Bile Acid Subspecies Are Correlated With Pruritus and Bilirubin Improvement in PFIC Patients Treated With Maralixibat: Data From MARCH and MARCH-ON

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Presenter Disclosure: Henkjan J. Verkade

	No, Nothing to Disclose
x	Yes, Please Specify:

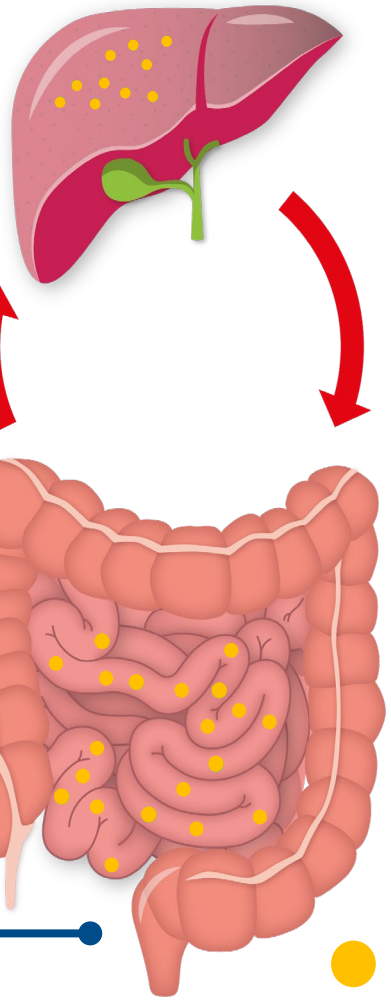
Company Name	Honoraria/ Expenses	Consulting / Advisory Board	Funded Research	Royalties/ Patent	Stock Options	Ownership/ Equity Position	Employee	Other (please specify)
Albireo/Ipsen		x	x					
Intercept		x						
Mirum Pharmaceuticals, Inc.		x	x					
Orphalan		x						
ProQR		x						
Rectify Therapeutics		x	x					
Vertex		x						

Enterohepatic Circulation of BAs

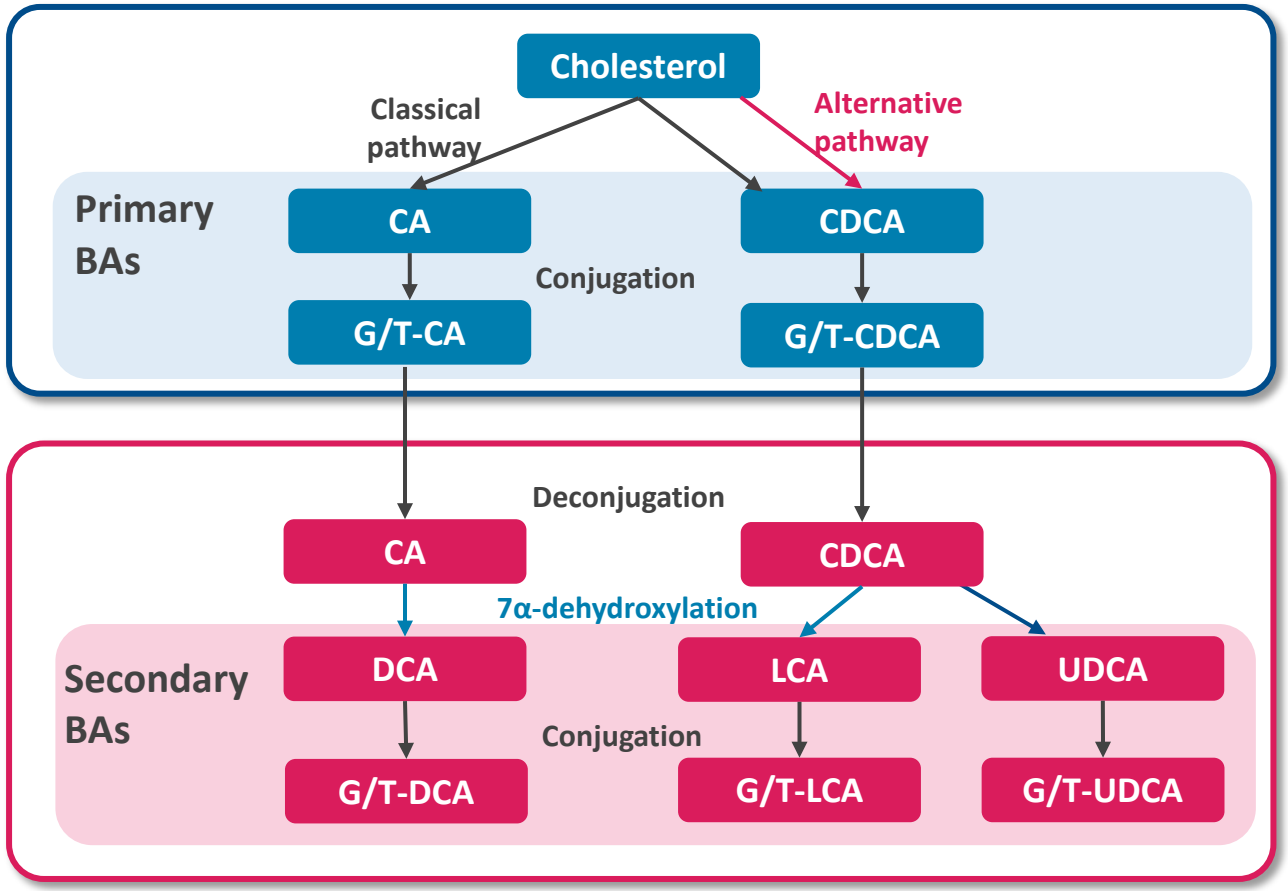
BAs are synthesised in the liver and stored in the gall bladder; *de novo* synthesis only accounts for 5% of BAs, with 95% reabsorbed and recirculated via the IBAT[1,2]

Reabsorption (>95%):
- Active uptake by IBAT in the ileum
- Passive absorption in the colon[2]

Excretion via faeces (~5%)



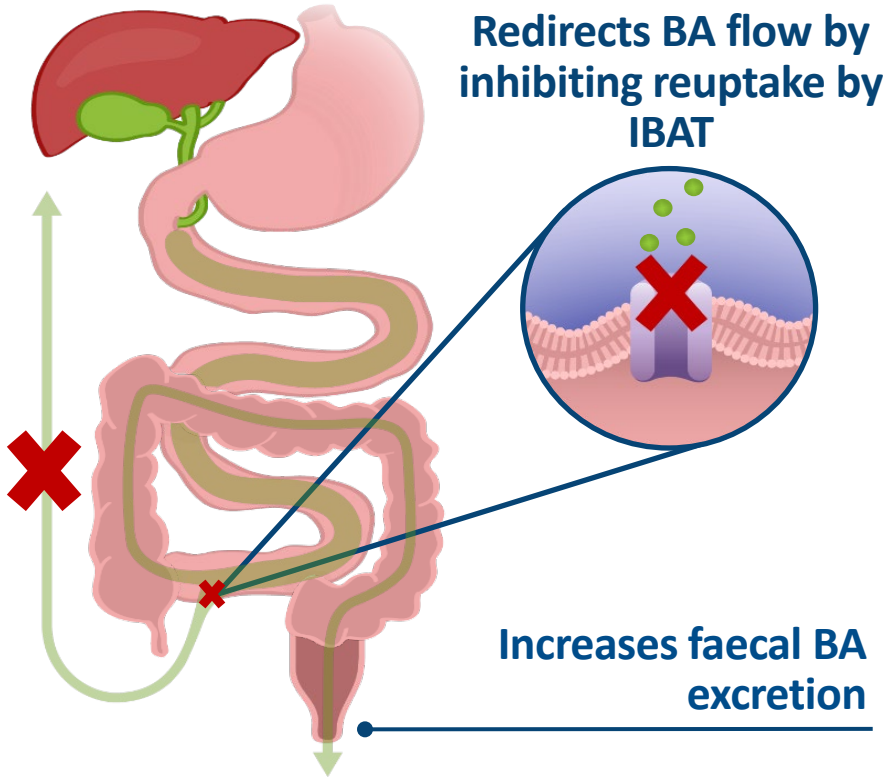
● = BA



BA, bile acid; IBAT, ileal bile acid transporter; IL-1, interleukin 1; sBA, serum bile acid; TNF-α, tumor necrosis factor α.

1. Kamath BM, et al. *Liver Int*. 2020;40:1812-1822. **2.** Di Ciaula A, et al. *Ann Hepatol*. 2017;16(Suppl. 1):s4-s14. **3.** Baker A, et al. *Clin Res Hepatol Gastroenterol*. 2019;43:20-36. **4.** Cai S-Y, et al. *Ann Transl Med*. 2021;9:737. **5.** Hirschfield GM, et al. *Gastroenterology*. 2010;139:1481-1496. **6.** Srivastava A. *J Clin Exp Hepatol*. 2014;4:25-36.

Maralixibat: IBAT Inhibitor That Interrupts Enterohepatic Circulation



Clinical effects of maralixibat in PFIC and Alagille syndrome

- ✓ Improvements in pruritus[1-4]
- ✓ Reduction in peripheral sBA[1-4]
- ✓ Improved transplant-free survival[1,2]

Maralixibat is approved for the treatment of PFIC in patients ≥3 months of age in the EU[5]

BA, bile acid; IBAT, ileal bile acid transporter; PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid.

1. Gonzales E, et al. *Lancet*. 2021;398:1581-1592. **2.** Sokol RJ, et al. *Hepatology*. 2023;78:1698-1710. **3.** Miethke AG, et al. *Lancet Gastroenterol Hepatol*. 2024;9:620-631. **4.** LIVMARLI® (maralixibat) [prescribing information]. Foster City, CA; Mirum Pharmaceuticals, Inc. July 2024. **5.** LIVMARLI® (maralixibat) [summary of product characteristics]. Amsterdam, Netherlands; Mirum Pharmaceuticals International B.V. Dec 2024.

Objective

- MARCH (NCT03905330) was a Phase 3, randomised, double-blind, placebo-controlled, 26-week trial investigating the efficacy and safety of maralixibat in participants with PFIC across the broadest range of PFIC types studied to date[1,2]
- Maralixibat in MARCH/MARCH-ON improved sBA, pruritus and bilirubin in most participants treated; however, there were responders and nonresponders, based on changes in ItchRO[Obs]) and sBA

To study the changes in sBA subspecies in sBA responders and non-responders in relation to changes in pruritus and direct bilirubin (BSEP patients)

PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid.

1. ClinicalTrials.gov identifier: NCT03905330. Updated December 11, 2023. Accessed March 13, 2025. https://clinicaltrials.gov/study/NCT03905330. **2.** Miethke AG, et al. *Lancet Gastroenterol Hepatol*. 2024;9:620-631. **3.** ClinicalTrials.gov identifier: NCT04185363. Updated February 14, 2025. Accessed March 13, 2025. https://www.clinicaltrials.gov/study/NCT04185363. **4.** Miethke A, et al. Oral presentation at AASLD 2023. **5**. D'Antiga L, et al. Presented at EASL 2024.

Methods

- Change from Baseline to Week 26 (averaged over the last 8-12 weeks) was calculated for all participants treated with maralixibat for 26 weeks in either MARCH or MARCH-ON
- Spearman correlation coefficients were determined to evaluate the relationship between changes in sBA subspecies and changes in Itch-Reported Outcome (Observer) (ItchRO[Obs]) and direct bilirubin
  - ItchRO(Obs) is a 0 to 4 scale, where 0 = no itch, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe[1]
  - A ≥ 1-point reduction in ItchRO(Obs) is considered clinically meaningful
- Participants were stratified into responders and nonresponders (based on changes in ItchRO[Obs]) and sBA after maralixibat treatment
  - ItchRO(Obs) response was defined as a ≥ 1-point reduction in ItchRO(Obs) from Baseline to the average of the final three 4-week periods in MARCH (Weeks 15-18, Weeks 19-22, and Weeks 23-26) or an average score of ≤ 1*
  - sBA response was defined as an average sBA level of < 102 µmol/L (if Baseline level was ≥ 102 µmol/L) or a ≥ 75% reduction from Baseline using the average from Weeks 18, 22, and 26*

*Participants were defined as nonresponders if the Baseline value or all 3 post-Baseline values were missing.
BSEP, bile salt export pump; FIC1, familial intrahepatic cholestasis-associated protein 1; ItchRO(Obs), Itch-Reported Outcome (Observer); MDR3, multidrug resistance protein 3; MYO5B, myosin Vb; PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid; TJP2, tight junction protein 2.
1. Kamath BM, et al. *Hepatol Commun*. 2020;4:1012-1018.

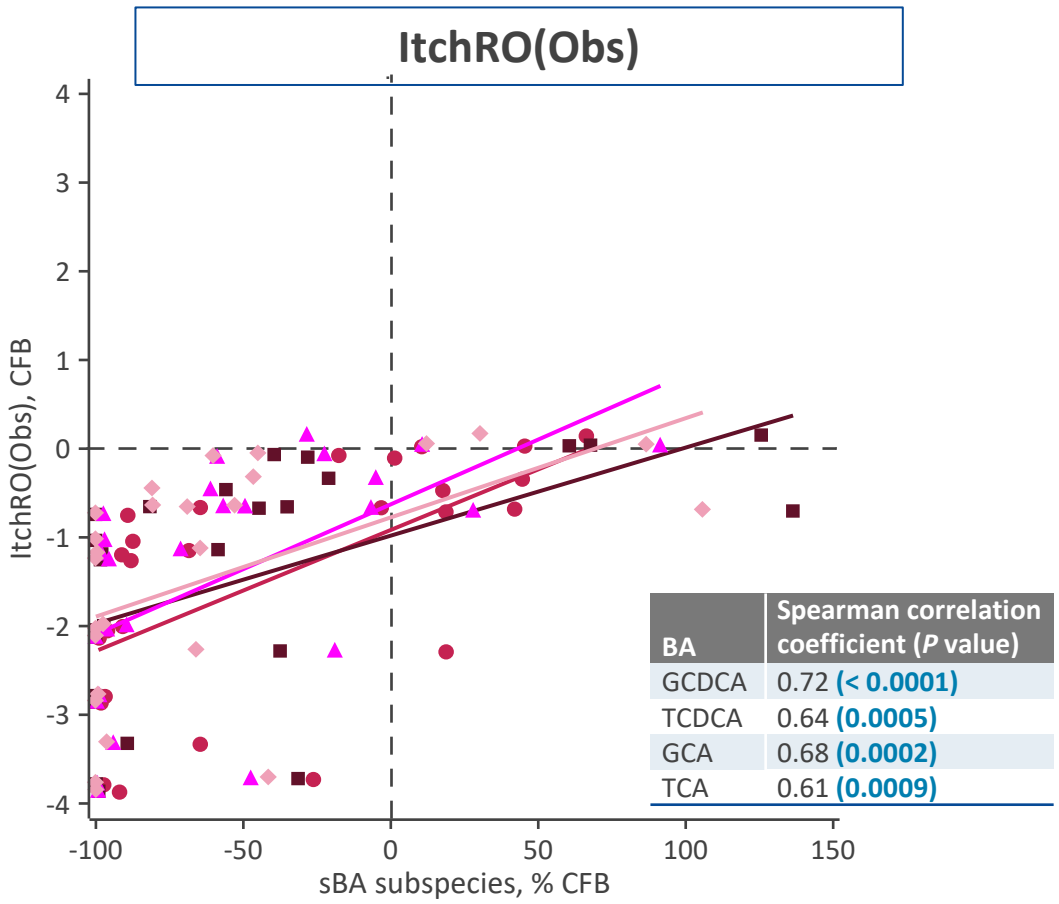
Baseline Characteristics in the BSEP Cohort

Parameter[a]	BSEP Cohort (N = 28)
Age, y	4 (2, 8)
Sex, male, %	35.7
Pruritus, ItchRO(Obs) score	2.9 (1.8, 3.6)
Total sBA, µmol/L	337 (209, 436)
Total bilirubin, µmol/L	27.4 (11.5, 61.6)
Direct bilirubin, µmol/L	19.2 (6.0, 44.5)
Height Z-score[b]	−1.2 (−1.8, −0.7)
Weight Z-score[b]	−2.0 (−3.0, −1.0)

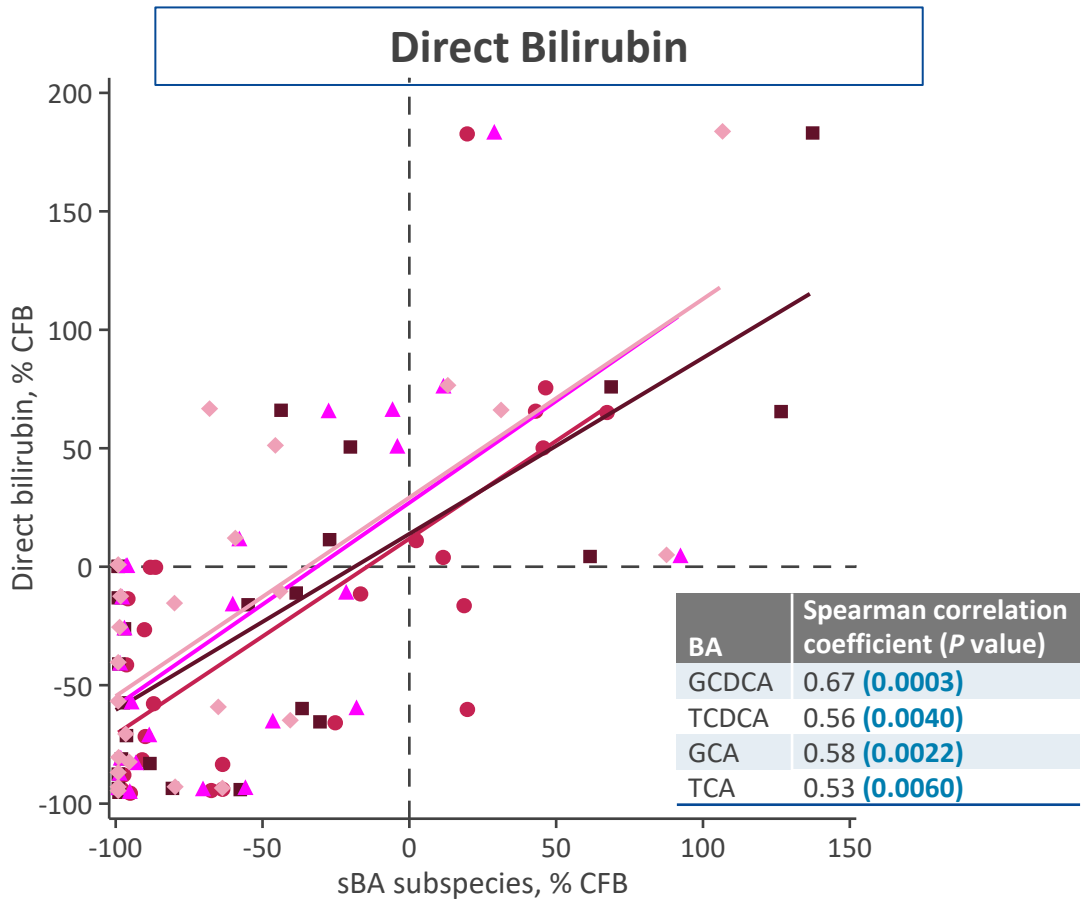
- Among the included participants, 89% (n = 25) were receiving UDCA

[a]All data are median (Q1, Q3) unless otherwise indicated. [b]Height and weight Z-scores are based on a participant's sex and age at the Baseline visit. The World Health Organization growth charts were used to derive Z-scores for participants younger than 24 months, and the Centers for Disease Control and Prevention growth charts were used to derive Z-scores for participants aged 24 months or older.
BESP, bile salt export pump; ItchRO(Obs), Itch-Reported Outcome (Observer); sBA, serum bile acid; UDCA, ursodeoxycholic acid.

Correlation of Conjugated Primary BAs With ItchRO(Obs) and Direct Bilirubin in the BSEP Cohort



BA	Spearman correlation coefficient (*P* value)
GCDCA	0.72 (< 0.0001)
TCDCA	0.64 (0.0005)
GCA	0.68 (0.0002)
TCA	0.61 (0.0009)



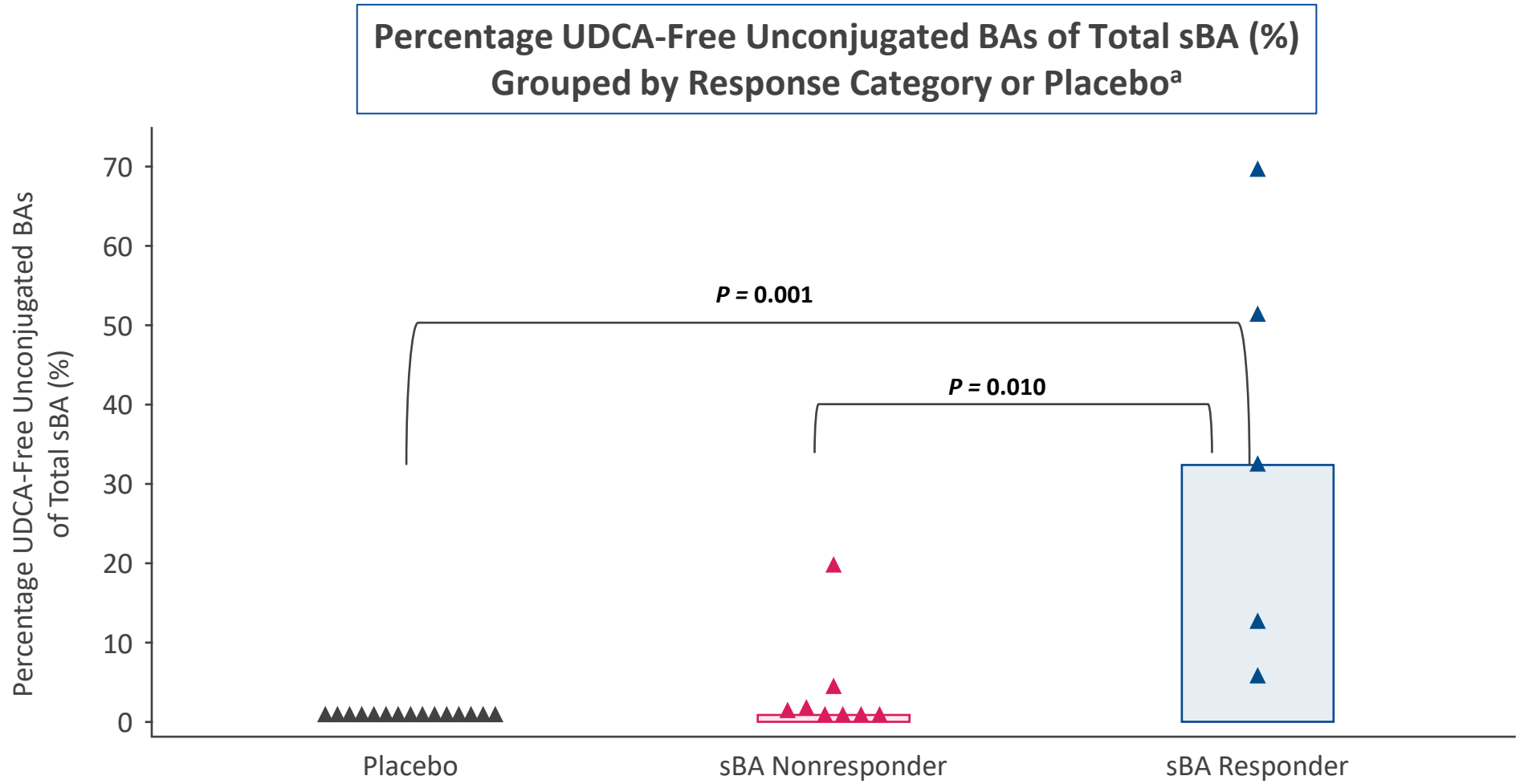
BA	Spearman correlation coefficient (*P* value)
GCDCA	0.67 (0.0003)
TCDCA	0.56 (0.0040)
GCA	0.58 (0.0022)
TCA	0.53 (0.0060)

● GCDCA ■ TCDCA ▲ GCA ◆ TCA Regression line — GCDCA — TCDCA — GCA — TCA

Conjugated primary BAs were positively correlated with markers of disease in the BSEP cohort

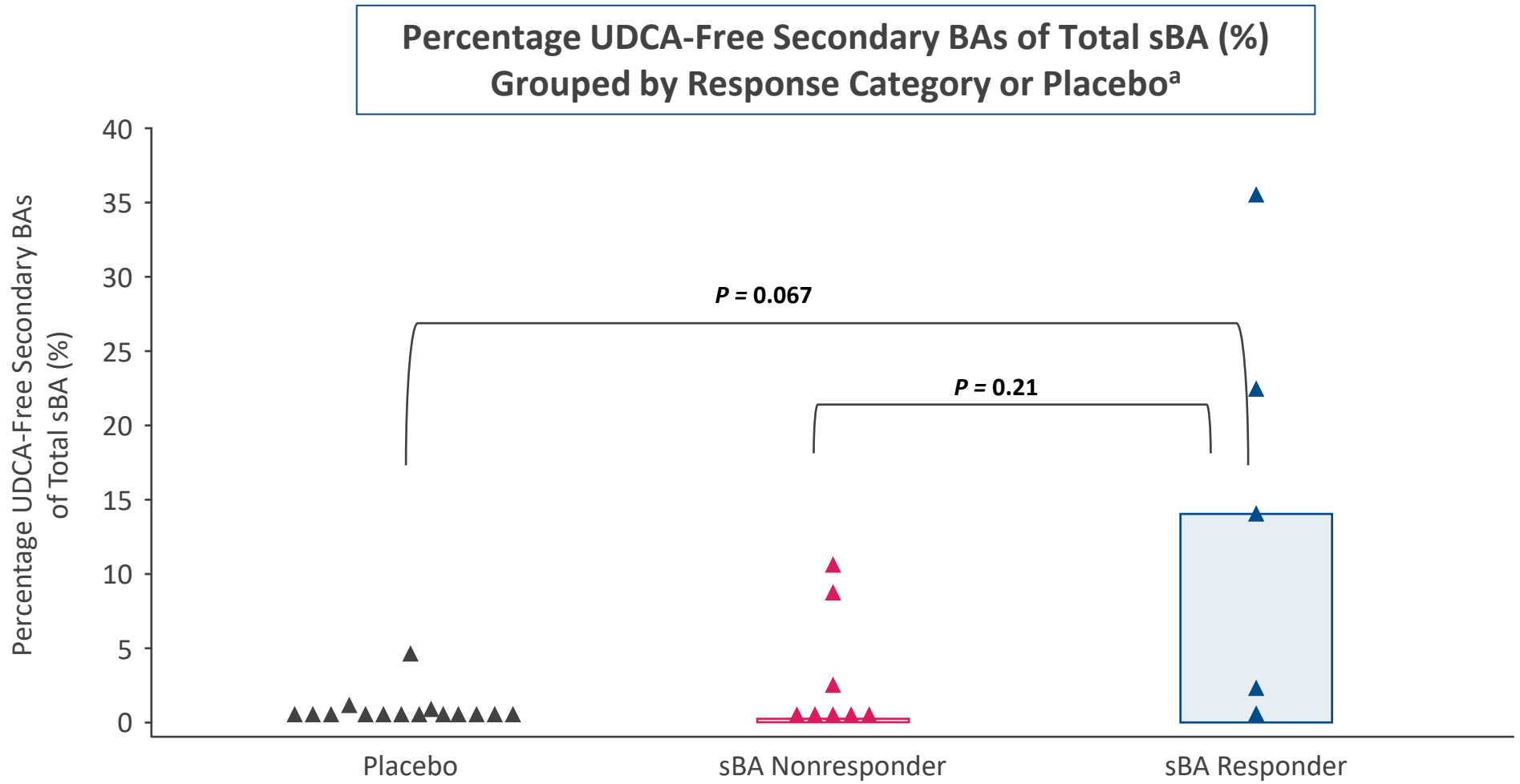
BA, bile acid; BSEP, bile salt export pump; CFB, change from Baseline; GCA, glycocholic acid; GCDCA, glycochenodeoxycholic acid; ItchRO(Obs), Itch-Reported Outcome (Observer); sBA, serum bile acid; TCA, taurocholic acid; TCDCA, taurochenodeoxycholic acid.

sBA Responders Had Higher Median UDCA-Free Unconjugated BAs of Total sBA Compared With Nonresponder and Placebo Groups in the BSEP Cohort



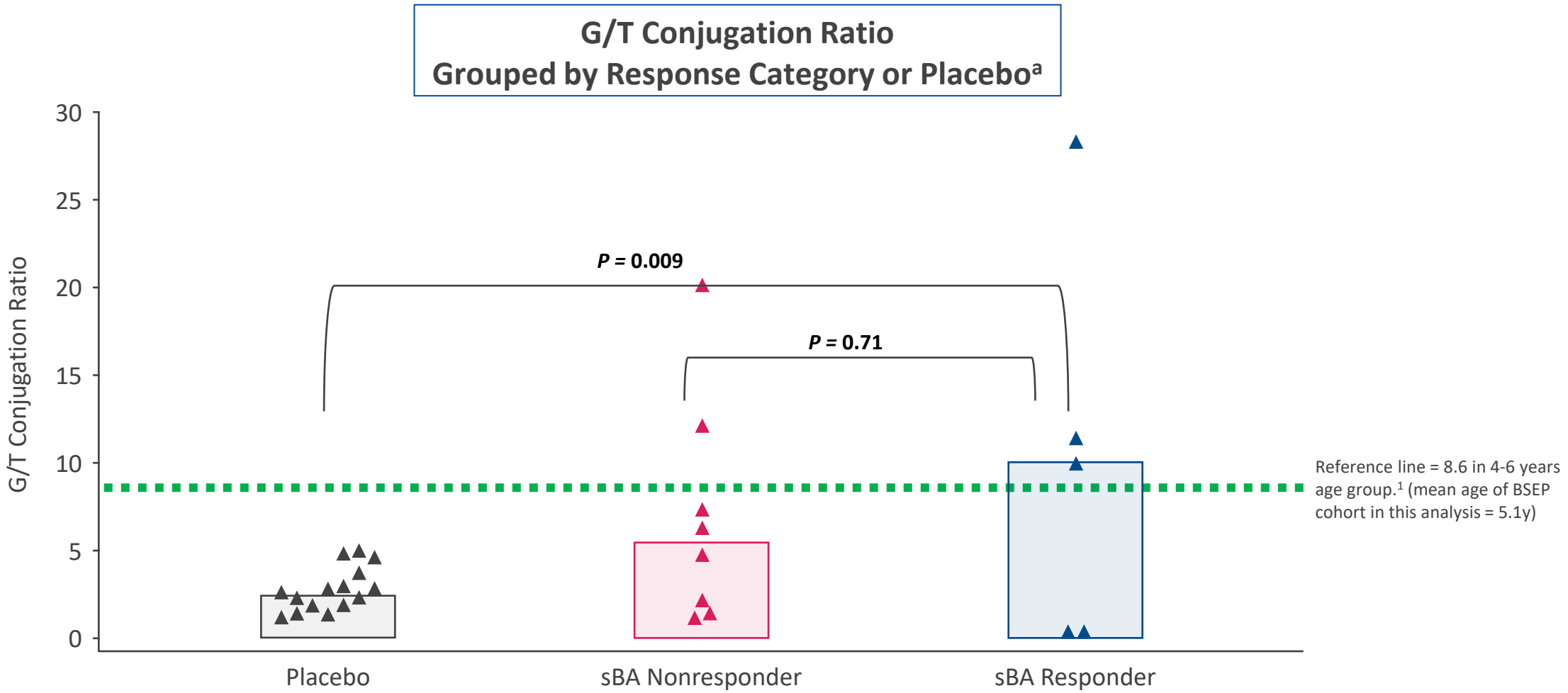
Individual points on the graph represent the individual study participants. The bars indicate the median value for each group.
[a]Unless specified otherwise, UDCA, GUDCA, and TUDCA are excluded when calculating total and secondary sBA values.
BA, bile acid; BSEP, bile salt export pump; sBA, serum bile acid; UDCA, ursodeoxycholic acid.

sBA Responders Had Higher Median UDCA-Free Secondary BAs of Total sBA Compared With Nonresponder and Placebo Groups in the BSEP Cohort



Individual points on the graph represent the individual study participants. The bars indicate the median value for each group.
[a]Unless specified otherwise, UDCA, GUDCA, and TUDCA are excluded when calculating total and secondary sBA values.
BA, bile acid; BSEP, bile salt export pump; GUDCA, glycoursodeoxycholic acid; sBA, serum bile acid; TUDCA, tauroursodeoxycholic acid; UDCA, ursodeoxycholic acid.

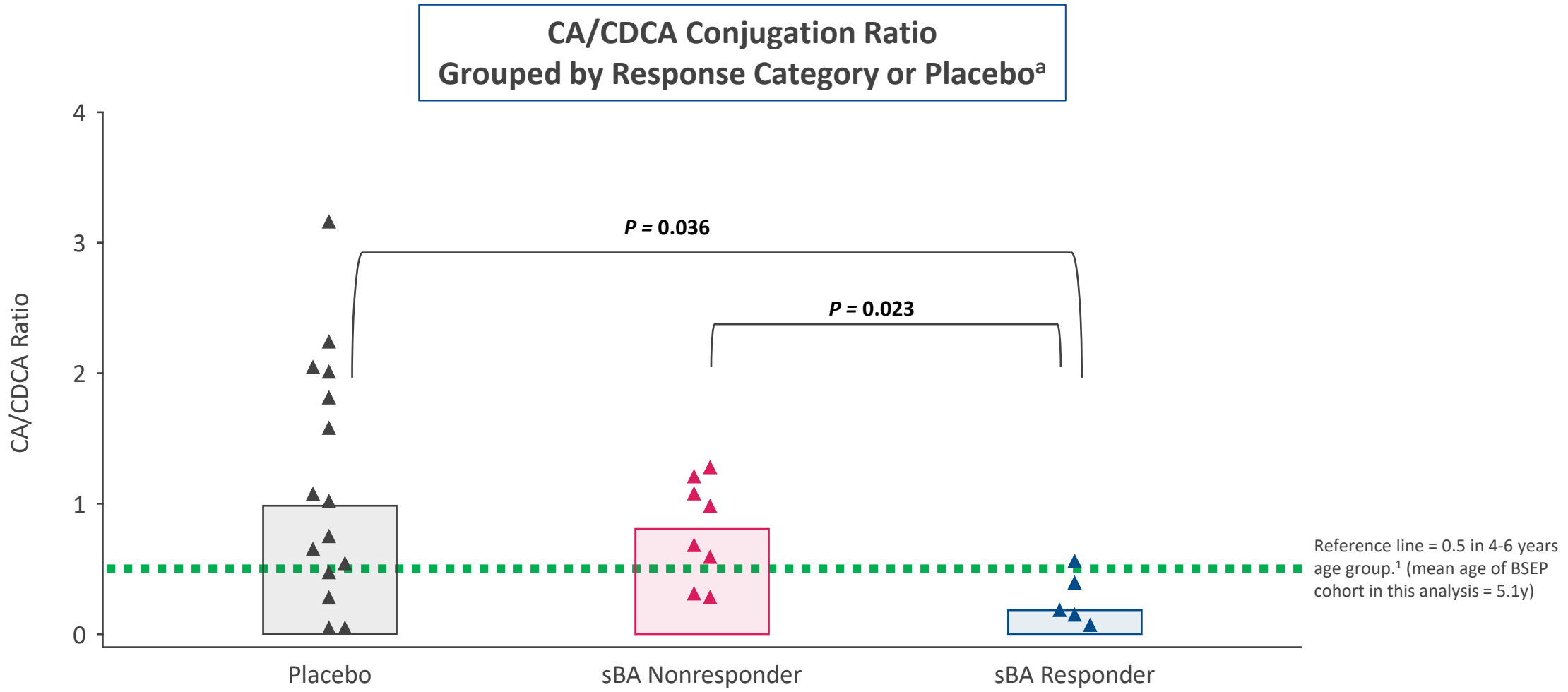
In sBA Responders, Median G/T Was Restored to Healthy Children Levels in the BSEP Cohort



Individual points on the graph represent the individual study participants. The bars indicate the median value for each group.
[a]G/T ratio is derived as the sum of GCDCA, GCA, GDCA, and GLCA divided by the sum of TCDCA, TCA, TDCA, and TLCA.
BSEP, bile salt export pump; GCA, glycocholic acid; GCDCA, glycochenodeoxycholic acid; GDCA, glycodeoxycholic acid; GLCA, glycolithocholic acid; G/T, glycine-to-taurine ratio; sBA, serum bile acid; TCA, taurocholic acid; TCDCA, taurochenodeoxycholic acid; TDCA, taurodeoxycholic acid; TLCA, taurolithocholic acid.

1. Niijma S. *Pediatr Res.* 1985;19(3):302-307.

sBA Responders Had Lower Median CA/CDCA Ratios Compared With Placebo and Nonresponder Groups in the BSEP Cohort



Individual points on the graph represent the individual study participants. The bars indicate the median value for each group.
[a]CA/CDCA ratio is derived as CA divided by CDCA.
BSEP, bile salt export pump; CA, cholic acid; CDCA, chenodeoxycholic acid; sBA, serum bile acid.
1. Niijma S. *Pediatr Res.* 1985;19(3):302-307.

Conclusions

- These results expand on previous research demonstrating a correlation between sBA and pruritus and identify changes in BA subspecies associated with improvements in pruritus and direct bilirubin, including negative correlations with unconjugated primary BAs and positive correlations with conjugated primary BAs
- In the BSEP cohort, serum composition of BA subspecies was significantly different between ItchRO(Obs) responders and the placebo group or ItchRO(Obs) nonresponders after treatment with maralixibat
  - Similarly, sBA responders showed significant differences in BA composition compared with the placebo group or sBA nonresponders in the BSEP cohort
- These data help elucidate the pathophysiology of how maralixibat may improve both pruritus and underlying liver health in patients with PFIC

BA, bile acid; BSEP, bile salt export pump; FGF-19, fibroblast growth factor 19; ItchRO(Obs), Itch-Reported Outcome (Observer); PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid.

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Disclosures

- HJV has nothing to declare
- AGM is a consultant and has a sponsored research agreement with Mirum Pharmaceuticals, Inc.
- SPH is a hepatic safety adjudication committee member at Albireo and has received a research grant from Mirum Pharmaceuticals, Inc.
- DBM, TN, CK, JS, WG, and PV are employees of and shareholders in Mirum Pharmaceuticals, Inc.
- RJT is a consultant for Mirum Pharmaceuticals, Inc., Albireo, Generation Bio, Rectify Therapeutics, and Alnylam and a shareholder in Generation Bio and Rectify Therapeutics

Thank You!