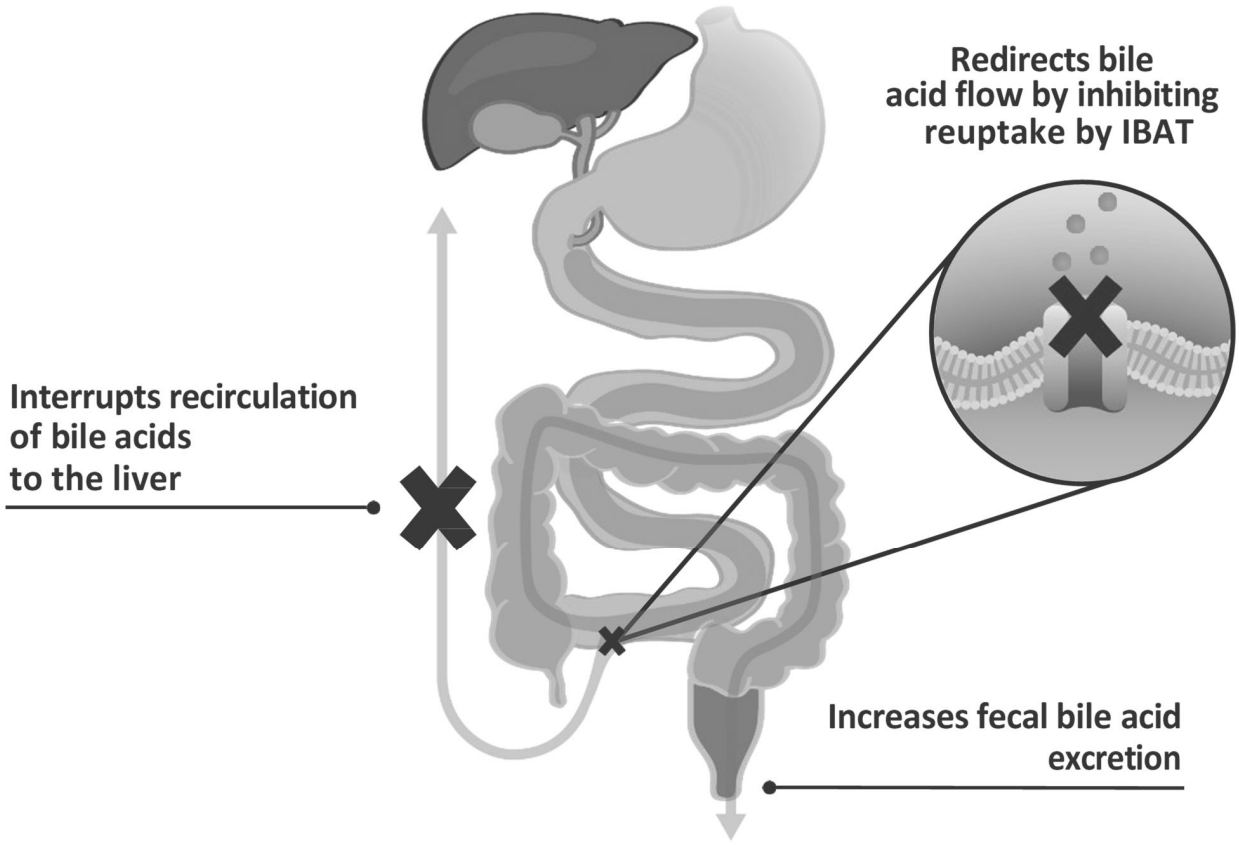
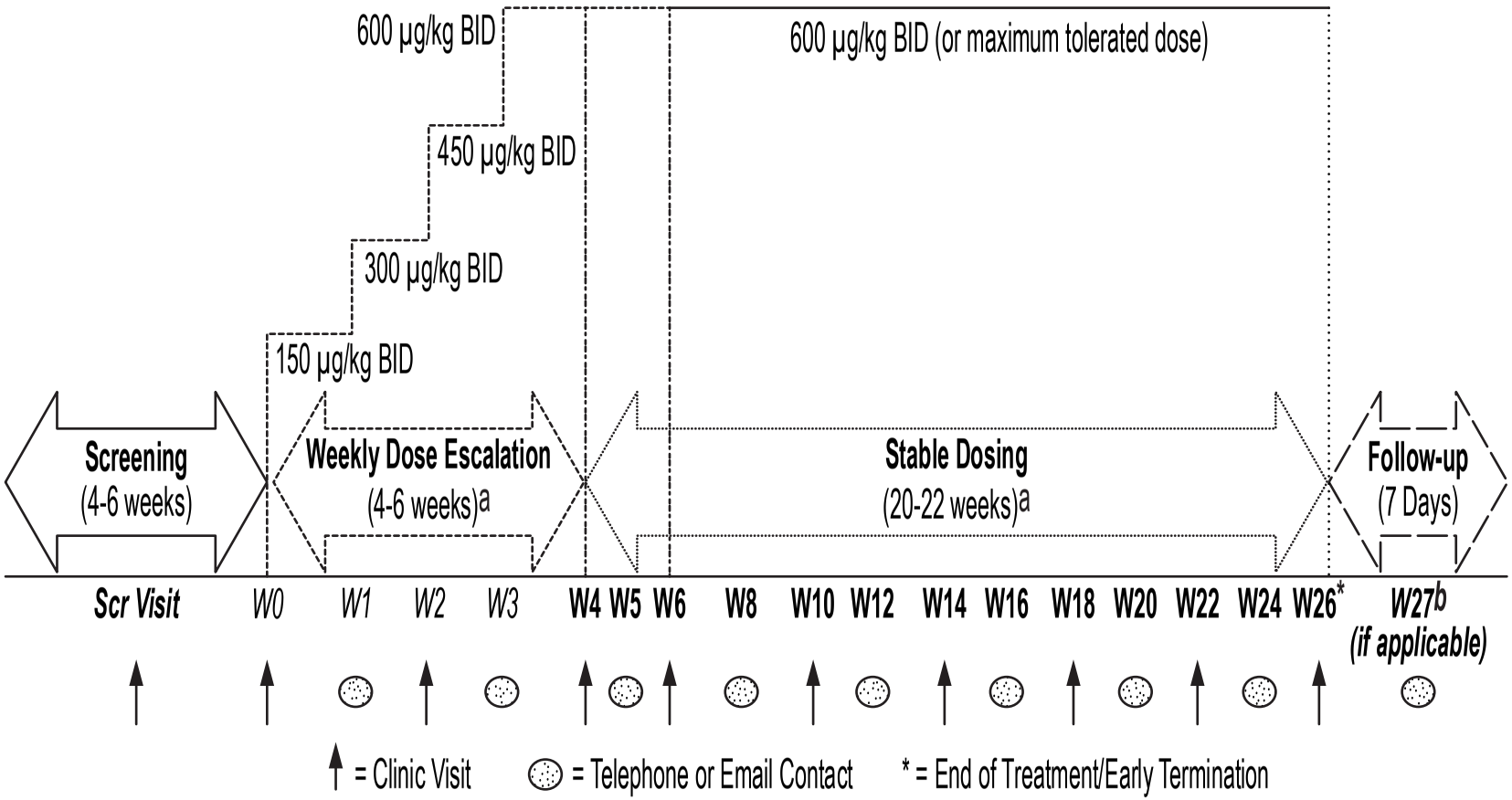
FIG. 1


Redirects bile
acid flow by inhibiting
reuptake by IBAT
Interrupts recirculation
of bile acids
to the liver
Increases fecal bile acid
excretion



a Dose escalation may occur over 4-6 weeks depending on tolerability. Stable dosing will occur over 20-22 weeks, depending on the duration of the dose escalation period.

b Safety follow-up visit for subjects not continuing into the extension study (MRX-503).

FIG. 2

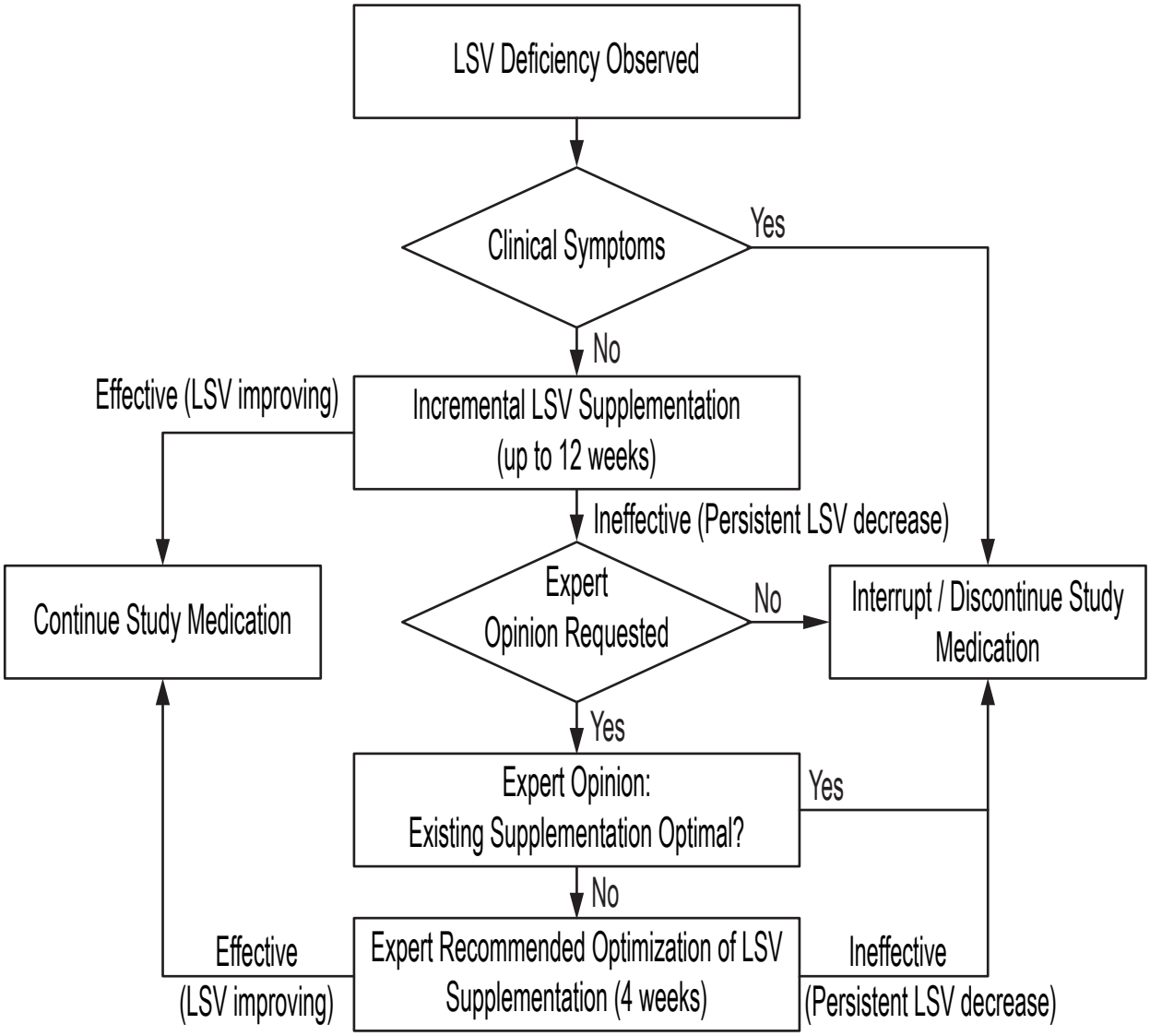

LSV Deficiency Observed
Clinical Symptoms
Yes
No
Effective (LSV improving)
Incremental LSV Supplementation
(up to 12 weeks)
Ineffective (Persistent LSV decrease)
Continue Study Medication
Expert
Opinion Requested
No
Interrupt / Discontinue Study
Medication
Yes
Expert Opinion:
Existing Supplementation Optimal?
Yes
No
Effective
(LSV improving)
Expert Recommended Optimization of LSV
Supplementation (4 weeks)
Ineffective
(Persistent LSV decrease)

FIG. 3

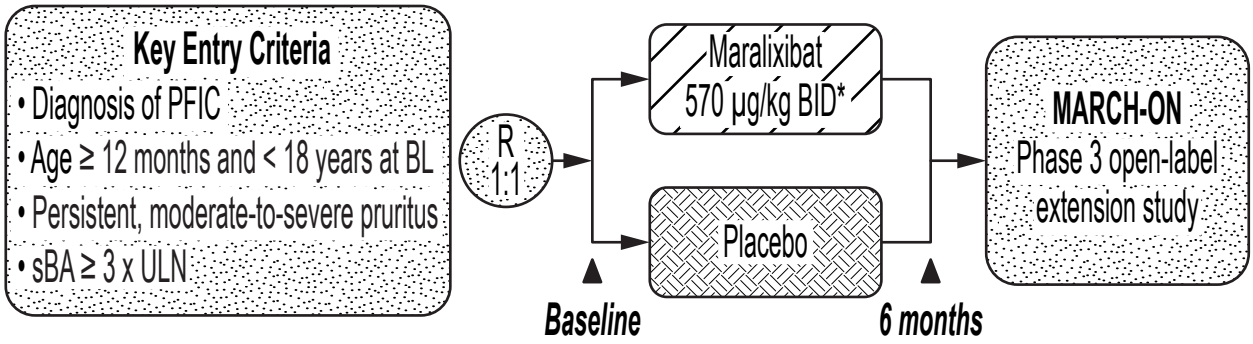


FIG. 4A



Primary Endpoint (BSEP cohort):

Mean change in morning ItchRO(Obs) severity score between Baseline and average of the last 12 weeks

Secondary Endpoints (BSEP and All-PFIC cohorts):

- Mean change in morning ItchRO(Obs) severity score between Baseline and average of the last 12 weeks in the All-PFIC cohort
- Mean change in total sBA level between Baseline and average of the last 12 weeks in the BSEP and All-PFIC cohorts
- Responder analyses of pruritus and sBA

Exploratory Endpoints (All-PFIC cohorts):

- Mean change from Baseline in total and direct bilirubin
- Mean change from Baseline in growth (height and weight Z-scores)

- Endpoints were analysed using a repeated measures model (MMRM) approach considering data from all study visits
- ItchRO(Obs) is a 0-4 scale; ≥ 1 point reduction is clinically meaningful
- The safety endpoints were assessed in the full-study population per incidence of AEs

FIG. 4B

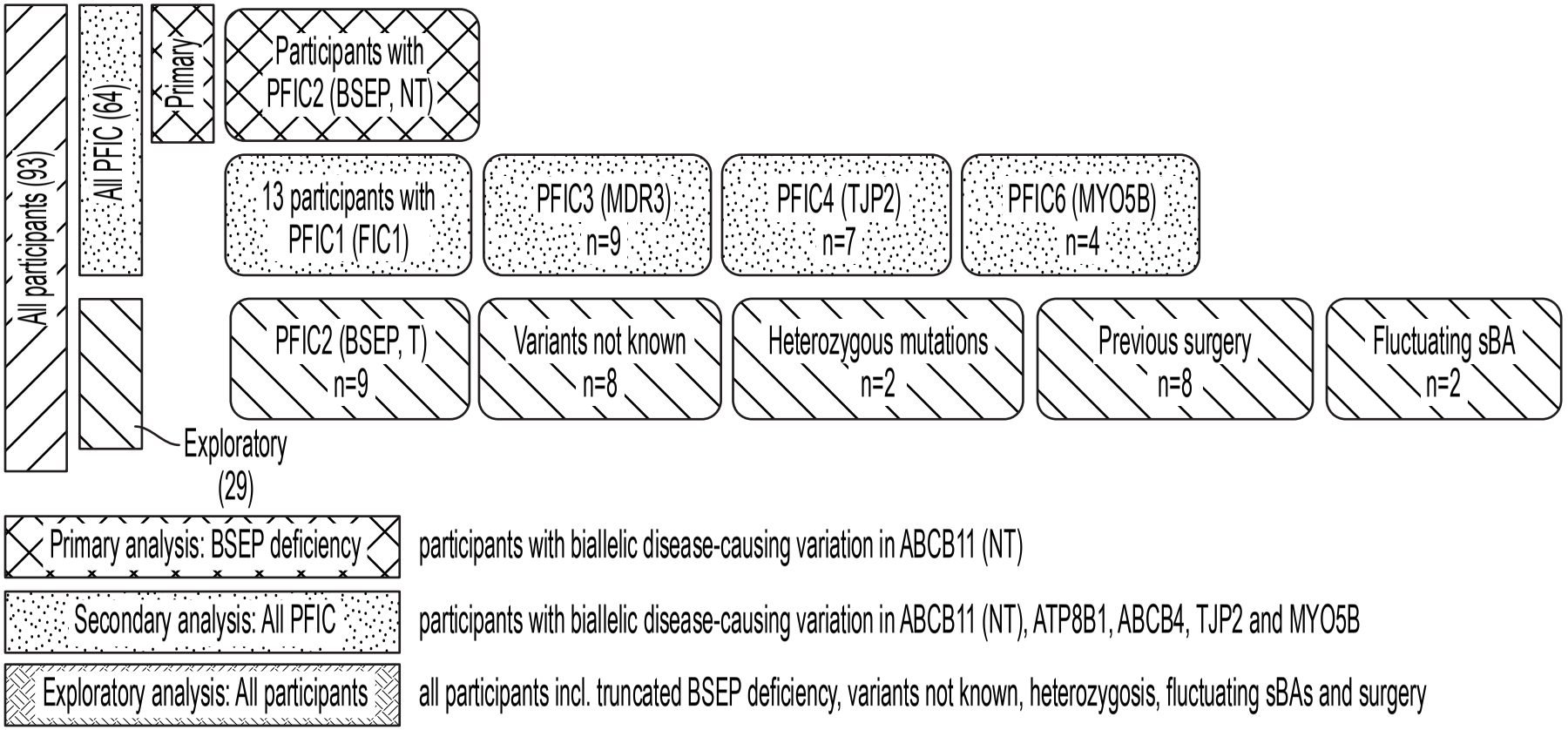
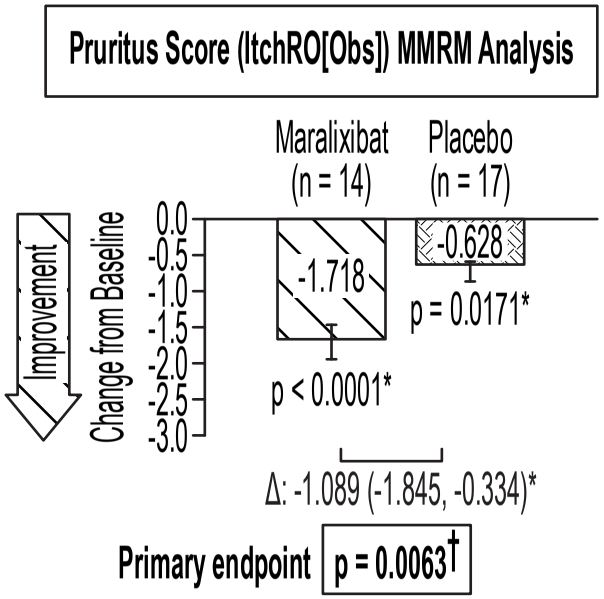
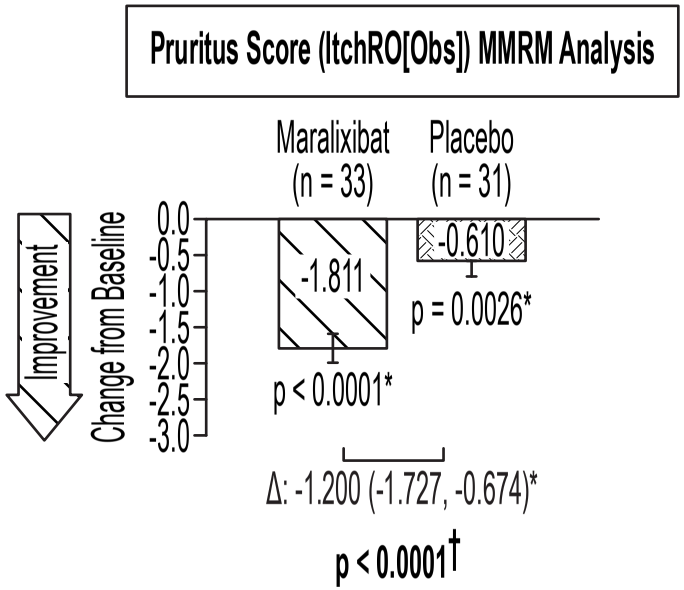

All participants (93)
All PFIC (64)
Primary
Participants with PFIC2 (BSEP, NT)
13 participants with PFIC1 (FIC1)
PFIC3 (MDR3) n=9
PFIC4 (TJP2) n=7
PFIC6 (MYO5B) n=4
Exploratory (29)
PFIC2 (BSEP, T) n=9
Variants not known n=8
Heterozygous mutations n=2
Previous surgery n=8
Fluctuating sBA n=2
Primary analysis: BSEP deficiency
participants with biallelic disease-causing variation in ABCB11 (NT)
Secondary analysis: All PFIC
participants with biallelic disease-causing variation in ABCB11 (NT), ATP8B1, ABCB4, TJP2 and MYO5B
Exploratory analysis: All participants
all participants incl. truncated BSEP deficiency, variants not known, heterozygosis, fluctuating sBAs and surgery

FIG. 5



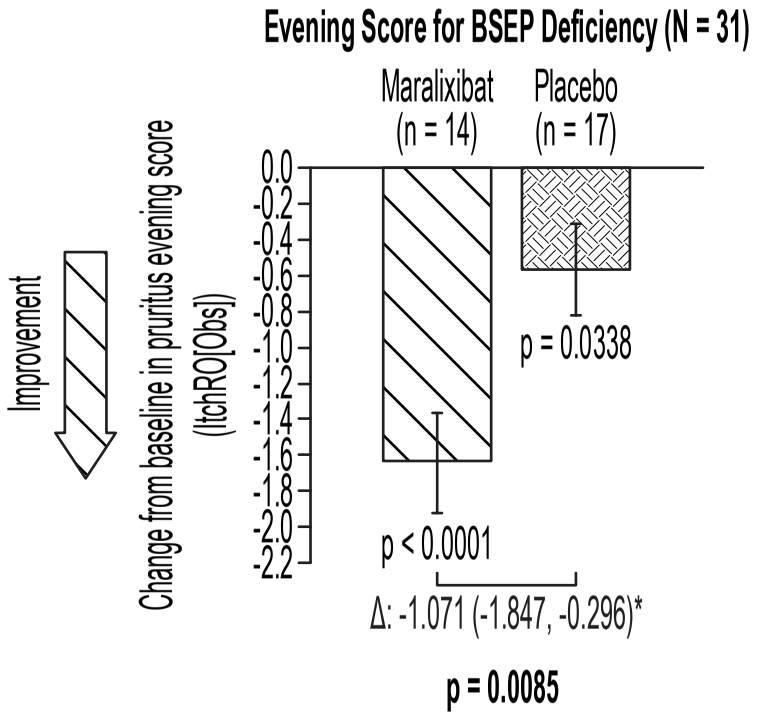


Data are LS mean (for bar plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (4-week intervals) using an MMRM. CI, confidence interval; ItchRO(Obs), Itch-Reported Outcome (Observer); LS, least squares; MMRM, mixed model repeated measures; PFIC, progressive familial intrahepatic cholestasis

*LS mean delta with 95% CI; †Maralixibat LS mean = placebo LS mean.

FIG. 6A

FIG. 6B



*Data are LS Mean with standard error bars (Baseline to Weeks 15-26).

FIG. 7A

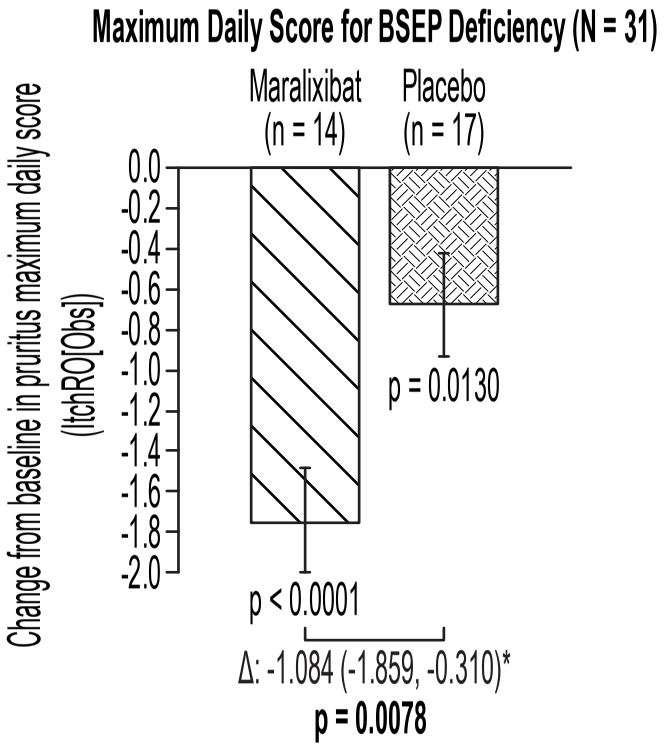
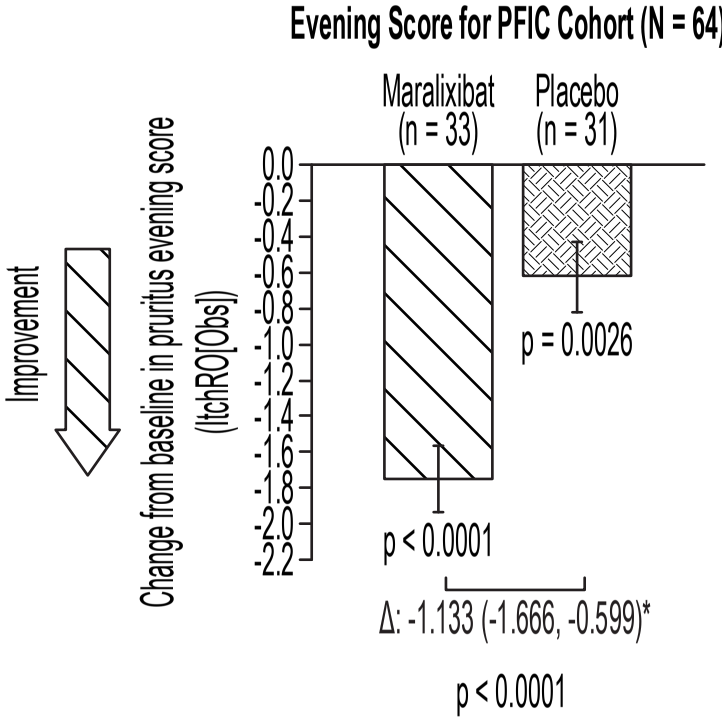


FIG. 7B



*Data are LS Mean with standard error bars (Baseline to Weeks 15-26).

FIG. 8A

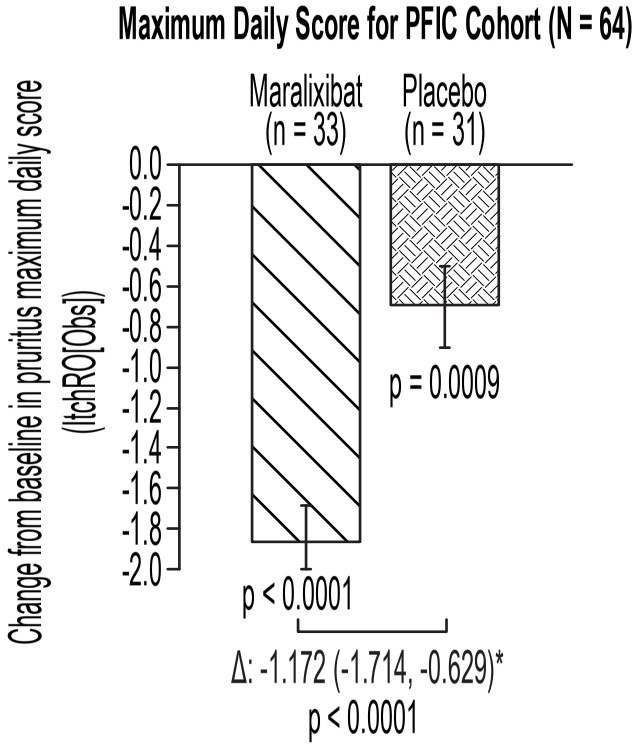


FIG. 8B

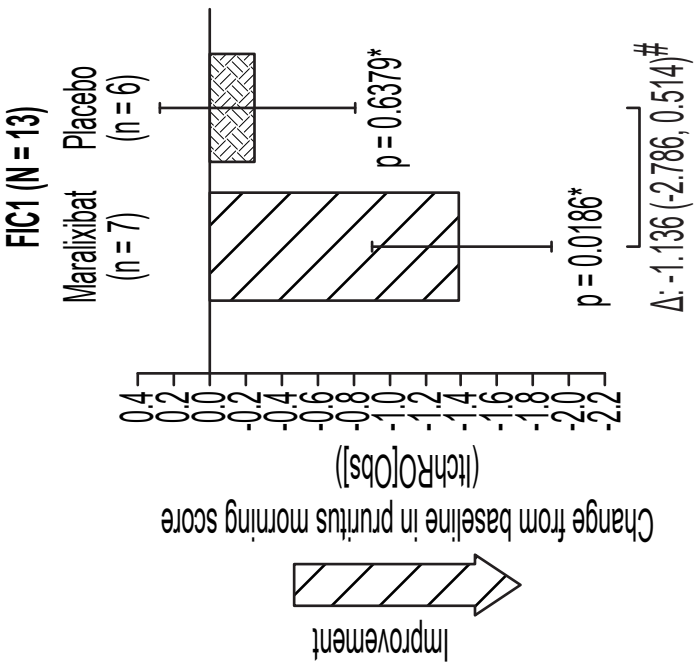

FIC1 (N = 13)
Maralixibat (n = 7)
Placebo (n = 6)
p = 0.6379*
p = 0.0186*
Δ: -1.136 (-2.786, 0.514)#
p = 0.1559**
Change from baseline in pruritus morning score (itchRO[Obs])
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
-1.6
-1.8
-2.0
-2.2
Improvement
Data are LS Mean with standard error bars.
* Change from Baseline to Week 15-26 LS Mean = 0
** Maralixibat LS mean = Placebo LS mean
# LS mean Delta with 95% CI

FIG. 9A

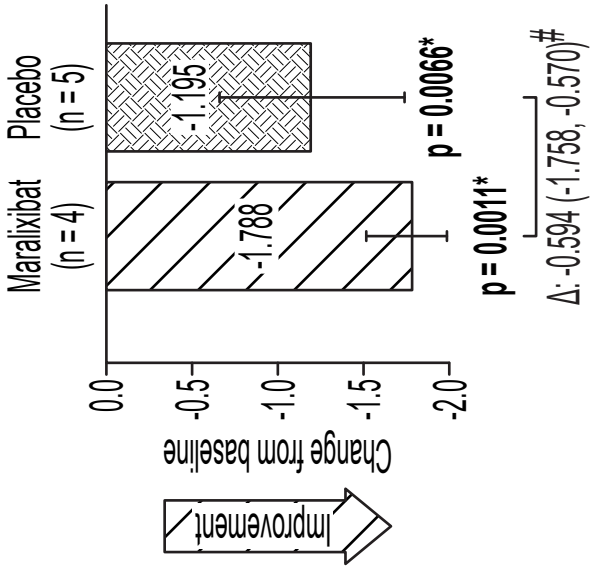

Maralixibat (n = 4)
Placebo (n = 5)
-1.788
-1.195
p = 0.0011*
p = 0.0066*
Δ: -0.594 (-1.758, -0.570)#
p = 0.2781**
Change from baseline
0.0
-0.5
-1.0
-1.5
-2.0
Improvement

FIG. 9B

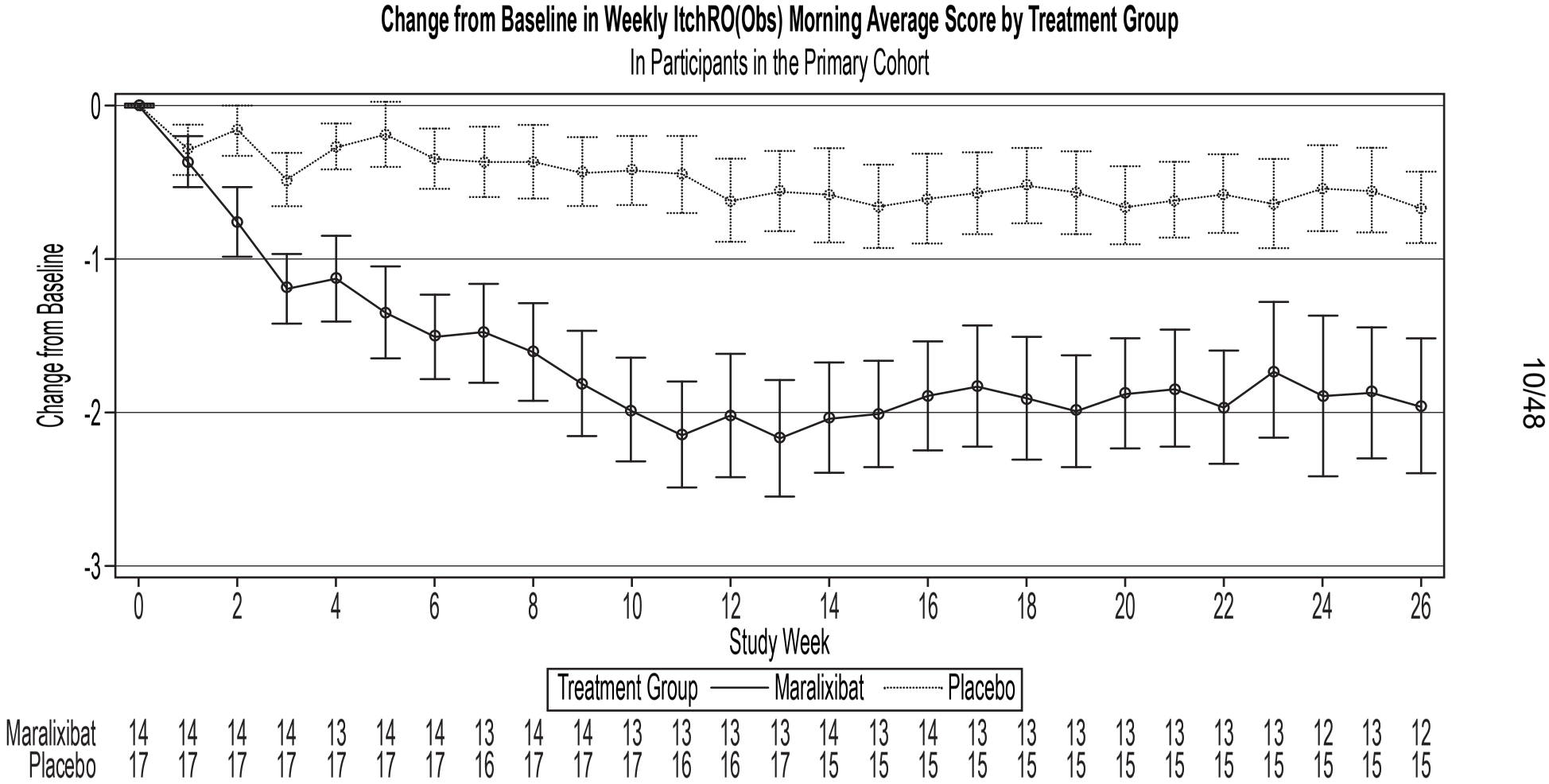

Change from Baseline in Weekly ItchRO(Obs) Morning Average Score by Treatment Group
In Participants in the Primary Cohort
Change from Baseline
0
-1
-2
-3
0
2
4
6
8
10
12
14
16
18
20
22
24
26
Study Week
Treatment Group
Maralixibat
Placebo
Maralixibat 14 14 14 14 13 14 14 13 14 14 13 13 13 13 14 13 14 13 13 13 13 13 13 13 12 13 12
Placebo 17 17 17 17 17 17 17 16 17 17 17 16 16 17 15 15 15 15 15 15 15 15 15 15 15 15 15

FIG. 10A

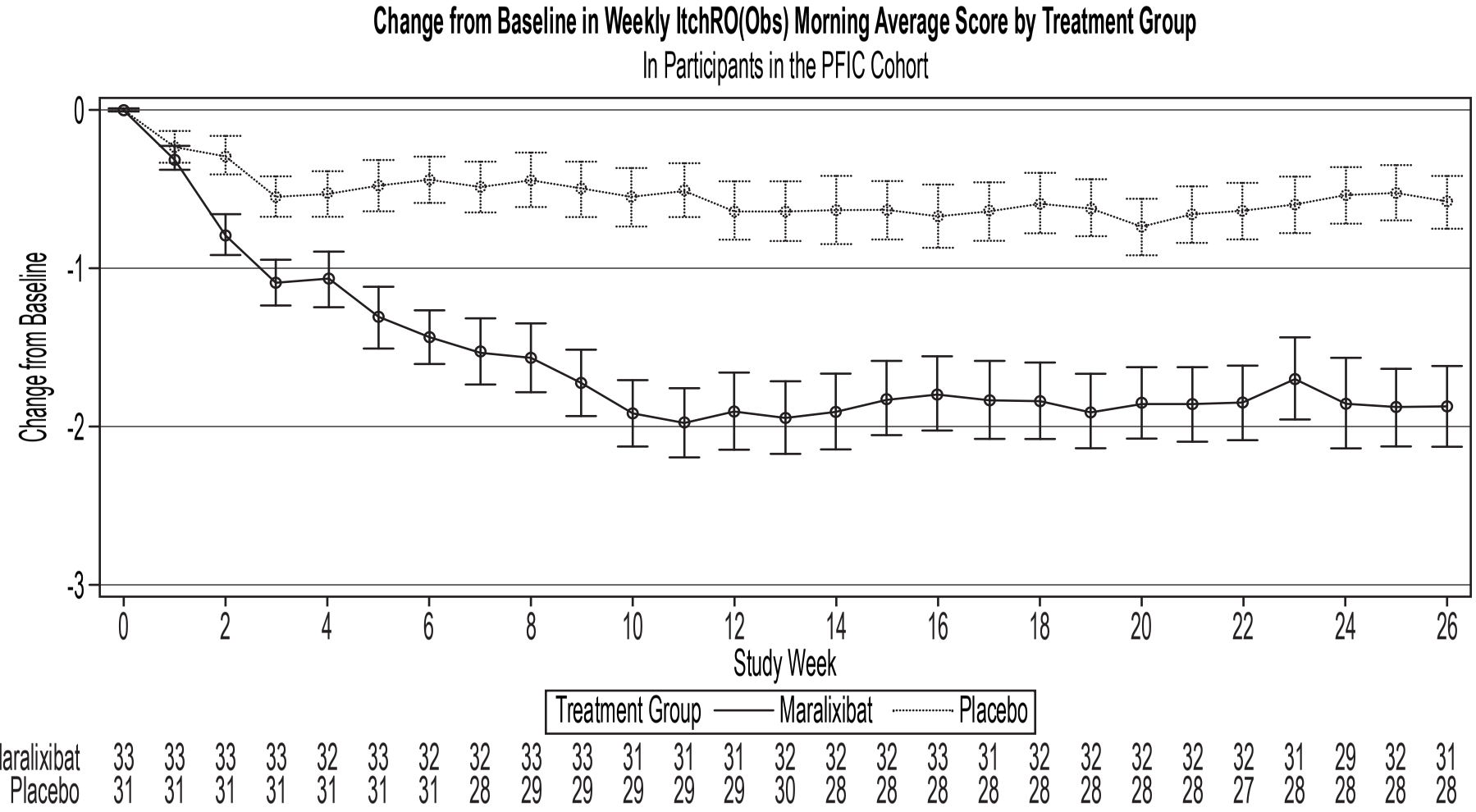

Change from Baseline in Weekly ItchRO(Obs) Morning Average Score by Treatment Group
In Participants in the PFIC Cohort
Change from Baseline
0
-1
-2
-3
0
2
4
6
8
10
12
14
16
18
20
22
24
26
Study Week
Treatment Group
Maralixibat
Placebo
Maralixibat 33 33 33 33 32 33 32 32 33 33 31 31 31 32 32 32 33 31 32 32 32 32 32 31 29 32 31
Placebo 31 31 31 31 31 31 31 28 29 29 29 29 29 30 28 28 28 28 28 28 28 28 27 28 28 28 28

FIG. 10B

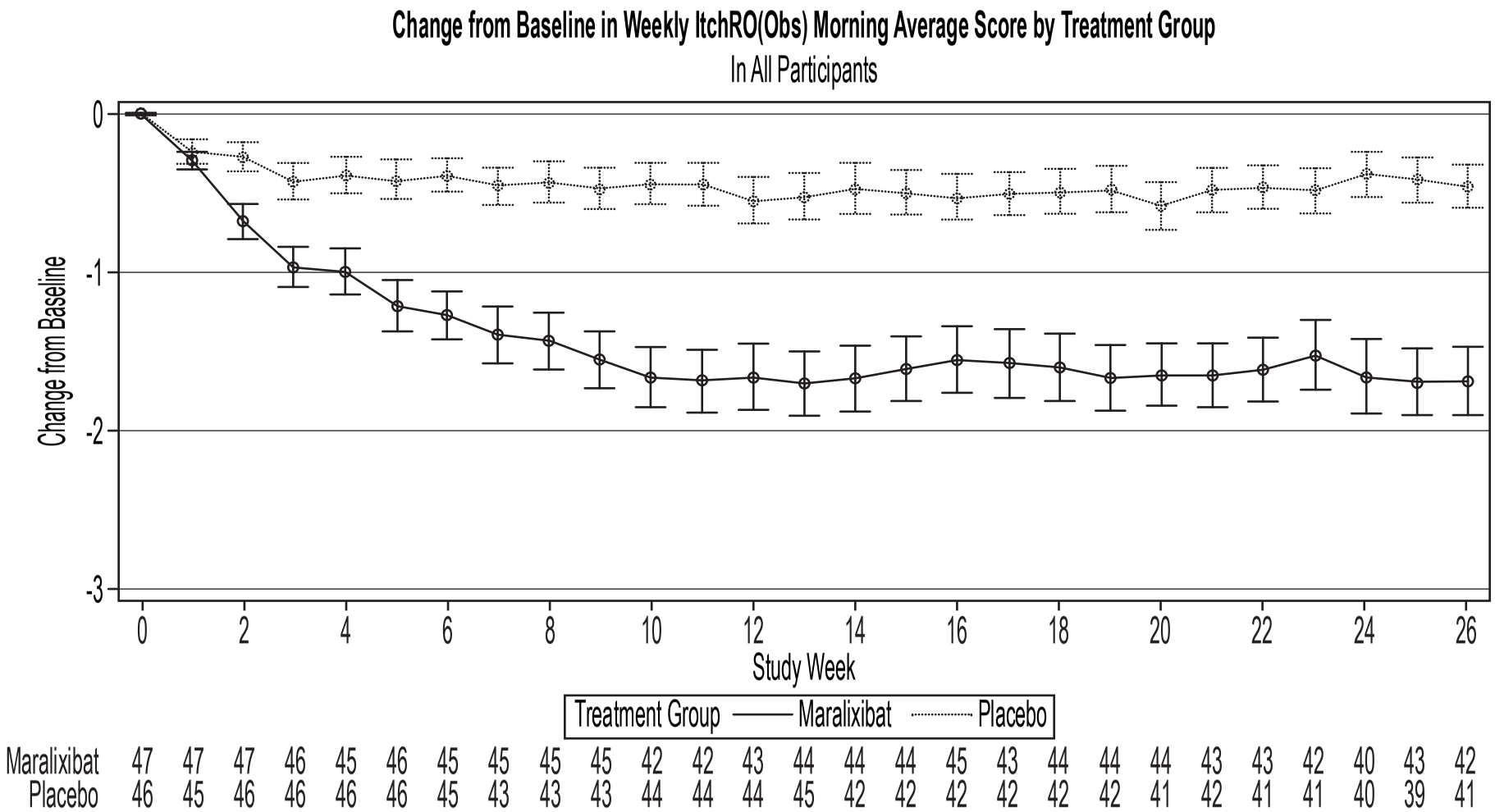
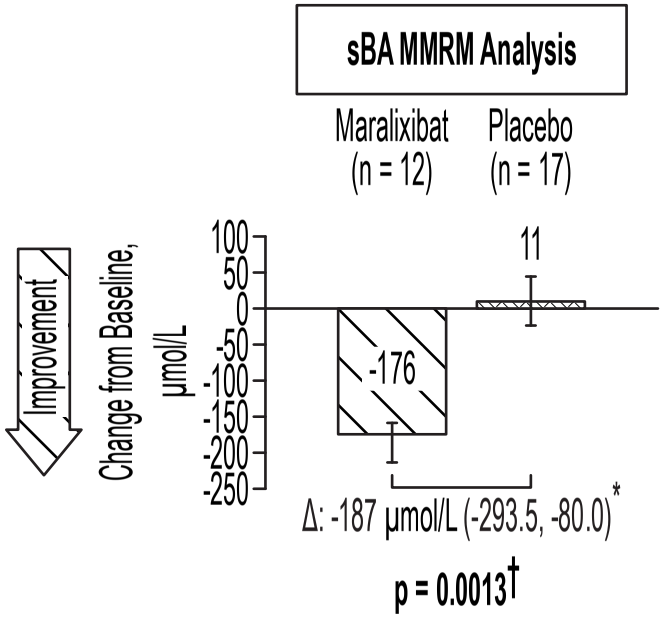
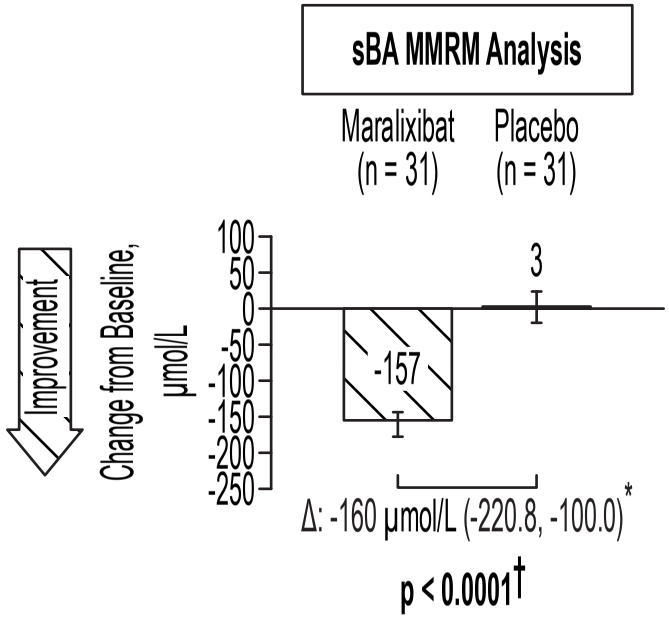

Change from Baseline in Weekly ItchRO(Obs) Morning Average Score by Treatment Group
In All Participants
Change from Baseline
0
-1
-2
-3
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week
Treatment Group
Maralixibat
Placebo
Maralixibat 47 47 47 46 45 46 45 45 45 45 42 42 43 44 44 44 45 43 44 44 44 43 43 42 40 43 42
Placebo 46 45 46 46 46 46 45 43 43 43 44 44 44 45 42 42 42 42 42 42 41 42 41 41 40 39 41

FIG. 10C





Data are LS mean (for bar plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (Weeks 18, 22 and 26) using an MMRM.

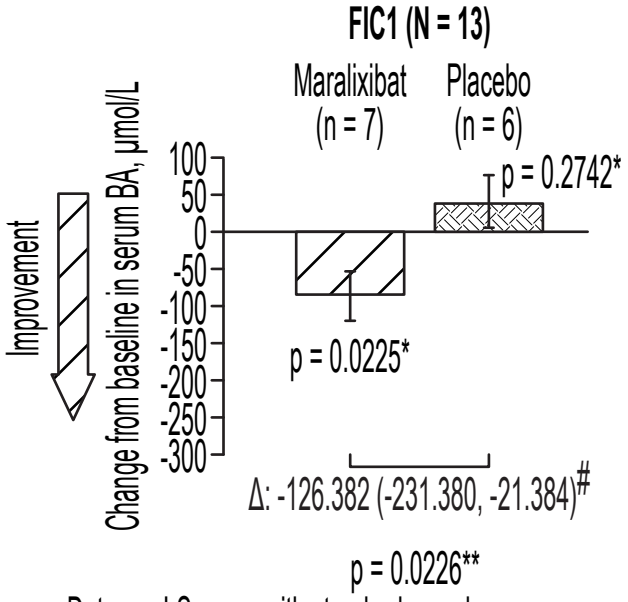
Two participants in the maralixibat group did not have baseline sBAs.

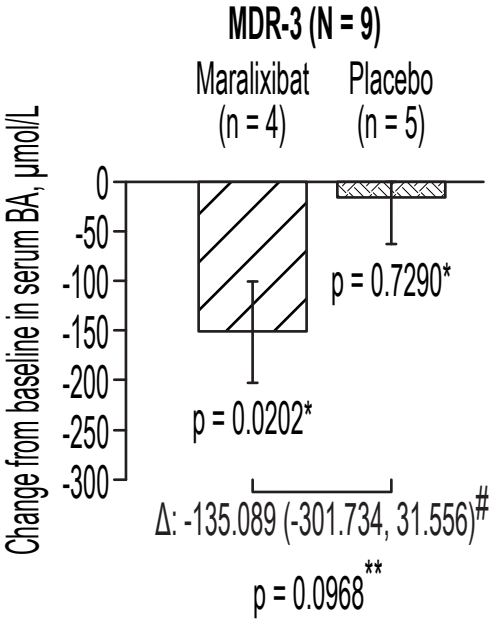
CI, confidence interval; LS, least squares; MMRM, mixed model repeated measures; PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid.

*LS mean delta with 95% CI; †Maralixibat LS mean = placebo LS mean.

FIG. 11A

FIG. 11B





Data are LS mean with standard error bars.

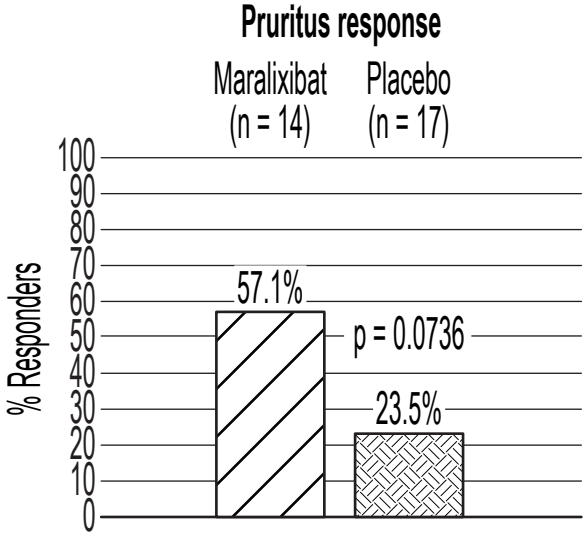
* Change from Baseline to week 18-26 LS Mean = 0

** Maralixibat LS mean = Placebo LS mean

LS mean Delta with 95% CI

FIG. 12A

FIG. 12B



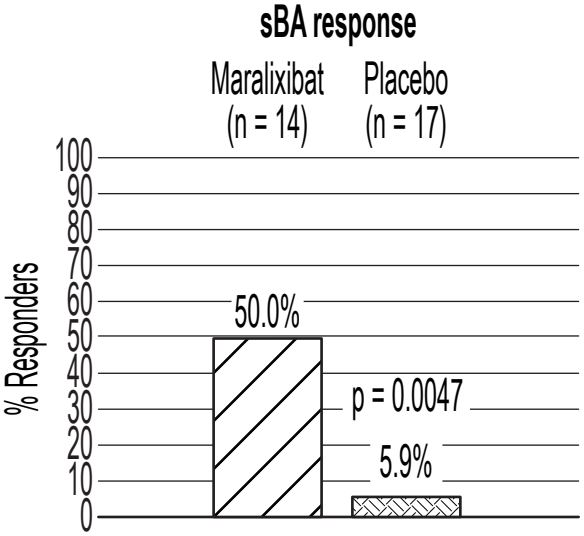


FIG. 13A

FIG. 13B

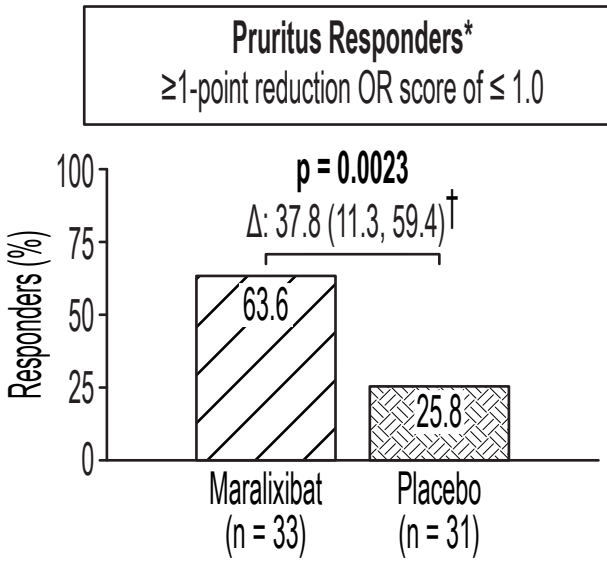


FIG. 14A

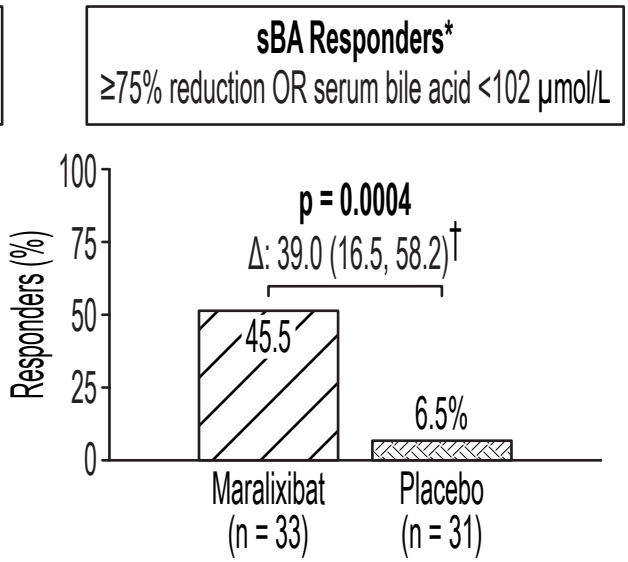


FIG. 14B

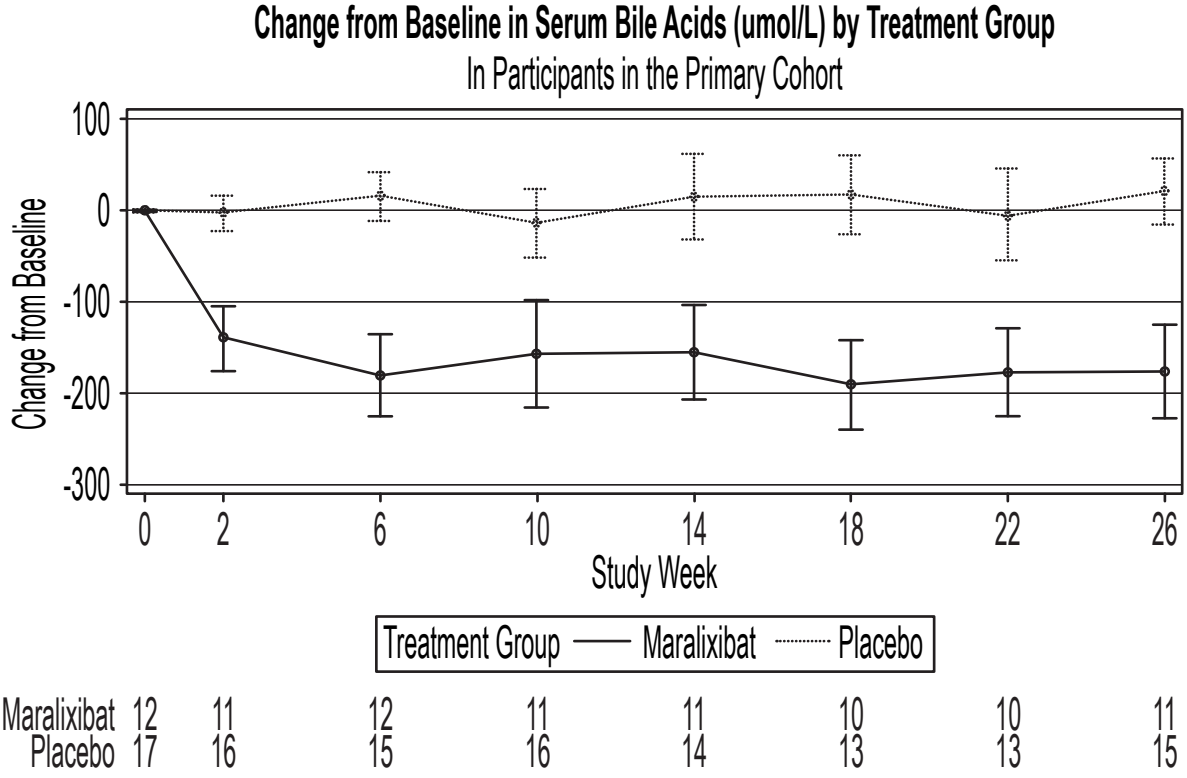


FIG. 15A

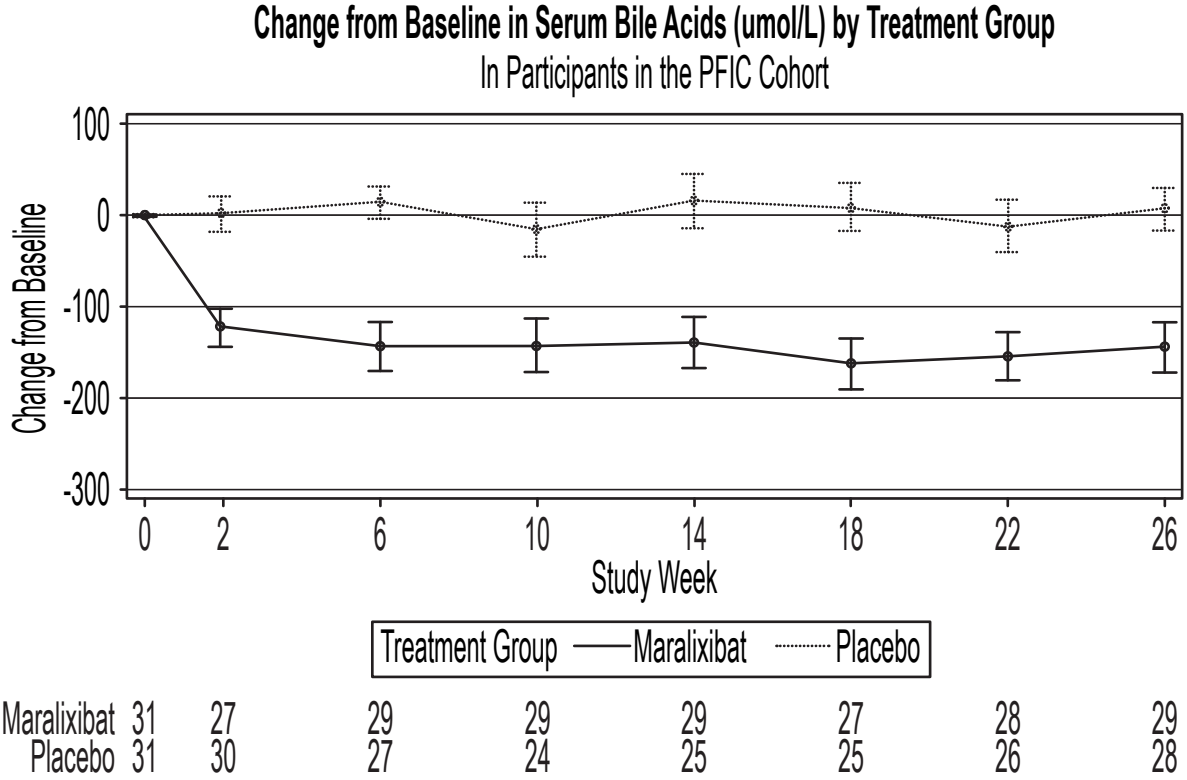


FIG. 15B

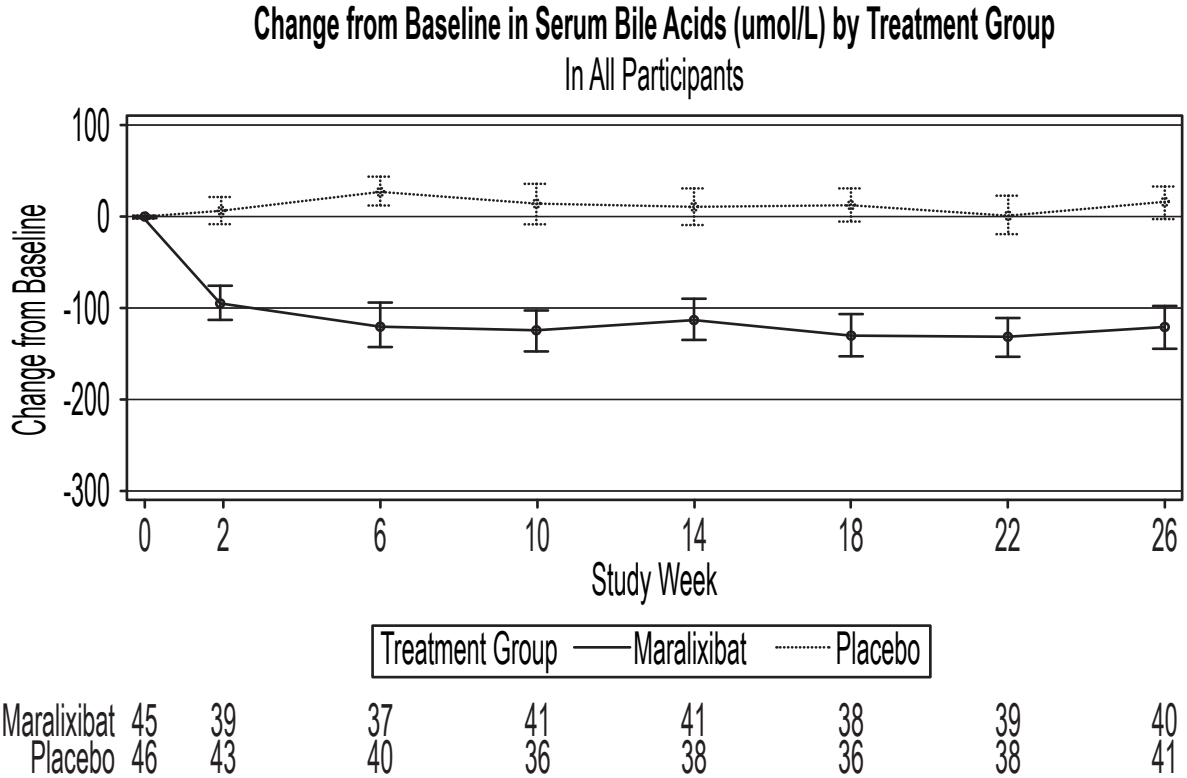


FIG. 15C

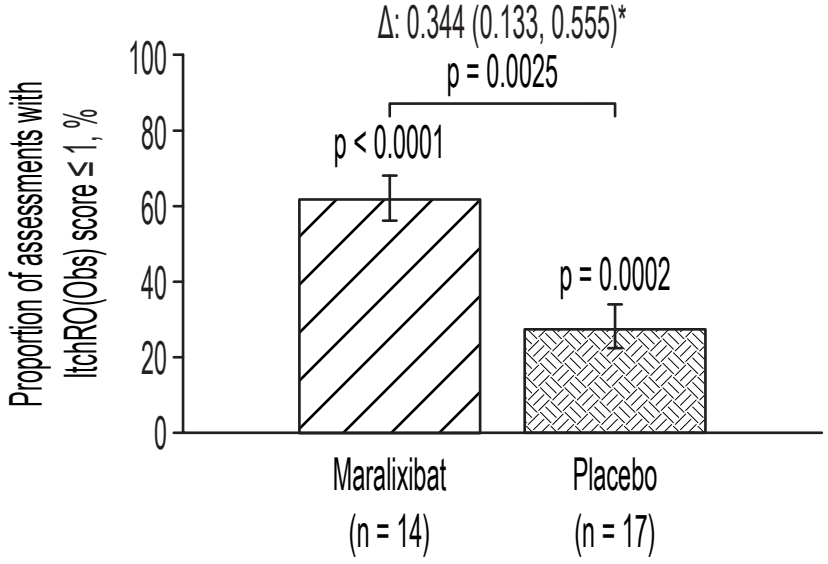


FIG. 16A

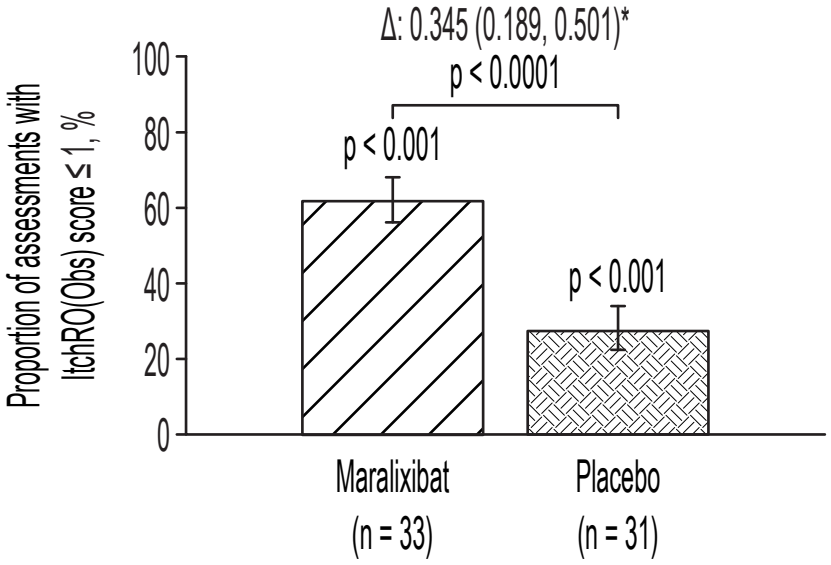


FIG. 16B

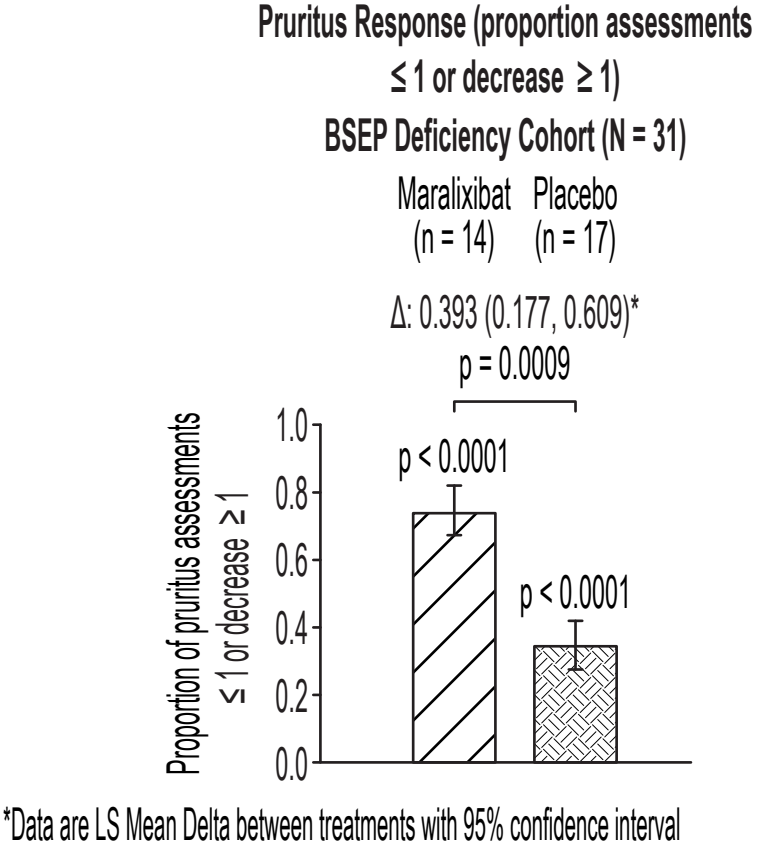


FIG. 17A

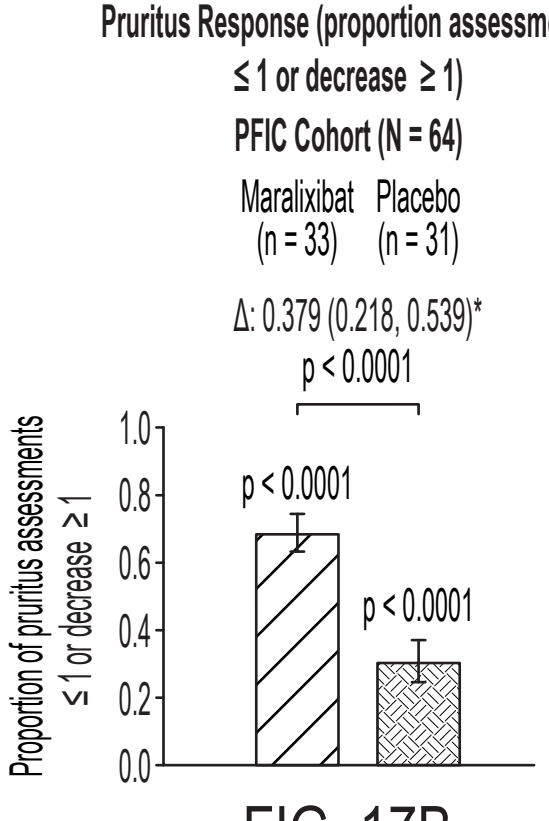


FIG. 17B

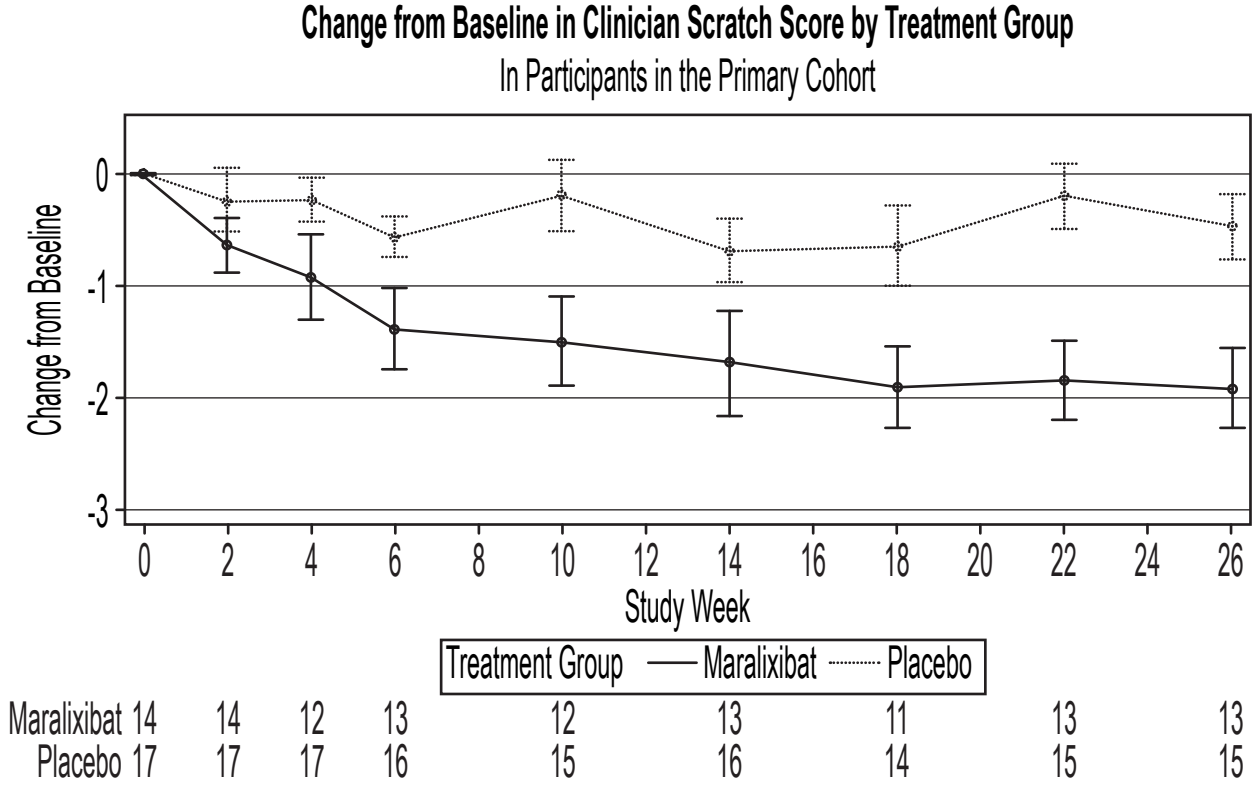


FIG. 18A

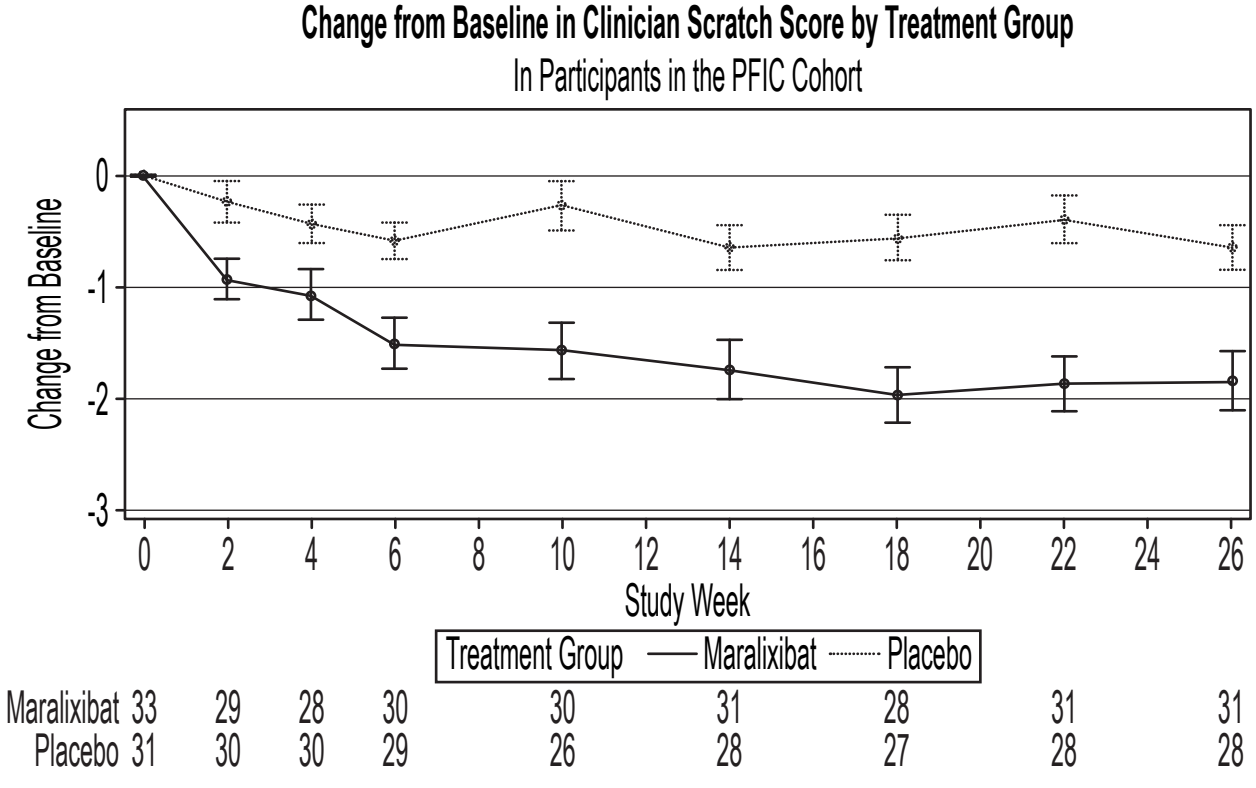
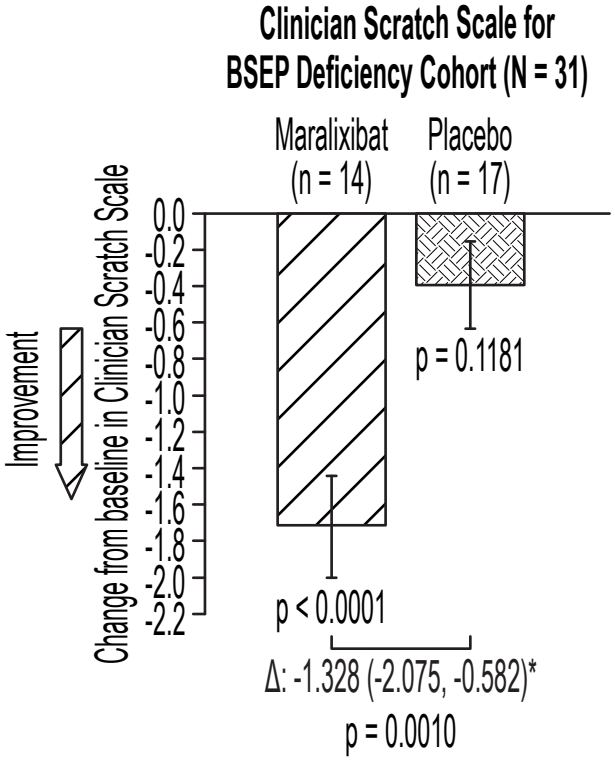


FIG. 18B



*Data are LS Mean Delta between Baseline and Week 26 with 95% confidence interval

FIG. 19A

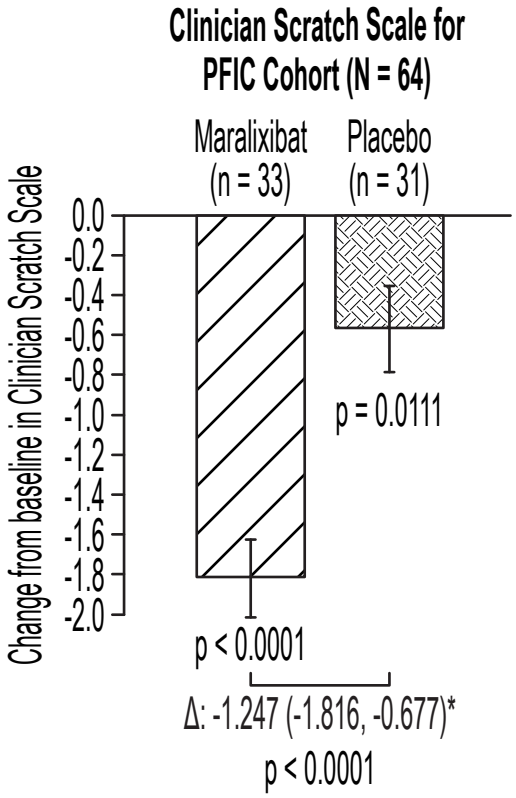
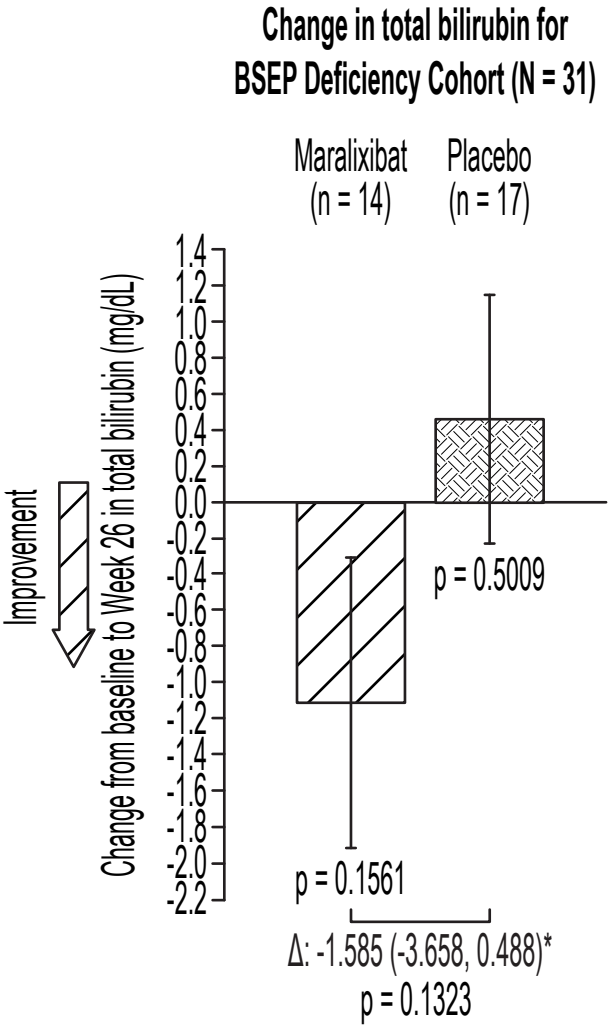

Clinician Scratch Scale for
PFIC Cohort (N = 64)
Maralixibat
(n = 33)
Placebo
(n = 31)
Change from baseline in Clinician Scratch Scale
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
-1.6
-1.8
-2.0
p = 0.0111
p < 0.0001
Δ: -1.247 (-1.816, -0.677)*
p < 0.0001

FIG. 19B



*Data are LS Mean Delta between Baseline and Week 26 with 95% confidence interval

FIG. 20A

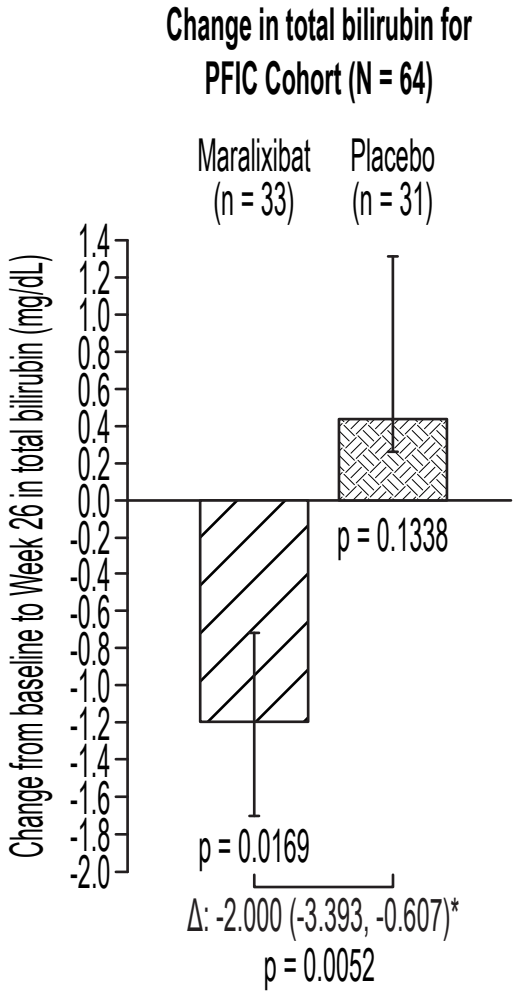

Change in total bilirubin for
PFIC Cohort (N = 64)
Maralixibat
(n = 33)
Placebo
(n = 31)
Change from baseline to Week 26 in total bilirubin (mg/dL)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
-1.6
-1.8
-2.0
p = 0.1338
p = 0.0169
Δ: -2.000 (-3.393, -0.607)*
p = 0.0052

FIG. 20B

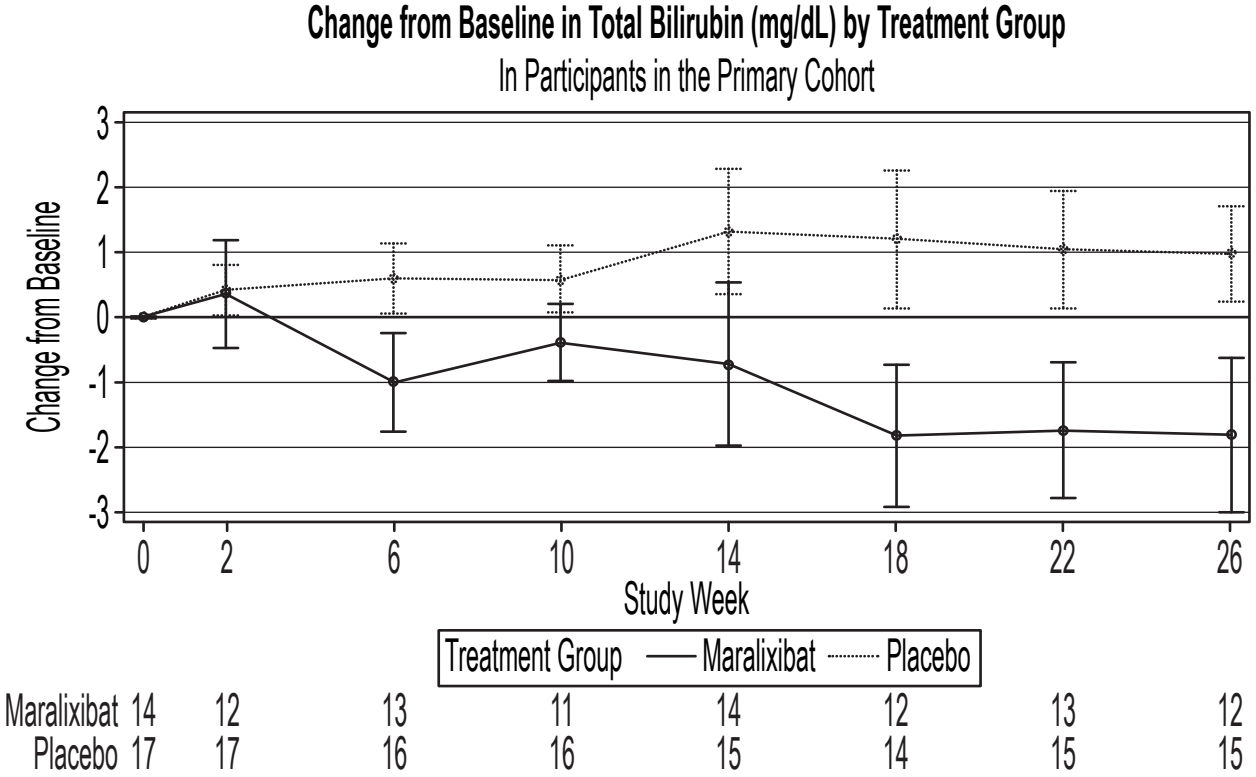


FIG. 21A

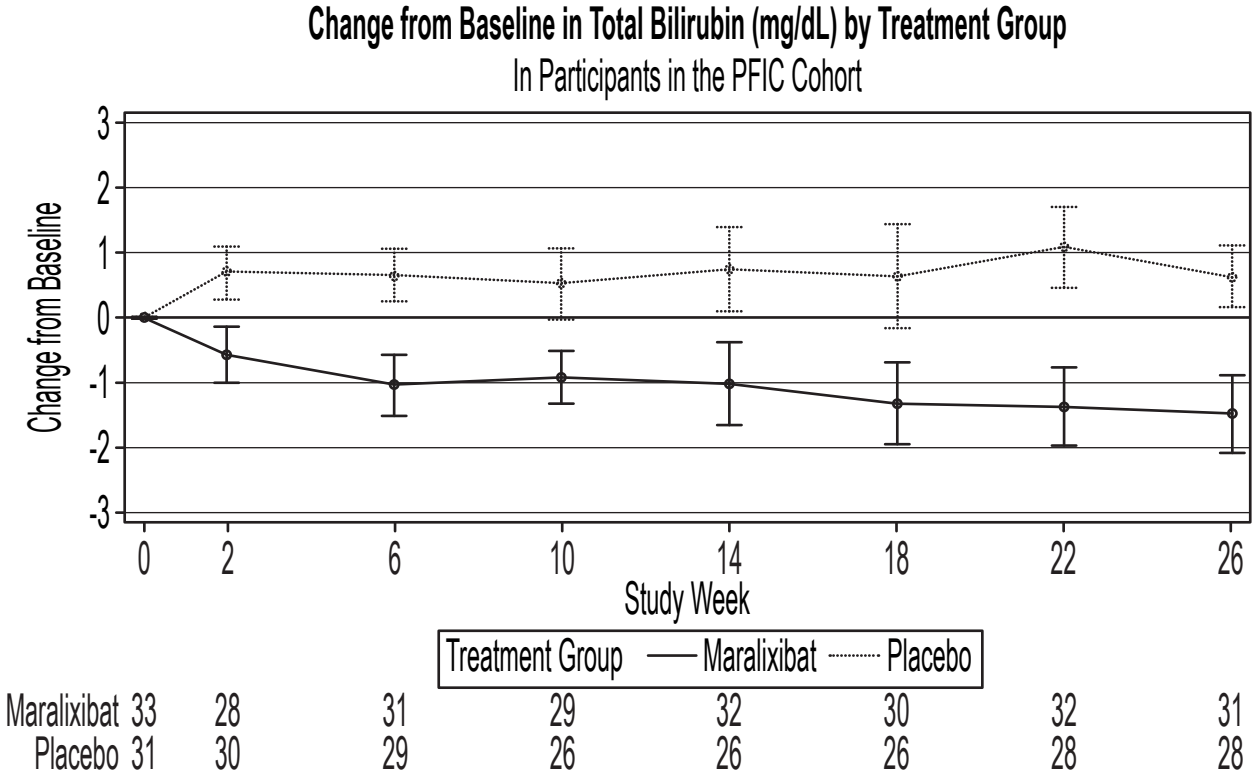
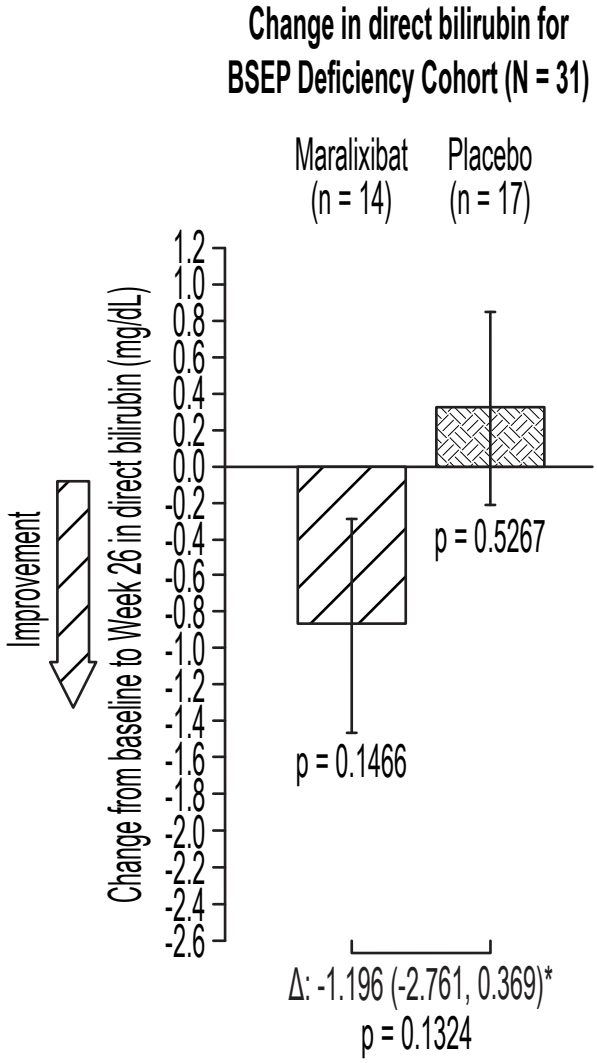


FIG. 21B



*Data are LS Mean Delta between Baseline and Week 26 with 95% confidence interval

FIG. 22A

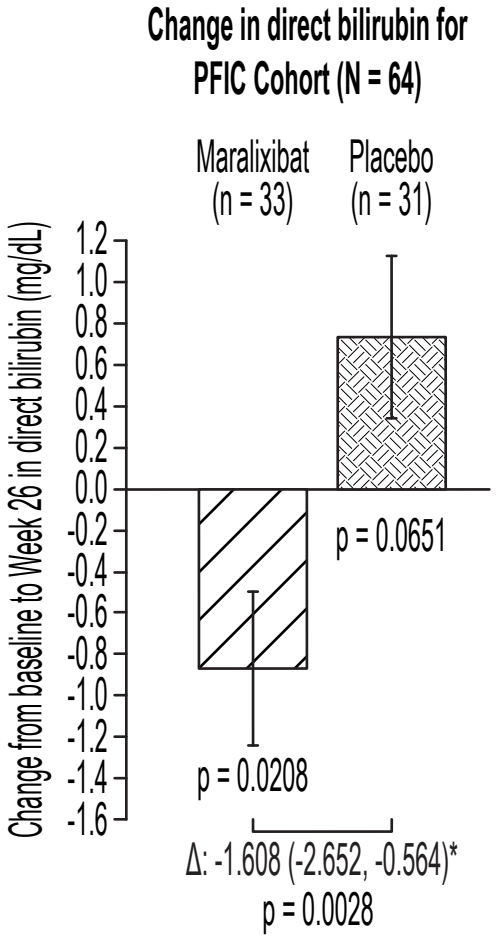
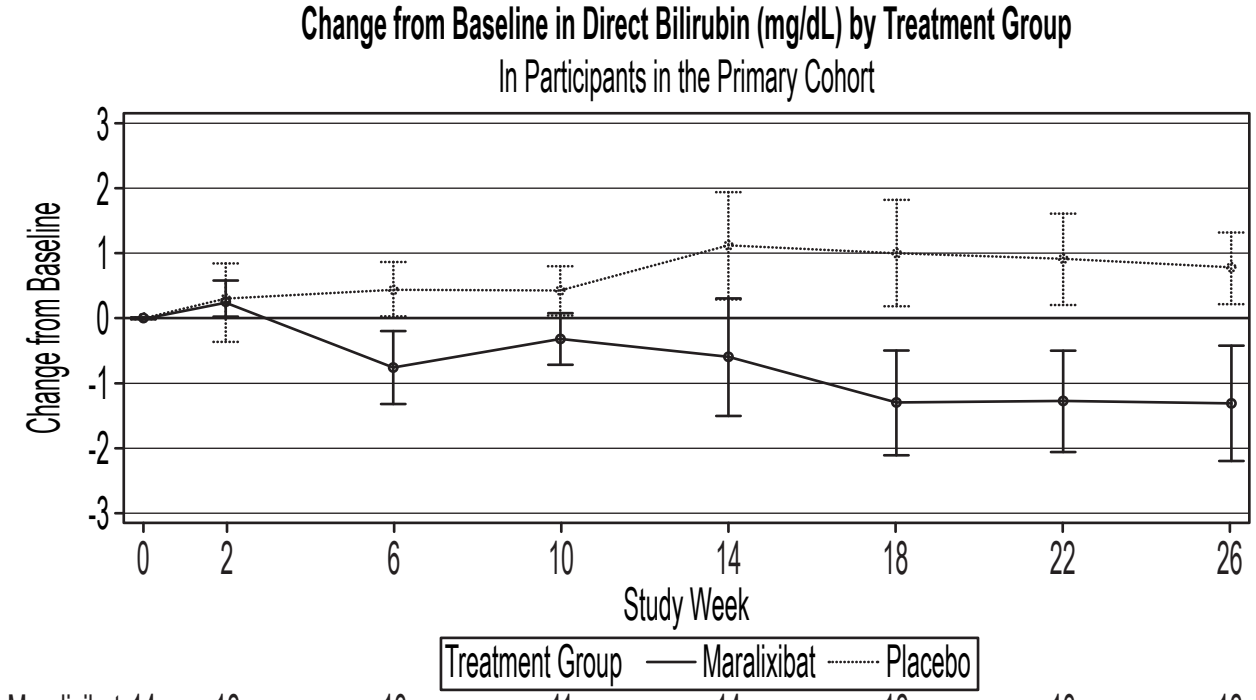
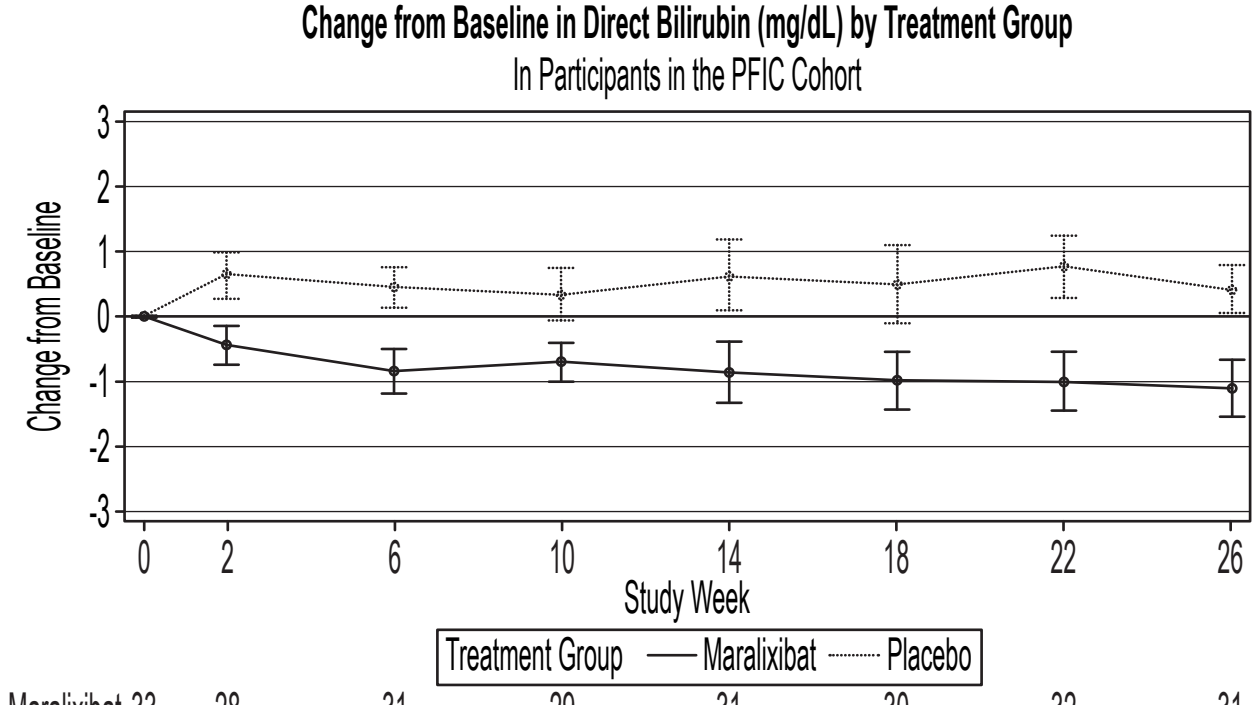

Change in direct bilirubin for
PFIC Cohort (N = 64)
Maralixibat
(n = 33)
Placebo
(n = 31)
Change from baseline to Week 26 in direct bilirubin (mg/dL)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
-1.6
p = 0.0651
p = 0.0208
Δ: -1.608 (-2.652, -0.564)*
p = 0.0028

FIG. 22B



Maralixibat	14	12	13	11	14	12	13	12
Placebo	17	17	15	16	15	13	14	15

FIG. 23A



Maralixibat	33	28	31	29	31	30	32	31
Placebo	31	30	28	26	26	25	27	28

FIG. 23B

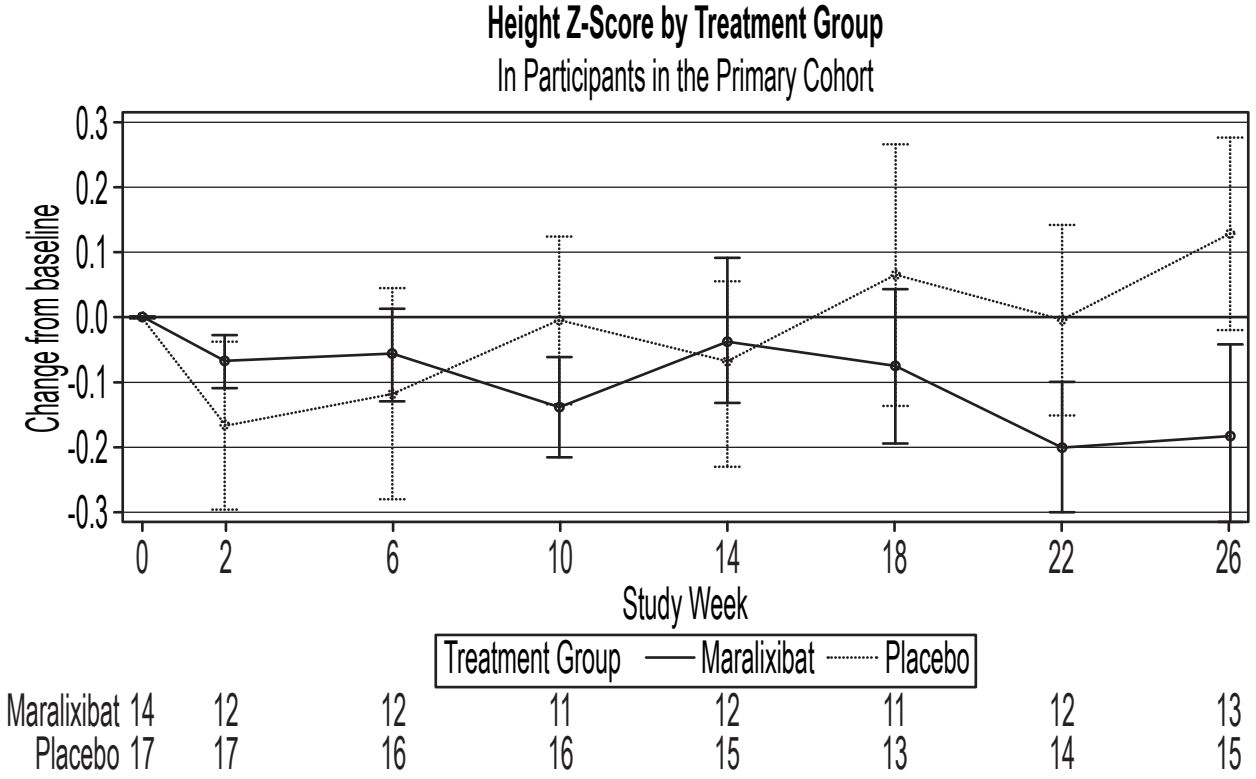


FIG. 24A

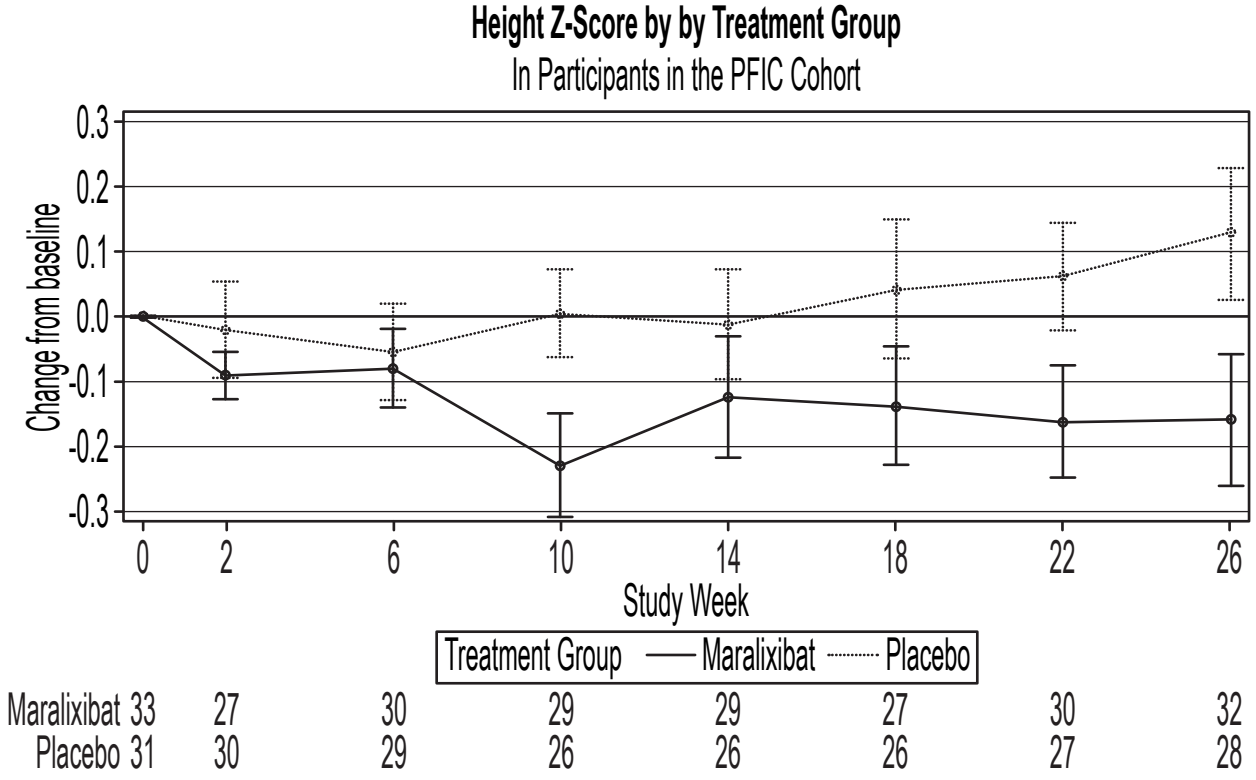
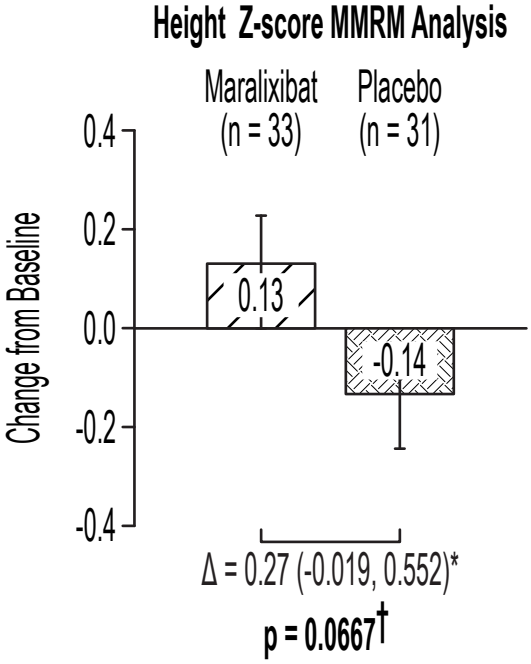


FIG. 24B



* LS mean delta with 95% CI; †Maralixibat LS mean = placebo LS mean

FIG. 24C

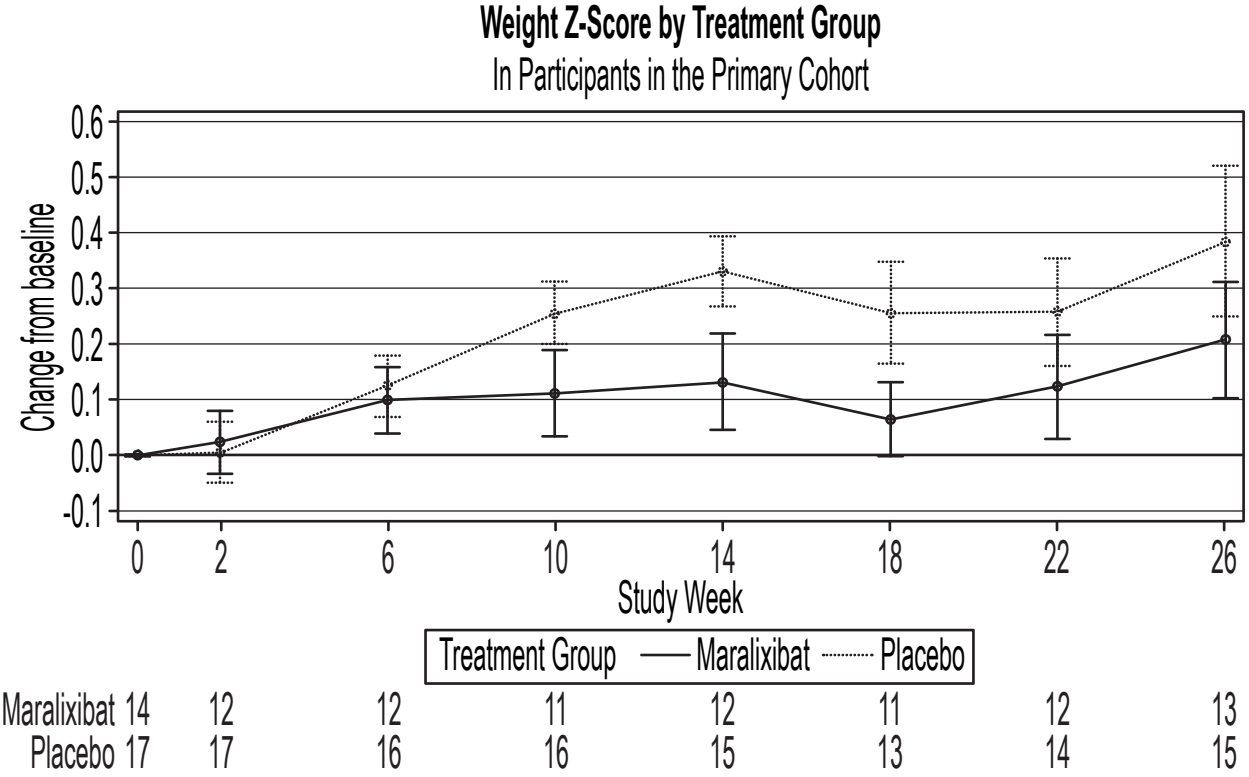


FIG. 25A

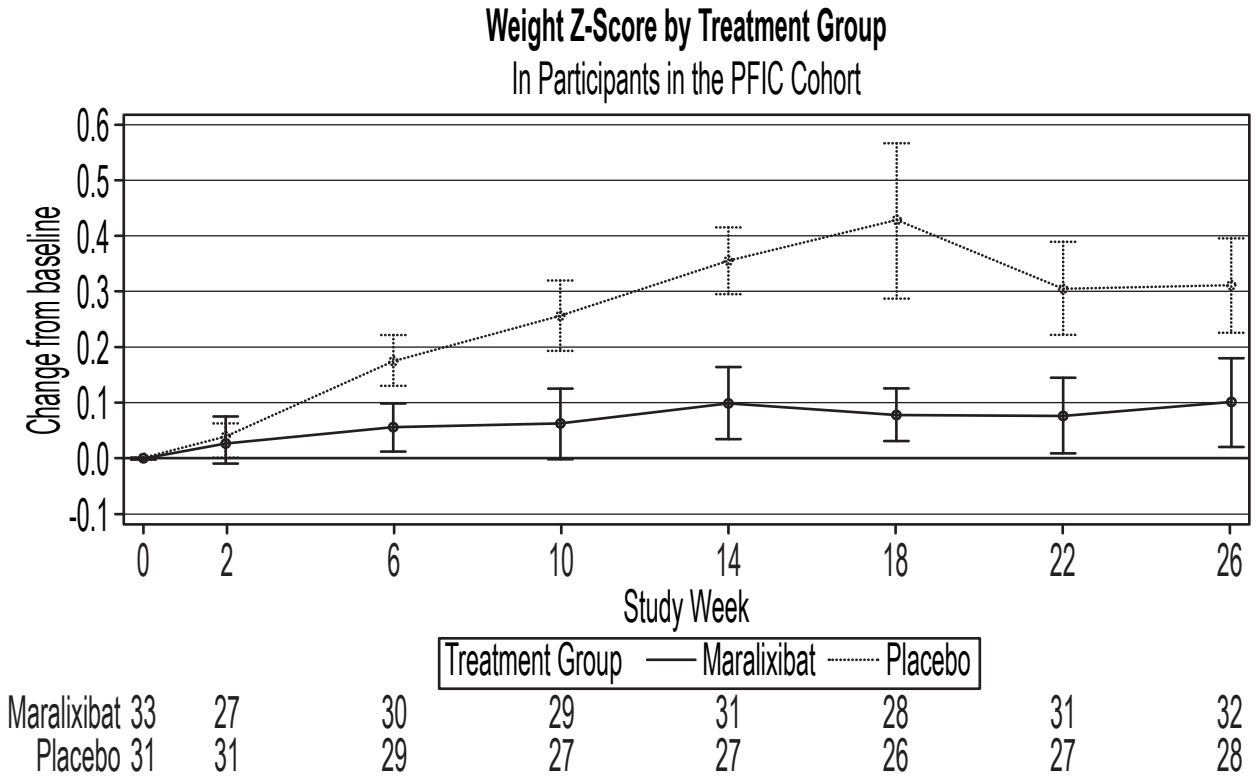


FIG. 25B

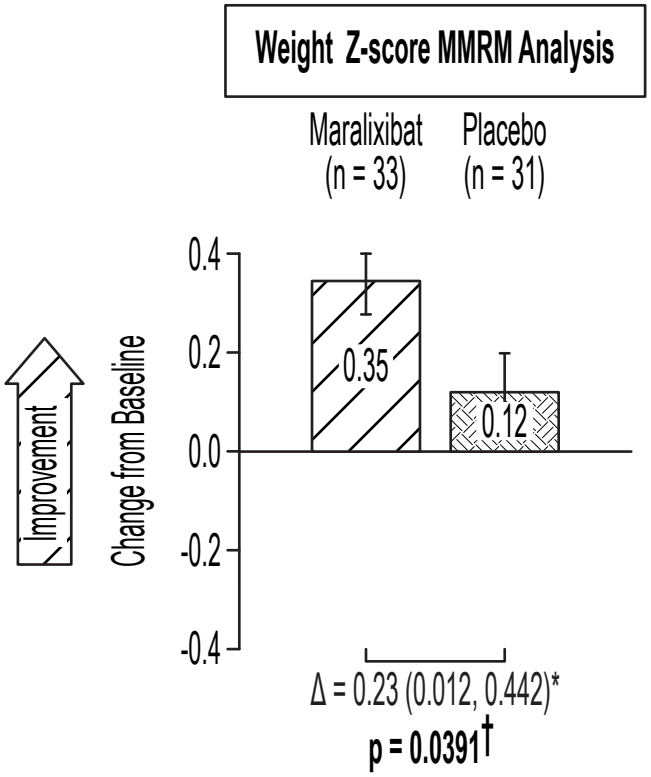
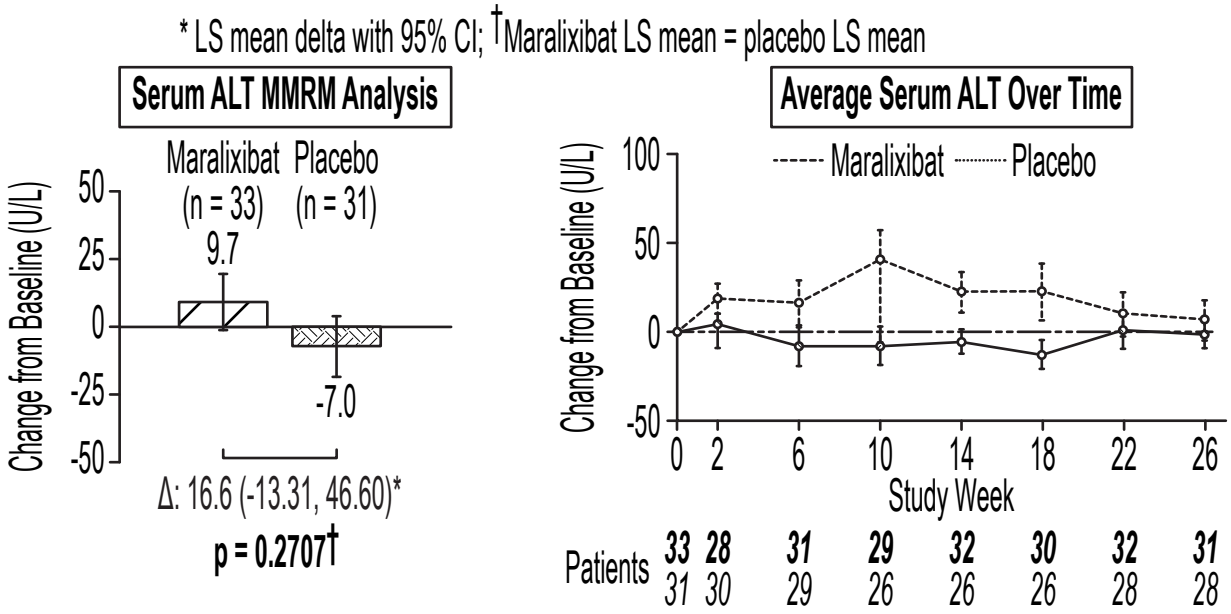


FIG. 25C



Data are LS mean (for bar plot) and mean (for line plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (weeks 18, 22, and 26) using a MMRM. ALT, alanine aminotransferase; LS, least squares, MMRM, mixed model repeated measures; PFIC, progressive familial intrahepatic cholestasis

*LS mean delta with 95% CI; †Maralixibat LS mean = placebo LS mean

FIG. 26A

FIG. 26B

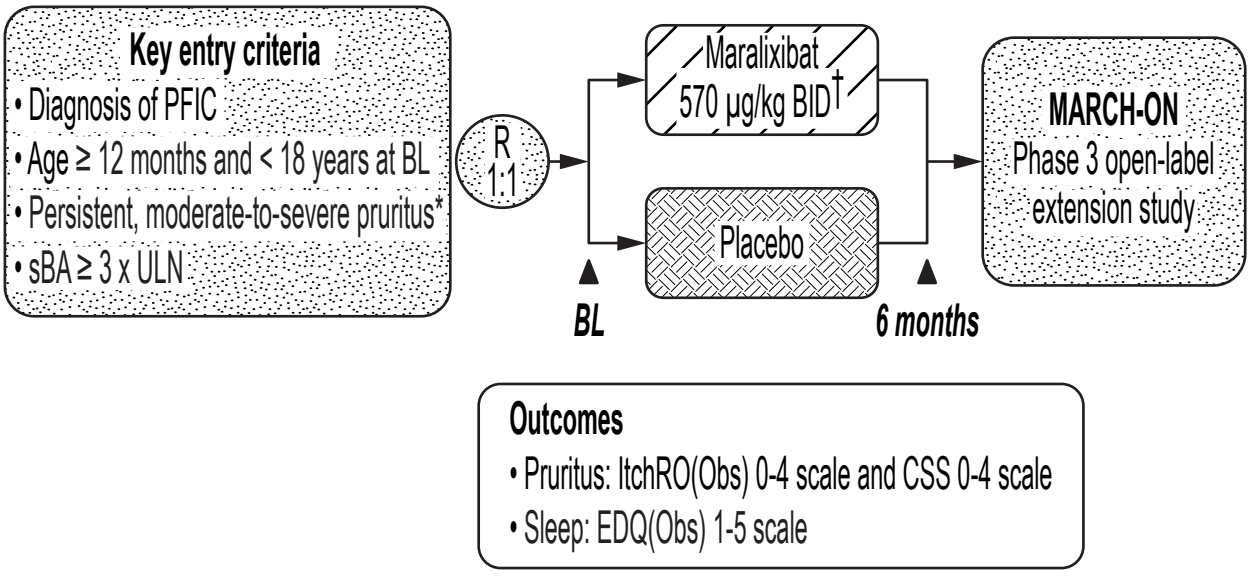


FIG. 27A

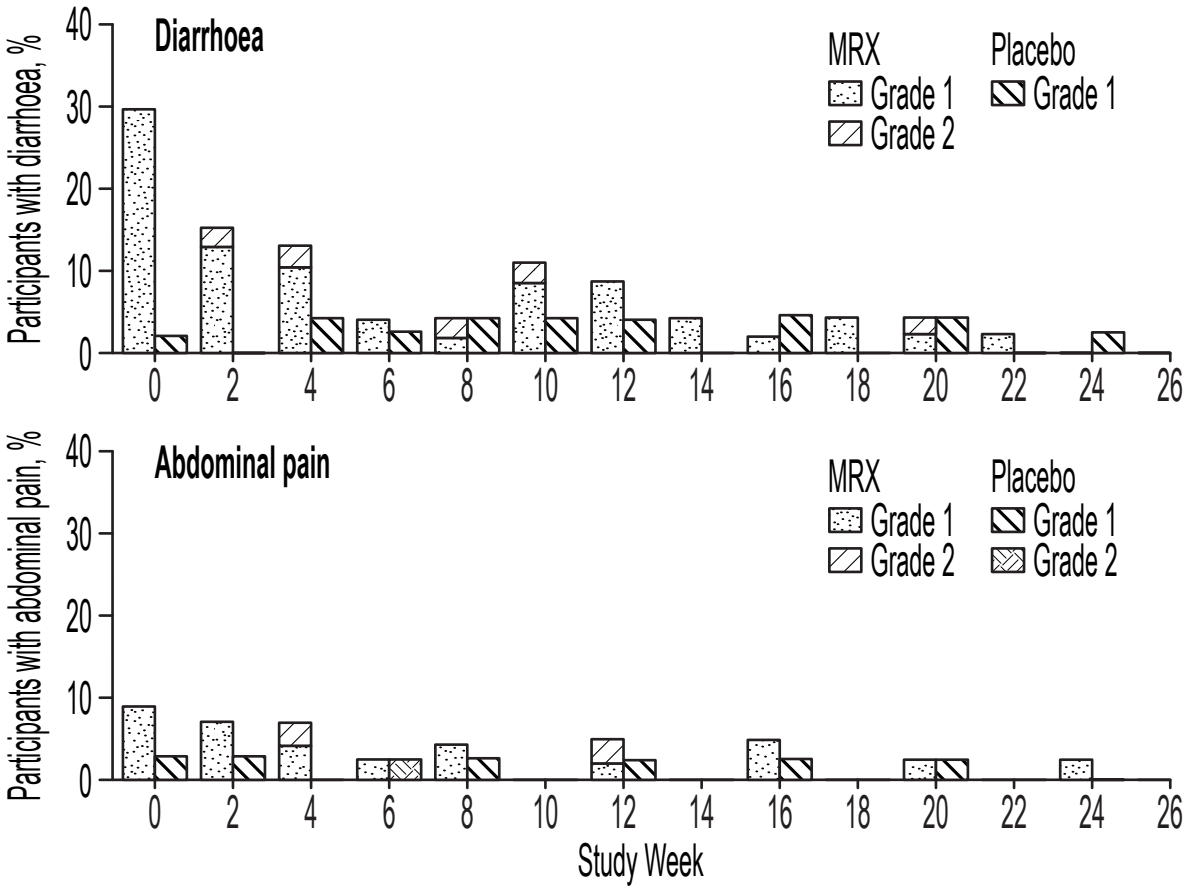
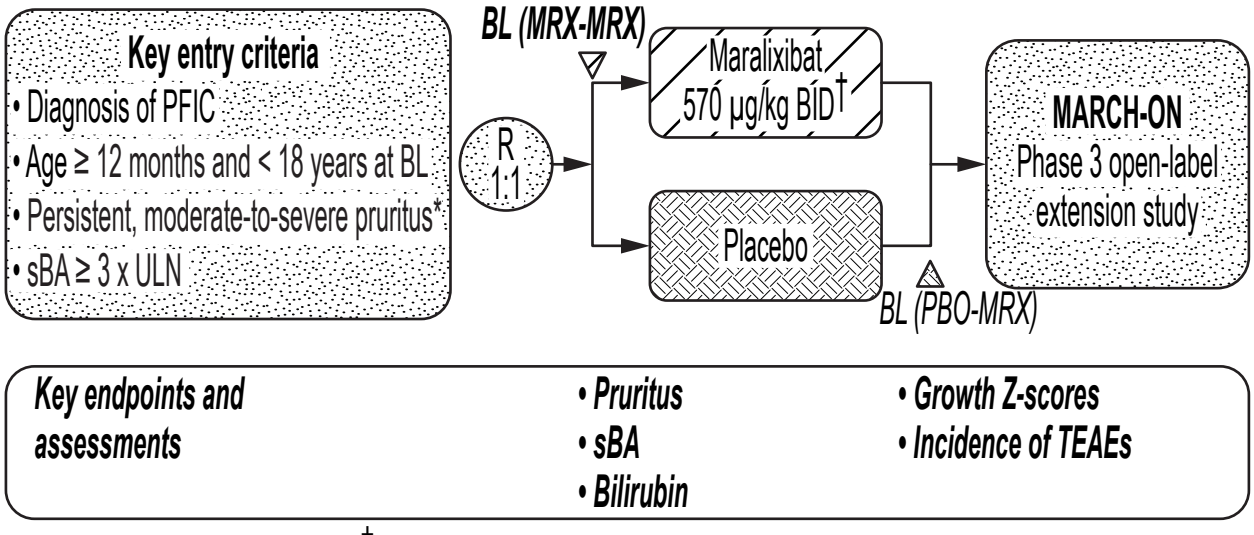
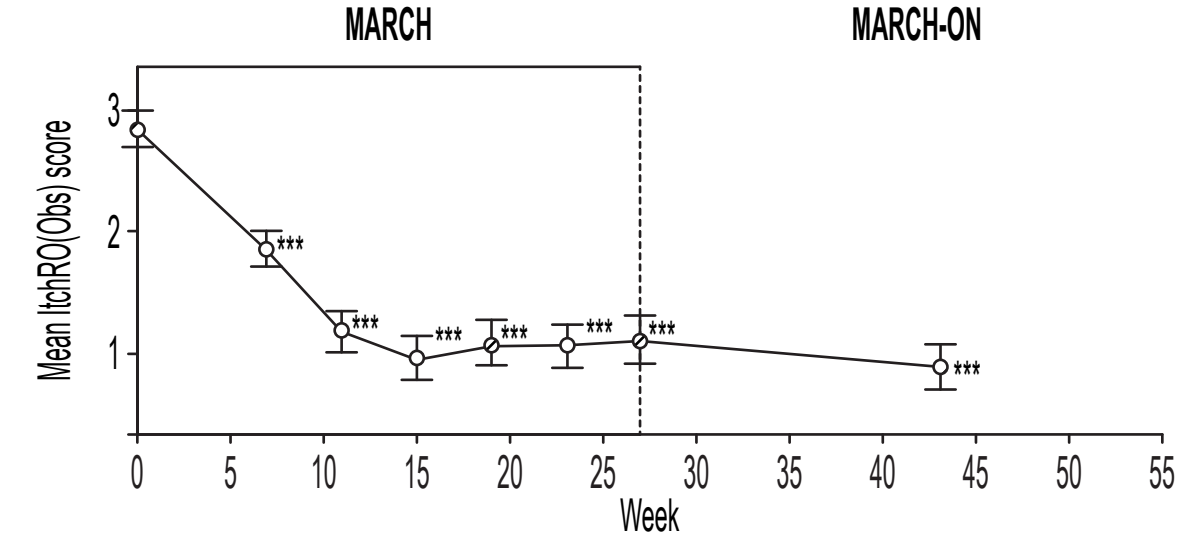


FIG. 28



*ItchRO(Obs) score ≥ 1.5; †Maralixibat 570 µg/kg is equivalent to 600 µg/kg maralixibat chloride
BL, baseline; MRX, maralixibat, PBO, placebo; R, randomised, TEAE, treatment-emergent adverse event

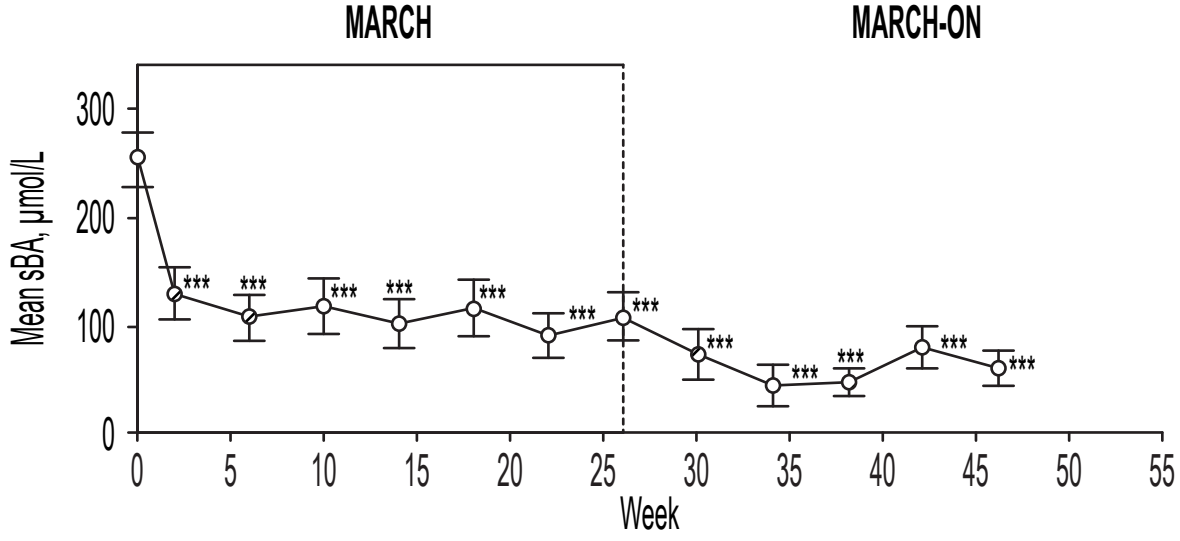
FIG. 29A



MRX-MRX	33		33	33	31	33	32	32				19	

***p < 0.001 from t-test. Error bars show the standard error of the mean.

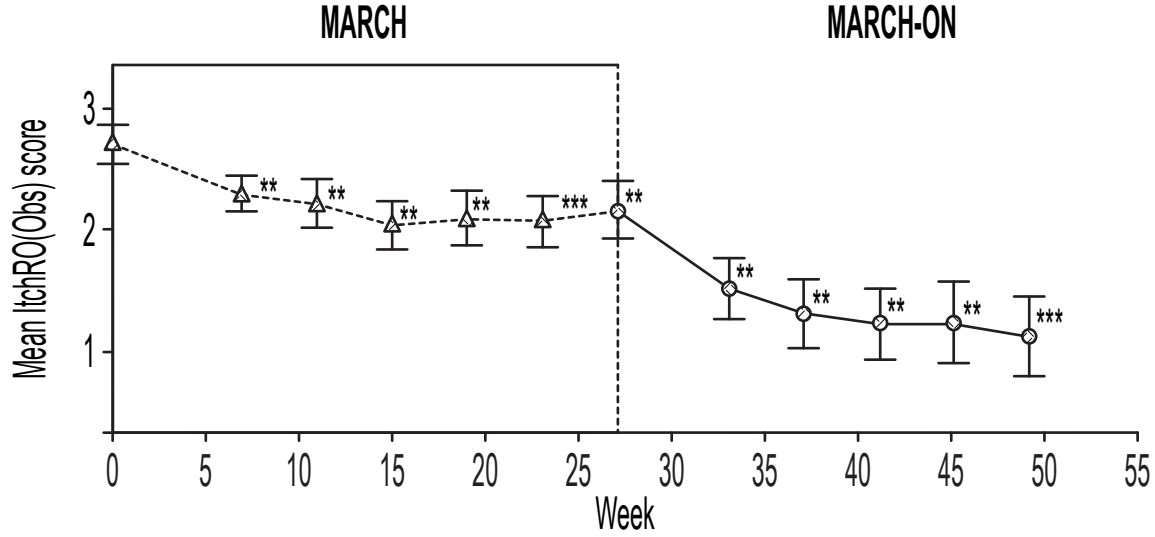
FIG. 29B



MRX-MRX	31	28	31	30	31	29	30	31	23	17	19	20	20

***p < 0.001 from t-test. Error bars show the standard error of the mean.

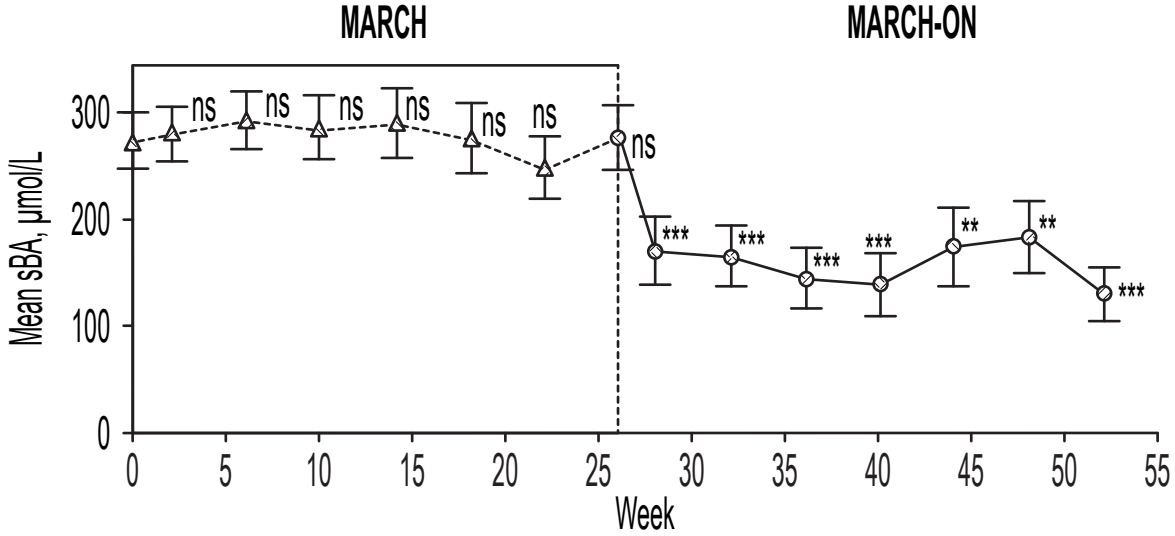
FIG. 29C



PBO-MRX 31 31 29 29 28 28 28 24 22 21 19 15

**p < 0.01; ***p < 0.001 from t-test. Error bars show the standard error of the mean.

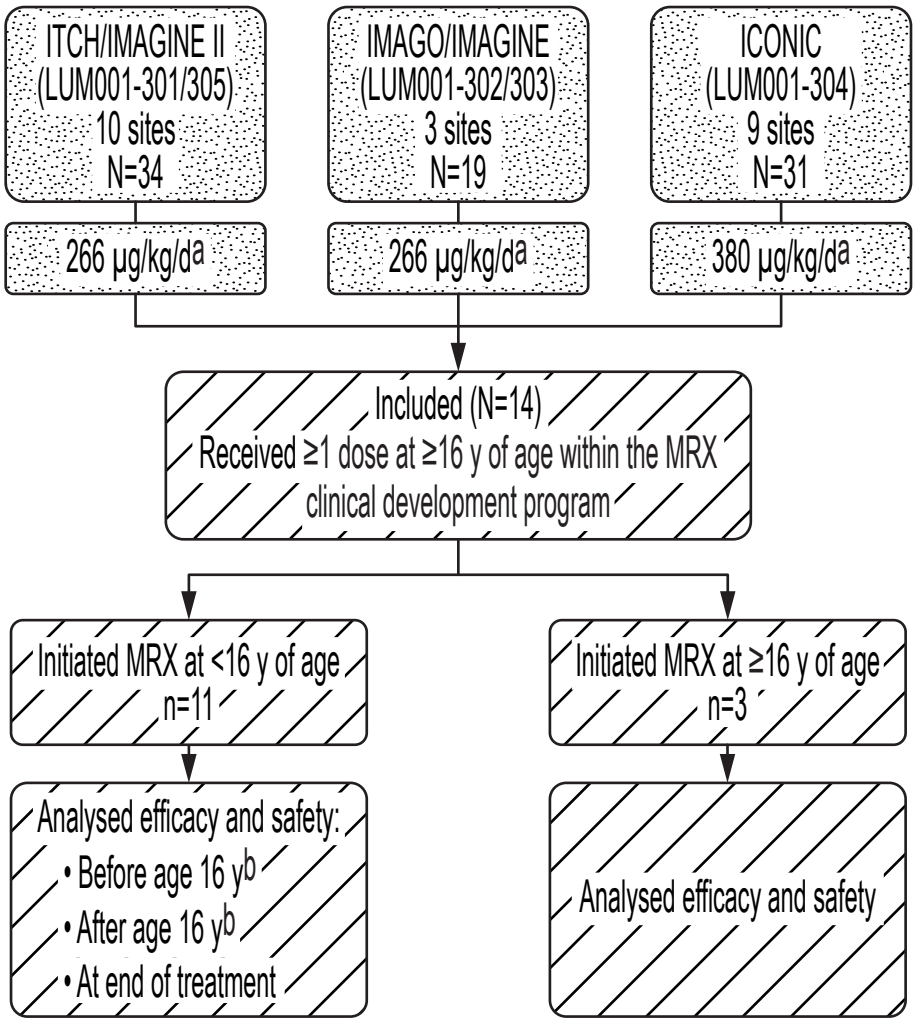
FIG. 29D



PBO-MRX 31 30 27 24 25 25 26 28 22 21 20 18 17 15 14

**p < 0.01; ***p < 0.001 from t-test. Error bars show the standard error of the mean. ns, not significant.

FIG. 29E



[a]All doses presented as MRX-free base. All patients received the daily dose appropriate for their weight, with an adult maximum dose of 28.5 mg/d.

[b]Before age 16 years is defined as the last data point prior to turning 16 years of age. After age 16 years is defined as the first data point after turning 16 years of age.

FIG. 30

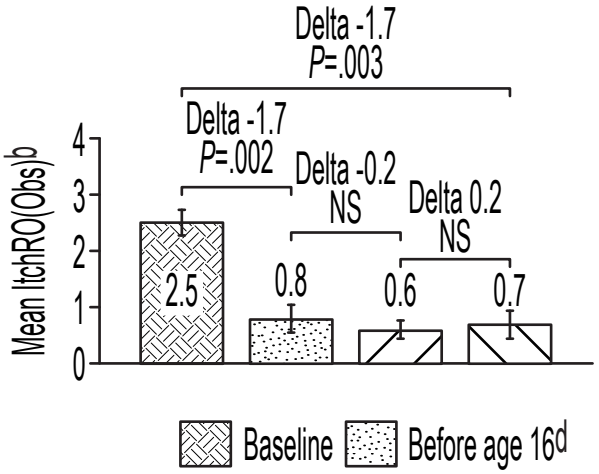


FIG. 31A

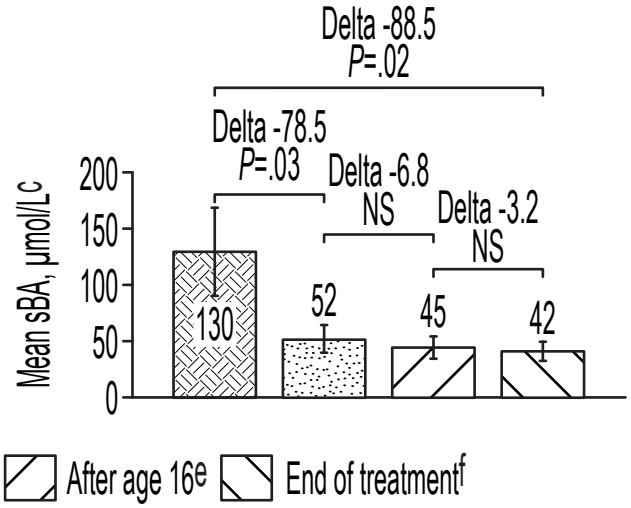


FIG. 31B

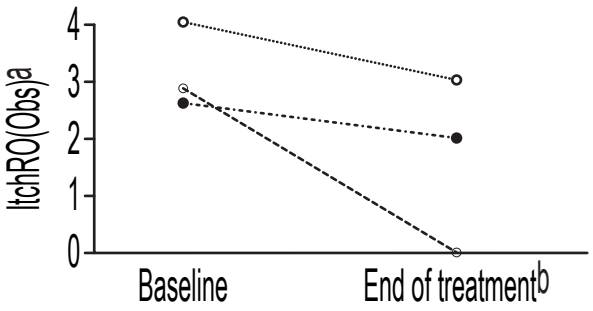


FIG. 32A

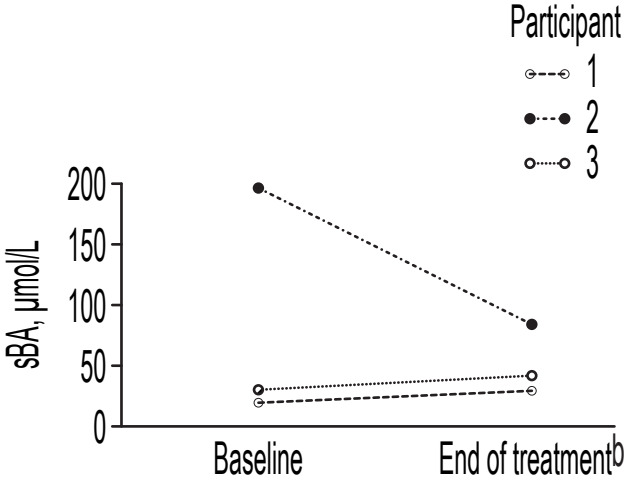
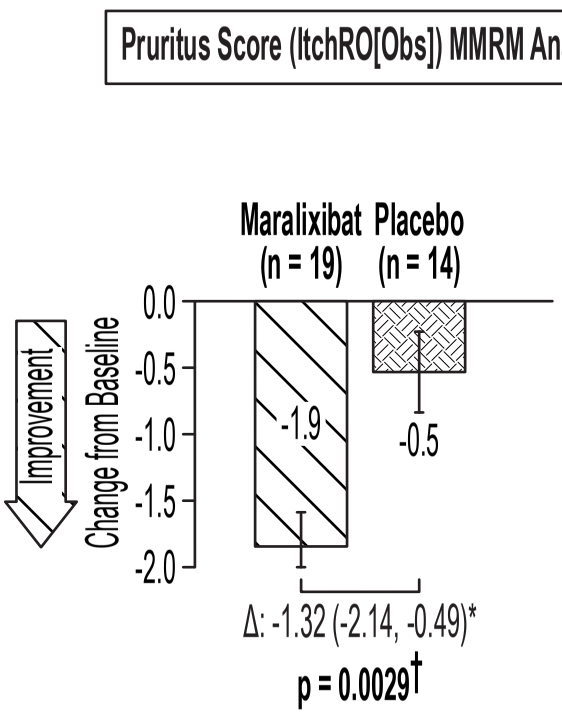
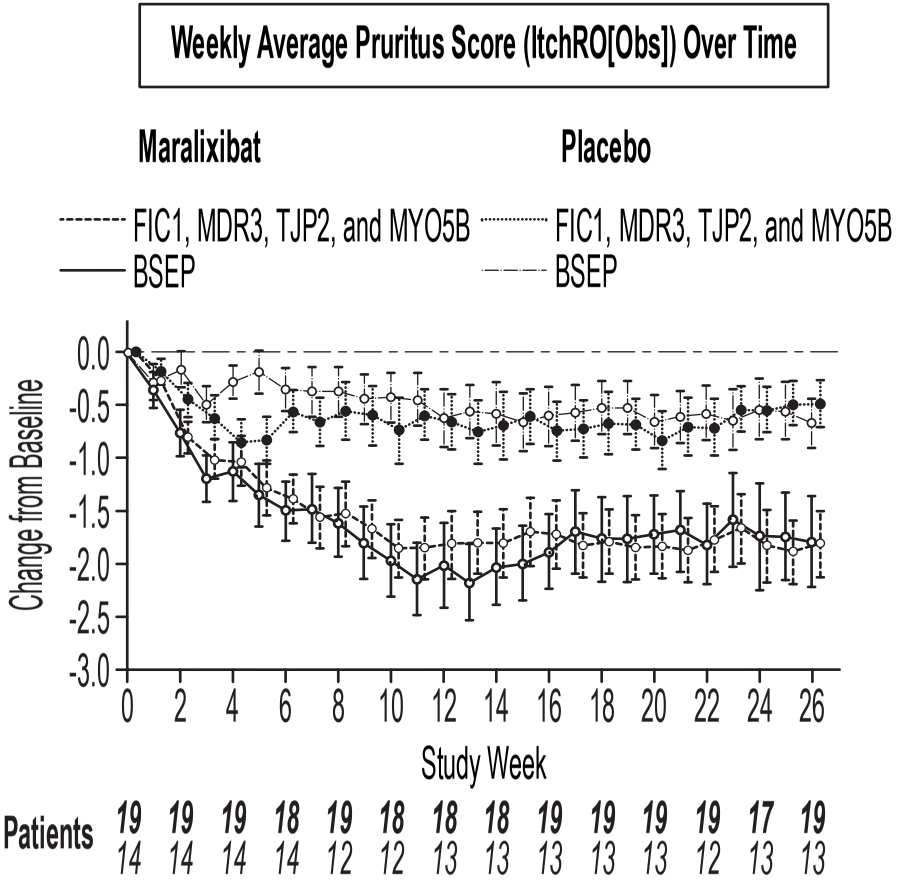


FIG. 32B



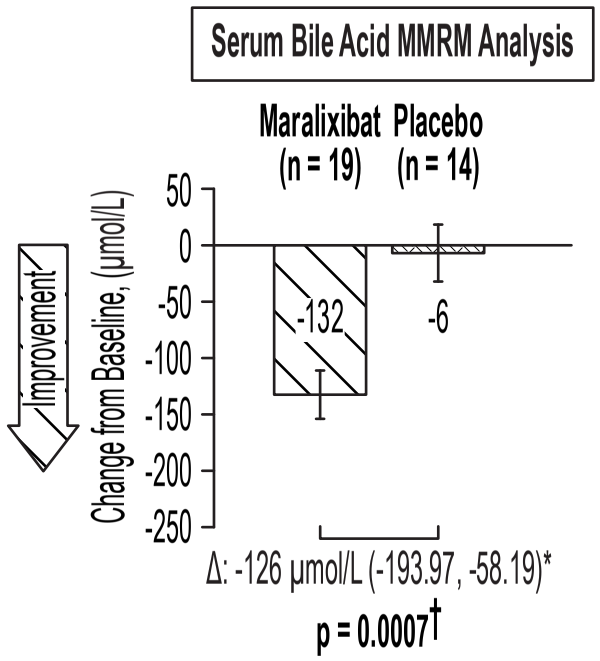


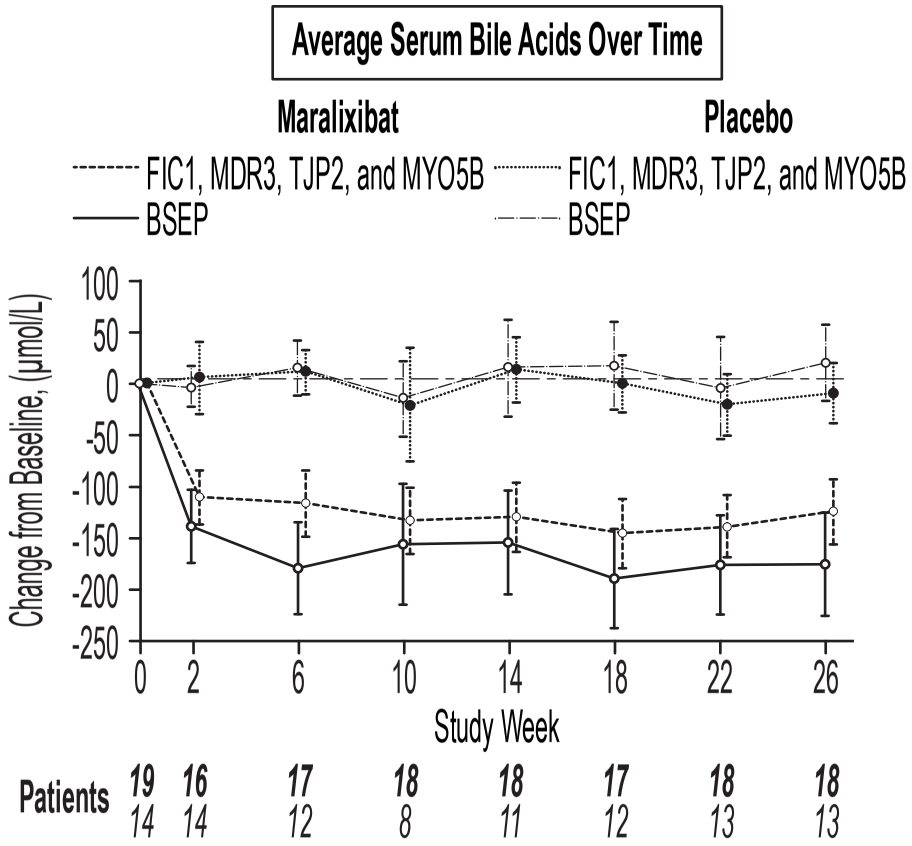
Data are LS mean (for bar plot) and mean (for line plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (4-week intervals) using a MMRM. FIC1, familial intrahepatic cholestasis-associated protein 1; ItchRO(Obs), Itch Reported Outcome (Observer); LS, least squares; MMRM, mixed model repeated measures; MDR3, Multi-drug resistant 3 protein; MYO5B, myosin VB; TJP2, tight junction protein 2

*LS mean delta with 95% CI; †Maralixibat LS mean = placebo LS mean

FIG. 33A

FIG. 33B





Data are LS mean (for bar plot) and mean (for line plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (weeks 18, 22, and 26) using a MMRM. FIC1, familial intrahepatic cholestasis-associated protein 1; LS, least squares; MMRM, mixed model repeated measures; MDR3, Multi-drug resistant 3 protein, MYO5B; myosin VB; TJP2, tight junction protein 2

*LS mean delta with 95% CI; †Maralixibat LS mean = placebo LS mean

FIG. 34A

FIG. 34B

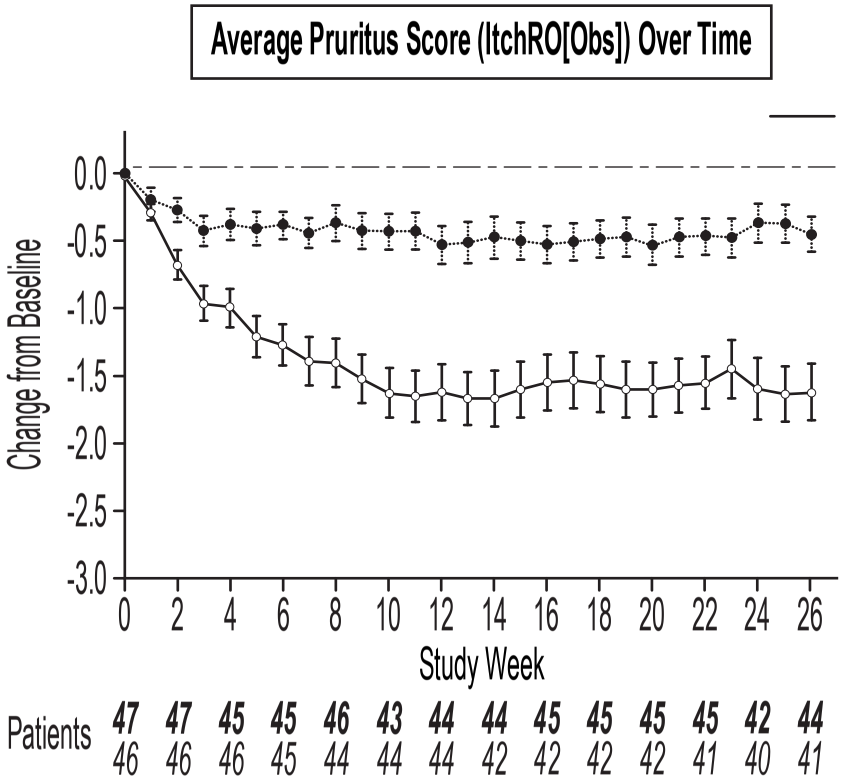


FIG. 35A

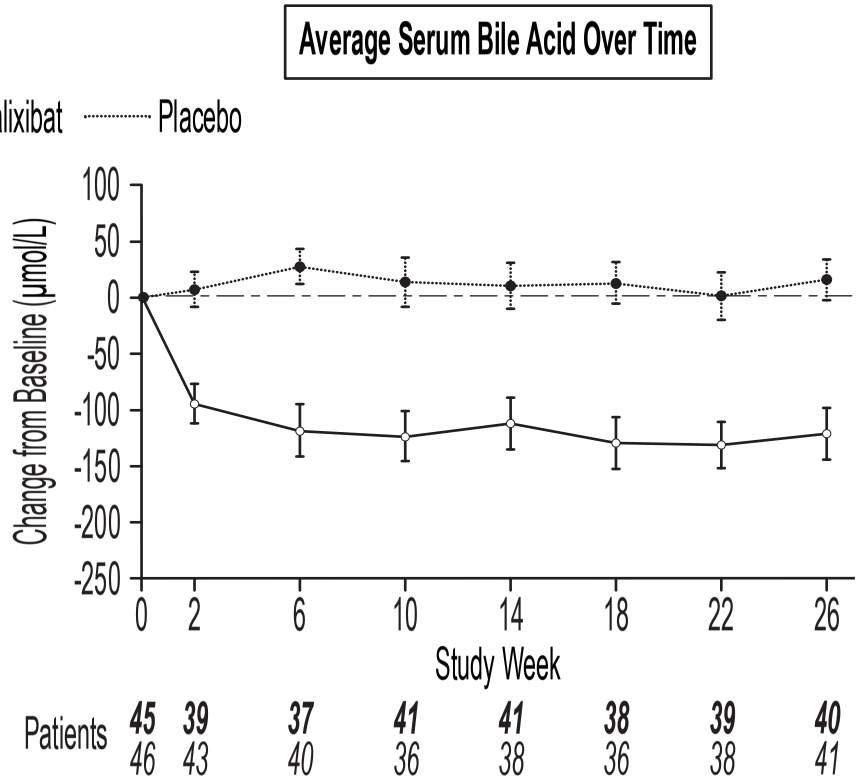
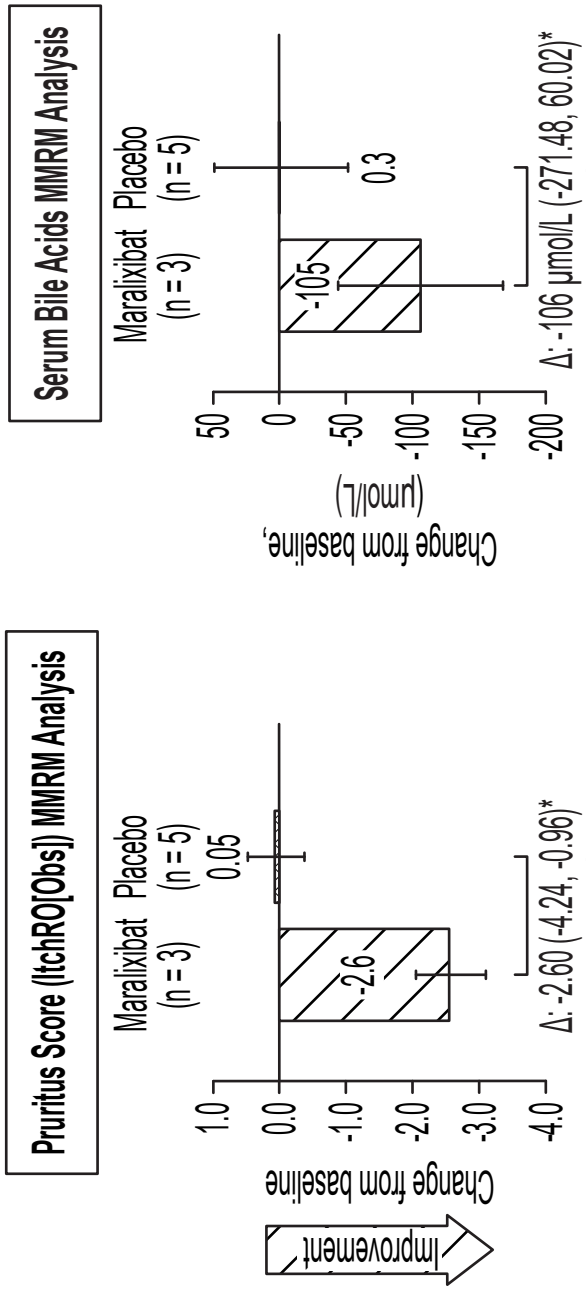


FIG. 35B

Data are means with standard error bars. Two participants in the maralixibat group did not have baseline serum bile acids. ItchRO(Obs), Itch Reported Outcome (Observer)

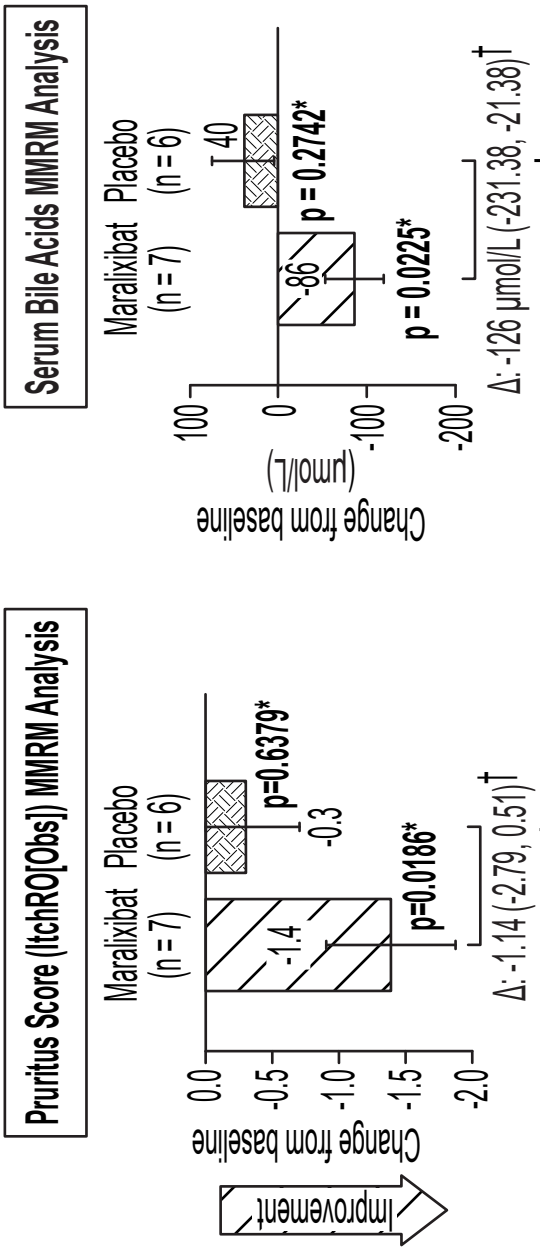


Data are LS Mean with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (4-week intervals for ItchRO, Weeks 18, 22, and 26 for sBA) using a repeated measures mixed effect model. LS, least squares; MMRM, mixed model repeated measures.

*LS mean Delta with 95% CI. †Maralixibat LS mean = Placebo LS Mean

FIG. 35C

FIG. 35D

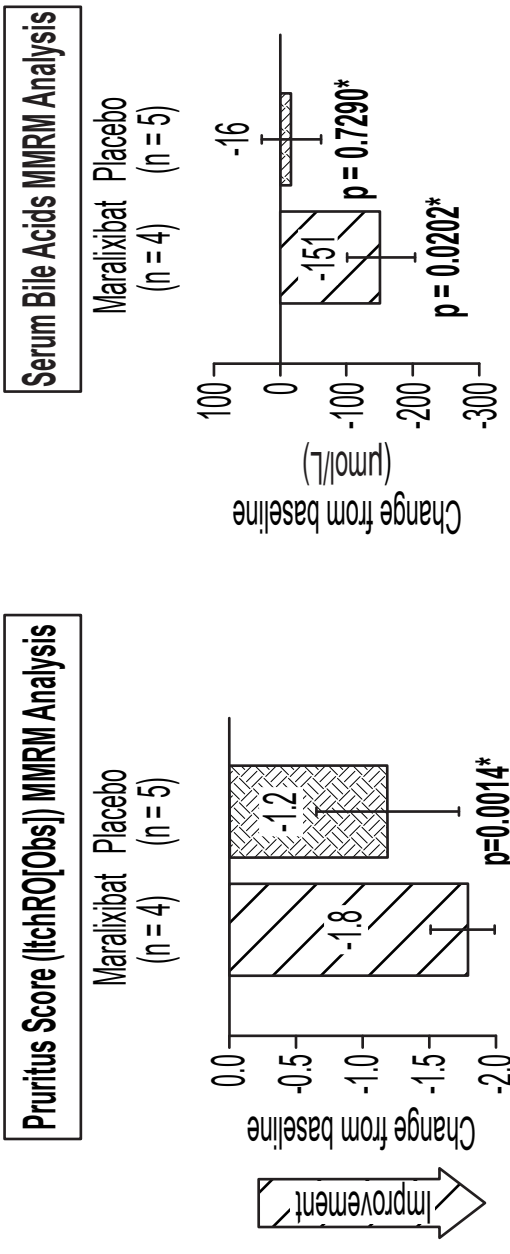


Data are LS Mean with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (4-week intervals for ItchRO, Weeks 18, 22, and 26 for sBA) using a repeated measures mixed effect model. FIC1, familial intrahepatic cholestasis-associated protein 1; LS, least squares; MMRM, mixed model repeated measures.

*Versus baseline. †LS mean Delta with 95% CI. ‡Maralixibat LS mean = Placebo LS Mean.

FIG. 35E

FIG. 35F

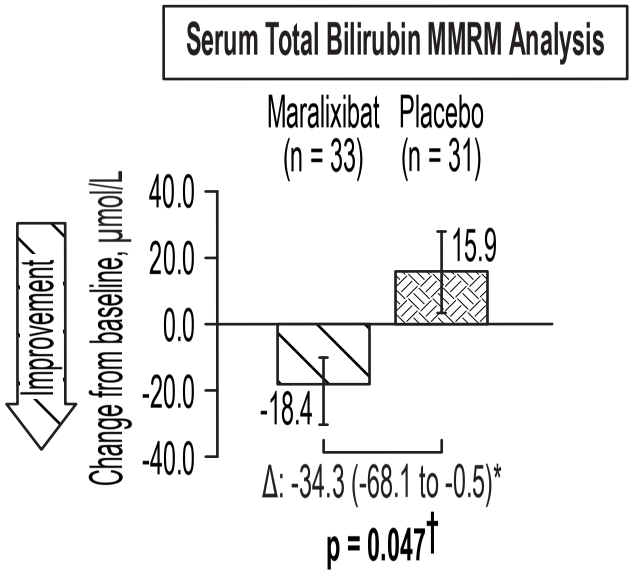


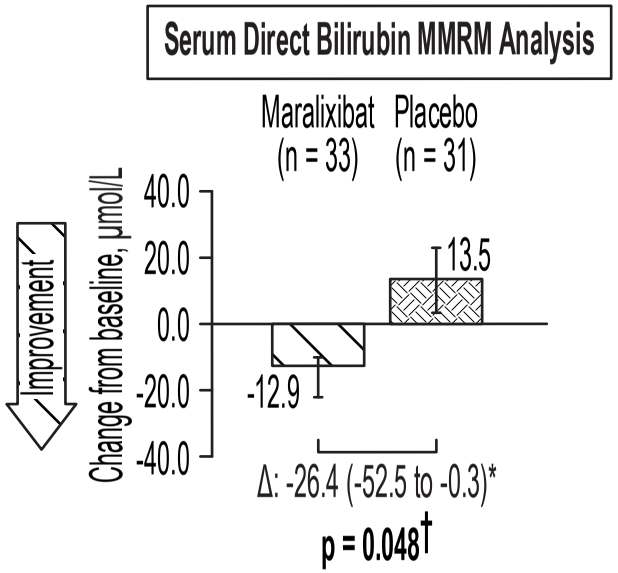
Data are LS Mean with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (4-week intervals for ItchRO, Weeks 18, 22, and 26 for sBA) using a repeated measures mixed effect model. LS, least squares; MDR3, Multi-drug resistant 3 protein; MMRM, mixed model repeated measures.

*Versus baseline. †LS mean Delta with 95% CI. ‡Maralixibat LS mean = Placebo LS Mean.

FIG. 35G

FIG. 35H





Maralixibat resulted in statistically significant improvements in total and direct bilirubin in the All-PFIC cohort

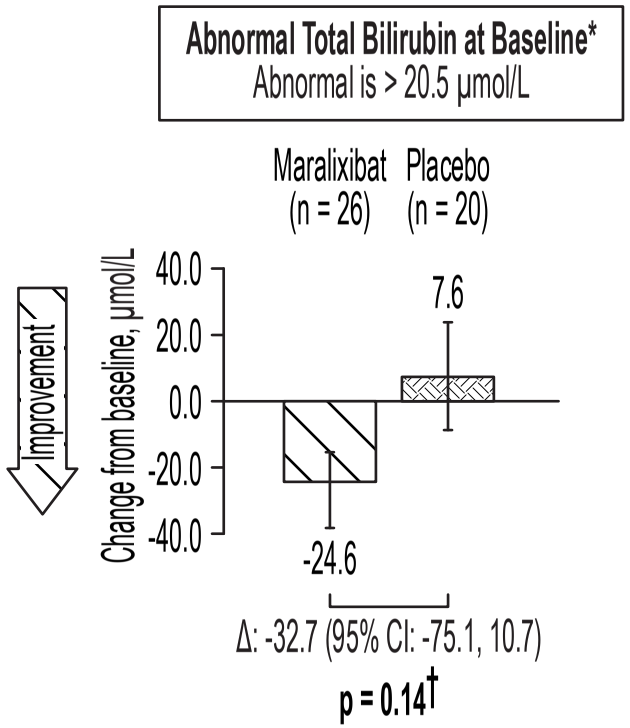
Data are LS mean with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last three time periods (Weeks 18, 22, and 26) using an MMRM approach.

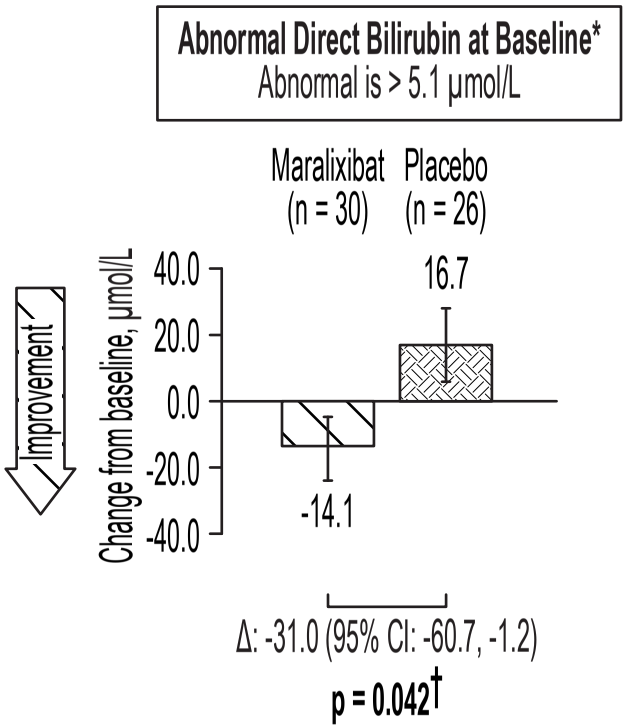
*LS mean Delta with 95% CI; †Maralixibat LS mean = Placebo LS Mean.

LS, least squares, MMRM, mixed-model repeated measures.

FIG. 36A

FIG. 36B





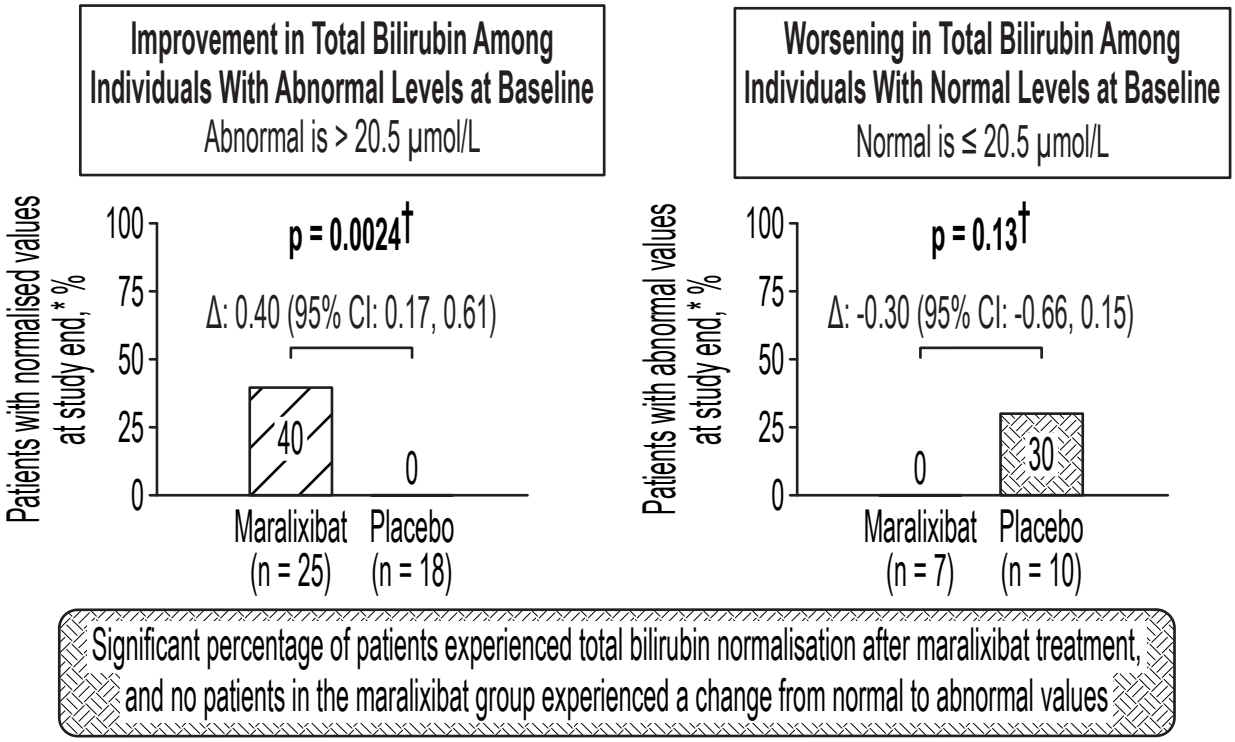
Maralixibat treatment resulted in improvements in bilirubin in patients who had abnormal bilirubin at Baseline

*Estimated change from an MMRM; numbers correspond to the average of weeks 18-26 (18, 22, and 26).

†Maralixibat LS mean = Placebo LS Mean. MMRM, mixed-model repeated measures.

FIG. 37A

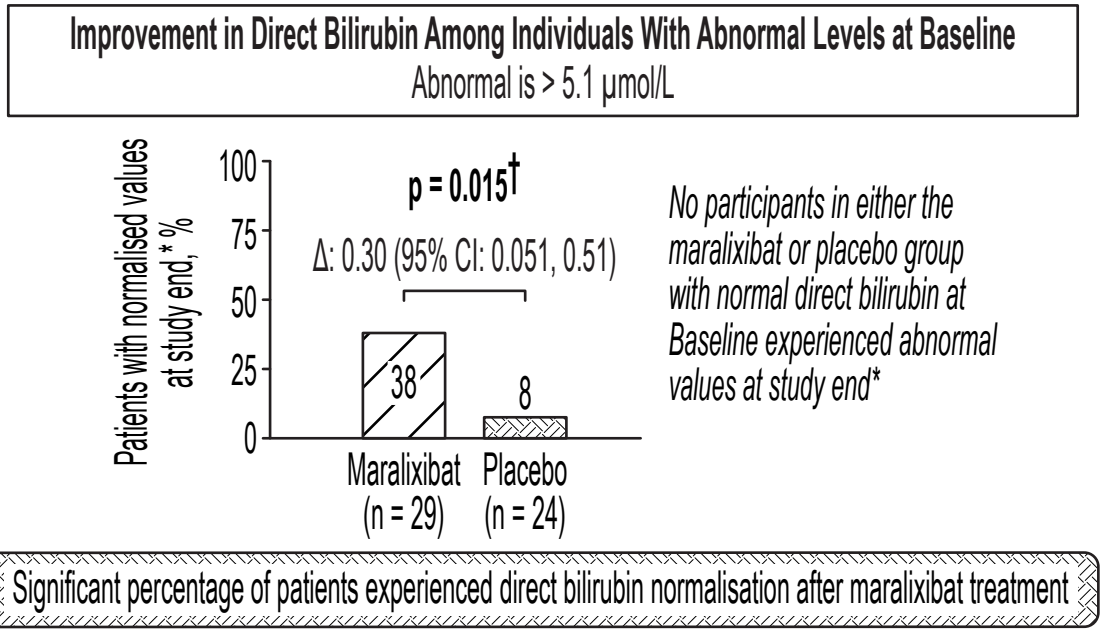
FIG. 37B



*The average of Weeks 18, 22, and 26. †Barnard's exact test.

FIG. 38A

FIG. 38B



*The average of Weeks 18, 22, and 26; †Barnard's exact test.
CI, confidence interval.

FIG. 39

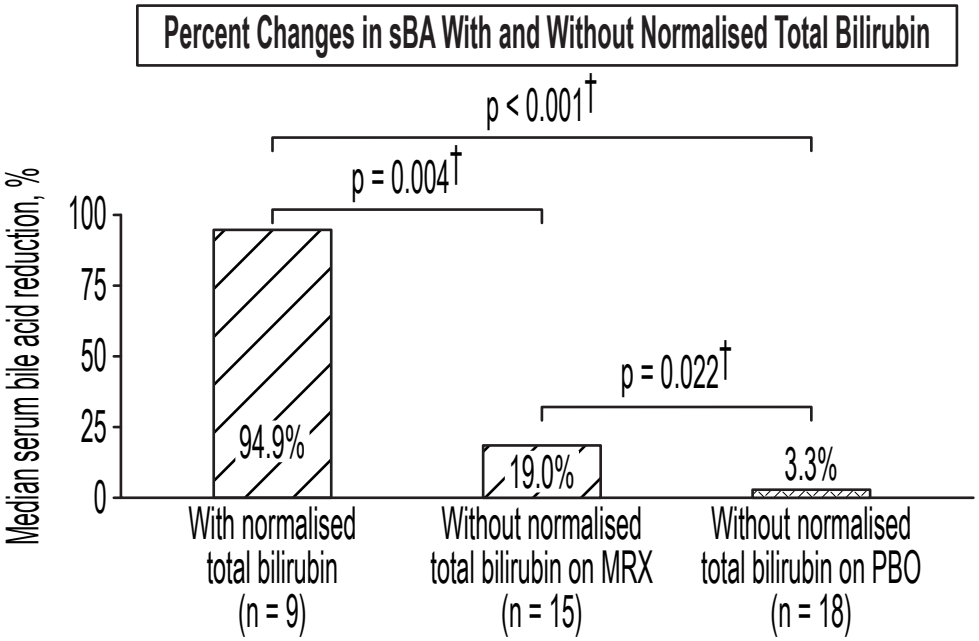


FIG. 40

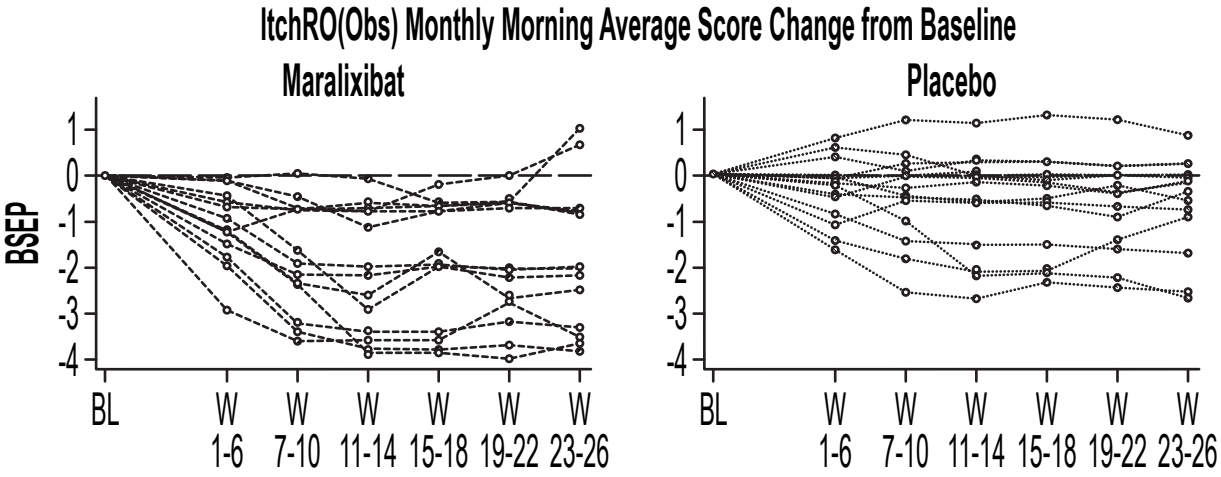


FIG. 41A

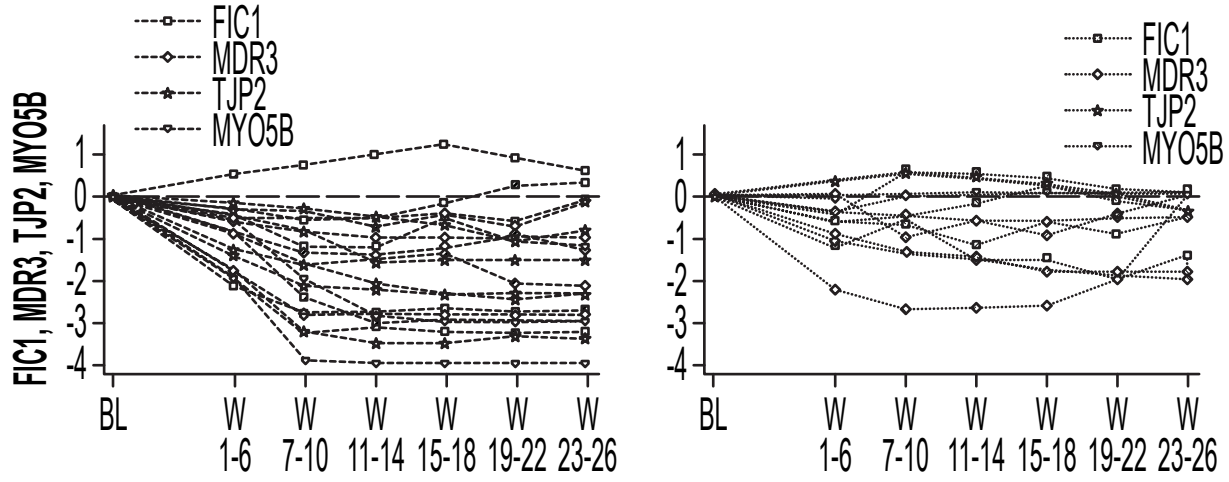


FIG. 41B

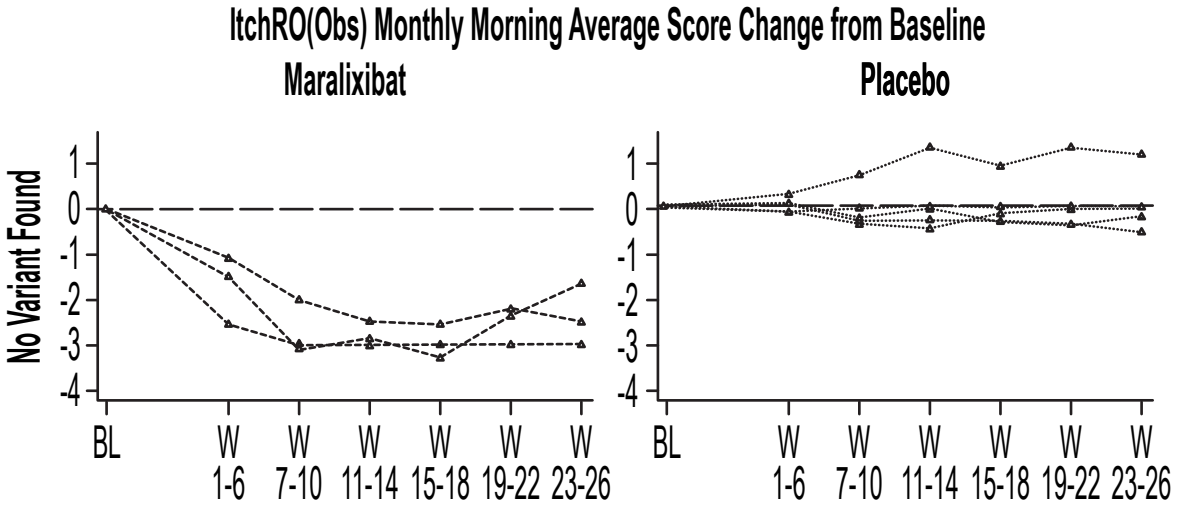


FIG. 41C

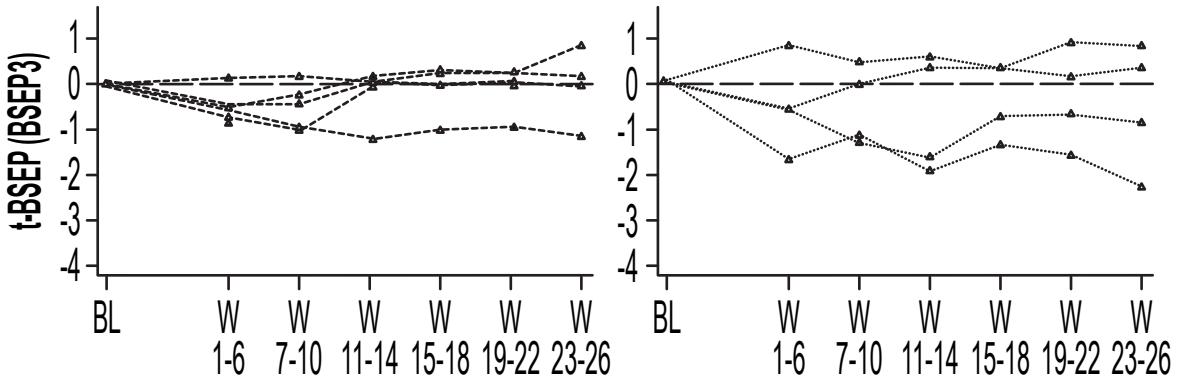


FIG. 41D

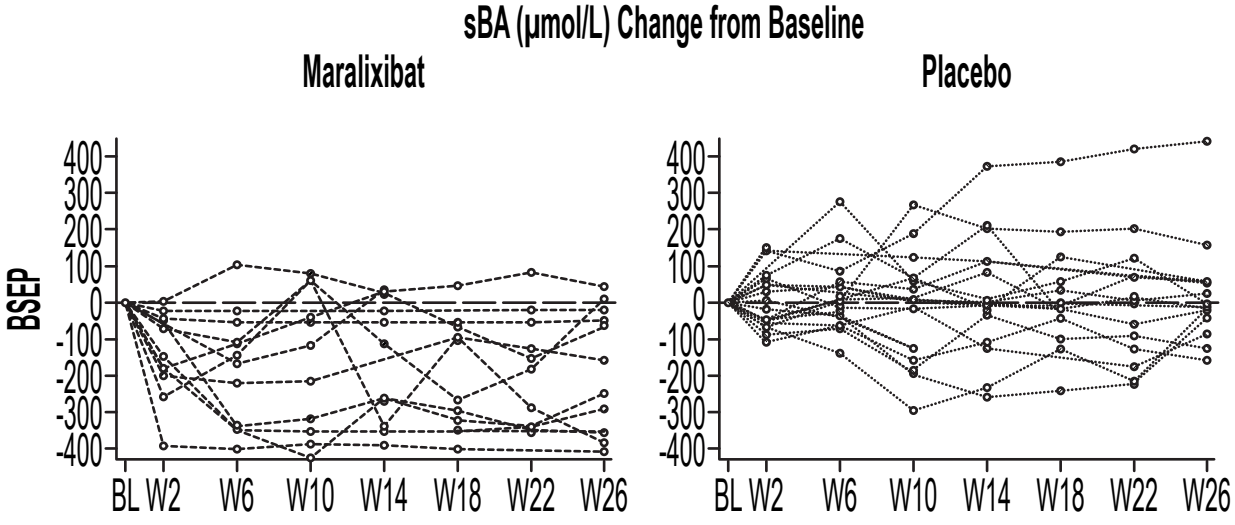


FIG. 42A

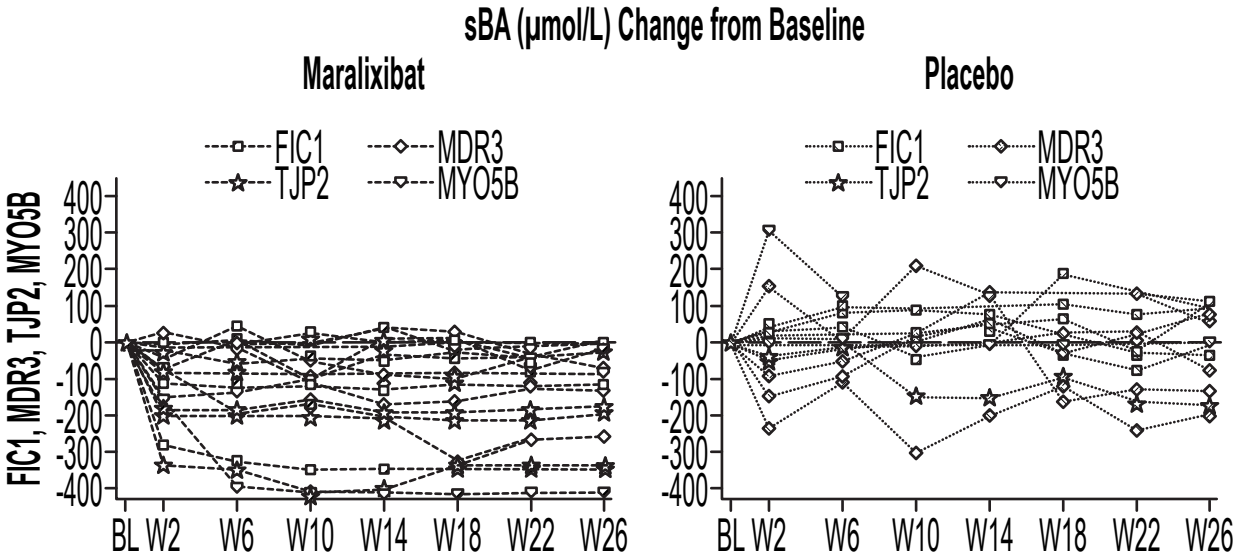


FIG. 42B

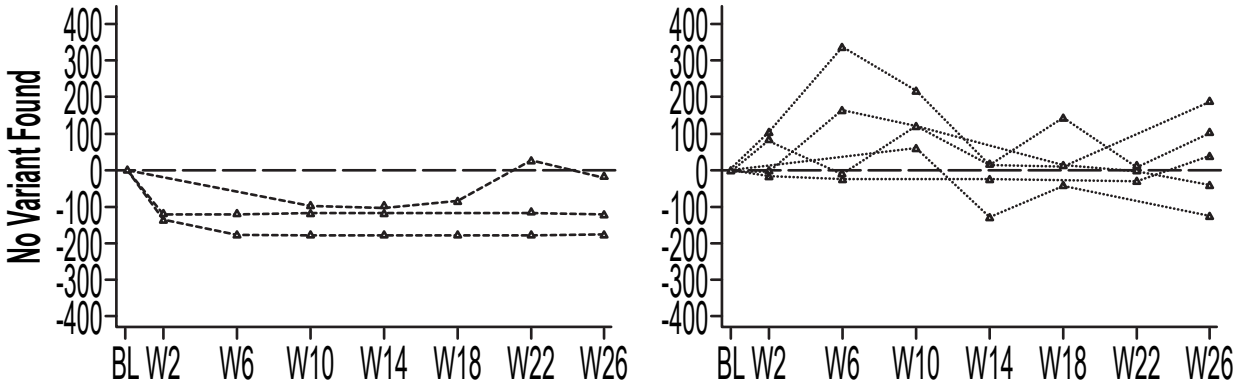


FIG. 42C

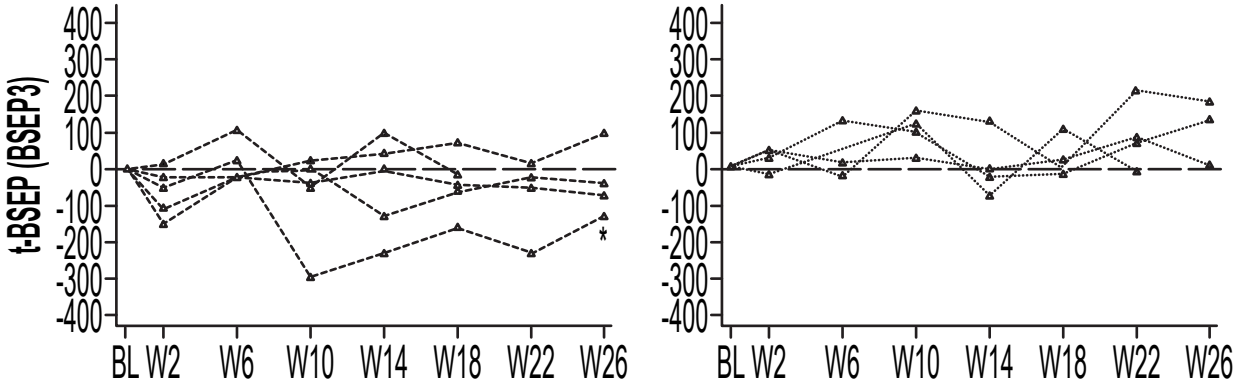


FIG. 42D