SAFETY MONITORING COMMITTEE CHARTER

SONOMA BIOTHERAPEUTICS, INC.

PROTOCOL ID
SBT777101-01

PROTOCOL TITLE
A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Activity of Single Ascending Doses of SBT777101 in Subjects with Rheumatoid Arthritis

US IND NUMBER:
029028

INVESTIGATIONAL PRODUCT (IP)
SBT777101

VERSION & EFFECTIVE DATE
V 1.0, 06-Jun-2023

SPONSOR AND CRO APPROVERS

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Richard Kay, MBChB, PhD Medical Monitor Medpace	Date
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VERSION HISTORY

VERSION DATE	VERSION NUMBER	SUMMARY
06-Jun-2023	V 1.0	Initial version.

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CONTENTS

1 INTRODUCTION

This Safety Monitoring Committee (SMC) Charter describes the responsibilities of the SMC and its processes for:

- Routine review of the safety profile of SBT777101; and,
- Recommendation for dose escalation and ongoing study conduct.

The initial SMC Charter and all subsequent versions will be filed in the study TMF following signature.

2 COMPOSITION OF THE SMC

The SMC will consist of at least the following individuals:

- All study Principal Investigators (PIs) with dosed patients being evaluated during an SMC review
- Sonoma Medical Monitor
- Medpace Medical Monitors
- An independent physician with expertise in rheumatoid arthritis (RA)
- An independent physician with expertise in chimeric antigen receptor T-cell (CAR T) therapy

The independent physician with expertise in RA will serve as primary SMC Chair. The physician with expertise in CAR T therapy will serve as backup Chair in the event the primary Chair is unavailable for a given SMC review session. The SMC Chair will be responsible for filling out the SMC Recommendation Form and providing to Medpace to circulate for signature.

Additional PIs may be included. Minimum attendees include at least one SMC Chair and PIs with subjects under review.

3 SMC RESPONSIBILITIES

SMC member responsibilities include the following:

- Review and approve the SMC Charter (see Appendix B). Signature on the Charter acknowledges the following:
    - Acceptance of the roles and responsibilities of serving on the SMC
    - Agreement to protect the confidentiality of study data and SMC discussions and recommendations
    - Agreement to disclose any actual or potential conflicts of interest in a timely manner
- Review all materials prior to an SMC, which include the following:
    - SMC Meeting agenda
    - The SMC Recommendation Form (See Appendix A)
    - All safety data provided to the SMC
- Convene regularly during the study—or ad hoc when a dose-limiting toxicity (DLT) has occurred in any trial subject—to review clinical study data and assess the benefit/risk profile of SBT777101.
- Provide recommendations regarding study conduct*, to include:
    - Initiation or cessation of dose escalation
    - Addition of dose levels, or other deviation(s) from the protocol-specified dosing scheme (including dose reduction)
    - Study continuation or discontinuation, including full study termination

*Sonoma Biotherapeutics will make final decisions regarding dose escalation and/or dose levels

4 OVERVIEW OF STUDY DESIGN

The SBT777101-01 study is a Phase I, open-label study to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary clinical activity of single ascending doses of SBT777101 in subjects with active RA.

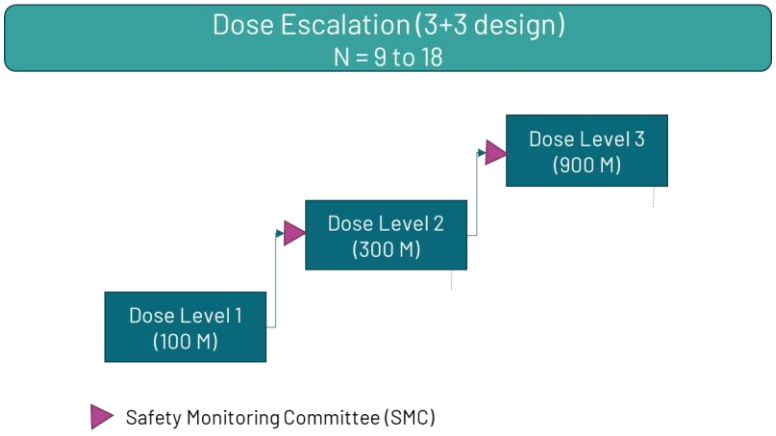
4.1 Overall Study Design

Eligible trial subjects will undergo apheresis and SBT777101 (the IP) will be manufactured for each subject. Each subject will receive a single dose of the IP on Day 1, after which subject safety will be followed for one year. Upon study completion (Week 48), subjects will be encouraged to roll over into an observational long-term follow-up study for up to 15 years in accordance with FDA guidance for gene therapies.

4.1.1 Dose Escalation

The study will follow a “3+3 dose escalation” design (see Figure 1); three eligible subjects will be enrolled and evaluated in each of three cohorts. No subject may receive treatment of SBT777101 until after the DLT monitoring period (28 days for dose escalation cohort subjects) has been completed for the prior subject. Dose escalation may not proceed until the DLT monitoring period (at least 28 days) has concluded for the final subject in a cohort. The SMC will oversee dose escalation.

Figure 1:



4.1.2 Replacement of Subjects

Subjects in dose escalation cohorts will be replaced for any of the following reasons:

- Received less than 85% of the planned study drug administration
- Discontinued, withdrew from, or lost to follow-up before completing the DLT evaluation period (up to study Day 28)

If a subject experiences a DLT, they will not be replaced.

4.1.3 Additional Subjects for PK and PD evaluations

After the dose escalation cohorts are complete, the Sponsor may enroll additional subjects (up to a total of 6) at one or more dose levels that do not exceed the highest dose level determined to be safe by the SMC, to obtain additional data if required to further define PK and PD properties to guide future dose selection.

4.1.4 Dose Levels

The planned dose levels during dose escalation are listed in the below table:

COHORT/DOSE LEVEL	TOTAL CAR^+ T CELLS
1 (Starting dose)	100×10^6
2	300×10^6
3 (Maximum dose)	900×10^6

If ≥1 subject in the first cohort (Dose Level 1) experiences a DLT, Sonoma Biotherapeutics and/or the SMC may approve and oversee enrollment of subjects into a cohort at a dose lower than the planned starting dose. Fewer or additional cohorts, lower than the maximum planned dose in Cohort 3, may be included based on safety observations and/or IP manufacturing limitations, with SMC approval.

4.2 Study Stopping Rules

The study will be paused, and the risk to other subjects evaluated, prior to a decision whether to continue or terminate the study if any of the following occurs:

- Death from any cause other than events clearly unrelated to IP
- Diagnosis of malignancy of T cell origin in any subject who received IP, until insertional mutagenesis is ruled out
- Incidence of the following in over one-third of subjects, regardless of duration:
    - Grade 4 cytokine release syndrome (CRS)
    - Grade ≥ 3 Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS)
    - Other grade ≥ 3 nonhematologic serious adverse events (SAEs) not related to disease progression or other underlying medical condition unrelated to study treatment
    - Grade >3 infection related to study treatment
    - Grade 4 vital organ toxicity not related to disease progression
- A decision to stop dose escalation or study activities has been recommended by the SMC in two cohorts for safety concerns
- The SMC determines that a pattern of adverse events (AEs) would preclude evaluation of any further dose cohorts or place subjects already in the study at increased safety risk

5 SMC RECOMMENDATIONS

The SMC will convene approximately 4 weeks after the first (sentinel) subject has been dosed in each dose escalation cohort and upon completion of a dose escalation cohort. It will also convene on an ad hoc basis if a DLT occurs. The SMC will provide recommendations on study conduct (i.e., escalate dose to the next planned cohort, cease dose escalation, additional dose levels, cease dosing). After each SMC review, the SMC will provide an SMC Recommendation Form (see Appendix A) to Sonoma to serve as formal documentation for their recommendation. This form will be filed to the study Trial Master File (TMF).

5.1 Dose-Limiting Toxicity (DLT)

Decisions regarding dose escalation will primarily be based on assessment of DLTs occurring in subjects enrolled in dose escalation cohorts. A DLT is defined as any of the following occurring within 28 days following IP infusion:

- Death

- Grade 4 CRS (any duration)
- Grade 3 CRS that does not improve to Grade ≤ 2 within 72 hours following adequate therapy
- Grade ≥ 3 ICANS (any duration)
- Grade ≥ 3 toxicity involving vital organs (e.g., cardiac, pulmonary)
- Grade 4 hematological toxicity that does not improve to Grade ≤ 2 within 28 days
- Grade ≥ 3 infections

5.2 Dose Escalation Decisions

The SMC will convene as soon as feasible following completion of the DLT observation period of the last subject dosed in the cohort to review available safety data. Following this review, the SMC will recommend whether dose escalation should proceed. The SMC will use the following as considerations for their recommendation:

- If a DLT is not seen in the first 3 subjects, then escalation to the next dose level may occur.
- If a DLT is seen in 1 of the first 3 subjects in any dose cohort, the cohort size will be expanded to a maximum of 6 subjects.
- Dose escalation will be temporarily halted if any of the following occur:
    - If more than 1 DLT occurs in ≤6 subjects in a dose cohort, any of the study stopping rules are met (see Protocol Section 3.5), or if cumulative safety data suggest an overall unacceptable toxicity profile, dose escalation will be discontinued and either the prior dose level will be considered the maximum tolerated dose (MTD), or an intermediate or lower dose level will be evaluated.

6 SMC MEETINGS

6.1 Meeting Materials

The Medpace Clinical Trial Manager (CTM) or delegate (i.e., project coordinator; PC) will provide the SMC members with materials in advance. The materials (e.g., to determine dose escalation decisions, etc.) should be distributed at least five business days prior (where possible) to allow adequate time for review. The materials will include the agenda and data review packet, and any additional information relevant to assessing the safety of trial subjects. All materials will be filed in the study TMF.

6.1.1 Data Review Packet

For each SMC, a packet of safety data will be provided to the SMC members. The process for generating the patient profiles, tables, figures, and listings containing the best available data will be described separately in the SMC Data Review Plan (DRP).

6.1.1.1 Minimum Required Data

The SMC will be provided with a data packet containing at least the following data:

- AEs and SAEs
- Basic demographics (i.e., age, gender)
- Medical/surgical history (including history specific to rheumatoid arthritis)
- Concomitant medications
- Prior medications (relevant to rheumatoid arthritis and/or the subject's clinical situation at the time of SMC review)

- Neurologic assessment via Immune Effector Cell-Associated Encephalopathy (ICE) score
- Abnormal and clinically significant safety laboratory tests (biochemistry, hematology, coagulation, and/or urinalysis)
- Abnormal and clinically significant 12-lead ECG results
- Abnormal and clinically significant vital signs

6.1.1.2 Additional/Supplemental Data

Additional data will be provided to the SMC as available and may include the following assessments (if the results are deemed abnormal and/or clinically significant by the Investigator):

- Safety laboratory tests (biochemistry, hematology, coagulation, and/or urinalysis) that are within normal limits or abnormal but deemed NOT clinically significant by the Investigator
- Markers of Inflammation (ferritin, IFNγ, CRP, ESR and/or IL-6)
- 12-lead ECG results that are within normal limits or abnormal but deemed NOT clinically significant by the Investigator
- Vital Signs that are within normal limits or abnormal but deemed NOT clinically significant by the Investigator

6.2 Meeting Facilitation

The SMC will convene to assess subject status and safety data. The assessment may take place offline or via scheduled teleconference.

6.2.1 Offline SMC Assessment

The SMC's assessment may be documented offline via email, except in the following circumstances:

- An event occurs that meets the definition of a stopping rule
- An event occurs that may meet the definition of a DLT and requires real-time discussion to determine whether dose escalation can occur, whether a cohort needs to be expanded, or whether a stopping rule has been met
- Evaluation of the need to terminate the study
- There is disagreement among the SMC members related to any of the above points

If any of the above circumstances are met, both independent physicians must attend the SMC review, with the RA physician serving as SMC Chair. When convening offline, at least one independent physician must attend to serve as Chair.

When convening offline, Medpace will provide the materials to the SMC members via email. SMC members are expected to review and provide their assessment to the SMC Chair within five business days of receipt. The SMC Chair will fill out the SMC Recommendation Form and return to the Medpace PC within one business day of receiving all SMC member assessment. The Medpace PC will file the Form to the study TMF. The SMC Chair will be responsible for calling a formal meeting if, in their opinion or the opinion of any SMC member, one of the above listed criteria are met. The SMC Recommendation Form will then be filled out at the formal SMC meeting. Documentation of all SMC-related discussions occurring via email will be filed in the study TMF once the Recommendation Form is received.

6.2.2 Convening Via Teleconference

6.2.2.1 Scheduling

When a formal SMC meeting is to be scheduled, the Medpace CTM or PC will schedule the SMC Meeting teleconference at a mutually agreeable time. The meeting will be facilitated by the Medpace CTM and/or PC, including attendance, introduction of attendees, and sharing of meeting materials.

6.2.2.2 Meeting Minutes

The Medpace CTM or PC will be responsible for taking formal meeting minutes and distributing to the attendees for review and edits within two business days following the conclusion of the meeting. Edits from all parties should be returned to the Medpace PC within two business days; otherwise, the minutes will be considered final. Finalized meeting minutes will be distributed to the SMC members and filed in the study TMF at finalization.

6.2.3 Recommendation Form

The SMC Chair will complete the SMC Recommendation Form for each SMC (see Appendix A). The Medpace CTM and/or PC will circulate the completed SMC Recommendation Form for signature by the Chair. The final, signed Recommendation Form will be forwarded to the SMC, Sonoma, Medpace, and investigative sites for filing in their Investigator Site File and for submission to IRBs in accordance with governing IRB guidelines. The Medpace CTM or PC will file the SMC Recommendation Form in the TMF.

7 APPENDIX A: SMC RECOMMENDATION FORM

Date of Recommendation (dd-MMM-yyyy)

To: Sonoma Biotherapeutics

From:

Safety Monitoring Committee Chair

Data Review Meeting Date:

(dd-MMM-yyyy)

The Safety Monitoring Committee has reviewed the accumulated data for the Sonoma Biotherapeutics SBT777101-01 trial and makes the following recommendation:

Recommendation for Cohort Reviewed:

☐ Sentinel Subject: Cohort:

- ☐ Enroll subjects 2 and 3 at current dose level
- ☐ Expand cohort size (specify in the "justification" section, below)
- ☐ Temporarily halt enrollment for this cohort (specify conditions under which enrollment may resume)
- ☐ Terminate enrollment for this cohort
- ☐ Enroll additional subjects at a different dose level than this cohort (not to exceed the maximum planned dose)
- ☐ Request additional data (specify in the "justification" section, below)
- ☐ Continue with modifications/amendment to the protocol (specify in the "justification" section, below)
- ☐ Terminate the study
- ☐ Other (please specify additional comments and/or recommendations in the “justification” section, below)

☐ End of Cohort: _____

- ☐ Proceed with dose escalation to the next planned cohort dose level
- ☐ Expand cohort size (specify in the "justification" section, below)
- ☐ Enroll additional subjects at a different dose level than this cohort (not to exceed the maximum planned dose)
- ☐ Request additional data (specify in the "justification" section, below)
- ☐ Continue with modifications/amendment to the protocol (specify in the "justification" section, below)
- ☐ Temporarily suspend enrollment until uncertainties are resolved
- ☐ Terminate the study
- ☐ Other (please specify additional comments and/or recommendations in the “justification” section, below)

☐ Ad hoc meeting

- ☐ Expand cohort size (specify cohort to be expanded and number of subjects)
- ☐ Enroll additional subjects at a lower or intermediate dose level (not to exceed the maximum planned dose)
- ☐ Request additional data (specify in the "justification" section, below)
- ☐ Continue with modifications/amendment to the protocol (specify in the "justification" section, below)
- ☐ Temporarily suspend enrollment until uncertainties are resolved
- ☐ Terminate the study
- ☐ Other (please specify additional comments and/or recommendations in the “justification” section, below)

Justification:

_____

_____ _____

SMC Chair Signature | Date (dd-MMM-yyyy)

8 APPENDIX B: SMC CHARTER SIGNATURE PAGE

A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Activity of Single Ascending Doses of SBT777101 in Subjects with Rheumatoid Arthritis

SMC Role (please check below):

☐ SBT777101-01 Principal Investigator

☐ Independent physician with expertise in (check one box below):

- ☐ Rheumatoid arthritis
- ☐ CAR T therapy

Name: _____

Affiliation: _____

By signing below, I certify that I have reviewed the SMC Charter V1.0 dated 06-Jun-2023 for the above study and approve it as written. I understand and accept my responsibilities as described in the Charter.

If applicable, I also certify that I have reviewed and understand prior SMC Review minutes and recommendations.

_____ _____

SMC Member Signature Date (dd-MMM-yyyy)