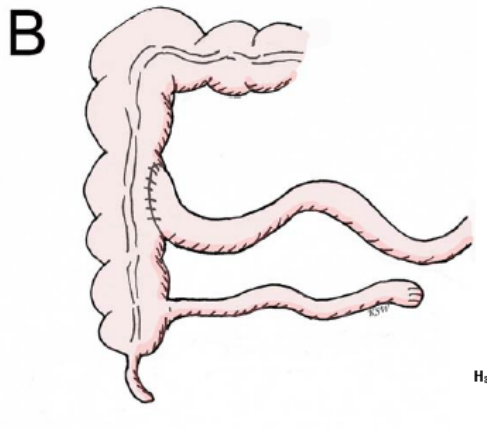
- Individual NIH NIDDK U01 grants to center principal investigators
- Site-specific NIH CTSA grants
- Cooperative Research and Development Agreement between the NIDDK and Lumena and Shire (which acquired Lumena)

Background

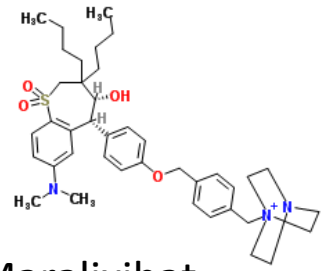
- Alagille Syndrome - systemic genetic disorder including bile duct paucity with severe cholestasis and pruritus
  - **Emerick** *Hepatology* 1999;29;822
- Pruritus refractory to medical therapy
- Surgical interruption of enterohepatic circulation can be effective
  - **Wang** *Hepatology* 2017;65:1645
- Homeostasis gone awry
  - **Hofmann** *Gut* 2003;52:1239
- ASBTi may mimic the effect of surgery
  - **Neimark** *JPGN* 2003;36:296



Biliary diversion



Ileal Exclusion



Maralixibat

Hypothesis

Interruption of the enterohepatic circulation of **bile acids,** in particular, mediates the effect of surgery

Therefore pharmacologic inhibition of ileal bile acid reclamation using the ASBTi, Maralixibat, would mimic the effect of surgery in Alagille Syndrome and ameliorate pruritus

Study Aims

- Amongst pediatric participants with Alagille Syndrome:
  - To evaluate the effect of Maralixibat versus placebo on pruritus as measured by the Itch Reported Outcome (ItchRO) instrument
  - To evaluate the safety and tolerability of Maralixibat
  - To evaluate the effect of Maralixibat versus placebo on serum bile acids
  - To explore the effect of Maralixibat versus placebo on other biochemical markers of cholestasis and liver disease

NCT01714726

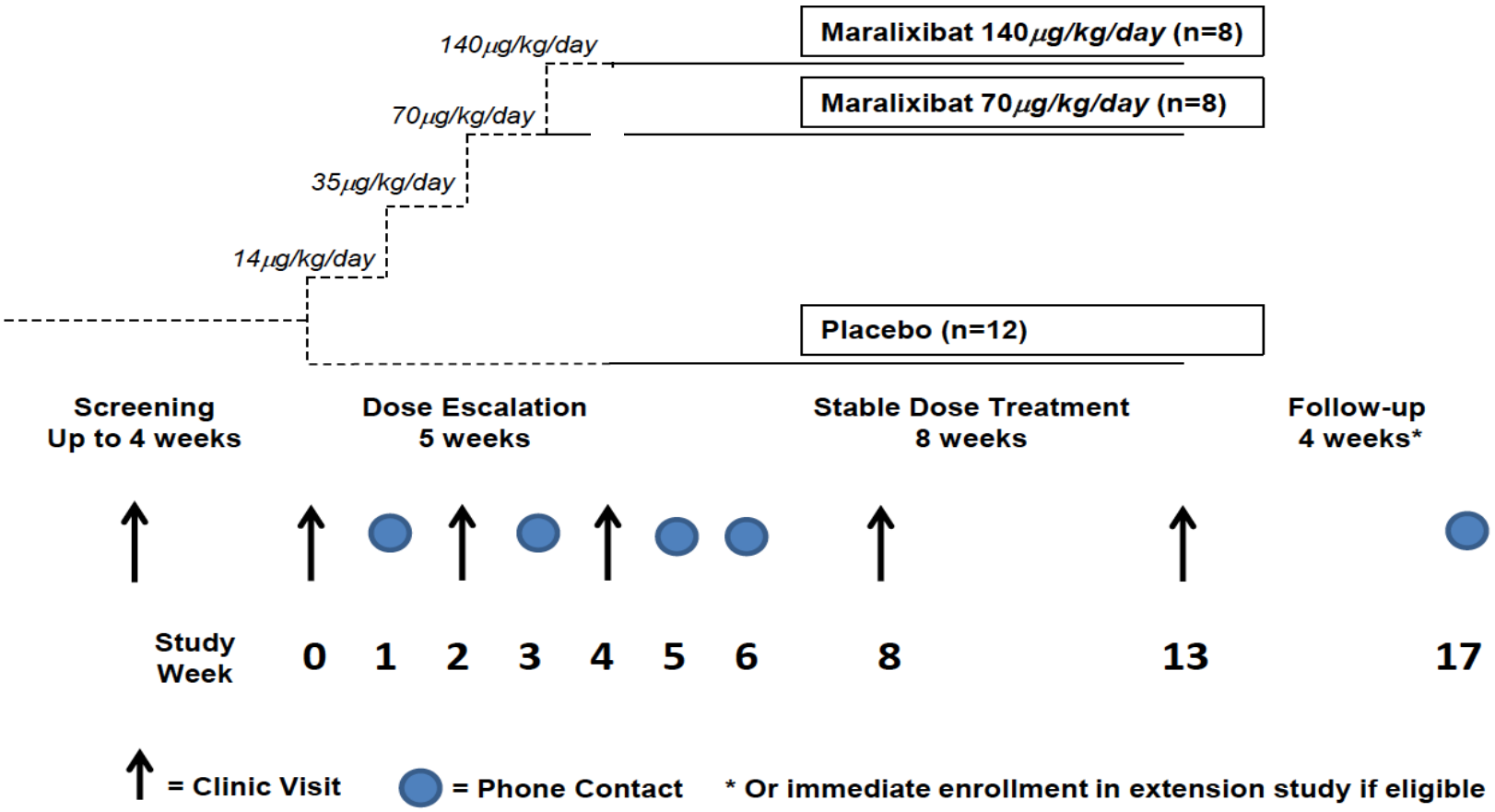
Major Entry Criteria

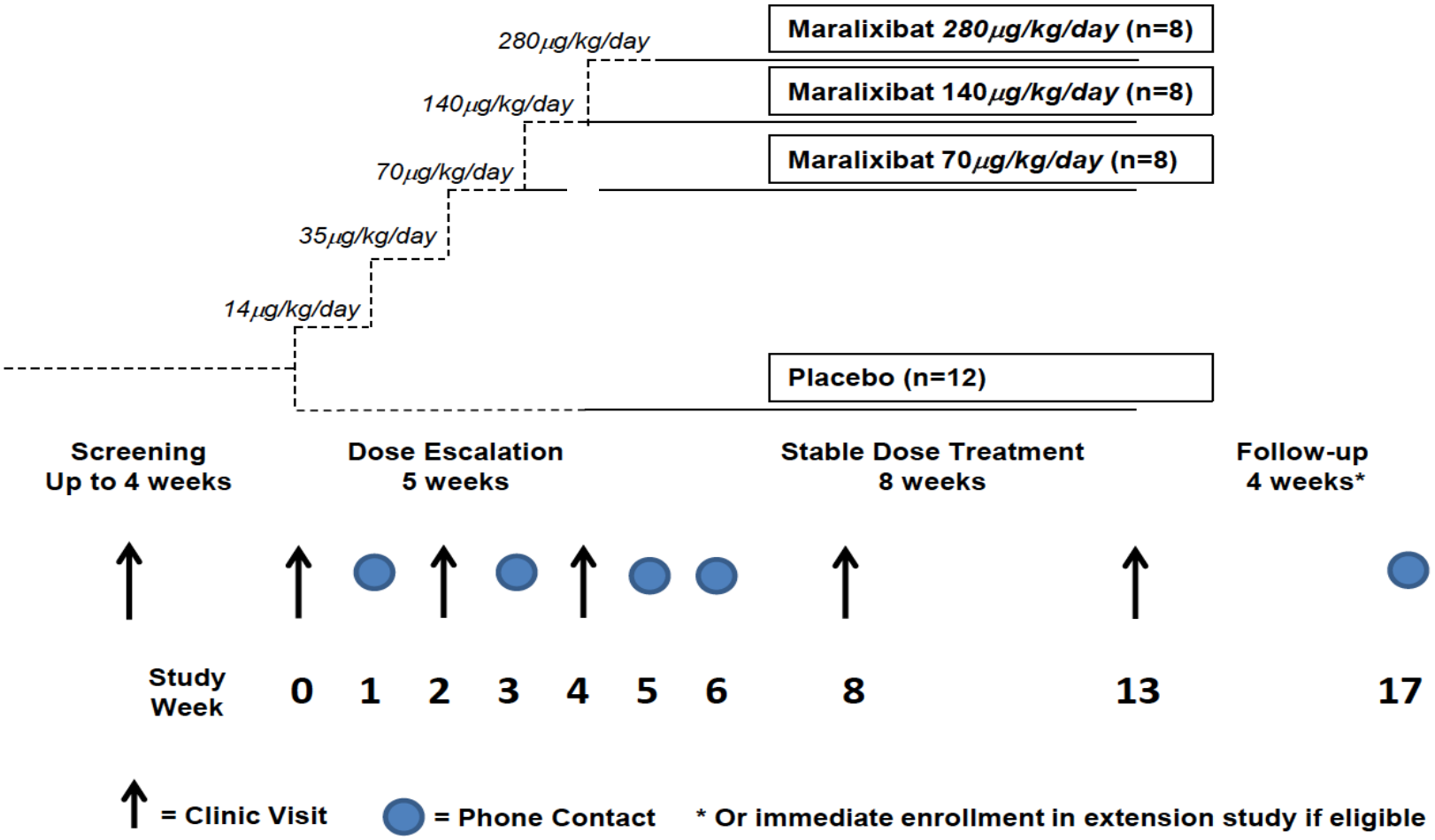
Inclusion

- Alagille Syndrome
- 1 to 18 years of age
- Cholestasis
- ItchRO (Obs) $\geq$ 2
- Consent/assent

Exclusion

- Significant chronic diarrhea
- Surgical interruption EHC
- Liver transplant
- ALT > 15x ULN
- Decompensated cirrhosis
- Bile acid or lipid resin
- Sodium phenylbutyrate


140μg/kg/day
Maralixibat 140μg/kg/day (n=8)
70μg/kg/day
Maralixibat 70μg/kg/day (n=8)
35μg/kg/day
14μg/kg/day
Placebo (n=12)
Screening
Up to 4 weeks
Dose Escalation
5 weeks
Stable Dose Treatment
8 weeks
Follow-up
4 weeks*
Study
Week
0
1
2
3
4
5
6
8
13
17
= Clinic Visit
= Phone Contact
* Or immediate enrollment in extension study if eligible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Study Week
0 1 2 3 4 5 6 8 13 17
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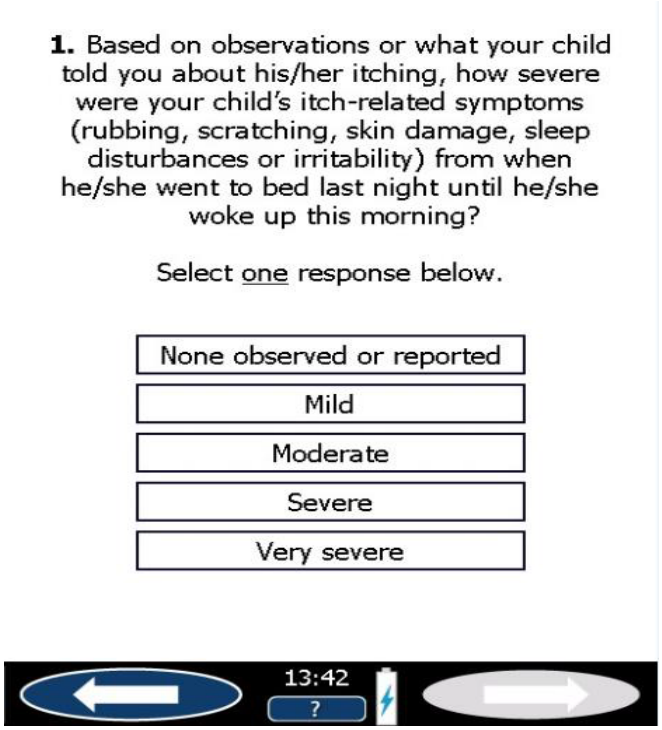
Assessment of Pruritus

ItchRO™



Kamath B, *Patient* 2017 (in press)

Clinician Scratch Scale (CSS)

Score	Description
0	None
1	Rubbing or mild scratching when undistracted
2	Active scratching without evident skin abrasions
3	Abrasions evident
4	Cutaneous mutilation, hemorrhage and scarring evident

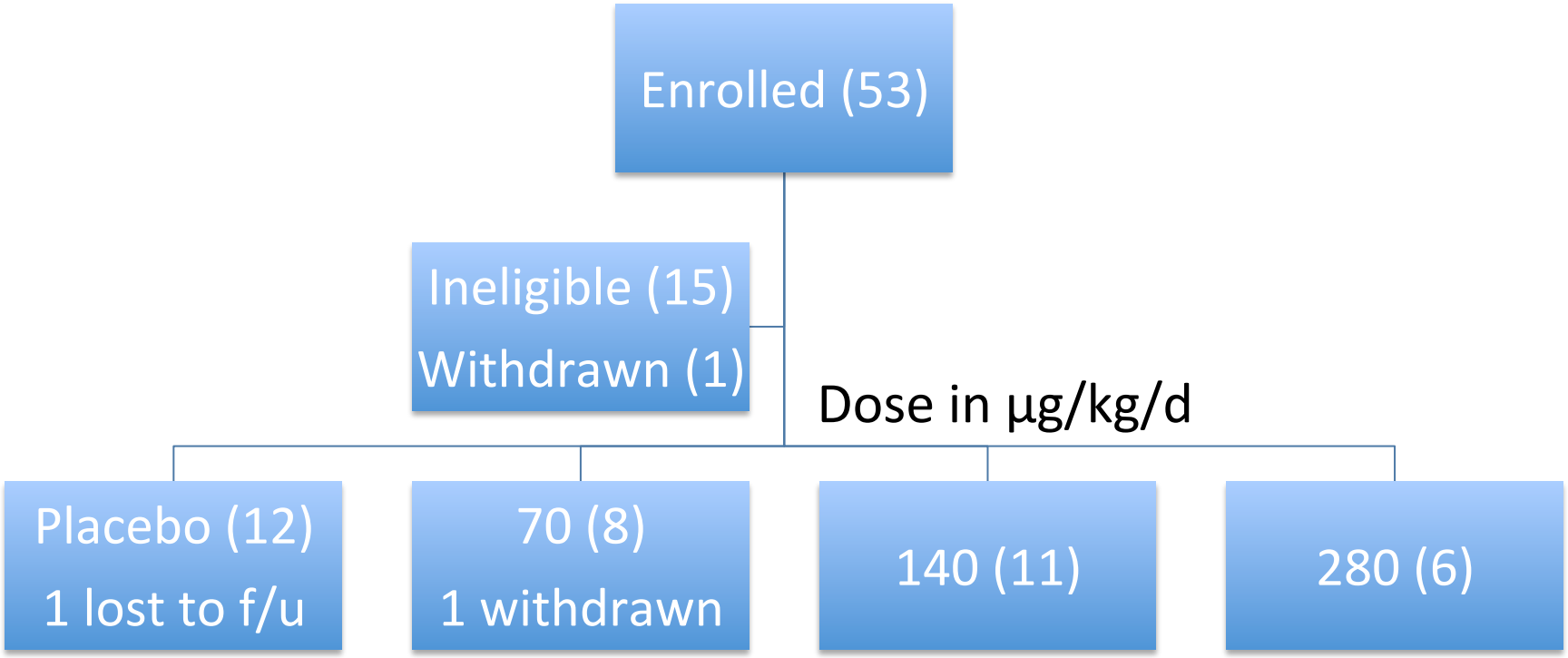
Whitington P, *Gastroenterology* 1988;95:130

ITCH End Points

- Primary: Change from baseline to week 13 in ItchRO(Obs)
- Secondary: Changes from baseline to week 13 in serum bile acids and liver biochemistries
- Exploratory: Changes from baseline over time in
  - Primary and secondary outcomes
  - Clinical Scratch Score (CSS)
- Safety

Statistical Analysis Plan

- For primary and key secondary end points,
  - **FIRST** compared two highest tolerated doses of Maralixibat vs placebo
  - Compared pooled Maralixibat doses vs placebo
  - Compared each Maralixibat dose group vs placebo
- Change from baseline to week 13 or end of treatment using ANCOVA (controlling for baseline)
- Modified ITT population (randomized, at least 1 treatment, at least 1 post-baseline efficacy assessment)


Enrolled (53)
Ineligible (15)
Withdrawn (1)
Dose in µg/kg/d
Placebo (12)
1 lost to f/u
70 (8)
1 withdrawn
140 (11)
280 (6)

Participant Characteristics

Demographics

Parameter	Maralixibat (N = 25)	Placebo (N = 12)
Age (yrs)	7.5	5.5
< 5 yrs	32%	50%
Female	40%	50%
Hispanic	20%	17%
White	80%	75%
Ht (z-score)	-1.71	-1.43
Wt (z-score)	-1.35	-1.21
Antipruritic	100%	100%

Laboratories

Parameter	Maralixibat (N = 25)	Placebo (N=12)
ItchRO (obs)	3.0	2.8
CSS	3.0	2.9
Serum bile acid (µM)	222	205
TB (mg/dL)	4.7	6.4
ALT (IU/L)	145	188
AST (IU/L)	138	172
GGT (IU/L)	531	419
Cholesterol (mg/dL)	372	476

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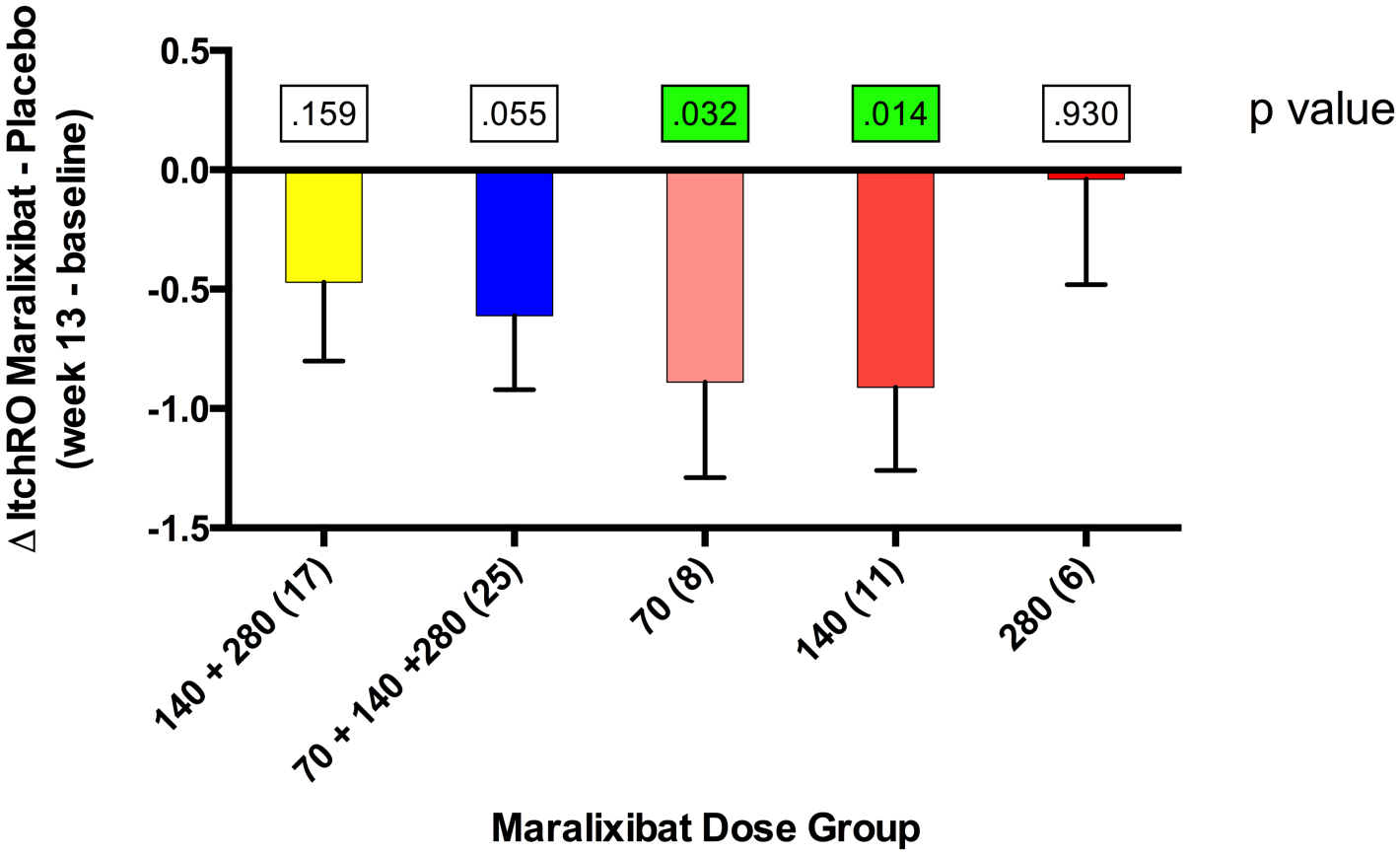
Primary End Point – ItchRO (Obs)



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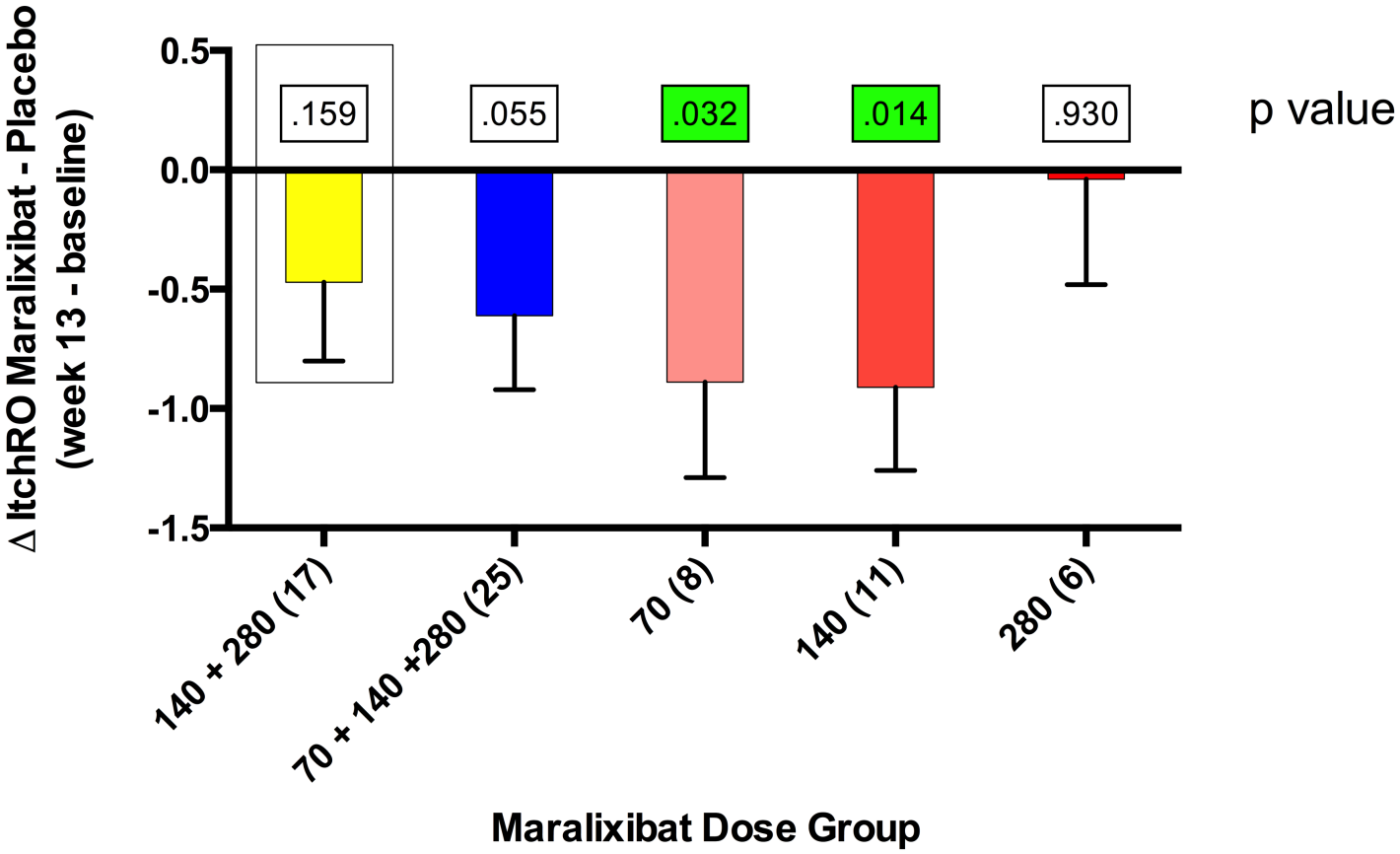

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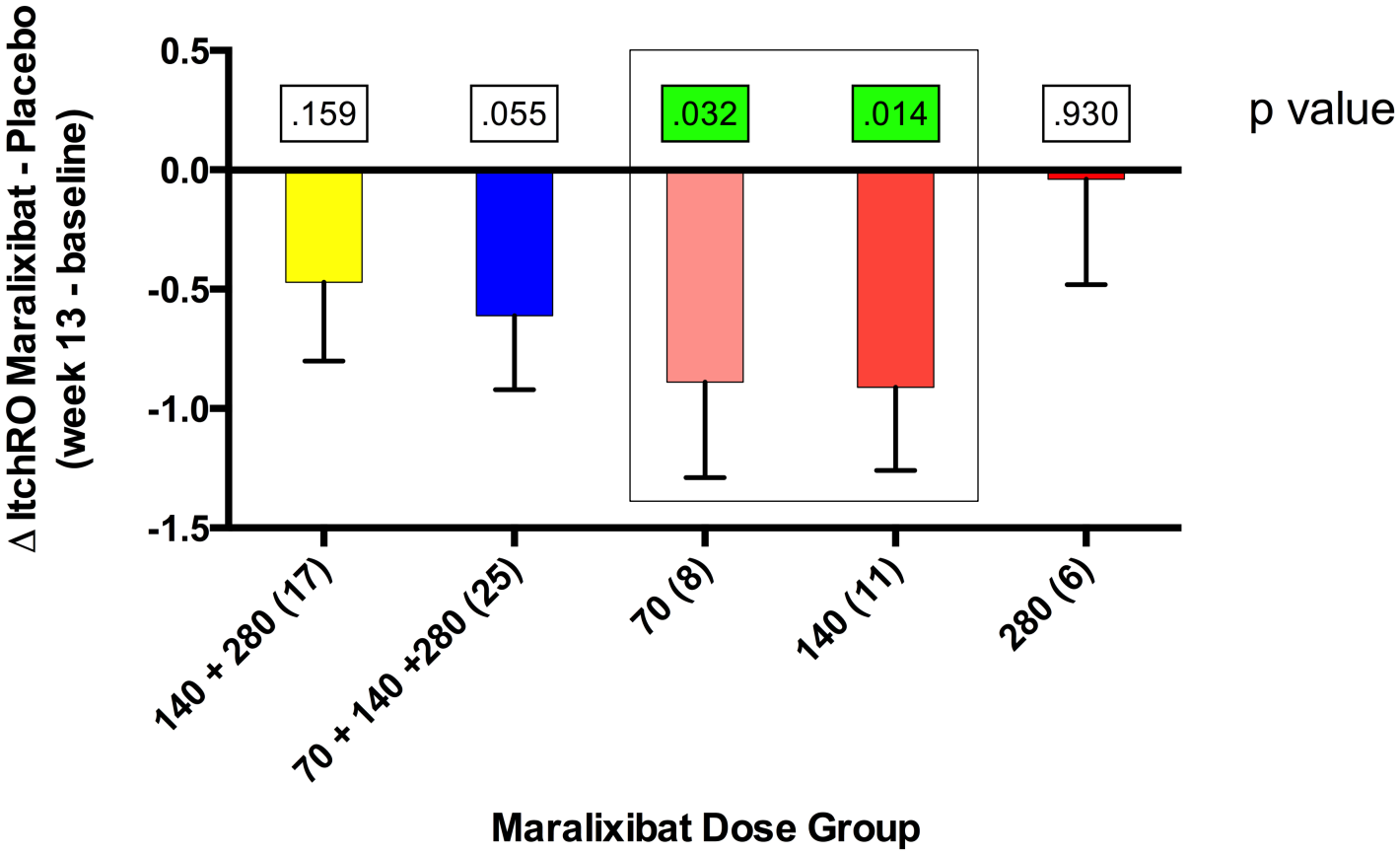

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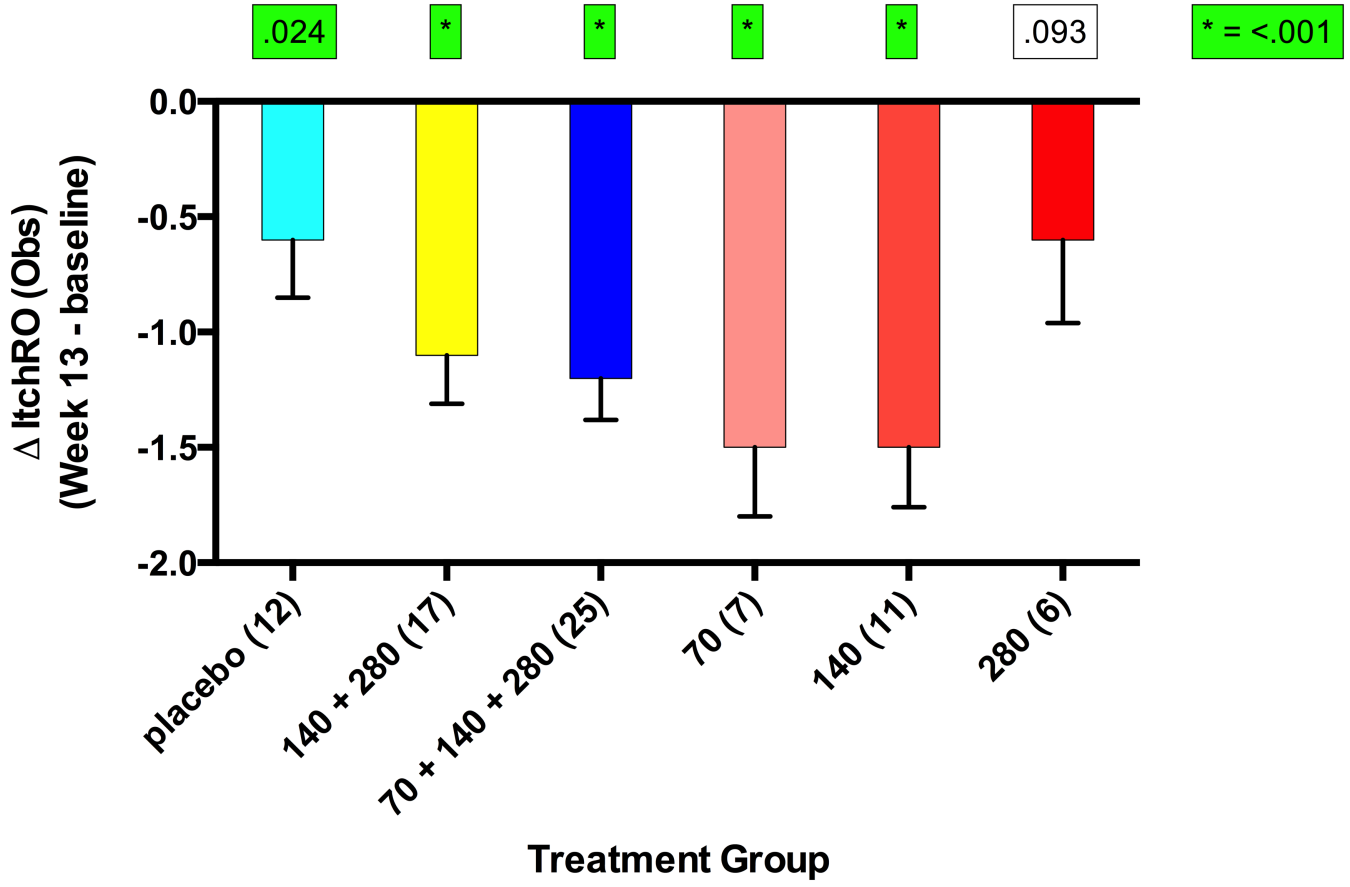
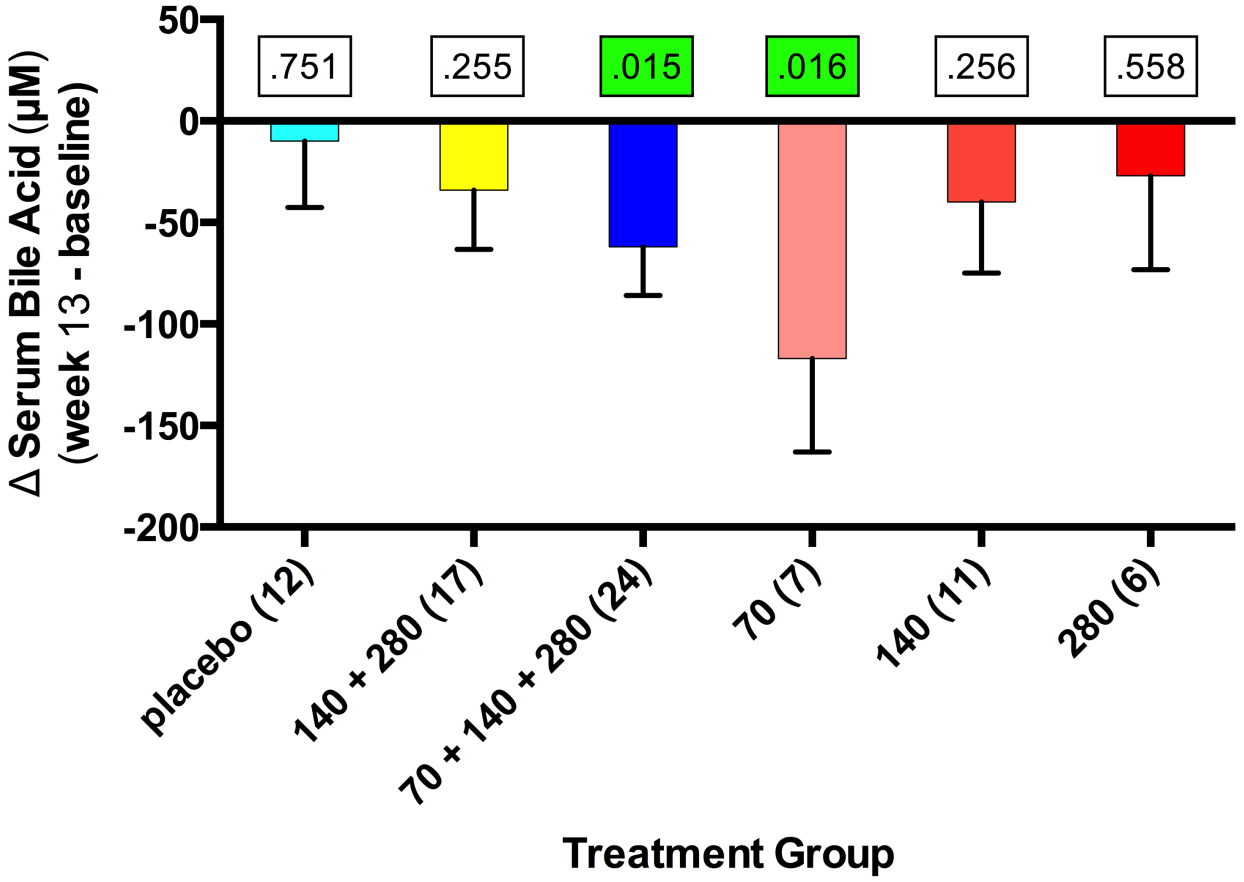


Secondary End Point – Serum Bile Acid



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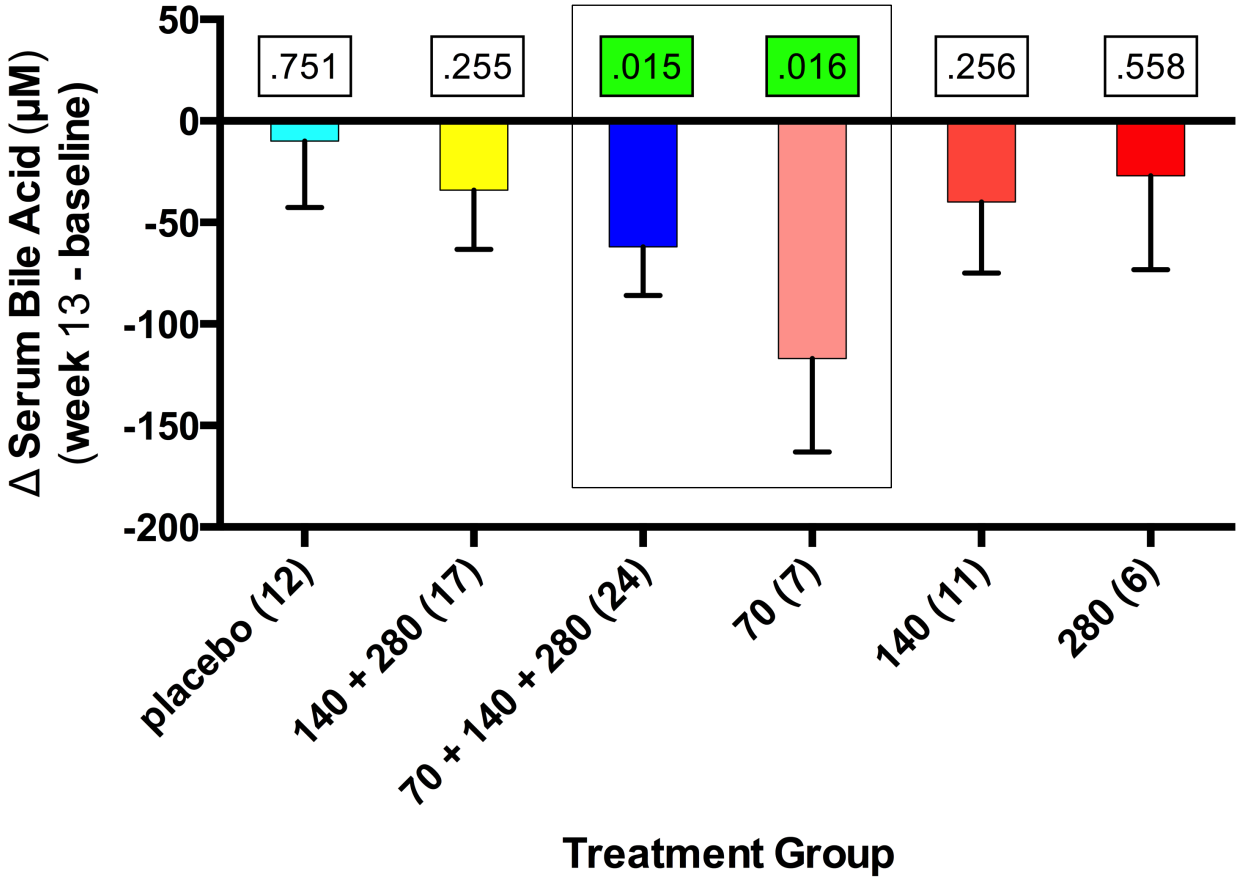
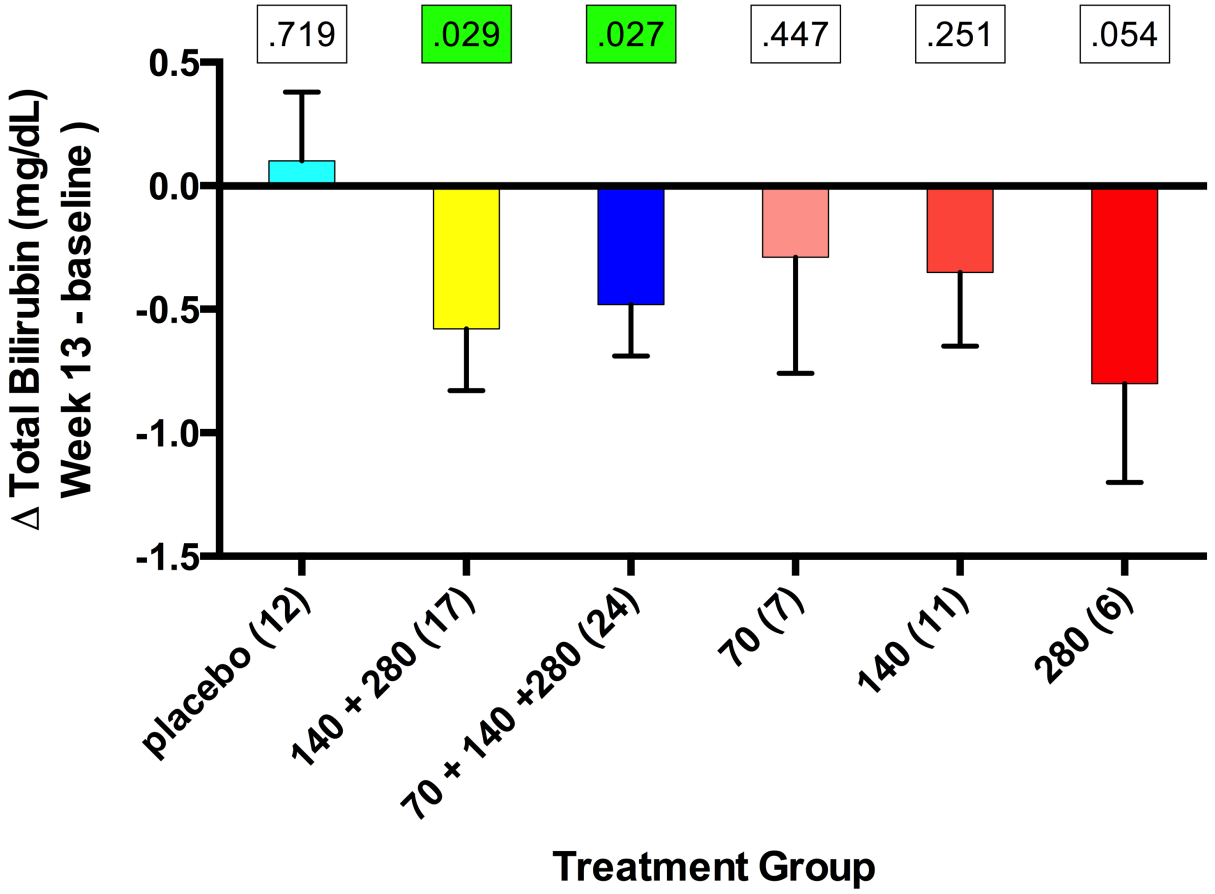


Secondary End Point – Total Bilirubin



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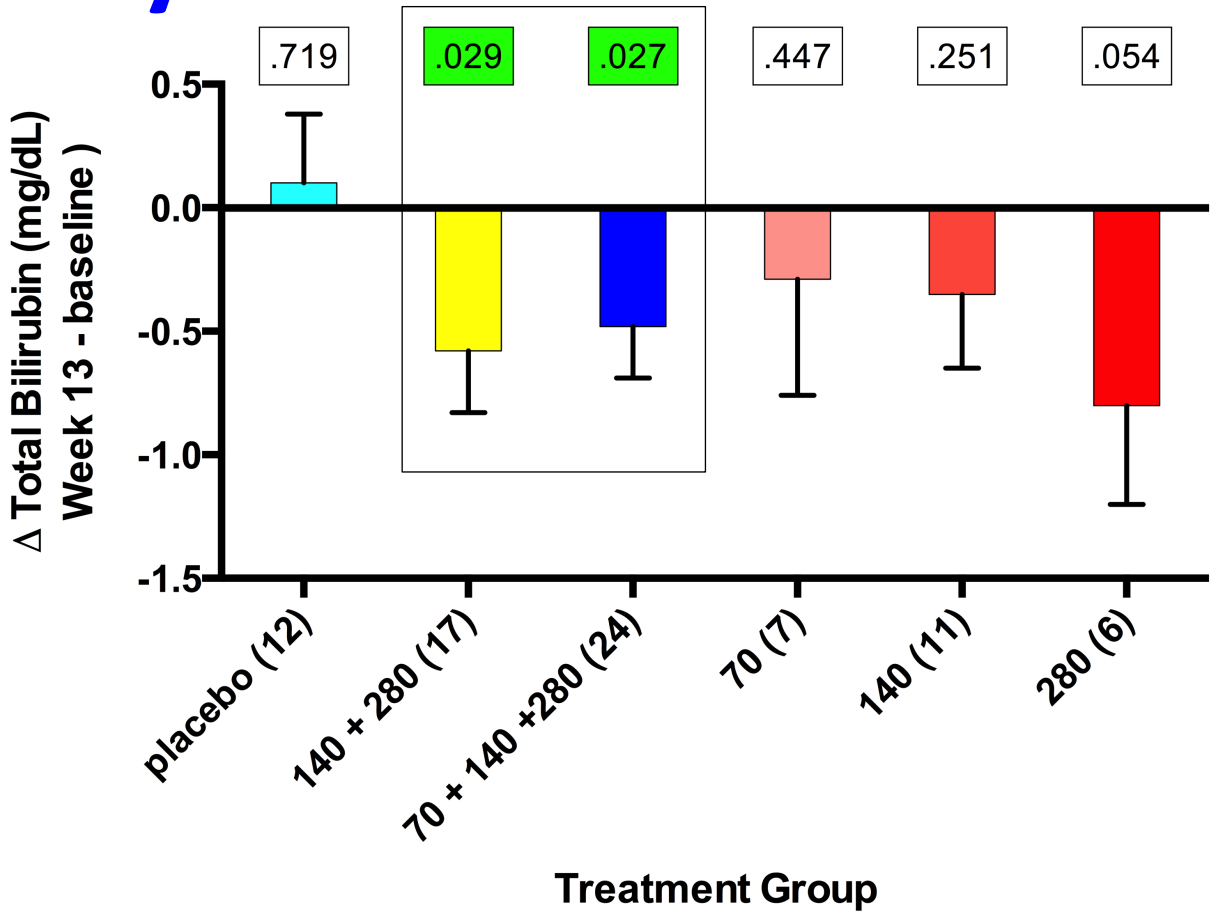
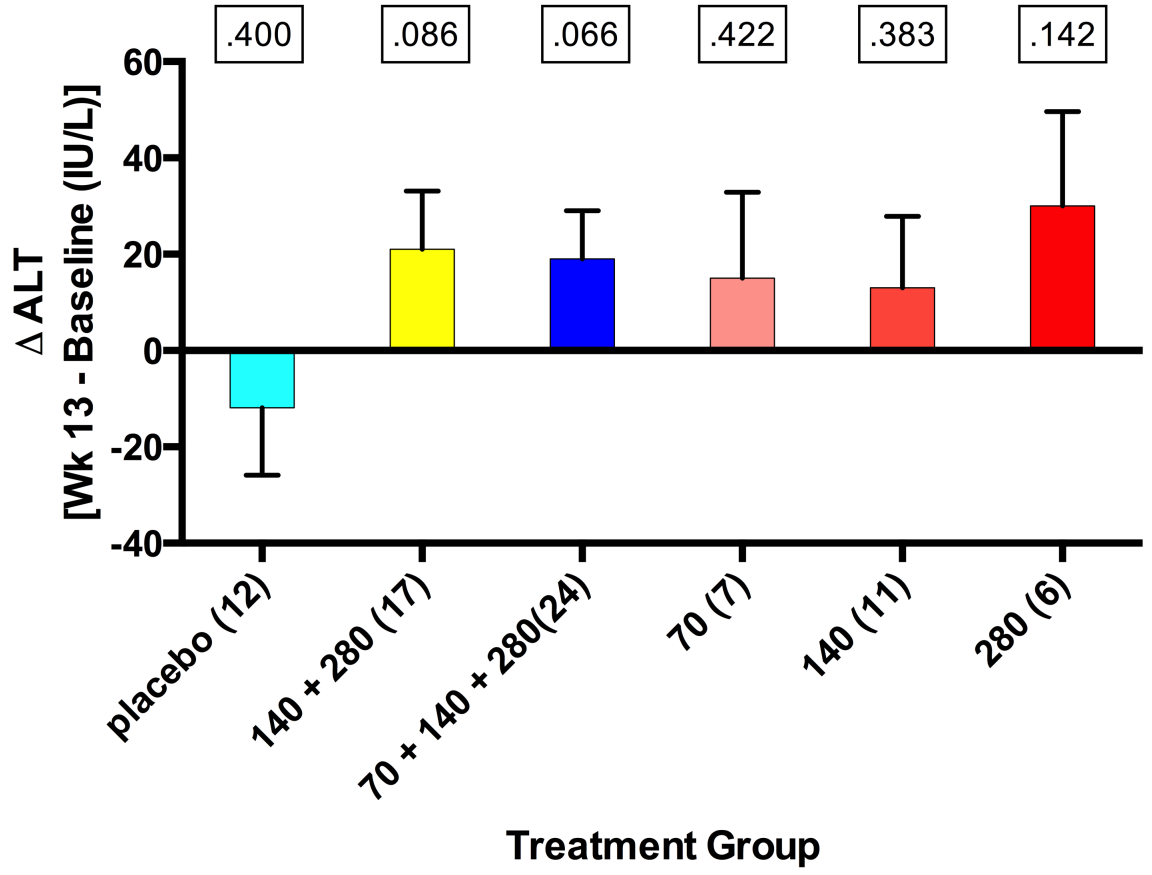
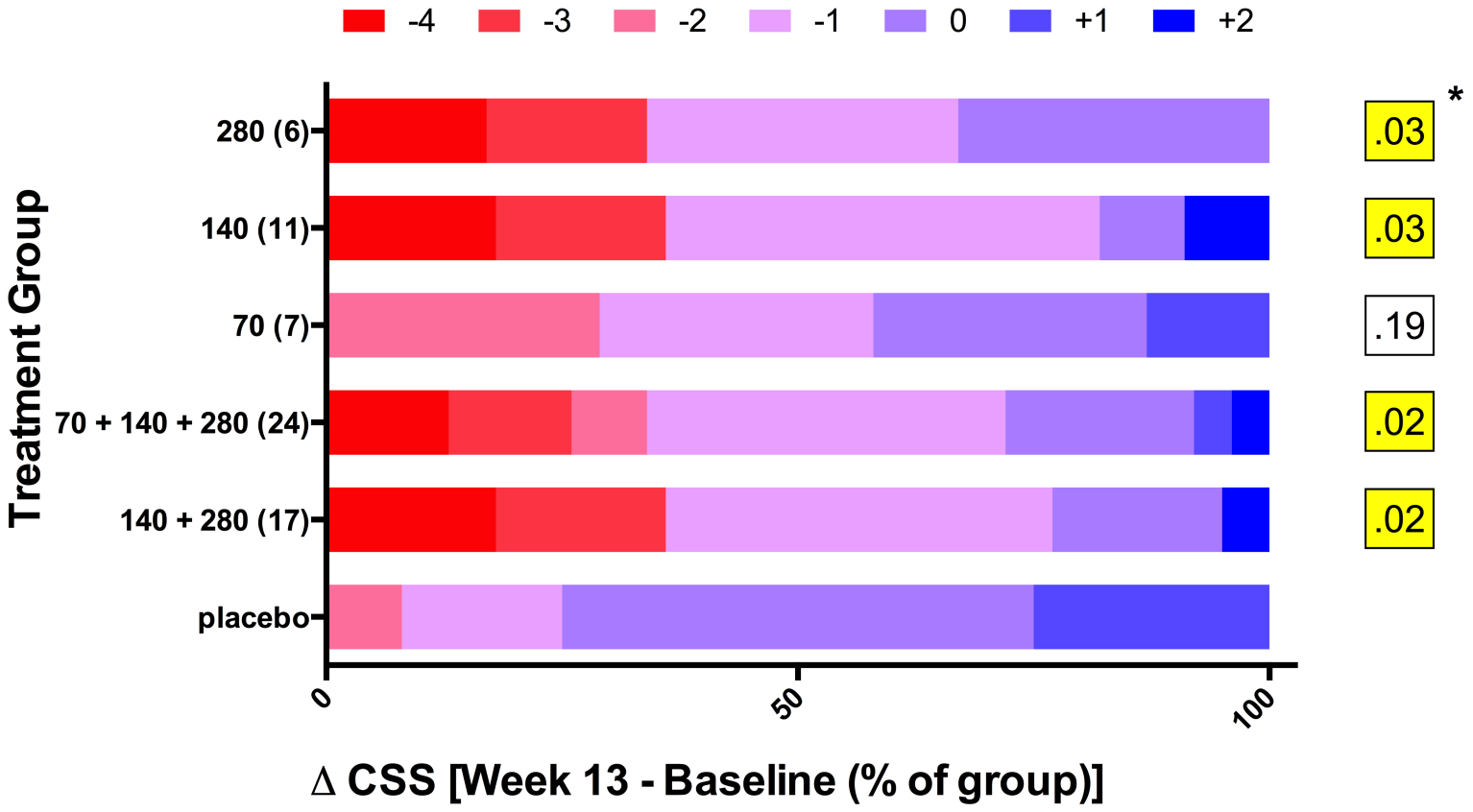


Secondary End Point - ALT

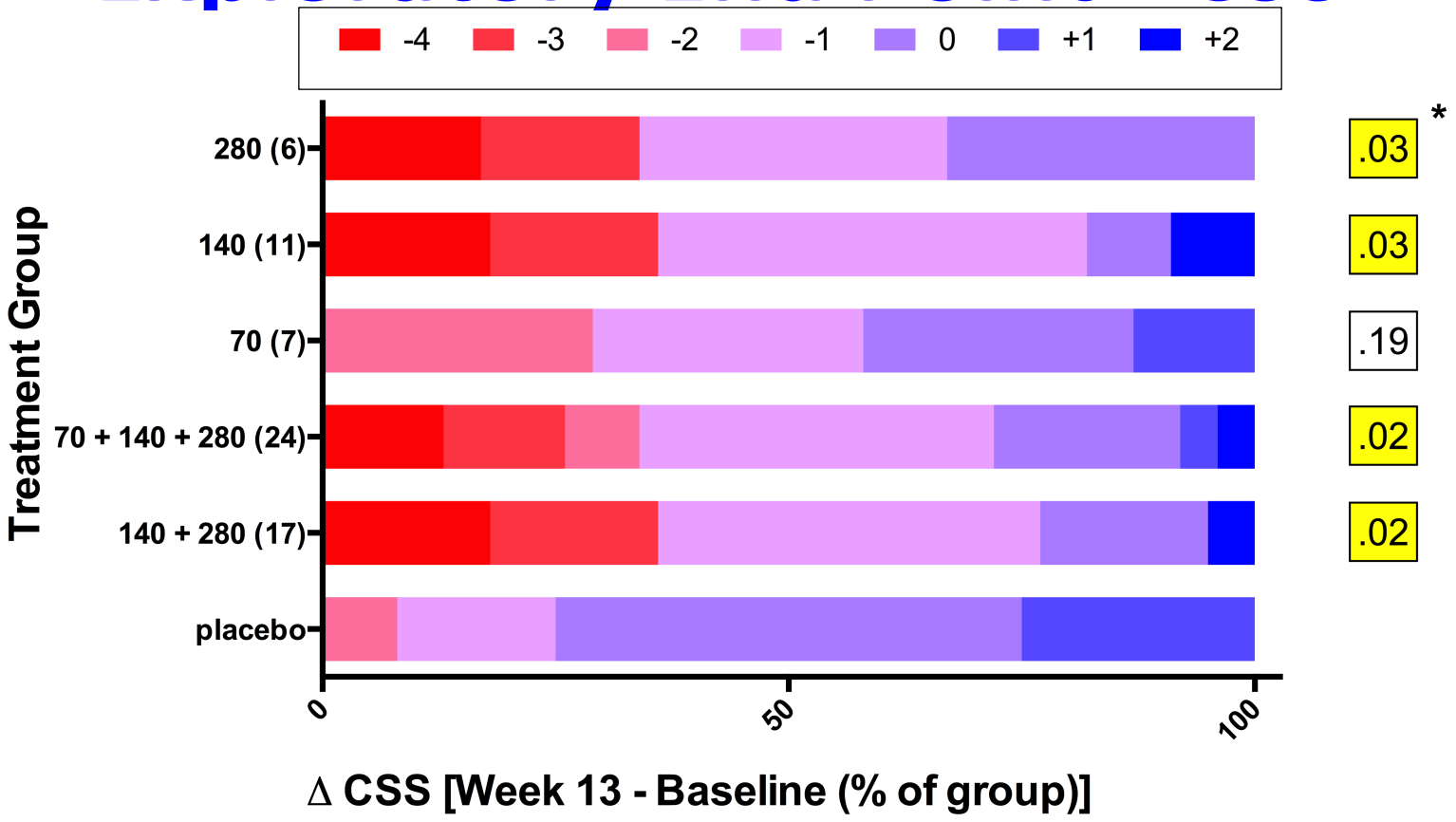


Exploratory End Point - CSS



* p-value relative to placebo

Exploratory End Point - CSS



* p-value relative to placebo

Safety - TEAE

- No deaths
- Serious TEAE – 1 Maralixibat
- Gastrointestinal-Related Events
  - Maralixibat – 52%
  - Placebo – 58%

Conclusions

- Although the pre-specified primary analyses of ItchRO were not all statistically significant, the data suggest that Maralixibat was safe and may reduce pruritus in Alagille Syndrome.
- Determination of optimal dosing and further assessments of safety and efficacy in children with cholestasis are warranted.