Efficacy and Safety of Odevixibat in Patients With Alagille Syndrome

Top-line Results From ASSERT, a Phase 3, Double-Blind, Randomized, Placebo-Controlled Study

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Disclosures

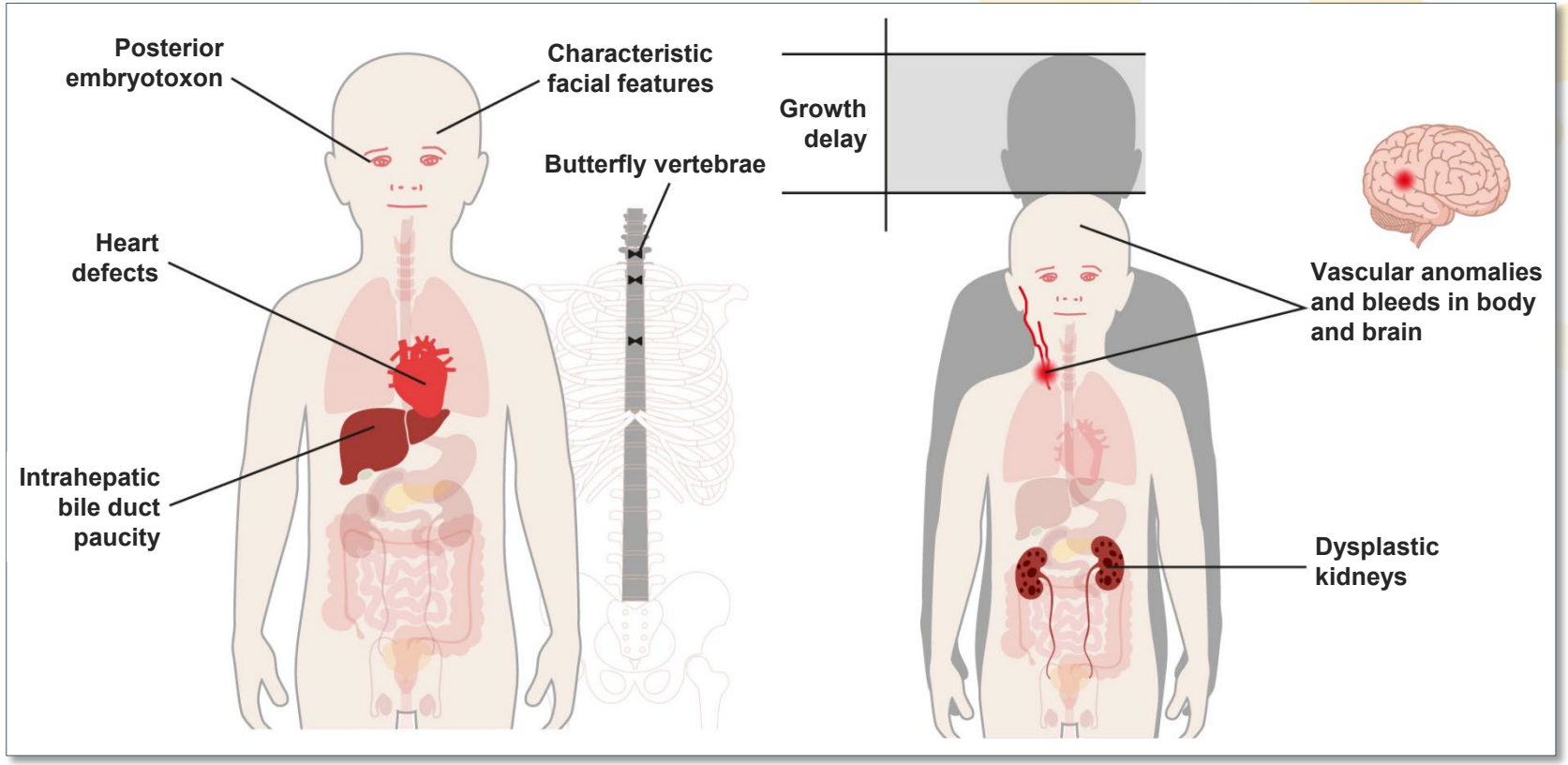
Nadia Ovchinsky

I disclose the following financial relationships with a commercial interest:

- Albireo – Consultant and research support

Introduction

- **ALGS**: Rare, multisystem disorder caused by mutations in *JAG1* or *NOTCH2*[1,2]
- **Odevixibat:** Potent, selective IBAT inhibitor, dosed once daily in oral capsules, under investigation for treatment of patients with ALGS



ALGS, Alagille syndrome; IBAT, ileal bile acid transporter.

1. Kamath BM, et al. *J Pediatr Gastroenterol Nutr.* 2018;67(2):148–56. 2. Kamath BM, et al. *Liver Int.* 2020;40:1812–22. Figure adapted from Mašek J, Andersson ER. *Development.* 2017;144(10):1743-63.

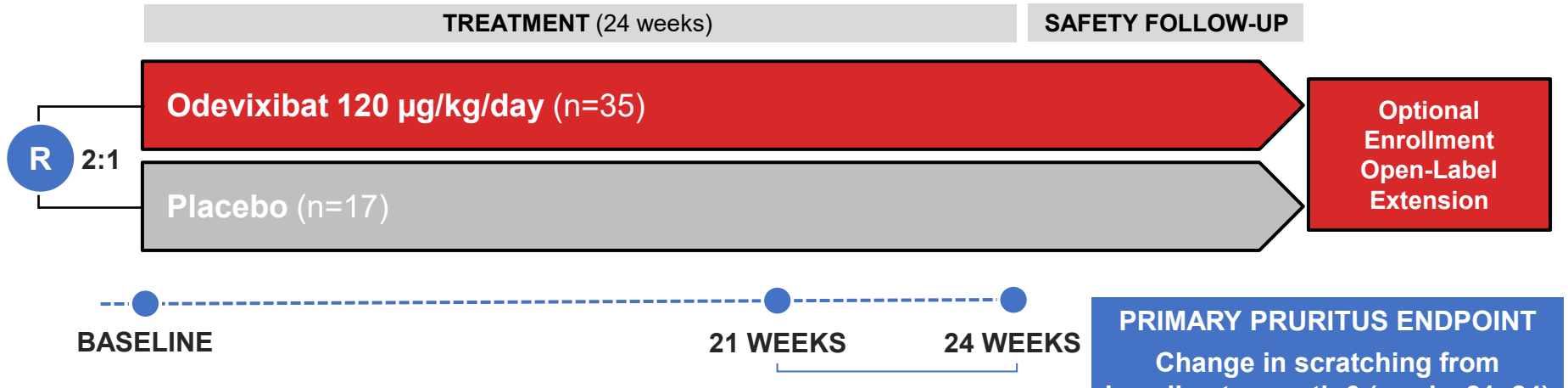
Objective and Study Design

Objective: To evaluate the efficacy and safety of odevixibat in patients with ALGS in the ASSERT trial (NCT04674761)

ASSERT: Phase 3, double-blind, randomized, placebo-controlled study of odevixibat in patients with ALGS

52 Patients

- Any age with a confirmed diagnosis of ALGS
- History of significant pruritus
- Elevated serum bile acid levels



PRIMARY PRURITUS ENDPOINT

Change in scratching from baseline to month 6 (weeks 21–24) as measured by the PRUCISION ObsRO caregiver instrument

ALGS, Alagille syndrome; ObsRO, observer-reported outcome; R, randomization.

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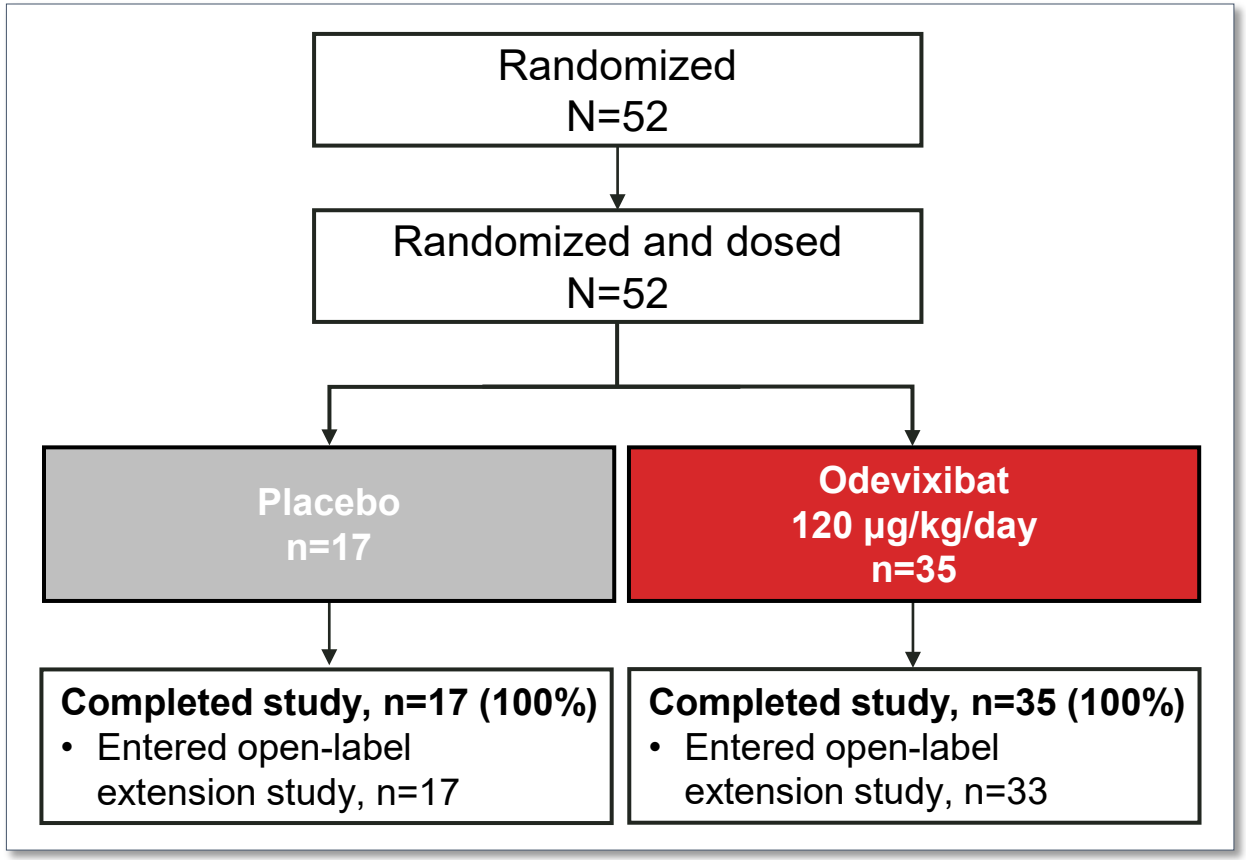
Patient Disposition and Exposure to Odevixibat



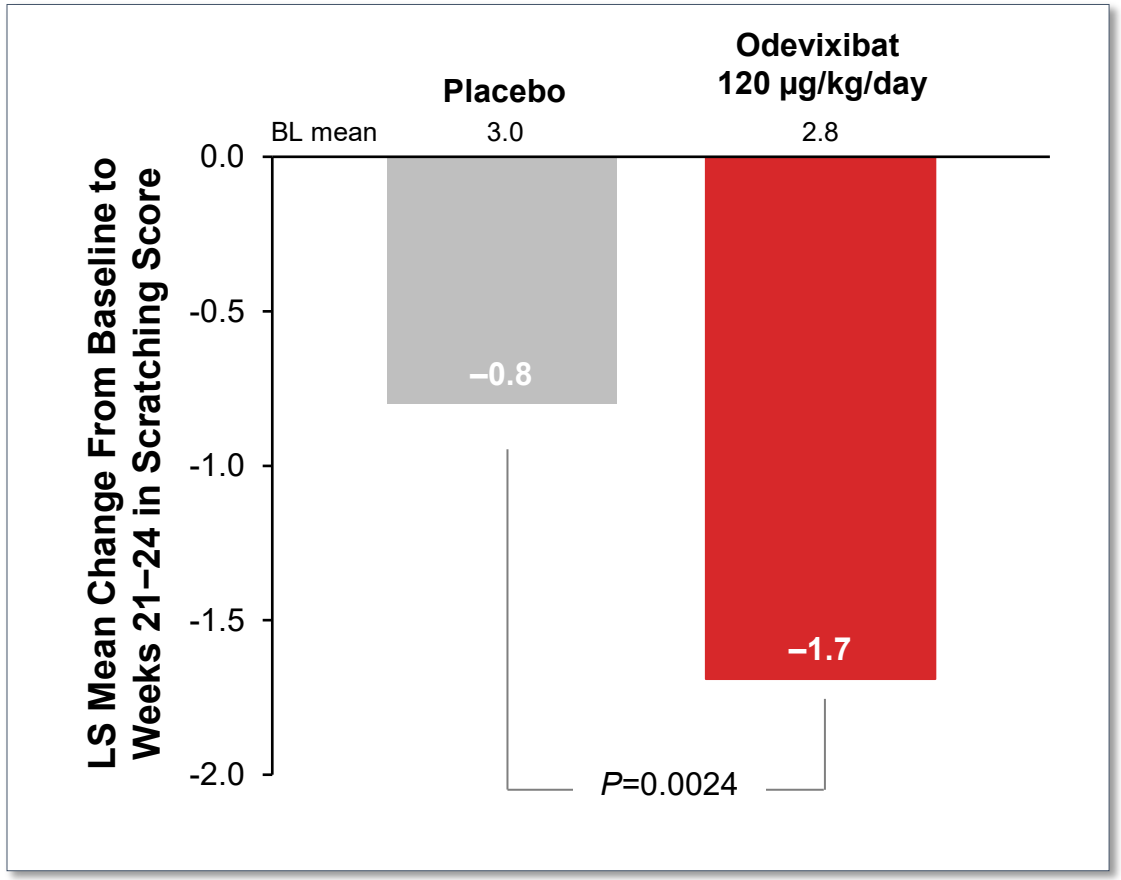
- All patients completed the study
- Median (range) exposure
  - Placebo: 24 (24–25) weeks
  - Odevixibat: 24 (21–26) weeks

Demographics and Baseline Characteristics

	Placebo n=17	Odevixibat 120 µg/kg/day n=35	Overall N=52
Age, mean (SD), years	**5.4** (4.4)	**6.7** (3.8)	**6.3** (4.0)
Male, n (%)	**6** (35)	**21** (60)	**27** (52)
Genetic testing, n (%)			
Mutation in *JAG1*	**16** (94)	**32** (91)	**48** (92)
Mutation in *NOTCH2*	**1** (6)	**3** (9)	**4** (8)
Pruritus score, mean (SD)	**3.0** (0.6)	**2.8** (0.5)	**2.9** (0.6)
Bile acids, mean (SD), µmol/L	**246** (121)	**237** (115)	**240** (116)
ALT, mean (SD), U/L	**149** (84)	**186** (83)	**174** (84)
AST, mean (SD), U/L	**161** (91)	**170** (81)	**167** (83)
Total bilirubin, mean (SD), mg/dL	**3.6** (3.3)	**3.0** (2.5)	**3.2** (2.8)
Total bilirubin, mean (SD), µmol/L	**62** (57)	**52** (43)	**55** (48)
Use of UDCA, n (%)	**16** (94)	**30** (86)	**46** (89)
Use of anti-pruritus medication, n (%)	**17** (100)	**34** (97)	**51** (98)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; UDCA, ursodeoxycholic acid.

Pruritus Was Significantly Improved With Odevixibat vs Placebo at Month 6 (Primary Endpoint)



Pruritus improvements were observed in patients with *JAG1* or *NOTCH2* mutations. Scratching score ranges from 0–4, with higher scores indicating worse symptoms. *P* value based on a mixed-model repeated measures analysis.
BL, baseline; LS, least squares.

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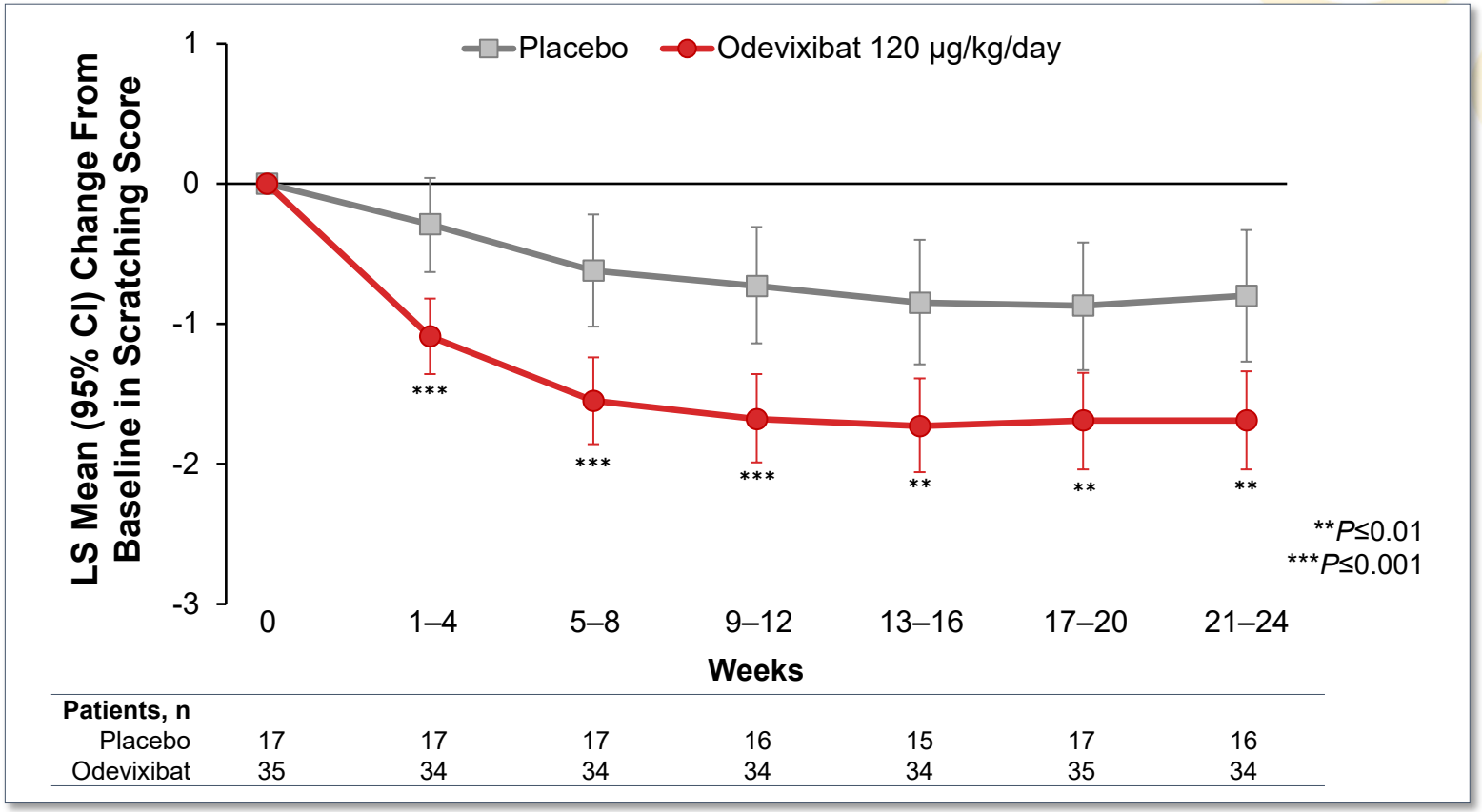
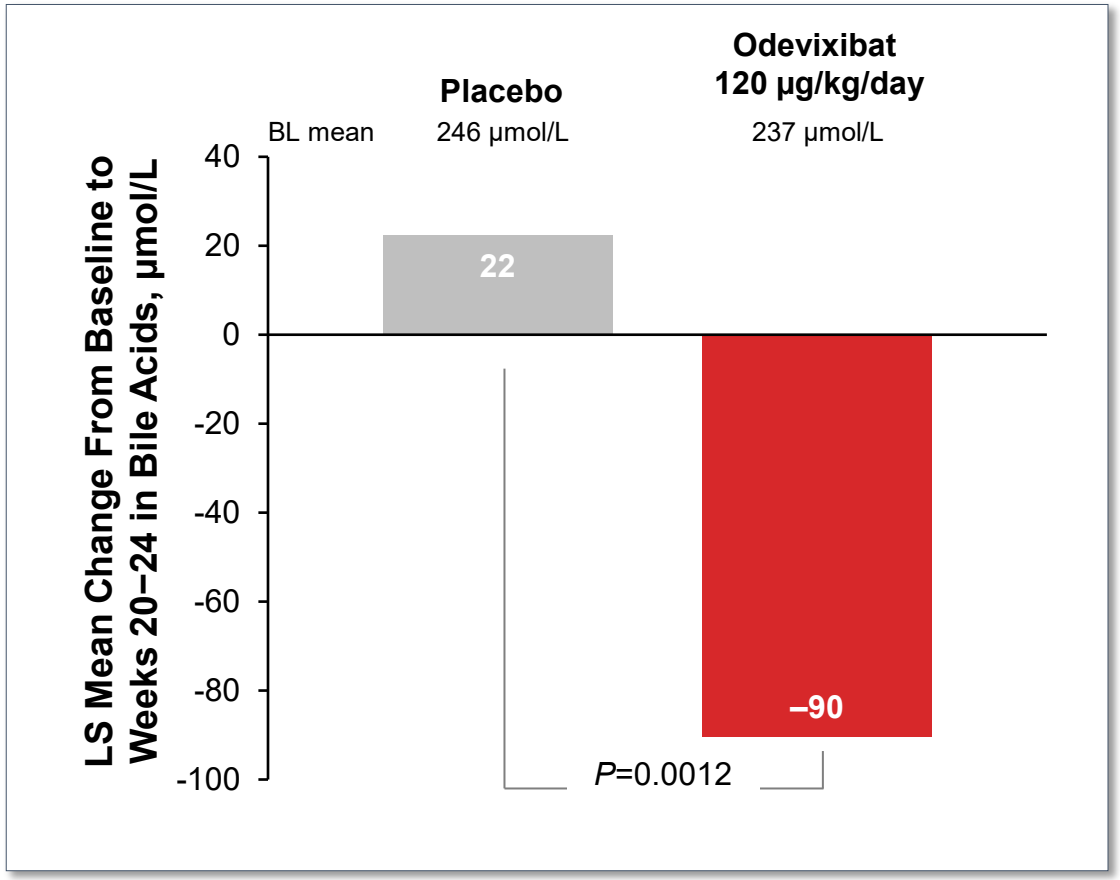
Improvements in Pruritus With Odevixibat Were Early, Rapid, and Sustained



Patients, n							
Placebo	17	17	17	16	15	17	16
Odevixibat	35	34	34	34	34	35	34

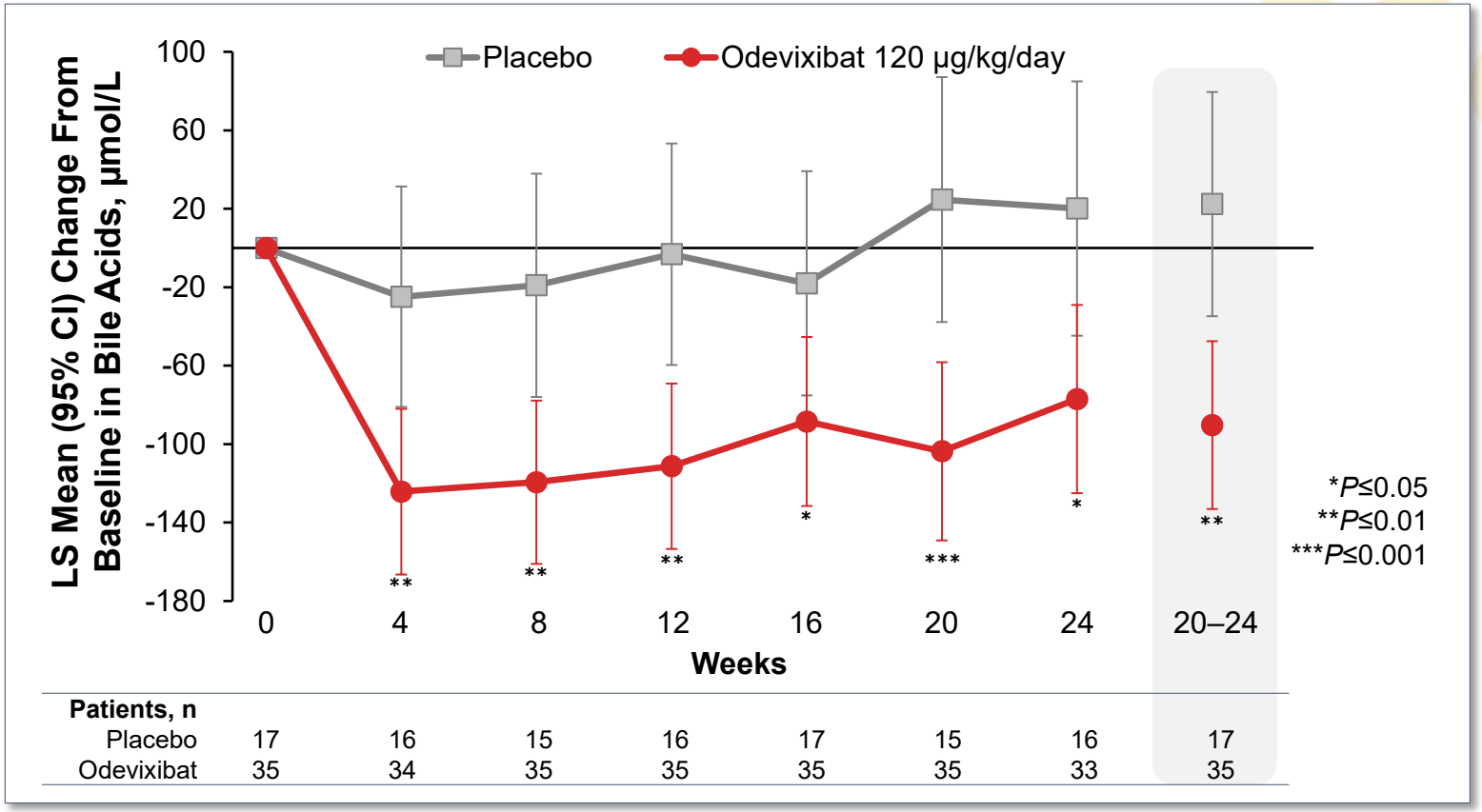
Scratching score ranges from 0–4, with higher scores indicating worse symptoms. *P* values based on a mixed-model repeated measures analysis.
LS, least squares.

Bile Acid Concentration Was Significantly Reduced With Odevixibat vs Placebo at Month 6 (Key Secondary Endpoint)



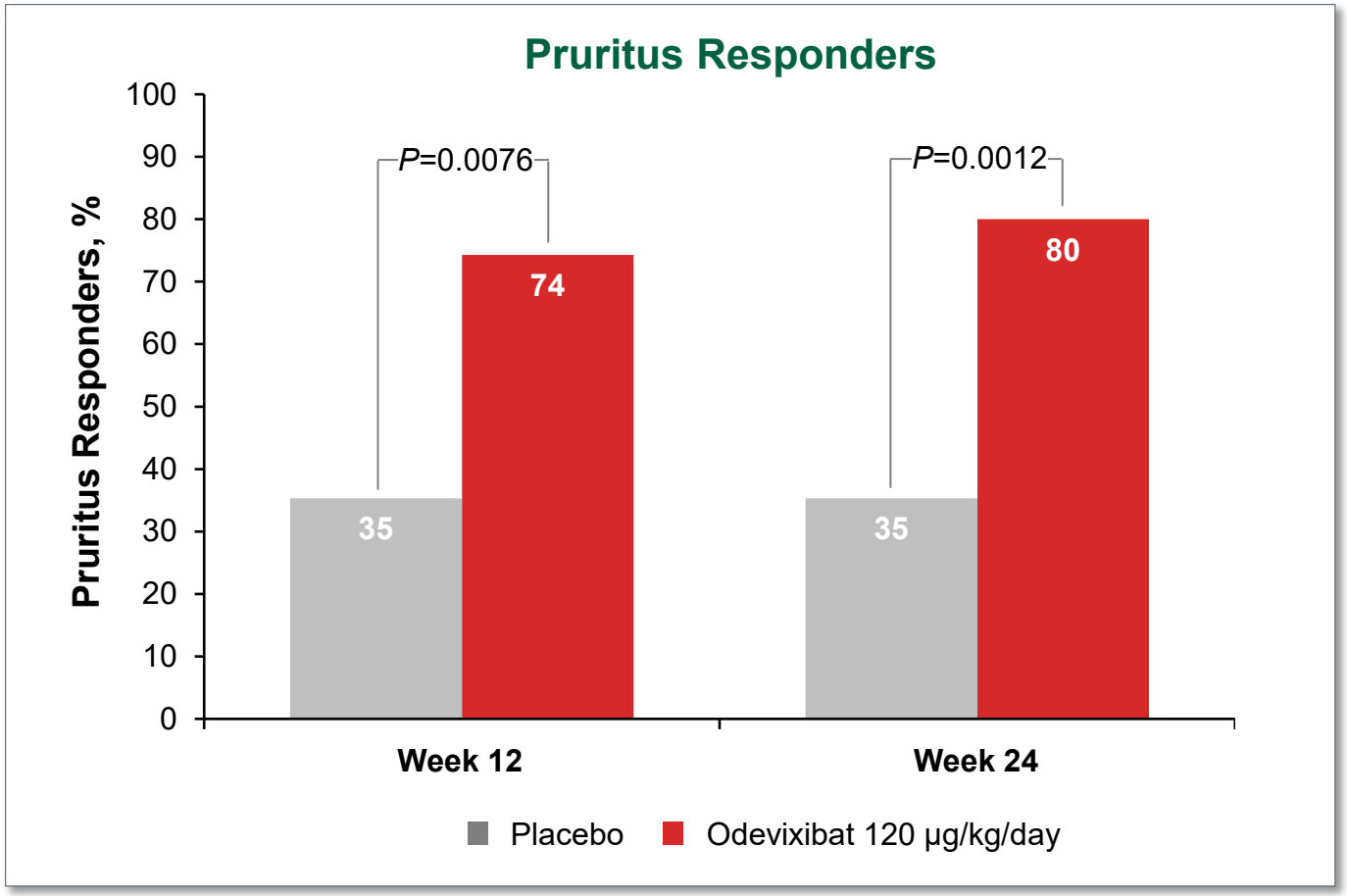
Bile acid reductions were observed in patients with *JAG1* or *NOTCH2* mutations. *P* values based on a mixed-model repeated measures analysis.
BL, baseline; LS, least squares.

Reductions in Bile Acids With Odevixibat Were Early, Rapid, and Sustained



P values based on a mixed-model repeated measures analysis.
LS, least squares.

More Patients Achieved a Clinically Meaningful Improvement in Pruritus With Odevixibat vs Placebo



Pruritus Response

Defined as ≥1-point reduction in monthly scratching score from baseline at 12 or 24 weeks

91% of odevixibat-treated patients achieved ≥1-point change at any time point over 24 weeks

P values based on Cochran-Mantel-Haenszel test.

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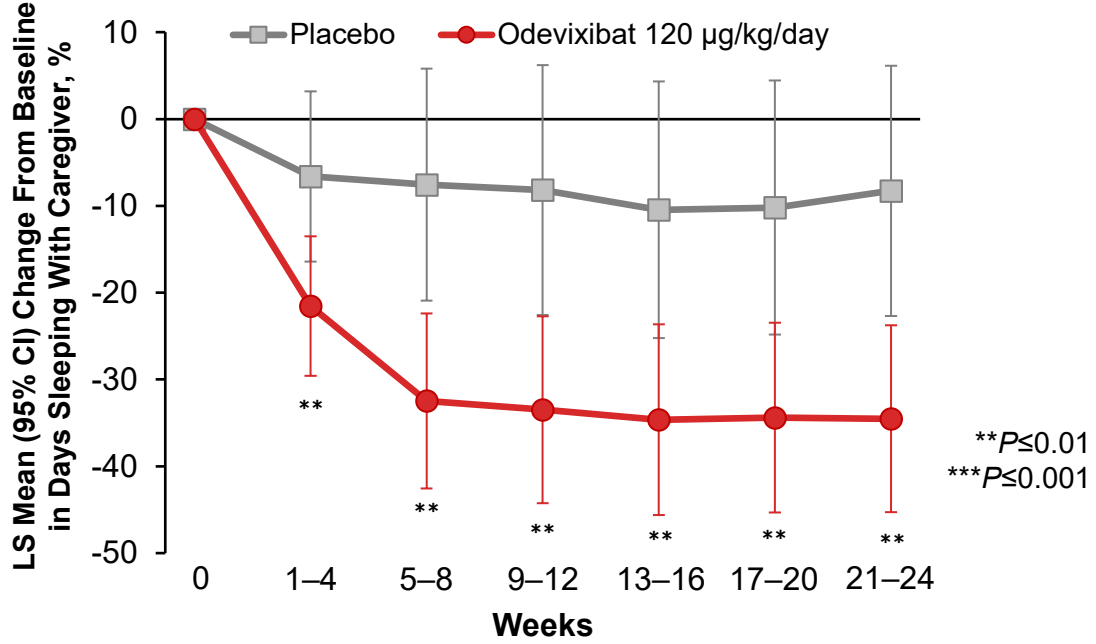
Most Sleep Parameters Were Significantly Improved With Odevixibat vs Placebo (Secondary Endpoint)

Days Sleeping With Caregiver (%)



**$P \leq 0.01$
***$P \leq 0.001$

Patients, n							
Placebo	17	17	17	16	15	17	16
Odevixibat	35	33	34	33	34	34	33

All Sleep Parameters

LS Mean Change From Baseline to Weeks 21–24	Placebo n=17	Odevixibat 120 µg/kg/day n=35
Days seeing blood due to scratching	–19%	–28%
Days with help falling asleep	–10%	–43%**
Days with soothing	–6%	–47%***
Days sleeping with caregiver	–8%	–35%**
Number of awakenings	0.2	–2.7
Days taking medication to induce sleep	4%	–3%
Daytime tiredness	–0.5	–1.1*

*$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$

Tiredness score ranges from 0–4, with higher scores indicating worse symptoms. *P* values based on a mixed-model repeated measures analysis.
LS, least squares.

Safety Summary

- Overall incidence of TEAEs was similar across the placebo and odevixibat-treated groups
- No deaths or TEAEs leading to study drug discontinuation were reported

Patients, n (%)	Placebo n=17	Odevixibat 120 µg/kg/day n=35
Any TEAE	12 (71)	26 (74)
Drug-related TEAEs	3 (18)	8 (23)
Severe TEAEs	2 (12)	5 (14)
Serious TEAEs	2 (12)	5 (14)
Drug-related serious TEAEs	0 (0)	1 (3)
Drug-related TEAEs in all patients, by preferred term		
Diarrhea	1 (6)	4 (11)
Vomiting	0 (0)	2 (6)
Abdominal pain	1 (6)	1 (3)
Abdominal pain upper	0 (0)	1 (3)
Hepatic enzyme increased	1 (6)	1 (3)
INR increased	1 (6)	1 (3)
Feces discolored	0 (0)	1 (3)
Frequent bowel movements	0 (0)	1 (3)
Hematemesis	0 (0)	1 (3)
Nausea	0 (0)	1 (3)
Blood triglycerides increased	0 (0)	1 (3)
Weight decreased	0 (0)	1 (3)

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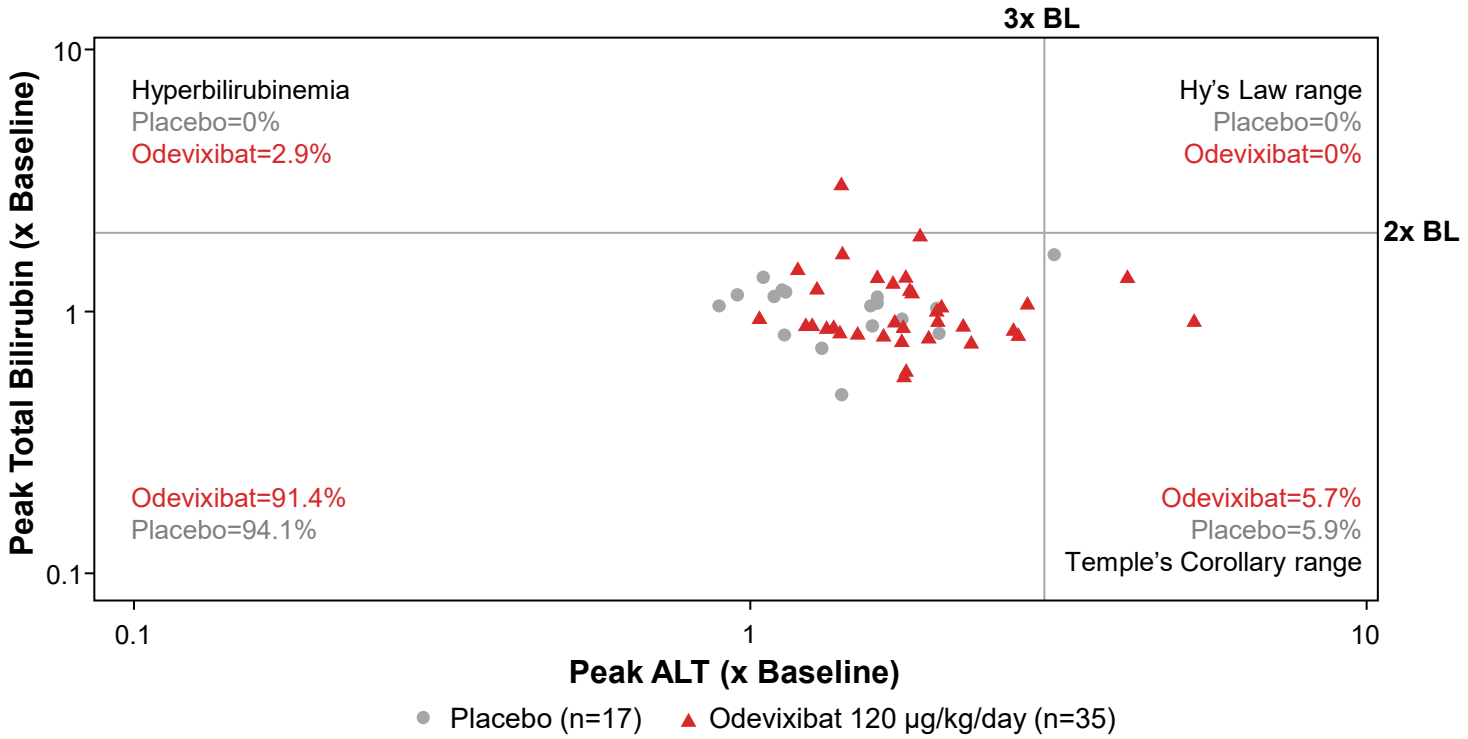
INR, international normalized ratio; TEAE, treatment-emergent adverse event.

Changes From Baseline in Hepatic Parameters

ALT and Total Bilirubin

	Placebo	Odevixibat 120 µg/kg/day
ALT, U/L		
Baseline, n	17	35
Mean (SD)	**149** (84)	**186** (83)
Change to week 24, n	17	34
Mean (SD)	**–2.8** (48)	**57** (84)
Total bilirubin, mg/dL		
Baseline, n	17	35
Mean (SD)	**3.60** (3.33)	**3.04** (2.54)
Change to week 24, n	17	34
Mean (SD)	**0.17** (0.88)	**0.001** (1.11)
Total bilirubin, µmol/L		
Baseline, n	17	35
Mean (SD)	**61.6** (57.0)	**52.0** (43.4)
Change to week 24, n	17	34
Mean (SD)	**2.8** (15.0)	**0.01** (19.0)

Modified eDISH Plot[1] for Post-Baseline Liver Function



Each data point represents maximum post-baseline ALT (per patient) and maximum post-baseline total bilirubin within 30 days of maximum ALT

ALT, alanine aminotransferase; BL, baseline; eDISH, evaluation of Drug-Induced Serious Hepatotoxicity.

1. Parks D, et al. *Pharmacoepidemiol Drug Saf.* 2013;22(6):571-8.

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Conclusions

- Odevixibat treatment for 24 weeks led to highly statistically significant and clinically meaningful improvements in pruritus as well as reductions in bile acid levels and improvements in sleep parameters in patients with ALGS
- Treatment effects were early, rapid, and sustained
- Odevixibat was generally well tolerated; overall incidence of TEAEs was similar with odevixibat and placebo
- No patients discontinued the study
- This randomized, placebo-controlled, pivotal, phase 3 study met its objectives of demonstrating the efficacy and safety of odevixibat in patients with ALGS

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ALGS, Alagille syndrome; TEAE, treatment-emergent adverse event.

Sincere thanks to the **patients** who participated in ASSERT, as well as their **families and caregivers**, the study **co-investigators and sub-investigators**, and the **staff members** at the **clinical centers** and those involved in data collection and analysis

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Key Takeaway

Odevixibat treatment led to significant, rapid, clinically meaningful, and sustained improvements in pruritus, as well as significant reductions in bile acids and improvements in sleep quality in patients with Alagille syndrome