BeiGene

Clinical Study Pharmacy Manual

Sponsor: BeiGene, Ltd.

Protocol: BGB-11417-301

Protocol Title: A Phase 3, Open-Label, Randomized Study of BGB-11417 (Sonrotoclax) Plus Zanubrutinib (BGB3111) Compared With Venetoclax Plus Obinutuzumab in Patients With Previously Untreated Chronic Lymphocytic Leukemia

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1. Introduction

1.1 Purpose of the Pharmacy Manual

The purpose of the Pharmacy Manual is to provide clear guidance on the receipt, storage, dispensing, destruction/return, and accountability of Investigational Product (IP) and drug-related supplies.

International Conference on Harmonization (ICH) Guidelines for Good Clinical Practices (GCP), U.S. Code of Federal Regulations Part 21, and all applicable local regulations will be followed during all study-related activities. All activities must be performed by qualified site personnel in accordance with the protocol, and all applicable amendments.

This document intends to ensure the Investigational Product is handled, stored, and dispensed within safety and efficacy parameters to the highest standard.

1.2 Roles and Responsibilities

1.2.1 Study Sponsor

BeiGene, Ltd. is the Sponsor of the clinical research trial. BeiGene, Ltd. is responsible for IP packaging, labeling, shipping, recall and authorization for use.

1.2.2 IP Distributor

The distributor in each country or region is different, however, has the same responsibility of receiving Investigational Product (IP), and managing IP labeling, shipment, storage, return and destruction. Depots are listed in the below table;

Table 1: Depot Names and Contacts

Country	Depot	Address and contact information
Australia and New Zealand	Zuellig Pharma SSG Australia Pty Ltd	**IP distribution:** 15 Lum Street, Export Park Adelaide Airport, South Australia 5950 Durnan,Tarsh Phone: +61 8 8150 0004 Tarsh.Durnan@zuelligpharma.com Huynh, Nga Phone: +61 8 8150 0020 nga.huynh@zuelligpharma.com

		IP orders/Shipments: Orders.ZPAU@zuelligpharma.com **IP return orders:** 15 Lum Street, Export Park Adelaide Airport, South Australia 5950 returns.zpau@zuelligpharma.com
USA/Canada	Fisher Clinical Services Inc.	**IP distribution:** 699 N. Wheeling Road, Mount Prospect, IL 60056, United States Matthew Mara Client Services Project Manager II Phone: 847-768-8120 matthew.mara@thermofisher.com **IP orders/Shipments:** Distribution.MountProspect@thermofisher.com **IP return orders:** Returns Center-Fisher Allentown Fisher Clinical Services, Attn: Return Operations 700B Nestle Way Breinigsville, PA 18031 ReturnDrug@thermofisher.com Phone: 484-538-2125 / 484-538-2161 Returns 3RD Party Depot in Canada McKesson Specialist Distribution 8449 Lawon Road, Unit 102, Milton, Ontario, L9T 9L1 Canada Tanya +1 905 827 1300 x 1103 Tanya.Guite@McKesson.ca cdpharma@ropack.com
Europe	Catalent Germany Schorndorf GmbH Catalent Pharma Solutions	**IP distribution:** Steinbeisstr. 1-2 73614 Schorndorf, Germany Nico Malerba Clinical Project Manager nico.malerba@catalent.com T +49 7181-7000- 283

		IP orders/Shipments: Schorndorf.DistributionRequests@catalent.com **IP return orders:** Catalent Germany Schorndorf GmbH Catalent Pharma Solutions Steinbeisstr. 1-2 73614 Schorndorf, Germany G-PS-SCH-CSSReturn@catalent.com For Italy site's expired drugs, use 3rd party depot in Italy. Alloga (Italia) srl Corso Stati Uniti 9/A 35127 Padova Italy resi@alloga.it Phone: +39 0498 700 344
United Kingdom	CATALENT CTS(EDINBURGH) LIMITED INCHWOOD	**IP distribution:** BATHGATE WEST LOTHIAN EH48 2EH UNITED KINGDOM PM: Callaghan, Connor Connor.callaghan@catalent.com **IP orders/Shipments:** Bathgate.DistributionRequests@catalent.com **IP return orders:** FOR UK RETURNS ONLY CATALENT CTS(EDINBURGH) LIMITED INCHWOOD BATHGATE WEST LOTHIAN EH48 2EH UNITED KINGDOM GMB-DC-GBL-BTHReturnsDept@catalent.com

Turkey	SMO GROUP TURKEY	**IP distribution:** Izmir Ataturk Organized Industrial Zone, 10053 str., No: 7/1, 35620, Cigli – Izmir, Turkey Canberk Isler Project Specialist, Turkey T: mob. +905447426771 tel. +902323980900 fax +902323283534 E: canberk.isler@smo-group.com **IP orders/Shipments:** depot-tr@smo-group.com **IP return orders:** SMO GROUP TURKEY Izmir Ataturk Organized Industrial Zone, 10053 str., No: 7, 35620, Cigli – Izmir, Turkey depot-tr@smo-group.com
South East Asia	FISHER CLINICAL SERVICES PTE.LTD.	**IP distribution:** 10 TOH GUAN ROAD #03-11/12 SINGAPORE 608838 Lim Chun Hwee (Ms) 林俊慧 Project Manager DID: +65 6807 0716 Fax: +65 6873 0862 chunhwee.lim@thermofisher.com Kristen Loo Project Coordinator Office (DID): +65 6807 0712 Email address: kristen.loo@thermofisher.com **IP orders/Shipments:** Distribution.Singapore@thermofisher.com **IP return orders:** IMP Drug Return Team Fisher Clinical Services Pte Ltd

		10 Toh Guan Road, #03-11/12, Singapore 608838 returns.singapore@thermofisher.com For Taiwan returns, please return to Taiwan LFS third-party depot. IMP Drug Return Team Logical Freight Solutions (LFS) 12F-3, No.176, Jian 1st Road, Zhonghe District, New Taipei City, Taiwan 235 Chunhwee.lim@thermofisher.com; Joanna.Koh@thermofisher.com; Kristen.Loo@thermofisher.com; FisherTw@mnx.com
Japan	Catalent Shiga K.K	**IP distribution:** 35 Hinokigaoka Minakuci-cho, Koga-city, Shiga, Japan 528-0068 Jiahui Ng Project Manager Phone: +81 537 29 1131 Fax: +81 537 29 1455 Email: JiaHui Ng JiaHui.NG@catalent.com Ai Asai Project Coordinator T (+81) 748-63-3300 | M (+81) 80-2397-1063 | F (+81) 748-63-3388 Asai, Ai Ai.Asai@catalent.com **IP orders/Shipments:** shiga.distributionrequests@catalent.com **IP return orders:** Catalent Shiga K.K 35 Hinokigaoka Minakuci-cho, Koga-city, Shiga, Japan 528-0068 Japan.ReturnRequests@catalent.com

China	Catalent Pharmaceutical Technology (Shanghai) Co.	**IP distribution:** Unit 4101/4202, 4# Building, No. 933 Shangfeng Road, Pudong New District, Shanghai 201201, China Timber Guan Project Manager Timber.Guan@catalent.com +86 18851127518 +86 21 5083 0607 **IP orders/Shipments:** Shanghai02.DistributionRequests@catalent.com **IP return orders:** Catalent Pharma Solutions 4# Building No.955 Shangfeng Road, Tangzhen, Pudong District, Shanghai, 201201, China Shanghai.ReturnRequests@catalent.com
Brazil	Marken Brazil Depot (Marken BRA)	**IP distribution:** Av. Vereador João de Luca, 1810 Jd. Prudência - São Paulo/SP Brazil - CEP: 04381-001 Lead PM (Daily contact) Max Qian | Project Manager Mobile +86 138 1108 3515 max.qian@marken.com (Depot Contact) Tatiana Romano TEL:+55 1156 704 901 tatiana.romano@marken.com **IP orders/Shipments:** CTDrequestsBRA@marken.com

		IP return orders: Av. Vereador João de Luca, 1810 Jd. Prudência - São Paulo/SP Brazil - CEP: 04381-001 CTDreturnsBRA@marken.com
Israel	Oximio-IL LTD.	**IP distribution:** 6 Bareket Street Industrial Park North Caesarea 3079863 Israel project.team@oximio.com **IP orders/Shipments:** Depot-il@oximio.com **IP return orders:** 6 Bareket Street Industrial Park North Caesarea 3079863 Israel Depot-il@oximio.com

1.2.3 Clinical Research Associate

The Clinical Research Associate (CRA) is responsible for training all site personnel that are delegated by the Principal Investigator the responsibility of handling IP and all pharmacy and study-related activities during the Site Initiation Visit. The CRA will monitor IP as described in the current Study Monitoring Plan and activities will include but are not limited to;

- review of temperature logs and storage conditions as per protocol
- review of shipping and receipt/return records,
- review of IP subject dispensing logs, IP inventory log
- confirmation of treatment compliance as per protocol during each routine monitoring visit

IP reconciliation is required to be completed by the CRA prior to any IP destruction during the study and at the close-out visit. The CRA will be responsible for arranging the supply of additional IP only in exceptional circumstances. For example, insufficient IP at the site due to higher than expected enrollment rate.

1.2.4 BeiGene Clinical Operations Manager or Designee

The BeiGene Clinical Operations Manager or designee is responsible for authorization of initial IP shipment by completing the Essential Documents (ESD) Checklist (VV-QDOC-00233; as outlined in *VV-QDOC-00234, Section 5.3.4*) located in the Pharmacy Binder and manual IP shipments if required. The Clinical Operations Manager or designee is responsible for activating the site in the IRT system.

1.2.5 Principal Investigator(s)

The Principal Investigator at each investigational site is responsible for ensuring all study procedures are conducted in accordance with the current protocol by delegating study IP related tasks to appropriately qualified, experienced and trained site personnel and according to all applicable local regulations. The Principal Investigator is ultimately responsible for the oversight and conduct of all study-related tasks, including IP management at his/her specific investigational site.

1.2.6 Study Pharmacist or Designee

For this study, the Pharmacist or designee that has been delegated the responsibility by the Principal Investigator will be responsible for managing IP at the investigational site. These tasks include, but are not limited to, receipt, storage, dispensing, accountability, disposition and return of IP.

Site personnel must be appropriately trained in the conduct of clinical studies prior to performing IP receipt and inventory, storage, dispensing, accountability and record keeping.

2. Investigational Product Instructions, Presentation, Preparation and Dispensation

2.2 BGB-11417 - Sonrotoclax Film-Coated Tablets

Sonrotoclax is formulated as film-coated, immediate-release tablets of 1, 5, 20, and 80 mg for oral administration.

Sonrotoclax is packaged in a child-resistant, high-density polyethylene bottle with a desiccant, induction seal and bottle label.

The contents of the label will be in accordance with all applicable local regulatory requirements.

The drug product is stored per the clinical label. The storage condition is supported by stability data conducted on the drug product.

Refer to Sonrotoclax Investigator's Brochure for details regarding administration, accountability, storage, and disposal.

2.2.1 Physical Description

Sonrotoclax drug products are supplied as film-coated, immediate-release tablets of 1, 5, 20 and 80 mg for oral administration.

Figure 1. 1 mg tablet and size

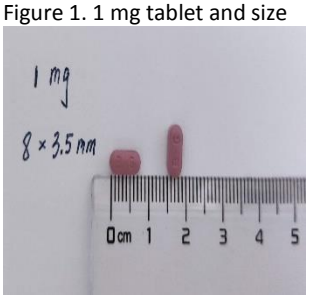


Figure 2. 5 mg tablet and size

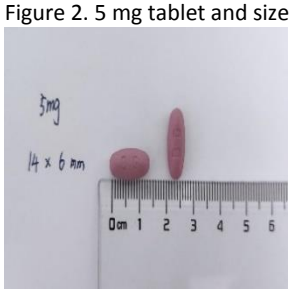


Figure 3. 20 mg tablet and size

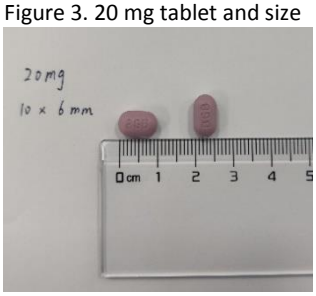
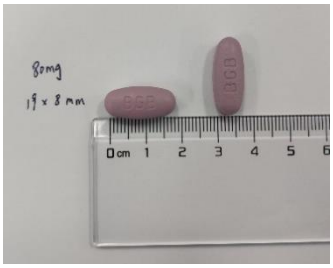


Figure 4. 80 mg tablet and size.



2.2.2 Packaging and labeling

The Sponsor will provide Sonrotoclax as film-coated tablets. The tablets will be packaged in high-density polyethylene (HDPE), white, opaque bottles. Each bottle will contain 30 tablets (1 mg, 5 mg, and 20 mg strength) or 31 tablets (80 mg strength) with desiccants. Each bottle will utilize a tamper-proof heat induction seal and a child-resistant closure. Below is the brief summarized information for the products packaging:

Packaging Configuration	**Dose Strength**			
	1 mg	**5 mg**	**20 mg**	**80 mg**
HDPE Bottle size	75cc	75cc	75cc	75cc
Tablets/bottle	30cts	30cts	30cts	31cts
Tablet coating color	Purple			

Figure 5 Example photograph of Sonrotoclax BGB-11417 demonstrating Packaging and Labelling – 1 mg

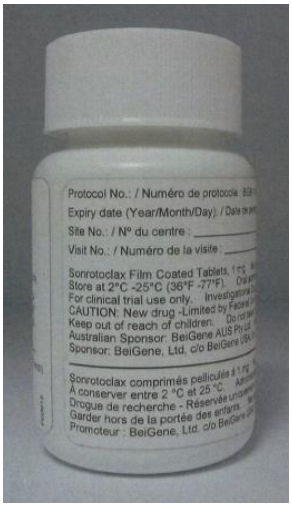


Figure 6 Example photograph of Sonrotoclax BGB-11417 demonstrating Packaging and Labelling – 5 mg

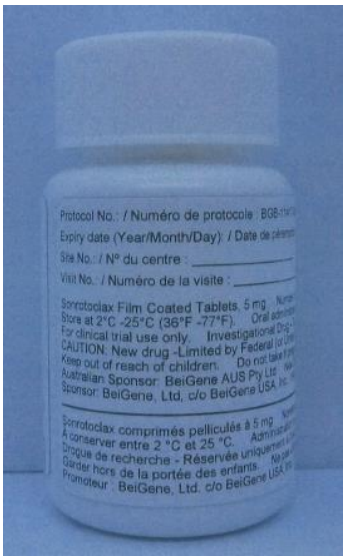


Figure 7 Example photograph of Sonrotoclax BGB-11417 demonstrating Packaging and Labelling – 20 mg

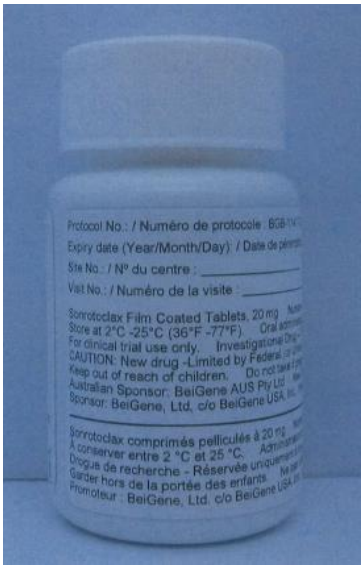
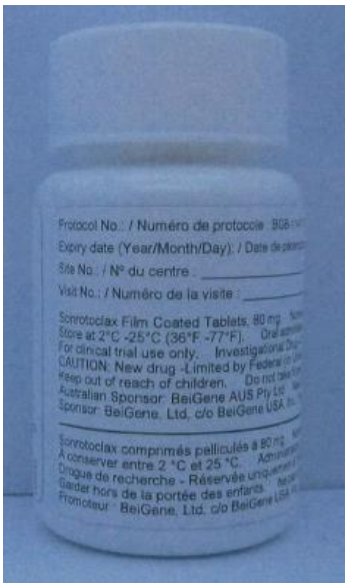


Figure 8 Example photograph of Sonrotoclax BGB-11417 demonstrating Packaging and Labelling – 80 mg



Each bottle will be identified by a manufacturing lot/batch number, will be labeled at a minimum with: Protocol ID, product name, strength and dosage, storage conditions, lot/batch number, expiry date, Sponsor name, and any other content required by local regulatory requirements.

2.2.3 Dispensing and Administration

Only qualified personnel that are trained on study procedures and that minimize undue exposure to themselves, and the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

The Pharmacist or designee should document the number of bottles and tablets dispensed using the IP Accountability Logs and IRT system (See Section 6 below). Patients should be made aware of the storage temperature requirements (See Section 3.3 below).

A Patient Diary should be provided to patients at each dispensation visit to record compliance of treatment. Patients must be instructed on how to complete the Patient Diary and also requested to bring it with them to the next visit for review or collection.

Sonrotoclax will only be administered to patients randomized to Arm A (refer to Protocol Version 0.0, Section 3.1). Sonrotoclax will be administered as a flat mg dose, rather than based on weight or body surface area. Doses for individual patients and visits will vary in this study in which individuals may be assigned to a different dose level, ramp-up schedule and/ or may require a dose reduction due to safety concerns (refer to Protocol Version 0.0, Section 5).

Depending on the assigned dose level and ramp-up schedule for a specific patient, patients may be issued more than one strength of sonrotoclax tablets.

2.2.4 Patient Dosing Instructions

The site personnel dispensing the tablets should review the dosing instructions with the patient at each visit to ensure the patient understands the dosing requirements correctly.

Sonrotoclax tablets will be administered orally, once daily (QD).

Dosing in the morning is preferred. Subjects should try to take the tablets at about the same time each day.

Tablets should be taken within 30 minutes after having a meal.

Tablets will be taken with 1 cup (approximately 240 mL) of water.

Patients should swallow the tablets whole and not chew or crush them.

If vomiting occurs after dosing, Sonrotoclax doses should not be replaced; unless all tablets come out intact within 15 mins of administration, in this case, another dose may be taken.

If a patient forgets to take Sonrotoclax for more than 8 hours, he/she should skip the dose and resume taking the drug the next day.

Patients must be asked to record their sonrotoclax daily dosing in the Sponsor-provided Patient Diary and report any missing doses or lost study drug at the next clinic visit.

Patients must be instructed to return the study drug packages that are empty, partially used or unused at each clinic visit.

Site staff should conduct a compliance check at each study visit, counting tablets if required. Patients should be questioned about any missing doses, lost drug and any discrepancies between the compliance check and the Patient Diary.

2.2.5 Dose Modifications

The dose reduction guidelines set forth in Table 2 below should be followed for hematologic (Protocol Version 0.0, Section 5.3.1.2) or non-hematologic (Protocol Version 0.0, Section 5.3.1.3) toxicities.

Dose holds and modifications during ramp-up are described in Protocol Version 0.0 Section 5.3.1.1.

If Zanubrutinib is discontinued permanently before Sonrotoclax dosing has been initiated, then no Sonrotoclax will be administered to the patient at any time during this study.

Table 2. Sonrotoclax Dose Reductions

Toxicity Occurrence	Target Dose Level	Sonrotoclax Dose upon Resumption of Dosing
First	0= target dose	Restart at 320mg
Second	-1 dose level	Restart at 160mg
Third	-2 dose level	Restart at 80mg
Fourth	Discontinue Sonrotoclax	Discontinue Sonrotoclax

2.3 BGB-3111 – Zanubrutinib Capsules

Zanubrutinib is formulated as capsule of 80 mg for oral administration. Zanubrutinib is packaged in a child resistant, high-density polyethylene bottle with induction seal and bottle label.

Zanubrutinib bottles must be stored at room temperature 15ºC to 30ºC (59°F to 86°F).

The contents of the label will be in accordance with all applicable local regulatory requirements.

Refer to Zanubrutinib Investigator's Brochure for details regarding intravenous administration, accountability, and disposal.

2.3.1 Physical Description

Zanubrutinib drug product contains BGB-3111 as the active pharmaceutical ingredient, microcrystalline cellulose as a filler, croscarmellose sodium as a disintegrant, sodium lauryl sulphate as a wetting agent, colloidal silica as a glidant, and magnesium stearate as a lubricant.

Zanubrutinib drug product is supplied as 80 mg strengths in capsules (size 0, opaque white capsules for 80 mg dose). Zanubrutinib capsules, 80 mg are white to off-white opaque hard capsules containing white to off-white powder, the product is supplied in child-resistant high-density polyethylene (HDPE) bottles with induction seals. The drug product is designed as an immediate-release dosage form.

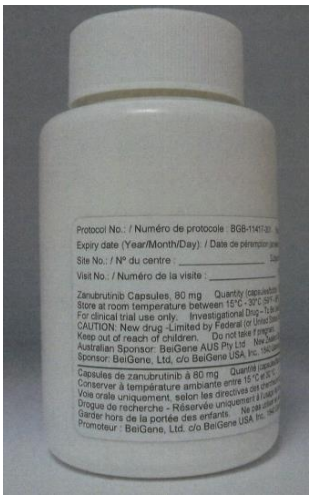
The manufacturing process includes standard pharmaceutical operations, mixing, sieving, and encapsulation.

2.3.2 Packaging and labeling

Zanubrutinib capsules, 80 mg will be supplied to the sites in 120-capsule bottles containing 80 mg capsules. Each bottle will be identified by a manufacturing lot/batch number.

Zanubrutinib/BGB-3111, supplied by BeiGene, will be labeled at a minimum with: Protocol ID, product name, strength and dosage, storage conditions, lot/batch number, expiry date, Sponsor name, and any other content required by local regulatory requirements.

Figure 9 Example photograph of BGB-3111 zanubrutinib demonstrating Packaging and Labelling



2.3.3 Dispensing and Administration

Only qualified personnel that are trained on study procedures and that minimize undue exposure to themselves, and the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

Study capsules will be dispensed for patients use in the Sponsor-provided HDPE bottles.

Zanubrutinib will only be administered to patients randomized to Arm A (refer to Protocol Version 0.0, Section 3.1).

The Zanubrutinib dose will be fixed during this study.

Patients will receive Zanubrutinib at 320 mg per day, dosed once or twice daily.

The dosing regimen must be selected by the investigator at or before the first administration of Zanubrutinib and cannot be modified for the duration of the study:

- Twice-daily Zanubrutinib should be administered as two 80 mg capsules by mouth twice a day (160 mg twice a day) with or without food unless reduced as recommended.
- Once-daily Zanubrutinib should be administered as four 80 mg capsules by mouth once a day (320 mg once a day) with or without food, unless reduced as recommended.

Dispense the appropriate number of Zanubrutinib bottles of each dosage strength required to support a patient's dosage requirements until their next visit. The Pharmacist or designee should document the number of bottles and capsules dispensed using the **IP Accountability Logs** and IRT system (See Section 6 below). Patients should be made aware of the storage temperature requirements (See Section 3.3 below). A **Patient Diary** or **Patient Diaries** should be provided to patients at each dispensation visit to record compliance of treatment.

Patients must be instructed on how to complete the **Patient Diaries** and requested to bring it with them to the next visit for review or collection.

2.3.4 Patient Dosing Instructions

The site personnel dispensing the capsules should review the dosing instructions with the patient at each visit to ensure the patient understands the dosing requirements correctly. Patients should be instructed to ensure the bottle is re-capped tightly after removing each dose.

Patients should take Zanubrutinib capsules with water at approximately the same time/s every day, with a minimum of 8 hours between consecutive doses. Zanubrutinib capsules should not be opened, broken, or chewed at any time. Zanubrutinib should be administered at the same time as Sonrotoclax, especially during the first 4 weeks of co-administration when PK sampling will occur. Sonrotoclax and Zanubrutinib may be taken in any order.

Study drug should be taken on site during PK sample schedule and time of administration recorded.

The Investigator is to instruct the patient to take the study drug exactly as prescribed and at the same time each day of dosing.

Patients must be asked to record their Zanubrutinib daily dosing in the Sponsor-provided **Patient Diary** and report any missing doses or lost study drug at the next clinic visit.

Patients must be instructed to return the study drug bottle(s) that are empty, partially used or unused at each clinic visit.

Site staff should conduct a compliance check at each study visit, counting tablets if required. Patients should be questioned about any missing doses, lost drug and any discrepancies between the compliance check and the **Patient Diary**.

2.3.5 Dose Modifications

In the event of adverse events attributed to Zanubrutinib and deemed intolerable by the Investigator, treatment should be either temporarily or permanently discontinued. Zanubrutinib may be held for a maximum of 28 days and restarted upon resolution of toxicity per investigator discretion. If, in the Investigator's opinion, it is in the patient's best interest to restart study drug after being held for > 28 days, then written approval must be obtained from the medical monitor or designee. More than one study drug hold is allowed. Dose interruption and modification guidelines are provided in the study protocol Version 0.0, section 5.3.2.

Table 3. Zanubrutinib Dose Reductions

Toxicity Occurrence	Dose Level	Zanubrutinib dosage (starting dose = 160 mg twice a day)	Zanubrutinib dosage (starting dose = 320 mg once a day)
First	0 = starting dose	Restart at 160 mg twice a day	Restart at 320 mg once a day
NOSecond	-1 dose level	Restart at 80 mg twice a day	Restart at 160 mg once a day
Third	-2 dose level	Restart at 80 mg once a day	Restart at 80 mg once a day
Fourth	Permanently discontinue Zanubrutinib	Permanently discontinue Zanubrutinib	Permanently discontinue Zanubrutinib

2.3 Venetoclax

Venetoclax is formulated as film-coated, tablets of 10, 50 and 100mg for oral administration (refer to Protocol Version 0.0, Section 5.1.3). The investigator is to instruct the patient to take the study drug exactly as prescribed and at the same time each day of dosing. Venetoclax will be provided by BeiGene or locally sourced.

Venetoclax will be administered by mouth once daily with food.

Venetoclax is packaged in blisters within child-resistant wallets.

Venetoclax should be stored as per labelling instructions.

Venetoclax will only be administered to patients randomized to Arm B (refer to Protocol Version 0.0, Section 3.1).

The contents of the label will be in accordance with all applicable local regulatory requirements.

The study drug must be kept at the temperature condition specified on the label.

Venetoclax will be dispensed by the study center personnel to patients every cycle to ensure adequate drug supply for administration at home throughout the Treatment phase as detailed in the Pharmacy Manual.

Patients will complete a daily pill diary for as long as they are receiving study treatment.

Patients must bring their diary cards to the site at each study visit so that they can be checked by study site personnel for compliance.

Patients will be requested to bring their unused medication, and all empty containers/packaging, to the center at each visit.

All doses and all dose changes including reasons for dose changes must be recorded on the patient IP accountability log.

For further details, see the manufacturer's prescribing information for Venetoclax.

2.4 Obinutuzumab

Obinutuzumab will be provided or locally sourced in vials containing concentrate for solution for infusion. The actual appearance and composition of the product may depend on the respective marketed product sourced for the participating countries.

Obinutuzumab will only be administered to patients randomized to Arm B (refer to Protocol Version 0.0, Section 3.1). The Pharmacist or designee should document the preparation and update the IP accountability log. The study/infusion nurse/study coordinator should update the infusion log during the infusion administration.

If a planned treatment is delayed, the delayed treatment should be administered as soon as possible thereafter with the schedule for subsequent doses adjusted to maintain the time intervals between doses. Patients who do not complete the Cycle 1 Day 1 treatment may proceed to the Cycle 1 Day 2 treatment.

Preparation of Obinutuzumab should occur according to institutional standards of care consistent with local country prescribing information. If the obinutuzumab is not approved in the study region, please follow below instructions and refer to Protocol Version 0.0 Section 5.2.2.2.

The obinutuzumab solution for intravenous solution should be prepared aseptically and diluted with 0.9% sodium chloride into a polyvinyl chloride or non-polyvinyl chloride polyolefin infusion bag. The prepared solution should be mixed by gentle inversion. It should not be frozen and administered immediately after preparation. If not used immediately, the solution may be

stored in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours. The solution should be inspected visually for any particulate matter and discoloration before administration.

Local country prescribing guidelines (i.e, Prescribing Information or Summary of Product Characteristics) should be followed throughout the study for obinutuzumab administration. In countries where local prescribing guidelines are not available the guidelines set in the Pharmacy Manual should be followed.

Obinutuzumab must be administered in a clinical setting (inpatient or outpatient). Full emergency resuscitation facilities should be immediately available, and patients should be under close observation at all times. Hypotension may occur during or immediately after infusions therefore, withholding antihypertensive treatment should be considered for 12 hours before obinutuzumab infusions and for the first hour after infusions.

Obinutuzumab should be given through a dedicated line, and IV infusion pumps should be used to control the infusion rate of obinutuzumab.

Obinutuzumab should not be given as an intravenous push or as a bolus.

All obinutuzumab infusions should be administrated ≥ 30 minutes after premedication with oral paracetamol and an antihistamine to mitigate the risks of infusion-related reactions (IRR) and Tumor Lysis Syndrome (TLS) (refer to Protocol Version 0.0, Section 8.1.3.1, Monitoring and Management of Infusion-Related Reaction and Table 16).

For the first dose of obinutuzumab [Cycle 1 Day 1 (C1D1)], premedication with corticosteroids is mandatory for all patients and must be administered ≥ 1 hour before the first dose.

For patients with a high lymphocyte count or bulky lymphadenopathy, the C1D1 infusion may be given over a longer period of time, or the dose may be split and given over more than 1 day. Two infusion bags should be prepared for the infusion on C1D1 and C1D2 (100 mg for C1D1 and 900 mg for C1D2). The first bag (100 mg) of obinutuzumab will be administered at an initial rate of 25 mg over 4 hours. If the first bag (100 mg) is completed without modifications of the infusion rate or interruptions, the second bag (900 mg) may be administered on the same day (no dose delay necessary, no repetition of premedication), provided that appropriate time, conditions, and medical supervision are available throughout the infusion. If there are any modifications of the infusion rate or interruptions during the first 100 mg, the second bag must be administered the following day (C1D2).

Note: If the local country label for obinutuzumab does not state that the 900 mg obinutuzumab can be infused on the same day (C1D1) as the 100 mg obinutuzumab infusion, these sites may infuse the 900 mg of obinutuzumab on C1D1 immediately after the 100 mg obinutuzumab infusion has been completed per the investigator`s discretion.

When both dosages (100 mg followed by 900 mg obinutuzumab infusion) are given on C1D1, TLS laboratory monitoring timepoints are calculated from the start time of the 100 mg obinutuzumab infusion (see protocol section 8.1.2). After the end of the first infusion, the IV line should remain in place for at least 2 hours in order to enable administration of medications

for management of IRRs or for resuscitative measures. If no adverse events occur after 2 hours, the IV line may be removed.

For subsequent infusions (C1D8 and onward), corticosteroid premedication should be given:

- To patients who experienced a Grade 3 IRR from the previous infusion
- To patients with lymphocyte counts > 25 x 10^9/L
- Or at the Investigator's discretion

For subsequent infusions (C1D8 and onward), the IV line should remain in place for at least 1 hour from the end of infusion, and if no adverse events occur after 1 hour, the IV line may be removed.

For patients who do not experience ≥ Grade 3 infusion-related symptoms with their previous infusion, premedication with corticosteroid for subsequent infusions may be omitted at the Investigator's discretion.

In the absence of IRRs/hypersensitivity, the rate of the infusion will be escalated in increments of 100 mg/hour every 30 minutes to a maximum rate of 400 mg/hour on Cycle 1, Day 8 onwards (refer to Protocol Version 0.0, Section 8.1.3.1.4, Subsequent Infusions of Obinutuzumab).

If the start of infusion is delayed or infusion-related symptoms occur that require delaying or stopping the infusion such that completing the infusion in a single day is not feasible, the infusion may be completed on the next day.

The reason for any deviation should be documented in the patient record.

Patients with preexisting cardiac and/or respiratory conditions or who have had a prior clinically significant cardiopulmonary adverse event with obinutuzumab should be monitored very carefully throughout the infusion and post infusion period. Patients with a history of clinically significant cardiac or respiratory disease are excluded per eligibility criteria.

The contents of the label will be in accordance with all applicable local regulatory requirements.

The study drug must be kept at the temperature condition specified on the label.

For further details, see the manufacturer's prescribing information for obinutuzumab.

3. Investigational Product (IP): Ordering, Shipping, Receiving, Storage, Return and/or Destruction

3.1 Ordering initial and additional Investigational Product

An initial IP shipment will be supplied to each site after the site has been activated within the IRT system.

After this initial supply, sites will automatically be re-supplied according to the status of active patients that the site has entered into the IRT system. Each time a patient is enrolled or discontinues treatment, this information must be entered into the IRT system to ensure an adequate supply of the drug at all times. Each time a shipment is received, acknowledgement of receipt must be made in the IRT system as soon as possible.

3.2 Acknowledgement of Receipt

Upon receiving the shipment, the Pharmacist or designee, should reconcile the shipment against the packing list and verify the temperature of the shipment.

Each shipping container should contain a temperature monitoring device, programmed to record the temperature within the container at set intervals. The temperature monitor will display an alarm symbol(s) if the temperature has been recorded outside of the specified range during the shipment. If multiple shipping containers have been received, each container will contain a separate temperature monitor. Each shipping container will need to be opened and the corresponding temperature monitor retrieved and stopped.

Please refer to the applicable Temperature Monitor Instruction Sheet, included in the shipment and provided by the vendor, for guidance on how to stop the device and retrieve the temperature data.

Complete the Acknowledgement of Receipt Form, also supplied with the shipment, and include information on temperature compliance or any excursions noted. Follow all instructions on the form, including returning a copy to the depot, if requested. File the signed & dated **Acknowledgement of Receipt Form** and any temperature excursion details in the 'Supplies' section of your Investigator Site File. The original packing list and temperature data should also be kept in the Investigator Site File for further verification. Note that all temperature excursions during shipment need to be reported expeditiously, as described in Section 4 below.

3.3 Shipping and Storage

Sonrotoclax must be transported and stored at 2 -25˚C (36-77˚F) according to the instructions on the label.

Bottles of Sonrotoclax tablets must be stored, at 2-25˚C (36-77˚F), according to the instructions on the label. The storage area should be secure with limited access. The temperature of the pharmacy's storage facility must be monitored during storage. If temperatures are recorded outside of this range, a temperature excursion will need to be reported expeditiously (see Section 4).

Once dispensed, bottles of Sonrotoclax tablets should be stored by the patient at 2-25˚C (36-77˚F), according to the label instructions.

Both IP receipt documentation and temperature logs will be reviewed by CRA's during routine monitoring visits to check compliance with the protocol and instructions in this manual.

Zanubrutinib must be stored at room temperature 15ºC to 30ºC (59-86ºF). The storage area should be secure with limited access. The temperature of the pharmacy's storage facility must be monitored during storage. If temperatures are recorded outside of this range, a temperature excursion will need to be reported expeditiously (see Section 4).

3.4 Returns and/or Destruction of Investigational Product

Follow the guidelines below for return/destruction of IP:

- All used and unused IP must be maintained at the clinical site for accountability and inventory purposes during the study conduct, i.e., returned bottles of IP from patients must be kept in a secure area for CRA verification. After the CRA has performed verification and drug accountability, bottles can be destroyed at the site or returned to the depot, if required.
- At site close-out, all remaining unused IP must be accounted for, all discrepancies explained and documented. No IP should be destroyed prior to CRA reconciliation completion and authorization for destruction or return to the depot if required.

BeiGene allows for the on-site destruction of IP if it is in accordance with the site's standard procedures. A copy of the site's standard operating procedures (SOPs) must be provided to the CRA for verification and be filed in the Investigator Site File (ISF). If a clinical site does not have appropriate destruction capabilities and procedures, the CRA will coordinate the return of the drug to the depot for destruction. If a copy of the site SOP is not available or cannot be provided to BeiGene, then a Note to File (NTF) must be completed to document the site's destruction process. The NTF must be provided to the CRA for verification and filed in the ISF. If

a copy of the site SOP is in the local language, no translation of the SOP will be required. Instead, an NTF needs to be completed in English to document the site's destruction process. https://myapplications.microsoft.com/

For sites that can destroy drug locally, authorization must be provided by the CRA after accountability and reconciliation have been completed in the IRT system before the IP can be destroyed. Documentation of destruction must be maintained and filed in the ISF. A destruction certificate is recommended to complete the accountability process.

For sites that will need to return used and unused IP, after completion of accountability and reconciliation, the CRA will create a return shipment within the IRT system and will prepare the shipment for return to the depot. The CRA will complete the relevant sections of an **IP Return Form** and send with the shipment.

Depot personnel will perform reconciliation between the returned IP and the **IP Return Form**, document the confirmation, and send the completed form back to the site for filing. This form is located in Section 11 (IP Destruction Documentation) of the Pharmacy Binder.

In addition to the above, any IP that is deemed as unusable or will not be dispensed (e.g. expired IP), may also be returned to depot following the same process.

4. Temperature Excursion

Suppose a temperature excursion is noted during IP shipping, storage at site, or reported by patients after dispensing. In that case, the site must **immediately** quarantine the impacted supply under the appropriate storage conditions, as indicated in Section 3.3, and contact the CRA. Also, the responsible Pharmacist or designee must record the impacted IP in the IRT system as quarantined. If the IP is in the patient's possession, the patient must be instructed to store the IP as instructed but **not** to take the IP until it has been confirmed whether it should be returned and replaced or is suitable to continue taking.

The site should report all IP temperature excursions as soon as possible, within **24 hours** upon discovery by completing the **Temperature Excursion Form** (See Appendix 1) provided in the Pharmacy Binder. The site should contact the CRA if the documented temperatures and/or duration of an excursion are not available for any reason.

The responsible Pharmacist or designee should complete and sign the **Temperature Excursion Form** (See Appendix 1), then save or scan to PDF and send via email to the mailbox below for evaluation. All relevant documents such as Temperature Log, Packing Slip, IRT/Inventory Report of Impacted IP, Temperature Log of back-up storage should also be scanned and attached to the Temperature Excursion Form. The CRA and BeiGene Clinical Operations Manager must be copied on the email.

Email completed Temperature Excursion Form to:

Temperature-Excursion @beigene.com

Email subject title: COUNTRY (Where the product is located and placed in quarantine), the product, protocol number and clinical site number. Example email subject line AUSTRALIA, SONROTOCLAX, SONROTOCLAX-301, site #00001

Attachment: Temperature Excursion Form and Temperature Log.

Please also ensure to copy the responsible CRA in the email.

5. Product Complaint/Deviation

In case of any quality issues with the IP, such as discoloration, particulate matter, etc., the bottle must be recalled and quarantined immediately for further clarification by Sponsor Quality Assurance (QA). The Pharmacist or designee should complete the relevant sections of the **Product Complaint Form** (Appendix 2) to record the issue and report to the CRA. The CRA must report all written, electronic or verbal information that indicates there may be an issue(s) with a product to QA via the following email: Productcomplaints@beigene.com. The **Product Complaint Form** needs to be attached to this reporting email, and the Supply Chain Lead should also be copied in the email to alert them of any potential product re-supply requirements. QA will coordinate the return of the complaint samples for evaluation, if necessary. Clinical Operations may be asked to request further information from the site and help coordinate re-supply. QA will make the final determination about the appropriate actions required, once the investigation has been completed.

6. Study Drug Accountability

The investigational medicinal product(s) (IMP[s]) for this study (Sonrotoclax, Zanubrutinib, Venetoclax, and obinutuzumab) will be provided by the sponsor, as required by local or country specific regulations.

In some instances, comparator drugs will be locally sourced.

The investigational site will acknowledge receipt of the IMP(s).

Any damaged shipments will be replaced, as appropriate.

Accurate records of all IMPs received, dispensed, returned, and disposed of should be recorded on the site's Drug Inventory Logs and in the IRT system (please refer to IRT guidelines).

7. Contingency Plan

In preparation for any unanticipated power outages or other emergencies, the investigational site should have a written back-up plan for storage of the IP. Proper chain-of-custody, security, and temperature controls must be maintained at all times. If there is a need for IP relocation, it must be reported to the CRA and/or the Study Sponsor to request for approval and process. IP must be stored in a controlled, locked, secure location at all times.

8. Revision History

Version	Author	Revision/Justification	Effective Date
1.0	**Bernadette Waller** Global Clinical Study Manager **Lee Nguyen** Clinical Supply Chain and Logistics Manager	Initial version	Date of Final Signature (see "Approvals" section)
1.1	**Bernadette Waller** Global Clinical Study Manager	Updated sections 2.2.2 & 2.3.2 Replaced bottle label images.	Date of Final Signature (see "Approvals" section)

9. Approvals

Role	Name	Signature
Medical Monitor	Tommi Salmi	DocuSigned by: Tommi Salmi Signer Name: Tommi Salmi Signing Reason: I approve this document Signing Time: 18-Dec-2023 | 16:27:35 PST 8752154FEF614F0D9277C93182610E73
Supply Chain	Lee Nguyen	DocuSigned by: Signer Name: Lee Nguyen Signing Reason: I approve this document Signing Time: 14-Dec-2023 | 15:47:51 PST 9004158C4208490397BEC7CCAE30C872
Global Clinical Study Manager	Bernadette Waller	DocuSigned by: Bernadette Waller Signer Name: Bernadette Waller Signing Reason: I approve this document Signing Time: 14-Dec-2023 | 14:56:09 PST E626ED88BBFA4F0E8F91CA86FC46D1CA

Appendix 1: Temperature Excursion Form

Appendix 2: Product Complaint Form

Appendix 3: GMP Deviation Form

Appendix 4: Blank Patient Diaries

Appendix 5: IP Accountability Logs (Site Inventory Log and Subject Dispensing Log, Infusion Log)

Appendix 6: Investigational Site Clinical Trial Material Order Form

Appendix 7: Obinutuzumab Label Instructions

Appendix 8: Venetoclax Label Instructions

DocuSign

Certificate Of Completion

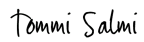
Envelope Id: F6BAF07AD7EC4B6F9FB7AD469BD5C2FE
Status: Completed
Subject: Complete with DocuSign: BGB-11417-301 Pharmacy Manual Version 1.1_15DEC2023_Final.docx
Source Envelope:
Document Pages: 31
Signatures: 3
Certificate Pages: 2
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC-08:00) Pacific Time (US & Canada)

Envelope Originator:
Elain LeNguyen
1900 Powell St. Suite 500
Emeryville, CA 94608
elain.lenguyen@beigene.com
IP Address: 163.116.211.49

Record Tracking

Status: Original
12/14/2023 2:52:27 PM
Holder: Elain LeNguyen
elain.lenguyen@beigene.com
Location: DocuSign

Signer Events	Signature	Timestamp
Bernadette Waller bernadette.waller@beigene.com Clinical Operations Manager BeiGene Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: E626ED88-BBFA-4F0E-8F91-CA86FC46D1CA Using IP Address: 1.145.71.236 Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 12/14/2023 2:54:50 PM Viewed: 12/14/2023 2:56:01 PM Signed: 12/14/2023 2:56:34 PM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Lee Nguyen lee.nguyen@beigene.com Senior Manager, Supply Chain & Logistics BeiGene Security Level: Email, Account Authentication (Required)	 Signature Adoption: Uploaded Signature Image Signature ID: 9004158C-4208-4903-97BE-C7CCAE30C872 Using IP Address: 163.116.132.113 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 12/14/2023 2:54:49 PM Viewed: 12/14/2023 3:47:10 PM Signed: 12/14/2023 3:48:18 PM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

Signer Events	Signature	Timestamp
Tommi Salmi tommi.salmi@beigene.com Medical Director BeiGene Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 8752154F-EF61-4F0D-9277-C93182610E73 Using IP Address: 84.248.174.6 Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 12/14/2023 2:54:50 PM Viewed: 12/18/2023 4:27:15 PM Signed: 12/18/2023 4:28:01 PM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
In Person Signer Events	**Signature**	**Timestamp**
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
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Certified Delivered	Security Checked	12/18/2023 4:27:15 PM
Signing Complete	Security Checked	12/18/2023 4:28:01 PM
Completed	Security Checked	12/18/2023 4:28:01 PM
Payment Events	**Status**	**Timestamps**