Final Review Memorandum

BLA: STN 125588\0\13, 14 and 15.

Date: 06-01-2017

To: Babita Mahajan, Ph.D., Scientific Lead, DETTD/PRB

Reviewer: Rana Nagarkatti, Ph.D., LEP/DETTD/OBRR

RPM: Iliana Valencia, MS, MCPM, Chief, RPMS, FDA/CBER/OBRR/IO

Through: Sanjai Kumar, Ph.D., Chief LEP/DETTD/OBRR

Through: Alain Debrabant, Ph.D., LEP/DETTD/OBRR

Sponsor / Product: Immugen, Inc: Blood donor screening test for evidence of Babesia microti by real-time polymerase chain reaction (PCR).

Purpose of the Submission: Response to the CR letter issued to Imugen Inc. (now Oxford Immunotec) on September 29, 2015.

Intended Use: The intended use as stated by the sponsor is, "*The Imugen B. microti AFIA (IFA) and NAT PCR are used as complementary tests for screening blood donors to determine B. microti infection as a means to reduce incidence of transfusion transmitted babesiosis*". The final intended use statement has not been provided.

Review Discipline: Pre-clinical and Clinical sections.

Recommendation: The sponsor's responses to the preclinical and clinical issues raised in the CR and 2 subsequent IRs (dated March 1 and March 23, 2017) are adequate. I recommend the approval of the BLA pending the satisfactory resolution of all issues raised in the CR that are being reviewed by the committee. In addition, the sponsor needs to provide an updated draft of the Package Insert for review.

Comments:

Brief summary of the BLA review timeline: FDA communicated a 49 item CR letter to Imugen on September 29, 2015. Imugen requested an extension of the response due date on September 16, 2016. FDA also received a partial response to

the CR letter on August 31, 2016, detailing the response to question 1 thru 6 of the issues in the clinical section of the CR letter. This partial response was reviewed by the clinical reviewers. On November 11, 2016, FDA communicated to Imugen that the response to the clinical section was adequate; however, clarifications regarding the selection of samples for determining clinical sensitivity and the total sample size for determining specificity were needed. On December 14, 2016, Imugen submitted a complete response to the CR letter. The comments below document my review of the clinical and pre-clinical sections of the sponsor's complete response and their response to the IRs. The ADD for the submission is June 14 2017.

Clinical Issues:

CR Issue #1: *You have not provided data for the clinical sensitivity of the Babesia NAT. In the clinical hold letter to IND 14532 dated December 10, 2010, we requested that you demonstrate the clinical sensitivity of this test in human samples that are blood-film positive for B. microti. Please provide data to demonstrate the clinical sensitivity of your assay in confirmed clinical Babesia positive samples.*

Imugen's Response: Imugen conducted NAT testing on 72 samples that were blood smear positive and 23 samples that were blood smear negative. The parasitemia in the samples ranged from 0.005% to 2.89%.

Comments: A subset of 72 samples from the clinically characterized archived pedigreed samples collected in Clinical Study 1 (a total of (b) (4) samples) were used to establish the clinical sensitivity of the NAT. These were pre-selected based on NAT, however, 72 samples that were smear positive were selected and used in a random and operator blinded manner for repeating the NAT assay to calculate clinical sensitivity. All 72 samples tested positive on the NAT assay and clinical sensitivity was calculated using the algorithm below (Attachment 1.3; DOC-RPT-42):

100% x (True Positives) / (False Negatives + True Positives)
Negatives= > 45 Ct
Positives= ≤ 45 Ct

Of the 23 negative samples one sample tested inconclusive on repeat testing.

Recommendation: The response is acceptable.

CR Issue #2: *In the clinical section, analysis of the data submitted in BAFSBLA.xlsx and MSTDONOR.xlsx, identified significant protocol deviations. The protocol for human 18S internal*

control testing (Page 259.17, document 021_Attachment 4-2-3-17 LAB-MOL-BPCR-10) states, "Ct values for the human 18S internal control should be (b) (4) *at a threshold setting of* (b) (4) *for all negative samples and controls. Any Babesia negative sample with a Hu18S Ct value of* (b) (4) *will be repeated from amplification. If the Ct value does not meet specifications after repeat testing, consult a supervisor." There are a total of 327 samples where the internal Hu18S PCR Ct ranged from* (b) (4) *Repeat testing was not performed on these samples as per the protocol.*

a. Please clarify why the SOP of repeat testing was not followed when Ct values for Hu18S were (b) (4) *for several of these specimens.*

Imugen's Response: Imugen responded prior to January 18, 2013 the Human 18S Ct value cut-off was set at (b) (4). On this date, the new cut-off of (b) (4) went into effect. As a result 326 samples were excluded from the analysis (Attachment 2.1) and excluded samples reported in the BCR-NAT-ATT-5 Excel worksheet.

Comments: The sponsor has provided the data requested.

Recommendation: The data is acceptable.

b. Please exclude these samples from data analysis and instead report them as protocol deviations and provide a separate excel worksheet with all excluded data. Alternatively, please perform new testing on samples where the SOP was not followed and submit the results for review to FDA.

Imugen's Response: The MSTDONOR.xlsx database was updated. To ensure a consistent evaluation at the current cut-off specification of (b) (4), all samples with Human 18S values (b) (4) that were not repeat-tested have been excluded (as indicated in BCR-NAT-ATT-5 Excel worksheet).

Comments: No comments.

Recommendation: The response is acceptable.

c. Please clarify what steps are taken by the supervisor to resolve out of specification results and how such test results are resolved and reported to the end user (i.e., blood establishments).

Imugen's Response: A CAPA was initiated to address the issue of a specimen that was found to be out of specifications and the protocol was clarified and staff retrained on the procedures. In addition, the ambiguity of arithmetic rounding at the cut-off value for the human 18S control regarding the determination of out of specification results was clarified. Sections 8.1 and 8.2 in LAB-MOL-BPCR-10

(Babesia microti Detection by Nucleic Acid Test for use on Blood Donor Screening Samples) were amended for clarification of the procedures.

Comments: No comments.

Recommendation: The response is acceptable.

CR Issue 3: *Similar to what is described above for Hu18S Ct Values, the protocol is not followed for Babesia specific amplification. For the Babesia NAT, the protocol (Page 259, 17, document 021_Attachment 4-2-3-17 LAB-MOL-BPCR-10) states that "Samples with Babesia-specific Ct values* (b) (4) *will be repeated. The original sample will be* (b) (4) *to the PCR plate." Further, the Figure 8.4.1.2: "Testing Flow Chart, 002 8-4-1 CSR study 1, Page 1595, indicated Babesia NAT will be repeated if Ct* (b) (4)

a.   *Please clarify at what Babesia-specific 18S Ct value the repeat testing is done (i.e.,* (b) (4)

Imugen's Response: The sponsor stated that CS1 was not intended to provide data for the calculation of clinical sensitivity and specificity. For the clinical studies used to establish sensitivity and specificity (Studies 2 and 3a), Imugen stated that Ct values due to an exponential curve (b) (4) would be repeated.

Comments: In the protocol LAB-MOL-BPCR-10: "Babesia microti Detection by Nucleic Acid Test for Use on Blood Donor Screening," (Attachment 2.5). All Babesia positive NAT specimens are repeated. Those samples with a Babesia-specific Ct value due to an exponential curve (b) (4) will be also be repeated. The protocol demonstrates the acceptable exponential curves in figures 8, 9 and 10 on page 23 of 26, LAB-MOL-BPCR-10 (version 1.18). In example of normal curves, if the exponential curve crosses the threshold at (b) (4) the sample will be (b) (4) and if one or more values in the retest are positive the sample is considered positive. The question of what constitutes an exponential amplification was raised in an IR letter (Issue#9, IR letter dated March, 23, 2017). Imugen responded with an updated LAB-MOL-BPCR-10 protocol, updated to version 1.19 from 1.18, to clarify which samples will be retested. In section 10.4 "*Interpretation of the Results*", section 10.4.3.3 states that *"A sample that crosses the threshold but does not demonstrate an exponential curve (no evidence of specific amplification) is considered negative. However, samples that cross the threshold but do not exhibit exponential amplification must be repeated from elution in order to achieve an "undetected" value that can successfully be transferred to* (b) (4) *and reported as "Negative"."* As the ambiguous samples with a non-exponential curve will be retested by NAT, the risk for transfusion transmission is reduced.

Recommendation: The response provided is acceptable.

CR Issue 4: *In the data provided in document MSTDONOR.xls, there are 707 samples where line item data for the Babesia 18S Ct and the Hu18S Ct value columns are blank. However, the donor test results are interpreted as "negative" (i.e., no Babesia DNA was detected for these 707 samples). This is a significant deviation from the IND protocol for these prospective blood donations. Please clarify why these specimens were not classified as invalid and why the testing was not repeated for these specimens rather than classifying them as Babesia negative. Please report these samples as invalid results and exclude them from analysis.*

Imugen's Response: Imugen responded that the Ct values were excluded from the MSTDONOR.xlsx due to a transcription error and not to a protocol deviation. The test results from the 707 samples that were missing Ct value data were re-examined, and were found to have valid Babesia and Human18S Ct values available in the test records. The updated MSTDONOR.xlsx file was provided.

Comments: The updated MSTDONOR.xlsx file was provided.

Recommendation: The response is acceptable.

CR Issue 7: *For each study's data summary, please display the data as a 2X2 table with results for the test under review in rows and the results of the comparator in columns. In cases where there are three outcomes (i.e., positive, negative, inconclusive) the data may be displayed in 2X3 or3X3 tables.*

Imugen's Response: Imugen has provided the requested data.

Comments: Imugen's response to the clinical study section of CR was reviewed as part of the partial response they submitted on November 11, 2016. The organization and analysis of clinical study results in 2x2 or 3x3 tables is acceptable and substantially improves the presentation of the clinical trial results. Additional clarifications regarding the donor testing results were provided

(b) (6)

Recommendation: The response is acceptable.

Pre-Clinical Issues:

CR Issue 9: *The analytical specificity/cross reactivity study has been conducted using seven bacteria species and one yeast species. Please expand the cross-reactivity studies to include the following pathogens (Plasmodium sp., Leishmania*

sp., Trypanosoma cruzi, and Borrelia burgdorferi) as agreed in the IND study protocols (IND#14532).

Imugen's Response: Imugen has provided additional data in DOC-RPT-31 and 35.

Comments: Imugen used Babesia negative and positive plasma samples that were spiked with 8 different bacterial species. Additional testing with 20 *P. falciparum* and 5 *T. cruzi* samples was also performed. The sponsor stated that Leishmania samples could not be procured. There was no interference detected in the NAT as *Babesia* negative samples remained negative after spiking and Babesia positive samples remained positive after spiking.

Recommendation: The response is acceptable.

Letter ready comments:

1.   Please provide an updated draft of the Package Insert.