IMGN151
(anti-FRα antibody-drug conjugate)

Study IMGN151-1001

PHARMACY MANUAL

Version Date: 03 Oct 2024

Version 6.0

CAUTION: IMGN151 is an Investigational New Drug – Limited by Federal (or United States) Law to Investigational/Clinical Trial Use Only. To be Used by Qualified Investigators Only. For Clinical Trial Use Only.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

The Pharmacy Manual is a reference guide for pharmacists, investigators, or their designees, and other study personnel participating in Protocol IMGN151-1001, sponsored by ImmunoGen, Inc. (ImmunoGen). The manual contains a description of pharmacy and drug-related procedures, including receipt and storage, formulation, dilution, preparation, administration, and accountability for IMGN151 (investigational medicinal product) and eye drops (non-investigational medicinal product). The manual is designed to provide in-depth information about pharmacy-related, study-specific procedures and serves as a quick reference guide during the study.

All site personnel who have an active study role relative to study drug receipt, preparation, and administration must be trained on the contents of this manual with documentation of training available for review in the Investigator Site File.

In the event that the patient is to receive drug at a satellite clinic, a mechanism must be established to ensure that study drug is dispensed only upon the order of the Investigator or a licensed clinician directly responsible to the Investigator as stated on Form FDA 1572 or equivalent. By completing and signing the order, the Investigator has certified that the study drug will be administered only to patients under his/her personal supervision or under the supervision of sub-investigators responsible to him/her as stated on Form FDA 1572 or equivalent.

In this study IMGN151 will be administered via intravenous (IV) infusion every 21 days. IMGN151 will be given at the dose levels according to the protocol.

Any departure from the guidance listed in this manual must be discussed with ImmunoGen prior to execution. This manual does not replace the study protocol.

2. DRUG SHIPMENT AND RECEIPT INSTRUCTIONS

The Interactive Response Technology (IRT) vendor, 4G Clinical, and Almac Group (product distribution) have been contracted by ImmunoGen to support drug supply/resupply management. Sites will confirm delivery of IMGN151 and eye drops shipments in the 4G Clinical portal as soon as received.

2.1. Receipt of Study Drug Shipments

Drug shipments are packaged in an insulated shipping container that maintains appropriate temperature conditions for the duration of the shipment and include an iTag Datalogger monitor that **should be stopped immediately upon receipt to avoid a false or incorrect temperature alarm from being triggered**.

Shipment Receipt Instructions for IRT and Non-IRT Orders:

If you are unable to upload data to TempEZ, email datalogger files to gatewaysupport@almacgroup.com and include the protocol number (IMGN151-1001) and site number in the subject line.

The following directions are also provided within the shipment.

1. Stop Datalogger immediately upon the opening of container.
2. Follow the iTag4 Bio Temperature Site Instructions included with the shipment to retrieve the temperature data.
3. Within 48 hours of receipt, upload the temperature monitor files into the temperature monitoring database (TempEZ). If there are issues connecting to the TempEZ website, files should be downloaded and sent to your clinical research associated (CRA)/Monitor and to **gatewaysupport@almacgroup.com** The instructional video can be found under this link: https://vimeo.com/619947265/0347f90c76. **include the protocol number (IMGN151-1001) and the site number in the subject line.**
4. If the order is placed using an IRT system (4G), receive shipment in 4G under the Supply Menu, select Shipments and find the shipment that has arrived. Under ‘More Actions’, select Receive Shipment. Follow all the past steps for uploading temperature monitor files to TempEZ.
5. If the shipment is in excursion, please keep the Datalogger until further instructed and refer to Section 2.3.

Please acknowledge shipment and receipt of all study drugs received in the 4G Clinical portal and upload the temperature monitor data as per the instructions provided. All documents packaged with the shipment should be reviewed and completed as instructed. For any additional questions or concerns, contact your CRA/Monitor and email ImmunoGen at

IMGNdrugresupply@immunogen.com. Please reference Section 10 when emailing IMGNdrugresupply@immunogen.com.

2.2. Temperature Allowances During Shipment

IMGN151 and eye drops are packaged in an insulated shipping container that maintains the conditions as outlined in Table 1.

Table 11: Study Drug Shipping Temperature Allowance

Study Drug and Eye Drops	Shipping Temperatures
IMGN151	2 to 8°C / 36 to 46°F
Eye Drops	15 to 25°C/59 to 77°F

2.3. Handling of Temperature Excursions During Shipment

If temperature excursions have occurred during the shipment of the ImmunoGen-supplied products, the datalogger will show an "alarm". If this occurs,

6. Physically quarantine the product at the appropriate long-term storage condition.
7. Receive the shipment into the 4G Clinical portal in 'Quarantine' status.
8. Ensure data is uploaded to the TempEZ system per Section 2.1
9. Complete the Temperature Excursion Form and e-mail the form to the CRA and IMGNdrugresupply@immunogen.com **and include the protocol number (IMGN151-1001) and the site number in the subject line.**
10. If the logger was not immediately stopped upon opening of the container, please note in the Details section of the Temperature Excursion Form.
11. Please note that the maximum and minimum temperatures should not be rounded to the nearest whole integer when completing the form.
12. Wait for final disposition status from ImmunoGen or CRA.

ImmunoGen will determine if the study drug is still acceptable for use and will notify the site accordingly.

- If the study drug is not acceptable for use, the inventory status will be updated accordingly in the IRT and new supply will be sent to the site.
- If the study drug is acceptable for use, the inventory status will be updated to Available in the IRT.

2.4. Drug Shipment and Receipt at Satellite Sites

Shipment between the pharmacy/main site and a satellite site is not recommended for either IMGN151 or eye drops. In the event of transport between the pharmacy/main study site and

satellite sites, written documentation of this procedure is required along with temperature monitoring during transit and is subject to ImmunoGen review and approval prior to any transport of study drug. Documentation requirements are outlined in below in Section 2.4.1.

2.4.1. Documentation of Chain of Custody for Study Drug and Eye Drops for Transport from the Main Site to the Satellite Site

a. The site must have a transport log for IMGN151 and eye drops used for this purpose at both the main and satellite sites.

b. The transport log(s) must include date/time of transport, manner of transport (e.g., personal vehicle, contracted courier, etc.), name of person/courier responsible for transport and manner of documentation of receipt at the satellite site.

c. 'Time out' for transport and 'time in' at receipt must be recorded for all transports.

d. Temperature monitoring of the drug during transport is required. Excursions outside of the 2-8°C range for IMGN151 must be evaluated against the allowable excursion limits in Table 3. Temperature during transit for eye drops must align with storage conditions listed on the label or a Temperature Excursion Form must be submitted.

e. A qualified courier with experience on biohazard material transportation is recommended. If site staff will be transporting IMGN151 and/or eye drops, the name of the person transporting the product(s) must be recorded as trained in the transfer of biohazard material on both the site Training Log and the site Delegation of Responsibilities Log.

2.5. Container/Closure Inspection

A Certificate of Analysis and a Certificate of Expiry are provided by the CRO. The lot expiry date for IMGN151 should be verified via the Certificate of Expiry. Shelf-life is supported by stability studies and is indicated on the carton and vial label (EU) or on the Certificate of Expiry (US).

Do not use after the expiration date printed on the label (EU) or on the Certificate of Expiry (US).

The IMGN151 vials should be visually inspected for damage (i.e., cracks or leaks). Any damaged material should be quarantined and a record of any damaged or suspected damaged drug should be documented in the Product Dispensing/Accountability Logs, or equivalent.

For all drug provided by ImmunoGen please notify Product.Complaints@ImmunoGen.com (Section 7) and your CRA of damage or suspected damage of vials/bottles. ImmunoGen may authorize the return shipment of unused or damaged drugs. To replace the damaged vials/bottles, please notify IMGNdrugresupply@immunogen.com **and include the protocol number (IMGN151-1001) and the site number in the subject line.** Please refer to Section 4 for more information on drug disposition and vial return.

3. IMGN151 OVERVIEW

3.1. Introduction

The active ingredient, IMGN151, is an antibody drug conjugate supplied by ImmunoGen as a sterile and preservative-free solution. The drug product yields a solution that is clear to slightly opalescent, colorless to pale yellow, and essentially free from foreign visible particles. Each 20 mL glass vial contains 180 mg of deliverable IMGN151 and will have a nominal drug concentration of 12 mg/mL. The composition for IMGN151 drug product per vial is presented in Table 2 below:

Table 22: Quantitative Composition of IMGN151 Drug Product (Per Vial)

Component	Quality Grade	Function	Concentration
IMGN151	In-house	Active ingredient	12 mg/mL (180 mg deliverable)
Acetate (from Acetic Acid)	Ph. Eur.-BP/JP/USP	Buffer agent	10 mM
Sodium Hydroxide	Ph. Eur.-NF/BP	Buffer agent	N/A
Sucrose	Ph. Eur.-NF/BP/JP	Stabilizer	9% w/v
Polysorbate 80	Ph. Eur.-NF/JP	Stabilizer	0.01% w/v
Water for Injection	Ph. Eur.	Diluent	N/A

BP = British Pharmacopeia; JP = Japan Pharmacopeia; NF = National Formulary; Ph. Eur. = European Pharmacopeia; USP = United States Pharmacopeia.

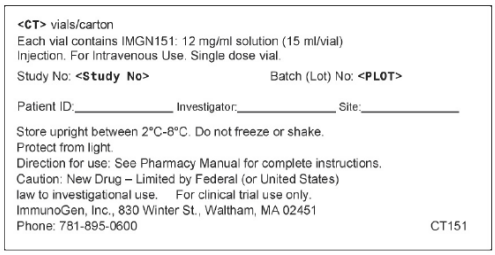
3.2. Packaging and Labeling

3.2.1. IMGN151

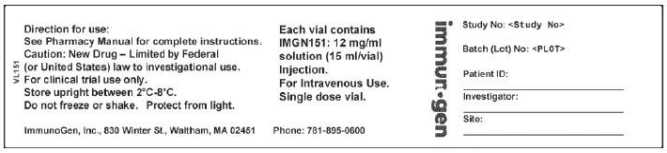
IMGN151 will be supplied in a sealed carton with 6 vials per carton. The container closure for each Type 1 glass vial consists of a latex-free butyl rubber stopper that has an ethylene tetrafluoroethylene (ETFE) fluoropolymer coating on the product contact surface and a 20 mm aluminum seal with a plastic Flip-off® top. Sample images of the IMGN151 carton and vial labels for the US are provided in Figure 1.

Figure 1: IMGN151 Carton and Vial Labels for the US

A) Carton Label



B) Vial Label



3.2.2. Eye Drops

Eye drops will be provided in the manufacturers' packaging and, where applicable per country requirements, will also contain study-related labeling to identify the product(s) as study supplies. Participants will be provided an eye care instructions sheet.

If required, the label on each carton of eye drops will include the following: a space to record the patient ID, investigator name, and site number. The label will also include the sponsor name and address, protocol number, a contact telephone number per local country requirements, the product (drug) name, strength, volume, number of units per carton, batch (lot) number, storage conditions, expiration date (where required). Limited use language that is country specific may be on the label as well. For example, "For Clinical Trial Use Only" or "Keep out of reach of children", could be found on some country specific labels.

If required, the label on each bottle of eye drops will include the following: a space to record the participant number, investigator name, and site number. The label will also include the company name and address, protocol number, a contact telephone number per local country requirements, the product (drug) name, strength, volume, batch (lot) number, storage conditions, expiration date (where required). Limited use language that is country specific may be on the label as well, similar to the carton labeling.

Country-specific regulations may result in changes or additions to the information listed above.

3.3. Storage and Stability

IMGN151 should be stored upright in the carton supplied at 2°C to 8°C (36°F to 46°F). DO NOT SHAKE OR FREEZE IMGN151 VIALS.

Exposure to high intensity light (i.e., UV light sources and direct sunlight) must be avoided. Exposure to light of normal (ambient) intensity (e.g., less than1000 lux) should be limited to a maximum of 8 hours.

Eye drops should be stored according to the manufacturers' labeling or storage instructions included on the study label.

3.3.1. Handling of Temperature Excursions During Storage

Table 3 provides information about on-site storage conditions for IMGN151 and the cumulative allowable time limits for specific temperature ranges. The total cumulative temperature excursion time for vials must be documented by the pharmacy in the applicable drug product accountability logs. Per Table 3, if an allowable temperature excursion is noted, the site does not need ImmunoGen approval to continue to store or dispense IP.

Should Pharmacy policy on reporting of excursions and this Manual disagree, the Manual reporting requirements must be followed unless the Pharmacy policy is more stringent. Records on refrigerator temperature data during study drug storage must be made available to the CRA/monitor and ImmunoGen upon request.

Table 33: IMGN151 Storage Temperature Excursions and Allowances

Temperature Range	Time Duration	Site can determine useability?	Comments
< 1.5°C	Any	No	Clinical Sites to quarantine product and send Temperature Excursion Form to CRA/Monitor and ImmunoGen[a1]to determine if product can be used[1].
1.5 to 8.4°C	Any	Yes	**Study drug can be used.**
8.5 to 25.4°C	Up to 6 hours (360 minutes) cumulative	Yes	**Study drug can be used.** Clinical sites to check cumulative time to ensure if less or equal to 6 hours (360 minutes). No Temperature Excursion Form required.
8.5 to 25.4°C	More than 6 hours (360 minutes) cumulative	No	Clinical sites to quarantine product and send Temperature Excursion Form and cumulative out of temperature time to CRA/Monitor and ImmunoGen[1]to determine if product can be used.
> 25.4°C	Any	No	Clinical Sites to quarantine product and send Temperature Excursion Form to CRA/Monitor and ImmunoGen to determine if product can be used[1].

IMP = investigational medicinal product.

[1]Contact ImmunoGen at IMGNdrugresupply@immunogen.com. **Please be sure to include the protocol number (IMGN151-1001) and site number in the email subject line.**

If a non-allowable temperature excursion occurs:

- Quarantine the product at 2°C to 8°C (36°F to 46°F)
- Update inventory status in the 4G IRT portal to 'Quarantined' for the impacted vials.
- Complete the Temperature Excursion Form and e-mail the form along with temperature data from the refrigerator to the CRA and IMGNdrugresupply@immunogen.com, **and reference the protocol number (IMGN151-1001) and the site number in the email subject line.**
- Please note that the maximum and minimum temperatures should not be rounded to the nearest whole integer when completing the form.
- Wait for final disposition status from ImmunoGen or CRA

ImmunoGen will determine if the study drug is still acceptable for use and will notify the site accordingly.

- If the study drug is not acceptable for use, the inventory status will be updated accordingly in the IRT, and new supply will be sent to the site.
- If the study drug is acceptable for use, the inventory status will be updated to Available in the IRT.

3.4. Precautions

IMGN151 is not expected to pose significant occupational safety risks to investigational and clinical staff under normal conditions of use and administration while following those procedures appropriate for the handling of cytotoxic agents (see Safety Data Sheet). As with any investigative agent, precautions should be taken to avoid direct contact with IMGN151. It is recommended that appropriate personal protective equipment be worn during preparation and administration. Do not deviate from procedures outlined in this Manual unless approved by ImmunoGen.

3.5. IMGN151 Preparation

All dispensing steps must be conducted to ensure product sterility. A Pharmacist or other appropriately licensed / authorized personnel must prepare IMGN151. IMGN151 IV preparation should be performed by qualified personnel using aseptic technique and in accordance with the country specific regulatory requirements (US: USP <797> & <800>). Refer to the SDS for hazard identification. Transport of study drug must be in accordance with local and country requirements for cytotoxic drugs. A pharmacy log with sufficient detail must be kept for each preparation to verify appropriate calculation and preparation and study drug inventory. All calculations and preparations must be double checked for accuracy before release of the study drug preparation. **Study drug vials are for single dose only.** The used study drug vial(s) may not be used for any additional participants even if dosed at the same time. The study drug vials do not contain any preservatives or antimicrobial agents. Precautions should be used to maintain

the sterility of the vials and the prepared study drug. Unused IMGN151 vials removed from the refrigerator and stored at ambient temperature can be returned to the refrigerator for later use, following the allowable storage guidelines outlined in Table 3.

Used vials are to be kept (at ambient temperature) for study drug reconciliation unless otherwise prohibited by site/local practices, documented (e.g., SOP), and such documentation is shared with the Sponsor and/or CRO. Accountability, Destruction and Method of Destruction should be documented and stored in the pharmacy binder and provided to the CRA upon request.

IMGN151 Dose Determination and Dispensing

All doses of IMGN151 must be diluted in sterile D5W prior to IV administration. IMGN151 diluted in D5W is stable within the concentration range of 0.3 mg/mL to 6.0 mg/mL, therefore the minimal allowable infusion concentration is 0.3 mg/mL and maximum allowable concentration for IV infusion is 6.0 mg/mL.

The calculated dose of IMGN151 administered will be based on the study participant's body weight at Cycle 1, Day 1 (C1D1) for dose escalation Cohort 1 and the study participant's BSA based on body weight and height at C1D1 for all remaining cohorts in dose escalation, and during dose optimization and dose expansion. Body weight will be measured at screening and Day 1 of each cycle. Body weight at C1D1 is the baseline weight. For subsequent cycles, significant (≥ 10%) change in body weight from baseline should prompt a recalculation of dose. A dose change with a new revised weight will become the baseline for any future dosing/changes. The most recent weight measured should be used for calculation. If a weight increase is noted in the most recent measurement, the value *should not* be used if it is attributed to fluid retention.

NOTE: Use the IMGN151 Dose and Total Infusion Volume Calculation Sheet (APPENDIX A) and perform the following calculations:

1. Determine the total amount of IMGN151 needed, based on the following:
2. Escalation Cohort 1:

IMGN151 Dose (mg) = Patient weight (kg) x Dose Level (mg/kg)

Rounding: Dose will be rounded to the nearest whole mg (normal rounding rules)

3. Escalation Cohorts 2-10, dose optimization and dose expansion:

IMGN151 Dose (mg) = Patient BSA (m^2) x Dose Level (mg/m^2)

Rounding: Dose will be rounded to the nearest whole mg (normal rounding rules)

4. Determine the volume of study drug needed, based on the following:

IMGN151 Volume (mL) = IMGN151 Dose (mg) / IMGN151 Concentration (12 mg/mL)

Rounding: Volume will be rounded to the nearest tenth decimal (normal rounding rules))

Refer to Table 4 to determine the final total IV bag volume needed for drug preparation.

Table 44: Determination of the Final Total IV Bag Volume of IMGN151 + D5W

IMGN151 Dose Level	Total IV Bag Volume (mL)
0.75 mg/kg	100[a1]
50 mg/m^2	100
100 mg/m^2	100
130 mg/m^2	100
160 mg/m^2	100
200 mg/m^2	100 or 250 dependent on BSA[a]
250 mg/m^2	250[a]
300 mg/m^2	250[a]
390 mg/m^2	250[a]
500 mg/m^2	250[a]

[a] Note the allowable concentration is 0.3 mg/ml to 6.0 mg/ml in the IV bag; thus, bag volumes may need to be adjusted accordingly. Note that the maximum allowable total dose is 1200 mg.

5. Determine the number of IMGN151 vials needed for the dose volume, based on the following:

Number of Vials = IMGN151 Volume (mL) / Extractable volume per vial (15 mL)

Rounding: Round up to the whole vial

6. Determine the volume of 5% Dextrose Injection USP (D5W) needed for dilution, based on the following:

Volume of D5W (mL) = Total IV Bag Volume (mL) - IMGN151 Volume (mL)

Rounding: Volume will be rounded to the nearest tenth decimal (normal rounding rules)

For patients enrolled into dose optimization, randomization will be done in the 4G IRT system (please refer to 4G User Guide for details). For all patients in dose escalation, optimization and expansion, the patient visit (e.g. C1D1, C2D1 etc.) should be recorded in the 4G IRT immediately prior to dispensing study drug. The 4G IRT system will then provide the quantity and lot number of IMGN151 to be dispensed. All dispensing steps must be conducted so that the product remains sterile, if applicable. A pharmacist or appropriately licensed / authorized individual must prepare IMGN151.

Follow institutional practices for labeling and ensure the Patient Identification number (Patient ID) is noted.

A study-specific Investigational Product Dispensing/Accountability Log will be supplied by ImmunoGen or the Contract Research Organization (CRO) for IMGN151 and eye drops supplied; however, the log may be replaced with an equivalent institutional form with ImmunoGen or CRO approval. At a minimum the Investigational Product Dispensing/Accountability Log should capture the patient's initials (as per regional regulations) and patient number, the dose (mg) required, the number of vials or units dispensed; the lot number, the time IMGN151 was removed from the refrigerator, and the date of dispensing, Sites may defer to their pharmacy's standard operating procedure (SOP) for accountability log processes provided that the SOP is available for ImmunoGen or CRO review. Materials

The components utilized for dilution, preparation, and administration of study drug should be suitable for the dosing volume and rates specified in Table 8. See examples of compatible materials in Section 3.9.

- IMGN151 vials assigned by IRT
- Polypropylene (PP) or polycarbonate (PC) syringes (appropriately sized for volumes)
- Sterile needles, pins or closed system transfer device (CSTD) for fluid transfer
- Diluent: 5% Dextrose Injection USP (for IMGN151 dilution and for pre-dose and post-dose flush)
- Infusion IV bag (empty or containing sterile 5% Dextrose Injection USP)
- IV tubing administration set with 0.2 or 0.22 µm in line filter
- IV Catheter
- Light protection for storage
- Infusion pump

3.6. IMGN151 Dilution with 5% Dextrose Injection USP (D5W)

Study drug vials are for single use only. Please note IMGN151 from different lots must not be mixed in a single administration. Keep separate pharmacy log sheets for different lots.

All doses of IMGN151 must be diluted in sterile D5W prior to IV administration. Please note IMGN151 is not compatible with saline solutions. IMGN151 must be diluted in D5W within the concentration range of 0.3 mg/mL to 6.0 mg/mL.

Note: refer to Section 3.6.1 for examples of dosing preparation.

1. Remove the required number of IMGN151 vials from the refrigerator approximately 30 to 60 minutes prior to preparation to allow the drug product to reach ambient temperature (18– 25°C). Keep protected from direct light.
2. The vial expiry date (EU) should be verified via the Certificate of Expiry, and a visual inspection of the vial(s) for cracks, leaks or any other damage should be done. The

expiry date will not be on the US Cartons/Vials, expiry date will be available in the IRT.

3. Gently invert/swirl to ensure content are well mixed. **Do NOT shake**.
4. If preparing the study drug in a sterile empty IV bag, draw up the required volume of IMGN151 and add to the empty IV bag. Then draw up the calculated balance of sterile 5% Dextrose Injection USP (D5W) and add to the IV bag with the study drug. Ensure that the total volume of infusion matches the total IV bag volume listed in Table 4. Gently mix the diluted drug solution by slowly inverting the bag at least 10 times to ensure complete mixing. **Do not shake or agitate.**
5. If preparing the study drug in a pre-filled D5W IV bag, withdraw the amount of D5W equivalent to volume of IMGN151 that will be added, plus IV bag overfill volume. Then add the required volume of IMGN151 to the D5W bag. Gently invert/swirl to ensure content are well mixed. **Do NOT shake or agitate**.
6. Label the prepared IMGN151 IV bag in accordance with local policy. Indicate the dose (mg) and volume to be infused.

Note: Once diluted in 5% Dextrose Injection USP, IMGN151 can be stored at 2°C to 8°C (under refrigeration). Protect the prepared IV bag from light. The infusion should be started within 24 hours from the time of preparation.

Do not reuse or administer to another patient. Used study drug vials should be retained separately at ambient temperature for study drug reconciliation if permitted by institutional practice; otherwise, dispose of used IMGN151 vials in the designated cytotoxic waste bin in accordance with institutional policy.

3.6.1. Examples of Drug Dosing/Preparation

Table 55: 75 mg Dose Preparation in 100mL IV Bag

Dose Level 50 mg/m^2								
BSA mg/m^2	**Dose** mg/m^2	**Drug Required (mg)**	**IMGN151 Vial Conc. (mg/mL)**	**Volume of IMGN151 (mL)**	**IMGN151 Vials (n)**	**D5W Volume (mL)**	**Total Volume (mL)**	**Final Concentration (mg/mL)**
1.5	50	75	12	6.3	1	93.7	100	0.75*

Table 66: 260 mg Dose Preparation in 100mL IV Bag

Dose Level 130 mg/m^2								
BSA mg/m^2	**Dose** mg/m^2	**Drug Required (mg)**	**IMGN151 Vial Conc. (mg/mL)**	**Volume of IMGN151 (mL)**	**IMGN151 Vials (n)**	**D5W Volume (mL)**	**Total Volume (mL)**	**Final Concentration (mg/mL)**
2.0	130	260	12	21.7	2	78.3	100	2.6

Table 77: 750 mg Dose Preparation in 250 mL IV Bag

Dose Level 300 mg/m^2								
BSA mg/m^2	**Dose** mg/m^2	**Drug Required (mg)**	**IMGN151 Vial Conc. (mg/mL)**	**Volume of IMGN151 (mL)**	**IMGN151 Vials (n)**	**D5W Volume (mL)**	**Total Volume (mL)**	**Final Concentration (mg/mL)**
2.5	300	750	12	62.5	5	187.5	250	3.0*

* Note the allowable concentration is 0.3 mg/ml to 6.0 mg/ml in the IV bag, thus bag volumes may need to be adjusted accordingly.

3.7. Administration Instructions

Prior to administration of study drug, the Investigator must review and confirm that the patient is eligible to participate in the study. Please refer to the protocol for further information about IMGN151 eligibility criteria.

Sites should follow local institutional policies for administration of IV chemotherapeutic agents. IMGN151 does not contain any preservative; therefore, study drug administration should begin within 24 hours after preparation and may be stored at 2 to 8°C, protected from light.

If the prepared study drug is stored at 2 to 8°C, it should be removed from the refrigerator at least 30 to 60 minutes prior to administration, to allow the solution to reach room temperature. Allow prepared study drug to reach room temperature without warming methods. The total time at room temperature may not exceed 8 hours, inclusive of infusion time with the study drug bag protected from light. No light protection for IV tubing is required.

IMGN151 should be administered as an IV infusion using a programmable calibrated IV infusion pump. **Do not piggyback into an IV line.** IMGN151 must not be administered as an IV push, bolus or as an uncontrolled rate infusion.

1. Prior to connecting study drug, flush patient's access with at least 30mL 5% Dextrose Injectable USP (IMGN151 is not compatible with saline solutions).
2. Program the IV pump in accordance with the infusion rates specified below:
    a. The first infusion of IMGN151 should be administered at a rate of 50 mL/hr for the first 30 minutes on Cycle 1 Day 1.
    b. If well tolerated, the infusion rate will be increased after 30 minutes to 100 mL/hour on Cycle 1 Day1.
    c. In subsequent cycles, IMGN151 may be infused at the highest tolerated rate up to 100 mL/hr. Infusion time will therefore vary depending on patient tolerability See Table 8 for a summary of infusion rates and times for each dose level.
    d. If patients develop infusion related reaction, site needs to slow the infusion rate or stop the infusion by following Protocol Section 5.5.2.
3. Proceed with post-dose 5% Dextrose Injection USP flush per Section 3.7.1.

Notes: Other methods of IV study drug administration using a pump are acceptable in accordance with institutional practice, as long as they can accurately deliver the prescribed volume/dose of IMGN151 at the indicated rate, and that all deliverable drug is accounted for.

Details of the dose level and the total dose administered should be documented in the source records as noted below:

- The start and stop times for each administration
- Infusion rate(s)
- Volume administered (at each rate, if applicable)
- Total volume administered
- The times of any interruption/decreases
- The reason if any administration is stopped prematurely

Table 88: IMGN151 Step Infusion Rate and Infusion Time at Different Dose Levels

IMGN151 Dose Level	Total IV Bag Volume (mL)	Step infusion rate for the first dose	Infusion time for the first dose (min)	Infusion rate for subsequent doses	Infusion time for subsequent doses (min)
0.75 mg/kg	100	50 mL/hr x 30 min then 100 mL/hr	75	100 mL/hr	60
50 mg/m^2	100	50 mL/hr x 30 min then 100 mL/hr	75	100 mL/hr	60
100 mg/m^2	100	50 mL/hr x 30 min then 100 mL/hr	75	100 mL/hr	60
130 mg/m^2	100	50 mL/hr x 30 min then 100 mL/hr	75	100 mL/hr	60
160 mg/m^2	100	50 mL/hr x 30 min then 100 mL/hr	75	100 mL/hr	60
200 mg/m^2	100 or 250 (depending on BSA)	50 mL/hr x 30 min then 100 mL/hr	75 or 165	100 mL/hr	60 or 150
250 mg/m^2	250[a]	50 mL/hr x 30 min then 100 mL/hr	165	100 mL/hr	150
300 mg/m^2	250[a]	50 mL/hr x 30 min then 100 mL/hr	165	100 mL/hr	150
390 mg/m^2	250[a]	50 mL/hr x 30 min then 100 mL/hr	165	100 mL/hr	150
500 mg/m^2	250[a]	50 mL/hr x 30 min then 100 mL/hr	165	100 mL/hr	150

[a] Note the allowable concentration is 0.3 mg/ml to 6.0 mg/ml in the IV bag, thus bag volumes may need to be adjusted accordingly. Note that the maximum allowable total dose is 1200 mg.

3.7.1. Post-IMGN151 Administration Flush with 5% Dextrose

When the IMGN151 infusion is complete, immediately flush the patient access with 30 mL of 5% Dextrose Injection USP to clear any residual IMGN151 from the catheter/CSTD.

Note: IMGN151 is NOT compatible with Saline solutions.

The start and stop time of the 5% Dextrose post-dose flush must be documented in the source records, as the stop time is considered the End of Infusion.

3.8. Eye Drop Administration

3.8.1. Lubricating Eye Drops

All participants will be instructed to use preservative-free lubricating artificial tears from C1D1 prior to and after dosing at least 4 times each day and continue through study treatment.

3.8.2. Vasoconstricting Eye Drops

If a participant develops corneal AEs of microcyst-like epithelial keratopathy ≥ Grade 2 (e.g., confluent keratopathy or keratopathy resulting in 3-line or more loss of BCVA), a prophylactic regimen of ocular vasoconstricting eye drops (brimonidine tartrate or equivalent adrenergic receptor agonist) should be added for subsequent cycles, unless the risks outweigh the benefits per the eye care specialist. Please see the clinical protocol for details.

3.8.3. Corticosteroid Eye Drops

If corneal AEs of microcyst-like epithelial keratopathy ≥ Grade 2 (e.g., confluent keratopathy or keratopathy resulting in 3-line or more loss of BCVA) are recurrent in participants on prophylactic vasoconstricting eye drops, a qualified medical professional or treating physician may choose to begin prophylactic corticosteroid eye drops in subsequent cycles. These participants should be instructed to use prophylactic corticosteroid eye drops for all subsequent cycles unless the risk outweighs the benefit. Please see the clinical protocol for details.

3.9. IMGN151 Compatibility and Incompatibility

IMGN151 is **NOT compatible** with the following:

- Saline solutions (0.9% sodium chloride)
- Heparin containing solutions
- Any other IV drug or IV electrolyte fluid
- IV fluids other than 5% dextrose have not been tested, and therefore, are not considered compatible
- PVC plasticized with di-2-ethyl-hexylphthalate (DEHP)

IMGN151 is **compatible** with the following:

- **Syringe/CSTD Components**: acrylonitrile-butadiene-styrene copolymer (ABS), PC, polyacetyl, polyisoprene, polytetrafluoroethylene (PTFE), PP, PVC, silicone, stainless steel, thermoplastic elastomer (TPE)
- **Infusion Sets:** (PVC or polyethylene (PE) lined/low absorption)

- **IV Filter 0.2 μm or 0.22 μm**: polyethersulfone (PES)
- **IV Catheters**: ethylene tetrafluoroethylene (ETFE), fluorinated ethylene propylene (FEP), polyurethane (PUR), Vialon biomaterial, non-PVC, non-DEHP, non-latex
- **IV Bags for dilution**: tris (2-Ethylhexyl) trimellitate (TOTM), polyolefin (PO) (e.g., polymer of ethylene and/or propylene)
- **IV solutions:** 5% Dextrose for Injection

The compatibility of IMGN151 with fluid contact materials which are not listed as acceptable or compatible is unknown and should not be used without ImmunoGen approval.

Contact ImmunoGen before the use of any unlisted equipment or fluid contact materials. Other equipment/materials should not be used without written agreement from ImmunoGen.

4. DISPOSITION AND DISPOSAL OF DRUG AND MATERIALS

The study/satellite site or pharmacy must maintain accurate records demonstrating dates and amount of both IMGN151 and eye drops (if applicable) received from ImmunoGen, who received study medication, and any study medications accidentally or deliberately destroyed.

After study drug accountability and reconciliation has been completed by the monitor (or as per institution policy for used study drug retention), open, partially used drug should be discarded in a suitable Biological Hazard waste container and subsequently incinerated/disposed according to institutional policy. A copy of the institution destruction policy will be filed in the investigator/pharmacist file.

Unused study drug remaining at study closure are also to be destroyed according to institutional policy, ideally after verification by the CRA/Monitor. The pharmacist will complete the Drug Destruction Memo and the accountability log or equivalent. Documentation of drug destruction must include the following: protocol number; site number; lot number(s); expiry date(s); quantity; the person responsible for destroying the drug; the date the drug was destroyed and the reason for its destruction are documented on the Drug Destruction Memo.

If IMGN151 and/or eye drops need to be returned for any reason to the depot, the site will register the shipment within 4G and follow the “Instruction for Return Shipments”. If vials need to be returned to ImmunoGen, the site will complete the Drug Return Form and email it to IMGNdrugresupply@immunogen.com, **please include the protocol number (IMGN151-1001) and the site number in the subject line of the email** . If there are any questions, please contact ImmunoGen (IMGNdrugresupply@immunogen.com) **and include the protocol number (IMGN151-1001) and the site number in the subject line and cc your CRA.**

5. DRUG SUPPLY AND REQUEST FOR RE-ORDER

ImmunoGen will provide the initial study drug supply once the site is authorized to receive study drug. The IRT vendor, 4G Clinical, has been contracted by ImmunoGen to support drug supply/resupply management for the study drug.

Activating a site in the 4G Clinical portal or screening a participant will trigger the initial study drug(s) shipment. 4G Clinical will communicate with the depot to send the study drug(s). Sites will confirm delivery of shipment in the 4G Clinical portal. Resupply shipments will be generated automatically based on actual and forecasted drug usage as calculated by the 4G IRT portal. In exceptional cases, sites can request the drug manually. Provide the CRA/Monitor and IMGNdrugresupply@immunogen.com **with the protocol number (IMGN151-1001) and site number in the subject line** with requested quantity, current inventory and reason for request. Upon approval, ImmunoGen will trigger a manual resupply in the 4G system.

It is anticipated that from the time of manual or IRT drug order to the time of drug receipt at the study center will be approximately **one week**. In the event additional drug is required within one week from the planned treatment of a participant, immediately contact your CRA/Monitor and ImmunoGen at IMGNdrugresupply@immunogen.com **with the protocol number (IMGN151-1001) and the site number in the subject line**.

Eye drop inventory will not be managed through the 4G system and should be monitored by the sites. ImmunoGen or Almac will trigger initial orders in 4G. The Resupply orders will be manually triggered by the sites through 4G or by contacting the CRA/Monitor. In an emergency situation, a resupply eye drop order can be requested by sending an email to IMGNdrugresupply@immunogen.com **with the protocol number (IMGN151-1001) and the site number in the subject line**.

Note: sites will only be able to manually order eye drops and not the IMGN151 drug.

5.1. Pharmacy Address Change

Should the address of the pharmacy change at any time throughout the trial, please contact your CRA.

6. DRUG ACCOUNTABILITY

Record the patient identification number (Patient ID) in the space provided on both the vial and carton label(s) for the unit(s) dispensed for that patient.

A separate Investigational Product Dispensing/Accountability Log or equivalent should be maintained for IMGN151 and each eye drop type. Vials or other dispensing units should be visually inspected for vial integrity (i.e., cracks or leaks) or other damage and a record of any damaged or suspect drug should be kept on the Investigational Product Dispensing/Accountability Log or equivalent.

All supplies for the study will be accompanied by accountability and shipping documents that must be maintained by the Pharmacist. This includes the Certification of Analysis for IMGN151 and the Certificate of Expiry (provided by the CRO), that must be maintained by the Pharmacist, or authorized site staff. Drug accountability monitoring will be performed by the CRA throughout the study. By prior arrangement, all study related files and logs, as well as access to study medication and storage areas, should be made available to the CRA/Monitor and ImmunoGen as requested. No documents should be destroyed, as these are required for the Trial Master File. At the end of the study, there will be a final reconciliation of all accountability records.

7. CLINICAL PRODUCT COMPLAINTS

If a product defect is observed, please complete the Clinical Product Complaint Form, located in the pharmacy binder. Quarantine affected material (in an area that meets the product's storage requirements) until ImmunoGen provides further guidance. Please take pictures/video showing the defect whenever possible. Email the form, along with the following information and attachments (as applicable) listed below, to Product.Complaints@ImmunoGen.com.

- Name and phone number
- Description of the defect (what was observed/when)
- Product name and lot Number
- Pictures and/or video of observed defect (if applicable)

Product defect includes any noticeable difference in the appearance, physical-chemical, or microbiological properties of the drug. Defects can be observed during storage, preparation, or administration.

8. SUPPORTING DOCUMENTATION (FORMS / TEMPLATES)

The following forms and templates are available for use by your site:

- Almac Drug Shipment and Acknowledgment Reference Guide
- Temperature Excursion Form
- Product Dispensing Accountability Logs for IMGN151 and eye drops
- Drug Destruction Memo
- Drug Return Form
- Instructions for Return Shipments
- Clinical Product Complaint Form & Completion Instructions

9. DRUG ADMINISTRATION AND SATELLITE SITES

In the event that the participant is to receive drug at a satellite clinic, a mechanism must be established to ensure that study drug is dispensed only upon the order of the Investigator or a licensed clinician directly responsible to the Investigator as stated on Form FDA 1572 or equivalent. By completing and signing the order, the Investigator has certified that the study drug will be administered only to participants under his/her personal supervision or under the supervision of sub-investigators responsible to him/her.

10. CONTACT INFORMATION

Please reference ImmunoGen or your CRA with any questions / concerns. Contact ImmunoGen at IMGNdrugresupply@immunogen.com **and include the protocol number (IMGN151-1001) and the site number in the subject line** and cc your CRA.

APPENDIX A: IMGN151 DOSE AND TOTAL INFUSION VOLUME CALCULATION SHEET

Dose Escalation Cohort 1	
Patient ID:	
Dose Level (mg/kg):	
Patient's Body Weight in Kg: *(Rounded to the tenth decimal place, e.g., values < .5 are to be rounded down to the nearest whole number and values ≥ .5 to be round up to nearest whole number)*	
IMGN151 to be dosed (rounded to whole mg): *(Dose level mg/kg × Body weight kg)*	
Volume of IMGN151 (mL): *(IMGN151 mg/ 12 mg/mL)*	
D5W bag volume (mL):	
Volume of D5W to be infused (mL): *(D5W bag volume – IMGN151 volume)*	
Total volume to be infused (mL): *(Volume of IMGN151 + Volume of D5W to be infused)*	
Final Concentration (mg/mL): (IMGN151 in mg/ Total volume to be infused in mL; needs to be within **0.3 and 6.0 mg/mL)**	

Dose Escalation Cohorts 2-10, Dose Optimization and Dose Expansion:	
Patient ID:	
Cohort Number (Dose Escalation) OR Dose Level (Dose Optimization) OR Cohort Letter (Dose Expansion)	
Dose Level (mg/m^2)	
BSA (m2) *See BSA equation below*	
IMGN151 to be dosed (rounded to whole mg) *(Dose level mg/m2 × BSA m^2)*	
Volume of IMGN151 (mL) *(IMGN151 mg/ 12 mg/mL)*	
D5W bag volume (mL)	
Volume of D5W to be infused (mL) *(D5W bag volume – IMGN151 volume)*	
Total volume to be infused (mL) *(Volume of IMGN151 + Volume of D5W to be infused)*	
Final Concentration (mg/mL): *(IMGN151 in mg/ Total volume to be infused in mL; needs to be within 0.3 and 6.0 mg/mL)*	

Patient's Body Surface Area (Mosteller's equation):

$$\text{BSA } (m^2) = \sqrt{\frac{Height\ (in) \times Weight\ (lb)}{3131}}$$

(Height in inch; weight in pound)

OR

$$\text{BSA } (m^2) = \sqrt{\frac{Height\ (cm) \times Weight\ (kg)}{3600}}$$

(Height in cm; weight in kg)

Online BSA calculator by Mosteller's formula: https://www.easycalculation.com/medical/bsa-Mostellers.php

APPENDIX B: STUDY IMGN151-1001 IV ADMINISTRATION GUIDANCE FOR INFUSIONIST

Appendix B
Study IMGN151-1001
IV ADMINISTRATION GUIDANCE FOR INFUSIONIST

Version Date: 02 Oct 2024

Version 6.0

CAUTION: IMGN151 is an Investigational New Drug – Limited by Federal (or United States) Law to Investigational/Clinical Trial Use Only. To be Used by Qualified Investigators Only. For Clinical Trial Use Only.

TABLE OF CONTENTS

LIST OF TABLES

11. INTRODUCTION

In this study, IMGN151 will be given as an IV infusion on Day 1 of each 21-day Cycle (Q3W) unless held for toxicity. IMGN151 is administered as a stepped IV infusion. Infusion rate and duration will vary depending on assigned dose level, total bag volume and participant's tolerability. The infusion rate may be adjusted for an infusion reaction as outlined in this document and as directed by the study site physician. Participant's dose level may be subject to modification/change by the study sponsor. The planned starting assigned dose levels and IV bag volumes are as follows but may be subject to change.

Table 99: Dose Levels and Corresponding Total IV Bag Volumes

IMGN151 Dose Levels	Total IV Bag Volume (mL)
0.75 mg/kg	100[a]
50 mg/m^2	100
100 mg/m^2	100
130 mg/m^2	100
160 mg/m^2	100
200 mg/m^2	100 or 250 dependent on BSA[a]
250 mg/m^2	250 [a]
300 mg/m^2	250 [a]
390 mg/m^2	250[a]
500 mg/m^2	250[a]

a Note the allowable concentration is 0.3 mg/ml to 6.0 mg/ml in the IV bag, thus bag volumes may need to be adjusted accordingly. Note that the maximum allowable total dose is 1200 mg.

12. ITEMS REQUIRED FOR IMGN151 ADMINISTRATION

- Study drug IV bag containing IMGN151
- Sterile empty IV bag or prefilled sterile IV bag of 5% Dextrose for injection, USP, 50, 100 or 250 mL for drug preparation and for line flush.
- All IV supplies for administration and to establish venous access via peripheral or central catheter, injection cap and line connectors. **Arterial infusion is not permitted**. Primary IV pump infusion set with maximum hold up volume (<23 mL). Tubing SHOULD BE A SHORT AS POSSIBLE, AND must not be longer than 3 meters (10 feet), with composition of either:

  - PVC and DEHP free (e.g., B.Braun catalogue #362032, or of similar composition), or
  - Low protein absorption IV tubing is not required but may be used.
  - Line connectors, and secondary IV set if required for the D5W flush.
  - Peripheral IV Catheter (BD Saf-T-Intima, BD Nexiva, BD Insyte or equivalent), central line catheter materials have not been evaluated for compatibility, therefore central line administration should only be considered if peripheral access is not available.
- A sterile 0.2-0.22µm in-line IV filter, Polyethersulfone (PES, Supor) membrane filter, no other filter types are permitted. (e.g., Baxter 2C8671, 2H8671 B.Braun 352205, 473993, 473993)
- Use of closed system transfer device (CSTD) for IV connections are permitted
- Programmable infusion pump
- Alcohol wipes, non-sterile gloves, and a sharps container

13. IMGN151 ADMINISTRATION PRECAUTIONS

- Participant's C1D1 dose is calculated by using body weight and height, as required, measured on C1D1. For any subsequent cycle, study team needs to check the participant's predose weight against the weight from the latest dosing visit (significant changes ≥ 10% will require re-calculation) and calculate/verify the dosage in accordance with the Pharmacy Manual. Complete all predose blood work and assessments per the protocol. Allow sufficient time for IMGN151 preparation and establish venous access.
- All patients will receive lubricating eye drops, immediately prior to and after dosing.
- Patient will be given acetaminophen or paracetamol 500 to 1000 mg (PO) or ibuprofen 400 mg to 600 mg PO, and diphenhydramine 25-50 mg IV (or equivalent H1 antagonist), dexamethasone 10 mg IV or equivalent (Cycle 1 administration required; later administration is at the discretion of the investigator) and Famotidine 40 mg PO or equivalent H2 antagonist at least 30 minutes prior to the infusion. Equivalent medications may be substituted based on institutional standard of care and availability.
- For subsequent study drug administration in a participant who had an IRR that was not adequately or only moderately controlled with acetaminophen and diphenhydramine, investigators may modify the premedication regimen according to standard institutional practice. Nonsteroidal premedication may be administered prior to the subsequent infusion, if warranted.
- Examine the IMGN151 bag for clarity and particles. Do not administer the prepared diluted IMGN151 if expired.

- Verify patency of the IV site, IMGN151 is to be infused **as a primary IV directly connected at a central or peripheral catheter or a Y-site**. The IMGN151 should not be connected to extension tubing and/or valve blocks for the infusion. **No other infusion fluid other than 5% Dextrose Injection is to be mixed with the IMGN151 during its administration. No other IV hydration (primary fluid) or other IV medications are to be administered during the IMGN151 infusion.**
- The preferred method of administration is direct connection to the catheter or through an injection port attached to the catheter. If a Y-site catheter is used, it must be thoroughly flushed, and no other medications may be given while the IMGN151 is being infused.
- Administration of IMGN151 must be through a 0.2-0.22µm in-line IV filter attached to the IV set. Care should be given to minimize the total IV-line/filter hold-up volume, in particular for 100 mL IMGN151 dosing bags.
- If using a primary IV infusion set, the IMGN151 IV infusion set with filter is to be primed, then placed in the pump, and the pump programmed prior to attaching the IV tubing to the study subject. Set the total pump volume to be delivered equal to the IMGN151 bag volume. Set the rate to the first step infusion rate.

Administration rate:

- **The first dose of IMGN151 is to be administered at a rate of 50 mL/hr for the first 30 minutes, if well tolerated then the rate can be increased to 100 mL/hr.**
- **If the first dose was well tolerated, then the second dose and all subsequent doses may start at 100 mL/hr.**
- **If the first dose (or repeat dose) is not well tolerated, start all subsequent infusions at a rate of 50 mL/hr for the first 30 minutes and limit the maximum rate to 100 ml/hr, or the maximum previously tolerated rate for all subsequent doses.**

Table 1010: IMGN151 Step Infusion Rate and Infusion Time at Different Dose Levels

IMGN151 Dose Level	Total IV Bag Volume (mL)	Step infusion rate for the first dose	Infusion time for the first dose (min)	Step infusion rate for subsequent doses	Infusion time for subsequent doses (min)
0.75 mg/kg	100	50 mL/hr x 30 min then 100 mL/hr	75	100 mL/hr	60
50 mg/m^2	100	50 mL/hr x 30 min then 100 mL/hr	75	100 mL/hr	60
100 mg/m^2	100	50 mL/hr x 30 min then 100 mL/hr	75	100 mL/hr	60
130 mg/m^2	100	50 mL/hr x 30 min then 100 mL/hr	75	100 mL/hr	60
160 mg/m^2	100	50 mL/hr x 30 min then 100 mL/hr	75	100 mL/hr	60
200 mg/m^2	100 or 250 (depending on BSA)	50 mL/hr x 30 min then 100 mL/hr	75 or 165	100 mL/hr	60 or 150
250 mg/m^2	250[a]	50 mL/hr x 30 min then 100 mL/hr	165	100 mL/hr	150
300 mg/m^2	250[a]	50 mL/hr x 30 min then 100 mL/hr	165	100 mL/hr	150
390 mg/m^2	250[a]	50 mL/hr x 30 min then 100 mL/hr	165	100 mL/hr	150
500 mg/m^2	250[a]	50 mL/hr x 30 min then 100 mL/hr	165	100 mL/hr	150

[a] Note the allowable concentration is 0.3 mg/ml to 6.0 mg/ml in the IV bag, thus bag volumes may need to be adjusted accordingly. Note that the maximum allowable total dose is 1200 mg.

NOTE: If hypersensitivity or an infusion reaction develops, the infusion of study drug should be stopped, and the treating physician or investigator immediately contacted for management and further infusion directions. If extravasation should occur stop the infusion. Apply light pressure and elevate the arm. At the discretion of the treating physician or investigator, a new IV site may be restarted in the contralateral limb and the infusion continued.

- When the IMGN151 infusion is started, record the time. When the IMGN151 bag is empty and before the drip chamber is emptied, pause the pump, attach a 5% Dextrose Injection bag (either by switching bags or though the IV-line secondary medication port) and immediately resume the infusion until the indicated IMGN151 bag volume

has been infused. Then flush the IV line with an additional 30 mL of 5% Dextrose Injection.

- The start and stop time of the 5% Dextrose post-dose flush must be documented in the source records, as the stop time is considered the End of Infusion.
- If the infusion was interrupted, record the time of interruption and the restart time if applicable.
- When the IMGN151 infusion is completed, **discard the IV set/flush bag in accordance with local policy, it must not be used for other IV infusions.**
- Subjects should continue to be observed for at least 6 hours after the first infusion, and at least 1 hour after each subsequent infusion.

14. PHARMACOKINETIC BLOOD SAMPLES

- Post infusion PK samples are to be drawn from the contralateral arm, either by direct venipuncture or through a separate PK catheter. If unavailable, a different port from a central venous catheter may be used.
- **PK samples should not be drawn from any catheter that was previously used to administer IMGN151**. If a catheter used to administer IMGN151 is used care should be taken to ensure adequate flushing of the catheter prior to the PK draw.
- PK draws are to use an appropriate blood discard tube/syringe in accordance with local policy. A discard blood sample must be collected prior to the PK sampling for any catheter blood draws. Flush the catheter after all blood draws in accordance with local policy.
- PK samples are to be processed immediately after draw. Details of processing are contained in the Lab Manual. Record the time of draw, processing, and weight of the subject on the PK Day.
- Post infusion PK sample collection is required at EOI, 2 h, 4 h and 6 h after EOI for cycle 1 and cycle 3. PK collection time needs to be considered when planning patient's C1D1 and C3D1 visits.
- Patients need to return to clinic on Days 2, 3, 8 and 15 for PK sample collection and other exams Cycle 1 and Cycle 3. Day 2 and Day 3 visits need to be considered when planning patient's C1D1 and C3D1 visit.
- Please see protocol for additional ADA and Biomarker sample collection.

15. MANAGEMENT OF IMGN151 INFUSION RELATED REACTIONS (IRR)

Treatment of IV infusion reactions:

> **Note:** These recommendations should not replace best medical practice. Institutional standards and guidelines for infusion related reactions should be followed.
>
> Subjects having severe reactions (Grade 3) hypersensitivity or allergic symptoms should not be re-challenged with study drug unless approved by the sponsor Medical Monitor.

Hypersensitivity/anaphylactic reactions could occur with administration of IMGN151. All doses of the study drug must be administered in the clinic under qualified medical staff supervision. Prophylactic pre-infusion medications should be given prior to study drug infusions. Medications for the treatment of hypersensitivity reactions must be available for immediate use to treat the reaction. If an administration reaction occurs, subjects should be observed until resolution of symptoms or until they are considered medically stable by the treating physician. Appropriate post reaction prophylactic medications should be provided to minimize a recurrence (break through) of the reaction. Subjects should immediately report any signs of hypersensitivity and/or skin reaction(s) to the study staff.

The following are treatment guidelines (which may be modified as needed by the investigator according to the best practices of medicine) for IRR. Note that for participants who have an infusion reaction requiring corticosteroid administration, corticosteroid administration should be used as prophylaxis on subsequent infusions.

Grade 1

- Slow the infusion rate by 50%.
- Monitor the participant for worsening of condition.
- Continue rate at 50% reduction and increase dose rate to the original rate by doubling the infusion rate after 30 minutes, as tolerated to the initial rate. Consideration can be given to beginning subsequent infusions at 50% rate and increasing as tolerated. The maximum infusion rate is 100 mL/hr.

Grade 2

- Stop the infusion.
- Administer diphenhydramine hydrochloride 25 to 50 mg IV (or PO if IV not available).
- Acetaminophen or paracetamol 500 to 1000 mg PO or ibuprofen 400 mg PO for fever.
- Oxygen and bronchodilators for mild bronchospasm.
- Resume the infusion at 50% of the prior rate once the infusion reaction has resolved or decreased to Grade 1. The rate may then be escalated to the original rate after 30

minutes, as tolerated. Consideration can be given to beginning all subsequent infusions at 50% rate and increasing as tolerated. The maximum infusion rate is 100 mL/hr.

- Monitor for worsening condition. If symptoms recur, discontinue the infusion; no further study drug will be administered at that visit.

Grade 3

- STOP THE INFUSION AND DISCONNECT THE INFUSION TUBING FROM THE PARTICIPANT.
- TO AVOID EXACERBATION OF INFUSION REACTION: DO NOT FLUSH THE TUBING/CATHETER – ASPIRATE RESIDUAL DRUG FROM THE VASCULAR ACCESS DEVICE.
- Administer diphenhydramine hydrochloride 25 to 50 mg IV (or PO if IV is not available), dexamethasone 20 mg IV (or equivalent), and other medications/treatment as medically indicated. Higher doses of corticosteroids (e.g., methylprednisolone 2 to 4 mg/kg IV or the equivalent) may also be considered for acute management.
- IV fluids, supplemental oxygen, and bronchodilators should be considered, as appropriate.
- If the Grade 3 infusion reaction occurs with study drug administration, it will be discontinued for that day. If symptoms have resolved to baseline within 12 hours, study drug may be infused the next day with approval of sponsor Medical Monitor. In addition, participants should be pre-medicated for this re-challenge and for any subsequent doses of study drug.
- Participants who have a Grade 3 infusion reaction that does not resolve within 12 hours despite medical management should not receive further study drug. Participants who experience a second Grade 3 infusion reaction at the time of study drug re-challenge will permanently discontinue study drug.
- Report the event as a serious adverse event (SAE), if appropriate.

Grade 4

- STOP THE INFUSION AND DISCONNECT THE INFUSION TUBING FROM THE PARTICIPANT.
- TO AVOID EXACERBATION OF INFUSION REACTION: DO NOT FLUSH THE TUBING/CATHETER – ASPIRATE RESIDUAL DRUG FROM THE VASCULAR ACCESS DEVICE.
- Administer diphenhydramine hydrochloride 50 mg IV (or PO if IV not available), dexamethasone 20 mg IV (or more as considered appropriate), and other medications/treatment and repeat as medically indicated.
- Give epinephrine or bronchodilators as indicated.

- Support ventilation and blood pressure as indicated. Report the event as an SAE.
- Participants who have a Grade 4 infusion reaction will not receive further study drug.

Grade 5

- Report the event as an SAE.

All administration reactions are managed by the treating study physician. The sponsor Medical Monitor should be notified immediately of any administration Grade 3/4 reactions and outcome, or infusion related allergic reactions independent of grade. Based on safety review by the sponsor's Medical Monitor/ the infusion rate may be amended/extended if any infusion related safety issues are identified.

16. PREMEDICATION AND PROPHYLAXIS

Premedication is required to mitigate the occurrence of infusion-related reactions (IRR). Equivalent medications may be substituted based on institutional standard of care and availability. Premedication should be given at least 30 minutes prior to infusion of study drug and include:

- Acetaminophen or paracetamol 500 to 1000 mg PO, or ibuprofen 400 to 600 mg PO
- Diphenhydramine 25 to 50 mg IV or equivalent H1 antagonist
- Dexamethasone 10 mg IV or equivalent (Cycle 1 administration required; later administration is at the discretion of the investigator)
- Famotidine 40 mg PO or equivalent H2 antagonist

For subsequent study drug administration in a subject who had an IRR that was not adequately or only moderately controlled with acetaminophen or paracetamol 500 to 1000 mg PO or ibuprofen 400 to 600 mg and diphenhydramine (or equivalent), investigators may modify the regimen according to standard institutional practice. Additional premedication, such as montelukast, may be administered prior to the subsequent infusion, if warranted, and infusion rate may be slowed to a minimum of 25 mL/h at investigator discretion. All medications must be recorded.

Participants experiencing an allergic study reaction (such as urticaria, angioedema or anaphylaxis) to study drug administration must have their study drug immediately stopped, the symptoms should be immediately treated in accordance with local practice. The participant should be medically monitored with an adequate follow-up time that symptoms have resolved, or the participant is felt to be medically stable before being released. Sponsor may require all subsequent treatments for an individual participant, or all subsequent participants receive prophylactic treatment.

To reduce the incidence of ocular symptoms after the dosing of IMGN151, all participants are also required to receive cool lubricating artificial tears immediately prior to and after dosing for 4-5 times each day starting from C1D1 and continuing throughout study treatment.

Participants with ocular symptoms should also be instructed to use topical ocular vasoconstricting eye drops (e.g., brimonidine tartrate 0.2% BID or equivalent adrenergic receptor

agonist) and/or corticosteroid eye drops. The instruction for using vasoconstricting and corticosteroid eye drops can be found in section 3.8 above.

17. STABILITY OF PREPARED IMGN151

IMGN151 does not contain any preservative; therefore, study drug administration should begin within 24 hours after preparation and may be stored at 2 to 8°C, protected from light.

Doses prepared in an IV bag are stable for up to 24 hours at 2 to 8°C protected from light. If the prepared study drug is stored at 2 to 8°C, it should be removed from the refrigerator at least 30 to 60 minutes prior to administration, to allow the solution to reach room temperature. Total time at room temperature may not exceed 8 hours, inclusive of infusion time with the study drug bag protected from light. No light protection for IV tubing is required.