Evidence to Support the Use of the Functional Assessment of Cancer Therapy – General Item GP5 (FACT GP5) to Assess Comparative Tolerability Endpoint: Results From the LIBRETTO-531 Trial

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Background and Objectives

- Functional Assessment of Cancer Therapy-General (FACT) Item GP5 is a validated and commonly used PRO measure of overall side-effect impact of cancer therapy.
- Increased bother from side effects is associated with lower quality of life (QoL) and a greater likelihood of treatment discontinuation.
- Understanding how patients interpret the term “bother” and how this is perceived by patients prior to starting systemic treatment is important.
- LIBRETTO-531 (NCT04213377) is a phase 3 study comparing selatrectinib vs. comparator of physician’s choice (cabozantinib or vandetanib) in patients with progressive, advanced, tyrosine kinase inhibitors (TKI)-naïve, Rearranged during Transfection (RET)-mutation positive medullary thyroid cancer (MTC).
- LIBRETTO-531 included a key secondary PRO endpoint comparing the proportion of time with high-side effect bother based on the GP5 rating of 3 or 4.
- Additional evidence supporting the item GP5 as a fit-for-purpose measure of tolerability in LIBRETTO-531 is needed.

Objectives

- To generate psychometric evidence supporting the use of GP5 to measure tolerability.
- To evaluate the appropriateness of the categorization of “high-side effect bother” using GP5 rating of 3 or 4 using data from LIBRETTO-531.

Methods

- Study design and data source:
  - Prospective analysis on blinded patient data (N=298, data cut-off date May 22, 2023) from a randomized, open-label, LIBRETTO-531 phase 3 trial.

- Patient population:
  - Adult (ages 18-75 years) patients with locally advanced, TKI-naïve, RET-classification (RET)-mutation positive MTC.

- Assessment schedule:
  - GP5 and PRO-CTCAE:
    - Data was collected at Cycle 1 Day 1 (baseline), then weekly post-baseline and at short-term follow-up.
  - EORTC QLQ-C30 and EQ-SD-5L:
    - Data was collected at Cycle 1 Day 1 (baseline), then at D1 of each cycle (28-day) post-baseline and at short-term follow-up.
  - All PRO measures were captured electronically using either a device provided to the patient or a device at the clinic site.

- Ability of the GP5 to detect change over time:
  - Time to first deterioration on PRO measures was defined as time to first post-baseline PRO measure that met the predefined change criteria.

- Known-group validity: Association between GP5 ratings and hospitalization:
  - Hospitalization was defined as any hospitalization (including planned hospitalization) during the first treatment cycle.

Results

- Reliability of FACT GP5:
  - During Cycle 2 (weeks 5-8) post-baseline:
    - ICCs ranged between 0.80-0.85.
    - Kappa coefficients ranged between 0.68-0.75.

- Distribution of QLQ-C30 functioning and QoL scores according to GP5 ratings at cycle 3:
  - Patients with higher GP5 scores showed association with lower QLQ-C30 scores (lower functioning and QoL).
  - Lower EQ-SD-5L VAS ratings (lower functioning).

- Characterization of high-side effect bother using PRO scores of functioning:
  - All three QLQ-C30 categories showed good ability to separate the QLQ-C30 Global health status/QoL and physical functioning (PF) scores between patients identified as having high-side effect bother.

- Known-group validity: Association between GP5 ratings and treatment discontinuation:
  - Level of bother (“Quite a bit” or “Very much”) with treatment side effects was higher at the assessment closer to treatment discontinuation ranging from 23.5% to 57.7% compared to only 4.7% in the benchmark group.

- Ability of the GP5 to detect change over time:
  - GP5 showed a good ability to detect change over time as participants with worsened symptomatic AE had higher post-baseline GP5 rating as compared to their own baseline rating and those among stable participants.

Conclusions

- The quantitative evidence generated from the psychometric analysis demonstrates that the GP5 has sufficient reliability, validity, responsiveness, and interpretation standards.
- The GP5 is a fit-for-purpose PRO measure for assessing patient-reported tolerability that is suitable for use in clinical trials among patients with RET-mutation positive MTC.
- Additional analysis may be required to assess fit-for-purpose of the GP5 in other cancer patient population.
- The categorization of “high-side effect bother” using a GP5 score 3 or 4 is appropriate for use in evaluating comparative tolerability in LIBRETTO-531.

Limitations

- Association between treatment adherence and GP5 was not observed due to the clinical trial setting.
- Interpretation of results based on hospitalization or focusing on consecutive high-side effect bother assessments, was limited due to low sample size.

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Note: Red circle indicates patients who reported stable symptomatic AE (no change from baseline) and patients who reported worsened symptomatic AEs from baseline.

Effect bother based on the GP5 rating of 3 or 4 is appropriate for use in evaluating comparative tolerability in LIBRETTO-531.