Team Leader Review Memorandum

The Exacerbation of Chronic Pulmonary Disease Tool (EXACT)
Patient Reported Outcome (PRO) Instrument

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EXECUTIVE SUMMARY

The Exacerbation of Chronic Pulmonary Disease Tool (EXACT-PRO) development has proceeded to the extent that the instrument is ready for additional testing specific to its intended application in terms of the patient population, condition, and other aspects of its measurement context for which the instrument was developed: evaluation of antibacterial drugs for the treatment of acute bacterial exacerbation of chronic bronchitis in patients with chronic obstructive pulmonary disease (ABECB-COPD). EXACT-PRO has demonstrated acceptable conceptual framework and content validity. The instrument is qualified for use as an endpoint in phase 2 trials enrolling patients with ABECB-COPD.

There were notable strengths to the information submitted for qualification. An earlier version of EXACT used a 23-item questionnaire and was developed based on patient interviews and demonstrated appropriate content validity. The instrument showed an ability to detect change over time when administered to patients receiving antibacterial treatment for ABECB-COPD. The scoring was done among 14 items: an item-reduction statistical analysis narrowed the questions from 23 to 14.

The developer submitted additional data for qualification review using the 14-item questionnaire with scoring of the 14 items. That is, the instrument was evaluated using a 14-item questionnaire and not the 23-item questionnaire that was contained in the original data. These data enrolled patients in 3 trials that were evaluating long-term treatments to prevent an exacerbation. This was not the context of use for EXACT, but did collect some information on patients experiencing ABECB-COPD. The 14-item EXACT questionnaire appeared so show a similar change from the peak of the exacerbation toward improvement over a one to two week period of time. This information serves as an important bridge between the 23-item and the 14-item EXACT.

There were several notable findings with the data submitted by the developer that raised concerns about the EXACT's reliability and ability to detect change. The EXACT scoring did not identify an exacerbation in approximately 50% of patients who were reporting a medically-treated exacerbation. There were no post-hoc analyses to explore reasons for this finding among 50% of exacerbations. For some patients receiving medical care for ABECB-COPD, the change in scoring of EXACT during treatment of

ABECB-COPD appeared to be within the day-to-day variability of the scoring. Although these trials did not evaluate the EXACT-PRO in the context of use, these findings raise some concern about EXACT's ability to detect change for the intended context of use for ABECB-COPD

Other concerns included the enrollment of patients into one trial that may not have had COPD (e.g., approximately 10% of patients in the Mpex trial were GOLD Stage 0). In addition, there was no documentation about whether the patient's exacerbation was ABECB-COPD or whether the exacerbation was due to environmental changes or allergy. Finally, the analysis population appeared to be a "per protocol" population and not an "intent-to-treat" population.

The developer should be encouraged to pursue instrument development. The EXACT reliability, other validity, and ability to detect change should be characterized within the context of use and in the intended population in order to be considered as a primary efficacy endpoint in phase 3 trials of ABECB-COPD. Therefore, EXACT can now be qualified as an endpoint in phase 2 trials evaluating antibacterial drugs for treatment of ABECB-COPD.

INTRODUCTION

Acute Bacterial Exacerbations of Chronic Bronchitis in patients with Chronic Obstructive Pulmonary Disease (ABECB-COPD) refers to a clinical diagnosis of bacterial infection superimposed on a chronic pulmonary condition. This situation is best described pathologically as bronchial inflammation associated with the isolation of pathogenic bacteria from sputum or bronchial lavage specimens. The acute component of ABECB-COPD is usually manifest as worsening of the same symptoms patients experience when they are not experiencing an acute infection.[1]

The primary emphasis of a clinical trial evaluating a new antibacterial drug for treatment of ABECB-COPD should be the effect of the antimicrobial drug on symptoms and self-reported signs that are important to patients. A well-defined and reliable method of assessing patient symptoms and self-reported signs should be used for ABECB-COPD trials. Accordingly, use of a well-defined and reliable patient-reported outcome (PRO) instrument is recommended as the primary outcome measure. It is in this context that the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) PRO was developed.

The instrument developer submitted summary data from their preliminary instrument development, patient interviews, and development of a draft 23-item EXACT. Datasets were submitted for the evaluation of the Rasch item pool reduction analyses that arrived at the 14-item EXACT and its scoring. After a review of these data, FDA review team determined that additional data on the use of the ***14-item*** EXACT in clinical trials would further support efforts towards an FDA qualification of the PRO instrument. A second follow-up submission included summary data using the 14-item EXACT in three phase 2 trials as well as datasets for review.

CONCEPTUAL FRAMEWORK OF EXACT

After appropriate literature reviews and preliminary consultations with academic clinicians and FDA medical officers involved in the review of investigational antibacterial drugs, the instrument developer conducted concept elicitation focus groups and cognitive debriefing interviews with 83 patients with COPD. The developers then conducted further cognitive debriefing interviews of "a draft instrument comprising 23 items, to be completed by patients as a daily, electronic diary each evening before

[1] See the following publications that provide definitions for COPD and ABECB-COPD: 1) American Thoracic Society, 1995, Standards for the Diagnosis and Care of Patients with Chronic Obstructive Pulmonary Disease, Am J Respir Crit Care Med; 152:S77-S120; 2) Donaldson GC, Wedzicha JA. COPD exacerbations- 1: Epidemiology. Thorax 2006;61:164-8; 3) Global Initiative for Chronic Obstructive Lung Disease (GOLD), updated 2006, Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease, which can be found at http://www.goldcopd.com; 4) the draft guidance for industry *Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment.*

bedtime."[2] This draft instrument was then administered to 410 patients with COPD. A total of 222 patients were experiencing an acute exacerbation and completed the EXACT over days 1-28 and again on days 60-67. A total of 188 patients were clinically stable with COPD and completed the EXACT over days 1-7. Thus a total of approximately 500 patients with COPD contributed overall to the evaluation of the draft instrument. The conceptual framework appears to have been adequate in capturing the concept domains in the intended treatment population of patients with ABECB-COPD.

CONTENT VALIDITY

The characteristics of the 83 patients who comprised the initial instrument development all had clinically-confirmed COPD with an exacerbation during the previous 6 months, and some within the previous 10 days. Additional subjects from minority groups were recruited to assess whether features of an instrument should account for any differences based on race. Only a small number were characterized as GOLD stage 1, while most fell within GOLD stages 2-4 indicating that patients had somewhat more severe disease in general. The instrument documented the input from elicitation focus groups and cognitive debriefing interviews from patients with COPD.

The 23-item draft questionnaire was administered to 410 patients at 40 clinics in the United States. The demographic characteristics of the patients were similar to the demographic characteristics of the 83 patients participating in the earlier instrument development phase. Approximately a dozen patients who were initially enrolled as "stable" were actually experiencing an acute exacerbation and were switched to the group of patients with COPD exacerbations. The study population appeared to be a reasonable representation of patients with COPD who would be evaluated in clinical trials that would assess efficacy of new products. Based on the responses to the 23 items, item-reduction analyses were conducted to arrive at a 14-item questionnaire. The 14-item questionnaire consists of three domains of "breathlessness", "cough and sputum", and "chest symptoms".

The Rasch analyses used to identify the 14 items for EXACT is beyond the scope of the expertise of medical reviewers in the Office of Antimicrobial Products. For additional review and comment, please refer to the reviews from Office of Biostatistics and the Office of New Drug's Study Endpoints and Labeling Development Team. However, Rasch analyses appear to be acceptable methods for item reduction in the evaluation of questionnaires.

The EXACT scores were evaluated among the patients experiencing ABECB-COPD. An evaluation of an averaged daily score from the start of the exacerbation to the tenth day of exacerbation showed a decline from a mean score of approximately 48 to a mean score of approximately 40, a difference in the mean score of approximately 8. The developer's

[2] Page 1 of the United BioSciences Corporation "Executive Summary" submission of February 23, 2009 described the 23-item EXACT as a "draft" instrument.

analysis by repeated measures ANCOVA models showed a statistically significant difference in the change of scores for this time period (p value less than 0.0001).

The EXACT appeared to show internal consistency in patients with stable COPD who are not experiencing an exacerbation. The EXACT also appeared to be sensitive to whether clinicians characterized the exacerbation as responding or not responding to therapy. The point estimates of the EXACT total scores for patients' report of mild, moderate, or severe exacerbation of COPD were 43, 48, and 55, respectively. However, the overlapping two-sided 95% confidence intervals (based on the reported standard deviations) limit an ability to draw strong conclusions about the reliability for EXACT total score to predict disease severity.

It is important to note that the conceptual framework of a PRO instrument will evolve and confirmed over the course of instrument development. When used in a placebo-controlled clinical trial the conceptual framework should again be confirmed by the observed relationships among items and domains.

After the review of the data provided on the 23-item instrument, the review team found that content validity was beginning to be established but concurred with the developer's characterization as a "draft" instrument. The review team found the EXACT development to be a promising outcome measure for ABECB-COPD and requested further information on the evaluation of the 14-item EXACT as the "final" instrument used in at least one clinical trial.

RELIABILITY, OTHER VALIDITY, AND ABILITY TO DETECT CHANGE

The developers submitted summary information and datasets from three phase 2 trials. The trials enrolled patients with stable COPD and followed them for COPD exacerbations, some of which may have been ABECB-COPD. One trial evaluated an inhaled formulation of an antibacterial drug administered monthly versus placebo, and the other two trials evaluated an investigational anti-inflammatory drug intended to stabilize COPD disease and reduce the number and extent of exacerbations, bacterial or otherwise. The trials followed patients over many months, and asked patients to participate in the daily use of EXACT.

The M-Pex Trial

In addition to the summary data provided by the instrument developer, the reviewers had access to the complete study report prepared by M-Pex and submitted to the open Investigational New Drug application. This phase 2 trial enrolled 322 stable COPD patients who were randomized to receive an inhaled formulation of levofloxacin (a systemic antibacterial drug approved for treatment of certain bacterial infections) or placebo in a 2:1 manner. They were followed for at least 6 months, and some patients were followed up to a year. The primary efficacy endpoint was the number and duration of "medically treated exacerbation" events. A medically treated exacerbation (MTE)

event was defined as, "symptomatic respiratory deterioration requiring treatment with antibiotic agents, systemic corticosteroids, hospitalization, or a combination of those treatments." A secondary endpoint was the EXACT-PRO exacerbation rates, defined as an increase of at least 12 points above baseline for at least 2 consecutive days or an increase of at least 9 points above baseline for at least 3 consecutive days. While there were no differences noted between the treatment groups on either the primary or secondary endpoint, the trial can still yield important information regarding the performance of the EXACT.

When first considering the demographic characteristics of the patient population, approximately 10% of enrolled subjects were characterized as GOLD stage 0. Thus, some trial participants did not have the disease of interest (COPD) and therefore do not contribute to further understanding of validity, reliability, or the ability to detect change with an instrument and its intended context of use. The instrument developers did not consider an evaluation where these trial participants were excluded from analyses. This finding greatly enhances the limitations of the results that describe reliability or the ability to detect change of EXACT scores.

A concern is the finding that 57% of MTEs did not have a corresponding EXACT event. Specifically, of the 136 MTEs that were recorded in the study in which patients reported symptomatic worsening to their health-care provider or to an emergency medical department, 59 (43%) also met the definition of an event by EXACT scoring.[3] Of the 77 (57%) patients without a corresponding EXACT scoring event, 12 had missing data on the EXACT score. Thus, 65 (48%) had an MTE event but did not meet EXACT scoring criteria for an event. The number of patients experiencing an MTE but did not have EXACT scoring that indicated an exacerbation (n=65) exceeded the number of patients with a corresponding EXACT event (n=59). The instrument developer points out that, "Validity refers to the extent to which the instrument measures what it is intended to measure." There is concern that the instrument is not measuring what it is intended to measure because about half of the patients experiencing an MTE did not have a corresponding EXACT event. The sponsor's demonstration of validity by comparison to other symptom scoring systems or to FEV_1 seems irrelevant. There were no further post-hoc analyses to explore hypothesis testing as to why the 65 events did not have an EXACT score that defined an event. The pre-defined 12-point increase over 2 days, or the 9-point increase over 3 days to define an EXACT event does not appear to be valid for the ascertainment of a new exacerbation event from baseline.

There were evaluations of baseline intra-individual variability when patients were not experiencing an event.[4] This important and potentially clinically meaningful evaluation of intra-individual variability did not appear to be incorporated in any analyses. A change in scoring greater than the change in individual variability alone may be considered to be a significant change or a significant event. Thus, one or two standard

[3] Tables 11A and 13 of the appendix, "Post-hoc Statistical Analysis Tables".
[4] See Table 5 "Summary of EXACT Total Score for Baseline Week and Final Week" on page 12 of the "Summary Report". For the M-pex trial, the intra-individual variability score was 4 with a standard deviation of 2.6.

deviations above the baseline variability, that is, a change of scoring of 6 or 8, might be considered to be clinically meaningful and fulfill a definition of an EXACT event. After all, the preliminary "draft" 23-item instrument used among patients being treated for ABECB-COPD showed a mean improvement in the 14-item EXACT score of 8 points over ten days of treatment (i.e., not 12 points or even 9 points). The sponsor, M-Pex pharmaceuticals, appeared to prespecify a sensitivity analysis in which an increase of 6 points would be used to define an EXACT event. Neither the instrument developer nor the sponsor presented the results of sensitivity analyses using an increase in 6 points as the EXACT event, even though the sponsor prespecified this type of analysis.

The comparison of the developer's data to the sponsor's compete study report showed consistency because the sponsor also stated that 136 MTEs were observed. However, this number of MTEs was derived from Efficacy Evaluable population that received at least 2 consecutive doses and had no protocol violations. Thus, the developer's dataset and analyses did not use the intent-to-treat population. This type of "per protocol" analysis excludes subject post-randomization and is subject to bias.

If the limitations and concerns of the performance of EXACT in defining the onset of an exacerbation can be completely set aside, it may be possible to focus only on the intended context of use as an efficacy outcome measure for the evaluation of antibacterial drugs for the treatment of ABECB-COPD. The developer presented the results of the EXACT scores during an exacerbation. The case report forms did not collect microbiological information at the time of the event to ascertain whether the exacerbation was nonbacterial or ABECB-COPD, but it may be reasonable to assume that the exacerbations behave similarly in terms of patients' symptoms and their improvement with therapy. For patients with exacerbations characterized as "moderate", the mean score of approximately 50 points at the onset of exacerbation is reduced by day ten to approximately 44 points, for a difference of about 6 points. For patients with exacerbations characterized as "severe", the mean score of approximately 54 points at the onset of exacerbation is reduced by day ten to approximately 44 points, for a difference of about 10 points.[5] When pooling moderate and severe exacerbations, patients who had an MTE with a corresponding EXACT score showed a mean score of approximately 56 at the onset of the exacerbation and at day 10 showed a mean score of approximately 47, for a decline in 9 points. The EXACT data are also shown for the patients that had treatment for an MTE but did not have a corresponding EXACT score.[6] In this subgroup, the mean score of approximately 46 showed a decline to approximately 42 at day 10. This change in 4 points falls within the intra-individual variability observed during baseline recordings of EXACT.

In comparison to the developer's data on the 23-item draft instrument using the scoring from 14 items, the data from the use of the final 14-item instrument appears to be roughly

[5] Figure 2 "Mean EXACT Total Scores (±SE) during Medically Treated Exacerbations (MTEs): Day 7 to Day 21 by EXACT Event Status" on page 23 of the Summary Report.

[6] Figure 2: "EXACT Total Scores during Medically Treated Exacerbations (MTEs)" on page 18 of the Post-hoc Statistical Analysis Tables.

similar. It may not be appropriate to compare the results in any formal manner because disease severity was not compartmentalized into "moderate" or "severe" in the earlier study and cross-study comparisons are problematic. The fact that the EXACT scoring during an exacerbation event, some of which may have been ABECB-COPD, appeared similar is a strength of the results of this evaluation and provides a "bridge" from the 14-item instrument scoring to the conceptual framework and preliminary work on content validity based on the 23-item draft instrument.

The AstraZeneca Trials

The two phase 2 trials also enrolled patients with stable COPD. A total of 1,346 patients were enrolled. In contrast to the M-Pex trial, none of the patients were Gold stage 0 and therefore all patients had a diagnosis of COPD. The trials used a definition of MTE nearly identical to the M-Pex trial: "patient-report of healthcare resource utilization for exacerbations of COPD, including clinical or emergency room visits with antibiotic and/or systemic corticosteroid treatment or hospitalization for exacerbation of COPD."

The concern in the M-Pex trial that the EXACT score did not identify about half of the patients with an MTE was also a concern in these two trials. Pooling the results of the 2 trials, 183 MTEs occurred during the 12 weeks of follow up. The number of patients with MTEs and a corresponding EXACT event was 88 (48%). A total of 82 patients (45%) experienced an MTE but did not have a corresponding EXACT event. These findings indicate that the instrument may not be measuring what it is intended to measure in terms of the context of use in defining a new exacerbation in a population of stable COPD patients using daily EXACT.

The two AstraZeneca trials enrolled a larger population of patients with COPD, and all of the patients had at least GOLD stage 1 or higher (i.e., no patients with GOLD stage 0 were enrolled). The intra-individual variability was smaller in these two trials with variability scores of 3.6 and 3.5. Thus, a change in the EXACT scoring of as little as 6 may be at least one standard deviation away baseline variability. As with the M-Pex trial, there were no other post-hoc analyses using different scoring parameters (e.g., a change in 6 points) to define an EXACT event.

Turning the attention to the data collected during the exacerbations (the EXACT-PRO's context of use in ABECB-COPD), the developer provided EXACT scores during MTEs.[7] Among patients with MTEs and a corresponding EXACT event in study AZ-12, the EXACT score was approximately 56 at the start of the exacerbation and declined to approximately 43 at day 10 of the exacerbation, for a difference in scoring of 13 points. The same subgroup of patients in AZ-20 showed an EXACT score of approximately 59 at the start of the exacerbation that declined to approximately 47 at day 10, for a difference in scoring of 12 points. The subgroup of patients in both trials with MTEs that did not have a corresponding event showed a lower score at the start of the exacerbation with a decline of only 4 or 5 points at day 10. This data is similar to the data from M-Pex,

[7] Figure 2: EXACT Total Scores during Medically Treated Exacerbations (MTEs) on page 18 of the Post-hoc Statistical Analysis Tables.

where the subgroup of patients with an MTE but no corresponding EXACT event showed, on average, a change in mean EXACT scores that falls very near or within intra-individual variability. The following Tables 1 & 2 summarize the results of reliability, validity, and ability to detect change.

Table 1: Medically Treated Exacerbations Adapted from Tables 11A and 13 in Post-hoc Statistical Analysis Tables

	M-Pex	AstraZeneca Trial 12	AstraZeneca Trial 20
Trial Population	235	749	597
Total number of MTEs	136	126	57
MTEs with a corresponding EXACT event*	59 (43%)	64 (51%)	24 (42%)
MTEs with missing data on the EXACT event*	12	9	4
MTEs that did not have EXACT event*	65 (48%)	53 (42%)	29 (51%)

*EXACT event was defined as 12-point increase over 2 days or the 9-point increase over 3 days

Table 2: EXACT Total Scores during MTEs Adapted from Figure 2 in the Post-hoc Statistical Analysis Tables

Trial	Characterization of MTE by EXACT scoring	Mean EXACT score at onset of exacerbation	Mean EXACT score at day 10 after the onset of exacerbation	Difference between mean EXACT scores at onset and at day 10
M-Pex trial	MTEs with a corresponding EXACT event*	56	47	9
	MTEs that did not have EXACT event*	46	42	4
AstraZeneca Trial 12	MTEs with a corresponding EXACT event*	56	43	13
	MTEs that did not have EXACT event*	50	45	5
AstraZeneca Trial 20	MTEs with a corresponding EXACT event*	59	47	12
	MTEs that did not have EXACT event*	51	47	4

*EXACT event was defined as 12-point increase over 2 days or the 9-point increase over 3 days

The instrument's reliability in terms of having day-to-day scores without variation appears poor when considering the subgroup with an MTE who did not meet criteria for an EXACT exacerbation event. When considering the instrument's ability to detect change, the subgroup of patients with an MTE that did not have a corresponding EXACT event showed a level of change over the course of their illness that might fall within intra-individual variability. However, the subgroup of patients who met the definition of an EXACT event appeared to demonstrate an ability to detect change that was beyond a change that might be considered to be intra-individual variability.

STRENGTHS AND WEAKNESSES OF EXACT

Strengths of the EXACT:

- Patients with MTEs who also had an EXACT-defined exacerbation event had changes in EXACT scores that demonstrated continued improvement over a ten day time period from the onset of the exacerbation, showing that the EXACT is able to detect a change that appears to be reliable and valid measurement of symptom improvement in this subgroup.
- The evaluation of the 14-item EXACT in the subgroup with MTE's who also had an EXACT-defined event during exacerbations appeared to show a similar improvement in scoring over a ten day time period from the onset in comparison to the 23-item draft instrument that was used in the earlier evaluations; this serves as an important "bridge" to the instrument's conceptual framework and early content validity.
- The trials confirmed an important characterization about patients' symptoms during and just after an exacerbation; the symptom score does not return to their baseline just before the exacerbation.
- The intra-individual variability and standard deviations begin to show what might be considered meaningful differences in EXACT scoring beyond the day-to-day variability in scoring.

Weaknesses of the EXACT

- A definition of a new exacerbation by the EXACT scoring as the 12-point increase over 2 days or the 9-point increase over 3 days captured only approximately 50% of patients being treated for an exacerbation (MTEs), calling into question the instrument's reliability and validity when using this definition of a new exacerbation.
- Patient who were being treated for MTEs, but did not have a corresponding EXACT event, showed an improvement in mean scoring over ten days from onset of only approximately 4 or 5 points, which may fall within the instrument's intra-individual variability of approximately 4 points.
- The M-Pex trial enrolled approximately 10% of patients without documentation of COPD (GOLD stage 0) and these patients did not appear to be excluded from instrument analyses.

- The "Efficacy Evaluable" population was used for the instrument analyses in the M-Pex trial; intent-to-treat populations are the preferred analysis populations.
- There was no documentation regarding the characterization as ABECB-COPD or an exacerbation due to non-bacterial causes such as exacerbations due to environmental changes or allergic conditions.
- There were no data that begin to demonstrate, or even begin to hypothesize, the potential treatment effect of an antibacterial drug by evaluating changes in EXACT scoring to be used for efficacy determinations in a clinical trial of an antibacterial drug for treatment of ABECB-COPD.

OTHER OBSERVATIONS ABOUT EXACT-PRO

- The treatment effect of an antibacterial drug over placebo in the treatment of ABECB-COPD is likely to be small. Experience in other disease areas where there is a small treatment difference over placebo indicated in some circumstances that a subgroup of patients have a much larger treatment effect, which is often important to identify. The EXACT scoring of many responses in the instrument as identical scores (e.g., the same score in items 10 and 11 for "severely", "extremely", and "too breathless to do these") may not permit identification of a subgroup that has a larger treatment effect. The amount of symptomatic improvement from not being capable to perform an activity at all to being moderately short of breath when performing the activity might be characterized differently, on an individual basis, in comparison to a patient who never lost an ability to perform an activity but recorded symptomatic improvement from severely to moderately short of breath. The current EXACT score on items 10 and 11 would be identical for these two individuals (1 point difference). Yet sleep disturbances and feeling tired have graded scoring for "severely" and "extremely" that would be capable of differentiating between two individuals where one shows symptomatic improvement from severe to moderate (1 point difference) and the other from extreme to moderate (2 point difference).
- A raw summed score may be capable of detecting a larger treatment difference in a subgroup of patients. The conversion table to the EXACT score may reduce an ability to show larger treatment differences in a subgroup.

Further modification of the instrument, as suggested in the iterative process of PRO development in Figure 3 of the FDA's PRO guidance, should consider these observations from patients who lack an ability to perform the activity because of the exacerbation and their symptomatic improvement.

SUMMARY

Development of EXACT-PRO has proceeded to a point where it is qualified for use in phase 2 trials. The PRO guidance states, "The adequacy of an instrument's development and testing is specific to its intended application in terms of population, condition, and

other aspects of its measurement context for which the instrument was developed." Accordingly, the next step in the EXACT-PRO development should be an evaluation of its use in the intended application: a phase 2 placebo-controlled trial in patients experiencing an ABECB-COPD to begin to demonstrate reliability, other construct validity, ability to detect changes, and ascertain whether further instrument iteration and modifications might be necessary. An estimate of the treatment difference on an EXACT-PRO score of an antibacterial drug versus placebo would enable appropriate efficacy assumptions and sample size calculations for a phase 3 trial. These would be important components of evaluations that might enable future qualification of EXACT as a phase 3 efficacy endpoint.