BACKGROUND
Beloranit, a methane aminopeptidase 2 inhibitor, is in development for the treatment of hyperphagia-related behaviors and obesity in individuals with Prader-Willi syndrome (PWS). PWS is a complex, rare genetic disorder that has many systemic effects. The hallmark of PWS is an incessant feeling of insatiable hunger, regardless of food intake (hyperphagia). Patients typically also have abnormal growth and development, intellectual disabilities, maladaptive and compulsive behaviors, and severe obesity without institution of behavioral adaptations that significantly impact the quality of life of the entire family. Due to their cognitive limitations, individuals with PWS are unable to reliably report the severity of their hyperphagia. Thus, a caregiver-reported measure focused on food-seeking behaviors is needed to support pharmaceutical development and labeling claims associated with hyperphagia in this patient population. The caregiver-completed Hyperphagia Questionnaire (HQ) is a 13-item instrument currently available in United States (US)-English, commonly used to assess food-seeking behaviors in PWS research.

OBJECTIVE
To develop and culturally adapt a modified version of the HQ, the HQ-CT for Clinical Trials (HQ-CT), for use in multinational PWS clinical trials.

METHODS
The international development of the HQ-CT comprised two key stages: the development of the HQ-CT in US English and the cultural adaptation of the US-English HQ-CT into 10 European languages (Figure 1).

Development of the HQ-CT in US English
1) Initial Modification of the HQ
2) Psychometric Evaluation
3) FDA Review
4) PWS Caregiver Review
5) Production of Final 9-item HQ-CT (US-English)

1) Initial Modification of the HQ
- The developers of the HQ and experts in clinical outcome assessments reviewed the HQ considering industry guidance related to clinical outcome assessments, including recommendations in the Food and Drug Administration (FDA) patient-reported outcome guidance. The objectives were to limit the concepts of measurement to behaviors that are observable by caregivers and that have the potential to change during the course of the trial.

2) Psychometric Evaluation
- The preliminary HQ-CT underwent psychometric evaluation using data collected in a phase 2, single-center, randomized, double-blind, placebo-controlled clinical trial of beloranit in patients with PWS. Analyses evaluated the internal consistency of composite HQ-CT scores (Cronbach’s alpha), construct validity ( Spearman correlations with additional measures), and preliminary responsiveness (effect size estimates for HQ-CT items). Item-total correlations and inter-item correlations were computed to inform the HQ-CT scoring algorithm. Due to small sample sizes, Cohen’s general rule of thumb was applied to characterize effect size estimates in change scores (i.e., 0.20, small; 0.50, moderate; 0.80, large).

3) FDA Review
- A review of the modified HQ-CT was conducted by the FDA.

4) PWS Caregiver Review
- The aim of the interviews was threefold: to inform any further refinements to facilitate ease of item comprehension and response by caregivers, to provide additional support for content validity of the HQ-CT, and to optimize the usability of the electronic-data capture device.
- In-depth qualitative interviews were conducted with 6 caregivers of overweight or obese adolescents or adults with PWS. The interviews had two main components: a concept elicitation interview and a cognitive debriefing of an electronic version of the HQ-CT.

5) Production of Final 9-item HQ-CT (US-English)
- The results from the initial modification of the original HQ were combined with the findings from the psychometric evaluation, FDA review, and caregiver review to transform the HQ into the HQ-CT.

RESULTS
Development of the HQ-CT in US English
1) Initial Modification of the HQ
- A preliminary 10-item HQ-CT was created following the development and labeling claims associated with hyperphagia in the food-seeking behaviors of patients typically also have abnormal growth and development, intellectual disabilities, maladaptive and compulsive behaviors, and severe obesity without institution of behavioral adaptations that significantly impact the quality of life of the entire family. Due to their cognitive limitations, individuals with PWS are unable to reliably report the severity of their hyperphagia. Thus, a caregiver-reported measure focused on food-seeking behaviors is needed to support pharmaceutical development and labeling claims associated with hyperphagia in this patient population. The caregiver-completed Hyperphagia Questionnaire (HQ) is a 13-item instrument currently available in United States (US)-English, commonly used to assess food-seeking behaviors in PWS research.

Cultural Adaptation of HQ-CT into 10 European Languages
- Industry-standard adaptation methods were used to ensure conceptual equivalence between the new language versions and the original source US-English instrument, while using everyday language suitable for the target culture. The cultural adaptation process included two key stages: initial translation and PWS caregiver review.

6) Translation
- Translation of the HQ-CT into the 10 European target languages used a forward-backward translation methodology, which was aided by a comprehensive instrument codebook. The process for producing the initial translations for all language versions involved the following steps: forward translation, harmonization, backward translation, conceptual equivalence review, and final adjustments (if needed).

7) PWS Caregiver Review
- Individual cognitive debriefing interviews were conducted with 5 caregivers of patients with PWS in each target country to assess the face and content validity of the translated HQ-CT.

The International Development of the Modified Hyperphagia Questionnaire
S Rebecca Crawford, T Michelle Brown, Sheri E Fehnel, Lynda C Doward, Lauren Nelson, Alice Chen, Terri Kim, Elizabeth Roof, Elisabeth M Dykens

RTI Health Solutions, Manchester, United Kingdom; RTI Health Solutions, Research Triangle Park, NC, United States; Zafgen Inc., Boston, MA; Vanderbilt University, Nashville, TN, United States