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# DAYBUE™ (trofinetide): Long-term Use in Rett Syndrome

This letter is provided in response to your specific request for information regarding data for the long-term use of trofinetide in individuals with Rett syndrome (RTT).

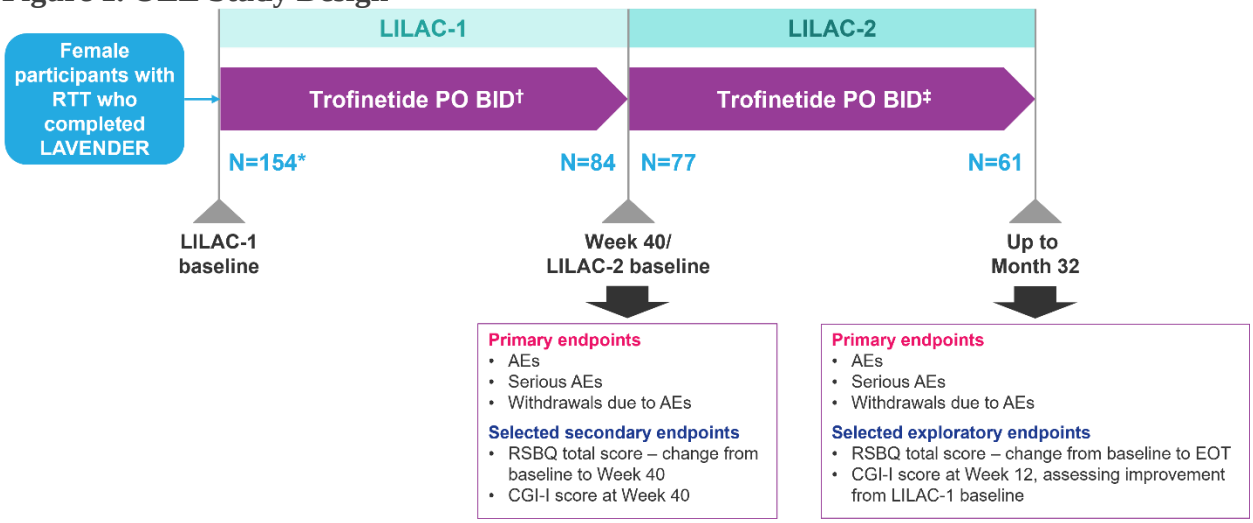
## Summary


- The long-term safety and tolerability of trofinetide in participants with RTT was assessed in two consecutive **open-label extension (OLE) studies**, LILAC-1™ and LILAC-2™.[1,2]
- LILAC-1 was a 40-week OLE enrolling eligible participants who completed the pivotal Phase 3 LAVENDER™ study (N=154).[1]
    - Overall, **70 (46%) participants discontinued the study**; 36% discontinued due to an adverse event (AE) and 3% due to lack of efficacy.[1]
    - The most **common AEs** were diarrhea (74.7%) and vomiting (28.6%). Diarrhea (n=33; 21.4%) was the most common AE leading to discontinuation of study drug, followed by vomiting (n=10; 6.5%).[1]
- LILAC-2 was a 32-month OLE enrolling eligible participants who completed the LILAC-1 study (N=77).[2]
    - Overall, **16 (20.8%) participants discontinued the study**; 6.5% discontinued due to an AE and 3.9% due to lack of efficacy.[2]
    - The most **common AEs** were diarrhea (53.2%), COVID-19 (27.3%) and vomiting (19.5%). Vomiting (n=2; 2.6%) was the most common AE leading to discontinuation of study drug. There were four deaths during the study, none of which were considered related to study drug.[2]
- The Rett Syndrome Behaviour Questionnaire (RSBQ) total score and Clinical Global Impression-Improvement score were assessed in LILAC-1 and LILAC-2 as part of the secondary and exploratory assessments of **long-term efficacy**, respectively.[1,3] These descriptive data should be interpreted cautiously and may represent chance findings given the limitations of the open-label study design and lack of control arm.


## Open-label Extension Studies in RTT

LILAC-1 was a 40-week, multicenter, OLE study in girls and women with a diagnosis of typical RTT according to the 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 (**Figure 1**).[1,4] Eligible participants completing LILAC-1 could enroll into LILAC-2, a 32-month, multicenter OLE study (**Figure 1**).[2] For both studies, the primary endpoint was the long-term safety and tolerability of trofinetide.[1,2]

**Figure 1. 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 from the antecedent study.*
*Abbreviations: AE=adverse event; BID=twice a day; CGI-I=Clinical Global Impression-Improvement; OLE=open-label extension; PO=oral; RSBQ=Rett Syndrome Behaviour Questionnaire; RTT=Rett syndrome.*

## Baseline Characteristics

At LILAC-1 baseline, the mean (standard deviation [SD]) overall age of participants was 11.0 (4.55) years and the mean (SD) baseline CGI-S score was 4.8 (0.78) (**Table 1**).[1] At LILAC-2 baseline, the overall mean (SD) age was 12.0 (4.38) years, and the mean (SD) CGI-S score was 4.8 (0.89).[2]

**Table 1. 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 for the LAVENDER study. RSBQ total score and CGI-S score were assessed at the baseline visit for the respective open-label extension study.*
*†N=76.*
*Abbreviations: CGI-S=Clinical Global Impression-Severity; PBO=placebo; RSBQ=Rett Syndrome Behaviour Questionnaire; SD=standard deviation; TROF=trofinetide.*

## Participant Disposition

Overall, 70 (46%) participants discontinued LILAC-1; 36% discontinued due to an adverse event and 3% due to lack of efficacy (**Table 2**).[1] In LILAC-2, 16 (20.8%) participants discontinued, reasons for which included an AE (n=5; 6.5%), death (n=4; 5.2%), and lack of efficacy (n=3; 3.9%).[2] Of the 61 participants who completed LILAC-2, 57 were transitioned over to commercially marketed trofinetide.[7]

**Table 2. 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) n (%) | Total (N=77) n (%) |
| **Completed the study** | 39 (45.9) | 45 (65.2) | 84 (54.5) | 61 (79.2) |
| **Early termination** | 46 (54.1) | 24 (34.8) | 70 (45.5) | 16 (20.8) |
| **Reason for early termination** | | | | |
| Adverse event | 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 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) |
| **Participant took commercially marketed trofinetide within 30 days after study completion** | 0 | 0 | 0 | 57 (74.0) |

*Abbreviations: PBO=placebo; TROF=trofinetide.*

# Long-term Safety Results

## LILAC-1

Overall in LILAC-1, 143 (92.9%) participants experienced AEs; 19 (12.3%) were serious AEs (**Table 3**). The most common serious AEs in the total population were seizure (3.2%) and pneumonia (2.6%).[1] One participant experienced two serious AEs that were considered related to study drug (urinary tract infection and dehydration).[6]

**Table 3. Summary of Adverse Events (LILAC-1 Safety Analysis Set)[6]**

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

*Abbreviations: AE=adverse event; PBO=placebo; TROF=trofinetide.*

The most common AEs in LILAC-1 were diarrhea (74.7%) and vomiting (28.6%) (**Table 4**). Most reports of diarrhea were of mild or moderate severity (95.6%); all reports of vomiting were mild or moderate in severity.[1]

**Table 4. Adverse Events ≥5% in Total Group (LILAC-1 Safety Analysis Set)[1]**

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

*Abbreviations: PBO=placebo; TROF=trofinetide.*

Diarrhea (n=33; 21.4%) was the most common AE leading to discontinuation of study drug, followed by vomiting (n=10; 6.5%).[1] Other AEs leading to discontinuation of study drug that were reported in more than 1 participant were weight decreased (n=3; 1.9%), seizure (n=2; 1.3%), and seizure cluster (n=2; 1.3%).[6]

Changes in laboratory parameters, vital signs, body weight, and electrocardiograms were generally small and similar for participants treated with trofinetide or placebo in LAVENDER. Potentially clinically important (PCI) changes in alanine aminotransferase (≥3 times the upper limit of normal [ULN]) were reported for 14 (9.3%) participants: none were more than 5 times the ULN and no instances met Hy's law criteria.[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 which 15 (53.6%) and 7 (25.0%) participants also reported diarrhea and vomiting, respectively.[1]

## LILAC-2

Overall, 72 (93.5%) participants experienced AEs in LILAC-2; 23 (29.9%) were serious AEs (**Table 5**).[2] No participants experienced a serious AE that was considered related to study drug. There were four deaths during the study, none of which were considered related to study drug. One participant experienced two fatal AEs, vomiting and aspiration, following the surgical placement of a gastrostomy tube. The remaining fatal AEs were experienced by one participant each: cardiac arrest, gastric ulcer hemorrhage, and sudden unexplained death in epilepsy.[2,7]

**Table 5. Summary of Adverse Events (LILAC-2 Safety Analysis Set)[7]**

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

*Abbreviation: AE=adverse event.*

The most common AEs in LILAC-2 were diarrhea (53.2%), COVID-19 (27.3%) and vomiting (19.5%) (**Table 6**). 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]

**Table 6. Adverse Events in ≥5% of Participants (LILAC-2 Safety Analysis Set)[7]**

| Preferred Term | Trofinetide (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) |

Seizure (n=5; 6.5%) was the most common serious AE, followed by vomiting, pneumonia, urinary tract infection and acute respiratory failure, which were each reported in 2 (2.6%) participants. Other serious AEs were reported in 1 participant each.[7] Vomiting (n=2; 2.6%) was the most common AE leading to discontinuation of study drug.[2] Other AEs leading to discontinuation of study drug were reported in 1 participant each: cardiac arrest, diarrhea, gastric ulcer hemorrhage, retching, sudden unexplained death in epilepsy, COVID-19, seizure, aspiration and pneumonia aspiration.[7]

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 7 (10.9%) participants at Week 52 and 4 (18.2%) participants at Week 104. Of the participants with a PCI decrease in weight at Week 52, 3 (42.9%) and 1 (14.3%) participant also reported diarrhea and vomiting, respectively. Of the participants with a PCI decrease in weight at Week 104, 1 (25.0%) also reported diarrhea.[2]

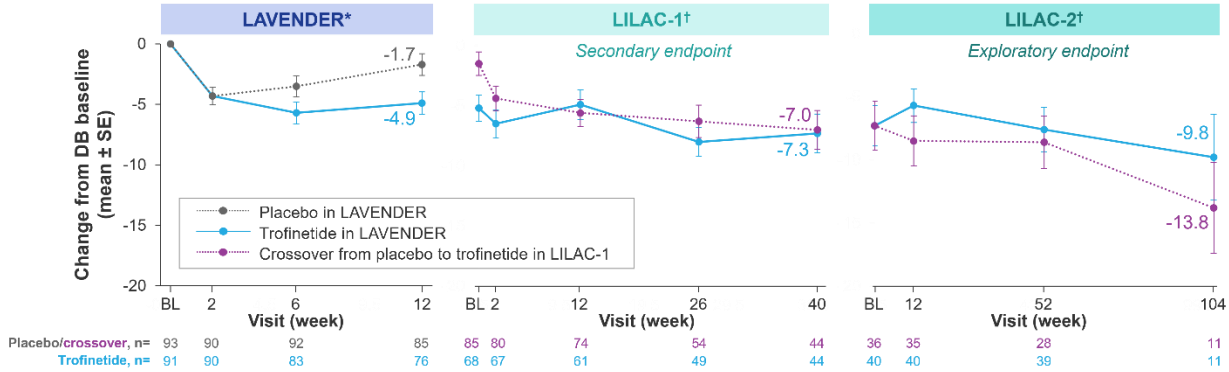
## Long-term Efficacy Results

The change from baseline to Week 40 in RSBQ total score and CGI-I score at Week 40 were assessed as secondary efficacy endpoints in LILAC-1.[1] In LILAC-2, the change from baseline to end of treatment in RSBQ total score and CGI-I score at Week 12 compared with the LILAC-1 baseline were assessed as exploratory efficacy outcomes.[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 control arm.

### RSBQ Total Score

The change in RSBQ total score from LAVENDER baseline through to LILAC-2 Week 104 is shown in **Figure 2**. In the overall population of LILAC-1, the mean (standard error [SE]) change in RSBQ total score from LAVENDER baseline to Week 40 was -7.1 (1.13).[1] In LILAC-2 overall, the mean (SE) change in RSBQ total score from LAVENDER baseline to Week 104 was -11.8 (2.45).[2]

**Figure 2. RSBQ Total Score Change from LAVENDER (DB) Baseline to LILAC-2 Week 104[1,2,5]**




**Full analysis set. Difference in least squares mean from the mixed-effect model for repeated measure analysis.*
*†Safety analysis set. Data are mean (SE).*
*Abbreviations: BL=baseline; DB=double blind; PBO=placebo; RSBQ=Rett Syndrome Behaviour Questionnaire; SE=standard error; TROF=trofinetide.*

### CGI-I Score

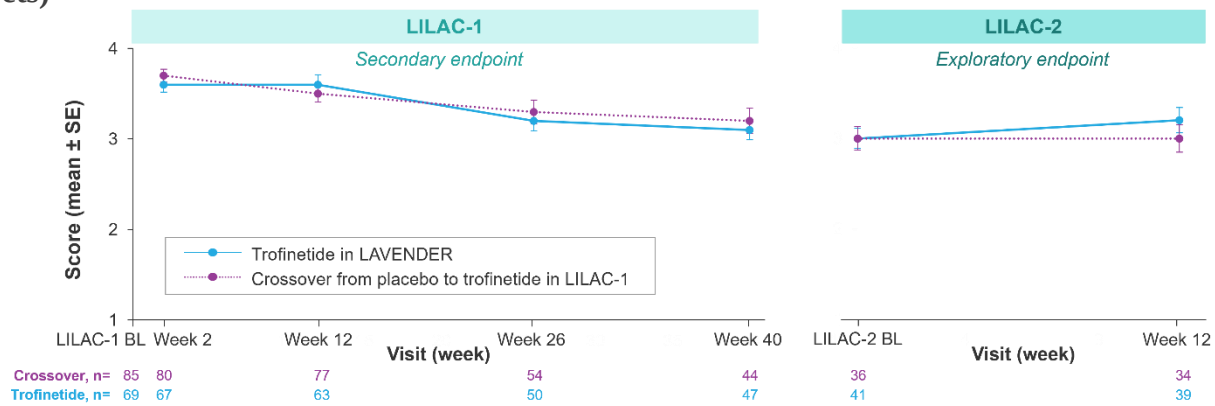
Mean (SE) CGI-I scores at LILAC-1 Week 40 and LILAC-2 Week 12 (both relative to LILAC-1 baseline) are summarized in **Table 7** and **Figure 3**.

**Table 7. CGI-I Endpoints in LILAC-1 and LILAC-2* (LILAC-1 and LILAC-2 Safety Analysis Sets)[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.*
*Abbreviations: CGI-I=Clinical Global Impression-Improvement; PBO=placebo; SE=standard error; TROF=trofinetide.*

**Figure 3. CGI-I Score from LILAC-1 Baseline* (LILAC-1 and LILAC-2 Safety Analysis Sets)[2]**

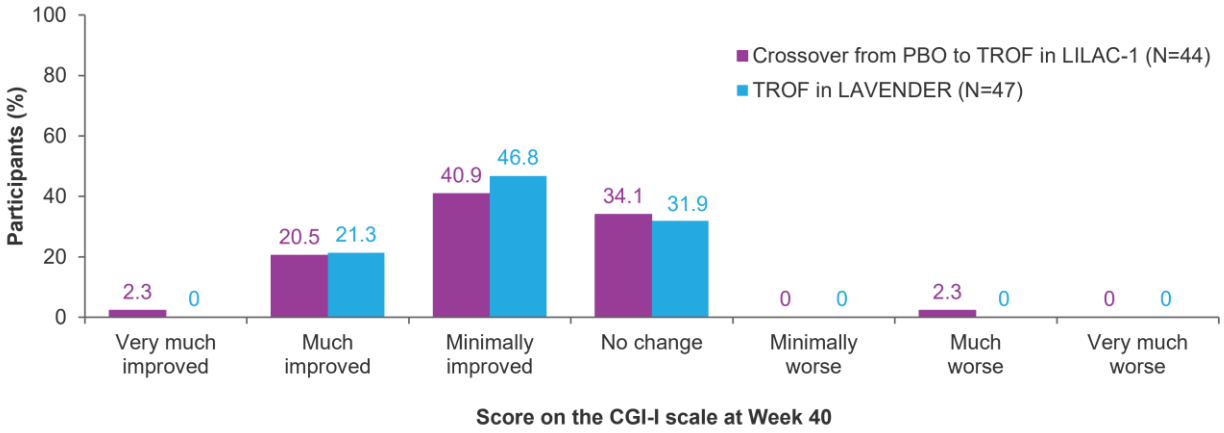



**Clinician rated improvement or worsening relative to LILAC-1 baseline.*
*Abbreviations: BL=baseline; CGI-I=Clinical Global Impression-Improvement; SE=standard error.*

### *CGI-I Responder Analysis*

In a secondary analysis of LILAC-1, 65.9% of the total group showed improvement in CGI-I at Week 40 compared with LILAC-1 baseline, with 68.1% treated with trofinetide in LAVENDER showing improvement and 63.7% treated with placebo in LAVENDER showing improvement (**Figure 4**).[1]

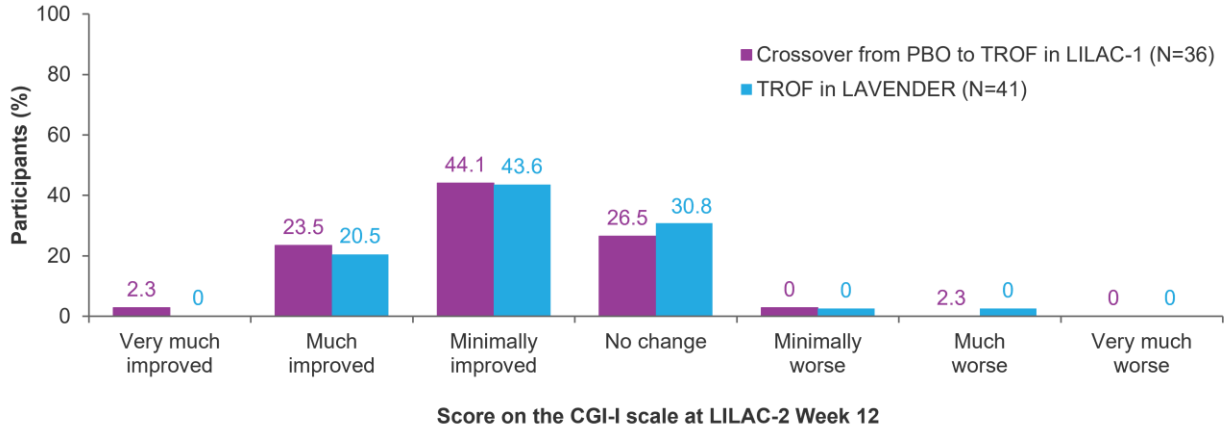
**Figure 4. CGI-I Responder Rates at LILAC-1 Week 40* (LILAC-1 Safety Analysis Set)[1]**




**Clinician rated improvement or worsening relative to LILAC-1 baseline.*
*Abbreviation: CGI-I=Clinical Global Impression-Improvement; PBO=placebo; TROF=trofinetide.*

At LILAC-2 Week 12, 64.1% of participants who rolled over from the trofinetide group in LAVENDER and 70.5% of participants who rolled over from the placebo group in LAVENDER showed improvement in CGI-I score when compared with LILAC-1 baseline (**Figure 5**).[7]

**Figure 5. CGI-I Responder Rates at LILAC-2 Week 12* (LILAC-2 Safety Analysis Set)[7]**




**Clinician rated improvement or worsening relative to LILAC-1 baseline.*
*Abbreviation: CGI-I=Clinical Global Impression-Improvement; PBO=placebo; TROF=trofinetide.*

### *CGI-I Shift Analysis (LILAC-1)*

A *post hoc* analysis was conducted for CGI-I scores in the subset of 44 participants who received trofinetide in both LAVENDER and LILAC-1 and completed both studies (**Table 8**). Of these participants, 33 (75%) showed some degree of improvement (CGI-I score of 1, 2 or 3) in one or both studies, while 11 (25%) had no change (CGI-I score of 4) in both studies.[9]

**Table 8. Shift in CGI-I Score from LAVENDER Week 12 to LILAC-1 Week 40 in Participants who Received Trofinetide in Both Studies[9]**

| | CGI-I Score at Week 12 of LAVENDER | CGI-I Score at Week 40 of LILAC-1 | Trofinetide (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) |

*Abbreviation: CGI-I=Clinical Global Impression-Improvement.*

## Limitations

These studies are limited by the 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] Furthermore, the results of these OLE studies should be interpreted with recognition of the following limitations: open-label design, lack of a control arm, attrition rate due to various reasons over the study duration, and inability to assess participants long term after discontinuation.

## References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