STATISTICAL ANALYSIS PLAN

A Phase 1/2, Multi-center, Open-label Study of IMGN632 Monotherapy Administered Intravenously in Patients with CD123 positive Acute Myeloid Leukemia and Other CD123-positive Hematologic Malignancies

Study Title:	A Phase 1/2, Multi-center, Open-label Study of IMGN632 Monotherapy Administered Intravenously in Patients with CD123 positive Acute Myeloid Leukemia and Other CD123 positive Hematologic Malignancies
Study Number:	IMGN632-0801
Product Name:	IMGN632
IND Number:	130889
Indication:	Acute myeloid leukemia, blastic plasmacytoid dendritic cell neoplasm, acute lymphoblastic leukemia, myelodysplastic syndrome, myeloproliferative neoplasms, hematologic malignancies
Sponsor:	AbbVie Inc. 830 Winter Street Waltham, MA 02451, USA
Study Version:	Original protocol, 07 August 2017 Protocol amendment 1, 05 September 2017 Protocol amendment 2, 09 October 2017 Protocol amendment 3, 13 October 2017 Protocol amendment 4, 29 June 2018 Protocol amendment 5, 05 November 2019 Protocol amendment 6, 04 February 2020 Protocol amendment 7, 07 January 2022 Protocol amendment 8, 21 October 2022 Protocol amendment 9, 30 May 2023
SAP Date:	02 October 2024
Version:	2.0

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
ADA	Antidrug antibody
AE	Adverse event
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase (SGPT)
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase (SGOT)
ATC	Anatomical Therapeutic Chemical
BOR	Best overall response
BPDCN	Blastic plasmacytoid dendritic cell neoplasm
C1D1	Cycle 1 Day 1
CCR	Composite complete remission
CD123+	Positive for expression of the CD123 antigen
CI	Confidence interval
CLS	Capillary leak syndrome
CML	Chronic myeloid leukemia
CMML	Chronic myelomonocytic leukemia
CR	Complete remission
CRc	Clinical complete remission
CRC	Cohort Review Committee
CRF	Case report form
CRh	Complete remission with partial hematologic recovery
CRi	Complete remission with incomplete recovery
CRMRD-	Complete remission without minimal residual disease
CS	Clinically Significant
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DoCR	Duration of composite complete remission
DoR	Duration of overall response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EFS	Event-Free Survival

Abbreviation	Explanation
EOT	End of treatment
IMGN	ImmunoGen, Inc.
IV	Intravenous(ly)
LVEF	left ventricular ejection fraction
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	Morphologic leukemia-free state
MRD	Minimal residual disease
mSWAT	Modified Severity Weighted Assessment Tool
MTD	Maximum tolerated dose
MUGA	Multigated acquisition
NCS	Not Clinically Significant
NE	Not evaluable
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PK	Pharmacokinetics
PR	Partial response
PT	Preferred term
Q1	first quantile
Q3	third quantile
QTc	Corrected QT interval
RFS	Relapse-Free Survival
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SD	Stable disease or standard deviation
SMQ	Standardised MedDRA Query
SOC	System organ classes
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
VOD	Veno-occlusive disease
WHO	Word Health Organization

1. INTRODUCTION

This statistical analysis plan is designed to outline the statistical methods in evaluating the safety, tolerability, and anti-leukemia activity of IMGN632 when administered as monotherapy to patients with CD123+ hematologic malignancies. Pharmacokinetic and pharmacodynamic analysis, biomarker analysis, and ECG analysis will be addressed in a separate analysis plan.

This document has been prepared using Protocol version 9.0 dated 30 May 2023, and has been updated per the FDA's feedback received in February 2024 Type B meeting and September 2024 Type B pre-BLA meeting.

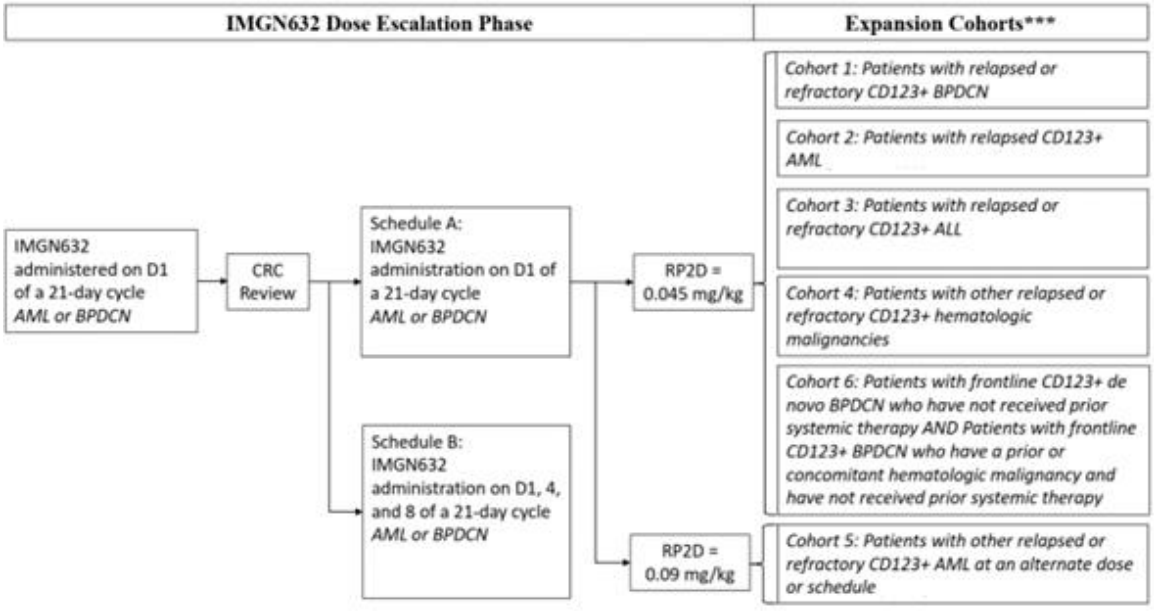
2. STUDY DESIGN

2.1 Overall Study Design

This is an open-label, multicenter, Phase 1/2 study to determine the maximum tolerated dose (MTD), recommended Phase 2 dose (RP2D), if different, and recommended dosing schedule for IMGN632 monotherapy and to assess the safety, tolerability, PK, immunogenicity, and anti-leukemia activity of IMGN632 when administered to patients with CD123+ hematologic malignancies.

This study is comprised of a dose escalation phase followed by a dose expansion phase. The dose escalation phase established the MTD(s) and/or RP2D(s) for IMGN632 when given on different schedules and explored the safety profile and anti-leukemia activity at selected RP2D(s) and recommended schedule(s). The dose expansion phase included treatment with IMGN632 at different dose levels and schedules in different disease populations (Figure 1).

Figure 1: Study Design Schema



*** Dose expansion cohorts were enrolled in patient populations as described by Cohorts 1 through 6. To select the RP2D, **C**ohort**s** 2 and 5 were used to further explore two dose levels of **S**chedule A in R/R AML, **i.e., C**ohort 2: 0.045 mg/kg, **C**ohort 5: 0.09 mg/kg. All other cohorts used the selected RP2D of 0.045 mg/kg Q3W. No patients were enrolled in Cohort 4.

For dose escalation, eligible patients were ≥ 18 years of age and had relapsed/refractory CD123+ AML or BPDCN. The dose escalation phase followed a standard 3 + 3 cohort design. Two dosing schedules were evaluated in this portion of the study:

- Schedule A: IMGN632 administered on Day 1 of a 21-day cycle
  - The starting dose for IMGN632 was 0.015 mg/kg. The dose escalation regimen ranged from 3-fold with the first dose escalation to 1.5-fold with the last dose escalation. The rationale for the 3-fold increase in dose between Cohort 1 and Cohort 2 was based upon the use of a non-cross-reactive toxicology species to determine the no observed adverse effect level (NOAEL) and the increased clearance of IMGN632 predicted in patients based on interspecies scaling.
- Schedule B: IMGN632 administered on an alternate dosing schedule (Days 1, 4, and 8 of a 21-day cycle)
  - The maximum starting dose for Schedule B was determined by the Cohort Review Committee (CRC) based on available safety, PD, and PK data from the last dose cleared on Schedule A or lower doses based on PK and CD123 saturation kinetics. IMGN632 was administered in equal fractions across Days 1, 4, and 8 of a 21-day cycle (e.g., 1/3 of the total dose administered on Schedule A on each of Days 1, 4, and 8).

Study enrollment opened with IMGN632 being administered on Schedule A (Table 1) and explored escalating doses of IMGN632 based on a modified Fibonacci escalation schema. Patients were enrolled into cohorts using a standard 3 + 3 design. During the escalation phase, a total of 65 patients were enrolled, 42 treated under Schedule A and 23 treated under Schedule B.

Table 1: Dose Escalation Cohorts – Schedule A (Day 1 every 3 weeks)

Dose Escalation Cohorts	IMGN632 (mg/kg/dose)	Fold Dose Increase Over Prior Dose Level
1	0.015	--
2	0.045	3
3	0.09	2
4	0.18	2
5	0.3	1.67
6	0.45	1.5

Table 2. Dose Escalation Cohorts – Schedule B (Days 1, 4, 8 every 3 weeks)

Dose Escalation Cohorts	IMGN632 (mg/kg/dose)	Fold Dose Increase Over Prior Dose Level
1	0.015	--
2	0.03	2
3	0.06	2

The MTD for a given schedule was defined as the highest dose at which fewer than 2 of 6 patients experience a dose-limiting toxicity (DLT) in a dose cohort. Based on input from the CRC review of data, including PK, PD, safety, and any signs of activity, up to 12 patients in total at a given dose level (at or below the MTD) may be enrolled to further characterize safety and identify the true DLT rate in addition to characterizing efficacy signals.

2.1.1 Selection of the RP2D and Dose Expansion Cohorts

Following escalation, two dose levels of IMGN632 on Schedule A were taken to expansion cohorts in relapsed/refractory AML to help select the RP2D, i.e., 0.045 mg/kg Cohort 2, 0.09 mg/kg Cohort 5. Based on safety, anti-leukemia activity, PK, and PD assessments the dose of 0.045 mg/kg administered on Day 1 of a 21-day cycle (Schedule A) was selected as the RP2D, and this dose was used in expansion Cohorts 1, 3, and 6.

The monitoring of DLTs across all expansion cohorts at the same dose level used a frequentist approach using a maximum probability of DLT of 20% as a stopping rule.

2.1.2 BPDCN Expansion Phase

Patients with BPDCN were enrolled into one of the following cohorts:

- Cohort 1: Patients with relapsed or refractory BPDCN who have received 1 to 3 prior systemic therapies (including tagraxofusp-erzs) or patients with frontline BPDCN enrolled before 26 October 2020
- Cohort 6: Patients enrolled after 26 October 2020 with frontline *de novo* BPDCN who had not received prior systemic therapy, and patients with frontline BPDCN who had a prior or concomitant hematologic malignancy and had not received prior systemic therapy

All patients received the RP2D of 0.045 mg/kg IMGN632 by IV infusion on Day 1 of a 21-day cycle. All 3 areas of potential disease involvement (skin, bone marrow, nodal/visceral) were assessed (mSWAT score from skin exam, blast % from bone marrow aspirate, SPD from PET-CT) to establish a response; subsequently repeated computerized tomography/positron emission tomography (CT/PET) scans were only performed on patients with nodal/visceral disease at baseline, or as indicated clinically. Bone marrow and skin assessments continued per schedule for all patients.

Table 3. BPDCN Expansion Phase Disease Assessment Schedule

Assessment	End of Cycle 1	End of Cycle 2	End of Cycle 4	End of Cycle 6	Subsequent Assessments
Bone marrow aspirate	X	X	X	X	Every 4 cycles (~ every 3 months) thereafter
CT/PET scan[a]		X	X	X	Every 4 cycles (~ every 3 months) thereafter
Skin mSWAT[b,c]	X	X	X	X	Every 2 cycles (~ every 6 weeks) thereafter

CT/PET = computed tomography/positron emission tomography; mSWAT = Modified Severity-Weighted Assessment Tool

a. CT/PET scans are performed for all patients on this schedule until CR is achieved then CT/PET will only be required for those patients with baseline nodal/visceral involvement.

b. A biopsy of normal-appearing skin is unnecessary to assign a CR. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a CR would exist.

c. Photographs of skin lesions are taken by Investigator or designee.

Pharmacokinetics will be evaluated, and the safety and tolerability of the drug will be closely monitored.

2.2 Sample Size

Overall, 179 patients were enrolled in the study.

2.2.1 Dose Escalation Phase

During the dose escalation phase, ascending doses of IMGN632 were evaluated to identify the MTD in each schedule using a traditional 3 + 3 design.

2.2.2 AML/ALL Expansion Phase

After data review and selection of the recommended dose(s) and schedule(s), the dose expansion phase of the study was opened. Patients with hematologic malignancies other than BPDCN enrolled in this study were assigned to 1 of the following 4 dose expansion cohorts.

Twenty-patient expansion cohorts (Cohorts 2 through 5) were selected to allow measurement of a target CR rate of 60% while having a 90% CI to exclude a low response rate of 30%. If the observed CR rate is 12/20 (60%), then the 90% CI for CR rate will be 39% to 78%. Assuming the true CR rate is 60%, then the probability of observing at least 9 complete responders (out of 20) is 94%.

- Cohort 2: Patients with relapsed AML
- Cohort 3: Patients with relapsed or refractory ALL
- Cohort 4: Patients with relapsed or refractory hematologic malignancies not included in the cohorts above (e.g., high-risk/very high-risk MDS, MPN, CMML, BP-CML)
- Cohort 5: Patients with relapsed or refractory (to non-intense therapies) AML at an alternate dose or schedule

2.2.3 BPDCN Expansion Phase

Sample size of the target population for formal efficacy analysis:

- [redacted]
- [redacted]

2.3. Investigational Study Drug

[redacted]

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Dose Escalation Phase

3.1.1 Primary Objective and Endpoints

- To determine the maximum tolerability of IMGN632 on the selected dosing schedule(s)
  - MTD and RP2D

3.1.2 Secondary Objectives and Endpoints

- To characterize the safety profile and tolerability of IMGN632 when given as a single agent across dose levels and schedules
  - Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and DLTs
- To characterize the PK of IMGN632, total antibody, and FGN849 (active catabolite)
  - PK parameters, including but not limited to observed maximum concentration (C_{max}) and area under the concentration versus time curve (AUC)
- To evaluate the potential immunogenicity of IMGN632
  - Antidrug antibody (ADA)
- To assess the anti-leukemia activity in AML patients:
  - Overall response rate (CR + CRh + complete remission with incomplete recovery [CRi] + morphologic leukemia-free state [MLFS] + partial response [PR]), complete remission rate (CR, CRh), composite complete remission (CCR) rate (CR, CRh, CRi), and time to event outcomes (duration of complete response [DoCR], duration of overall response [DoR], event-free survival [EFS], relapse-free survival (RFS), and OS)

3.2 AML/ALL Expansion Phase (Cohorts 2, 3 and 5)

3.2.1 Primary Objectives and Endpoints

- To assess the rate of CR in AML and ALL patients:

3.2.2 Secondary Objectives and Endpoints

- Key secondary: To assess the DoCR for patients with CR in AML and ALL patients
- To assess the rate of CR + CRh
- To assess the rate of CR + CRh + CRi
- To assess the rate of overall response: CR + CRh + CRi + MLFS + PR
- To assess the duration of overall response: CR + CRh + CRi + MLFS + PR
- To assess the EFS
- To assess the RFS
- To assess the OS
- To characterize the safety profile and tolerability of IMGN632 when given as a single agent at specified dose levels and schedules

  - Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and DLTs
- To characterize the PK of IMGN632, total antibody, and FGN849 (active catabolite)
  - PK parameters, including but not limited to observed maximum concentration (C_{max}) and area under the concentration versus time curve (AUC)
- To evaluate the potential immunogenicity of IMGN632
  - Antidrug antibody (ADA)

3.3 BPDCN Expansion Phase (Cohorts 1 and 6)

3.3.1 Primary Objective and Endpoints

- To assess the rate of composite CR (CCR) in frontline *de novo* BPDCN patients in Cohort 6
  - CR + clinical CR (CRc)

3.3.2 Secondary Objectives and Endpoints

- Key Secondary: To assess the DoCR for patients with CR/CRc in frontline *de novo* BPDCN patients in Cohort 6
- To assess the rate of CCR separately in all frontline and R/R BPDCN patients: CR + CRc
- To assess the DoCR separately for relapsed/refractory and all frontline patients with CR or CRc in Cohorts 1 and 6
- To characterize the safety profile and tolerability of IMGN632 when given as a single agent at the RP2D level
- To assess the rate of (CR+CRc+CRh)
- To assess the duration of (CR+CRc+CRh)
- To assess ORR: (CR+CRc+CRh+CRi+PR)
- To assess the duration of overall response (DoR)
- To assess the time to (CR+CRc)
- To assess the time to (CR+CRc+CRh)
- To assess the time to overall response (CR+CRc+CRh+CRi+PR)
- To assess OS
- To assess the percent of BPDCN patients able to bridge to stem cell transplant (SCT) in the frontline and relapsed/refractory populations separately

- To assess the DoCR by SCT (yes vs no) separately in all frontline and R/R BPDCN patients
- To characterize the PK of IMGN632, total antibody, and FGN849 (the active catabolite)
- To evaluate the potential immunogenicity of IMGN632
  - ADA
- To assess transfusion independence (if data is available)
  - Conversion rate to independence of red blood cell (RBC) and platelet transfusion relative to baseline

3.4 Exploratory Objectives and Endpoints Escalation and Expansion Phases

- To characterize the PD profile of IMGN632, by assessing target saturation by IMGN632 and persistence of saturation, during the dose escalation portion of the study
  - CD123 receptor occupancy in blood and bone marrow by flow cytometry

Additional analyses and subsequent results of the exploratory assessments may be reported in separate documents and not included in the SAP or Clinical Study Report (CSR), respectively.

3.5 Estimands for Primary and Key Secondary Objectives in AML

3.5.1 Estimands for Primary Objective

Table 4: Estimands for Primary Objective

Objective: To assess the efficacy of IMGN632 in relapsed/refractory AML population		
Estimand: The CR rate in the relapsed/refractory AML patients during the IMGN632 treatment		
ESTIMAND ATTRIBUTES	ESTIMAND	ANALYSIS
Population	All relapsed/refractory AML patients	All relapsed/refractory AML patients treated at the RP2D (0.045 mg/kg every 3 weeks) who received at least one dose of IMGN632 and who were eligible based on the screening criteria (mITT).
Treatment condition	IMGN632 0.045 mg/kg administered on Day 1 of a 21-day cycle (every 3 weeks)	
Endpoint (variable)	CR as assessed by investigators	
Population-level summary	CR rate, defined as the number of patients who achieve a CR divided by the number of patients in the mITT population	Proportion of CR and a two-sided 95% confidence interval using Clopper-Pearson exact method for binominal data
Intercurrent events (IE)	**Strategy for IE**	**Handing of missing assessment**
Study treatment discontinuation	While on treatment Only response assessment on or prior to IE will be used.	Patients without any response assessments will be treated as a non-responder.

3.6 Estimands for Primary and Secondary Objectives in BPDCN

3.6.1 Estimands for Primary Objective

Table 5: Estimands for Primary Objective

Objective: To assess the efficacy of IMGN632 in frontline *de novo* BPDCN population		
Estimand: The CR/CRc rate in the frontline *de novo* BPDCN patients during the IMGN632 treatment		
ESTIMAND ATTRIBUTES	ESTIMAND	ANALYSIS
Population	All frontline *de novo* BPDCN patients	All frontline *de novo* BPDCN patients in Cohort 6 (enrolled after 26 October 2020) who received at least one dose of IMGN632 and who were eligible based on the screening criteria (mITT)
Treatment condition	IMGN632 0.045 mg/kg administered on Day 1 of a 21-day cycle (every 3 weeks)	
Endpoint (variable)	CR/CRc as assessed by investigators	
Population-level summary	CR/CRc rate, defined as the number of patients who achieved a CR/CRc divided by the number of patients in the mITT population.	Proportion of CR/CRc and a two-sided 95% confidence interval using Clopper-Pearson exact method for binominal data
IE	**Strategy for IE**	**Handing of missing assessment**
Study treatment discontinuation	While on treatment Only response assessments on or prior to IE will be used.	Patients without any response assessments will be treated as a non-responder.

3.6.2 Estimands for Key Secondary Objective

Table 6. Estimands for Key Secondary Objective

Objective: To assess the efficacy of IMGN632 in frontline *de novo* BPDCN population		
Estimand: The DoCR in the frontline *de novo* BPDCN patients during the study		
ESTIMAND ATTRIBUTES	ESTIMAND	ANALYSIS
Population	All frontline *de novo* BPDCN patients	All frontline *de novo* BPDCN patients in Cohort 6 (enrolled after 26 October 2020) who received at least one dose of IMGN632 and who were eligible based on the screening criteria and achieved CR or CRc.
Treatment condition	IMGN632 0.045 mg/kg administered on Day 1 of a 21-day cycle (every 3 weeks)	
Endpoint (variable)	DoCR based on investigator assessments	
Population-level summary	DoCR, defined only for patients who achieved a CCR and will be measured from the date of initial remission (CR or CRc, whichever occurs first) to relapse or death due to progression, whichever occurs first	Kaplan-Meier method for survival function estimate
IE	**Strategy for IE**	**Handing of missing assessment**
Death	Composite	Relapse or death after two or more consecutive missed disease assessments is considered censoring
Start of a new anti-cancer therapy prior to relapse or death	Treatment policy All data collected after IE will be included.	
Study treatment discontinuation	Treatment policy All data collected after IE will be included.	

4. DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

4.1 Baseline Definition

Study Day 1 (i.e., Cycle 1 Day 1) will be designated as the first day a patient receives the study drug. The baseline value is defined as the last non-missing value on or before the date of the first dose of the study drug.

4.2 Definition of Study Days

Unless otherwise noted, study days of an evaluation are defined as the number of days relative to the first dose date.

- If the evaluation date is on or after the first dose date, then study days are calculated as (evaluation date - first dose date + 1).
- If the evaluation date is before the first dose date, then relative study days are calculated as (evaluation date - first dose date).

4.3 Definition of Treatment Period

The treatment period is defined as the time from the first dose of the study drug through 30 days after the last dose or prior to the subsequent therapy, whichever occurs first.

4.4 Clinical Laboratory Tests

- Clinical laboratory results beyond the detectable limits will be reported as detectable limits for calculating descriptive statistics.
- All the laboratory test results will be included in the data listings as reported.

4.5 Safety Data Handling

For all safety data, no imputation methods will be used to replace missing data unless otherwise stated in this document. Only observed data will be used for analyses.

4.5.1 Handling Partial Dates for Adverse Event

For records with missing adverse event (AE) onset date, the following procedure will be employed to determine whether the AE is treatment-emergent:

- No imputation if the date is completely missing.
- Known year, but month and day missing: If the year is the same as the year of the first study drug dose, and the AE end date is missing (Partial AE end dates should be imputed before applying this rule) or ongoing or after the first study drug dose date, use first study drug dose date. Otherwise, use January 1 of the year.

- Known year and month, but day missing: If the year and month are the same as the year and month of the first study drug dose, and the AE end date is missing (Partial AE end dates should be imputed before applying this rule) or after the first study drug dose date, use the first study drug dose date. Otherwise, use the 1st day of the month.

AE end date imputation:

- No imputation if the date is completely missing.
- Known year, but month and day missing: December 31 of the year.
- Known year and month, but day missing: Last day of the month.

4.5.2 Handling Partial Dates for Non-AE (including death)

For records with a missing start date, the following procedure will be employed:

- If a date is missing the day portion (e.g., July 2015), the incomplete date will be imputed by using the first day of the month (e.g., 01 July 2015).
- If a date is missing the day and month portion (e.g., 2015), the incomplete date will be imputed as the first day of the year (e.g., 01 January 2015).

For records with a missing end date, the following procedure will be employed:

- If a date is missing the day portion (e.g., July 2015), the incomplete date will be imputed by using the last day of the month (e.g., 31 July 2015).
- If a date is missing the day and month portion (e.g., 2015), the incomplete date will be imputed as the last day of the year (e.g., 31 December 2015).

After the above imputation, the following rules are used.

- The final imputed death date is the later date of last known alive date + 1 and imputed death date from above procedure. The last known alive date is derived per Section 7.6.1.7.
- In case of a medication where the start date is completely missing, it is considered as prior medication. In addition to the start date being completely missing, if the stop date is also completely missing or the stop date is on or after the first dose date, it will also be considered as a concomitant medication.

4.6 Multiple Assessments for the Same Assessment Time Point

In the case of multiple observations at a specific visit, the following rules are used:

- Take the data point that is closest to the nominal visit day.

- Take the one after the nominal visit day if multiple data points have the same equal distance from the nominal visit day.

5. PLANNED ANALYSIS

5.1 Interim Analyses

A futility analysis was conducted on the first 14 patients in Cohort 1.

Interim analyses were performed in frontline *de novo* BPDCN patients enrolled in Cohort 6.

5.1.1 Relapsed/Refractory BPDCN Patients Enrolled in Cohort 1

[redacted]

5.1.2. Frontline *de novo* BPDCN Patients Enrolled in Cohort 6

[redacted]

[redacted]

Table 7. O'Brien-Fleming Boundaries

[redacted]

Table 8. Probability of Early Stopping at Different True CR/CRc Rates

[redacted]

5.2 Final Analyses and Reporting

All final planned analyses per the protocol and this analysis plan will be performed only after database lock.

6. ANALYSIS POPULATIONS

6.1 Primary Analysis Population (Frontline *De Novo* BPDCN Patients)

The Primary Analysis Population (PAP) includes all frontline BPDCN patients who have not received prior systemic therapy prospectively enrolled after 26 October 2020, meeting with the FDA and do not have an identified prior or concomitant hematologic malignancy (PCHM) at or prior to the time of their screening bone marrow assessment. These patients are a subset of the frontline BPDCN patients enrolled in Cohort 6. To be included in the PAP, patients need to receive at least one dose of IMGN632 and meet the screening criteria. The three frontline patients (2 *de novo*, 1 PCHM) enrolled before 26 October 2020 are excluded from the PAP but included in the broader frontline BPDCN groups.

The primary study endpoint is the composite CR (CR+CRc) rate with the supporting secondary endpoint of DoCR (CR+CRc) in the PAP.

6.2 Safety Population

The Safety Population will include all patients who received any dose of IMGN632. All safety analyses will be performed on the Safety Population.

6.3 Modified Intent-to-Treat (mITT) Population

The mITT Population includes all patients who were eligible based on the screening criteria and who received at least one dose of IMGN632.

All efficacy analyses will be performed on the mITT Population.

6.4 Analysis Data Presentation

Table 9 illustrates the relationship between each population and the analyses for which the data from the population will be used:

Table 9. Analysis Populations

Analysis Population	Analysis				
	Baseline	Patient Disposition	Efficacy	Safety	Immunogenicity
Safety	X	X		X	
mITT	X	X	X		X

The safety results will be summarized by the following structures:

- By indication (all dose levels and schedules)

All BPDCN Patients	All AML/ALL	All Patients

- By dose level (all indications): Schedules A and B, respectively

Schedule A	0.015 mg/kg	0.045 mg/kg	0.09 mg/kg	0.18 mg/kg	0.3 mg/kg	0.45 mg/kg
Schedule B	0.015 mg/kg	0.03 mg/kg	0.06 mg/kg			

- By indication at the RP2D

Frontline *De novo* BPDCN Patients (Primary Analysis Population)	Total Frontline BPDCN Patients (prospective)*	Total Frontline *De novo* BPDCN Patients	Total Frontline PCHM BPDCN Patients	Total Frontline BPDCN Patients	Total R/R BPDCN Patients	Total BPDCN Patients	Total AML/ALL Patients	Total Patients at RP2D

*The three frontline patients (2 *de novo*, 1 PCHM) who were enrolled prior to 26 October 2020 are not included in this population.

The efficacy results for BPDCN patients will be summarized in the following structure. The efficacy results for AML patients will be summarized separately by dose level for Schedules A and B.

- By indication at the RP2D

Frontline *De Novo* BPDCN Patients (Primary Analysis Population)	Total Frontline BPDCN Patients (prospective)*	Total Frontline *De Novo* BPDCN Patients	Total Frontline PCHM BPDCN Patients	Total Frontline BPDCN Patients	Total R/R BPDCN Patients

*The three frontline patients (2 *de novo*, 1 PCHM) who were enrolled prior to 26 October 2020 are not included in this population.

The below analyses will be performed for Dose Escalation of Schedule A.

- Overall of TEAEs
- TEAEs by SOC and PT
- All deaths

7. STATISTICAL CONSIDERATION

All analyses described in this plan are considered a priori analyses in that they have been defined prior to locking the database. All other analyses, if any, designed subsequently to locking the database, will be considered post hoc analyses and will be described as exploratory analyses in the Clinical Study Report.

All summaries and statistical analysis will be performed using SAS v9.4 or later.

7.1 General Statistical Procedures

Categorical variables will be summarized with the number and percentage of patients with a response in the category. Percentages will be based on the number of patients in the given population as noted. The number of patients with missing information will also be included. Percentages will be reported to one decimal place.

A 2-sided 95% exact binomial (Clopper-Pearson) confidence interval (CI) for categorical variables without multiplicity adjustment will be provided where appropriate for efficacy analysis.

Continuous variables will be summarized with the number of patients (n), mean, standard deviation (SD), median, first quantile (Q1), third quantile (Q3), minimum (min), and maximum (max). Mean, median, Q1 and Q3 will be reported to 1 more decimal place than the raw data, while the SD will be reported to 2 more decimal places than the raw data. Minimum and maximum will be reported with the same number of decimals as the original data.

Unless otherwise stated, demographic and baseline characteristics, disposition, drug exposure, and safety data will be summarized for each initial dose level assigned and overall by treatment schedule and overall without distinguishing the study phases (for all patients enrolled in the study).

Data not summarized in the tables will be listed only. Listings will be provided for all available data and will be sorted by study phase, patient number, visit and schedule if applicable.

7.2 Patients Disposition and Protocol Deviation

7.2.1 Patient Disposition

The number and percentage of patients who discontinued the study drug or the study completely with primary reasons for discontinuation will be provided.

7.2.2 Protocol Deviations

The number and percentage of patients with major protocol deviations will be provided.

Major protocol deviations will be listed for the Safety Population.

7.3 Demographics and Baseline Characteristics

All baseline characteristic summary statistics and analyses are based on characteristics prior to the first dose of study drug. Distributions of the continuous demographic and baseline characteristic variables will be summarized with the number of non-missing observations, mean, standard deviation, and median, as well as the minimum and maximum values.

For the categorical demographic and baseline characteristic variables, the frequency and percentages of patients within each category will be summarized. The number of patients with missing information will also be summarized.

7.3.1 Demographics

The following patient demographics collected at the screening visit will be summarized:

- Age (years), calculated as an integer of (first dose date – birthdate +1)/365.25
- Age category (18 - < 65, ≥ 65, 65 - < 75, ≥ 75)
- Sex
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Missing)
- Race (White, Black or African American, Asian, Not Reported)
- Height (cm) at baseline
- Weight (kg) at baseline
- BMI (kg/m2) at baseline
- Baseline ECOG performance status
- Baseline grades of WBC, ANC, platelets and hemoglobin
- Baseline hepatic function (normal: BILI ≤ ULN and AST ≤ ULN; mild impairment: BILI ≤ ULN and AST > ULN or ULN < BILI ≤ 1.5*ULN; moderate impairment: 1.5*ULN < BILI ≤ 3*ULN; severe impairment: BILI > 3*ULN)
- Baseline renal function (normal: creatinine clearance ≥ 90 mL/min; mild impairment: 60 - < 90 mL/min; moderate impairment: 30 - < 60 mL/min; severe impairment: < 30 mL/min)

7.3.2 Medical History

The medical history will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA) (Version 24.0 or later), associating lower-level terms with preferred terms (PTs) and system organ classes (SOCs) by the primary hierarchy.

The number and percentage of patients experiencing any medical conditions will be tabulated by SOC and PT. If a PT or SOC was reported more than once for a subject, the subject will be counted once in the incidence for that PT or SOC.

7.3.3 Disease Characteristics and Prior Therapy

Baseline disease characteristics will be summarized for BPDCN and AML/ALL patients separately:

- Bone marrow blasts percentage at baseline (BPDCN/AML/ALL)
- Skin lesion involvement at baseline assessed by mSWAT (BPDCN only)
- Nodal/visceral (liver, spleen) involvement assessed by CT/PET (BPDCN only)
- Baseline organ involvement (BPDCN only)
    - Bone Marrow
    - Peripheral Blood
    - Skin
    - Lymph node
    - Visceral

A summary of the following elements will be provided for BPDCN and AML/ALL patients separately:

- Time from initial diagnosis to first dose date (years), calculated as (first dose date – initial diagnosis date + 1)/365.25
- History/type of disease (secondary versus *De novo*)
- Patient status at baseline (first Relapse, primary refractory, relapsed-refractory, untreated)
- Prior exposure to tagraxofusp-erzs (BPDCN patients only)
- Prior stem cell transplants (SCT)
- Transfusion dependence at baseline, defined as 2 or greater separate instances of red blood cell transfusions and/or 2 or greater separate instances of platelet transfusions that occurred within56 days on or before Cycle 1 Day 1.

Prior systemic therapy for BPDCN and AML/ALL patients will be summarized separately as follows:

- Prior systemic therapy type
- Number of prior systemic therapy regimens (1, 2, 3, 4 and > 4)
- Regimen number (as a continuous variable)

- Time from last dose date of most recent therapy to first dose (months), calculated as (first dose date - last dose date of most recent therapy + 1)/30.5
- Reasons for most recent therapy given
- Number of cycles of most recent therapy
- Best response of most recent therapy
- Reason discontinued most recent therapy

7.4 Prior and Concomitant Medications

Medications will be coded by Anatomical Therapeutic Chemical (ATC) Classification based on the March 2021 or later version of the World Health Organization (WHO) Drug Dictionary.

Prior medications are defined as any medications, other than study treatments, with a start date prior to the first dose of the study drug. In cases where a medication is started before the first dose and is ongoing after the first dose, that medication is considered both a prior medication and a concomitant medication.

Concomitant medications are medications, other than study drugs, being taken during the treatment period (see Section 4.3). Medications that started before the first dose of the study drug and were ongoing on the date of the first dose will be considered concomitant medications.

The number and percentage of patients who have taken prior or concomitant medications will be summarized separately by ATC Level 1 and preferred term (PT) pharmacological subgroup (ATC Level 3). A subject will be counted only once for the medication taken more than once.

7.5 Prior and Concomitant Procedures

All procedures will be coded using MedDRA version 18.0 or later.

A prior procedure is defined as a procedure that occurred before the first dose date; Concomitant procedures are defined as procedures occurring during the treatment period (see Section 4.3).

The number and percentage of patients who have prior or concomitant procedures will be summarized separately by SOC and PT. A subject will be counted only once for the procedure received more than once.

7.6 Efficacy Analyses

7.6.1 Efficacy Outcomes for BPDCN

The best overall response (BOR) is the best response designation recorded by the investigator/site for a patient between the date of the first dose of IMGN632 and the date of relapse, or the date of the start of a new anti-cancer therapy, whichever occurs first. The patients without any response assessments will be treated as non-responders and their BORs will be set to not evaluated (NE).

The patient's BOR assignment will be based on the order: CR>CRc>CRh>CRi>PR>SD>PD.

The primary efficacy endpoint is to assess the CCR (CR+CRc) rate in the Primary Efficacy Analysis Population (frontline *de novo* BPDCN population enrolled after 26 October 2020).

Unless otherwise specified, an exact 95% CI for the binary variable (e.g., composite remission rate) will be calculated using the Clopper–Pearson method. The descriptive statistics will be presented for time to response (e.g., time to CCR).

7.6.1.1 BPDCN Composite Complete Remission (CCR) Rate

The CCR is defined as a complete response of CR or CRc.

If a patient has multiple types of remissions, the date of the CCR is the date of the earliest remission. For example, in BPDCN, if a patient had a CRi, CR, and CR at Cycle 1, 2, and 3 respectively, the date of the CCR is the date of the first CR (at Cycle 2) for this patient.

The CCR rate will be calculated as the number of patients who achieve a CCR divided by the number of patients in the corresponding population. The patients without any response assessments will be treated as non-responders.

Time to CCR is defined as time from date of first dose of study drug to the first date of CR or CRc.

The primary analysis of CCR rate will be based on the investigator assessments. A sensitivity analysis of CCR rate will be performed using the Sponsor derivations of CR and CRc.

For the CRc assessment, the Sponsor's derivation will define the response criteria for skin by adding marked clearance as ≥ 75% reduction of mSWAT from baseline and ≤ 10% residual overall BSA. No biopsy results will be used for the CRc derivation since no biopsy was required per the protocol for the CRc assessment. For the Sponsor's derivation of CR/CRc, the baseline and post-baseline involved disease areas will be defined as the last assessment of involved disease areas at screening. The response date at each post-baseline disease assessment will be defined as the date of the last assessment of involved disease areas. The details of the Sponsor's derivation are included in Table 10. The time to Sponsor's derived CR/CRc will also be evaluated.

Table 10. Sponsor's Criteria for CR and CRc

Response	Disease Assessment Areas	Sponsor's Criteria for CR and CRc
CR or CRc	Bone Marrow	Blast ≤5%
CR or CRc	Peripheral Blood	Hematology lab results from Peripheral Blood within 14 days after Bone Marrow procedure date: Neutrophil count > 1×10^9/L and platelet count > 100×10^9/L
CR	Skin	100% clearance of all skin lesions from baseline and no new lesions
CRc	Skin	Marked clearance as percent reduction from baseline ≥ 75% in mSWAT score and ≤ 10% of BSA for skin area with disease. Biopsy results are not used for CRc derivation since no biopsy was required per the protocol for the CRc assessment.
CR or CRc	Nodal Masses	Regression to normal size on computed tomography (CT)
CR or CRc	Spleen Liver	Not palpable, modules disappeared

7.6.1.2 BPDCN Other CCR Rates

Similar to the CCR rate, other complete remission rates will be calculated for CR+CRc+CRh and CR+CRc+CRh+CRi, respectively.

The patients without any response assessments will be treated as non-responders.

7.6.1.3 BPDCN Overall Response Rate (ORR)

The ORR is defined as the proportion of patients with the BOR of CR, CRc, CRh, CRi, or PR.

The patients without any response assessments will be treated as non-responders.

7.6.1.4 BPDCN Duration of Composite Complete Remission (DoCR)

The DoCR is defined only for patients who achieve a CCR (CR or CRc) and will be measured from the date of initial remission (CR or CRc, whichever occurs first) to relapse or death from any cause, whichever occurs first.

The censoring rules to calculate DoCR are summarized in Table 11.

The following DoCR sensitivity analyses will be performed:

1) Only include death due to progression.
2) Censor at a new anti-cancer therapy excluding SCT.
3) Use the Sponsor-derived response including assessment date.

The KM method will be used to summarize DoCR, including KM curves, and medians with corresponding 95% confidence interval (CI).

Table 11. DoCR Analysis Rules

Situation	Date of Event or Censoring	Outcome
Relapse	Relapse	Event
Death	Date of death	Event
No relapse and no death at follow-up	Date of the last disease assessment	Censored
Relapse or death after two or more consecutive missed disease assessments*	Date of last disease assessment with documented non-relapse prior to relapse or death	Censored

* Up to 6 cycles: The disease assessment is every 6 weeks with 1-week window. Two consecutive missed assessments will be 12 weeks (84 days). If relapse or death due to progression occurred after 91 days (+ 7-day window) from the last non-relapse assessment, it will be considered censoring at last non-relapse assessment. After 6 cycles, the disease assessment will be every 12 weeks with a 1-week window. The duration for 2 missed consecutive assessments will be 175 days.

Last Disease Assessment for BPDCN: the latest date of disease assessment in any area (skin, CT, bone marrow or CBC). For Peripheral/CBC blood test, both PLT count and ANC will be checked.

7.6.1.5 BPDCN Duration of Overall Response (DoR)

The DoR is defined only for patients who achieve the overall response defined in Section 7.6.1.4.

The DoR will be measured from the date of initial response to relapse, or death from any cause, whichever occurs first. If a patient had multiple types of responses, the DoR should be calculated from the earliest (initial) response. The earliest response may not be the best overall response. For example, if a patient had a PR, CRi, CR, CR at Cycle 1, 2, 3 and 4 respectively, the earliest response is the PR at Cycle 1, not the CR as the BOR at Cycle 3.

The analysis method and censoring rules to calculate DoR are the same as DoCR. The following DoR sensitivity analyses will be performed:

1) Only include death due to progression.
2) Censor at a new anti-cancer therapy excluding SCT.

7.6.1.6 BPDCN Transfusion Independence Conversion Rate

Transfusion dependence at baseline will be defined as 2 or greater separate instances of red blood cell transfusions and/or 2 or greater instances of platelet transfusions that occurred within 56 days on or before Cycle 1 Day 1 (C1D1).

Transfusion independence will be defined as any 56-day period after C1D1 in which the patient does not receive either a red blood cell or platelet transfusion.

The rate of conversion with 95% CI from transfusion dependence at baseline to any 56-day period of transfusion independence post treatment will be calculated separately.

The number (percentage) of patients with transfusion dependence at baseline and independence at post-baseline baseline will also be summarized.

7.6.1.7 Overall Survival (OS)

The OS is defined for all mITT patients and will be measured from the date of the first dose until death from any cause. For a patient who is not known to have died by the end of the study follow-up, observation of OS will be censored on the date he or she was last known to be alive. The last known alive date will be determined by selecting the last available date of the following study procedures: start date of adverse event, bone marrow collection, disease assessment, vital signs assessment, electrocardiogram assessment, clinical laboratory collection, study drug administration, start date of concomitant or post-treatment medicine or procedure, transfusion, survival follow-up, end of study, biospecimen sample collection, skin lesion assessment, date of PET/CT, and performance status.

Patients who do not have any follow-up since the date of the first dose will be censored on the date of the first dose.

The KM method will be used to summarize OS, including KM curves, and medians with corresponding 95% confidence interval (CI).

7.6.1.8 BPDCN Efficacy Subgroup Analyses

Subgroup efficacy analyses will be performed as follows for primary endpoint:

- Post-treatment stem-cell transplant (yes versus no) (stem-cell transplant is considered consolidation for on-trial remission, with "bridging to transplant") for frontline and r/r BPDCN patients separately
- Prior tagraxofusp-erzs treatment (yes versus no) for the relapsed/refractory BPDCN patients
- Age group (18 to < 65, 65 - < 75, >= 65, ≥= 75)
- Baseline renal status (normal, mild impairment, moderate impairment, severe impairment)
- Baseline hepatic status (normal, mild impairment, moderate impairment, severe impairment)
- Race (White, Black or African American, Asian, Not Reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Missing)

7.6.2 Efficacy Outcomes for AML/ALL

The BOR is the best response designation recorded by the investigator/site for a patient between the date of the first dose of IMGN632 and the date of relapse, or the date of the start of a new

anti-cancer therapy, whichever occurs first. The patients without any response assessments will be treated as non-responders and their BORs will be set to NE.

The patient's BOR assignment will be based on the order:

CR>CRh>CRi>MLFS>PR>SD>PD.

An exact 95% CI for the response rate will be calculated using the Clopper-Pearson method.

7.6.2.1 AML/ALL CCR Rate

The CCR is defined as a complete response of CR, CRh, or CRi. The CCR rate will be calculated as the number of patients who achieve a CCR divided by the number of patients in the corresponding population. The patients without any response assessments will be treated as non-responders.

7.6.2.2 AML/ALL ORR

The ORR is defined as the proportion of patients with the BOR of CR, CRh, CRi, MLFS, or PR. The patients without any response assessments will be treated as a non-responder.

7.6.2.3 AML/ALL DoCR

The DoCR is defined only for patients who achieve a CR and will be measured from the date of initial remission to relapse or death from any cause, whichever occurs first.

7.6.2.4 AML/ALL DoR

The DoR is defined only for patients who achieve the overall response defined in Section 7.6.2.3. The DoR will be measured from the date of initial response to relapse, or death from any cause, whichever occurs first.

7.6.2.5 AML/ALL Transfusion Independence Conversion Rate

Transfusion dependence at baseline will be defined as 2 or greater separate instances of red blood cell transfusions and/or 2 or greater separate instances of platelet transfusions that occurred within 56 days on or before Cycle 1 Day 1 (C1D1).

Transfusion independence will be defined as any 56-day period after C1D1 in which the patient does not receive either a red blood cell or platelet transfusion.

The rate of conversion with 95% CI from transfusion dependence at baseline to any 56-day period of transfusion independence post treatment will be calculated separately.

The number (percentage) of patients with transfusion dependence at baseline and independence at post-baseline baseline will also be summarized.

7.6.2.6 AML/ALL EFS

The EFS is defined as the time from the first dose to the date of relapse for those who achieved CR, treatment failure, or death from any cause, whichever occurs first.

7.6.2.7 AML/ALL RFS

The RFS is defined as the time from the first dose to the date of relapse or death from any cause, whichever occurs first.

7.6.2.8 AML/ALL OS

The OS is defined for all enrolled patients and is measured from the date of the first dose until death from any cause.

7.6.2.9 AML/ALL Subgroup Analysis

The subgroup analysis will be performed for post-treatment stem-cell (yes versus no) (stem-cell transplant is considered consolidation for on-trial remission, with "bridging to transplant").

7.7 Safety Analyses

The safety analysis will be summarized for data collected during treatment period (see Section 4.3) for Safety population.

7.7.1 Study Drug Exposure

Patients enrolled in Schedule A received IMGN632, administered IV, on Day 1 of a 21-day cycle. Patients enrolled in Schedule B received equal fractions of IMGN632 on Days 1, 4, and 8 of a 21-day cycle, where each day is 1/3 of the total dose to be administered in the cycle.

Study treatment exposure will be summarized as follows:

- Number of treatment cycles
- Duration of treatment (weeks)
  - Schedule A: (last infusion date - first infusion date +21)/7
  - Schedule B: (last infusion date - first infusion date +14)/7
- Any infusion interruption
- Any infusion reaction
- Total cumulative dose (mg), defined as sum of actual dose administered in all cycles
- Actual dose intensity (mg/kg/dose)
  - Schedule A: total cumulative dose (mg)/baseline weight (kg)/total treatment duration (weeks)
  - Schedule B: total cumulative dose (mg)/baseline weight (kg)/total treatment duration (weeks)
- Relative dose intensity (%) = actual dose intensity/planned dose intensity*100%

7.7.2 Adverse Events

All adverse events (AEs) will be coded by SOC and PT using MedDRA (version 24.0 or later). The severity of AE will be assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

A treatment emergent adverse event (TEAE) is defined as any new AE that begins or any pre-existing conditions that worsens in severity during treatment period (see Section 4.3). An AE

occurred on the same day of first dose will be considered as a TEAE unless the time of the AE is before the time of first dose.

In addition, AEs starting more than 30 days after the last dose of study drug that were determined by the investigators to be related to the study drug should also be considered TEAEs. The CTCAE grade change for a later AE record and an earlier AE record which have the same preferred term and the later AE started on the same date of earlier AE ended or 1 day after the earlier AE ended at are linked. The linked AE occurring more than 30 days after last dose of study should also be considered as TEAE.

AE of special interest (AESI): infusion-related reactions. Any symptom or sign occurring within 24 hours of infusion and suggestive of an infusion-related reaction should be promptly reported. The AESIs will be summarized based on the investigator assessment.

AEs that are definitely, probably, or possibly related to the study drug will be considered as related to the study drug. AEs with missing or unknown relationship to the study drug are considered as related to the study drug. AEs with the closest relatedness to the study drug will be used for summaries.

Number and percentage of patients with TEAEs by maximum CTCAE grade will be summarized.

An overview of TEAEs will be provided including:

- Any TEAEs
- Any study drug-related TEAEs
- Any Grade 3+ TEAEs
- Any study drug-related Grade 3+ TEAEs
- Any serious TEAEs
- Any study drug-related serious TEAEs
- Any TEAEs leading to dose reduction
- Any TEAEs leading to dose delay
- Any study drug-related TEAEs leading to dose reduction
- Any study drug-related TEAE leading to dose delay
- Any TEAEs leading to permanent discontinuation of study drug
- Any study drug-related TEAEs leading to permanent discontinuation of the study drug
- Any TEAEs leading to death
- Any study drug-related TEAE leading to death
- Any AESI
- Any Grade 3+ AESI

- Any hypersensitivity (SMQ Narrow) occurring on the same day of IMGN632 infusion or 1 day after
- Any anaphylactic reaction (SMQ Narrow) occurring on the same day of IMGN632 infusion or 1 day after
- Any liver-related events per SMQ
- Any DLTs

The following events will be summarized by SOC, PT, and Grade:

- TEAEs
- Study drug-related TEAEs
- Grade 3+ TEAEs
- Study drug-related Grade 3+ TEAEs
- Serious TEAEs
- Study drug-related serious TEAEs
- TEAEs leading to dose reduction
- Study drug-related TEAEs leading to dose reduction
- TEAEs leading to dose delay
- Study drug-related TEAEs leading to dose delay
- TEAEs leading to permanent discontinuation of study drug
- Study drug-related TEAE leading to permanent discontinuation of study drug
- TEAE leading to death
- Study drug-related TEAE leading to death
- AESI
- Grade 3+ AESI
- DLTs
- TEAEs of Hemodynamic Edema, Effusions, and Fluid Overload (SMQ Broard) plus the PTs of Face Edema, Swelling of face, Periorbital Edema, Lip Swelling, Edema genital, Scrotal Edema, Scrotal Swelling.
- TEAEs of neutropenia (PTs neutropenia and neutrophil count decreased)
- TEAEs of anemia (PTs anaemia and haemoglobin decreased)
- TEAEs of thrombocytopenia (PTs thrombocytopenia and platelet count decreased)
- Hypersensitivity (SMQ Narrow) occurring on the same day of any IMGN632 infusion or 1 day after

- Anaphylactic reaction (SMQ Narrow) occurring on the same day of any IMGN632 infusion or 1 day after

Analyses of TEAEs will be performed for each of the important identified and important potential risks for IMGN632 as defined by the criteria in Table 12.

Table 12. Important Identified and Potential Risks for IMGN632

Risk Category	Risk	Criteria for Identification
Important identified	Infusion-related reaction	• Hypersensitivity (SMQ Narrow) occurring on the same day of any IMGN632 infusion or 1 day after • Anaphylactic reaction (SMQ Narrow) occurring on the same day of any IMGN632 infusion or 1 day after (Analyzed separately)
	Edema	Hemodynamic Edema, Effusions, and Fluid Overload (SMQ Broad) plus the PTs of Face Edema, Swelling of face, Periorbital Edema, Lip Swelling, Edema genital, Scrotal Edema, Scrotal Swelling.
	Veno-occlusive disease	PTs of VOD and VOLD
Important potential	Cytopenia	Neutropenia: neutropenia and neutrophil count decreased (PTs) Anemia: anaemia and haemoglobin decreased (PTs) Thrombocytopenia: thrombocytopenia and platelet count decreased (PTs)
	Febrile neutropenia	Febrile neutropenia (PT)
	Infections	Infections and infestations (SOC)

Liver-related events will be summarized by PT, and Grade, including PTs in the following SMQs:

- Cholestasis and jaundice of hepatic origin (SMQ narrow)
- Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ narrow)
- Hepatitis, noninfectious (SMQ narrow)
- Liver related investigations, signs, and symptoms (SMQ narrow) and the following PTs:
  - Venoocclusive liver disease
  - Venoocclusive disease

For selected TEAEs, outcome, time to onset, time to resolution will be summarized. Incidence for IRRs pre and post implementation of additional steroid prophylaxis regimen will be summarized.

7.7.3 Clinical Laboratory Results

Laboratory test results within the treatment period (including hematology, coagulation, serum chemistry) will be categorized to their CTCAE Version 4.03 toxicity grades.

Shift tables from baseline to worst post-baseline CTCAE grade (high or low, as applicable, scheduled or unscheduled) will be summarized. The following abnormality tables for each laboratory tests related to CTCAE will also be included:

- Shifts from Grade 0 (normal) at baseline to Grade 1 - 4 post-baseline (maximum) and worsening from an abnormal baseline value of at least one grade up post-baseline (maximum).
- Shifts from Grade 0 - 2 at baseline to Grade 3 or 4 post-baseline (maximum) and from Grade 3 at baseline value to Grade 4 post-baseline (maximum).

For the above shift tables, a baseline grade of 0 (normal) will be imputed for all patients with at least one post-baseline but missing a baseline value for each lab test.

Clinically significant values in liver function tests will be summarized by the following categories (Table 13) using the maximum post-baseline lab values during the treatment period. The denominator for the summaries will be the number of patients who had at least 1 non-missing post-baseline value during the treatment period.

Table 13. Clinically Significant Values in Liver Function Tests

AST > 3 × ULN > 5 × ULN > 10 × ULN > 20 × ULN	ALT > 3 × ULN > 5 × ULN > 10 × ULN > 20 × ULN
AST or ALT > 3 × ULN > 5 × ULN > 10 × ULN > 20 × ULN	Total bilirubin (TBL) > 1 × ULN > 2 × ULN
(AST or ALT) and ALP and TBL (concurrent[a]) AST or ALT > 3 × ULN and ALP < 2 × ULN and TBL > 2 × ULN	Alkaline phosphatase (ALP) > 1.5 × ULN
(AST or ALT) and TBL (concurrent[a]) AST or ALT > 3 × ULN and TBL > 1.5 × ULN AST or ALT > 3 × ULN and TBL > 2 × ULN	

AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; ULN = Upper limit of normal

a. Concurrent means that all the associated liver function tests must be from the same visit or +/- 72 hours.

Lab tests and abnormal lab values including urinalysis and pregnancy tests will be provided in listings.

7.7.4 Vital Signs

Vital signs (including temperature, pulse rate, systolic blood pressure, diastolic blood pressure, and respiratory rate) will be classified into 4 or 5 categories (low, borderline low, normal, borderline high, or high) according to (Table 14) below. Shift tables based on this classification will be summarized from baseline to the worst post-baseline visit value.

Table 14. Classification of Vital Signs

Vital Sign	Low	Borderline Low	Normal	Borderline High	High
Heart Rate (beats per minute)	< 50	50-59	60-90	91-99	≥ 100
Systolic blood pressure (mmHg)	< 80	-	80-120	121-139	≥ 140
Diastolic blood pressure (mmHg)	< 60	-	60-80	81-89	≥ 90
Respiratory Rate (breaths per minute)	< 12	-	12-20	21-24	≥ 25
Temperature (°C)	< 35.0	35.0-36.4	36.5-37.2	37.3-37.9	≥ 38.0

7.7.5 Capillary Leak Syndrome (CLS)

The summary of patients meeting CLS criteria will be provided.

CLS is defined as capillary leak syndrome (preferred term) reported as an adverse event or those meeting 2 or more of the criteria in Table 15 with at least 2 criteria having a start date (time is not needed) within 7 days of each other during the treatment period.

Table 15. CLS Criteria

Criteria	Variable	Value	
Hypoalbuminemia	PT	Hypoalbuminemia	
	Lab result	Albumin (any value ≤ 3 g/dL)	
Edema	HLT	Oedema	
	PT	Ascites Eyelid oedema Face oedema Fluid overload Fluid retention Generalized oedema Hypervolaemia Laryngeal oedema	Oedema Oedema peripheral Periorbital oedema Peripheral swelling Swelling Swelling face Weight increased
	VS result	Weight (any increase > 5 kg from baseline)	
Hypotension	PT	Hypotension Hypovolemia	
	VS result	Systolic blood pressure (any value < 90 mmHg)	
	Concomitant medication (PT)	Dopamine Ephedrine Epinephrine Norepinephrine	Norepinephrine bitartrate Phenylephrine Vasopressin
Cytokine release syndrome (CRS)/ Infusion related reaction (IRR)	PT	Cytokine release syndrome Infusion related reaction Cardiac arrest Cardiopulmonary failure Multi-organ failure Multiple organ dysfunction syndrome	
HLT = High Level Term level of MedDRA; PT = preferred term; VS = vital sign			

7.7.6 BPDCN Safety Subgroup Analyses

The incidence of TEAEs will be assessed for the following subgroup (but not limited to):

- Age group (18 to < 65, 65 - < 75, >= 65, ≥= 75)
- Baseline renal status (normal, mild impairment, moderate impairment, severe impairment)
- Baseline hepatic status (normal, mild impairment, moderate impairment, severe impairment)
- Race (White, Black or African American, Asian, Not Reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Missing)

8. IMMUNOGENICITY

Anti-IMGN632 seroconversion refers to the development of anti-drug antibodies (ADA) that bind to IMGN632 and is based upon positive results in both screening and confirmatory ADA assays. The ADA and neutralizing antibody (nAb) assessment will be categorized as follows:

- Treatment-emergent ADAs: Patients who had a baseline-negative ADA result and who developed ADAs at any time after initial administration of drug.
- Treatment-enhanced ADAs: Patients who had a baseline positive ADA result in whom the assay signal was enhanced (greater than baseline titer by ≥ 4 folds) at any time after initial drug administration.
- Treatment-unaffected ADA: Patients who had a baseline-positive ADA result in whom the assay signal was not enhanced (not greater than baseline titer ≥ 4 folds) at any time after initial drug administration.
- Seronegative: a patient who tests negative at all visits.
- Treatment-emergent nAb negative: Treatment-emergent nAb status was defined as "negative" if subject was treatment-emergent or treatment-enhanced ADA positive and had no positive post-baseline nAb assessment.
- Treatment-emergent nAb positive: Treatment-emergent nAb status was defined as "positive" if subject was treatment-emergent or treatment enhanced ADA positive and had at least one positive post-baseline nAb assessment.

The effects of immunogenicity on the pharmacokinetics (PK) will be evaluated by comparing between-subject and within-subject concentrations or PK parameters based on the ADA status. Efficacy endpoint CR/CRc rate will be analyzed by the ADA and neutralizing antibody status.

TEAEs related to infusion-related reactions by SOC/SMQ and PT will be summarized based on the ADA status.

APPENDIX A. LIST OF SAP SIGNATORIES

Name	Title	Role/Function Area
[redacted]		

Document Approval

Study IMGN6320801 - Statistical Analysis Plan Version 2 - 02Oct2024 (E3 16.1.9)

Version: 1.0 **Date:** 02-Oct-2024 **Company ID:** 20241002-0900f9f6885bbdbc-1.0-en

Signed by:	Date:	Meaning of Signature:
[redacted]	02-Oct-2024 22:02 UTC	[redacted]
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	02-Oct-2024 21:14 UTC	
	02-Oct-2024 20:31 UTC	