Statistical Analysis Plan Addendum

A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with Acute Respiratory Distress Syndrome Associated with COVID-19

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Addendum to the Statistical Analysis Plan for the ACTIVE 3b/TESICO Trial
May 1, 2022

According to the TESICO protocol, no interim monitoring for futility was planned. When the trial was designed, futility assessments were not planned because completing the trial, in the absence of safety concerns, could provide valuable information for future investigations, rapid enrollment was anticipated, and the primary endpoint requires 90 days of follow-up to classify patients into the appropriate category of the ordinal outcome. Randomized patients who have not completed 90 days of follow-up would not contribute to an interim assessment of futility with respect to the primary outcome. Two paragraphs from section 11.3.1 of the protocol are cited below:

> "First, in many cases, potential agents may be relevant not only to COVID-19-associated ARDS but to other forms of ARDS. As such, even if an agent did not achieve its efficacy endpoint, enrollment to the planned sample size is expected to provide important insights relevant to future investigations in ARDS. These insights may especially pertain to potential effects among subgroups of patients or less common safety events of interest.
>
> Second, the primary endpoint of this trial requires 90 days of follow-up since the final classification of a patient's recovery requires knowledge of their status on Day 90. While this duration of follow-up for the primary endpoint is essential for a patient-centered result at the conclusion of the trial, in the context of the anticipated rapid enrolment of the trial, this endpoint is infeasible to use for stopping boundaries for either efficacy or futility on the basis of conditional power."

As a consequence of the enrollment decline since January 2022, most randomized patients have now completed 90 days of follow-up. For example, as of April 24, 2022, 466 of the planned 640 patients (73%) have been enrolled to the aviptadil/placebo group and 457 (98%) of those patients will have a day-90 anniversary by May 25, the date of the next Data and Safety Monitoring Board (DSMB) review.

It is costly to maintain the infrastructure of the TESICO trial. For example, the team continues to work with NRx on new manufacturing supply chains for drugs, continues to ship aviptadil to study sites when current supplies reach their expiry date, and continues to maintain staff at our international coordinating centers.

Therefore, we considered it important to develop a plan for assessing futility for the TESICO trial.

The purpose of this addendum to the Statistical Analysis Plan (SAP) is to document the results of the sample size re-estimation which was carried out in March 2022 using blinded (pooled outcome data for the aviptadil and placebo groups combined), and to describe our plan for futility assessments that will be carried out for future meetings of

the DSMB.

Sample Size Re-estimation for TESICO

Marginal (both treatment groups combined) category proportions for the Day 90 primary ordinal outcome were provided on March 22, 2022 by the unblinded TESICO statisticians to the blinded leadership of TESICO for the initial 352 patients enrolled and followed to day 90. These proportions are given in the 2nd column of the table below. The 3rd column gives the marginal proportions that had been assumed in the design for estimating sample size.

Category Status at Day 90	**Observed pooled category proportions (n=352)**	**Hypothesized pooled category proportions; OR=1.5; alpha = 0.05 (2-sided); power=0.80; and total n=602; increased to 640 to allow for some missing data and patients who withdraw before their infusion**
1 (home off oxygen ≥ 77 consecutive days)	**.196**	**.145**
2 (home off oxygen 49-76 consecutive days)	**.168**	**.254**
3 (home off oxygen 1-48 consecutive days)	**.134**	**.171**
4 (not hospitalized, at home on oxygen or not at home)	**.106**	**.096**
5 (hospitalized for medical care or in hospice care	**.056**	**.047**
6 (dead)	**.341**	**.289**
	1.00	**1.00**

The formula for total sample size (n) assuming 1:1 allocation of treatments based on Whitehead (Stat Med 1993) is given below. The sum of the cubed marginal proportions (the p_i's and numbers in the table) for the 6 categories is in the denominator of the formula. Other parameters were fixed as stated at the top of the 3rd column above. Using this formula, solving for Z_β, power was re-estimated.

$$n = 12 (Z_{\alpha/2} + Z_\beta)^2 / \ln(OR)^2 [1 - \Sigma p_i^3]$$

Using the observed marginal proportions, power is slightly less than 0.80 for n=602. The sample size for 0.80 power is 608 with the category percentages in the 2nd column.

In the report for the February 2022 meeting of the DSMB, the percentage of patients with unknown recovery status at day 90 was 9.4%. This is somewhat higher than planned.

The observed percentage of deaths at day 90 in the table above is 5% higher than the pooled estimate used for sample size. This is likely due to enrolling more patients on non-invasive or mechanical ventilation or ECMO than anticipated. We assumed 80% of patients would enter on a high flow nasal cannula (HFNC), 5% on non-invasive ventilation (NIV), and 15% on mechanical ventilation or ECMO (VENT). Mortality for these 3 groups in the control group was assumed to be 30%, 40% and 45%, respectively.

Among the 352 patients who completed day 90, 195 (55%) are on HFNC at entry. At the time of the February DSMB meeting, the percentages on HFNC, NIV, and VENT at study entry were 53%, 6% and 41%, respectively. Using the original mortality estimates, the 90-day mortality estimate for the control group assuming these percentages persist is 36.8%. Assuming an OR of 1.5, the resulting aviptadil mortality would be 28.0%. The pooled estimate using these percentages assumed for the aviptadil (28.0%) and placebo (36.8%) groups is 32.4%, close to the observed pooled rate of 34.1%.

Recommendation: No change in sample size is required if missing data at day 90 can be reduced to 5%. The goal should remain 640 participants.

Futility Assessment Plan for TESICO

As a guideline, we propose futility be assessed at the May 25, 2022 DSMB meeting using conditional power estimates for the primary 6-category ordinal outcome. We also propose that the recommendation by the DSMB on futility consider the time required to complete enrollment in the trial in addition to conditional power. For example, if enrollment can be completed in 3 months, then conditional power > 0.10 might be acceptable for continuing the trial; if the completion of enrollment requires another 12 months, then conditional power of > 0.50 might be more appropriate.

For the May 25 review we assume the following:

- Outcome data will be available for 70% of the 640 planned patients.
- By the time of the meeting, the number enrolled to the aviptadil/placebo group will increase by 6 patients to 472. This leaves an additional 168 patients to enroll.
- Enrollment will be completed in 7 months by December 31, 2022 (an average of 24 patients per month from June through December). This assumption is based on steady enrollment of 15 new sites in Brazil which will begin enrollment in July or August, enrollment in Europe which may begin in September, and an increase

in enrollment in the U.S. The rate required to complete enrollment by the end of 2022 is similar to that for the month of February 2022 when it was 22.

We propose that conditional power be estimated based on assuming the following for the 30% of patients (largely not enrolled) without day 90 information (future data):

- Assume an odds ratio (OR) of 1.5 as in the design for future data.
- Assume the OR observed for the future data.

<u>As a guideline</u>, it is recommended that conditional power be at least 0.20 based on either of the 2 assumptions to continue the trial.

It is also recommended that the DSMB consider other information in making their recommendation. For example, the following results should be considered:

- The magnitude of the OR required for the remaining 30% of patients in order to obtain a significant result.
- The observed mortality differences between treatment groups (mortality is an important secondary endpoint).
- Subgroup findings for the primary endpoint for the two disease strata by oxygen requirement at baseline (high flow nasal cannula and non-invasive ventilation versus mechanical ventilation and ECMO).
- The primary safety outcome at day 28.
- A repeat of the aforementioned analyses excluding participants who were not infused (currently 9 patients) in the event a modified intention to treat (mITT) analysis is carried out instead of an ITT analysis.

If the review on May 25 leads to a recommendation to continue the trial as planned, we would like the DSMB to reassess futility using conditional power in August 2022, irrespective of how much additional data (completed day 90 visits) are available. If the rate of enrollment has not increased substantially by August and it is unlikely that enrollment will be completed by December 31, 2022, we recommend using conditional power > 0.5 as the criteria for continuing the trial. Conditional power estimates will be estimated in the same way and similar supporting analyses will be provided for the August DSMB review.

The results of the sample size re-estimation and the plan for futility assessments were shared with the DSMB on April 28, 2022, and they responded on April 29, 2022 that they agreed with “staying with the current sample size of 640” and “with the guidelines for futility as spelled out”. They also stated the following: “The Board affirms the study teams’ recognition that what is suggested are guideline for the Board to use rather than rules.”