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 4.0, 24-Jul-2024

SPONSOR AND CRO APPROVERS

Richard Kay, MBChB, PhD Medical Monitor Medpace	Date
Ann Woolfrey, MD Medical Monitor Medpace	Date
Sarah Baxter, MD, PhD Medical Director Sonoma Biotherapeutics	Date
Ari Bitton Director, Clinical Operations Sonoma Biotherapeutics	Date
Sabrina Fox-Bosetti Vice President, Clinical Operations Sonoma Biotherapeutics	Date
Ashley Huston, BS Director, Clinical Trial Management Medpace	Date

VERSION HISTORY

VERSION DATE	VERSION NUMBER	SUMMARY
06-Jun-2023	V 1.0	Initial version.
10-Aug-2023	V 2.0	Added caption in section 2 clarifying that voting members will not have conflicts of interest related to SBT777101. Revised section 6.1.1.2 to clarify circumstances surrounding when additional/supplemental data would be provided to the SMC. Removed reference to “Data Review Plan”; added section 6.1.2 describing SMC data exports and format. Revised section 6.2.1 to clarify that SMC offline assessment may take place via email or via a secured online communication platform.
24-Jul-2024	V 3.0	Revised throughout to maintain consistency with Sonoma SMC Charter for protocol SBT777101-02, including: • Formatting changes throughout • Composition of the SMC (including differentiation between closed vs. open sessions, Core Committee vs. Advisory Team, and SMC composition including Chair definitions) • Defined Responsibilities of the Core SMC Committee and Advisory Team • Updated Appendices Clarified that study Principal Investigators, as non-voting members, should sign the SMC Charter Signature Page as acknowledgement of their role on the SMC.

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CONTENTS

1 INTRODUCTION

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

- Routine (and ad hoc) 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 two bodies:

2.1 SMC Core Committee

The SMC Core Committee is an independent committee that will provide recommendations to the Sponsor in closed session. The Core Committee will consist of:

- An independent physician with expertise in rheumatoid arthritis (RA)
- An independent physician with expertise in chimeric antigen receptor T-cell (CAR T) therapy
- An independent third physician with clinical trial expertise

The independent SMC Core Committee (voting members) will decide on SMC Core Committee recommendations in a closed session. The independent physician with expertise in RA will serve as primary SMC (Core Committee and Advisory Team) Chair and facilitator. The independent physician with expertise in CAR T therapy will serve as backup Chair in the event the primary Chair is unavailable for a given SMC (Core Committee and Advisory Team) review session. The SMC Core Committee Chair will be responsible for filling out the SMC Core Committee Recommendation Form (Appendix A) and providing to Medpace to circulate for signature. To minimize potential bias and ensure safety of subjects, the voting members of the SMC Core Committee will not have financial, professional, or other potential conflicts of interest in the success or failure of SBT777101.

2.2 SMC Advisory Team

The SMC Advisory Team will provide data to the independent SMC Core Committee in open session. The Advisory Team will consist of:

- Study Principal Investigators (PIs) or designee with dosed subjects being evaluated during an SMC Review
- Sonoma Medical Monitor(s)
- Medpace Medical Monitor(s)
- Additional PIs or Sub-Investigators may be included as non-voting advisors to the SMC.

Minimum attendees for a SMC review meeting include at least two SMC Core Committee Members, Sonoma Medical Monitor(s) and Medpace Medical Monitor(s).

3 SMC RESPONSIBILITIES

SMC Core Committee member responsibilities include the following:

- Review and approve the SMC Charter via the SMC Charter Signature Page (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:
    - All safety data provided to the SMC.
    - The SMC Recommendation Form (see Appendix A).
- Convene regularly during the study to review clinical study data and assess the benefit/risk profile of SBT777101. In addition, the SMC Core Committee will convene on an ad hoc basis when a dose-limiting toxicity (DLT) has occurred in at least one subject, when a study stopping criterium has been met, or when either the Sponsor, an investigator, or another entity (i.e., FDA, IRB, etc.) requests a meeting.
- 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, interruption, or discontinuation, including full study termination.

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

All study PIs are expected to acknowledge their understanding of, and non-voting role on, the SMC by reviewing the SMC Charter, filling out and signing the Charter Signature Page (see Appendix B), and filing a copy of the SMC Charter and a complete Signature Page in their site files.

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.

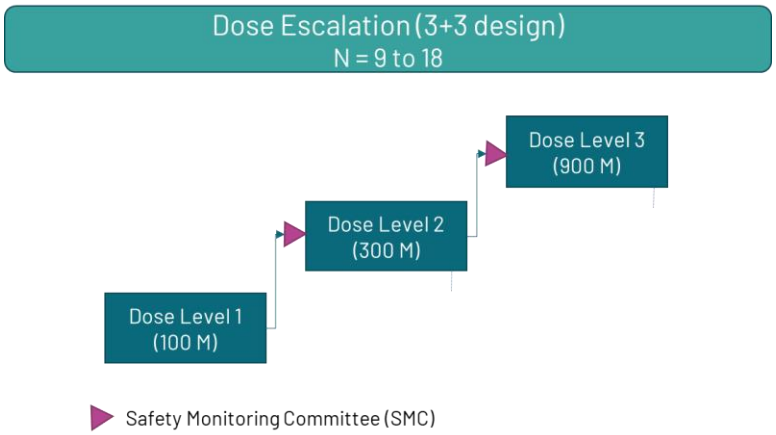
4.1 Overall Study Design

Eligible trial subjects will undergo apheresis and SBT777101 (the IP) will be manufactured for each subject (autologous cell therapy). Each subject will receive a single dose of the IP on Day 1, after which subject safety will be followed for approximately 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, and the SMC has reviewed all relevant data, when applicable. 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:



M = millions of CAR^{+} Treg cells

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; not exceeding 24) 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 Core Committee 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.

Alternatively, the SMC Core Committee may recommend that dose escalation may be delayed, paused, or modified as deemed appropriate.

5 SMC (CORE COMMITTEE) RECOMMENDATIONS

The SMC (Core Committee and Advisory Team) will convene approximately 4 weeks after the first (sentinel) subject has been dosed in each dose escalation cohort and must convene upon completion of a dose escalation cohort. It will also convene on an ad hoc basis if a DLT occurs, a stopping rule is met, or there are any other reasons to meet. The SMC Core Committee will provide recommendations on study conduct (i.e., escalate dose to the next planned cohort, cease dose escalation, additional dose levels, cease dosing, etc.) in writing (SMC Recommendation Form, see Appendix A) to the Sonoma Medical Director to serve as formal documentation for their recommendation (refer to section 6.2.3).

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 Core Committee and Advisory Team 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 Core Committee will recommend whether dose escalation should proceed. The SMC Core Committee 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 Core Committee and Advisory Team with materials in advance. The materials will include a summary of the safety data 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 meeting, a packet of safety data will be provided to the SMC Core Committee and Advisory Team members. The process for exporting the best available data will be described in section 6.1.2.

6.1.1.1 Minimum Required Data

The SMC Core Committee and Advisory Team members will be provided with a data packet containing the most recent 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
- Abnormal and clinically significant physical exam findings

6.1.1.2 Additional/Supplemental Data

Additional data will be provided to the SMC Core Committee and Advisory Team members as available and when deemed clinically meaningful. The determination of providing such additional data will be made by the Sponsor and/or Medpace Medical Monitors and will be based upon actual clinical scenarios and/or laboratory findings.

6.1.2 SMC Data Format and Exports

The data provided to the SMC Core Committee and Advisory Team members for review will be provided, at minimum, in the following formats:

- Patient profiles
- Summary of key findings

- Appropriate Tables and Listings

Medpace will generate raw data listings and patient profiles consisting of cumulative data for all enrolled subjects as of the requested data cut-off date. The study medical monitor(s) will review the raw data listings and patient profiles and generate a summary of findings for the SMC. The SMC Core Committee and Advisory Team members will receive the summary of key findings, patient profiles, and raw data listings for review.

6.2 Meeting Facilitation

The SMC Core Committee and Advisory Team members will convene to assess subject status and safety data. The assessments will take place via scheduled teleconference to the extent possible.

6.2.1 Offline SMC Assessment

The independent SMC Core Committee's assessment may be documented offline, except in the following circumstances:

- Review of each sentinel subject and fully enrolled cohorts.
- 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.

If any of the above circumstances are met, at least two of the SMC Core Committee members must attend the SMC Core Committee review, with the RA physician serving as SMC Core Committee Chair and facilitator.

When convening offline, Medpace will provide the materials to the SMC members (Core Committee and Advisory Team) via encrypted email, SharePoint, or other secure online communication platform. SMC members (Core Committee and Advisory Team) are expected to review and provide their assessment to the SMC Core Committee Chair via email within five business days of receipt. The SMC Core Committee Chair will fill out the SMC Recommendation Form (see Appendix A) and return the form to the Medpace PC within one business day of receiving the assessment from all members of the SMC Core Committee. The Medpace PC will file the Form to the study TMF. The SMC Core Committee Chair will be responsible for calling a formal meeting if, in their opinion or the opinion of any SMC Core Committee member, one of the above listed criteria are met. The SMC Core Committee Recommendation Form will then be filled out at the formal SMC meeting. Documentation of all SMC-related discussions (Core Committee and Advisory Team) 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 (Core Committee and Advisory Team) meeting is to be scheduled, the Medpace CTM or PC will schedule the 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 Core Committee Chair will complete and sign the SMC Core Committee Recommendation Form for each closed session of the independent SMC Core Committee (see Appendix A) and share the document with the Medpace CTM and/or PC.
- The Medpace CTM and/or PC will forward the signed form to all members of the SMC and to Sonoma.
- This Form will be reviewed by Sonoma Medical Director, and, at their discretion, it will be forwarded to the 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 (Core Committee) Recommendation Form in the TMF. Ultimately, the final decision regarding whether to accept the recommendations of the SMC rests with Sonoma Biotherapeutics.

7 APPENDIX A: SMC (CORE COMMITTEE) 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 Core Committee has reviewed the accumulated data for the Sonoma Biotherapeutics SBT777101-01 trial and makes the following recommendations:

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
- ☐ Clinical trials

Name: _____

Affiliation: _____

By signing below, I certify that I have reviewed the SMC Charter V3.0 dated 26-Jun-2024 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.

_____ _____

Signature Date (dd-MMM-yyyy)