

**A Multicenter, Adaptive,
Randomized, Blinded Controlled
Trial of the Safety and Efficacy of
Investigational Therapeutics for
Hospitalized Patients With
COVID-19 (Trial H3: BRII-196/
BRII-198)**

**Version 1.0
20 November 2020**

NCT05780424

Appendix H3: BR11-196+BR11-198 – version 1.0 (20 November 2020)

The content of this appendix is confidential and should only be viewed by persons covered by the CDA entered between BR11 and NIAID in relation to the TICO / ACTIV-3 study.

This appendix provides detailed information pertaining to the study of this investigational agent. If not stated otherwise, the text in the master protocol gives the approach that will be taken to study this agent.

H.3.1. Introduction and rationale for studying the agent

BR11-196 and BR11-198 are two fully human immunoglobulin G (IgG)-1 monoclonal antibodies (mAb) derived from antibodies P2C-1F11 and P2B-1G5, respectively, that were isolated directly from human B cells of a convalescent COVID-19 patient [1-3]. These mAbs target distinct epitopes in the SARS-CoV-2 receptor binding domain (RBD) in the coronavirus spike (S) glycoprotein. SARS-CoV-2 S uses the angiotensin-converting enzyme 2 (ACE2) to enter cells via interaction with the RBD [4]. Therefore, mAbs against the RBD will prevent virus binding to ACE2, blocking virus entry and virus infection. BR11-196 and BR11-198 are potent in neutralizing SARS-CoV-2 viruses in pseudo-virus as well as live virus neutralization assays. The targeting of different epitopes in the viral antigen by the BR11-196 and BR11-198 cocktail is a strategy to reduce the generation and selection of resistant virus as compared to single antibody. Further, the fragment crystallizable (Fc) region of BR11-196 and BR11-198 is engineered with a triple-amino-acid (M252Y/S254T/T256E [YTE]) substitution to allow an extended half-life [5, 6]. The introduction of YTE also reduces the binding activity against Fc γ receptors by approximately 3 folds, thereby minimizing the potential risk of Fc-mediated antibody-dependent enhancement (ADE).

Brii Biosciences (BriiBio) is a multinational biopharmaceutical company that discovers and develops innovative medicines to address unmet public health needs with a focus on infectious diseases. BriiBio operates in the US headquartered in Durham, NC and operates in China headquartered in Beijing, with facilities and staff also in San Francisco, CA and Shanghai.

Neutralizing mAbs that can inhibit viral replication and potentially mitigate the severity of disease caused by viral infection represent an important therapeutic option in the treatment of known and emerging infectious diseases. Whereas one antiviral agent (remdesivir) has been demonstrated to have clinical benefit in the target population for this trial and is now part of standard-of-care (see Appendix I), it is plausible that additional antiviral effects from the combination of the neutralizing mAbs BR11-196 and BR11-198 together with the remdesivir may provide additive, if not synergistic, antiviral effect and hence, contribute to improvement in time to sustained recovery.

BriiBio is evaluating the safety, tolerability, and pharmacokinetics (PK) of each antibody in two randomized, placebo-controlled, single-ascending-dose, Phase 1, first in human studies at three dose levels of BR11-196 (750 mg, 1500 mg, 3000 mg) in study BR11-196-001 (NCT04479631)[7] and three dose levels of BR11-198 (750 mg, 1500 mg, 3000 mg)

in study BR11-198-001 (NCT04479644)[8]. In each study of 16 healthy volunteers, the active formulation is injected into an IV bag of normal saline before being administered intravenously. Subjects of each dose cohort, for each respective study, are randomized in a ratio of 3:1 to receive either the active formulation or placebo (normal saline). Subjects remain as inpatients at the clinical investigational site for sample collection and assessments for 7 days post-dose and thereafter return to the clinic at designated visit times for additional sample collection and assessments, with the last visit scheduled on Day 181. A Safety Review Committee (SRC) performs ongoing reviews of safety and tolerability based on data collected in pre-planned cohorts to guide the progress of the study and ensure the safety of the subjects. Both studies completed enrollment of planned subjects and preliminary safety, tolerability, and PK data from these studies are supportive of the dose selected for use in this study.

H3.1.1 *Potential risk and benefits from BR11-196+BR11-198*

Anticipated risk is considered low, based on the known mechanism of action for human-derived neutralizing antibodies in acute viral disease states. BR11-196 and BR11-198 are highly specific mAb directed at foreign (non-human) epitope(s). The parent antibodies were isolated from B lymphocytes of a naturally convalescent SARS-CoV-2-infected patient. Hence, BR11-196 and BR11-198 have undergone natural positive and negative selection pressures *in vivo*, unlike humanized antibodies generated in mice. Therefore, off-target binding, tissue cross-reactivity and immunogenicity are considered unlikely, which is further supported by the absence of binding to membranes of monkey and human tissues in tissue cross-reactivity studies. The complementarity determining regions (CDRs) of BR11-196 are identical to the parent mAb P2C-1F11. BR11-198 is only different in one amino acid in the CDR3 of precursor mAb, P2B-1G5 (to reduce manufacturing development risk). In the Fc domain of BR11-196 and BR11-198, three clinically validated amino acid modifications (M252Y/S254T/T256E [YTE]) were introduced to extend half-life [5, 6].

BR11-196 targets a discontinuous binding site that contains 23 amino acid residues in the RBD of the spike protein that are located in the interface of the ACE2 receptor binding site (11 of 23 amino acids are known to bind to this receptor). BR11-198, however, has minimal competition with ACE2 and BR11-196 but strong competition with S309 (VIR-7831), a mAb specifically recognizing the core domain of RBD. These results indicate that BR11-198 exerts its neutralizing ability through the binding to the core domain in the RBD of the spike protein. Therefore BR11-196 and BR11-198 target the RBD through distinct, non-competitive, complementary neutralizing mechanisms. *In vitro* studies suggest that the two antibodies act additively, if not synergistically [2, 3]. Additionally, the combination of two antibodies, like BR11-196 and BR11-198, reduced the chance of resistant escape mutants of SARS-CoV-2, *in vitro*, compared to antibodies being studied alone [9].

Potential risks for infusion of an IgG1 mAb directed toward a microbial pathogen are mostly associated with either infusion-related immediate and non-immediate hypersensitivity reactions, or infusion-related cytokine release syndrome. Signs and symptoms of infusion-related immediate hypersensitivity reactions may include, but are

not limited to: anaphylaxis, angioedema, bronchospasm, chills, diarrhea, hypotension, itching, skin rash, shortness of breath, urticarial, tachycardia, and throat irritation or chest tightness. Additional signs and symptoms associated with cytokine release syndrome may also include fever, headache, myalgia, nausea, and vomiting.

A theoretical risk is that BR11-196 or BR11-198 may cause antibody-dependent enhancement (ADE) of viral replication (section 3.2 of the master protocol). This is based on responses observed to some monoclonal antibody therapies used in other unrelated viral diseases, namely Dengue and Zika virus infections. Unlike ADE associated with Dengue and Zika virus infections, this phenomenon has not been clearly established for coronavirus infections, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), and has not been reported to date with SARS-CoV-2. Additionally, limited experience with the use of convalescent serum as a treatment for patients with severe COVID-19 has not indicated safety concerns [10]. BR11-196 and BR11-198 will be administered to patients at sufficiently high dose levels to neutralize SARS-CoV-2 and avoid sub-neutralizing concentrations in the presence of virus that are typically associated with ADE. In addition, there was no ADE observed in over 20,000 COVID-19 patients who were treated with convalescence plasma [11] and in the recently published study in infants who received YTE-containing RSV mAb over 1 year *in vivo* entering second RSV season [12]. With a total of 37 representative tissues from human and cynomolgus monkeys, BR11-196 and BR11-198 had no cross reactivity at concentration up to 10 ug/mL and this is consistent with highly specific affinity to the RBD region of the spike protein of SARS-CoV-2 virus. Both BR11-196 and BR11 198 with YTE modification in Fc regions exhibited reduced binding activity by approximately three-fold to human Fcγ receptors (FcγRIIIa-F158/V158 and FcγRIIIa-H131/R131), and no ADCC activity in the assay using primary NK cells in the presence of BR11-196 [2, 3]. These results suggest BR11-196 and BR11-198 may have a reduced risk of potential Fc-mediated ADE.

As of 24 August 2020, all healthy volunteers who were administered study drug in the BR11-196-001 (NCT04479631)[7] and BR11-198-001 (NCT04479644)[8] studies are under follow-up. A total of 16 subjects were randomized in the ongoing BR11-196-001 study and completed dosing: 750 mg (3 subjects), 1500 mg (6 subjects), 3000 mg (3 subjects), and placebo (4 subjects). A total of 17 subjects were randomized in the ongoing BR11-198-001 study of which 16 subjects completed dosing: 750 mg (3 subjects), 1500 mg (6 subjects), 3000 mg (3 subjects), and placebo (4 subjects). The demographic profile of subjects across dose levels in the BR11-196-001 and BR11-198-001 studies was comparable with respect to mean age (mean age of subjects by study: 32 and 33 years, respectively), gender (81% and 88% male, respectively), racial distribution (88% and 94% Han Chinese, respectively), and mean body mass index (22 kg/m², in both studies). At the dose level of up to 3000 mg, both BR11-196 and BR11-198 were well tolerated. No infusion-related reaction, hypersensitivity reaction, or adjustment of infusion rate due to AEs during the administration have been reported. No SAEs or AEs of Grade 3 or above (Common Terminology Criteria for Adverse Events (CTCAE); a grading system) have been reported. No medical interventions were needed.

Most lab abnormalities were transient and returned to normal range or baseline level within 2 weeks without any clear pattern nor correlation to dose.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of BR11-196 and BR11-198 may be found in the Investigator's Brochure(s) (IB) [2, 3] and Participant Information Leaflet.

Given the data on BR11-196 and BR11-198 from the on-going Phase 1 studies, the well-described safety profile of other therapeutic monoclonal antibodies, the pre-clinical safe toxicology profile, and the limited disease directed therapeutic options for patients with COVID-19 illness, the overall benefit-risk assessment of this study is considered favorable.

H3.1.2 Motivation for agent selection by the ACTIV Trial Oversight Committee (TOC)

The ACTIV-2/3 Agent Selection Committee (ASC) reviewed the Bii Biosciences SARS-CoV-2 neutralizing antibody cocktail (BR11-196 and BR11-198) voted in favor of the agent proceeding into ACTIV-2 and ACTIV-3, and the TOC endorsed that recommendation. Bii Bioscience's BR11-196 and BR11-198 antibodies were supported because Bii Biosciences presented strong preclinical data for viral neutralization, Live virus neutralization BR11-196 IC₅₀ 0.024 µg/ml, BR11-198 IC₅₀ 0.030 µg/ml and Live virus neutralization BR11-196 IC₉₀ ≤ 0.296 µg/ml. BR11-198 IC₉₀ ≤ 0.490 µg/ml. BR11-196 and BR11-198 are human neutralizing immunoglobulin G1 that bind distinct epitopes in receptor binding domain (RBD) in spike protein of SARS-CoV-2 virus. They are M257Y/S259T/T261E (YTE) modified isoforms of monoclonal antibodies derived from B cells of a recovered COVID-19 patient. BR11-196 neutralizes SARS-CoV-2 by directly blocking the binding of receptor ACE2 to RBD for viral entry. The structural analysis of BR11-196 Fab complexed with the RBD protein provided insights into the neutralization mechanism. It revealed a highly conserved conformational antigenic site comprised of 23 contact residues in RBD and 11 of them are used by ACE2 to bind SARS-CoV-2. Unlike BR11-196, BR11-198 demonstrated no or little competing capacity with ACE2 and BR11-196, indicating two antibodies have distinct and non-overlapping epitopes, and neutralize virus through different mechanisms. As expected, when evaluated in the live virus microneutralization assay in combination, they displayed moderate additive effect. While the YTE modification improves the half-life of antibodies to provide prolonged duration of protection and extended therapeutic treatment window, it reduces binding activity to human Fcγ receptors, thereby minimizing the potential risk of Fc-mediated antibody-dependent enhancement.

In addition, the ASC appreciated that Bii Bioscience was targeting date for Investigational New Drug (IND) submission was early September, and that its Phase 1 study should be complete by mid-September, with the candidate agent ready to enter ACTIV clinical trials by late September pending Phase 1 results. In addition, BR11-196 and BR11-198 will be the first cocktail to be tested in ACTIV, exciting the ASC to assess a few combination agents. Finally, the ASC found the manufacturing and scalability strategy for Bii Biosciences sufficient for the full trial and beyond.

Brii statement regarding plans for licensure: BriiBio is a biopharmaceutical company whose goal is to bring important medical breakthroughs to as many patients in as many countries as possible. It would therefore be BriiBio's general intent to pursue licensure in countries where the trial occurs. In the case of the COVID-19 pandemic, the actual decision to pursue licensure will be impacted by other factors which may include: status of the COVID pandemic in the country and medical need, availability of other therapies including vaccines, available drug supply and other supply feasibility issues, and other regulatory considerations.

H3.1.3 Justification for dose chosen for BRII-196 and BRII-198

The 1000 mg / 1000 mg clinical doses of the BRII-196 and BRII-198 combination therapy in the Phase 2/3 study is selected by considering the *in vitro* and *in vivo* pharmacology results, hypothesized *in vivo* target coverage requirements, predicted human serum drug concentration profiles, available safety data, including nonclinical toxicology data and preliminary clinical safety, and tolerability results from the ongoing Phase 1 studies in healthy adult participants.

Based on the potent and unique RBD binding properties and *in vitro* antiviral neutralization activity, BRII-196 can be used as the main clinical efficacy component of the combination therapy. BRII-198 also demonstrated potent antiviral neutralizing activity *in vitro*, has a non-competitive RBD target binding epitope that is different from BRII-196 and does not block the binding of ACE2 to the RBD region. These unique properties of BRII-198 make it a potentially important additional clinical efficacy component in the combination therapy in order to achieve a more effective treatment of COVID-19 patients infected with WT and different mutations of SARS-CoV-2 viruses and to minimize potential viral escape risk. Similar to reported data from other anti-SARS-CoV-2 antibodies [13, 14], preliminary results indicated BRII-196 and BRII-198 combination therapy (1:1 ratio) treatment led to effective viral clearance and less body weight loss in the *in vivo* hACE-2 mouse model. Based on the above considerations, it is believed that the equivalent dose strategy of the BRII-196 and BRII-198 combination therapy will efficiently utilize unique characteristics of both antibodies that will lead to anticipated clinical efficacy.

Based on previous experience with other antiviral neutralizing mAbs [15-17], as well as preliminary *in vivo* efficacy data in the hACE2 hamster model, it is hypothesized that drug coverage of 10-30 folds of *in vitro* IC₉₀ at the sites of infection, e.g. nasal cavity and lung, is needed for effective treatment of COVID-19 patients. Literature reported biodistribution coefficients of monoclonal antibodies in the nasal cavity and lung are about 3-4% [15] and 10-15% [18] of the corresponding serum drug concentrations, respectively. Based on this assessment, the target minimal serum BRII-196 and BRII-198 concentrations are 100-300 folds of *in vitro* IC₉₀ for at least 3-weeks, the target duration considered suitable for neutralizing antibody therapy [19, 20].

A population PK model was built and applied to predict human PK profiles of BRII-196 and BRII-198. To support fixed dose strategy, body weight has been incorporated as a covariate in the population PK model, and the covariate analysis suggested minimal impact of body weight to the pharmacokinetics of BRII-196 and BRII-198. The model predicted terminal half-life is 89.2 days (10th-90th percentile: 65.2 - 124 days) that is in

the reported range of other YTE mAbs in human [5, 6]. Interim data from the ongoing BR11-196 and BR11-198 Phase 1 studies in the healthy adult participants is consistent with the predicted concentration – time profiles at dose levels of 750 and 1500 mg. The proposed dose of 1000 mg of each antibody is predicted to have sufficient target coverage individually over minimally 3-week period.

In addition, the nonclinical and preliminary clinical safety data also support the proposed dose of 1000 mg / 1000 mg for BR11-196 and BR11-198. BR11-196 and BR11-198 were well tolerated after two weekly doses of 100 or 300 mg/kg in the GLP 14-day toxicity studies with 56-day recovery. The “No-Observed Adverse Effect Level” (NOAEL) was 300 mg/kg for BR11-196 and BR11-198, the highest dose level tested in the studies. At the proposed dose of 1000 mg, the safety margins for BR11-196 were approximately 6.8-fold (human equivalent dose (HED)), 34-fold (C_{max}) and 23-fold (AUC). The corresponding safety margins for BR11-198 were approximately 6.8-fold (HED), 29-fold (C_{max}) and 23-fold (AUC). In addition, the combined dose of BR11-196 and BR11-198 was well tolerated in a single dose acute toxicity study in rats with the NOAEL at 300 mg/kg for each antibody. In the *in vitro* tissue cross reaction (TCR) study using representative human and cynomolgus monkey tissues, BR11-196 and BR11-198 had no cross reactivity with both human and cynomolgus tissues at concentrations up to 4-10 folds of the optimal positive staining concentrations. At the dose level of up to 3000 mg, both BR11-196 and BR11-198 were well tolerated in the ongoing Phase 1 studies in the healthy adult participants.

Based on the PK and PK/PD assessment and the available nonclinical and clinical safety profile, the following doses of BR11-196 and BR11-198 was chosen for study in ACTIV-3: 1000 mg and 1000 mg, respectively.

This dose is selected to minimize potential concerns about underdosing and thus failing to detect an efficacy signal for an efficacious therapy. There are no significant safety concerns about using the 1000 mg dose of each of the antibodies, as side effects in antibody therapy are not generally dose-dependent.

H3.2. Agent specific eligibility criteria

In addition to the inclusion and exclusion criteria outlined in the master protocol, the following patients will be excluded: 1) pregnant women; and 2) nursing mothers. In addition, prior to the initial futility assessment which is performed when approximately 150 participants have been enrolled on BR11-196/BR11-198 and 150 on placebo, patients on high-flow oxygen or non-invasive ventilation (category 5 of the pulmonary ordinal outcome) will be excluded. These patients may be eligible for the trial if the initial futility assessment is passed by this agent.

H3.3. Description of investigational agent

H3.3.1. Administration and duration

See the PIM and Pharmacy Procedures for details about administration and duration. See also section [H3.5](#) below for guidance on the clinical management of the infusion, including infusion-related reactions.

A dedicated line should be used for infusion of BR11-196 and BR11-198 and they should not be mixed or administered with other medications.

The recommended infusion rate is ≤ 4 mL/min. The infusion rate may be reduced as deemed necessary if an infusion reaction is observed.

Participants will be closely monitored during the infusion and for at least 2 hours after completion of the infusion. Additional monitoring may be necessary based on clinical judgement of the study investigator(s) and/or site staff, and in accordance with the master protocol. The site must have resuscitation equipment, emergency drugs and appropriately trained staff available during the infusion and for at least 2 hours after the completion of the infusion.

If a participant has not already received the relevant dose of remdesivir at the day of enrolment, and has no contraindications to start remdesivir, it is recommended (but not required) that the relevant dose of remdesivir is infused after the infusion of BR11-196/placebo and BR11-198 /placebo is completed.

H3.3.2. Formulation and preparation

Both BR11-196 and BR11-198 sterile drug products are packaged in glass vials with a concentration of 30 mg/ml and should be stored upright and in the carton at 2-8 °C, protected from light.

The pharmacy will dispense 1000 mg of each agent (see [Table H3.1](#)). Placebo is normal saline. The study medication is prepared by an unblinded pharmacist at the local pharmacy. To ensure blinding of the participant and clinical staff a colored sleeve will be placed over the infusion bags. Preparation of study treatment and blinding procedures are described in the PIM and Pharmacy Procedures.

BR11-196 and BR11-198 should be prepared and dispensed as soon as possible after randomization. Both infusions must be completed (including flush of line) within 4 hours after preparation if the solution for injection has been stored at room temperature, or within 24 hours if the solution has been stored under refrigerated conditions.

Table H3.1. Study medication overview.

Intervention Name	Placebo	BR11-196	BR11-198
Dose Formulation	0.9% sodium chloride solution	Solution in single-use vial (30 mg/mL)	Solution in single-use vial (30 mg/mL)
Dosage Level(s) (mg)	Not applicable	1000 mg	1000 mg
Route of administration	IV infusion	IV infusion	IV infusion
Use	Placebo	Experimental	Experimental
IMP and NIMP	IMP	IMP	IMP
Sourcing	Commercially available 0.9% sodium chloride solution	manufacture and testing performed by WuXi Biologics Co. Ltd	manufacture and testing performed by WuXi Biologics Co. Ltd

Packaging and Labeling	Commercially available 0.9% sodium chloride solution	Study Intervention will be provided in glass vials and will be labeled appropriately	Study Intervention will be provided in glass vials and will be labeled appropriately
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H3.3.3 Supply, distribution, and accountability

Procedures for ordering and accepting drug, for maintaining inventory of BR11-196+BR11-198, and for breaking the blind in the event of a medical emergency will be described in the Pharmacy Procedures.

H3.3.4. Contraindicated medications

No medication is known to be contraindicated in patients receiving the investigational agent.

H3.3.5. Precautionary medications

The clinical site should have necessary equipment and medications for the management of any infusion reaction (see section [H3.5](#) below).

Premedication for infusions is not planned. However, if an infusion reaction occurs during administration or if the participant has a medical history suggesting a potential benefit from premedication, the study investigator(s) should determine the appropriate premedication.

The investigators and sponsor may decide to recommend premedication, if the frequency of infusion reactions among participants warrants it. If minor infusion reactions are observed, administration of acetaminophen, 500 mg to 1000 mg, antihistamines and/or other appropriately indicated medications may be given prior to the start of infusions for subsequent participants. The decision to implement premedication for infusions in subsequent participants will be made by the investigator and sponsor and recorded in the study documentation. Any premedication(s) given will be documented as a concomitant therapy.

H3.4. Clinical and laboratory evaluations

H3.4.1 Timing of Assessments

Appendix B outlines the clinical and laboratory monitoring. Assessment and reporting of AEs (section 10.1.1), SAEs (section 10.1.2) and unanticipated problems (section 10.1.3) and their severity, causality (section 10.1.5) and expectedness (section 10.1.6) is performed as outlined in the relevant section of the master protocol.

The half-life of BR11-196 and BR11-198 is 90 days. As outlined in the master protocol, the primary endpoint is assessed through day 90, but follow-up will be extended to 18 months for BR11-196 and BR11-198 to collect hospitalizations and deaths (section 9.1.2).

H3.4.2 Immunogenicity Assessments

At the visits specified in the master protocol (Days 0, 28, and 90) venous blood samples will be collected to determine antibody production against BR11-196+BR11-198. Immunogenicity may be assessed by a validated assay designed to detect ADAs in the

presence of BR11-196+BR11-198. Antibodies may be further characterized for their ability to neutralize the activity of BR11-196+BR11-198. Remaining volume from the PK sample may also be used for immunogenicity assessments as needed.

H3.4.3. Pharmacokinetic Assessments

At the visits specified in the master protocol (Days 0, 1, 5, 28, and 90) venous blood samples will be collected to determine BR11-196+BR11-198 serum concentration for pharmacokinetic assessment. The PK/Immunogenicity assessment will require 2 mL of the serum collected, as described in the Master Protocol Appendix B as “Research Sample Storage”. PK samples may be assessed by a validated assay at a bioanalytical lab. The PK assessment will use the same 2 ml serum aliquot specified in the Immunogenicity assessment section above ([H3.4.2](#)). Analysis of samples from placebo-treated subjects is not planned. Remaining sample used for PK may be pooled and used for exploratory metabolism or bioanalytical method experiments as deemed appropriate.

H3.5. Clinical management issues

All participants should be monitored closely for 2 hours after the infusion, as there is a risk of infusion reaction and hypersensitivity (including anaphylaxis) with any biological agent.

H3.5.1. Symptoms and Signs

Symptoms and signs that may occur as part of an infusion reaction, include, but are not limited to, fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and dizziness.

Infusion-related reactions’ severity will be assessed and reported using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected version 2.1 [\[21\]](#)

H3.5.2. Site Needs

The clinical site should have necessary equipment, medications, adequately qualified and experienced staff with appropriate medical cover for the management of any infusion reaction, which may include, but is not limited to, oxygen, IV fluid, epinephrine (adrenaline), acetaminophen (paracetamol) and antihistamine.

The pharmacy must use amber-colored Ultraviolet Light-Inhibiting (UVLI) protective bags to place over the infusion bag. The pharmacy will be provided with labels to be placed on the IV bag before dispensing (refer to the Pharmacy Procedures).

The pharmacy is required to provide normal saline and IV bags, similarly shrouded.

H3.5.3. Management of Infusion Reactions including Discontinuation

Investigators will use their clinical judgement and standard of care to evaluate and manage all infusion reactions. If an infusion reaction occurs, then supportive care should be used in accordance with the signs and symptoms. If a severe and potentially life-threatening infusion reaction occurs with BR11-196+BR11-198/placebo, its use should be permanently discontinued.

If a participant is not infused with BR11-196+BR11-198/placebo or the complete infusion is not given, all follow-up procedures and reporting's outlined in the master protocol (Appendix B for overview), should be adhered to as indicated.

H3.5.4. Adverse Events of Special Interest (AESI)

The following are AESIs for the agent BR11-196+BR11-198 or placebo for BR11-196+BR11-198:

- Infusion-related reactions
- Allergic/hypersensitivity reactions

H3.6. References

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