STUDY OPERATIONS MANUAL

SONOMA BIOTHERAPEUTICS

PROTOCOL ID
SBT777101-01

DATE
22-Jan-2024

VERSION
V 2.0

VERSION HISTORY

VERSION DATE	VERSION NUMBER	SUMMARY
28-Aug-2023	V 0.1	Initial draft
03-Nov-2023	V 1.0	Final V1.0
22-Jan-2024	V 2.0	Revised section 2.3 to reflect Sonoma as the sole recipient of the Subject Eligibility Form. Added section 4.1.1 "Screen Failures" to direct sites to the eCRF completion guidelines on how to enter data for screen failed subjects. Revised section 5.2 to note that DLTs must be reported within 24 hours. Revised section 5.4 to refer sites to the SMC Charter for full details on the SMC. Minor formatting changes throughout.

CONTENTS

INTRODUCTION

Medpace will be assisting Sonoma Biotherapeutics with managing the SBT777101-01 study. The study will be managed according to Medpace Standard Operating Procedures (SOPs).

The purpose of this Study Operations Manual is to:

- Provide clarity and guidance for operational and logistical aspects associated with this protocol.
- Ensure protocol adherence.
- The Study Operations Manual may be updated and/or revised as needed. The most recent approved version will take precedence over any previous version(s).
- The guidance within this manual does not replace an understanding of or adherence to the requirements contained in the approved Protocol, Investigator Brochure, applicable regulations, local and institutional (site) guidelines and requirements, or Standard Operation Procedures (SOPs) governing this study.

1 COMMUNICATION

All communication regarding this study should be routed to the appropriate contacts listed in the table below. For detailed contact information, please refer to the Project Team List.

COMMUNICATION PATH	
Primary contacts for all study and protocol related issues	Sonoma Clinical Operations Lead with your Medpace CRA in CC
Secondary contact for all protocol related issues if your CRA or Sonoma is not available	Medpace Clinical Trial Manger (CTM) & Sonoma Clinical Operations email
Primary contacts for lab supply related issues	Your Medpace CRA with Sonoma Clinical Operations Lead in CC

IMPORTANT STUDY EMAILS	
Sonoma Clinical Operations	ClinicalOperations@Sonomabio.com
Sonoma Patient Operations	PatientOps@Sonomabio.com

2 PRE-SCREENING / PATIENT ELIGIBILITY PROCESS

2.1 Pre-screening and Cohort Slot Requests

Prior to the signing of informed consent, when a site has identified a possible candidate for the study, please use the following steps to request a screening slot:

Important: Do not screen any subjects until you receive written confirmation from a representative of Sonoma!

1. Fill out a SBT777101-01 Pre-Screening Slot Request Form. The Slot Request Form will require you to fill out information regarding the potential patient, including (but may not be limited to):
    - Site information, including PI, Site Name and Site #

- General background questions on the potential subject, including YOB, date of RA diagnosis (as known), any previous screening history (for this study) and a review of current RA medications (if known).
- Planned or projected dates for the screening (consenting) visit as well as biopsy visit. The biopsy collection visit should be planned for no later than 7-10 days from date of screening.

  Note – changes to the planned/projected dates should be communicated to Sonoma Clinical Operations in a timely manner after the form has been submitted and/or approved. Planning for downstream activities such as apheresis, slot assignment and dosing are contingent upon the screening and biopsy dates with results.

2. Please send the Pre-Screening Slot Request Form to the Sonoma team at ClinicalOperations@Sonomabio.com for review. When possible, please submit the Pre-Screening Slot Request Form at least 7 days in advance of the consenting visit in to allow as much time for the coordination of downstream activities.

3. Once the form is received, Sonoma Clinical Operations will initiate communications between the Research Coordinator, Sonoma Patient Operations, and the site's Apheresis Clinic to schedule a hold date for apheresis collection.

   3.1 Please note – Scheduling apheresis collection is a site driven process and will require coordination between the Site Research Coordinator and Apheresis Clinic, with input for cell manufacturing availability and protocol windows from Sonoma Patient & Clinical Operations. Sonoma Clinical Operations will assist, as requested/needed.

4. The Pre-Screening Slot Request Form will be returned to you by Sonoma Clinical Operations. After receiving the returned form, please bring the subject in for their screening/consenting visit. Once returned to the site the Pre-Screening Form will contain key pieces of information:

   4.1 The Subject ID assignment

   4.2 The hold (planned) date for the subject's apheresis collection with agreement between the clinical site and Sonoma. Should this date change due to any reason, please communicate with ClinicalOperations@Sonomabio.com to update the team with your CRA in copy.

2.2 Screening Visit(s)

5. Please reference the protocol Schedule of Assessments for all screening assessments + protocol section 7.3 for the preferred order of assessments during screening (and subsequent) visits.

6. Once screening assessments are complete, and the subject is ready for eligibility review, proceed to section 2.2 (below).

2.3 Subject Eligibility Form

Each subject will need a fully completed and signed Subject Eligibility Form to be considered eligible for IP dosing. Please plan for sufficient time for submission and review of the Eligibility Form, as review and approval for each part of the eligibility will take approximately 24-72 hours. Part 1 of the eligibility form will take the longest time to complete and review, with supplemental (redacted) source documentation per below.

- The eligibility form has three parts:
  - Pre-biopsy
  - Pre-apheresis, and
  - Pre-infusion
- Subjects cannot move into the pre-apheresis or pre-infusion phases unless the previous part(s) have been fully completed, sent for review, and signed by the site's PI and a representative from Sonoma Biotherapeutics.

- The subject will not be fully eligible for IP infusion unless all three parts of the eligibility form are completed and signed.

The Subject Eligibility Form needs to be returned to ClinicalOperations@Sonomabio.com only.

The following documents should be sent alongside the eligibility form when submitting Part 1 of the form:

- A copy of the subject's labs with **all** patient-identifying health information redacted.
- A completed copy of the 28SJC_28TJC Source Form + DAS28 online calculator form (for the DAS28 online calculator instructions, refer to section 2.2.1 below)
- A redacted copy of the ECG results during screening
- Redacted copies of pertinent medical history (12 month prior to consent)
- Redacted copies of historical and concomitant medications for
    - All known RA treatments
    - All other medications 30 days prior to consent

When Submitting Parts 2 & 3 of the Subject Eligibility Form, please submit redacted source documentation to ClinicalOperations@Sonomabio.com for any/all applicable changes to the subject's treatment and medical history, including (but not limited to):

- Any new lab results with **all** patient-identifying health information redacted.
- Redacted copies of pertinent medical history
- Redacted copies of concomitant medications

2.3.1 DAS28 Calculation Process

The DAS28-CRP is calculated online via: https://www.4s-dawn.com/DAS28/

To complete this form, follow the instructions on the page to select the patient's current tender joints and swollen joints based on the provided DAS28 worksheet completed by the PI who performs the assessment. The calculator will also ask for the Patient Global Health Score – this is synonymous with the Patient Global Assessment of Arthritis measure on the Visual Analog Scale (VAS; Section 2.2.2).

Once this form is complete, please attach a printout of this to the subject's eligibility worksheet. This printout is considered the subject's source data and the score will also need to be entered into the EDC by site staff.

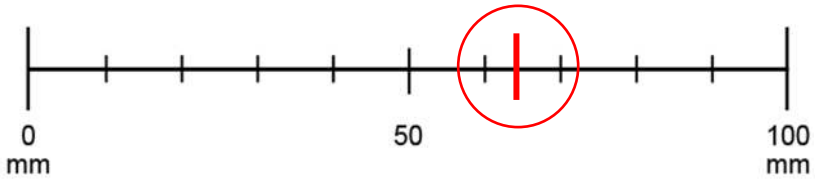
To retrieve a printout of the calculator, you can either take a screen capture of the page (Windows: Windows + Shift + S; Mac: Command + Shift + 4) or use the "print to PDF" function on the webpage.

- To print the screen to a PDF, you will need to view the advanced print settings and select the option to include background graphics for the image to transfer properly.

2.3.2 Visual Analog Scale (VAS)

The VAS contains three measures – the Patient's Global Assessment of Arthritis, the Patient's Assessment of Arthritis Pain, and the Physician's Global Assessment of Arthritis.

For both patient measures, the patient should be instructed to draw a single, solid, straight line perpendicular to the scaled line to indicate their response to the question. An example of an ideal line for this scale is as follows:



The physician should then repeat this exact process for the physician measure.

Please use the clear ruler provided in your site's Welcome Pack *every time* you measure this line to maintain consistency across study sites and users. Then record the measured VAS score on the blank space corresponding to that VAS question. Each VAS score should be in the range of 0-100 and should not contain any decimals.

The VAS is also utilized in calculating the DAS28 using the online calculator. Please note that "Patient Global Health" on the calculator is synonymous with "Patient Global Assessment of Arthritis" utilized in this study.

2.4 Screening Synovial Biopsy Collection

As part of the eligibility process, each subject will need to undergo a synovial biopsy during the screening period. To help minimize risk to the subject it is recommended that Part 1 of the Subject Eligibility Form be submitted in advance of the biopsy collection. The biopsy visit should be planned for no later than 7-10 days from date of screening.

Please refer to the SBT777101 Synovial Biopsy Manual for collection, processing, and shipping requirements.

3 MEDICATION GUIDANCE

Each part of the screening (initial screening, apheresis and prior to IP administration) will require a subject to experience a washout period for specific medications related to the treatment of RA. Any current medications should be kept at stable doses from 30 days prior to screening. Of note, any subjects with prior cell or gene therapy treatment are excluded from study participation.

Please refer to protocol section 5 for full guidance on concomitant therapy during the course of the study, including:

- Refer to Section 5.2.2 and Table 3 of the protocol for a list of prohibited medications.
- Refer to protocol Section 5.2 for guidelines on concomitant medications for the treatment of RA.
- Refer to protocol Section 5.2.4 and Table 5 for guidance on rescue therapies for subjects on study.

Please contact the Medical Monitor with your CRA and Sonoma Clinical Operations ClinicalOperations@Sonomabio.com in copy for any questions as it relates to management of concomitant medications, including medications for RA and rescue therapy/therapies.

4 SITE OPERATIONS

4.1 Pre-Apheresis Eligibility

Before apheresis occurs, the site should ensure the following requirements have been met:

- Biopsy results are available, and Sonoma has approved the subject for eligibility (Eligibility Part 1).
- Ensure the expected washout duration of any medication prohibited before and/or during apheresis has been met. Refer to protocol Section 5.2.2, Table 3.
- Complete and submit Part 2 of the Subject Eligibility Form:

- Part 2 of the Subject Eligibility Form must be sent to ClinicalOperations@Sonomabio.com for review and approval prior to initiation of apheresis to confirm changes in medical history and concomitant medication(s).

  Note – Please plan for sufficient time for submission and review of the Eligibility Form, as review and approval of eligibility for part 2 will take approximately 24-72 hours.

- Receive the reviewed, signed and completed (Part 2) Subject Eligibility Form from Sonoma. After receiving Part 2 of the form from Sonoma, the subject is officially enrolled in the study.
- Sonoma Biotherapeutics Patient Operations (PatientOps@sonomabio.com) will initiate a Subject Record Form in advance of the collection. The Subject Record Form will collect baseline information about your site and the subject and should be limited between the site and Sonoma Patient Operations during communications.

  Note - Please do not share the Subject Record Form with Sonoma Clinical Operations, as the form will contain PHI. For an example of the Subject Record Form, please refer the Sonoma Apheresis Collection Protocol.

4.1.1 Screen Failures

4.2 In the event of participant screen failure, please refer to the CCG guidelines for further instructions on how to proceed. Apheresis Collection

Apheresis collection will be completed by the affiliated apheresis unit for each clinical site. For complete guidelines on collection, processing and shipment of specimen by apheresis team personnel, please refer the Sonoma Apheresis Collection Protocol.

4.3 Infusion Scheduling

Scheduling the date of infusion is a site driven process between the Clinical Research Coordinator and the Cell Therapy Unit, with input from Sonoma Patient and Clinical Operations accounting for manufacturing release and protocol windows. Once apheresis collection has been completed, please plan for approximately 6-7 weeks (~42-45 days) until IP availability.

Please confirm with Sonoma Biotherapeutics Patient Operations (patientops@sonomabio.com) confirming availability of IP release and delivery dates align with targeted date for IP infusion. Please ensure your CRA and ClinicalOperations@Sonomabio.com are in copy of communications.

4.4 Pre-Infusion Eligibility

Before IP Infusion occurs, the site must ensure the following requirements have been met and documented appropriately:

- Bring the subject in/complete the pre-infusion visit: Subject eligibility must be reconfirmed between study Days -10 and -4 to confirm that it is safe and appropriate for the subject to receive the study drug.
- Prior to IP Infusion, ensure the subject has fully completed the expected washout duration of any medication prohibited before and/or during IP administration. Refer to protocol Section 5.2.2, Table 3.
- Ensure the Subject Eligibility Form is fully completed (Parts 1, 2, and 3), and signed by both site and Sonoma personnel.

  Note – Please plan for sufficient time for submission and review of the form, as review and approval of eligibility for part 3 will take approximately 24-72 hours.

4.5 Day of Infusion

4.5.1 Pre-Infusion

Pre-Infusion activities and assessments are managed by cell therapy and/or clinical research personnel, depending on delegation. The following coordination of efforts and evaluations should be performed prior to IP administration:

- Please confirm with your cell therapy unit that IP has been received in accordance with the SBT777101 IP Manual and is available for infusion.
- Please ensure that all medication washout requirements have been met prior to dosing. Refer to Protocol Section 5.2.2 Table 3.
- Baseline evaluations and assessments: Refer to the protocol Schedule of Assessments for all assessments to complete on Study Day 1. On Day 1, all assessments should be performed prior to dosing, unless otherwise specified.

  Note: other safety laboratory evaluations (e.g., clinical chemistry, hematology, urinalysis, coagulation, etc.) are not required, but should be repeated if a clinically meaningful change to the subject's history since the most recent evaluations (i.e., Pre-Infusion Day -10 to -4) are suspected or confirmed.

Upon completion of all pre-dose assessments and evaluations, refer to section 4.2 of the SBT777101 IP Manual for pre-medication guidance.

Note - Do not open the LN2 shipper until the time of thaw, following subject eligibility confirmation and pre-medication administration, and just prior to the administration of SBT777101 to the subject.

Refer to Section 4.3 of the SBT777101 IP Manual for Day of Infusion Criteria.

4.5.2 IP Preparation and Administration

IP Preparation and Administration is managed by your site's clinical cell therapy clinic personnel. Refer to Section 4.4 of the SBT777101 IP Manual for Investigational Product Handling and Preparation instructions.

Ensure the IP is thawed and prepared according to the instructions listed in section 4.5 of the IP Manual. Once fully thawed, SBT777101 infusion must be completed within 3 hours.

Once the IP is prepared and transported to the patient's bedside, IP administration begins. Vital signs must be measured within 60 minutes prior to infusion (within 15 minutes is preferred), then at least every 15 minutes during the infusion. For further instructions, please refer to the Schedule of Assessments in the protocol.

4.5.3 24-Hours Post-Infusion

All subjects will be directly and continuously monitored in an inpatient setting for the first 24-hours post-IV administration of SBT777101. Subjects will undergo constant cardiopulmonary monitoring post receipt of study drug. For further instructions regarding post-infusion patient monitoring, please refer to the Protocol and Protocol Schedule of Assessments.

4.5.4 Preferred Order of Study Assessments

Please refer to section 7.3 of the protocol for the preferred order of assessments.

4.5.5 Patient Temperature Diaries

Subjects are required to measure and record their temperatures in the patient diary at least once daily. Sites are required to review patient diaries at each visit. There are a total of 12 Patient Temperature Diaries per patient.

Please note that each visit comes with a numbered range of days this visit could occur (on SOA, e.g., ± 2 days), so these diary days overlap to accommodate those who may attend a visit at the very beginning or tail end of this window. The distribution and collection schedule of the patient temperature diaries is as follows:

WEEKS COVERED	DAYS COVERED	DISTRIBUTED AT:	COLLECTED AT:
1	1-8	Study Day 2 Visit	Study Week 1 Visit
2	8-16	Study Week 1 Visit	Study Week 2 Visit
3	15-23	Study Week 2 Visit	Study Week 3 Visit
4	22-30	Study Week 3 Visit	Study Week 4 Visit
5-6	29-44	Study Week 4 Visit	Study Week 6 Visit
7-8	43-63	Study Week 6 Visit	Study Week 8 Visit
9-10	49-72	Study Week 8 Visit	Study Week 10 Visit
11-12	71-86	Study Week 10 Visit	Study Week 12 Visit
13-18	85-133	Study Week 12 Visit	Study Week 18 Visit
19-24	119-175	Study Week 18 Visit	Study Week 24 Visit
25-36	162-260	Study Week 24 Visit	Study Week 36 Visit
37-48	245-343	Study Week 36 Visit	Study Week 48 Visit

The patient daily temperatures are not recorded in EDC but instead are evaluated for AEs and other safety concerns and filed into source for CRA review.

5 SAFETY

5.1 AE/SAE Reporting

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostic reports) related to the event. For further information, please see Appendix E in the Protocol.

Safety Contact Information:

Medpace Clinical Safety SAE Reporting Line – US

Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3

Fax: +1-866-336-5320 or +1-513-570-5196

Email: Medpace-safetynotification@medpace.com

5.2 Site Reporting Responsibilities

- Document all AEs, SAEs, and pregnancies in the subject's source.
- Ensure the Investigator documents the causality assessment for each AE or SAE.
- Report SAEs immediately (within 24 hours) upon awareness.
- Report DLTs immediately (within 24 hours) upon awareness.
- Enter AEs into EDC within 5 business days.
- Report subject pregnancy immediately (within 24 hours) upon awareness to Medpace Clinical Safety and complete Exposure in Utero Form.
- Promptly respond to queries from Medpace Clinical Safety and provide additional or follow-up information, clarification, or supporting medical/hospital records with PII redacted.

5.3 Cell Therapy Risk Mitigations

Subjects will be assessed clinically for adverse events during the conduct of this study using the CTCAE Grading Scale (Appendix E in the Protocol).

CRS and neurotoxicity adverse events will be assessed using the American Society for Transplantation and Cellular Therapy (ASTCT) grading scales (Appendix F and Appendix G in the Protocol).

5.4 Safety Monitoring Committee (SMC)

The SMC is convened to provide routine review of the safety profile of SBT777101 and provide recommendations for dose escalation and ongoing study conduct. Refer to the SMC Charter for full details regarding the SMC.

The current SMC Charter and Member Signature Page will be provided in your site's welcome pack. Upon receipt, the PI should review the SMC Charter and sign the SMC Member Signature Page. Please scan the signed Signature Page to your CRA and Sonoma Clinical Operations. File the original in your site's ISF.