# 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

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## Background

- LIBRETTO-531 (NCT04211337) is a randomized, open-label, Phase 3 trial comparing selpercatinib to physician's choice of cabozantinib or vandetanib in participants with progressive, advanced, kinase inhibitor-naïve, *RET*-mutant medullary thyroid cancer.[1]
- Comparative tolerability, measured as proportion of time on-treatment with "**high side effect (SE) bother**", as assessed by the **Functional Assessment of Cancer Therapy (FACT) – General Physical Item 5 (GP5)** was a key secondary alpha-controlled patient-reported outcome in LIBRETTO-531.[1]
- 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.[2]
- 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

**To explore:**

**a. participants' perception of bother, burden, and tolerability, and**

**b. clarity of the GP5 and association of GP5 response options with "high SE bother."**

## Study Design and Analysis

A qualitative, non-interventional, cross-sectional study with participants from LIBRETTO-531 study receiving treatment and with no disease progression

↓

Semi-structured 1:1 interviews (30–60mins) in the participant's native language

↓

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

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

The GP5 Item
"**I am bothered by side-effects of treatment**"

| 5-item Likert scale | |
|---|---|
| 0 | Not at all |
| 1 | A little bit |
| 2 | Somewhat |
| 3 | Quite a bit |
| 4 | Very much |

Recall period: 7 days

### *Analysis*

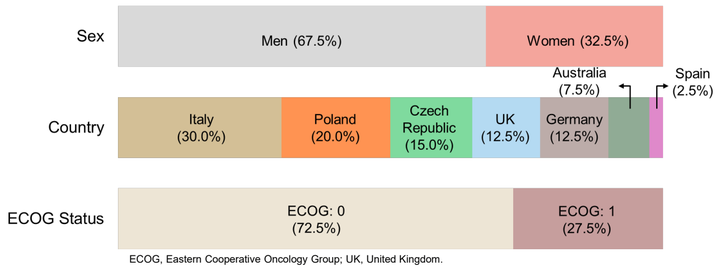
- Interview transcripts were thematically analyzed with inductive and deductive coding using ATLAS.ti.
- All transcripts were analyzed in groups of 5. Saturation analysis was reached once no new information or theme occurred.

## Demographics and Clinical Characteristics

Mean age **55.5 ± 13.6** years

Time between first day of treatment in the trial and the interview date **62.7 ± 37.1** weeks

Total number of participants interviewed = 40




ECOG, Eastern Cooperative Oncology Group; UK, United Kingdom.

## Concept elicitation

### *Participant Reported Symptomatic SEs*

- Sixty-three symptomatic SEs were identified across 12 domains.

| Attention/Memory |
|---|
| Difficulty finding words |
| Short term memory loss |

| Cutaneous |
|---|
| Acne/pimples* |
| Blisters/sores** |
| Bruising |
| Burning sensation |
| Callouses (hands/feet)* |
| Dry skin* |
| Graying hair* |
| Hair loss* |
| Hives** |
| Itching* |
| Peeling/flaking skin |
| Peeling/splitting nails |
| Rash** |
| Skin infection** |
| Skin redness |

| Fatigue** |
|---|
| Physical fatigue |
| Mental fatigue |
| Feeling tired |
| Weakness |

| Oral |
|---|
| Burning in mouth |
| Difficulty chewing |
| Dry mouth*,** |
| Pain in mouth** |
| Taste loss/changes* |
| Tinging in mouth |
| Mouth ulcers/sores*,** |

| Nose and Throat |
|---|
| Dry nose |
| Dry throat |
| Nasal congestion |
| Sore throat |

| Gastrointestinal |
|---|
| Abdominal pain/cramps** |
| Bloating** |
| Constipation** |
| Decreased appetite* |
| Diarrhea* |
| Increase appetite |
| Indigestion |
| Nausea*,** |
| Vomiting |
| Weight gain*,** |
| Weight loss |

| Sexual |
|---|
| Erectile dysfunction** |

| Cardio/circulatory |
|---|
| Cold hands/feet** |
| Heart palpitations |
| Body swelling* |

| Miscellaneous |
|---|
| Dizziness |
| Fever |
| Insomnia |
| Rigid body at night |
| Shortness of breath |
| Sweating |
| Vision problems |

| Neurological |
|---|
| Nerve pain** |
| Tingling/numbness |

| Urinary |
|---|
| Bladder pain** |
| Dark urine** |

| Pain |
|---|
| Headache |
| Leg cramps |
| Joint pain |
| Muscle cramps/aches |

*Least bothersome ** Most bothersome

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

| Themes | Participants (n) |
|---|---|
| **Bother** | |
| Interfere with daily activities | 29 |
| Cause physical discomfort | 26 |
| Increase 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 |
| **Burden** | |
| Burden implies a greater degree of SE severity or interference in daily activities in general | 31 |
| Interfere with daily activities more than bothersome SEs | 18 |
| Burdensome SEs are | |
| More severe | 14 |
| Longer duration | 7 |
| More frequent | 4 |
| Burdensome SEs cause a greater cognitive effort and/or have a greater and more negative impact on mental health or emotional well-being than bothersome SEs | 8 |
| **Tolerability** | |
| Tolerability is related to bother and/or burden | 31 |
| The efficacy of the treatment is considered when determining how tolerable its SEs are | 20 |
| SEs are tolerable if they don't significantly interfere with daily activities | 18 |
| SEs are tolerable if they are bearable | 18 |
| Treatment benefits weighed against the harms of SEs to assess extent of SE tolerability | 16 |
| SEs are tolerable if their severity is none to mild | 8 |
| The SEs and clinical efficacy of other treatments are compared to SEs and clinical efficacy of one's own treatment when determining how tolerable its SEs are | 6 |

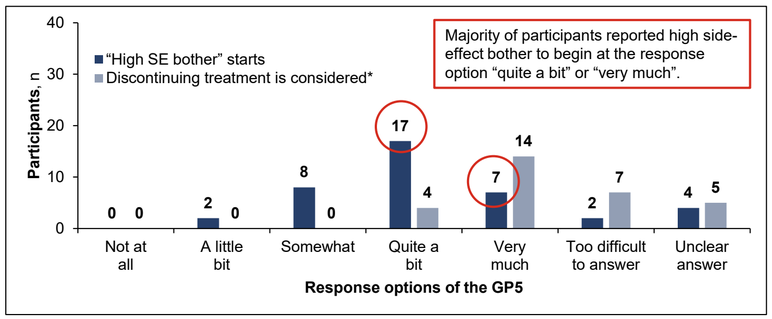
- No new information was identified (saturation) after completing analysis of the second group (10 transcripts).
- Most participants defined SE bother based on the symptoms and impacts of SEs.
- Participants defined SE burden as **more severe**, had **longer duration**, **more frequent**, required **greater cognitive effort** and **greater negative impact** on well-being compared with SE bother.

## Cognitive debriefing

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

| Response option | Participant interpretation | | | | | | | Illustrative participant quotes |
|---|---|---|---|---|---|---|---|---|
| | Cognitive/emotional experience of SEs | Physical experience of SEs | | | | Daily activity interference | Consider dose delay/dose modification/ discontinuing treatment | |
| | | SE existence/ Number of SEs | Severity | Duration | Frequency | | | |
| 0 – Not at All | No worries, problems, concerns, or bother (n=22)<br>Minor annoyance (n=1)<br>Have coped with/gotten used to it (n=3) | SEs not present (n=12) | Not severe (n=4) | Short (1 – 2 week) (n=1) | | No impacts (n=8) | | **Cognitive/emotional experience of SEs**: "Well, not at all, for me, means I haven't got – I don't know what to say. How can you say not at all? I have no concerns at all. It's not on my mind. Nothing's happening to me, basically, other than normal things"<br>**SE existence**: "Not at all means that I don't feel absolutely anything, that there's no repercussion, no SE following the treatment"<br>**Daily activity interference**: "It would mean that I feel as I did before I started treatment, I may have developed acne, for example, or this change in hair color, but it does not hinder my functioning in any way" |
| 1 – A Little Bit | No bother (n=8)<br>Light bother (n=20)<br>Can endure it (n=2) | | Mild severity (n=14)<br>20-25% of discomfort (n=1) | Short duration (few minutes – few weeks) (n=5) | Low frequency (1–7 times/week) (n=10) | No impacts (n=7)<br>Light impacts (n=9) | | **Cognitive/emotional experience of SEs**: "I'm not worried about it, because I'm feeling healthy. I feel good. So yeah, I'm a little bit worried, because I have the cancer, but I'm not really – yeah, I feel healthy"<br>**Severity**: "Mild side-effects that are worth mentioning but not severe"<br>**Duration/Frequency**: "Well, again, like in my case, the person has a bloated belly, it's nothing serious, it just bothers, but only for an hour, half an hour, two hours once or twice a month, I guess" |
| 2 – Somewhat | Causes moderate bother or annoyance (n=26)<br>Bother turns into burden (n=4)<br>Can still cope with it or bear it (n=6) | Experiencing multiple SEs (n=2) | Moderate severity (n=4)<br>40% of discomfort level (n=1)<br>Mild severity (n=1) | Constant (n=5)<br>Few hours (n=2) | High frequency (3–7 times/week) (n=8) | Need to change/reduce daily activities (n=15)<br>Do not have to change/reduce daily activities (n=2) | | **Cognitive/emotional experience of SEs**: "Well, somewhat would mean I'm not handling the drug. Like I've got a few problems. Yeah, I'm starting to worry. Maybe it's not working. Maybe these SEs are a bit too much"<br>**Daily activity interference:** "If I had to answer somewhat, it would mean that at least once during that day, it had affected what I do during the day. It would have been something that lasted for a few hours or a day or meant that I had to rest or put my feet up or whatever. So that would be somewhat to me" |
| 3 – Quite a Bit | Causes a lot of bother (n=11)<br>Feeling burden (n=3)<br>Unbearable (n=4)<br>Can be endured (n=1) | Experiencing multiple SEs (n=1) | Strong severity (n=11)<br>70% of discomfort level (n=1) | Constant (n=3) | High frequency (2–10 times/week) (n=7)<br>Persistent or recurrence of SEs (n=3) | Big impact (n=20)<br>Reduced quality of life (n=2) | Consider discontinuing treatment (n=1) | **Cognitive/emotional experience of SEs**: "So if all of a sudden, things started changing a lot more, I would definitely be more worried"<br>**Daily activity interference**: "I cannot eat like I used to before, I have difficulty swallowing, I eat yoguris, I can still eat some food, but it causes me pain, I don't have much saliva, I have to support myself with water, in the same way calluses are quite painful, I try not to walk too much, I am limited"<br>**Severity**: "Well, that it's not as good as it was, that it's worse, that it's gotten worse, well… That my skin would crack more and it wouldn't be the same" |
| 4 – Very Much | High bother (n=9)<br>Feeling burden (n=1)<br>Unbearable/Unable to cope (n=8) | Experiencing multiple SEs (n=1) | Extreme severity (n=11)<br>80% or more of discomfort level (n=1) | Constant (n=2)<br>Lasts a week (n=1) | Daily (n=3) | Big changes in lifestyle (n=18) | Change dose/drug (n=3)<br>Consider discontinuing treatment (n=2)<br>Decide to discontinue treatment (n=3) | **Daily activity interference:** "If it was affecting me very much, that'd be a big change in my lifestyle then. I'd be thinking I can't do this. I can't go out of the house. I can't go to work. Or even if I do, I can't carry on as normal"<br>**Severity**: "And then I had difficulties to see, because there was this puffiness under the eyes, and the legs were so swollen that I could not put on the shoes" |

### *GP5 Response Options Participants Associated with High SE Bother and Treatment Discontinuation*




*Question was not asked to 10 participants due to cross-cultural translation challenges, moderator error, or based on moderator discretion due to the sensitive nature of the question.

### *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

- Many participants (n=36) were interviewed after being on treatment for ≥1 year, while some (n=4) were interviewed 10–14 weeks after treatment initiation. Hence, participants' perception could be associated with recall bias.
- Participants answered questions on dose escalation and treatment discontinuation hypothetically since not all participants changed dose or discontinued treatment. Hence, results are subject to hypothetical bias as participants might act differently during the time of actual dose escalation or treatment discontinuation.

## 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.**

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2. US FDA. Published Jun 2021. Accessed Apr 12, 2024. https://www.fda.gov/media/149994/download.

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