

From Development to Early Real-World Use: Clinical and Formulation Rationale

for DAYBUE® Stix in Rett Syndrome

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INTRODUCTION

- Trofinetide is approved for the treatment of Rett syndrome (RTT) by the US Food and Drug Administration (FDA) based on the efficacy and safety results of LAVENDER, LILAC, and LILAC-2¹⁻³
 - At the time of the approval, trofinetide was available as DAYBUE®, a ready-to-use oral solution⁴
- Real-world experience has revealed challenges with DAYBUE® use in some patients with RTT regarding excipient sensitivity, taste, large dosing volume, dietary restrictions, and refrigerated storage/portability
- DAYBUE® Stix, a trofinetide powder for oral solution that can be constituted with water or water-based beverages over a range of volumes, was designed to address the real-world challenges of DAYBUE®
 - DAYBUE® Stix was approved by the FDA in December 2025⁴

OBJECTIVE

- To summarize the data supporting DAYBUE® Stix development and present early learnings on the real-world use of DAYBUE® Stix

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ACKNOWLEDGMENTS

The study was supported by Acadia Pharmaceuticals Inc. (San Diego, CA, USA). Medical writing support was provided by Juan Sanchez-Cortes, PhD, of Evidence Scientific Solutions, Inc., and funded by Acadia Pharmaceuticals Inc.

DISCLOSURES

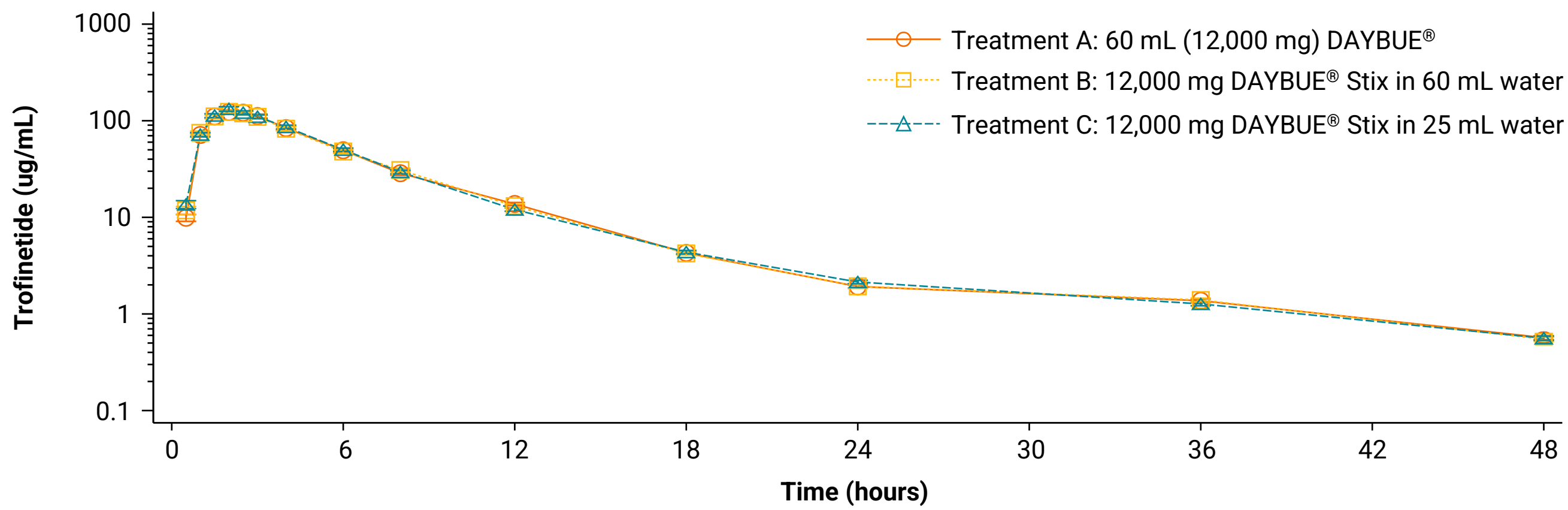
MD, RT, LC, and AP are employees and stakeholders in Acadia Pharmaceuticals Inc.

RESULTS

Bioequivalence of DAYBUE® and DAYBUE® Stix

- The results of a randomized, phase 1 study determined the bioequivalence of DAYBUE® and DAYBUE® Stix⁵
 - In total, 38 healthy adults took 3 versions of trofinetide: (A) 60 mL (12,000 mg) DAYBUE®; (B) 12,000 mg DAYBUE® Stix constituted in 60 mL water; and (C) 12,000 mg DAYBUE® Stix constituted in 25 mL water (Figure 1)
 - Each solution was orally administered on separate days in an ABC or BAC sequence
 - Each dosing period lasted 3 days separated by a washout period of 5 days, for a total period of 19 days
 - Trofinetide blood concentration was measured over 48 hours after each dose using high-performance liquid chromatography
 - Bioequivalence criteria (90% confidence interval of geometric mean ratio for maximum observed concentration of the drug and area under the plasma concentration–time curve falling within 80% and 125%) were met for all treatment groups (Figure 1)
 - The safety profile of DAYBUE® and DAYBUE® Stix were similar and consistent with other phase 1 studies of DAYBUE® in healthy subjects
 - The results of this study demonstrated that DAYBUE® and DAYBUE® Stix can be used interchangeably and support that DAYBUE® Stix can be constituted using adjustable volumes

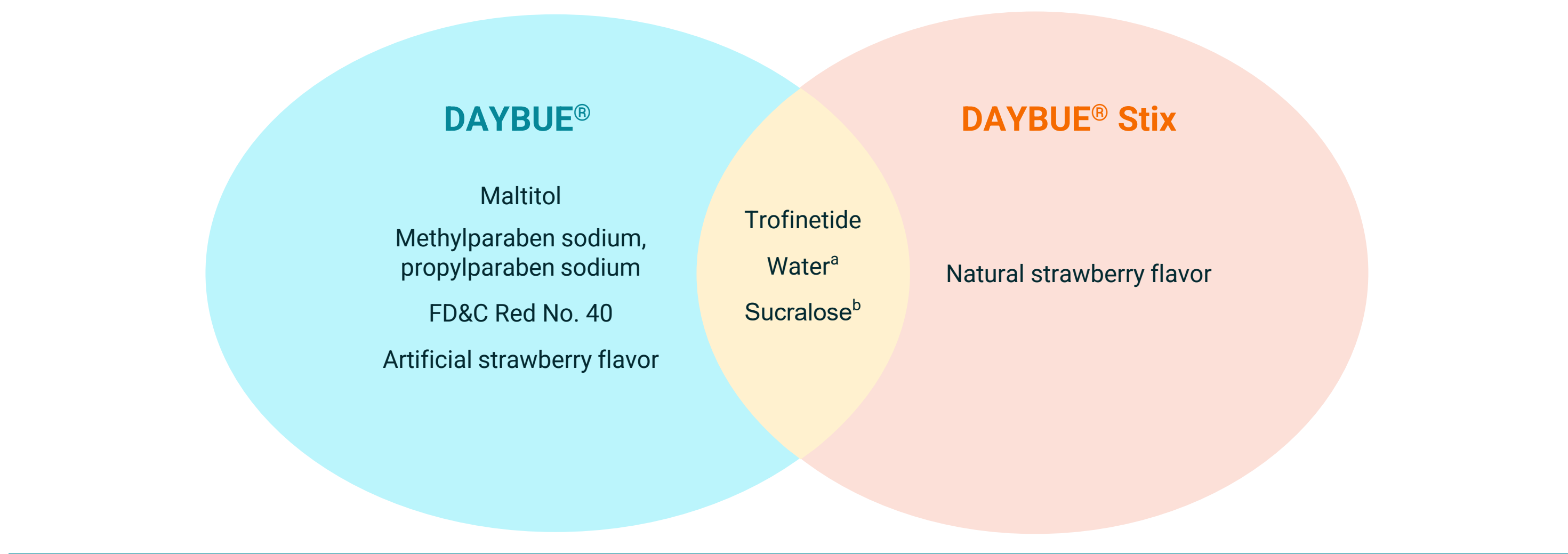
Figure 1. Bioequivalence of DAYBUE® and DAYBUE® Stix



Ingredients in DAYBUE® and DAYBUE® Stix

- DAYBUE® Stix consists of the same active ingredient (trofinetide hydrate [≥95% w/w]) and the same medium (water) as DAYBUE® with fewer excipients than DAYBUE® (Figure 2)⁵
 - DAYBUE® Stix does not contain maltitol as a sweetener
 - DAYBUE® Stix does not contain antimicrobial agents (methylparaben sodium and propylparaben sodium) or dyes (FD&C Red No. 40)
 - DAYBUE® Stix is flavored with natural strawberry flavor, whereas DAYBUE® is flavored with artificial strawberry flavor

Figure 2. Ingredients in DAYBUE® and DAYBUE® Stix



^aFixed medium and volume with DAYBUE®; medium can be water or water-based across a range of volumes with DAYBUE® Stix; ^bDAYBUE® contains more sucralose than DAYBUE® Stix.

Carbohydrate Content in DAYBUE® and DAYBUE® Stix

- The different excipient composition changes the carbohydrate burden of trofinetide treatment from 0.03 g of carbohydrates/mL in DAYBUE® to 0.04 g of carbohydrates/g in DAYBUE® Stix
 - Across recommended doses, DAYBUE® contributes 1.5–3.6 g of carbohydrates/day and DAYBUE® Stix contributes 0.40–0.96 g of carbohydrates/day

Palatability of DAYBUE® Stix With Water-Based Beverages

- The flavor quality of DAYBUE® Stix constituted in a variety of common water-based beverages was evaluated in an open-label taste assessment
 - The juices and hydration beverages assessed were identified through polling of patient groups and included fruit juices, teas, and sports drinks (Figure 3)
 - A 12-g dose of DAYBUE® Stix was constituted in 25, 60, and 120 mL for each beverage
 - Flavor characteristics were evaluated by 9 sensory panelists using the Flavor Profile Method of sensory analysis⁶
 - Flavor quality varied between the different beverage vehicles (Figure 3)
 - Sourness and astringency of the samples increased with increasing trofinetide concentration
 - Consumption of miracle berries before tasting DAYBUE® Stix for oral solution powder resulted in the highest flavor quality
 - Sweet tea, Mott’s for Tots, Tropicana Light, and Welch’s Grape had the same aggregate amplitude as the miracle berries, but with higher scores for sourness and astringency
 - The 2 viscous vehicles, HyFiber and ThickenUp Clear, helped mitigate sourness and astringency

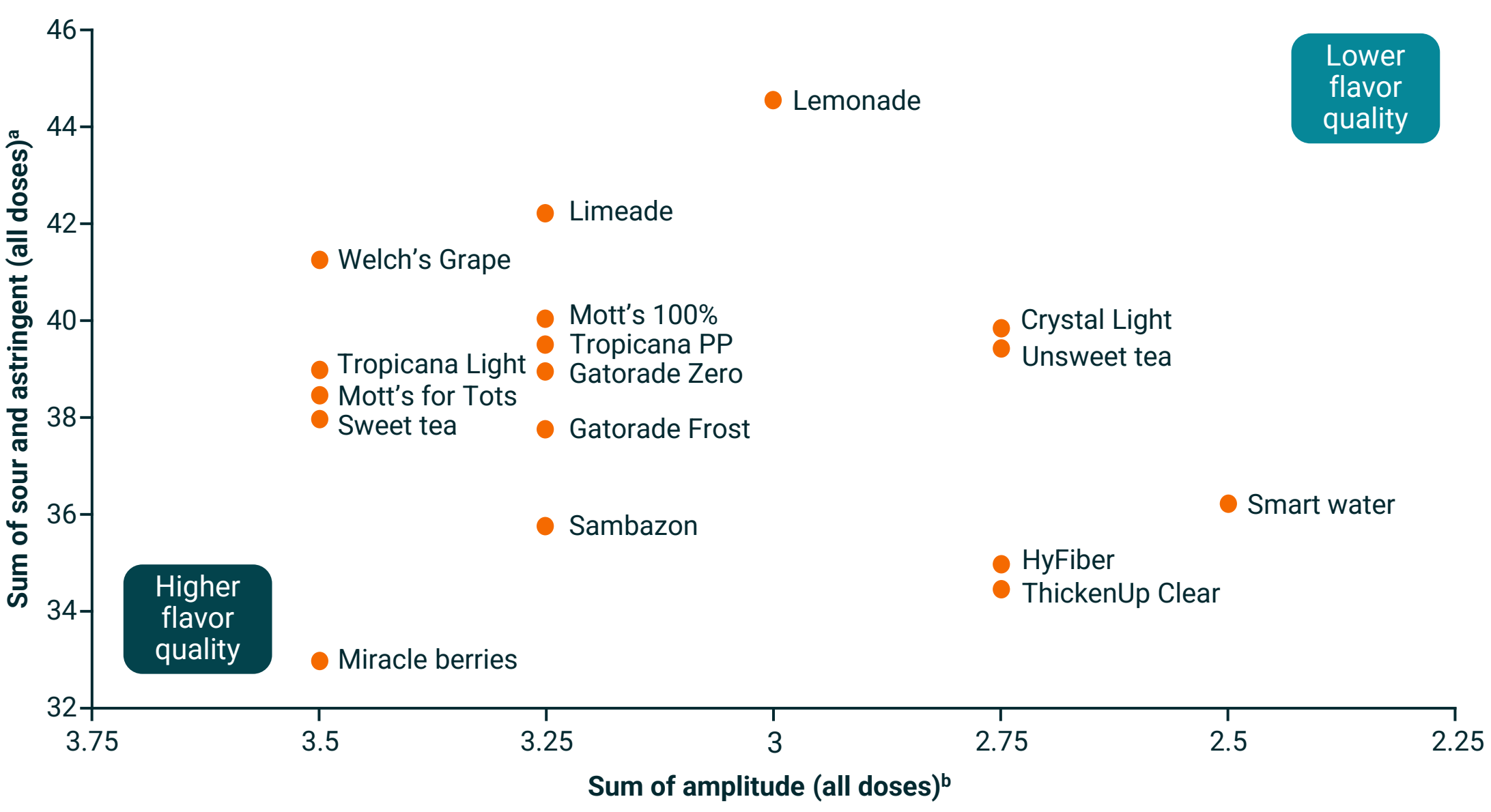
Early Clinician Perceptions of DAYBUE® and DAYBUE® Stix

- Early insights from 7 key opinion leaders in RTT point to clinicians and caregivers favoring DAYBUE® Stix over DAYBUE® (Table 1)
 - The advisors shared that DAYBUE® Stix is generally preferred by caregivers (n = 3), is easier for caregivers to administer (n = 3), and that they strongly recommend it to caregivers of patients with RTT (n = 4)
 - Although some advisors did not have enough experience with DAYBUE® Stix (n = 5), some of them shared that, in their experience, DAYBUE® Stix has a better tolerability profile than DAYBUE® (n = 2)

Real-World DAYBUE® Stix Insights From LOTUS

- In total, 29 patients with RTT enrolled in LOTUS have been treated with DAYBUE® Stix (Figure 4)
 - Of these patients, 25 switched from DAYBUE® to DAYBUE® Stix, 2 had discontinued DAYBUE® and restarted treatment with DAYBUE® Stix, and 2 patients were treatment naïve before initiating DAYBUE® Stix
 - In these patients treated with DAYBUE® Stix in LOTUS, normal stools were common, followed by constipation and diarrhea
 - The most common type of diarrhea reported by caregivers was loose stools

Figure 3. Flavor Quality of DAYBUE® Stix in Water-Based Beverages

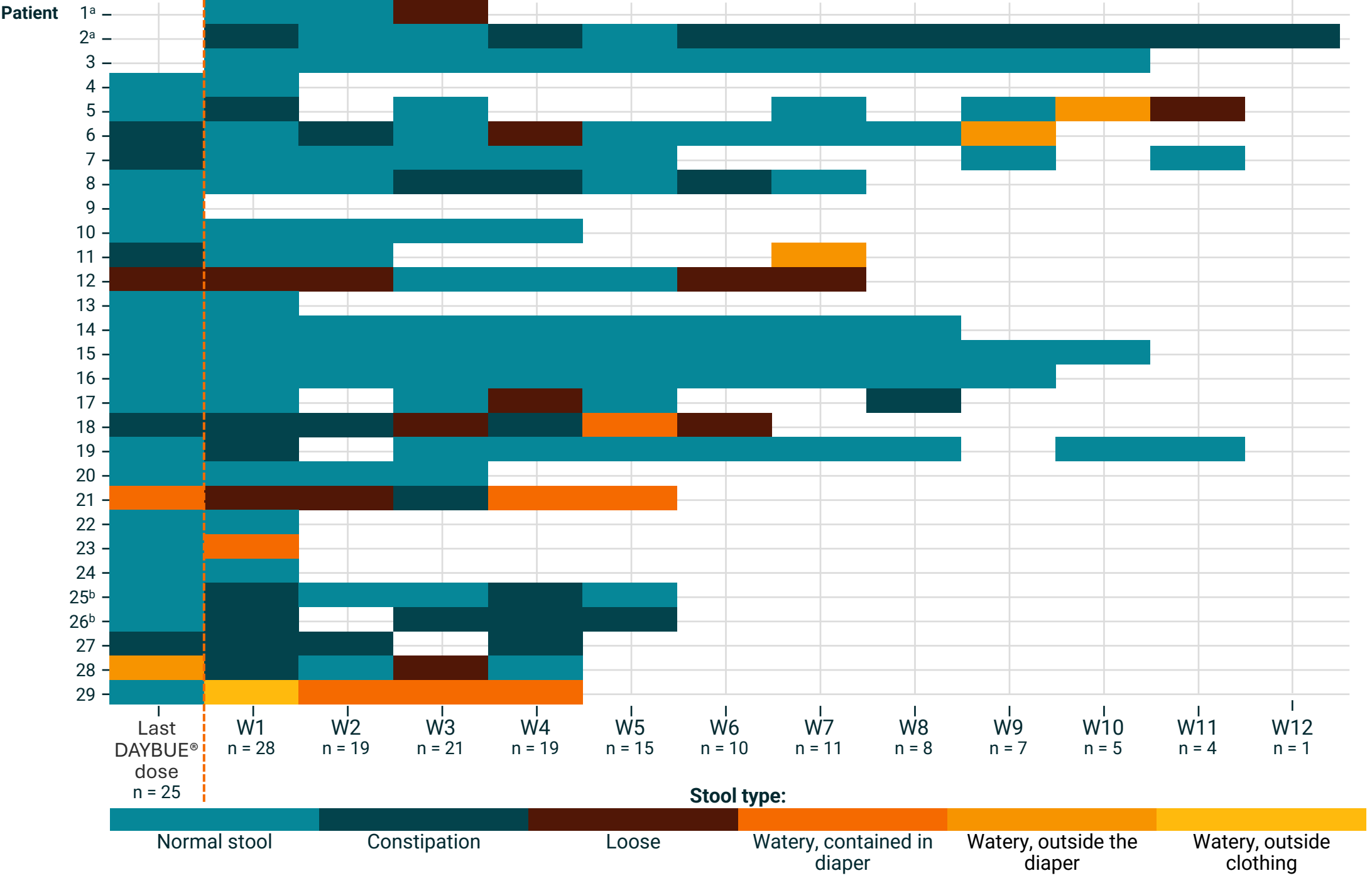


^aSum of sour and astringent intensities (basic sour taste and puckering) of all preparation volumes (120 mL + 60 mL + 25 mL); ^bSum of amplitude rating (balance and fullness of all preparation volumes (120 mL + 60 mL + 25 mL); higher score is better.

Table 1. Clinician Perceptions of DAYBUE® and DAYBUE® Stix (n=7)

	DAYBUE®	DAYBUE® Stix	They are about the same	Not enough experience
Comparing ease of administration between DAYBUE® and DAYBUE® Stix				
Generally more preferred by caregivers	-	3	-	4
Seems to be more palatable	-	3	-	4
Easier for caregivers to administer	2	3	2	-
Comparing dosing between DAYBUE® and DAYBUE® Stix				
Easier for patients to achieve their weight-banded dose	2	1	1	3
Easier to titrate	3	-	4	-
Comparing tolerability and clinical benefit between DAYBUE® and DAYBUE® Stix				
Results in less vomiting	-	-	-	7
Results in less diarrhea	-	1	-	6
Results in better/more detectable clinical benefit	-	-	1	6
Is more tolerable	-	2	-	5
Strongly recommended to patients	-	4	1	2

Figure 4. Stool Type in Patients From LOTUS Treated With DAYBUE® Stix



^aPatient was treatment naïve at the time of DAYBUE® Stix initiation; ^bPatient discontinued DAYBUE® and restarted on DAYBUE® Stix. W, Week.

CONCLUSIONS

Trofinetide is now available in 2 formulations: DAYBUE® and DAYBUE® Stix

- DAYBUE® Stix addresses real-world administration needs in RTT

The integration of bioequivalence, formulation, and taste support the role of DAYBUE® Stix as a flexible and patient-centered treatment option for RTT

Real-world insights from RTT experts and caregivers in the LOTUS study suggest favorable usability by caregivers and manageable tolerability