**Participant Interpretation of GP5 Response Options Illustrative Participant Quotes**

Themes Identified in Association with Side-effect Bother, Burden, and Tolerability

- **Themes**
  - **Burden**
    - Interference with daily activities: 29
    - Cause physical discomfort: 26
    - Increased cognitive effort and cause annoyance/inconvenience: 13
    - Cause additional mental health problems/negative emotions: 10
    - Treatment benefits weighed against the harms of SEs to assess extent of SE bother: 5
    - Affect appearance in a stigmatizing way: 4
  - **Minor annoyance**
    - Burnt: 21
    - Difficulty finding words: 18
    - Difficulty breathing: 9
    - Difficulty swallowing: 4
    - Difficulty with speech: 4
    - Graying hair: 2
    - Headache: 2
    - Increase appetite: 2
  - **Moderate severity**
    - Difficulty finding words: 20
    - Difficulty breathing: 20
    - Difficulty swallowing: 20
    - Difficulty with speech: 16
    - Difficulty finding words: 16
    - Difficulty breathing: 16
    - Difficulty swallowing: 10
    - Difficulty with speech: 10
    - Difficulty finding words: 4
    - Difficulty breathing: 4
    - Difficulty swallowing: 4
    - Difficulty with speech: 4
    - Difficulty finding words: 4
    - Difficulty breathing: 4
    - Difficulty swallowing: 4
    - Difficulty with speech: 4
  - **Severe**
    - Difficulty finding words: 20
    - Difficulty breathing: 20
    - Difficulty swallowing: 20
    - Difficulty with speech: 20
    - Difficulty finding words: 20
    - Difficulty breathing: 20
    - Difficulty swallowing: 20
    - Difficulty with speech: 20
    - Difficulty finding words: 16
    - Difficulty breathing: 16
    - Difficulty swallowing: 16
    - Difficulty with speech: 16
    - Difficulty finding words: 16
    - Difficulty breathing: 16
    - Difficulty swallowing: 16
    - Difficulty with speech: 16
  - **Very much**
    - Difficulty finding words: 16
    - Difficulty breathing: 16
    - Difficulty swallowing: 16
    - Difficulty with speech: 16
    - Difficulty finding words: 16
    - Difficulty breathing: 16
    - Difficulty swallowing: 16
    - Difficulty with speech: 16
    - Difficulty finding words: 10
    - Difficulty breathing: 10
    - Difficulty swallowing: 10
    - Difficulty with speech: 10
    - Difficulty finding words: 10
    - Difficulty breathing: 10
    - Difficulty swallowing: 10
    - Difficulty with speech: 10
  - **High side effect**
    - Difficulty finding words: 10
    - Difficulty breathing: 10
    - Difficulty swallowing: 10
    - Difficulty with speech: 10
    - Difficulty finding words: 10
    - Difficulty breathing: 10
    - Difficulty swallowing: 10
    - Difficulty with speech: 10

**Concept elicitation**

Participants described their experience of side effects since initiating study treatment. The interviewer probed further for details, when required.

**Conceptualization**

Participants provided feedback on the GP5, including item clarity, the recall period, their interpretation, and perspectives on the difference between response options.

**Analysis**

Interview transcripts were thematically analyzed with inductive and deductive coding using ATLAS.ti.

**Content Validity of FACT-GP5 to Assess Treatment Tolerability in Participants with Progressive, Advanced, Kinase Inhibitor-naïve, RET-mutant Medullary Thyroid Cancer: Qualitative Interview Sub-study of the LIBRETTO-531 Trial**

**Background**

LIBRETTO-531 (NCT02411337) is a randomized, open-label, Phase 3 trial comparing cabozantinib to physician’s choice of zolimoetabib or Vandetanib in participants with progressive, advanced, kinase inhibitor-naive, RET-mutant medullary thyroid cancer.

**Comparative treatment tolerability was measured as a composite of time on treatment with high “side effect” bother, as assessed by the Functional Assessment of Cancer Therapy (FACT) – General Physical Health subscale (GP5). A high score on the GP5 was a key secondary alpha-controlled patient-reported outcome in LIBRETTO-531.**

**DRAFT FDA guidance on “Core Patient-Reported Outcomes in Cancer Clinical Trials” identifies the GP5 as a possible potential summary measure of overall SE impact. However, additional evidence supporting the GP5 as a fit-for-purpose measure of patient-reported tolerability in the context of the LIBRETTO-531 study is needed.**

**Objectives**

• Most participants defined SE bother based on the symptoms and impacts of SEs.

b. clarity of the GP5 and association of GP5 response options with “high SE bother.”

**Design and Analysis**

A qualitative, non-interventional, cross-sectional study with participants from the FACT-GP5 study receiving treatment and with no disease progression (n=40) was conducted.

**Participants**

- **Participant’s Understanding of GP5, Retrieval of Information, and Feedback for Response Options**

  **40/40 participants reported that the GP5 content was clear and that nothing additional would be needed to make it easier to understand.**

  **38/40 participants reported that it was easy to recall and retrieve information to answer the GP5.**

  **37/40 participants reported the response options were appropriate.**

**Limitations**

- Overall, findings demonstrated content validity of the GP5 item for assessing the tolerability and the definition of “high SE bother.”

- **This qualitative evidence supports the GP5 item as a fit-for-purpose measure for patient-reported tolerability in LIBRETTO-531.**

**Conclusions**

- Overall, findings demonstrated content validity of the GP5 item for assessing the tolerability and the definition of “high SE bother.”

- **This qualitative evidence supports the GP5 item as a fit-for-purpose measure for patient-reported tolerability in LIBRETTO-531.**