Maralixibat improves xanthomas and hypercholesterolaemia in children with Alagille syndrome: an integrated analysis from two clinical trials

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Faculty Disclosure

	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)
Mirum Pharmaceuticals		X						

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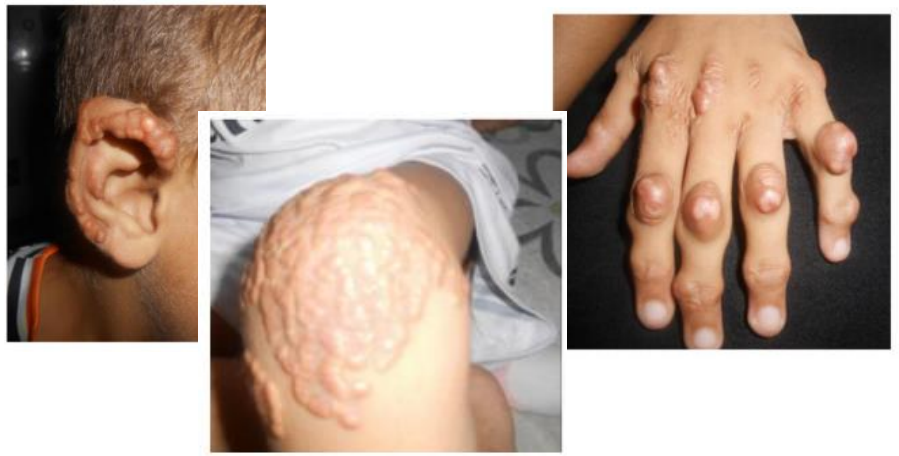
- Postdoctoral Clinical Fellow in the Division of Pediatric Gastroenterology, Hepatology, and Nutrition at The Johns Hopkins University School of Medicine and Johns Hopkins Children's Center
- Primary research interests include endoscopy and hepatology
- Starting as Assistant Professor at Indiana University School of Medicine (Riley Hospital for Children) with a focus on advanced endoscopy after completion of fellowship in June 2023

Xanthomas in Alagille Syndrome

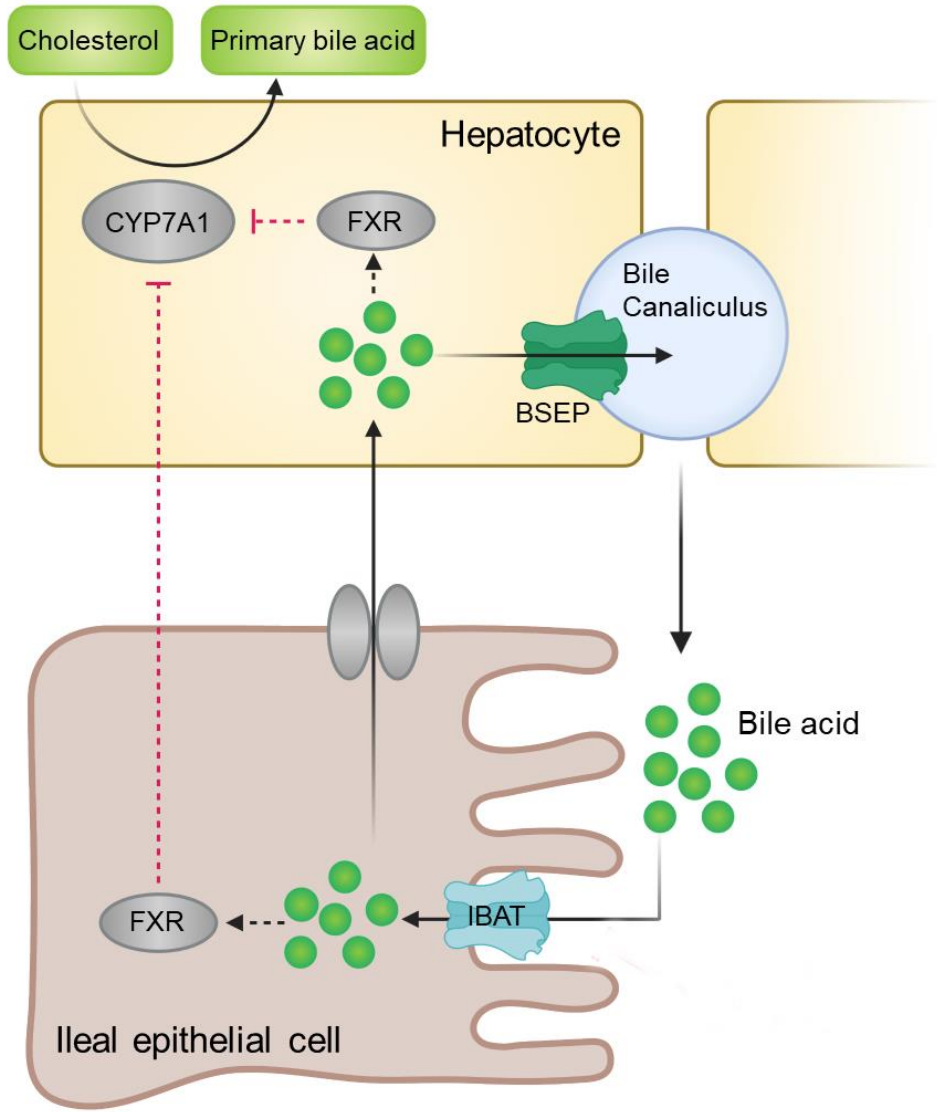
- Alagille syndrome (ALGS) is a rare, debilitating, autosomal dominant disorder with a broad range of clinical manifestations[1]
- Key clinical features include cholestasis, failure to thrive, xanthomas, and progressive liver disease
  - All can lead to liver transplant or death[1]
- Xanthomas are a uniquely burdensome presentation of ALGS, occurring in 24%-42% of patients[2,3]
  - Can be debilitating and disfiguring – associated with overall reduced quality of life[4,5]
  - An indication for liver transplantation in approximately half of liver transplant recipients with ALGS[2,4]
  - Currently, no approved medical therapies available to treat xanthomas, although surgical diversion may provide some benefit



ALGS, Alagille syndrome.

1. Saleh M, et al. *Appl Clin Genet.* 2016;9:75-82. **2.** Vandriel SM, et al. *Hepatology.* 2023;77(2):512-529. **3.** Kamath BM, et al. *J Pediatr Gastroenterol Nutr.* 2018;67(2):148-156. **4.** Lykavieris P, et al. *Gut.* 2001;49(3):431-435. **5.** Gonzales E, et al. *Lancet.* 2021;398(10311):1581-1592.

Cholesterol Conversion to Bile Acids

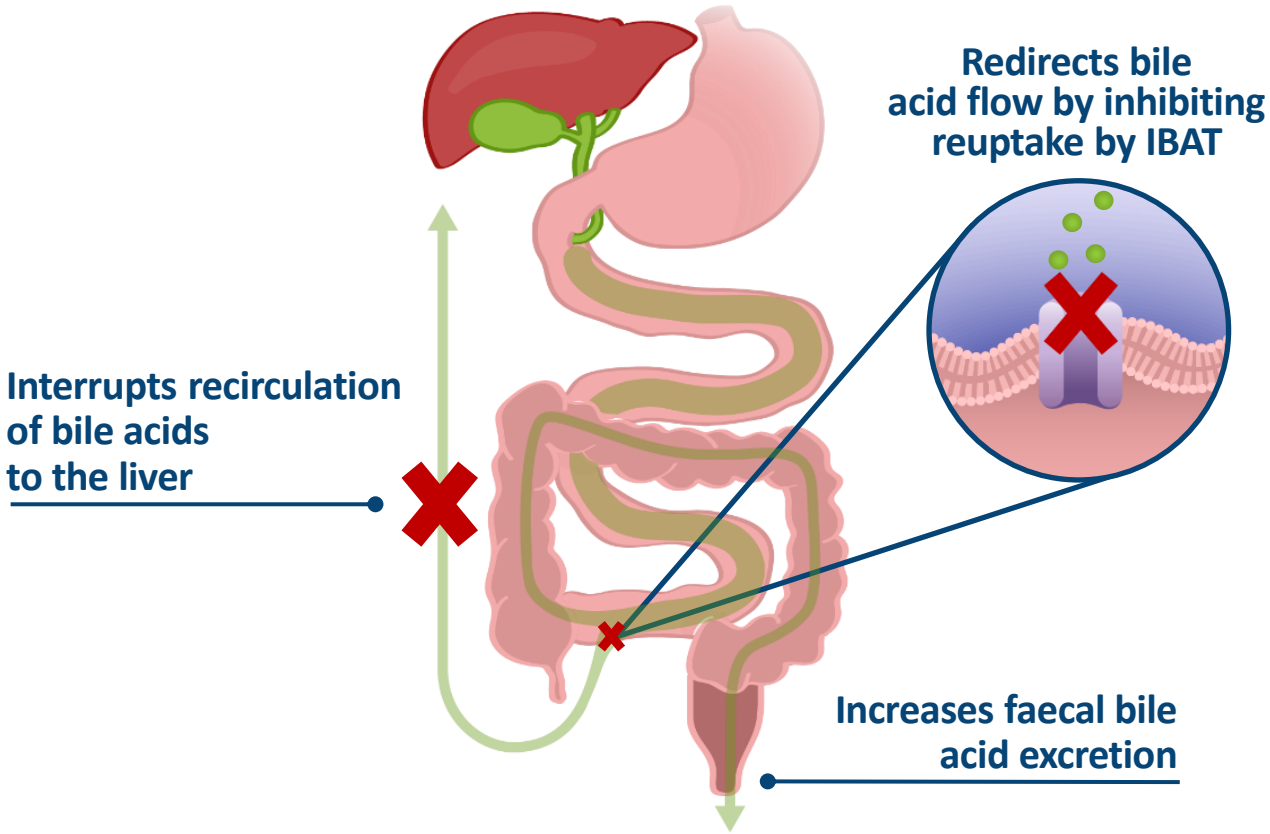


Bile acid synthesis:

- ✓ **Cholesterol is converted to primary bile acids in the liver**
- ✓ **Bile acids are taken up by ileal cells and recirculated back to the liver**
- ✓ **Bile acids in ileal cells and hepatocytes inhibit the synthesis of primary bile acids from cholesterol**

BSEP, bile salt export pump; CYP7A1, cholesterol 7-α-hydroxylase; FXR, farnesoid X receptor; IBAT, ileal bile acid transporter.
Schaap FG, et al. *Nat Rev Gastroenterol Hepatol*. 2014;11(1):55-67.

Maralixibat, an Oral, Minimally Absorbed, IBAT Inhibitor Interrupts Bile Acid Recirculation[1]



Clinical effects of IBATi in cholestasis[1,2]:

- ✓ Improvements in pruritus (itch)
- ✓ Reductions in serum bile acids
- ✓ Improved transplant-free survival

Maralixibat is approved for the treatment of cholestatic pruritus in patients with ALGS ≥2 months of age in the EU and ≥3 months of age in the US[1,3]

IBAT, ileal bile acid transporter.

1. LIVMARLI. Prescribing information. Mirum Pharmaceuticals, Inc.; 2023. **2.** Hansen BE, et al. Presented at NASPHGAN 2022. **3.** LIVMARLI. Summary of product characteristics. Mirum Pharmaceuticals, Inc.; Dec 2022.

IBAT Inhibitors, Xanthomas, and Cholesterol: What Is Known

- Xanthomas are thought to be caused by impaired bile acid excretion from the liver
  - Results from accumulation of precursors in bile acid synthesis like cholesterol
- IBAT inhibitors such as maralixibat have been shown to pharmacologically reduce serum bile acid levels, which could impact the presence of xanthomas and cholesterol
- Multiple clinical trials of maralixibat have shown:
  - Significant decrease in serum bile acids over >5 years of follow-up[1,2]
  - Significant improvements in both xanthomas and cholesterol[1,2]

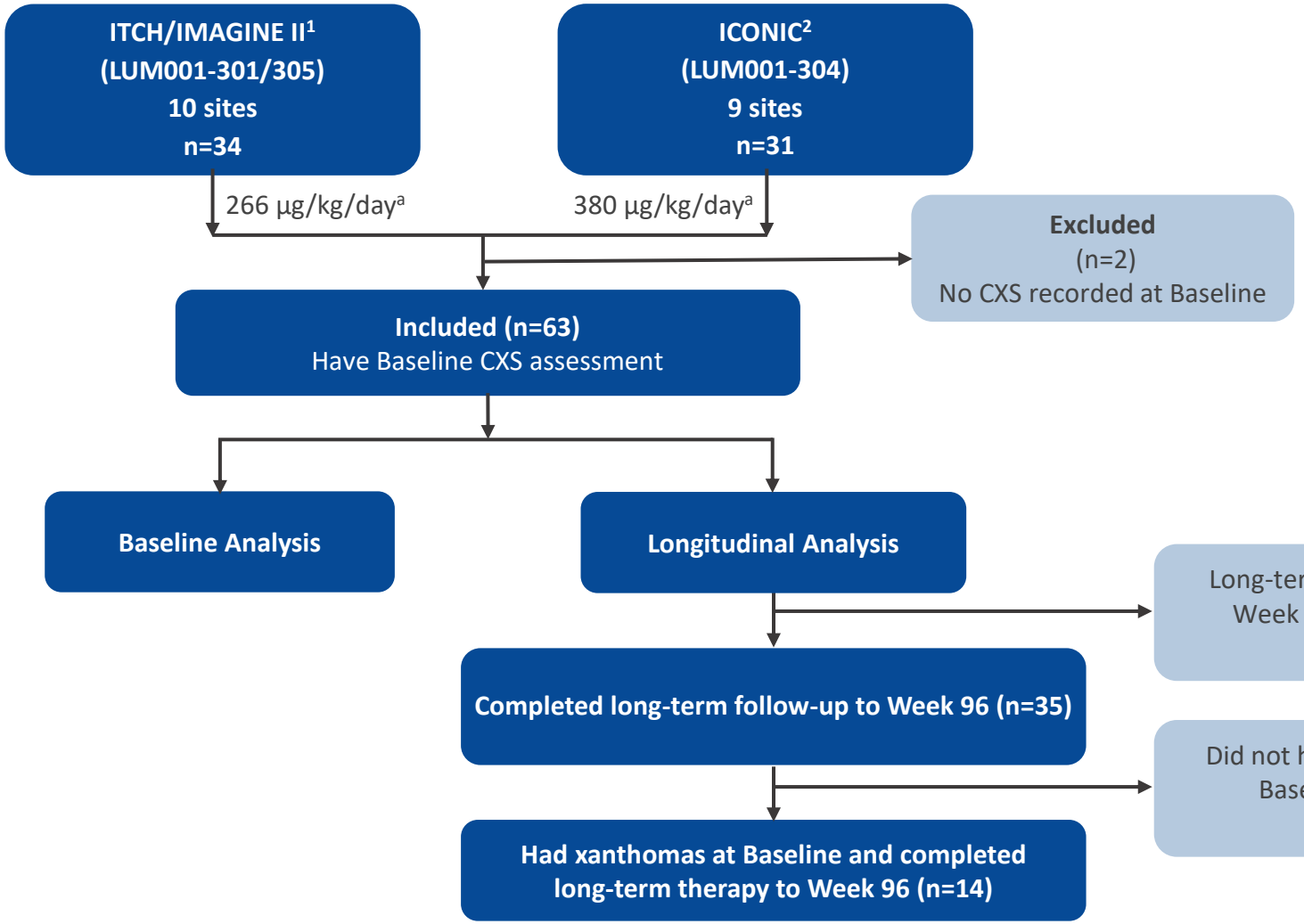
1. Data on File. Mirum Pharmaceuticals, Inc. **2.** Gonzales E, et al. *Lancet*. 2021;398(10301):1581-1592.

Study Aim

To characterise xanthomas at Baseline and assess the impact of maralixibat on xanthomas using integrated data from the maralixibat ALGS clinical trials program

Data on File. Mirum Pharmaceuticals, Inc.

Methods



Endpoints

- Baseline characteristics
- Response to MRX treatment:
  - CXS trends over time
  - Change from Baseline to Week 96:
    - Total cholesterol, HDL, LDL
    - HRQoL (PedsQL-SF and PedsQL-PF)
  - Predictors of treatment response

[a]All doses presented as MRX free-base.
CXS, Clinician Xanthoma Scale; HDL, high-density lipoprotein; HRQoL, health-related quality of life; LDL, low-density lipoprotein; MRX, maralixibat; PedsQL-SF, Pediatric Quality of Life Inventory–Social Functioning; PedsQL-PF, Pediatric Quality of Life Inventory–Physical Functioning.
1. Data on File. Mirum Pharmaceuticals, Inc. **2.** Gonzales E, et al. *Lancet.* 2021;398(10301):1581-1592.

CXS Assessment

Improvement

Scale	Descriptor	Characteristics
0	None	No evidence of xanthomatosis
1	Minimal	<20 scattered individual lesions
2	Moderate	>20 lesions that do not interfere with or limit activities
3	Disfiguring	Large numbers of lesions that by their large numbers or size cause distortion of the face or extremities
4	Disabling	Xanthomas that interfere with function (such as hand use or ability to walk) because of excess size or number

Xanthoma responder is defined as an individual who dropped their CXS by ≥1 point from Baseline

A nonresponder is defined as an individual who had the same or increase in CXS

CXS, Clinician Xanthoma Scale.
Gonzales E, et al. *Lancet.* 2021;398(10301):1581-1592.

Baseline Characteristics

Characteristic, median (Q1, Q3)	CXS 0 (n=36)	CXS 1-2 (n=17)	CXS 3-4 (n=10)	*P* value*
Age, mo	6 (4, 11)	5 (4, 9)	2.5 (2, 5)	.03
Laboratory assessments				
sBA, µmol/L	143 (48, 287)	243 (114, 412)	506 (329, 623)	.0004
Total bilirubin, mg/dL	1.7 (0.9, 4.2)	5.5 (0.9, 11.1)	11.9 (8.9, 14.4)	<.0001
Direct bilirubin, mg/dL	1.1 (0.5, 3.5)	4.6 (0.8, 8.4)	9.4 (7.6, 10.0)	<.0001
GGT, U/L	275 (176, 472)	360 (242, 964)	597 (506, 834)	.02
ALT, U/L	122 (88, 183)	193 (125, 226)	173 (152, 249)	.008
Total cholesterol, mg/dL	282 (235, 333)	361 (282, 460)	1004 (613, 1389)	<.0001
LDL, mg/dL	155 (121, 182)	178 (134, 203)	207 (155, 257)	.056
HDL, mg/dL	66 (37, 75)	32 (20, 68)	21 (18, 26)	.0005
PedsQL				
Average social functioning	77.5 (65, 90)	72.5 (47.5, 77.5)	62.5 (50, 77.5)	.02
Average physical functioning	75 (56.3, 84.4)	61 (43.8, 73.4)	65.6 (40.6, 67.2)	.04

*Jonckheere-Terpstra test for trend.
ALT, alanine transaminase; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PedsQL, Pediatric Quality of Life Inventory; sBA, serum bile acid; Q1, first quartile; Q3, third quartile.
Data on File. Mirum Pharmaceuticals, Inc.

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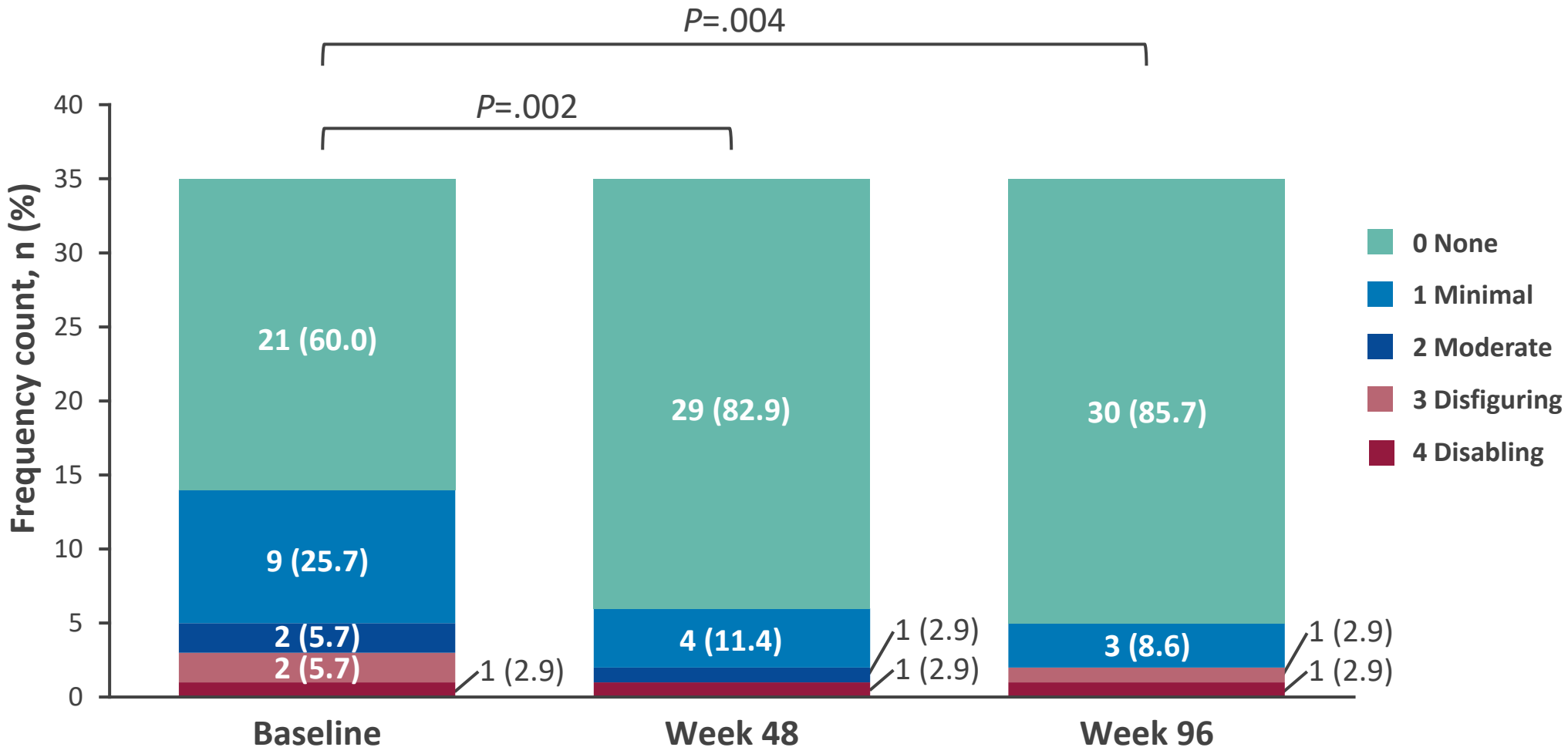
Increased xanthomas at Baseline were associated with worsening biomarkers of disease severity and quality of life

*Jonckheere-Terpstra test for trend.
ALT, alanine transaminase; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PedsQL, Pediatric Quality of Life Inventory; sBA, serum bile acid; Q1, first quartile; Q3, third quartile.
Data on File. Mirum Pharmaceuticals, Inc.

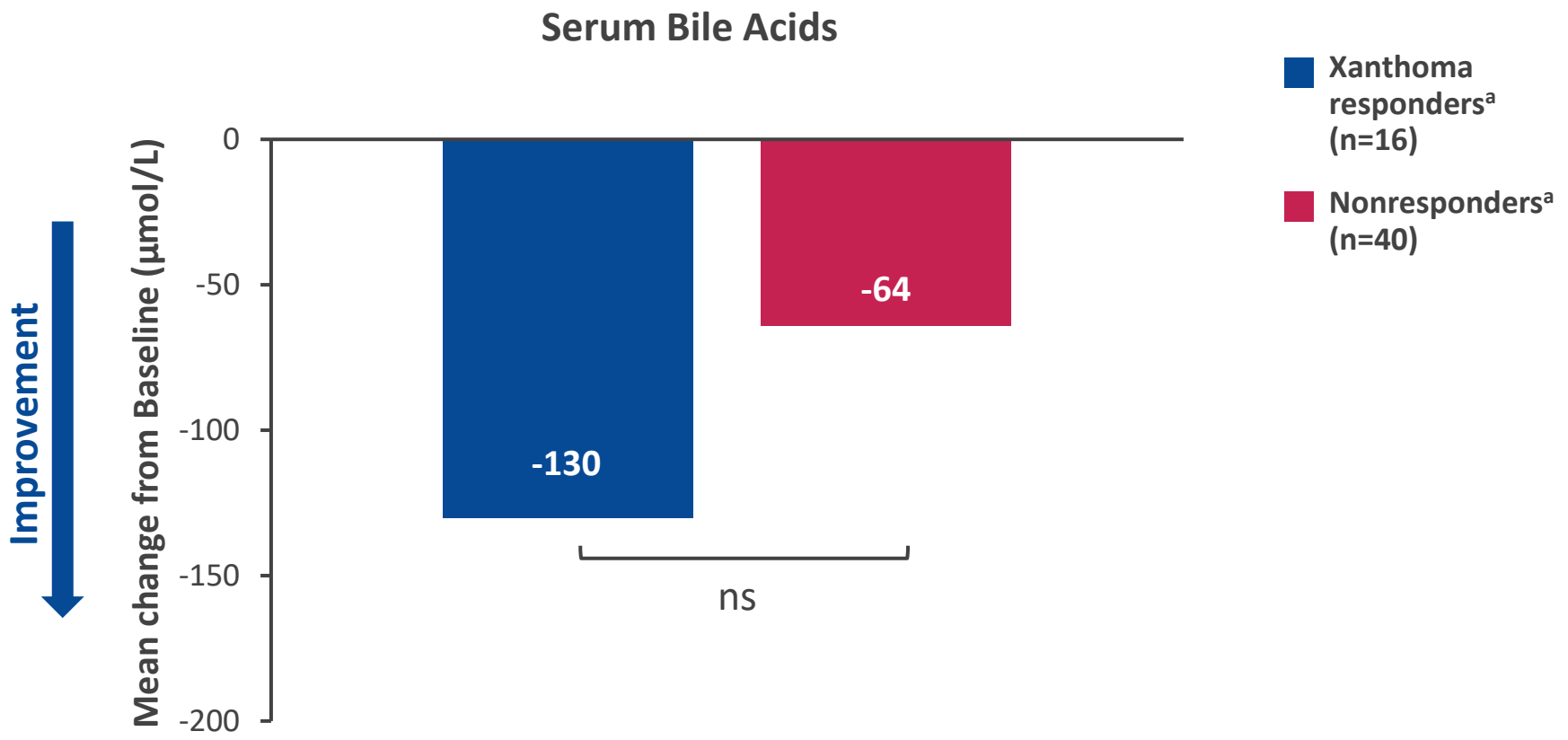
Xanthoma Severity Over Time in Participants With Long-Term Follow-Up on Maralixibat (n=35)[1,2,a]



[a]Includes data from all participants from ICONIC and ITCH clinical trials who completed long-term follow-up (n=35).

1. Data on File. Mirum Pharmaceuticals, Inc. **2.** Gonzales E, et al. *Lancet*. 2021;398(10311):1581-1592.

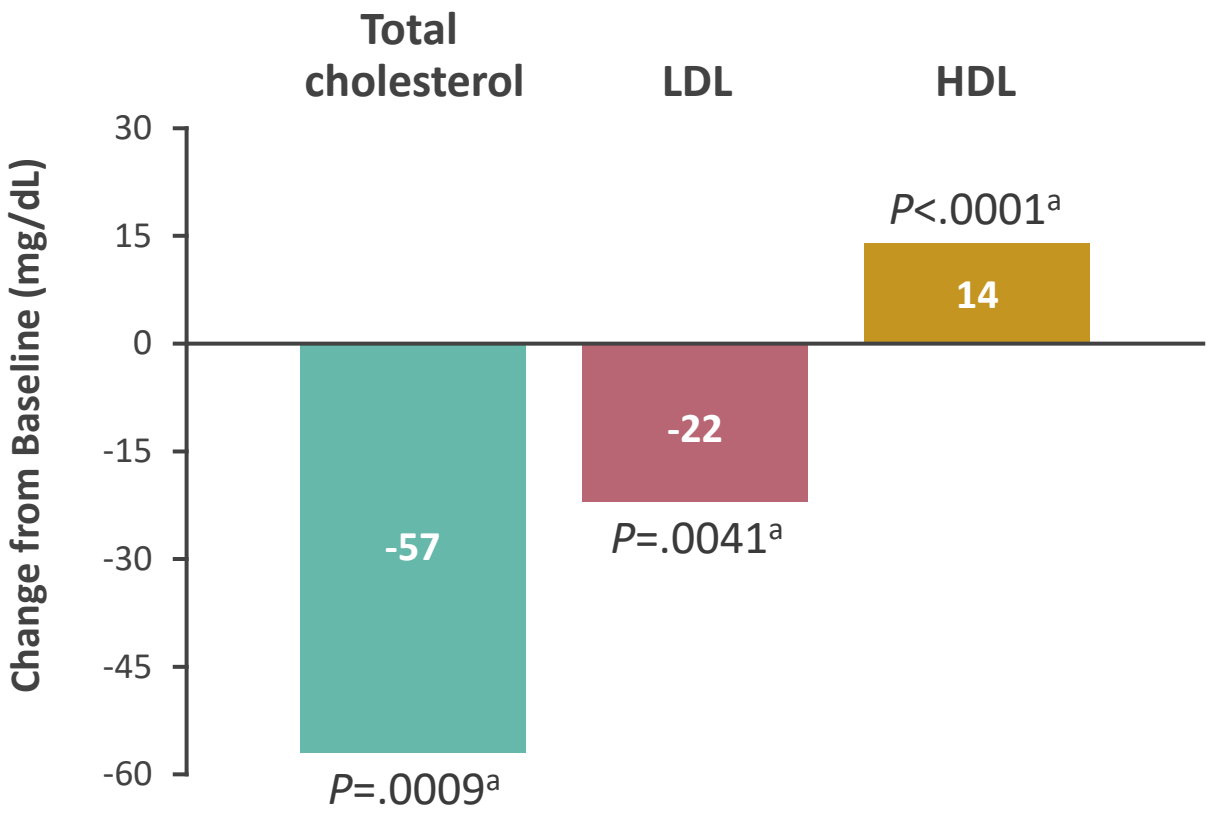
Change From Baseline to Week 48: Serum Bile Acids



Numerical differences in serum bile acids were observed between xanthoma responders and nonresponders

[a]Xanthoma responder defined as individual who dropped their CXS by ≥1 point from Baseline to Week 48. A nonresponder had the same or increase in CXS. Analysis only included people who had xanthomas at Baseline, and with CXS and sBA available at Week 48.
sBA, serum bile acid; ns, not significant.
Data on File. Mirum Pharmaceuticals, Inc.

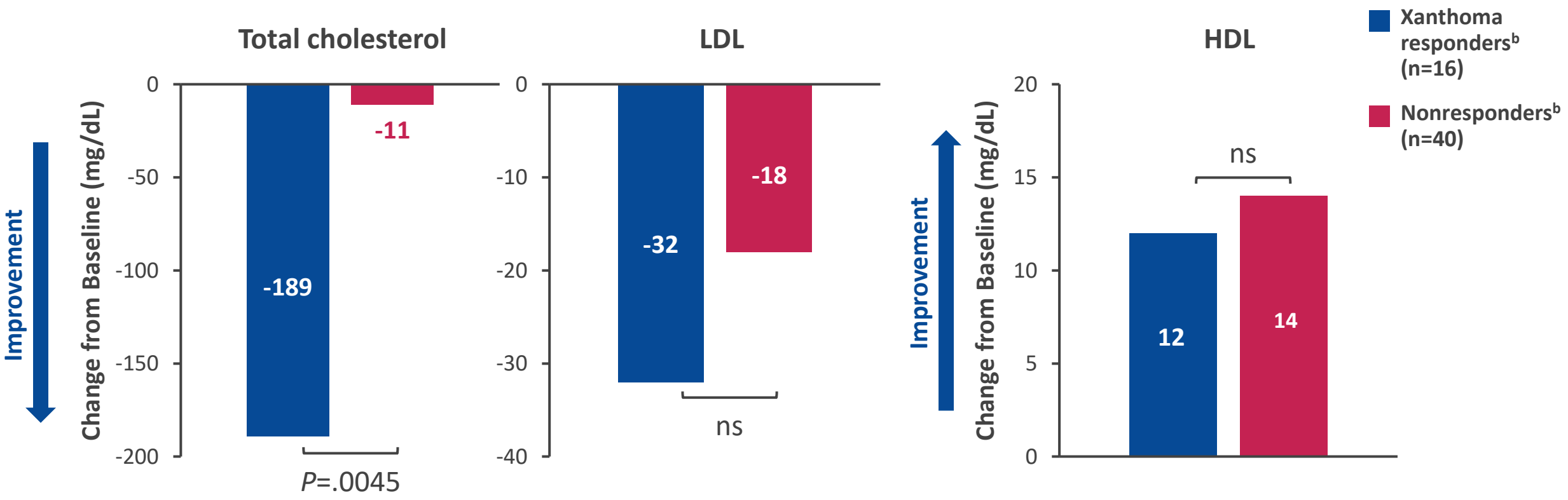
Change From Baseline to Week 96: Total Cholesterol, LDL, and HDL (n=35)



Change from baseline in total cholesterol, LDL, and HDL was statistically significant after maralixibat treatment

[a]*P* values Baseline versus Week 96.
HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Data on File. Mirum Pharmaceuticals, Inc.

Change From Baseline to Week 48: Total Cholesterol, LDL, and HDL



At 48 weeks, n=56 patients had data available for xanthoma response and cholesterol

Maralixibat treatment resulted in a significant decrease in total cholesterol in xanthoma responders compared with nonresponders[a,b]

[a]Analysis only included people who had xanthomas at Baseline, and CXS and cholesterol assessed at Week 48. [b]Xanthoma responder defined as individual who dropped their CXS by ≥1 point from Baseline to Week 48. A nonresponder had the same or increase in CXS.
HDL, high density lipoprotein; LDL, low density lipoprotein; ns, not significant.
Data on File. Mirum Pharmaceuticals, Inc.

Pruritus Response From Baseline to Week 48

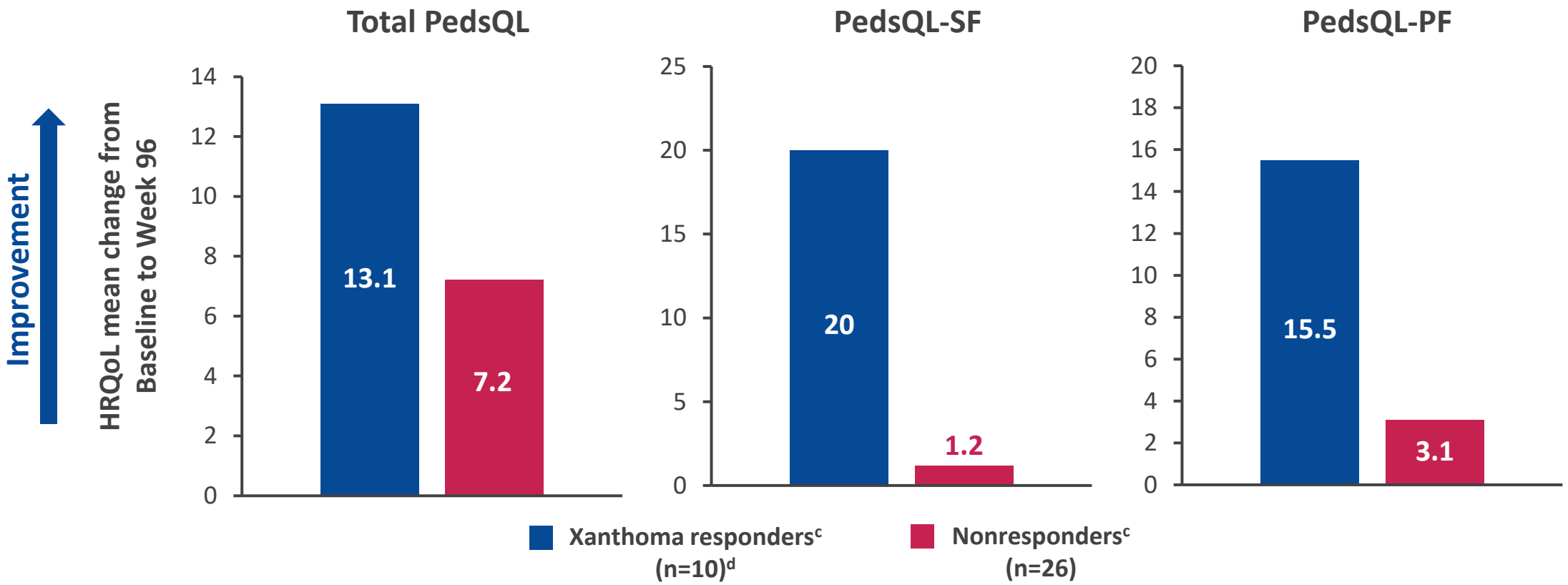
		Xanthoma response[a]			
		Xanthoma responders	Nonresponders	Total	
Pruritus response	≥1-Point reduction in ItchRO, n (%)	8 (89)	11 (61)	19	*P*=.04[b]
	<1-point reduction in ItchRO, n (%)	1 (11)	7 (39)	8	
	Total, n	9	18	27	

Xanthoma responders experienced a greater decrease in pruritus upon maralixibat treatment compared with nonresponders[c]

[a]Xanthoma responder defined as individual who dropped their CXS by ≥1 point from Baseline to Week 48. A nonresponder had the same or increase in CXS. [b]Chi-square test of all 4 values.
[c]Analysis included people who had xanthomas at Baseline, and with CXS and pruritus assessed at Week 48.
ItchRO, itch-reported outcome.
Data on File. Mirum Pharmaceuticals, Inc.

Change from Baseline to Week 96 in QoL by Xanthoma Response[1,a]

Minimal clinically important difference (MCID): 4–5 points[2,b]



Xanthoma responders demonstrated clinically meaningful improvements in quality of life upon maralixibat treatment compared with nonresponders

[a]Analysis only included people who had xanthomas at Baseline and had QoL data at Week 96. Data are difference in means. [b]MCID for the HRQoL assessments ranges from 4 to 5 points, depending on the scale, as validated in previous analyses. [c]Xanthoma responder defined as individual who dropped their CXS by ≥1 point from Baseline to Week 96 which was an n=21 for Total QoL. A nonresponder had the same or increase in CXS. [d]Of 10 xanthoma responders, 10 had Total QoL and 9 had PedsQL-SF and PF assessments.

HRQoL, health-related quality of life; MCID, minimal clinically important difference; ns, not significant; PedsQL-SF, Pediatric Quality of Life Inventory–Social Functioning; PedsQL-PF, Pediatric Quality of Life Inventory–Physical Functioning; QoL, quality of life.

1. Data on File. Mirum Pharmaceuticals, Inc. **2**. Varni JW, et al. *Ambul Pediatr.* 2003;3:329-341.

Limitations

- Although significant reductions in total cholesterol levels were observed, the clinical impact of these reductions is unclear
- These data do not include measurements of lipoprotein X to better understand which changes in cholesterol were occurring
- The CXS was used as a marker of xanthoma severity, though a degree of subjectivity exists when calculating this score
- The sample size is small overall, particularly for longitudinal analyses
  - Some of the long-term measurements are missing

Conclusions

- This is the first longitudinal analysis of xanthomas in patients with ALGS correlating QoL parameters to xanthoma scores
- In patients with ALGS, higher CXS at Baseline were associated with worsened biomarkers of ALGS and reduced QoL
- Consistent with its mechanism of action, maralixibat treatment reduced xanthomas, hypercholesterolaemia, and serum bile acids
- Changes in xanthomas were associated with improvement in QoL in patients with ALGS after maralixibat treatment
- Earlier treatment may help prevent development of severe xanthomatosis and hypercholesterolaemia

SCAN HERE

Data on File. Mirum Pharmaceuticals, Inc.

Acknowledgements

- The authors would like to thank the clinical trial participants, their families, and investigators for their participation in the maralixibat clinical studies to date
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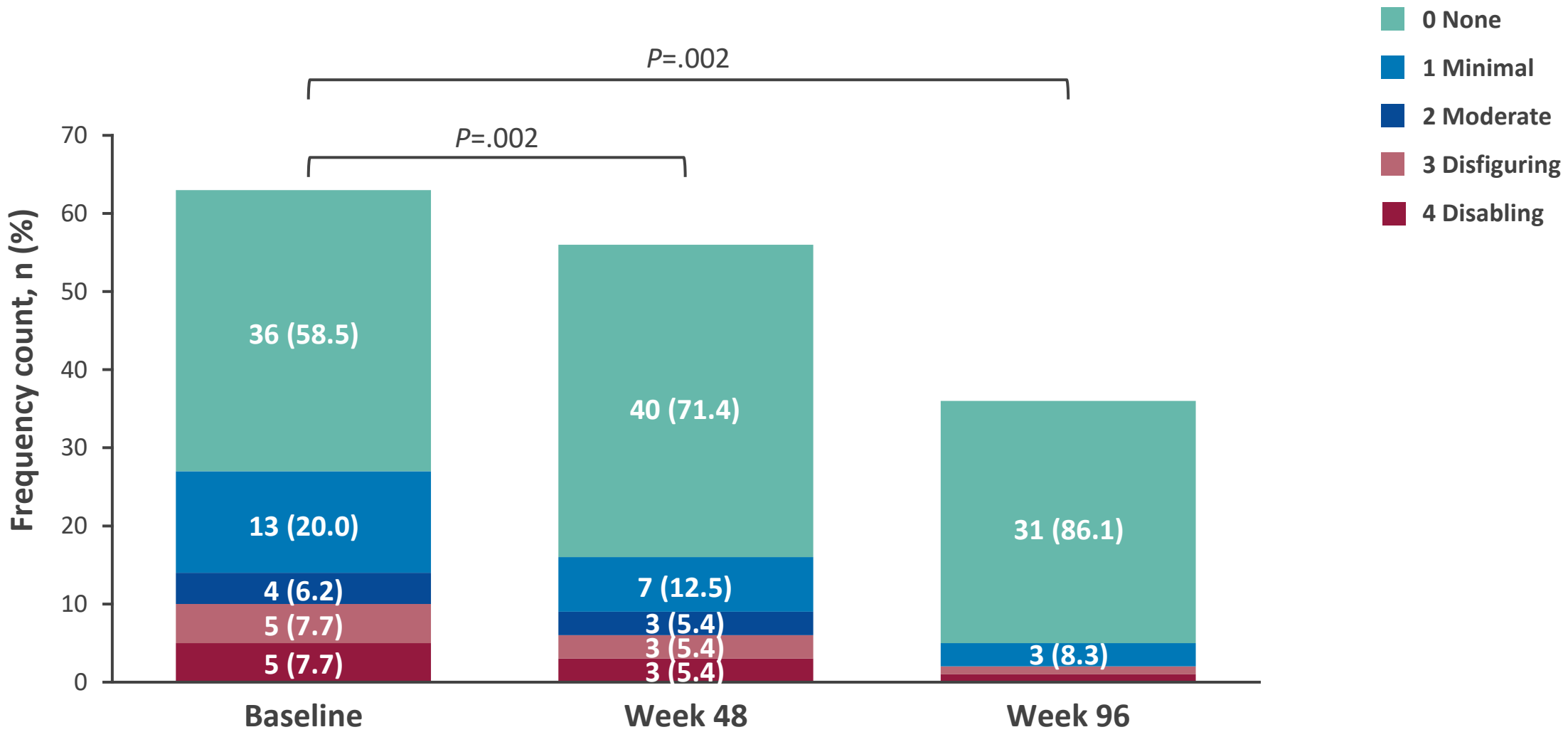
Author Disclosures

- W Karnsakul is a consultant for Mirum Pharmaceuticals, Inc.
- D Mogul and R Aguilar are employees of and shareholders in Mirum Pharmaceuticals, Inc.

Thank you!

Back-up

Xanthoma Severity Over Time in All Participants Treated With Maralixibat (N=65)[1,2,a]



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