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For further information regarding Indication and Important Safety Information for DAYBUE and DAYBUE STIX, please click here: Prescribing Information.

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DAYBUE® (trofinetide): Results from open-label extension studies

The long-term safety and tolerability of TROF in participants with RTT were assessed in two consecutive OLE studies, LILAC-1™ and LILAC-2™ [1,2]

LILAC-1

40-week OLE enrolling eligible participants who completed the pivotal Phase 3 LAVENDER™ study (N=154)[1]

Primary Endpoint: Most common AEs[1]

- **Diarrhea (n=115; 74.7%)** — Most common AE leading to discontinuation of the study drug (n=33; 21.4%)
- **Vomiting (n=44; 28.6%)** — Second most common AE leading to discontinuation of the study drug (n=10; 6.5%)

- Overall, 70 (46%) participants discontinued the study.[1]
  - 55 (36%) due to an AE
  - 5 (3%) due to lack of efficacy

LILAC-2

32-month OLE enrolling eligible participants who completed the LILAC-1 study (N=77)[2]

Primary Endpoint: Most common AEs[2]

- **Diarrhea (n=41; 53.2%)**
- **COVID-19 (n=21; 27.3%)**
- **Vomiting (n=15; 19.5%)** — Most common AE leading to discontinuation of the study drug (n=2; 2.6%)

- There were four deaths during the study, none of which were considered related to the study drug.[2]
- Overall, 16 (20.8%) participants discontinued the study.[2]
  - 5 (6.5%) due to an AE
  - 3 (3.9%) due to lack of efficacy

- The RSBQ total score and CGI-I score were assessed in LILAC-1 and LILAC-2 as part of secondary and exploratory assessments of long-term efficacy, respectively.[1,3]

LILAC-1*[,1]

-7.1 (1.13)	**RSBQ Total Score:** Change from LAVENDER baseline to Week 40
3.1 (0.09)	**CGI-I Score:** Change from baseline to Week 40

LILAC-2*[,2]

-11.8 (2.45)	**RSBQ Total Score:** Change from LAVENDER baseline to Week 104
3.1 (0.10)	**CGI-I Score:** Change from baseline to Week 12

*Mean (SE)

These descriptive data should be interpreted cautiously and may represent chance findings given the limitations of the open-label study design and lack of a control arm.[1,3]

DAYBUE® (trofinetide): Results from open-label extension studies

LILAC-1

- 40-week, multicenter, OLE study[1]
- Girls and women with a diagnosis of typical RTT according to Rett Syndrome Diagnostic Criteria with a documented disease-causing mutation in the *MECP2* gene who elected to roll over from the pivotal Phase 3 study, LAVENDER[1,4]

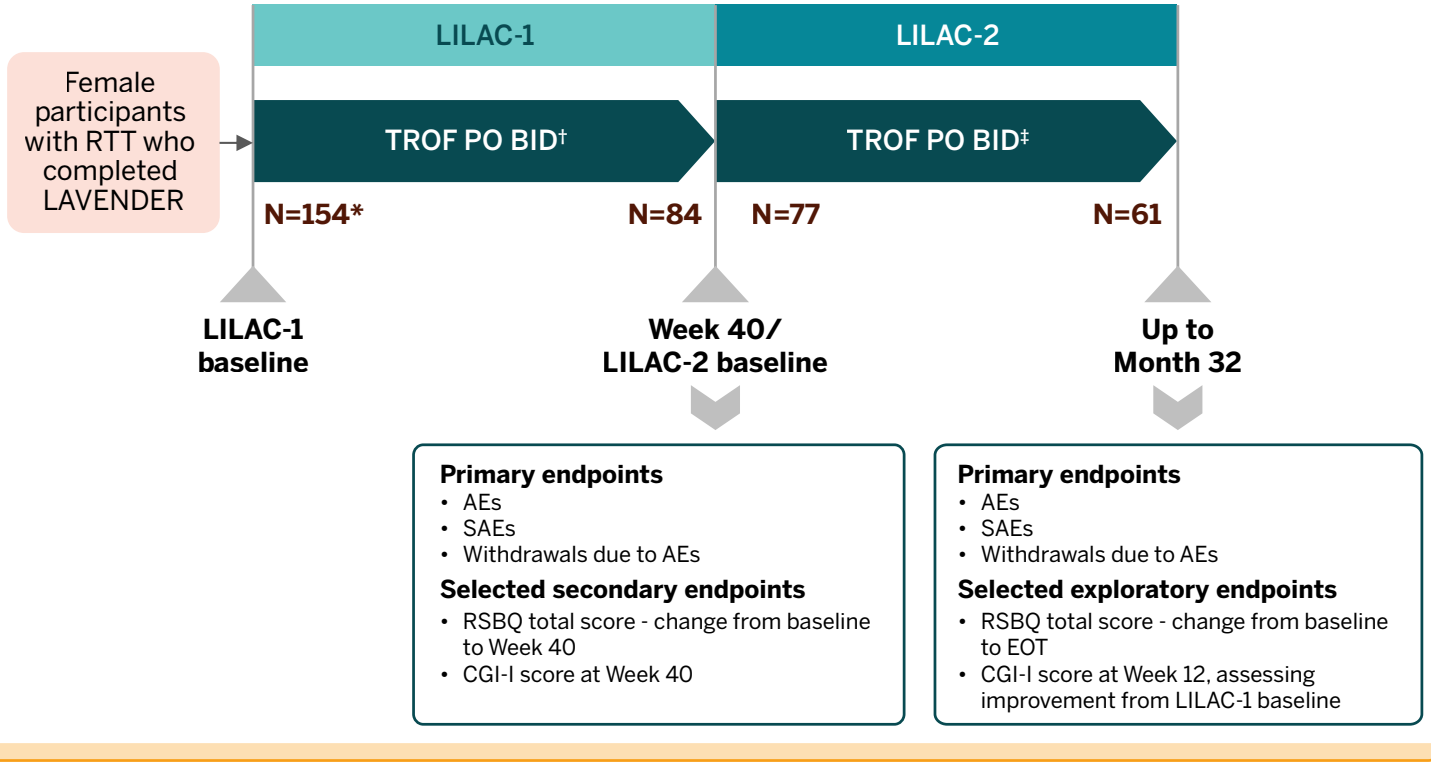
LILAC-2

- 32-month, multicenter, OLE study[2]
- Eligible participants completing LILAC-1[2]

Primary endpoints: AEs, SAEs, and withdrawal due to AEs[1,2]

Selected exploratory secondary endpoints: RSBQ total score and CGI-I score[1,2]

OLE study design[1-3,5]



*Of the 187 participants who were randomized in the LAVENDER study, 155 completed the study and 154 elected to roll over to the open-label LILAC-1 extension study (85 who received placebo in LAVENDER, and 69 who received trofinetide in LAVENDER).

†Dose based on participant's body weight at baseline, except for subjects whose assigned dose in LAVENDER was decreased for tolerability reasons who will remain on that same dose in LILAC-1 and have their dose increased during the study, if tolerated, to the dose level based on weight.

‡The assigned dose for this study was the participant's final dose in the antecedent study.

Abbreviations and References

DAYBUE® (trofinetide): Results from open-label extension studies

Selected baseline demographics and disease characteristics* (LILAC-1 and LILAC-2 safety analysis sets)[1,2,6,7]

	LILAC-1			LILAC-2
	PBO in LAVENDER (N=85)	TROF in LAVENDER (N=69)	Total (N=154)	Total (N=77)
Age, years (mean ± SD)	11.0 ± 4.51	10.9 ± 4.63	11.0 ± 4.55	12.0 ± 4.38
Primary race, n (%)				
White	82 (96.5)	61 (88.4)	143 (92.9)	71 (92.2)
Black or African American	0	1 (1.4)	1 (0.6)	1 (1.3)
Asian	1 (1.2)	4 (5.8)	5 (3.2)	1 (1.3)
Native Hawaiian or other Pacific Islander	0	1 (1.4)	1 (0.6)	0
Other	2 (2.4)	2 (2.9)	4 (2.6)	4 (5.2)
RSBQ total score (mean ± SD)	42.8 ± 12.99	39.5 ± 11.87	41.3 ± 12.57	36.4 ± 12.68†
CGI-S score (mean ± SD)	4.8 ± 0.77	4.9 ± 0.79	4.8 ± 0.78	4.8 ± 0.89

*Participant demographics were assessed at the screening visit in the LAVENDER study. The RSBQ total score and CGI-S score were assessed at the baseline visit in the respective OLE study. †N=76.

Comorbidities reported in participants with an incidence >10% in LILAC-1 and LILAC-2[6,7]

	LILAC-1			LILAC-2
	PBO in LAVENDER (N=85)	TROF in LAVENDER (N=69)	Total (N=154)	Total (N=77)
Constipation, n (%)	66 (77.6)	50 (72.5)	116 (75.3)	56 (72.7)
Seizure, n (%)	44 (51.8)	32 (46.4)	76 (49.4)	31 (40.3)
GERD, n (%)	37 (43.5)	31 (44.9)	68 (44.2)	38 (49.4)
Gastrostomy, n (%)	37 (43.5)	28 (40.6)	65 (42.2)	37 (48.1)
Diarrhea, n (%)	18 (21.2)	31 (44.9)	49 (31.8)	34 (44.2)
Epilepsy, n (%)	16 (18.8)	16 (23.2)	32 (20.8)	23 (29.9)

Abbreviations and References

DAYBUE® (trofinetide): Results from open-label extension studies

Participant disposition (LILAC-1 and LILAC-2 safety analysis sets)[2,6,7]

	LILAC-1			LILAC-2
	PBO in LAVENDER (N=85)	**TROF in LAVENDER (N=69)**	**Total (N=154)**	**Total (N=77)**
Completed the study, n (%)	39 (45.9)	45 (65.2)	84 (54.5)	61 (79.2)
Early termination, n (%)	46 (54.1)	24 (34.8)	70 (45.5)	16 (20.8)
Reason for early termination, n (%)				
AE	36 (42.4)	19 (27.5)	55 (35.7)	5 (6.5)
Death	0	0	0	4 (5.2)
Lack of efficacy	4 (4.7)	1 (1.4)	5 (3.2)	3 (3.9)
Non-compliance with the study drug	1 (1.2)	2 (2.9)	3 (1.9)	2 (2.6)
Participant withdrew consent	3 (3.5)	2 (2.9)	5 (3.2)	0
Other: Not related to COVID-19	2 (2.4)	0	2 (1.3)	2 (2.6)

61
participants completed the LILAC-2 study

Within 30 days after study completion

57 (74%)
participants consumed commercially approved TROF

Abbreviations and References

DAYBUE® (trofinetide): Results from open-label extension studies

Summary of AEs[6]

	PBO in LAVENDER (N=85)	TROF in LAVENDER (N=69)	Total (N=154)
Any AE, n (%)	82 (96.5)	61 (88.4)	143 (92.9)
Any SAE, n (%)	10 (11.8)	9 (13.0)	19 (12.3)
Any related AE, n (%)	73 (85.9)	52 (75.4)	125 (81.2)
Any related SAE, n (%)	0	1 (1.4)	1 (0.6)
Any AE leading to discontinuation of the study drug, n (%)	36 (42.4)	19 (27.5)	55 (35.7)
Any severe AE, n (%)	12 (14.1)	3 (4.3)	15 (9.7)
Any fatal AE	0	0	0

AEs ≥5% in the total group[1]

	PBO in LAVENDER (N=85)	TROF in LAVENDER (N=69)	Total (N=154)
Diarrhea, n (%)	71 (83.5)	44 (63.8)	115 (74.7)
Vomiting, n (%)	29 (34.1)	15 (21.7)	44 (28.6)
COVID-19, n (%)	9 (10.6)	8 (11.6)	17 (11.0)
Seizure, n (%)	9 (10.6)	5 (7.2)	14 (9.1)
Upper respiratory tract infection, n (%)	9 (10.6)	4 (5.8)	13 (8.4)
Pyrexia, n (%)	7 (8.2)	5 (7.2)	12 (7.8)
Decreased appetite, n (%)	6 (7.1)	5 (7.2)	11 (7.1)
Irritability, n (%)	4 (4.7)	6 (8.7)	10 (6.5)
Urinary tract infection, n (%)	6 (7.1)	4 (5.8)	10 (6.5)
Weight decreased, n (%)	5 (5.9)	4 (5.8)	9 (5.8)

Most reports of diarrhea were of mild or moderate severity (95.6%); all reports of vomiting were mild or moderate in severity

Most common SAEs in the total population[1]

Seizure (3.2%)

Pneumonia (2.6%)

- One participant experienced two SAEs that were related to the study drug: Urinary tract infection and dehydration[6]

Most common AEs leading to drug discontinuation[1]

Diarrhea
Most common (n=33; 21.4%)

Vomiting
Second most common (n=10; 6.5%)

Other AEs[6]

- Weight decreased (n=3; 1.9%)
- Seizure (n=2; 1.3%)
- Seizure cluster (n=2; 1.3%)

- Changes in laboratory parameters, vital signs, body weight, and electrocardiograms were generally small for and similar between participants receiving TROF and those receiving PBO in LAVENDER.[5]
- PCI changes in alanine aminotransferase (≥3 times the ULN) were reported in 14 (9.3%) participants; none were more than five times the ULN, and no instances met Hy's law criteria.[1,8] A PCI decrease in weight (≥7% change from LAVENDER baseline) was reported in 28 (18.2%) participants at any point during the study; of these, 15 (53.6%) and 7 (25.0%) participants also reported diarrhea and vomiting, respectively.[1]

Abbreviations and References

DAYBUE® (trofinetide): Results from open-label extension studies

Summary of AEs[7]

	TROF (N=77) n (%)
Any AE	72 (93.5)
Any SAE	23 (29.9)
Any related AE	42 (54.5)
Any related SAE	- -
Any AE leading to discontinuation of the study drug	9 (11.7)
Any severe AE	10 (13.0)
Any fatal AE*	4 (5.2)

Most common AEs[2]

Diarrhea (n=41; 53.2%)

COVID-19 (n=21; 27.3%)

Vomiting (n=15; 19.5%)

All reports of diarrhea were of mild or moderate severity; most reports of vomiting (n=14; 93.3%) were mild or moderate in severity[2]

Most common SAEs[7]

Seizure (n=5; 6.5%)

Vomiting (n=2; 2.6%)

Pneumonia (n=2; 2.6%)

Acute respiratory failure (n=2; 2.6%)

Urinary tract infection (n=2; 2.6%)

AEs ≥5% in the total group[7]

Preferred Term	TROF (N=77) n (%)
Diarrhea	41 (53.2)
COVID-19	21 (27.3)
Vomiting	15 (19.5)
Pyrexia	13 (16.9)
Urinary tract infection	13 (16.9)
Seizure	11 (14.3)
Constipation	9 (11.7)
Upper respiratory tract infection	9 (11.7)
Influenza	7 (9.1)
Cough	6 (7.8)
Pharyngitis streptococcal	6 (7.8)
Pneumonia	5 (6.5)
Irritability	5 (6.5)
Gastroenteritis viral	4 (5.2)
Viral upper respiratory tract infection	4 (5.2)
Nasal congestion	4 (5.2)
Flatulence	4 (5.2)
Electrocardiogram QT prolonged	4 (5.2)
Weight decreased	4 (5.2)
Decreased appetite	4 (5.2)
Dehydration	4 (5.2)
Lethargy	4 (5.2)

Most common AEs leading to drug discontinuation[2]

Vomiting (n=2; 2.6%)
Most common

Other AEs reported in one participant each:[7]

- Cardiac arrest
- Seizure
- Diarrhea
- Retching
- Gastric ulcer hemorrhage
- COVID-19
- Sudden unexplained death in epilepsy
- Aspiration and pneumonia aspiration

- In general, changes in vital signs and hematology and chemistry parameters were small, appeared to be mild and transient, and were self-limiting. A PCI decrease in weight (≥7% decrease) relative to LAVENDER baseline was reported in seven (10.9%) participants at Week 52 and four (18.2%) participants at Week 104. Of the participants with a PCI decrease in weight at Week 52, three (42.9%) and one (14.3%) participants also reported diarrhea and vomiting, respectively. Of the participants with a PCI decrease in weight at Week 104, one (25.0%) also reported diarrhea.[2]

*There were four deaths during the study, none of which were considered related to the study drug. One participant experienced two fatal AEs, vomiting and aspiration, following surgical placement of a gastrostomy tube. The following remaining fatal AEs were experienced by one participant each: cardiac arrest, gastric ulcer hemorrhage, and sudden unexplained death in epilepsy.[2,7]

Abbreviations and References

DAYBUE® (trofinetide): Results from open-label extension studies

LILAC-1

Mean (SE) change in RSBQ total score from LAVENDER baseline to Week 40:

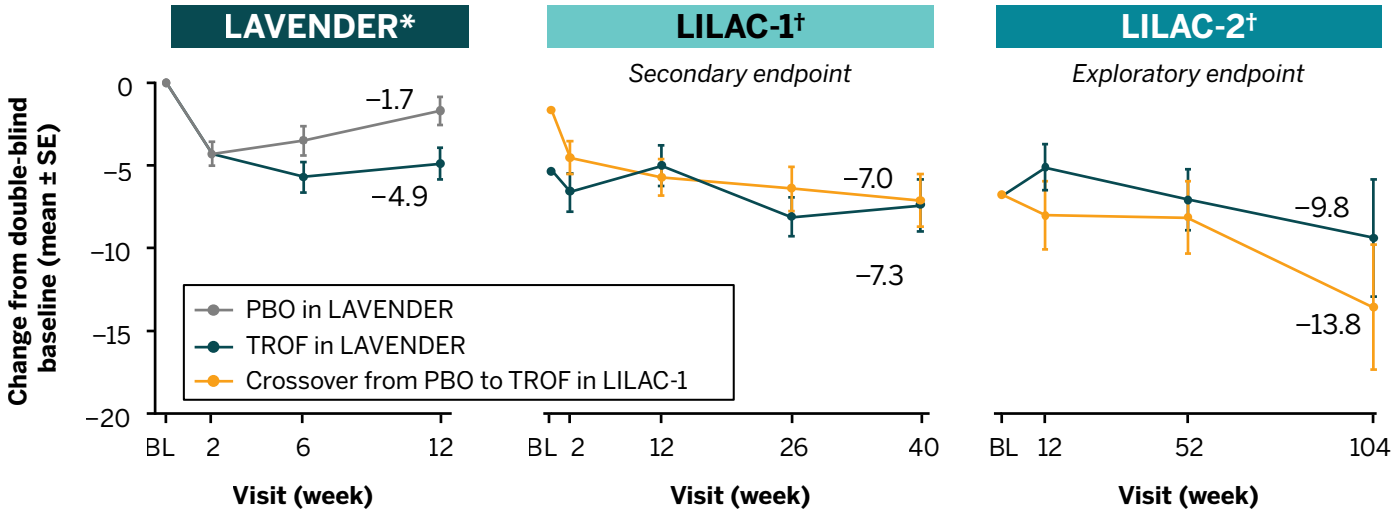
−7.1 (1.13)[1]

LILAC-2

Mean (SE) change in RSBQ total score from LAVENDER baseline to Week 104:

−11.8 (2.45)[2]

RSBQ total score change from LAVENDER (DB) baseline to LILAC-2 Week 104[1,2,5]



PBO/crossover, n=	93	90	92	85	85	80	74	54	44	36	35	28	11
TROF, n=	91	90	83	76	68	67	61	49	44	40	40	39	11

LILAC-1: Change from baseline to Week 40 in the RSBQ total score was assessed as a secondary efficacy endpoint.[1]

LILAC-2: Change from baseline to EOT in the RSBQ total score compared with LILAC-1 baseline was assessed as an exploratory efficacy outcome.[3]

These descriptive data should be interpreted cautiously and may represent chance findings given the limitations of the open-label study design and lack of a control arm.

*Full analysis set. Difference in least squares mean from a mixed-effect model for repeated measure analysis.

†Safety analysis set. Data are mean (SE).

Abbreviations and References

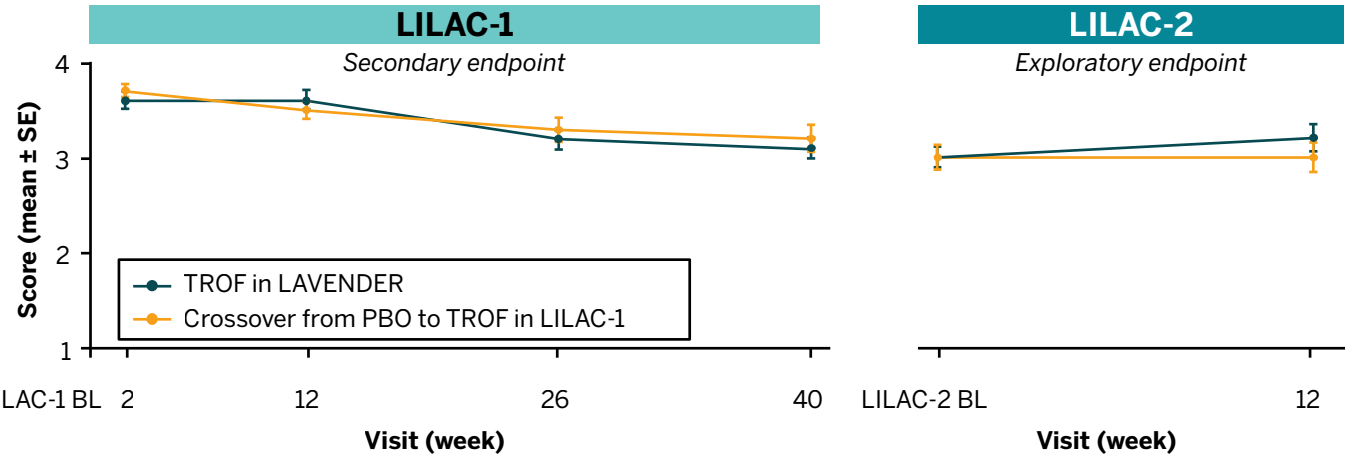
DAYBUE® (trofinetide): Results from open-label extension studies

CGI-I endpoints in LILAC-1 and LILAC-2*[6,7]

		PBO in LAVENDER	TROF in LAVENDER	Total
LILAC-1 Week 40	N	44	47	91
	Mean (SE)	3.2 (0.14)	3.1 (0.11)	3.1 (0.09)
LILAC-2 Week 12	N	34	39	73
	Mean (SE)	3.0 (0.15)	3.2 (0.14)	3.1 (0.10)

*Clinician-rated improvement or worsening relative to LILAC-1 baseline.[1,2]

Mean CGI-I score from LILAC-1 baseline*[1,2]



Crossover, n=	85	80	77	54	44	36	34
TROF, n=	69	67	63	50	47	41	39

LILAC-1: CGI-I score at Week 40 was assessed as a secondary efficacy endpoint.[1]

LILAC-2: CGI-I score at Week 12 compared with LILAC-1 baseline was assessed as an exploratory efficacy outcome.[3]

These descriptive data should be interpreted cautiously and may represent chance findings given the limitations of the open-label study design and lack of a control arm.

*Clinician-rated improvement or worsening relative to LILAC-1 baseline.

Abbreviations and References

DAYBUE® (trofinetide): Results from open-label extension studies

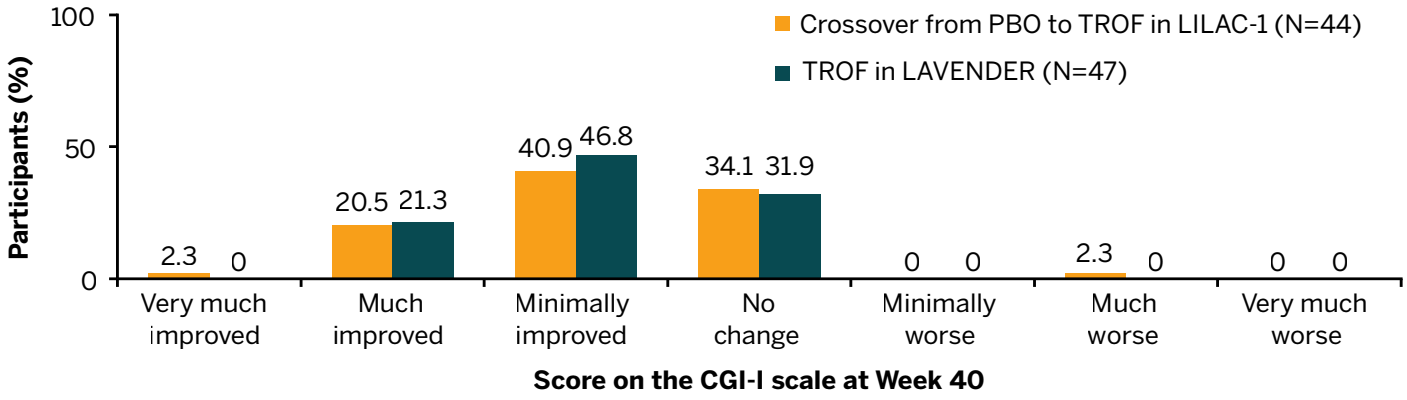
LILAC-1[1]

65.9% of the total group showed improvement in the CGI-I score at Week 40 vs baseline

63.7% treated with PBO in LAVENDER showed improvement

68.1% treated with TROF in LAVENDER showed improvement

CGI-I responder rates at LILAC-1 Week 40*[,1]



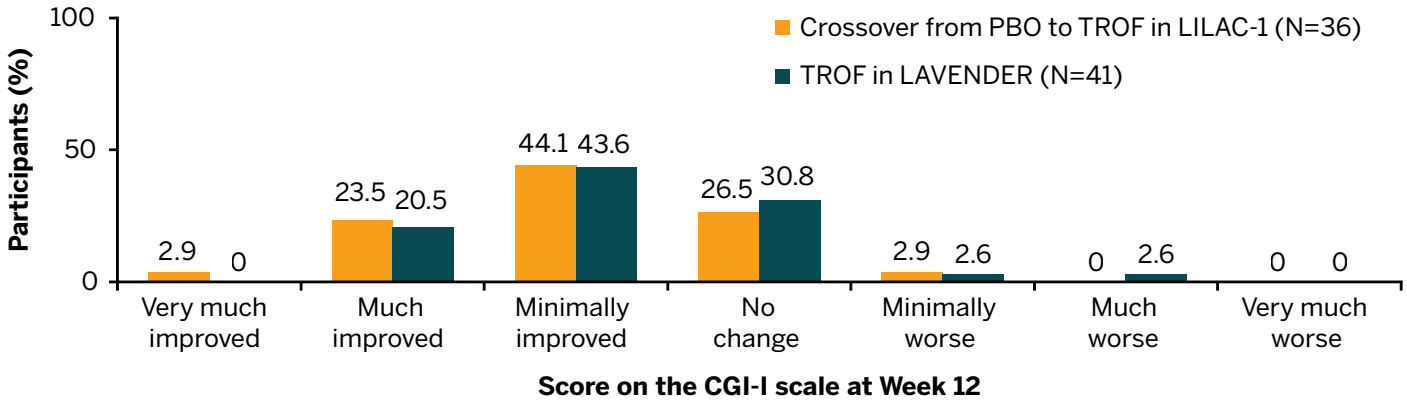
*Clinician-rated improvement or worsening relative to LILAC-1 baseline.

LILAC-2

64.1% of participants who rolled over from the TROF group in LAVENDER showed improvement at Week 12*[,7]

70.5% of participants who rolled over from the PBO group in LAVENDER showed improvement at Week 12*[,7]

CGI-I responder rates at LILAC-2 Week 12*[,7]



*Clinician-rated improvement or worsening relative to LILAC-1 baseline.[2]

Abbreviations and References

DAYBUE® (trofinetide): Results from open-label extension studies

CGI-I shift analysis (LILAC-1)

- A post hoc analysis of the CGI-I score was conducted in the subset of 44 participants who received TROF in both LAVENDER and LILAC-1 and completed both studies.[9]
- Of these participants, 33 (75%) showed some degree of improvement (CGI-I score of 1, 2, or 3) in one or both studies, whereas 11 (25%) experienced no change (CGI-I score of 4) in both studies.[9]

Shift in CGI-I score from LAVENDER Week 12 to LILAC-1 Week 40 in participants who received TROF in both studies[9]

	CGI-I Score at Week 12 of LAVENDER	CGI-I Score at Week 40 of LILAC-1	TROF (N=44) n (%)
Improvement in both studies	1, 2, 3	1, 2, 3	14 (31.8)
No change in LAVENDER, improvement in LILAC-1	4	1, 2, 3	16 (36.4)
Improvement in LAVENDER, no change in LILAC-1	1, 2, 3	4	3 (6.8)
No change in either study	4	4	11 (25.0)

Abbreviations and References

DAYBUE® (trofinetide): Results from open-label extension studies

- Exclusion of male participants and participants aged <5 years[1]
- All scores are limited to participants who were still included in the trial (there was no imputation of missing data)[2]
- Results of these OLE studies should be interpreted with recognition of the following limitations:[2]
  - Open-label design
  - Lack of a control arm
  - Attrition rate due to various reasons over the study duration
  - Inability to assess participants long term after discontinuation

Abbreviations and References

Abbreviations

X

AE, adverse event; **BID,** twice a day; **BL,** baseline; **CGI-I,** Clinical Global Impression-Improvement; **CGI-S,** Clinical Global Impression-Severity; **COVID-19,** coronavirus disease 2019; **EOT,** end of treatment; **GERD,** gastroesophageal reflux disease; **OLE,** open-label extension; **PBO,** placebo; **PCI,** potentially clinically important; **PO,** oral; **RSBQ,** Rett Syndrome Behaviour Questionnaire; **RTT,** Rett syndrome; **SAE,** serious adverse event; **SD,** standard deviation; **SE,** standard error; **TROF,** trofinetide; **ULN,** upper limit of normal.

References

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