NCT03054870

ADDENDUM TO STATISTICAL ANALYSIS PLAN
FOR
PROTOCOL CYC-009

A Comparison of Technegas® and Xenon 133 Planar Lung Imaging in Subjects Referred for Ventilation Scintigraphy

Study Drug: Technegas®

Sponsor: Cyclomedica Australia Pty Ltd.
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[redacted]

Original Protocol (Version 1.1) **Date:** 4 October 2016

Protocol Amendment 1 **Date:** 2 November 2018

APPROVAL SIGNATURE

This analysis plan was reviewed and has the approval of:

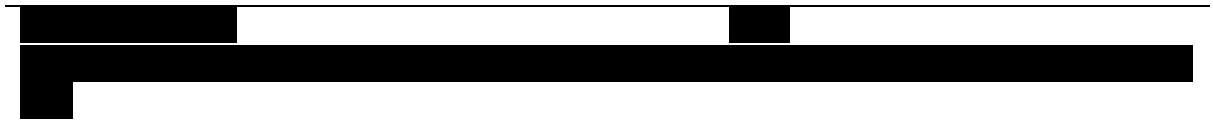
Sponsor's Study Statistician

[redacted]

APPROVAL SIGNATURE

This analysis plan was reviewed and has the approval of:

Sponsor's Responsible Party



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1. REASON FOR SAP ADDENDUM

On March 26, 2020, Cyclomedica Australia Pty Ltd submitted an original 505(b)(2) New Drug Application (NDA), 022335, for the drug product, Technegas® (Technetium Tc-99m Carbon Aerosol), the TechnegasPlus Technegas® Generator and Pulmotec carbon crucible used in the TechnegasPlus Technegas® Generator to produce Technegas®. Technegas® and its generator, including the crucible, are regulated as diagnostic radiopharmaceutical drugs pursuant to 21. C.F.R. 315.2.

Following the FDA filing review, it was determined by the Agency that the application was sufficiently complete to permit a substantive review. The CYC-009 study, whose protocol has been formally agreed upon by FDA under a Special Protocol Agreement, is not yet completed; an interim report of safety data was included in the NDA submission but no interim report of efficacy data was included. Given that the trial is now approximately 80% complete and blinded reads of images of 200 subjects have been performed, the Agency requested that a formal interim efficacy analysis of the available blind read data be conducted by an independent third-party statistician.

This addendum to the CYC-009 Statistical Analysis Plan (SAP), Version 2, describes how the sponsor intends to respond to this request.

2. TRIAL INTEGRITY

As of March 31, 2020, 225 subjects enrolled in the study, but as a result of the Coronavirus Disease 2019 (COVID-19) pandemic, enrollment in the study was suspended by the sites. Sixteen (16) of the 225 subjects withdrew prior to receiving Technegas, and data for the remaining 209 subjects are complete. The target number of enrolled subjects who receive both a Techegas and Xenon ventilation scan is 240. Blinded reads of subjects' ventilation scan images have been conducted in blocks of 40 subjects and to date, five blocks of subjects' images (n = 200 subjects) have been read by the three blinded readers. The independent read database is being hosted by an electronic data capture (EDC) vendor and is being securely maintained in a validated database system with an audit trail. Once a reader commits a record to the independent read database, the record cannot be modified. Refer to the Image Review Charter CYC-009 for more details. To date, the independent read data have remained blinded.

Analysis populations remain as described in SAP Section 5. The Full Analysis Set (FAS) will be the primary efficacy analysis data set. The Per Protocol Set (PPS) will be a secondary data set for analysis of efficacy data.

Efficacy endpoints are unchanged and are described in SAP Section 6.1. The **primary efficacy endpoint** is percent agreement between Technegas and Xe-133 obtained from blinded readers' ventilation assessments of matching image views.

The primary efficacy endpoint, percent agreement (PA) between Technegas and Xe-133, from analysis of each of the three blinded readers' ventilation scores for the matched image views, will be subjected to the following test of null (H_0) versus alternate hypotheses (H_A), (SAP Section 7.1):

$$H_0: PA \leq 60\% \text{ versus } H_A: PA > 60\%$$

For the study to be deemed a success, the null primary efficacy hypothesis must be rejected for at least two of the blinded readers (SAP Section 7.2).

Neither the primary efficacy endpoint or the secondary prespecified endpoints are modified in this addendum.

3. INTERIM ANALYSIS METHODOLOGY

Study CYC-009 is an ongoing study with planned enrollment of 240 subjects that have completed the Xe-133 and Technegas imaging. To date, blinded reads have been performed by three independent readers of 200 subjects who have completed the study. A not previously planned interim analysis of these available blind read efficacy data will be performed at the request of FDA. Based on review of the various methodologies, the alpha spending function method of DeMets and Lan[1,2] is determined to be appropriate for this situation, and the function which approximates the O'Brien-Fleming boundary will be used.[3] Given that 200 of 240 subjects have completed the blind-read and one-sided total alpha of 0.025 specified for the primary efficacy endpoint in the original SAP, this proposed method would test for significance at the one-sided alpha =0.0141 at the interim stage of the requested interim analysis (critical value is lower bound of 97.18% confidence interval), and at the one sided alpha=0.0210 at the final stage (critical value is lower bound of 95.80% confidence interval).

In general, efficacy data will be analyzed in accordance with the methods described in SAP Section 10.5. For each reader, binary agreement scores will be analyzed using a generalized linear model with SAS®[4] PROC GENMOD. The logit function (log odds ratio) will be specified as the link function, and subject will be specified as a repeated measure to allow for correlations between lung regions within a subject. The estimate of the intercept of the model using generalized estimating equation (GEE) methodology will provide an overall estimate of the agreement and a confidence interval in terms of the log odds ratio; simple algebra will be used to obtain the corresponding estimates and confidence intervals in terms of percent agreement (PA).

Sample SAS code is provided below [redacted]

The non-inferiority hypothesis to be tested is:

H_0: PA ≤ 60% versus H_A: PA > 60%

where 60% is the non-inferiority margin. If the null hypothesis is rejected based on the lower boundary from the 97.18% confidence interval for PA exceeding 60%, Technegas will be considered non-inferior to Xe-133 with respect to assessing pulmonary ventilatory distribution.

4. INTERIM ANALYSIS DECISION RULES

FDA has requested that one of the following four decisions be reached based on the interim efficacy analysis. The rules by which one of the four potential decisions will be selected are as follows:

i. **Successful outcome, trial terminates**
Two (2) or more of the 3 blinded readers reject the null hypothesis for PA, for

matched views PA.

ii. **Not yet successful outcome, trial continues**
Successful outcome criterion as described in (i) is not met, but 2 or more of the 3 blinded readers demonstrate that PA > 50% for matched views PA.

iii. **Non-successful outcome, trial terminates (futility outcome)**
Outcome criteria described in either (i) or (ii) are not met; evidence does not support PA > 50%.

iv. **"Close Enough"**
The results of the analysis are not statistically significant to allow for a decision as in (i) but are 'close enough', in that at least two of the three readers have a PA greater than 0.60 and a p-value of less than 0.025 is realized, and it is clinically obvious that given the same results, a slightly larger sample size or not utilizing the adjustment due to the unplanned interim analysis, would have resulted in a statistically significant result.

5. INDEPENDENT THIRD PARTY STATISTICIAN

The interim analysis of the blinded read data will be performed by an independent third party statistician. The EDC vendor will provide the statistician with a private and secure portal to access and download unblinded read data, which will be maintained in a secure location to which only the independent statistician has access. All data access will continue to be compliant with 21 C.F.R. Part 11.

The independent statistician will analyze all primary and secondary efficacy endpoints for both FAS and PPS populations as described in the SAP Sections 10.5.1 and 10.5.2, except that any inferential testing of the non-inferiority hypothesis will be tested using one-sided alpha equal to 0.0141.

In addition, descriptive statistics will be provided for subject disposition, demographic data, and clinical reason for imaging.

A statistical report will be written by the statistician including subject data listings of data analyzed or summarized. The report will be provided only to the Data Efficacy Monitoring Committee (DEMC). The sponsor and their contracted partners involved with any aspect of the study will remain blind to the efficacy results at this time.

6. DATA EFFICACY MONITORING COMMITTEE

At the request of FDA, a DEMC will be formed by the sponsor to review the interim efficacy statistical report prepared by the independent third party statistician. The DEMC will consist of three members each with expertise in clinical trials, including a statistician. The members will have no prior financial affiliation with the sponsor and have had no prior involvement in the CYC-009 trial. The DEMC will make a recommendation to the sponsor based on their review of the results of the interim analyses and the decision rules provided above. Details on DEMC membership and their role with respect to the study will be specified in the CYC-009 DEMC Charter that will be provided to and agreed upon by each DEMC member prior to conduct of the DEMC.

7. FINAL ANALYSIS

If enrollment continues to completion, the final analysis will be conducted in accordance with the final SAP Version 2, except that inferential hypothesis testing of PA efficacy endpoints will be tested at one-sided alpha=0.0210.

8. REFERENCES

1 Lan KG and DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983; 70: 659-663

2 DeMets DL and Lan KG. Interim analysis: the alpha spending function approach. *Statistics in Medicine* 1994; 13: 1341-1352

3 O'Brien PD and Fleming TR. A Multiple Testing Procedure for clinical trials. *Biometrics* 1979; 35: 549-556

4 SAS Software Release 9.4 (TS1M2). Copyright© 2002-2012 by SAS Institute Inc., Cary, NC, USA