Reply

ReQuest™: Reply to Dr. Revicki and Prof. Talley

K.D. Bardhan^a H. Mönnikes^b V. Stanghellini^c D. Armstrong^d P. Berghöfer^e T.D. Bethke^e
G. Gatz^e

^aRotherham District General Hospital, Rotherham, UK; ^bDepartment of Medicine, Division Hepatology, Gastroenterology, and Endocrinology, Charité Medical Center – Campus Virchow Hospital, Medical School of Free University and Humboldt University, Berlin, Germany; ^cS. Orsola-Malpighi University Hospital, Bologna, Italy; ^dMcMaster University, Hamilton, Canada; ^eALTANA Pharma AG, Constance, Germany

We are grateful to Dr. Revicki and Prof. Talley for their incisive questions and constructive comments. The issues raised are broad, concern the validation process and would be difficult to reply to in detail within the confines of a letter. Their questions, however, encourage us to prepare a separate and detailed report on methodology. So we will limit our replies here.

General Comments

Several different approaches are used in psychometrics, each with its own specific methodology. Item Response Theory for example is a modern development. We however have based ReQuest™ on the Classical Test Theory because it is well established and because this approach is favoured by the regulatory authorities when constructing an instrument to serve as the study end-point in treatment of gastroesophageal reflux disease (GERD).

We applied the Classical Test Theory approach in four steps as follows:

- First, the full range of symptom descriptions was collected from different sources, including GERD patients, and without prejudging the relevance of any description. Unlike previous questionnaires, ReQuest™ was designed specifically to include all manifestations of GERD, whatever patients felt was part of their illness, and not only those

traditionally believed to be part of the GERD spectrum.

This yielded 67 symptom descriptions, which then were condensed into 6 dimensions based on expert clinical opinion, and to which a seventh dimension, general well-being, was added.

Lower abdominal/digestive complaints, one of the dimensions, appear at first sight not to be related to reflux. Yet this was complained of by more than half of the patients with erosive and non-erosive reflux disease (n = 6,043).

- Next, the clinical trials were conducted in patients with erosive and non-erosive GERD and the results analysed as described, the second and third steps [1–3].
- The final step was to use the clinical data from the trials to refine the instrument by factor analysis and item reduction. Again, all symptom descriptions were included and without prejudgement as to their relevance in GERD. The analysis is entirely mathematical, so individual clinicians' influence is avoided. This identified that 7 (of the 67) items did not add significantly to the total picture, hence were excluded. The remaining 60 items clustered into 20 factors. These factors in turn correlated well with the dimensions. Thus, the mathematical-statistical process of factor analysis confirmed the clinical-empirical approach used to create the dimensions.

Placebo-controlled studies are planned. These, along with patho-physiology investigations, will address some of the issues raised, for example the minimal clinically important differences.

Specific Comments

Factor Analysis

Each of the 20 factors represents a cluster of associated or related symptom descriptions *statistically* derived from the original 67 we started with. Each factor, furthermore, was clinically relevant as judged by experts.

Over-factoring – presumably meaning the creation of an excessive number of factors, some an artifact and irrelevant – is avoided as the process is entirely mathematical. We did not pre-specify the number of factors: it just happened to be the case that the mathematics yielded 20.

Scoring of ReQuest™ Dimensions

The symptom burden is calculated from the Visual Analog and Likert Scales as a *weighted* product of Intensity × Frequency. The weighting is achieved by the application of a constant derived from multivariate analysis, which optimises between sensitivity, reliability and the ability to detect changes specific to the day the instrument is applied. (This will be discussed further in

the detailed report on methodology.) This modification explains why the 'the reported score does not seem to reflect this scoring system'. We apologise for not having made the process clear in the original report.

ReQuest™ Sub-Scales

The two sub-scales ReQuest™-GI and ReQuest™-WSO, both validated, were constructed to 'fine-tune' the instrument. The ReQuest™-GI measures gastro-intestinal symptoms in general and correlates with the GSRS scale (Gastrointestinal Symptom Rating Scale). The placebo-controlled studies will help separate the reflux-associated symptoms from others. The ReQuest™-WSO reflects the other symptoms, those thought to be more closely related to psychological aspects, and correlates with the PGWB scale (Psychological General Well-Being index scale).

ReQuest™ Long Questionnaire

The individual items were scored simply as 'present' or 'absent'. Note that the main purpose of the Long Questionnaire was to serve as a means of validating the Short Questionnaire.

Responsiveness Index

The symptom burden of GERD would be expected to fluctuate, both spontaneously and as a result of PPI treatment, during the 31 days of observation (baseline 3 days; treatment 28 days). The Responsiveness Index attempts to distinguish between the two. 'Stability' refers to the range within which such changes are deemed spontaneous, anything greater being attributed to treatment. The measurement of stability is, however, to some extent arbitrary, for it is based on an individual investigators' assessment – and such judgements vary between investigators.

We assessed stability by measuring fluctuations in the intensity of symptoms (based on the visual analog score). Importantly, sensitivity analysis confirmed that altering the range of such estimates had relatively little effect on the Responsiveness Index.

Minimal Clinically Important Differences

The forthcoming placebo-controlled studies will give a better appreciation of such differences and of their clinical relevance.

Clumsy English Phraseology Point taken!

The fact remains that these were the words used by patients interviewed and then translated into different languages, the accuracy of translation being validated. Importantly, the phraseology was understood, clumsy or not!

References

- 1 Bardhan KD, Stanghellini V, Armstrong D, Berghöfer P, Gatz G, Mönnikes H: Evaluation of GERD symptoms during therapy. Part 1. Development of the new GERD questionnaire ReQuest™. *Digestion* 2004;69:229–237.
- 2 Mönnikes H, Bardhan KD, Stanghellini V, Berghöfer P, Bethke TD, Armstrong D: Evaluation of GERD symptoms during therapy. Part 2. Psychometric evaluation and validation of the new questionnaire ReQuest™ in erosive GERD. *Digestion* 2004;69:238–244.
- 3 Bardhan KD, Stanghellini V, Armstrong D, Berghöfer P, Gatz G, Mönnikes H: International validation of ReQuest™ in patients with endoscopy-negative gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2004; 20:891–898.