CLINICAL STUDY PROTOCOL

TITLE PAGE

Protocol Title:	An Open-Label, Multi-Center, Single-Arm, Phase 1 Study Evaluating the Safety and Pharmacokinetics of Dinutuximab Beta as Maintenance Therapy in Chinese Patients with High-Risk Neuroblastoma
Protocol Number:	BGB-dinutuximab beta-101
Phase:	1
Investigational Products:	Dinutuximab beta (BGB-dinutuximab beta), 13-Cis-Retinoic Acid
IND Number:	Not applicable
EUDRACT Number:	Not applicable
Proposed Indication(s):	High-risk neuroblastoma
Sponsor:	BeiGene (Beijing) Co., Ltd. Room 101, 201, 402, 502, Building 1, No. 30 Science Park Road Zhong-Guan-Cun Life Science Park Changping District Beijing, 102206 China
Sponsor Medical Monitor:	[redacted] Telephone: [redacted] Email: [redacted]
Original Protocol Version 0.0:	15 June 2020
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FINAL PROTOCOL APPROVAL SHEET

An Open-Label, Multi-Center, Single-Arm, Phase 1 Study Evaluating the Safety and Pharmacokinetics of Dinutuximab Beta as Maintenance Therapy in Chinese Patients with High-Risk Neuroblastoma

BeiGene, Ltd., Approval:

(See electronic signature)	*(See electronic signature)*
Sponsor Medical Monitor	Date

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INVESTIGATOR SIGNATURE PAGE

Protocol Title: An Open-Label, Multi-Center, Single-Arm, Phase 1 Study Evaluating the Safety and Pharmacokinetics of Dinutuximab Beta as Maintenance Therapy in Chinese Patients With High-Risk Neuroblastoma

Protocol Identifier: BGB-dinutuximab beta-101

This protocol is a confidential communication of BeiGene, Ltd., and its subsidiaries. I confirm that I have read this protocol, I understand it, and I will work according to this protocol and the terms of the clinical study agreement governing the study. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.

Instructions for Investigator: Please SIGN and DATE this signature page prior to implementation of this sponsor-approved protocol. PRINT your name, title, and the name and address of the center in which the study will be conducted.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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SYNOPSIS

Name of Sponsor/Company: BeiGene (Beijing) Co., Ltd.
Investigational Products: Dinutuximab beta, 13-Cis-Retinoic Acid
Title of Study: An open-label, multi-center, single-arm, Phase 1 study evaluating the safety and pharmacokinetics of dinutuximab beta as maintenance therapy in Chinese patients with high-risk neuroblastoma
Protocol Identifier: BGB-dinutuximab beta-101
Phase of Development: 1
Number of Patients: Approximately 8 patients
Study Centers: Approximately 1 to 3 centers in China
Study Objectives: **Primary:** • To assess the safety and tolerability of ≤ 5 treatment cycles of dinutuximab beta in combination with 13-cis-retinoic acid (RA) as maintenance therapy in Chinese patients with high-risk neuroblastoma • To characterize the pharmacokinetics (PK) of dinutuximab beta in Chinese patients **Exploratory:** • To explore the preliminary anti-tumor activity and event free survival rate (EFS), of ≤ 5 treatment cycles of dinutuximab beta in combination with 13-cis-RA as maintenance therapy in Chinese patients with high risk neuroblastoma, if applicable
Study Endpoints: **Primary:** • Adverse events (AEs) characterized by type, frequency, severity (as graded by the National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 5.0), timing, seriousness, and relationship to study drug(s); and other safety assessments • PK parameters of dinutuximab beta, including but not limited to area under the concentration-time curve (AUC), maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), time to C_{max} (t_{max}), and half-life ($t_{1/2}$) if data permits **Exploratory:** • EFS is defined as the time from initiating study drug(s) to disease progression, death from any cause, relapse, secondary malignancy as assessed by investigators, including EFS rate at 6 months as measured by Kaplan-Meier method

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Study Design

This is an open-label, multi-center, single-arm, Phase 1 study evaluating the safety and pharmacokinetics of dinutuximab beta as maintenance therapy in Chinese patients with high-risk neuroblastoma.

After providing written informed consent, completing all screening assessments, and being confirmed as eligible for study participation, approximately 8 patients will be enrolled to receive dinutuximab beta plus 13-cis-RA therapy:

- Dinutuximab beta at 100 mg/m^2/cycle will be given as continuous long-term infusion (LTI) for 10 days from Day 1 to Day 11 in every 35-day cycle.
- Patients will receive 13-cis-RA 160 mg/m^2/day, divided into close to 2 equal doses and given orally twice a day for 14 days, starting on the next day after completion of dinutuximab beta infusion.
- Up to 5 cycles of administration will be applied for both dinutuximab beta and 13-cis-RA.

Study Assessments:

- AEs will be characterized by type, frequency, severity (as graded by the NCI CTCAE version 5.0), timing, seriousness, and relationship to study drug will be recorded; other safety assessments to be performed including vital signs, physical examinations, ophthalmologic examination, performance status, laboratory safety tests, etc.
- Blood samples will be collected on Day 1, 3, 8, 11, 15 (optional), 22 (optional), and 29 in Cycle 1, and on Day 1 and 11 in Cycle 2, 3, and 4 to characterize the PK of dinutuximab beta.
- Tumor assessments or monitoring will be performed by the investigators at Screening Visit, end of treatment Cycle 3, and end of treatment visit. International Neuroblastoma Response Criteria (INRC) (Brodeur et al 1993) is recommended as a reference for response evaluation in patients evaluable for tumor assessment.

Duration of Patient Participation:

Patients will receive study drugs until the completion of the 5 treatment cycles (ie. 25 weeks), tumor relapse, progressive disease (PD), unacceptable toxicity, death, or other discontinuation criterion is met.

Study Population:

Patients aged ≥ 12 months with high-risk neuroblastoma who have previously received induction chemotherapy and achieved at least a partial response followed by myeloablative therapy and stem cell transplantation

Key Eligibility Criteria:

- Patients aged ≥ 12 months
- Diagnosis of high-risk neuroblastoma according to the International Neuroblastoma Staging System (INSS) criteria, ie, INSS Stage 4 without *MYCN* amplification (MNA) and aged ≥ 18 months; or INSS Stage 2-4 with MNA
- Patients who have previously received induction chemotherapy and achieved a partial or complete response followed by myeloablative therapy and stem cell transplantation

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Investigational Products, Dose, and Mode of Administration:

Dinutuximab beta

- Dinutuximab beta at 100 mg/m^2/cycle will be given as continuous long-term infusion (LTI) for 10 days from Day 1 to Day 11 in every 35-day cycle.
- Up to 5 cycles of infusion will be administered.

13-cis-RA

- 13-cis-RA will be given orally at a dose of 160 mg/m^2/day, divided into close to 2 equal doses twice a day for 14 days, started on the next day after completion of dinutuximab beta infusion.
- Up to 5 cycles of oral administration will be applied.

Reference Therapy, Dose, and Mode of Administration:

Not applicable

Statistical Methods:

Analysis Sets

- The Safety Analysis Set will include patients who have received at least 1 dose of study drug.
- The PK Analysis Set will include patients who have at least one available post-baseline PK data in Safety Analysis Set.

Safety Analyses

Safety is the primary endpoint and will be assessed by adverse events as characterized by type, frequency, severity (as graded by the NCI-CTCAE version 5.0), time, seriousness, and relationship to study drug(s), vital signs and laboratory abnormalities. Extent of exposure, physical examinations, and ECG findings will also be used in determining the safety profile. Descriptive statistics will be used to analyze all safety data in the Safety Analysis Set.

Pharmacokinetic Analyses

Serum concentration-time data of each patient will be tabulated and graphically presented on linear semi-logarithmic scales. PK parameters will be determined using a standard non-compartmental method in PK analysis set. Descriptive statistics will be used, including means, standard deviations, medians, ranges, geometric mean, and coefficient of variation (CV) % associated to the geometric mean as appropriate.

Exploratory Efficacy Analyses

No formal hypothesis testing is planned in this trial. Tumor assessment based on investigator assessment will be used to calculate EFS as well as time-point estimates including EFS-6m by Kaplan-Meier method. 95% confidence intervals will be constructed to describe the precision of the point estimates of interest (eg, median EFS, EFS-6m) if estimable.

A listing of patients in Safety Analysis Set will be provided.

Sample Size Consideration

The study plans to enroll approximately 8 patients as recommended for PK studies by CDE technical guidance on clinical pharmacokinetic study of chemical drugs (Center of Drug Evaluation (CDE) of National Medical Products Administration (NMPA) 2005). Therefore, a sample size of approximately 8 patients is proposed in this single arm study for PK assessment consideration.

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
C_{max}	maximum serum concentration
CT	computed tomography
ECG	electrocardiogram
eCRF	electronic case report form
EOT	End-of-Treatment (Visit)
GD2	disialoganglioside 2
GCP	Good Clinical Practice
ICF	informed consent form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
PK	pharmacokinetic(s)
ULN	upper limit of normal

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1. INTRODUCTION AND RATIONALE

1.1. Neuroblastoma

Neuroblastoma commonly refers to a spectrum of neuroblastic tumors (including neuroblastoma, ganglioneuroblastoma, and ganglioneuroma). Neuroblastomas have a rather heterogeneous character and may vary in terms of location, histopathologic appearance, and biologic characteristics as well as in their clinical behavior; which can cover a broad spectrum from spontaneous regression to maturation, to a benign ganglioneuroma, or to an aggressive disease with metastatic dissemination leading to death (Chinese Children Cancer Group and Pediatric Surgery Society of Chinese Medical Association 2015).

Neuroblastoma is mainly a pediatric disease that currently represents the third most common form of childhood cancer after leukemia and brain tumors. It is the most common solid extracranial tumor in the pediatric population, representing 8% to 10% of all childhood tumors (Papaioannou et al 2005; Colon et al 2011).

Most patients with neuroblastoma are diagnosed under the age of 5 years, and most present with metastatic disease and/or high-risk features. The incidence is 10.2 cases per million children under 15 years of age, and nearly 500 new cases are reported annually in the United States (US) (Colon et al 2011). In the European Union (EU), the annual incidence of neuroblastoma in the pediatric population (0 to 14 years) is 0.12 in 10,000 people and that in the general population is 0.03 in 10,000 people. International reports have shown that the incidence rates of neuroblastoma are highest among high-income countries in Europe and North America and lower in low-income countries in Africa, Asia, and Latin America (Lacayo et al 2019). The lower incidence of neuroblastoma in developing, low-income countries could be attributed to underdiagnosis.

High-risk neuroblastoma, a mainly pediatric disease, remains one of the major challenges in pediatric oncology and is characterized at diagnosis by metastatic disease beyond 18 months of age and unfavorable biological features e.g. v-myc myelocytomatosis viral related oncogene (*MYCN*) amplification as the most prominent one (Cohn et al 2009). Despite the introduction of novel treatment strategies, including high-dose chemotherapy followed by autologous bone marrow or stem cell transplantation, the outcome of these patients remains poor, relapses occurring even after such extensive chemotherapeutic interventions (Maris et al 2010; Modak et al 2010; Qarziba EU SmPC).

Since the majority of patients with high-risk disease eventually experience local or systemic relapse even after achieving complete remission after first-line therapy, much attention has been focused on maintenance treatment of minimal residual disease (MRD). Maintenance treatment consists of biological therapies that include differentiation-inducing agents such as retinoid derivatives or immunotherapy with monoclonal antibodies. Retinoids induce terminal differentiation of neuroblastoma cells and apoptosis in vitro. Today, 13-cis-retinoid acid (RA) given 2 weeks per month over 6 months post-transplantation is part of most high-risk protocols.

Development of effective maintenance therapeutic strategies appears to be the only realistic way to further improve outcome in this disease. In this regard, there has been growing interest in major areas of adjuvant therapy of malignant diseases, including tumor-specific immunotherapy.

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One concept in the treatment of neuroblastoma is the application of monoclonal antibodies directed against neuroblastoma cells. The chimeric monoclonal antibody (mAb) ch14.18, which recognizes the disialoganglioside (GD2) on neuroblastoma cells, is expressed by almost all neuroblastoma cells. This antibody could therefore have an important role in the treatment of neuroblastoma.

The first chimeric anti-GD2 antibody was produced in murine, non-secreting myeloma cells (ch14.18/SP2/0, dinutuximab) (Gillies et al 1989) and later, the ch14.18 construct was recloned into Chinese hamster ovary (CHO) cells leading to dinutuximab beta (ch14.18/CHO).

In a phase 3 study, patients with high-risk neuroblastoma who had a response to induction therapy and stem-cell transplantation were randomly assigned to receive standard therapy (6 cycles of 13-cis-RA) or immunotherapy (6 cycles of 13-cis-RA and five concomitant cycles of ch14.18/SP2/0 in combination with alternating GM-CSF and interleukin-2). Immunotherapy was superior to standard therapy with regard to rates of event free survival (EFS) (66 ± 5% versus 46 ± 5% at 2 years, p=0.01) and overall survival (86 ± 4% versus 75 ± 5% at 2 years, p=0.02 without adjustment for interim analyses) (Yu et al 2010).

1.2. Dinutuximab Beta

Dinutuximab beta is a mouse-human chimeric monoclonal IgG1 antibody that is specifically directed against the carbohydrate moiety of GD2. Dinutuximab beta has been shown *in vitro* to bind to GD2-expressing neuroblastoma cell lines and to induce both complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity. Dinutuximab beta is indicated for the treatment of high-risk neuroblastoma in patients ≥ 12 months who have previously received induction chemotherapy and achieved at least a partial response followed by myeloablative therapy and stem cell transplantation (SCT); as well as in patients with a history of relapsed or refractory neuroblastoma with or without residual disease (Qarziba EU SmPC).

A summary of nonclinical and clinical data for dinutuximab beta is provided below; additional data are presented in the Dinutuximab Beta Investigator's Brochure.

1.2.1. Nonclinical Data for Dinutuximab Beta

Specific antigen binding (K_{Diss}=15 to 22 nM) of dinutuximab beta to GD2 has been shown *in vitro* via surface plasmon resonance (SPR) as well as via a competition ELISA analysis (EC_{50}=4.5 ng/mL). *In vitro* effector function studies also showed dinutuximab beta-triggered cytolytic activities on LAN-1 (neuroblastoma) cells in a complement-dependent cytotoxicity assay (EC_{50}= 57 ng/mL), in an antibody-dependent cell-mediated cytotoxicity assay (EC_{50}=2.0 ng/mL), and in a whole blood test of cytolytic activity (EC_{50}=64.6 ng/mL), respectively.

The *in vivo* antitumor activity of dinutuximab beta was demonstrated in a syngeneic mouse model. Dose-dependent and antigen-specific suppression of metastases was demonstrated in mice treated with dinutuximab beta 4 and 12 mg/kg/day for 5 consecutive days. The anti-tumor effect could be abrogated by depletion of NK cells, confirming that antibody-dependent cell-mediated cytotoxicity is the main cause of dinutuximab beta-triggered anti-tumor activity.

No stand-alone safety pharmacology studies have been performed with dinutuximab beta in accordance with ICH guideline S9 2016. However, tests of neurological, cardiovascular, and

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respiratory function parameters including repeated-dose toxicity studies in guinea pigs and cynomolgus monkeys showed no test item-related changes.

1.2.2. Clinical Pharmacology

The pharmacokinetics of dinutuximab beta based on 10-day continuous intravenous infusion of 10 mg/m^2/day (equal to a total dose of 100 mg/m^2/course) were evaluated in Studies APN311-303 and APN311-202. Mean plasma C_{max} levels for Cycle 1 were reached on the last day of infusion, with a C_{max} mean ± SD of 13.36 ± 5.89 µg/mL in APN311-303 and 11.91 ± 4.25 µg/mL in APN311-202. The volume of distribution was stated to be 5 to 6.5 L/m^2. In Study APN311-202, C_{max} proportionally increased over the dose range of 10 to 30 mg/m^2/day.

While no excretion or metabolism studies have been conducted to date, the expected metabolic pathway for dinutuximab beta involves its degradation into small peptides and individual amino acids by ubiquitous proteolytic enzymes. The half-life ($t_{1/2}$) for Cycle 1 of dinutuximab beta was around 190 hours (ie, 8 days), with a $t_{1/2}$ median (range) of 186.52 (70.13-295.37) hours in APN311-303 and 178.01 (77.14-396.23) hours in APN311-202. Pharmaceutic(s) (PK) parameters for Cycles 2 to 5 were similar to those for Cycle 1, but with a tendency to increased C_{max} and AUC values from cycle to cycle due to a slight drug accumulation. The mean accumulation ratio for C_{max} and AUC increased from Cycle 2 to 5, with the range of 1.29 to 1.57 and 1.32 to 1.61, respectively.

1.2.3. Preliminary Efficacy and Safety Data With Dinutuximab beta

Efficacy

The efficacy of dinutuximab beta for the treatment of neuroblastoma was evaluated in 5 clinical studies. The main compassionate-use Study APN311-303 showed therapeutic efficacy of dinutuximab beta administered as a continuous 10-day infusion in patients with relapsed and refractory neuroblastoma and in those who had received first-line therapy only. The efficacy of dinutuximab beta was confirmed in 4 additional complementary studies that provided efficacy data for both relapsed/refractory and first-line patients for continuous infusion versus short-term (8 h) infusion and for patients receiving concomitant interleukin-2 (IL-2) treatment with immunotherapy versus immunotherapy alone.

Dinutuximab beta either given as short-term infusion (STI) (5 x 8 hours) or long-term infusion (LTI) (10 days, 24 hours) demonstrated significant clinical benefits to patients with high-risk neuroblastoma in terms of ORR, EFS, and overall survival (OS). The overall response rate (ORR), EFS and OS across studies are presented in Table 1. In historic control groups, OS at 2 years was between 20% and 30%.

Table 1: Efficacy of Dinutuximab Beta in Clinical Studies in European Patients

	Study APN311-						
	303[a]	**202[a]**		**201[b]**	**101[bc]**	**302[b]**	
	(N=54)	**V1 (N=44)**	**V2 (N=76)**	**(N=35)**	**(N=15)**	**w/o IL2 (N=187)**	**with IL-2 (N=198)**
Evaluable (N) for response	37	32	45	20	12	65	70

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	Study APN311-						
	303[a]	202[a]		201[b]	101[bc]	302[b]	
	(N=54)	V1 (N=44)	V2 (N=76)	(N=35)	(N=15)	w/o IL2 (N=187)	with IL-2 (N=198)
Response (CR, PR, VGPR)	41%	50%	56%	75%	33%	44%	51%
Evaluable (N) for EFS+OS	53	44	76	35	ND	180	190
EFS at 3 years	31%	41%	54%	40%	ND	55%	61%
OS at 3 years	66%	54%	77%	55%	ND	64%	69%

[a] Continuous 24-hour infusion. [b] 8-hour infusion. [c] No IL-2 co-treatment
V1, first part of Study 202, based on Original Protocol; V2, second part of Study 202, based on Protocol Amendment 1.0; CR, complete response; EFS, event free survival; IL-2, interleukin 2; N, number of patients; ND, not determined; OS, overall survival; PR, partial response; VGPR, very good partial response; w/o, without.
Resource: Dinutuximab Beta Investigator's Brochure.

The efficacy was independent of disease state at baseline. However, compared to multimodality treatment for relapsed/refractory neuroblastoma without immunotherapy, treatment including dinutuximab beta showed significant advantages. Also, the effects were independent of IL-2 co-administration. Monotherapy with dinutuximab beta showed similar survival outcomes as combination treatment with IL-2 when used as part of the maintenance phase of first-line therapy for high-risk neuroblastoma patients (study APN311-302). The results are also comparable to therapy with ch14.18/SP2/0 (ch14.18 monoclonal antibody produced in murine SP2/0 cells) plus intravenous IL-2 and granulocyte macrophage colony-stimulating factor although this asset was assessed in a population of complete responders only (Yu et al 2010).

Safety

The most prominent adverse reaction with dinutuximab beta is severe neuropathic pain, especially during the first courses, due to the binding of dinutuximab beta to GD2 on nerve cells. Standard pain management including opioids, gabapentin, and nonsteroidal anti-inflammatory drugs should thus be established by experienced physicians when dinutuximab beta is administered. Hypersensitivity reactions are commonly observed with monoclonal antibody treatment and were also frequently observed with dinutuximab beta treatment (63%) including pyrexia, pruritus, tachycardia, and hypertension. Capillary leak syndrome is a common adverse reaction of IL-2 and has also occurred frequently with dinutuximab beta (40%). Other frequently reported adverse events (AEs) varied across studies but commonly included constipation, nausea, vomiting, cough, increased liver enzymes, anemia, decreased neutrophils, and decreased platelets. Most AEs were Grade 1 to Grade 3; Grade 4 events occurred with incidences between 6% and 45% across studies. A continuous treatment regimen led to a clearly improved pain-toxicity profile compared with the 8-hour infusion regimen. The omission of subcutaneous IL-2 as co-treatment with the 8-hour infusion regimen greatly reduced side effects. To ensure patient's safety, administration of dinutuximab beta must be performed by a healthcare professional well experienced in managing severe allergic reactions including anaphylaxis. Infusion of dinutuximab beta must be initiated in an environment where full resuscitation services are immediately available.

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1.3. Study Rationale

High-risk neuroblastoma is a rare disease in China and has a poor prognosis. Compared with medical treatment in western countries, the diagnosis and treatment of neuroblastoma in China needs to be improved. Dinutuximab beta is approved as Qarziba in the EU and is on the list of urgently needed drugs issued by the Center for Drug Evaluation (CDE) in 2018. Although dinutuximab beta, as a monoclonal antibody, is unlikely to show ethnic differences (Zhao et al 2012; Navid et al 2010), this study was proposed in Chinese patients to assess pharmacokinetics and safety and verify any ethnic differences with regard to use and dosage. The study is designed to provide PK data in 8 Chinese patients and to confirm the safety and tolerability of dinutuximab beta when administered as a continuous infusion at a dose of 10 mg/m^2/day for 10 days for up to five 35-day cycles.

1.3.1. Rationale for Selection of Dose

The approved dose and schedule of dinutuximab beta to be used in this study was selected based on previous studies in which the same dose and schedule of dinutuximab beta 10 mg/m^2/day for 10 days in 35-day cycles was used. In Study APN311-101, a dose of 100 mg/m^2/cycle was confirmed (8-hour infusion, 5 days). In Study APN311-202, the dose schedule of 100 mg/m^2/cycle (10 mg/m^2/day, 10-day continuous infusion) was used as a starting point; this dose was then confirmed as safe and efficacious in the dose schedule finding part and the confirmatory part.

A population PK analysis was conducted on the data obtained from Studies APN311-101, -202, and -303. Median values of body surface area (BSA) were used for PK simulation of different age groups (< 2 years to > 18 years). The predicted typical exposure (C_{max} and AUC_{24h}) was similar in all subjects ≤ 12 years and decreased slightly for older patients, which in turn supported the dose justification based on BSA for a wide age range.

The effect of race on the exposure of IgG1 mAb is often insignificant after the difference in body weight or BSA has been taken into account (Zhao et al 2012). Therefore, the exposure of dinutuximab beta is not likely to be ethnically different as the dosing is based on BSA. Further, the C_{max} in the Japanese study APN311-102 (N = 9) was similar to that in Studies APN311-202 and -303 that used the schedule of dinutuximab beta 10 mg/m^2/day for 10 days in 35-day cycles. Therefore, the same dose and schedule was selected for use in this study for Chinese patients.

Recent data from Study APN311-302 showed that the addition of IL-2 in combination with dinutuximab beta infusions does not increase event-free survival (EFS) and overall survival (OS) in high-risk neuroblastoma patients but does show an inferior safety profile compared with dinutuximab beta alone. The focus of this study is to evaluate PK in Chinese patients; coadministration with IL-2 is not expected to affect the PK characteristics of dinutuximab beta but may increase toxicity. Therefore, IL-2 is not included as a cotreatment in this study.

1.4. Benefit-Risk Assessment

For patients with high-risk neuroblastoma, treatment options are limited. Treatment with an anti-GD2 antibody (dinutuximab beta) is globally known to prolong EFS and OS and is used as the standard-of-care of maintenance treatment throughout the USA and EU.

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To date, over 1489 patients with neuroblastoma have been treated with short-term (8-hour) infusions or continuous (24-hour) infusions of dinutuximab beta in combination with IL-2 or as a single-agent treatment. Response to treatment with dinutuximab beta has been consistently shown in all completed clinical studies to date.

Dinutuximab beta is associated with considerable but manageable toxicities. The most prominent adverse reaction with dinutuximab beta is neuropathic pain. Skilled pain management including the use of morphins is a prerequisite when dinutuximab beta is administered. Additional dinutuximab beta-related frequent toxicities include pyrexia, hypersensitivity reactions, pruritus, capillary leak syndrome, cytokine release syndrome, hypotension, and tachycardia. A continuous infusion regimen of dinutuximab beta over 10 days, ie, a lower dinutuximab beta concentration per hour of infusion, leads to an improved pain-toxicity profile; meanwhile, omission of co-treatment IL-2 can also reduce side effects and result in better compliance. Noteworthy, administration of this compound must be performed by well-trained physicians with experience in treating oncologic pediatric patients and severe allergic reactions. Patient safety during and after administration must be closely monitored.

All possible benefits and risks will be discussed thoroughly with the patient and/or his/her legally authorized representative. The ICF will be signed by patient and/or his/her legally authorized representative before study entry.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of dinutuximab beta can be found from Qarziba EU SmPC.

In conclusion, the benefit of outcome improvements outweighs the risk related to dinutuximab beta infusion when treating patients with high–risk neuroblastoma.

1.5. Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and in accordance with Good Clinical Practice (GCP) standards.

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2. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the safety and tolerability of ≤ 5 treatment cycles of dinutuximab beta in combination with 13-cis-retinoic acid (RA) as maintenance therapy in Chinese patients with high-risk neuroblastoma	Adverse events (AEs) characterized by type, frequency, severity (as graded by the National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 5.0), timing, seriousness, and relationship to study drug(s); and other safety assessments
To characterize the pharmacokinetics (PK) of dinutuximab beta in Chinese patients	PK parameters of dinutuximab beta, including but not limited to area under the concentration-time curve (AUC), maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), time to C_{max} (t_{max}), and half-life ($t_{1/2}$), if data permits.
Exploratory	
To explore the preliminary anti-tumor activity and event free survival rate (EFS), of ≤ 5 treatment cycles of dinutuximab beta in combination with 13-cis-RA as maintenance therapy in Chinese patients with high risk neuroblastoma, if applicable	EFS is defined as the time from initiating study drug(s) to disease progression, death from any cause, relapse, secondary malignancy as assessed by investigators, including EFS rate at 6 months as measured by Kaplan-Meier method

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3. STUDY DESIGN

3.1. Summary of Study Design

This is an open-label, multi-center, single-arm, Phase 1 study evaluating the safety and pharmacokinetics of dinutuximab beta as maintenance therapy in Chinese patients with high-risk neuroblastoma.

Potential patients will be screened for eligibility before study enrollment (screening period ≤ 28 days). The study will recruit approximately 8 patients who will be hospitalized (with a full resuscitation equipment) on Day 1 of each cycle and will receive continuous infusion of dinutuximab beta administered at a dose of 10 mg/m^2/day for 10 consecutive days in 35-day cycles (total dose 100 mg/m^2/cycle). Patients must be administered in a unit with a full resuscitation equipment. Patients will be discharged from the hospital at the investigator's discretion. Patients will continue to receive 13-cis-RA 160 mg/m²/day, divided into close to 2 equal doses and given orally twice a day for 14 days after completion of dinutuximab beta infusion.

Patients may receive up to five 35-day cycles in the absence of relapse, disease progression or unacceptable toxicity.

Refer to Figure 1 for an overview of the study design and Appendix 1 for details on study assessments and procedures that will be carried out during the study.

The maximum duration of participation (Screening Visit to Safety Follow-up Visit) for individual patients will be approximately 35 weeks. Each patient will participate in the screening period (≤ 28 days), study intervention infusion period (≤ 25 weeks), and a post-infusion period (≤ 6 weeks). Additional clinical follow-up might be needed depending on findings during the study.

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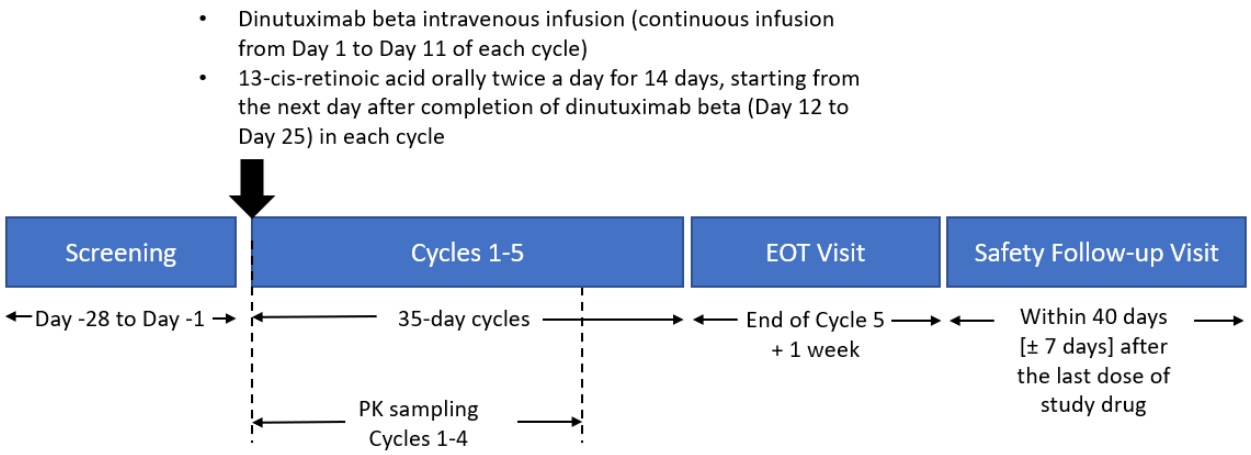
Figure 1: Study Schema



Abbreviations: EOT, end of treatment; PK, pharmacokinetic(s).

All patients will be closely monitored for AEs throughout the study and for 40 days after the last dose of study drug. AEs will be graded according to the NCI-CTCAE version 5.0. Refer to Section 9 for additional and specific information regarding AE monitoring and reporting.

PK analysis will be performed for dinutuximab beta.

Tumor assessments or monitoring will be performed by the investigators at Screening Visit, end of treatment Cycle 3, and end of treatment Visit per their clinical practice. International Neuroblastoma Response Criteria (INRC) (Brodeur et al 1993) is recommended as a reference for response evaluation (Section 8.4) in patients evaluable for tumor assessment. Refer to Section 7.6 for additional considerations regarding treatment continuation and withdrawal. Patients who, at the time of progression, have an ongoing AE that leads to treatment discontinuation and who have completed the scheduled Safety Follow-up Visit will be followed up until the event resolves, the investigator assesses the event as stable, the patient is lost to follow-up, or the patient starts a new anticancer therapy, end of study, whichever comes first.

Patients who have discontinued study drug(s) should return to the site for an End-of-Treatment (EOT) Visit as detailed in Section 7.4. After the EOT Visit, patients will have scheduled follow-up visits for safety (Appendix 1).

Study procedures and assessments are further detailed in Section 7 and Section 8, respectively, and the Schedule of Assessments can be found in Appendix 1.

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4. STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 4.1 and Section 4.2. The sponsor will not grant any eligibility waivers.

4.1. Inclusion Criteria

Each patient must meet all the following inclusion criteria to be considered eligible for participation in this study:

1. Signed informed consent form (ICF) and ability to comply with study requirements: patient or his/her parent/guardian must be capable of giving signed informed consent/assent as described in Section 14.3 including compliance with the requirements and restrictions listed in the ICF and in this protocol.
2. Age ≥ 12 months at consent
3. Diagnosis of high-risk neuroblastoma according to the International Neuroblastoma Staging System (INSS) criteria, ie, INSS Stage 4 without *MYCN* amplification (MNA) and aged ≥ 18 months; or INSS Stage 2-4 with MNA
4. Patients who have previously received induction chemotherapy and achieved a partial or complete response followed by myeloablative therapy and stem cell transplantation. Stem cell transplantation should be completed within 120 days of dinutuximab beta first administration. The date patients complete the last stem cell transplantation is defined as day zero (Day 0).
5. Not receiving standard or experimental treatments within 2 weeks before study treatment start and full recovery from the short-term major toxic effects of any prior treatment
6. Consistency of contraceptive use by men or women with local regulations regarding the methods of contraception for those participating in clinical studies

   NOTE: The reliability on sexual abstinence for male and/or female enrollment eligibility needs to be evaluated in relation to **the duration of the clinical study and the preferred and usual lifestyle of the patient**. Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
7. Females of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study, and 180 days after the last dose of study drug(s), and have a negative urine or serum pregnancy test ≤ 7 days of the first dose of study drug(s) (Appendix 4).
8. Nonsterile males must be willing to use highly effective method of birth control for the duration of the study and for 180 days after the last dose of study drug(s) (Appendix 4).
   - A sterile male is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility.
   - Males with known “low sperm counts” (consistent with “subfertility”) are not to be considered sterile for purposes of this study.

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9. Life expectancy of ≥ 12 weeks
10. Performance status ≥ 70% (Lansky Score or Karnofsky, see Appendix 3)
11. Laboratory tests:
    - ANC ≥ 1.5 x 10^9/L, platelets ≥100 x 10^9/L, and hemoglobin > 80 g/L
    - ALT and AST ≤ 2.5 x upper limit of normal (ULN) or < 5 x ULN if hepatic metastases are present; and total bilirubin < 1.25 x ULN
    - Creatinine clearance or radioisotope glomerular filtration rate (GFR) > 60 mL/min/1.73m^2
12. Negative test for hepatitis B surface antigen (HBsAg).
13. Pulse oximetry > 94% on room air

4.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from this study:

1. Hypersensitivity to ≥ 1 component of dinutuximab beta antibody or against mouse proteins
2. Actively progressive disease (not stabilized) or recurrent disease at the time of inclusion into the study
3. Significant intercurrent illnesses and/or any of the following:
    - Symptoms of congestive heart failure or uncontrolled cardiac rhythm disturbance
    - Significant psychiatric disabilities or uncontrolled seizure disorders
    - Active infections or active peptic ulcer, unless these conditions are corrected or controlled
    - Clinically significant neurologic deficit or objective peripheral neuropathy (> Grade 2)
    - Clinically significant, symptomatic pleural effusions
4. Previous treatment with anti-GD2 antibody before enrolling in this study
5. Any condition that required systemic treatment with either corticosteroids or other immunosuppressive medication ≤ 14 days before the first dose of study drug(s).
6. Concurrent treatment with any non-study anticancer therapies
7. Patients with active hepatitis C infection should be excluded. Note: Cured hepatitis C patients (as defined by a positive hepatitis C virus (HCV) antibody test and negative HCV RNA test) can be enrolled
8. Known history of HIV infection

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. Dinutuximab Beta

Formulation

Infusion: A volume of 4.5 ± 0.25 mL, which corresponds to a minimum extractable dose of 20 mg/vial, is filled into 6-mL type 1 glass vials.

Table 2: Dinutuximab Beta Formulation

Content	**4.5 ± 0.25 mg/mL**
Buffer	20 mM histidine, 5% sucrose, 0.01% Tween 20, water for injection
pH	5.5-6.5

The vials are closed with halobutyl rubber stoppers and sealed with aluminum flip-off caps. The actual antibody content of the respective batch of dinutuximab beta is indicated on the label on the vials.

Packaging, Labeling, And Handling

Dinutuximab beta will be supplied in a commercial presentation by sponsor.

The contents of the label will be in accordance with all applicable local regulatory requirements. The study drug must be kept at the temperature condition as specified on the label. Refer to the Pharmacy Manual for details regarding administration, accountability, and disposal. Please also refer to Dinutuximab Beta's Prescribing Information for other details regarding Dinutuximab beta.

5.1.2. 13-cis-retinoic acid

The 13-cis-RA (TeeWasH®), a liquid-filled capsule, will be supplied by sponsor. Management (ie, handling, storage, administration, and disposal) of 13-cis-RA will be in accordance with relevant local guidelines and/or prescribing information. The contents of the label will be in accordance with all applicable local regulatory requirements.

For the other details regarding 13-cis-RA, please refer to the local label of 13-cis-retinoic acid or Pharmacy Manual accordingly.

5.2. Dosage, Administration, and Compliance

Accurate records of all study drug(s) received, dispensed, returned, and disposed of should be maintained in the site's Drug Inventory Log. Refer to the Pharmacy Manual for details of study drug management, drug preparation, storage, and administration.

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5.2.1. Dinutuximab Beta

Dosage

Total dose: 100 mg/m^2/cycle

Patients may receive up to five 35-day cycles in the absence of disease progression or unacceptable toxicity.

Dinutuximab beta is administered at a dose of 10 mg/m^2/day as a 24-hour continuous infusion for 10 days (total dose 100 mg/m^2/cycle) for five 35-day cycles.

Preparation of Infusion

The solution for infusion must be prepared under aseptic conditions. The solution must not be exposed to direct sunlight or heat.

The patient-specific daily dose of dinutuximab beta is calculated based on BSA. Dinutuximab beta should be diluted aseptically to the patient-specific concentration/dose with sodium chloride 9 mg/mL (0.9%) solution for infusion, containing 1% human albumin (eg, 5 mL of 20% human albumin per 100 mL of 0.9% sodium chloride solution).

For continuous infusions, the solution for infusion can be prepared freshly on a daily basis, or sufficient for up to 5 days of continuous infusion. The daily dose is 10 mg/m^2. The amount of solution to be infused per day (within a treatment course of 10 consecutive days) should be 48 mL; with 240 mL for a 5-day dose. It is recommended to prepare 50 mL solution in a 50 mL syringe, or 250 mL in an infusion bag suitable for the employed infusion pump, ie, an overfill of 2 mL (syringe) or 10 mL (infusion bag) to allow for dead volumes of the infusion systems.

Administration of The Infusion

The solution for infusion should be administered via a peripheral or central intravenous line. Other intravenously co-administered agents should be delivered via a separate infusion line. The container should be inspected visually for particulates before administration. It is recommended that a 0.22 micrometer in-line filter is used during infusion.

For continuous infusions, any medical device suitable for infusion at a rate of 2 mL per hour can be applied, eg, syringe infusion pumps/infusors, electronic ambulatory infusion pumps. Note that elastomeric pumps are not considered suitable in combination with in-line filters.

The investigator may need to reduce or delay doses or stop treatment if certain side effects occur. It allows the investigator to decrease at 50% of the previous dose or interrupt the infusion. In this instance, the total amount does not need to equal 240 hours of infusion per cycle ideally (total dose of 100 mg/m^2/cycle). The investigator must record the reasonable reason for providing any alternative dose during treatment.

Refer to Qarziba EU SmPC for storage of the diluted solution and disposal.

Compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit along with information provided by the patient and documented accordingly. The investigator and/or

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study personnel will keep accurate records of the quantities of agents dispensed and used by each patient. This information must be captured in the source document at the end of each cycle.

5.2.2. 13-cis-retinoic acid

Patients will receive 13-cis-RA (TeeWasH®) at a total daily dose of 160 mg/m²/day, administered in close to 2 equal oral doses twice a day for 14 days after completion of dinutuximab beta infusion. Doses will need to be rounded to the nearest 10 mg. Capsules come as 10 mg sizes and can be emptied into a high fat food such as ice cream or chocolate mousse to administer. Investigators can adjust the dose of 13-cis-RA for the patient's conditions by following the 13-cis-RA prescription or investigators' experience in using 13-cis-RA. If the total daily doses are odd numbers of 13-cis-RA capsules, the number of capsules for each time can be unequal. In that case, if the daily doses are 11 capsules, patients would receive 5 capsules in the morning and 6 capsules in the evening or 6 capsules in the morning and 5 capsules in the evening.

Suggested supportive care for 13-cis-RA:

- Topical vitamin E should be applied to the lips twice a day during 13-cis-RA oral administration therapy if cheilitis develops
- Patients should avoid direct sun exposure while on 13-cis-RA
- Patients should avoid exposure to vitamin A products during 13-cis-RA

5.3. Overdose

In the case of overdose, patients should be carefully observed for signs or symptoms of adverse reactions and supportive care administered, as appropriate.

5.4. Dose Delay or Modification

Dose modification

This protocol allows some alteration from the currently outlined infusion schedule of dinutuximab beta, but the maximum cumulative exposure will not exceed 100 mg/m^2/cycle.

Based on the Investigator's evaluation of the severity of adverse drug reactions to dinutuximab beta, patients may undergo a dose reduction of 50% or a temporary interruption of the infusion. As a consequence, either the infusion period is prolonged or, if tolerated by the patient, the infusion rate may be increased up to 3 mL/h (continuous infusion), in order to administer the total dose.

Regarding the dose modification of 13-cis-RA, please refer to local label of 13-cis-retinoic acid.

Table 3: Recommended Dinutuximab Beta Dose Modification

Adverse reaction	Severity	Treatment modification
Any	**Grade 1 or 2**	Decrease infusion rate to 50%. After resolution, resume infusion at original rate.

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Hypersensitivity reaction	eg, Hypotension	Interrupt infusion and administer supportive measures. After resolution, resume infusion at original rate.
Dilated pupils with sluggish light reflex ± photophobia		Interrupt infusion. After resolution, resume infusion at 50% rate.
Any	**≥ Grade 3**	Interrupt infusion and administer supportive measures. Resume infusion at 50% rate if adverse drug reaction (ADR) resolves or improves to Grade 1 or 2 within 3 days of onset. If 50% dose reduction is tolerated for ≥ 1 day, consider advancing infusion to full rate as tolerated. If toxicity (≥ Grade 3) recurs at 50% dose reduction, treatment should be discontinued. If toxicity (≥ Grade 3) recurs while at 100% infusion rate, stop infusion and reduce dose to 50% if toxicity resolves or improves to ≤ Grade 2 within 3 days of onset. Do not increase dose to 100% again.
Capillary leak syndrome		Interrupt infusion and administer supportive measures. Resume at 50% rate if ADR resolves or improves to Grade 1 or 2.
Capillary leak syndrome requiring ventilator support; allergic reaction (anaphylaxis), skin toxicity, severe neuropathic pain, any other Grade 4 toxicity (which does not recover to Grade 1 or 2 or baseline within 5 weeks)	Grade 4	Discontinue infusion. Contact sponsor to confirm if patient may continue infusion at the start of the subsequent cycle.

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6. PRIOR AND CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter and prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving within 30 days before the first dose of dinutuximab beta:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.1. Premedication

Antihistamine premedication (eg, diphenhydramine) should be administered by intravenous injection approximately 20 minutes or orally based on the physician's judgment before starting each dinutuximab beta infusion. It is recommended that antihistamine administration be repeated every 4 to 6 hours as required during dinutuximab beta infusion.

Patients should be closely monitored for anaphylaxis and allergic reactions, particularly during the first and second treatment course.

Pain

Neuropathic pain usually occurs at the beginning of the treatment and premedication with analgesics, including intravenous opioids, before each infusion of dinutuximab beta is required. A triple therapy including nonopioid analgesics (according to World Health Organization guidelines), gabapentin, and opioids is recommended for pain treatment. The individual dose may vary widely.

Nonopioid analgesics

Nonopioid analgesics should be used permanently during the treatment, eg, paracetamol or ibuprofen (refer to local label for details regarding administration).

Gabapentin

The patient should be primed with 10 mg/kg/day, starting 3 days before dinutuximab beta infusion. The daily dose of gabapentin is increased to 2 x 10 mg/kg/day orally the next day and to 3 x 10 mg/kg/day orally the day before the onset of dinutuximab beta infusion and thereafter. The maximum single dose of gabapentin is 300 mg. This dosing schedule should be maintained as long as required by the patient.

Oral gabapentin should be tapered off after weaning off intravenous morphine infusion at the latest after dinutuximab beta infusion therapy has been stopped.

6.2. Continuous Morphine Infusion Schedule

Opioids are the standard pain treatment given alongside dinutuximab beta to prevent severe visceral and neuropathic pain. The amount of opioid required in the continuous infusion setting

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is less than that in the short-term infusion setting. The first day and cycle usually requires more amount of opioid than subsequent days and cycles. Opioids should therefore be started and then gradually weaned off according to the needs of the patient. Except for respiratory depression and sedation, the AEs in children and in adults are essentially the same (nausea, vomiting, constipation, pruritus, urinary retention, and lowered seizure threshold). The safety and efficacy of continuous intravenous administration of opioids for pain management are well established for all age groups. The risk of dependence is classified as low.

Tramadol should be used for moderate to severe pain, but for severe to very severe pain, morphine is preferred unless it is poorly tolerated by certain individuals, in which case other opioids can be used.

During the first cycle, intravenous morphine should initially be given as follows:

A morphine sulphate bolus (0.02 to 0.05 mg/kg/h) should be administered before the start of continuous infusion of dinutuximab beta. Thereafter, it is recommended to administer morphine sulphate at a continuous infusion rate of 0.03 mg/kg/h on the first day. The morphine dose can ideally be tapered on a daily basis over the first 5 days (to 0.02 mg/kg/h to 0.01 mg/kg/h to 0.005 mg/kg/h). Boluses can be either self-administered or administered by a nurse at 0.02 mg/kg/dose. If continuous morphine is required for > 5 days, the dose should be decreased at the end of treatment by 20% each day. It is expected that intravenous morphine can be rapidly tapered off. Depending on the individual patient's pain tolerance, subsequent cycles can be started with intravenous morphine, including the bolus loading dose, and tapered until a safe and well-tolerated outpatient pain management regimen is in place; for example,

- Oral morphine: administered at a dose of 0.2 to 0.4 mg/kg every 4 to 6 hours
- Oral tramadol: if pain is well-controlled on low doses of oral morphine
- Transdermal fentanyl patches: in centers where these are used regularly for pain control. The equivalent morphine to transdermal fentanyl dose rate in µg/h will be calculated based on the current use of intravenous morphine according to the manufacturers guidance and the dose will be gradually decreased according to pain symptoms.

The use of long-acting morphine is not recommended in this situation as it takes 48 hours to stabilize the dose, which is not practical.

6.3. Prohibited Concomitant Medications

The following medications are prohibited during the study or as otherwise noted:

- Any chemotherapy, hormonal anticancer therapy, radiotherapy, or experimental anticancer medications other than those that are study related, until patients have completed end of study assessments at the Safety Follow-up Visit or have discontinued study drug with dinutuximab beta prematurely
- Systemic glucocorticoids or other drugs with known immunosuppressive activity within 2 weeks of starting and 1 week after completing treatment with dinutuximab beta except to treat life-threatening conditions

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- The use of intravenous immunoglobulin (IVIG), because IVIG may interfere with the dinutuximab beta-mediated antibody-dependent cellular cytotoxicity, within 2 weeks of starting and 1 week after completing treatment with dinutuximab beta
- Tetracycline is prohibited when the patient is taking 13-cis-RA

6.4. Medications to Be Used With Caution

Potential interaction between study drug and concomitant medication

No interaction studies have been performed. Monoclonal antibodies (mAbs) are considered to have a low potential for drug-drug interactions with other therapeutic proteins or small molecules, as mAbs are mainly delivered by parenteral administration and are metabolized via the reticuloendothelial system or target-mediated disposition to peptides and amino acids. Therefore, as an intravenous IgG1 mAb, the concern for drug-drug interactions of dinutuximab beta is very low. However, in Study APN311-201, dinutuximab beta induced the release of cytokines, in particularly that of IL-6 and TNFα. Cytokines can affect expression levels of cytochrome P450 (CYP450), and IL-6 is known to decrease the activity of CYP450. A risk for indirect reduction of CYP450 activity may occur due to higher TNFα and IL-6 levels. Therefore, interactions with concomitantly used small molecules metabolized by CYP450, cannot be excluded. Caution should be applied when dinutuximab beta is co-administered with CYP450 substrates with a narrow therapeutic index.

If CYP450 substrates will be used, the medical monitor and clinical pharmacologist should be consulted. Please refer to Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (FDA 2016) for a complete list of CYP450 substrates.

For 13-cis-RA, detail information could consult the relevant prescribing local label of 13-cis-retinoic acid.

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7. STUDY PERIODS, VISITS, OR PROCEDURES

7.1. Screening Period

Screening evaluations will be performed ≤ 28 days before the first dose of study drug. A patient who agrees to participate in this study will sign the ICF before undergoing any study-specific screening assessment. Refer to Section 8.1 for instructions regarding screening assessments.

7.1.1. Informed Consent and Screening Log

Voluntary, written informed consent for participation in the study must be obtained before performing any study-specific procedures. ICFs for enrolled patients and for patients who are screened but not enrolled will be maintained at the study site.

The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

7.2. Enrollment

Prior to enrollment, the investigator is responsible for assessing and confirming that each patient meets all inclusion eligibility criteria for this study and that none of the exclusion criteria apply. All results from the screening procedures and relevant medical history must be available and reviewed by the investigator before eligibility can be determined. No eligibility waivers will be granted.

Sponsor verification of patient eligibility will be managed by way of source data verification in accordance with International Council for Harmonisation (ICH) E6.

The sponsor's medical monitor will support the investigator and/or site staff by answering any queries or questions relating to protocol eligibility criteria.

7.3. Treatment Period

Patients enrolled by the sponsor will be treated as described in Section 5.2.

Refer to Section 7.6 for additional considerations regarding treatment continuation and withdrawal.

Assessments before the start of dinutuximab beta infusion on Day 1 of each cycle:

- Oxygen-Saturation measurement
- Physical examination including vital signs, height, and weight
- Performance status
- 12-Lead ECG
- Chest X-ray
- Complete blood count including differential count*
- Biochemistry*

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- Urinalysis*
- Pregnancy test in WOCBP
- Blood sampling for PK (30 minutes before infusion) in Cycle 1, 2, 3 and 4

*If clinical chemistry, hematology, coagulation and urinalysis at screening are not performed ≤ 7 days before study drug administration on Day 1 of Cycle 1, these tests should be repeated and reviewed before study drug administration. After Day 1 of Cycle 1, results are to be reviewed within 72 hours before study drug administration.

Assessments during dinutuximab beta infusions:

- Performance status (on each infusion day)
- Blood sampling for PK (infusion starting time ±1 hour on Day 3 and Day 8 in Cycle 1)
- The following assessments must be regularly repeated during dinutuximab beta infusions according to routine medical care procedures to ensure safe treatment of the patients:
  - Physical examination including vital signs
  - Complete blood count (including differential count) and biochemistry on Day 8
- Electrocardiography (ECHO) or multigated acquisition scan (MUGA) scan as clinically indicated

On Day 11 of each cycle, evaluations and blood sampling must be done <u>just before the end</u> of dinutuximab beta infusion, ie, within a couple of minutes before the end of infusion. Evaluations must include the following:

- Physical examination including vital signs
- Performance status
- 12-Lead ECG
- Complete blood count (including differential count) and biochemistry
- Blood sampling for PK (5 minutes before the end of infusion) in Cycle 1, 2, 3 and 4

Assessments after dinutuximab beta infusions:

- Complete blood count (including differential count) and biochemistry (Days 15, 22, and 29)
- Blood samples for PK (Day 15 and Day 22 [optional], and Day 29 in Cycle 1)

The guidelines for pain control must be followed strictly for the whole study duration. If a patient has an unacceptable pain-toxicity profile, he/she might need more intense pain treatment such as intravenous morphine after Day 5. If this is the case, in the following cycles, the treatment team should again try to taper intravenous morphine.

AEs and concomitant medications are documented throughout all phases.

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7.4. End-of-Treatment Visit

Patients completing all 5 cycles should undergo the following assessments at the end (± 1 week) of the last cycle:

- Complete physical examination (including vital signs)
- Ophthalmologic examination by an ophthalmologist
- ECHO or MUGA scan
- 12-Lead ECG
- Complete blood count (including differential count) and biochemistry
- Urinalysis
- Coagulation profile
- Performance status
- Tumor evaluation will be done (using MRI [magnetic resonance imaging] and/or CT scan and/or ^{123}I-MIBG scan and/or ^{18}F-FDG-PET and/or bone marrow assessment)

Patients who discontinue study intervention early (receiving < 5 cycles) should also undergo EOT assessments, if clinically reasonable.

The EOT Visit is to be conducted ≤ 7 days after the investigator determined that the patient must permanently discontinue study drug. If routine laboratory tests (eg, hematology, clinical chemistry) were completed ≤ 7 days before the EOT Visit, these tests do not need to be repeated. A tumor assessment is not required at the EOT Visit if ≤ 6 weeks have passed since the last assessment. If EOT Visit did not occur until the planned Safety Follow-up Visit, then it can be used as replacement for the Safety Follow-up Visit.

Post-study treatment is allowed after the EOT Visit, at the discretion of the investigator, according to the treatment guideline and the local practice.

See Section 7.4 for assessments to be performed for the EOT Visit.

See Section 7.5.1 for details on the Safety Follow-up Visit.

7.5. Follow-up Periods

7.5.1. Safety Follow-up Period

Patients who permanently discontinue study drug will be asked to return to the clinic for the Safety Follow-up Visit, which is required to be conducted within 40 days [± 7 days] after the last dose of study drug or before the initiation of new anticancer therapy, whichever occurs first.

All AEs, including serious adverse events (SAEs), will be collected as described in Section 9.5.

See Appendix 1 for assessments to be performed at the Safety Follow-up Visit.

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7.5.2. Loss to Follow-up

If attempts to contact the patient by telephone are unsuccessful, additional attempts should be made to obtain protocol-required follow-up information: it may be possible to obtain the information from other contacts such as referring physicians or relatives. Attempts to establish contact should be documented in the patient's source documents. If a patient cannot be contacted despite all attempts, the patient will be considered lost to follow-up, and death information should be obtained through a public record search if local agencies permit.

7.6. Discontinuation From Study Treatment or From the Study

7.6.1. Patient Discontinuation From Study Treatment (End of Treatment for an Individual Patient)

Patients have the right to discontinue study drug at any time for any reason. In addition, the investigator has the right to discontinue a patient from study drug at any time. Patients who discontinue study drug for reasons other than relapse or progressive disease (PD) should be followed for assessments of preliminary anticancer activity (Section 8.4) and safety (Section 8.2), if possible.

The primary reason for discontinuation from study drug should be documented on the appropriate eCRF. Patients may discontinue study drug for reasons including but not limited to the following:

- Relapse
- PD
- AE
- Patient decision
- Pregnancy
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety if he or she were to continue the study drug
- Use of any concurrent anticancer therapy, including chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents (including Chinese [or other Country] herbal medicine and Chinese [or other Country] patent medicines) for the treatment of cancer [regardless of cancer type])
- Patient noncompliance
  - Study site staff should first counsel patients who are significantly noncompliant (eg, missing 2 treatment cycles) on the importance of study drug compliance and drug accountability. The investigator may, in consultation with the medical monitor, discontinue patients from treatment who are consistently noncompliant.

Treatment with dinutuximab beta should be permanently discontinued if the following toxicities occur:

- Grade 3 or 4 anaphylaxis

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- Prolonged Grade 2 peripheral motor neuropathy
- Grade 3 peripheral neuropathy
- Grade 3 vision eye toxicity
- Grade 4 hyponatremia (< 120 mEq/L) despite appropriate fluid management
- Recurrent or Grade 4 capillary leak syndrome (requires ventilator support)

If dinutuximab beta or 13-cis-RA is discontinued permanently before cycle 5 for reasons other than relapse or PD, the other drug could be continued per the study protocol.

7.6.2. Patient Discontinuation From the Study (End of Study for an Individual Patient)

Patients may discontinue from the study for reasons that include but are not limited to the following:

- Patient withdrawal of consent
- Death
- Lost to follow-up
- Completion of all study assessments

7.7. End of Study

The end of study is defined as the timepoint when the final data point is collected from the last patient in the study. This is when the last patient dies, withdraws consent, completes all study assessments, or is lost to follow-up, whichever comes first. Alternatively, the end of study is when the sponsor decides to terminate the study.

The sponsor has the right to terminate this study at any time. Reasons for terminating the study early include but are not limited to the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Overall patient enrollment is unsatisfactory

The sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients must be seen for an EOT Visit and Safety Follow-up Visit as described in Section 7.4 and Section 7.5.1.

The investigators may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the study.

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8. STUDY ASSESSMENTS

A table of scheduled study assessments is provided in Appendix 1. Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented in the medical record for each patient.

Where applicable, dosing will occur only if the clinical assessment and local laboratory test values (that must be available before any dosing) have been reviewed and found to be acceptable per protocol guidelines.

8.1. Screening Assessments

Screening evaluations will be performed ≤ 28 days before the first dose of study drug(s) (refer to Appendix 1 for details). Patients who agree to participate will sign the ICF before undergoing any study-specific screening assessment. The screening period begins on the first day that a screening assessment is conducted. Screening evaluations may be repeated as needed within the screening period. The investigator is to assess patient eligibility according to the latest screening assessment results.

Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before the first dose of study drug(s) may be used for the purposes of screening rather than repeating the standard-of-care tests unless otherwise indicated.

Procedures conducted only during the Screening Visit are described in this section. For the description of assessments that are conducted during screening as well as throughout the study, refer to Safety Assessments (Section 8.2), PK Assessments (Section 8.3), Tumor and Response Evaluations (Section 8.4) sections.

Rescreening under limited conditions may be allowed after consultation with BeiGene (eg, when a patient's laboratory result narrowly misses a laboratory criterion and it is correctable and not due to rapidly deteriorating condition or PD). Rescreening is allowed only once.

8.1.1. Oxygen-Saturation measurement

Patients will undergo an oxygen-saturation measurement (on room air). The measurements will be kept in the patients' records as source documents. The findings will be recorded in the eCRF.

8.2. Safety Assessments

8.2.1. Vital Signs

Vital signs will include measurements of body temperature (˚C), pulse rate, and blood pressure (systolic and diastolic). Pulse rate and blood pressure will be measured while the patient is in a spine position after resting for 5 minutes.

8.2.2. Physical Examinations

During the Screening Visit, a complete physical examination will be conducted, including evaluations of 1) the head, eyes, ears, nose, and throat; 2) cardiovascular; 3) dermatological; 4) musculoskeletal; 5) respiratory; 6) gastrointestinal; and 7) neurological systems. Any

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abnormality identified during screening will be graded according to NCI-CTCAE version 5.0 and recorded in the eCRF with appropriate disease/condition terms.

At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed. New or worsened clinically significant abnormalities are to be recorded as AEs in the eCRF. Refer to Section 9.2 for AE definitions, reporting, and follow-up requirements.

8.2.3. Ophthalmologic Examination

Patients will undergo an eye examination by an ophthalmologist. The findings of each examination will be recorded in the eCRF. Any significant abnormality present at screening should be recorded as medical history if assessed at the screening visit or as an AE if occurring after screening.

8.2.4. Performance Status

Patients will be assessed for performance status. For children ≤ 16 years of age, a Lansky Play-Performance Scale (Lansky et al 1985) will be used, and for those > 16 years of age, the Karnofsky Performance Scale (Mor et al 1984) will be used (Appendix 3).

8.2.5. Laboratory Safety Tests

Local laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted as outlined in Appendix 2 per the timepoints shown in Appendix 1.

If clinical chemistry, hematology, coagulation and urinalysis at screening are not performed ≤ 7 days before study drug administration on Day 1 of Cycle 1, these tests should be repeated and reviewed before study drug administration. After Day 1 of Cycle 1, results are to be reviewed within 72 hours before study drug administration.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically relevant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically abnormal during participation in the study or within 40 days after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified where possible and the sponsor notified.
- All protocol-required laboratory assessments as defined in Appendix 2 must be conducted in accordance with the laboratory manual and the Schedule of Assessments (Appendix 1).
- If laboratory values from laboratory assessments not specified in the protocol and performed at the institution's local laboratory result in the need for a change in patient

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management or are considered clinically relevant by the investigator (eg, are considered an SAE or an AE or require dose modification), then the results must be recorded in the eCRF.

8.2.6. Echocardiography/Multigated Acquisition Scan

Patients will undergo ECHO/MUGA scanning. The ECHO/MUGA scan recordings will be kept in the patient's records as source documents. The findings of each examination will be recorded in the eCRF. Any significant abnormality present at screening should be recorded as medical history if assessed at the screening visit or as an AE if occurring after screening.

8.2.7. Electrocardiograms

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper or electronic copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

All ECGs are to be obtained before other assessments scheduled at that same time (eg, vital sign measurements, blood draws). The patient should rest in a semirecumbent supine position for ≥ 10 minutes in the absence of environmental distractions that may induce changes in heart rate (eg, television, radio, conversation) before each ECG collection.

At each timepoint (see Appendix 1), 3 consecutive 12-lead ECGs should be performed approximately 2 minutes apart to determine the mean QT interval corrected for heart rate using Fridericia's formula (QTcF) interval.

8.2.8. Adverse Events

AEs will be graded and recorded throughout the study according to NCI-CTCAE version 5.0. Characterization of toxicities will include severity, duration, and time to onset.

All AEs, including SAEs, will be collected as described in Section 9.5.

8.3. Pharmacokinetic Assessment

Blood will be collected to characterize the PK of dinutuximab beta. Blood sampling (1 ml) for PK assessment will be collected at the timepoints specified in Table 4. The actual collection date and time of each blood sample will need to be recorded on the eCRF.

Table 4: Dinutuximab Beta PK Sampling Schedule

Cycle	**Cycle 1 (35 days per cycle)**							**Cycle 2, 3, and 4**	
Time	D1 Predose	D3	D8	D11	D15[a]	D22[a]	D29[a]	D1 Predose	D11
Window Allowed	-30 mins[b]	± 1 h[c]	± 1 h[c]	-5 mins[d]				-30 mins[b]	-5 mins[d]
PK Serum Sample	X	X	X	X	X	X	X	X	X

Abbreviation: PK, pharmacokinetic(s).

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[a] PK sampling on Day 15 and Day 22 in Cycle 1 is optional. That adjustment needs to be aligned with pharmacologists. PK sampling on Day 29 in Cycle 1 is required even if the infusion time will be delayed or extended.
[b] 30 minutes before starting infusion.
[c] Infusion starting time ± 1 hour.
[d] 5 minutes before the end of infusion, even if the infusion time will extend to the next days.

Blood samples for PK analysis will be collected into serum separator tube (SST) collection tubes. Shipping, storage, and handling of samples will be managed through a central laboratory. Samples will be shipped to the designated bioanalytical laboratory for quantification of serum dinutuximab beta concentrations. Full details on sample collection, processing, storage, and shipment will be provided in the laboratory manual.

8.4. Tumor and Response Evaluations

Tumor assessments or monitoring will be performed by the investigators at Screening Visit, end of treatment Cycle 3 and end of treatment Visit per their clinical practice. INRC (Brodeur et al 1993) is recommended as a reference for response evaluation in patients evaluable for response.

Tumor imaging will be performed ≤ 28 days before the first dose of study drug(s). Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before the first dose of study drug(s) may be used for the purposes of screening rather than repeating the standard-of-care tests.

Tumor assessments may include MRI and/or CT scan and/or ^{123}I-MIBG scan and/or ^{18}F-FDG-PET and/or bone marrow assessment.

All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening must be used throughout the study (eg, the same contrast protocol for CT scans).

8.5. Biomarkers

Not applicable.

8.6. Visit Windows

All visits on Day 1 of every cycle must occur within ± 3 days from the scheduled date, unless otherwise noted (see Appendix 1). All assessments will be performed on the day of the specified visit unless an acceptable time window is specified. Assessments scheduled on the day of study drug administration (Day 1) of each cycle should be performed before study drug infusion unless otherwise noted. Laboratory results must be reviewed before dosing.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other event, the visit should be scheduled for the nearest feasible date (the visit window is provided in Appendix 1), with subsequent visits conducted according to the planned schedule.

8.7. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or the investigator's request and may include vital signs/focused physical examination; Lansky Play-Performance

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Scale/Karnofsky Performance Scale (see Section 8.2.4 and Appendix 3); AE review; concomitant medications and procedures review; radiographic assessments; physical examination of liver, spleen, and lymph nodes; disease-related constitutional symptoms; and hematology and clinical chemistry laboratory assessments. The date and reason for the unscheduled visit must be recorded in the source documentation.

If an unscheduled visit is necessary to assess toxicity or for suspected PD, then diagnostic tests may be performed based on the investigator assessment as appropriate, and the results of these tests should be entered on the unscheduled visit eCRF.

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9. SAFETY MONITORING AND REPORTING

The investigator is responsible for the monitoring and documentation of events that meet the criteria and definition of an AE or SAE as provided in this protocol.

9.1. General Plan to Manage Safety Concerns

9.1.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies and clinical data with dinutuximab beta were considered.

9.1.2. Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 x baseline value) in combination with either an elevated total bilirubin (> 2 x ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered an indicator of severe liver injury. Therefore, investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST increase > 3 x baseline value in combination with total bilirubin > 2 x ULN (of which 35% is direct bilirubin)
- Treatment-emergent ALT or AST increase > 3 x baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the AE eCRF and reported to the sponsor immediately (ie, ≤ 24 hours after learning of the event).

9.1.3. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all AEs, defined and graded according to NCI-CTCAE version 5.0.

All enrolled patients will be evaluated clinically and with standard laboratory tests at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs (see Table 5), vital signs, physical examinations, ophthalmologic examination, performance status, laboratory measurements (hematology, clinical chemistry, etc), and other assessments including those listed in Appendix 2.

At the start of each cycle, study drug(s) will be administered only after clinical laboratory results have been reviewed. Administration of dinutuximab beta will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available (for additional information, see Section 5.2).

Investigators are instructed to report all AEs (includes pregnancy-related AEs).

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in Section 9.6.

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9.2. Adverse Events

9.2.1. Definitions and Reporting

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug(s), whether considered related to study drug(s) or not.

Examples of AEs include:

- Worsening of a chronic or intermittent pre-existing condition, including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- Detection or diagnosis of a new condition after study drug(s) administration even though the condition might have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug(s) or a concurrent medication (overdose per se should not be reported as an AE or SAE)

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results, and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all patient identifiers will be blinded on the copies of the medical records before submission to the sponsor.

9.2.2. Assessment of Severity

The investigator will assess the severity for each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon NCI-CTCAE version 5.0.

Toxicities that are not specified in NCI-CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Note: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (eg, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]); whereas, seriousness is classified by the criteria based on the regulatory

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definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 9.5.2.

9.2.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug(s) and the occurrence of each AE or SAE using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug(s) should be considered and investigated. The investigator should consult the Dinutuximab Beta's Prescribing Information in the determination of his/her assessment.

There may be situations when an SAE has occurred and the investigator has only limited information to include in the initial report to the sponsor. However, it is very important that the investigator always assesses causality for every SAE before transmission of the SAE report to the sponsor because the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may subsequently change his/her opinion of causality considering follow-up information and may amend the SAE report accordingly.

The causality of each AE should be assessed and classified by the investigator as "related" or "not related" based on all information available at the time of reporting. An AE is considered related if there is "a reasonable possibility" that the AE may have been caused by the study drug(s) (ie, there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of study drug/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug(s)
- Biological plausibility
- An AE should be considered "related" to study drug(s) if any of the following criteria are met; otherwise, the event should be assessed as "not related":
  - There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
  - There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
  - There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug[s]). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

9.2.4. Follow-up of Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each patient and provide further information to the sponsor on the patient's condition.

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All AEs and SAEs documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up, or the patient withdraws consent. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a patient dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any postmortem findings, including histopathology.

New or updated information should be reported to the sponsor according to the SAE instructions provided by the sponsor within the timeframes outlined in Section 9.5.2.

9.2.5. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, complete blood count, coagulation, or urinalysis) or other abnormal assessments (eg, ECGs, x-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and that significantly worsen during the study. The definition of "clinically significant" is left to the judgment of the investigator. In general, these are the laboratory test abnormalities or other abnormal assessments that:

- are associated with clinical signs or symptoms, or
- require active medical intervention, or
- lead to treatment interruption or discontinuation, or
- require close observation, more frequent follow-up assessments, or further diagnostic investigation.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, alkaline phosphatase and bilirubin 5 x ULN associated with cholestasis), only the diagnosis (ie, cholestasis) should be recorded on the AE eCRF.

If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the AE eCRF unless the etiology changes. The initial severity of the event should be recorded and the severity or seriousness should be updated any time the event worsens.

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9.3. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  Note: The term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE that hypothetically might have caused death if it was more severe.
- Requires hospitalization or prolongation of existing hospitalization

  Note: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.
- Results in disability/incapacity

  Note: The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgement (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following are NOT considered to be SAEs:

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline
- Hospitalization for social/convenience considerations
- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience

9.4. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction is a serious adverse reaction that is both unexpected (ie, not present in the study drug's reference safety information) and meets the definition of a serious adverse drug reaction, the specificity or severity of which is not consistent with those noted in the Dinutuximab Beta's Prescribing Information.

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9.5. Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

9.5.1. Adverse Event Recording Period

After informed consent has been signed but before the administration of the study drug(s), only SAEs should be reported.

After the first dose of study drug(s), all AEs and SAEs, regardless of relationship to study drug, will be reported until 40 days after last dose of study drug. All SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

AEs and SAEs should be recorded according to the details in Table 5. For the follow-up period for AEs, see Section 9.2.4. For the definition of treatment-emergent adverse events (TEAEs), see Section 10.2.2.

Table 5: Guidance for Duration of Recording New or Worsening Adverse Events

Event Type	Record new or worsening events that occur during this period	
	Begin	End
SAEs [a]	Signing of informed consent	Up to 40 days after last dose of study drug; initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever comes first
All nonserious AEs	First dose of study drug	Up to 40 days after last dose of study drug; initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever comes first

Abbreviations: AE, adverse event; SAE, serious adverse event.
[a] All SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

9.5.2. Reporting Serious Adverse Events

9.5.2.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 6.

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Table 6: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for sending initial report	Documentation method	Timeframe for sending follow-up report	Documentation method	Reporting method
All SAEs	Within 24 hours of first knowledge of the SAE	SAE report	As expeditiously as possible	SAE report	Email or fax SAE report form

Abbreviations: SAE, serious adverse event.

9.5.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she is to report the information to the sponsor within 24 hours, as outlined above in Section 9.5.2.1. The SAE report will always be completed as thoroughly as possible, including all available details of the event and forwarded to the sponsor or designee within the designated timeframes.

If the investigator does not have all information regarding an SAE, he/she is not to wait to receive additional information before notifying the sponsor or designee of the SAE and completing the form. The form will be updated when additional information is received.

The investigator must always provide an assessment of causality for each SAE as described in Section 9.2.3.

The sponsor will provide contact information for SAE receipt.

9.5.2.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will report all SAEs to the sponsor in accordance with the procedures detailed in Section 9.5.2.1. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a drug under clinical investigation.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the IRB/IEC.

All suspected unexpected serious adverse reactions (as defined in Section 9.4) will be submitted to all applicable regulatory authorities and investigators for dinutuximab beta studies.

When a study center receives an initial or follow-up safety report or other safety information (eg, revised Investigator's Brochure) from the sponsor, the investigator or designated responsible person is required to promptly notify his/her IRB or IEC. The investigator should place copies of safety reports from the sponsor in the investigator site file.

9.5.3. Eliciting Adverse Events

The investigator or designee will ask patients about AEs by asking the following standard questions:

- How are you feeling?

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- Have you had any medical problems since your last visit?
- Have you taken any new medicines since your last visit?

9.5.4. Progressive Disease

As PD is expected in this study population, the term "disease progression" should not be reported as an AE term. Instead the symptoms, signs, or clinical sequelae that result from PD should be reported as the AE term(s). For instance, in a patient who presents with pleural effusion resulting from PD of metastasis to the lungs, the event term should be reported as "pleural effusion" instead of "disease progression." If a patient experiences fatal multiorgan failure due to PD, the term "multiorgan failure" should be reported as the SAE with death as the outcome, instead of "fatal disease progression" or "death due to disease progression." All nonserious AEs, SAEs, and deaths, regardless of relatedness to PD, should be recorded and reported.

9.5.5. Deaths

Death is an outcome and not usually considered an AE. If the only information available is death and the cause of death is unknown, then the death is reported as an AE (eg, "death," "death of unknown cause," or "death unexplained").

9.5.6. Recording Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving study drug(s) or within 180 days after the last dose of dinutuximab, a pregnancy report form must be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous, should always be reported as a SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drug(s) should be recorded and reported as a SAE.

9.5.7. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Independent Ethics Committees

The sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, IRBs, and IECs based on applicable legislation.

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the following reference safety information documents:

- Dinutuximab Beta's Prescribing Information
- local label of 13-cis-retinoic acid

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9.5.8. Recording Infusion-Related Reactions

The symptoms of infusion-related reactions may include but are not limited to fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Each of the individual signs and symptoms of an infusion reaction should be recorded as a separate AE in the eCRF and identified as an infusion-related reaction. Refer to the eCRF completion guidelines for details.

9.6. Risks Associated With Dinutuximab Beta

Hypersensitivity Reactions

Severe infusion-related reactions including cytokine release syndrome (CRS) and anaphylactic and hypersensitivity reactions may occur despite the use of premedication. Occurrence of a severe infusion-related reaction (including CRS) requires immediate discontinuation of dinutuximab beta therapy and may necessitate emergency treatment.

CRS frequently manifests itself within minutes to hours of initiating the first infusion and is characterized by systemic symptoms such as fever, hypotension, and urticaria.

Anaphylactic reactions may occur as early as within a few minutes of the first infusion with dinutuximab beta and are commonly associated with bronchospasm and urticaria.

Treatment of Hypersensitivity Reactions

Antihistamines, epinephrine (adrenaline), and prednisolone for intravenous administration should be immediately available at the bedside during administration of dinutuximab beta to manage life-threatening allergic reactions. Treatment for such reactions should include prednisolone and epinephrine administered by intravenous bolus every 3 to 5 minutes as necessary according to clinical response. In case of bronchial and/or pulmonary hypersensitivity reaction, epinephrine (adrenaline) inhalation is recommended and should be repeated every 2 hours according to clinical response.

Capillary Leak Syndrome

Capillary leak syndrome (CLS) is characterized by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space. CLS usually develops within hours after initiation of treatment, whereas clinical symptoms (ie, hypotension, tachycardia) are reported to occur after 2 to 12 hours. Careful monitoring of circulatory and respiratory function is required.

Neurological Disorders of The Eye

Eye disorders may occur as dinutuximab beta binds to optic nerve cells. No dose modification is necessary in the case of an impaired visual accommodation that is correctable with eyeglasses, as long as this is judged to be tolerable.

Treatment must be interrupted in patients who experience Grade 3 vision toxicity (ie, subtotal vision loss per toxicity scale). In case of any eye problems, patients should be referred promptly to an ophthalmology specialist.

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Peripheral Neuropathy

Occasional occurrences of peripheral neuropathy have been reported with dinutuximab beta. Cases of motor or sensory neuropathy lasting > 4 days must be evaluated and non-inflammatory causes such as disease progression, infections, metabolic syndromes, and concomitant medication should be excluded.

Treatment should be permanently discontinued in patients experiencing any objective prolonged weakness attributable to dinutuximab beta administration. For patients with moderate (Grade 2) neuropathy (motor with or without sensory), treatment should be interrupted and may be resumed after neurologic symptoms resolve.

Systemic Infections

Patients are likely to be immunocompromised as a result of prior therapies. As they typically have a central venous catheter in situ, they are at risk of developing systemic infection. Patients should have no evidence of systemic infection and any identified infection should be controlled before starting therapy.

Hematologic Toxicities

Occurrence of hematologic toxicities such as erythropenia, thrombocytopenia, or neutropenia has been reported with dinutuximab beta. Grade 4 hematologic toxicities improving to ≤ Grade 2 or baseline values by start of next treatment course do not require dose modification.

Laboratory Abnormalities

Regulatory monitoring of liver function and electrolytes is recommended.

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10. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

10.1. Statistical Analysis

10.1.1. General Consideration

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarized using descriptive statistics, including N, mean, standard deviation, median, minimum, and maximum values. Geometric mean and geometric coefficient of variation (CV) % will be included for PK parameters, where applicable. Coefficient of variation will not be presented for change-from-baseline results.

All derivations, statistical analyses, summaries, and listings will be generated using SAS Version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina). Non-compartmental PK parameter calculations will be performed using Phoenix® WinNonlin® (Certara, Princeton, New Jersey). Graphics may be prepared using the same versions of SAS, or Phoenix WinNonlin, or with SigmaPlot 12.5, or higher (Systat Software, Inc., San Jose, California).

10.1.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Table 7: Populations for Analysis

Population (Analysis Set)	Description
Safety Analysis Set	The Safety Analysis Set (SAS) will include patients who have received at least 1 dose of study drug.
Pharmacokinetic (PK) Analysis Set	The PK Analysis Set (PKS) will include patients who have at least one available post-baseline PK data in Safety Analysis Set.

The safety analysis set (SAS) will be the primary analysis set for all safety analyses and the pharmacokinetic analysis set (PKS) will be used in pharmacokinetic analysis.

The safety analysis set (SAS) will be the primary analysis set for all efficacy analyses.

10.1.3. Patient Disposition

The number of patients treated, discontinued from study drug(s) and/or the study, and those with important protocol deviations will be counted in SAS. The primary reason for study drug(s) and/or study discontinuation will be summarized according to the categories in the eCRF. The end-of-study status (dead, withdrew consent, or lost to follow-up) at the data cutoff date will be summarized using the data from the eCRF.

Important protocol deviations will be summarized and listed by category.

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10.1.4. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the Safety Analysis Set and descriptive statistics.

Baseline patient characteristics will include a summary of the following:

- Patient demographics
- Baseline disease characteristics
- Prior anti-cancer therapies

Other patient characteristics will be summarized as deemed appropriate.

10.1.5. Prior and Concomitant Medications

Prior medications will be defined as medications that stopped before the day of first dose of study drug(s). Concomitant medications will be defined as medications that 1) started before the first dose of study drug(s) and were continuing at the time of the first dose of study drug(s), or 2) started on or after the date of the first dose of study drug(s) up to 40 days after the patient's last dose (as of the Safety Follow-up Visit). Concomitant medications will be coded using the World Health Organization Drug Dictionary drug codes and will be further coded to the appropriate Anatomical Therapeutic Chemical code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class. A listing of prior and concomitant medications will be provided.

10.2. Safety Analyses

Safety is the primary endpoint and will be assessed by AEs as characterized by type, frequency, severity (as graded by the NCI-CTCAE version 5.0), time, seriousness, and relationship to study drug(s), vital signs and laboratory abnormalities. Extent of exposures, Physical examinations, and ECG findings will also be used in determining the safety profile. TEAEs will be reported as the number (percentage) of patients with TEAEs by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables) and changes from baseline will be determined for laboratory parameters and vital signs.

Safety data will be summarized using the SAS.

10.2.1. Extent of Exposure

Extent of exposure to each study drug will be summarized descriptively as the number of cycles received (number and percentage of patients), duration of exposure (days), cumulative total dose received per patient (mg), dose intensity, and relative dose intensity.

The number (percentage) of patients requiring treatment interruption, dose delay, and drug discontinuation because of AEs will be summarized. Frequency of the above dose adjustments and discontinuation will be summarized by category. Reasons for dose modifications will be summarized as well.

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Patient data listings will be provided for all dosing records and for calculated summary statistics.

10.2.2. Adverse Events

The AE verbatim descriptions (investigator's description from the eCRF) will be coded using MedDRA. AEs will be coded to MedDRA (version 20.1 or higher) lowest level term, preferred term, and primary system organ class.

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug(s) and up to 40 days following last dose of study drug or initiation of new anticancer therapy, whichever occurs first.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by system organ class and preferred term. A patient will be counted only once by the highest severity grade per NCI-CTCAE version 5.0 within a system organ class and preferred term, even if the patient experienced ≥ 1 TEAE within a specific system organ class and preferred term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug(s).

Treatment-related AEs include those events considered by the investigator to be related to study drug or with missing assessment of the causal relationship. SAEs, deaths, ≥ Grade 3 TEAEs, treatment-related TEAEs, and TEAEs that led to treatment discontinuation, treatment interruption, or dose delay will be summarized.

10.2.3. Laboratory Analyses

Clinical laboratory (eg, hematology, clinical chemistry) values will be evaluated for each laboratory parameter as appropriate. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be provided. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by visit with the maximum postbaseline change.

Laboratory parameters that are graded by NCI-CTCAE version 5.0 or higher will be summarized by NCI-CTCAE grade. In the summary of laboratory parameters by NCI-CTCAE grade, parameters with NCI-CTCAE grading in both high and low directions (eg, calcium, glucose, magnesium, potassium, and sodium) will be summarized separately.

10.2.4. Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure, pulse rate, and body temperature) and changes from baseline will be presented by visit for all visits. Vital signs will be listed by patient and visit.

10.2.5. Ophthalmologic Examination

Ophthalmologic examination results will be listed by patient if available.

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10.2.6. Physical Examinations

Physical examination results will be listed by patients.

10.3. Pharmacokinetic Analyses

Blood samples will be collected on Day 1, 3, 8, 11, 15 (optional), 22 (optional), and 29 in Cycle 1, and on Day 1 and 11 in Cycle 2, 3 and 4 to measure serum concentrations of dinutuximab beta. Serum concentration-time data of each patient will be tabulated and graphically presented on linear semi-logarithmic scales. PK parameters will be determined using a standard non-compartmental analysis method in PK analysis set. Descriptive statistics will be used, including means, standard deviations, medians, ranges, geometric mean, and CV % associated to the geometric mean as appropriate. A listing of patients excluded from the analysis set and individual data points excluded from the analysis will be provided.

PK parameters will include, but are not limited to the following as allowed by data:

- C_{max} (ng/mL): Maximum serum concentration
- t_{max} (hour): Time to maximum serum concentration
- C_{min} (ng/mL): Minimum serum concentration
- $t_{1/2}$ (hour): Half-life
- AUC_{0-t} (ng·h/mL): Area under the serum concentration-time curve from zero to the last measurable concentration
- $AUC_{0-\infty}$ (ng·h/mL): Area under the serum concentration-time curve from zero to infinity

10.4. Exploratory Efficacy Analyses

No formal hypothesis testing is planned in this trial. Tumor assessment based on investigator assessment will be used to calculate EFS as well as time-point estimates including EFS-6m by Kaplan-Meier method. 95% confidence intervals will be constructed to describe the precision of the point estimates of interest (e.g. median EFS, EFS-6m) if estimable.

Event-free survival (EFS) is defined as the time from initiating study drug(s) to disease progression, death from any cause, relapse, secondary malignancy as assessed by investigators.

A listing of patients in Safety Analysis Set will be provided.

10.5. Other Exploratory Analyses

Not applicable.

10.6. Sample Size Consideration

The study plans to enroll approximately 8 patients as recommended for PK studies by Center of Drug Evaluation (CDE) technical guidance on clinical pharmacokinetic study of chemical drugs (CDE of National Medical Products Administration (NMPA) 2005). Therefore, a sample size of approximately 8 patients is proposed in this single-arm PK study.

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10.7. Interim Analyses

Not applicable.

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11. STUDY COMMITTEES

Not applicable.

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12. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The investigator must maintain adequate and accurate records to ensure that the conduct of the study may be fully documented. Such records include but are not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/IEC and governmental approvals. In addition, at the end of the study, the investigator will receive patient data, which will include an audit trail containing a complete record of all changes to such data.

12.1. Access to Information for Monitoring

In accordance with International Council for Harmonisation GCP guidelines, the study monitor must have direct access to the investigator's source documentation to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries in the eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected during these monitoring visits are resolved.

12.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene may conduct inspections or audits any time during or after completion of this clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor or its designee immediately. The investigator agrees to provide to representatives of a regulatory agency or BeiGene access to records, facilities, and personnel for the effective conduct of any inspection or audit.

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13. QUALITY ASSURANCE AND QUALITY CONTROL

13.1. Regulatory Authority Approval

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements or file the protocol to the appropriate regulatory agency before the study is initiated at a study center in that country.

13.2. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her personnel to the auditor/inspector to discuss findings and any relevant issues.

13.3. Study Site Inspections

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits may be performed periodically by the sponsor's or the contract research organization's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

Site visits will be conducted by the sponsor or an authorized representative to inspect study data, patients' medical records, and eCRFs. The investigator is to permit national and local health authorities; sponsor study monitors, representatives, and collaborators; and IRB/IEC members to inspect all facilities and records relevant to this study.

13.4. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug(s). This includes acknowledgment of receipt of each shipment of study drug(s) (quantity and condition), patient drug dispensation records, and returned or destroyed study drug(s). Dispensation records will document quantities received from BeiGene's designated depot or its designee and quantities dispensed to patients, including batch/lot number, date dispensed, patient identifier number, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure that it complies with BeiGene requirements specified in the Pharmacy Manual. At appropriate times during the conduct of the study or at the end of the study following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet BeiGene's requirements specified in the Pharmacy Manual for disposal, arrangements will be made between the site and BeiGene or its representative for destruction or return of unused study drug supplies.

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All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

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14. ETHICS/PROTECTION OF HUMAN PATIENTS

14.1. Ethical Standard

This study will be conducted by the principal investigator and the study center in full conformance with the International Council for Harmonisation E6 guideline for GCP and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the patient. The study will also comply with the requirements of the International Council for Harmonisation E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

14.2. Institutional Review Board/Independent Ethics Committee

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted, reviewed, and approved by the IRB/IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC. Copies of the IEC/IRB correspondence and approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to the sponsor promptly.

The principal investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments. In addition to the requirements for reporting all AEs to the sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and IRB/IEC. Investigators may receive written Investigational New Drug Safety Reports or other safety-related communications from the sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/IEC and archived in the site's study file.

14.2.1. Protocol Amendments

Any protocol amendments will be prepared by the sponsor. All protocol modifications must be submitted to competent authorities according to local requirements and to the IRB/IEC together with, if applicable, a revised model ICF in accordance with local requirements. Written documentation from competent authorities (according to local requirements) and from the IRB/IEC and required site approval must be obtained by the sponsor before changes can be implemented, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (eg, change in medical monitor or contact information).

Information on any change in risk and/or change in scope must be provided to patients already actively participating in the study, and they must read, understand, and sign each revised ICF confirming their willingness to remain in the study.

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14.3. Informed Consent

The sponsor's sample ICF will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The final IRB/IEC-approved ICFs must be provided to the sponsor for health authority submission purposes according to local requirements.

The ICFs must be signed and dated by the patient (if the patient is capable) and patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained before participation in the study.

The ICFs will be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/IEC-approved consent forms must be provided to the sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the ICFs (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study. For any updated or revised ICFs, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised ICFs for continued participation in the study.

A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICFs must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

14.4. Patient and Data Confidentiality

The investigator, institution, sponsor, and site will maintain confidentiality and privacy standards for the collection, storage, transmission, and processing of patients' personal and medical information by following applicable laws and regulations related to the confidentiality, use, and protection of such information, including the ICH Good Clinical Practice Guideline, as implemented locally. Such laws may be more stringent than the requirements in this protocol.

The investigator and site shall code the personal and medical information obtained during the study with a unique patient identification number assigned to each patient enrolled in the study. The investigator must ensure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Unless required to be provided by laws or regulations or specifically requested in exceptional circumstances by the sponsor or its representatives, the investigator and site must ensure that any personal and medical information transmitted to sponsor or its service providers is: 1) required by the protocol, and 2) appropriately de-identified (eg, via redaction and/or coding with the patient identification number) to ensure the following information about patients are NOT shared:

- names or initials (full or partial);
- *full* dates of birth;
- contact information (such as phone numbers or home or email addresses);

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- numerical identifiers (eg, hospital or medical record, government, health insurance, or financial account numbers) other than patient identification numbers assigned as part of this study;
- geographic identifiers smaller than a state, province, or local equivalent (such as city, county, zip code, or other equivalent geographic identifiers); or
- information about marital status, family, or household members; employment, sex life, sexual preference, or other sensitive data that is not relevant to the study.

Patient personal and medical information obtained during this study is confidential and may only be disclosed to third parties as permitted by the signed ICF (or a separate authorization for the use and disclosure of personal health information that has been signed by the patient), unless permitted or required by law.

In limited circumstances, such as in connection with insurance purposes or patient support services ancillary to certain study sites (eg, for patient travel or reimbursement), the investigator and site may provide certain of this personal information to the sponsor or its representatives. Such personal information may not be provided as part of the study protocol (eg, as part of the eCRF, on samples or reports submitted to the central lab, on safety reporting forms [except in China], or on product dispensing logs provided to the sponsor, etc).

Investigator and site must use only the specific forms and clinical trial systems, (eg, the electronic data capture [EDC] system and any secure file transfer platforms [SFTPs]) designated by sponsor for sharing and transfers of personal and medical information.

In the event of a breach of the confidentiality of a patient's personal and medical information, the investigator, site, and sponsor, as appropriate, shall fulfill all mediation steps and reporting obligations under applicable laws. If the sponsor identifies personal or medical information that was not properly de-identified, it may be required to report the disclosure under local applicable laws.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes where allowed by local law or the patient's signed ICF.

Information generated during this study must be available for inspection upon request by representatives of the United States Food and Drug Administration (US FDA), the China National Medical Products Administration (China NMPA), and all other national and local health authorities; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

The investigator agrees that all information received from the sponsor, including but not limited to the Investigator's Brochure, this protocol, eCRFs, the investigational drugs, and any other study information, are confidential and remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

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If a written contract for the conduct of the study that includes confidentiality or privacy provisions inconsistent with this section is executed, that contract's provisions shall apply to the extent they are inconsistent with this section.

14.5. Financial Disclosure

Investigators are required to provide the sponsor with sufficient accurate financial information in accordance with regulations to allow the sponsor to submit complete disclosure or certification to the absence of certain financial interest of the clinical investigators and/or disclose those financial interests, as required, to the appropriate health authorities. This is intended to ensure financial interests and arrangements of the clinical investigators with BeiGene that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. Investigators are responsible for providing information about their financial interests before participation in the study and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (ie, last patient, last visit).

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15. DATA HANDLING AND RECORD KEEPING

15.1. Data Collection and Management Responsibilities

15.1.1. Data Entry in the Electronic Case Report Form

All study-related data collected or received by the investigator or study team shall be promptly entered into the eCRFs. In no event should the entry of the study data into the eCRF be later than what is stipulated in the site contract after the data is collected or received by the investigator or study team without prior communication with and approval by the sponsor.

15.1.2. Data Collection

Data required by the protocol will be entered into an electronic data capture (EDC) system.

Data collection in the eCRF should follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The e-signature of the investigator or designee must be provided in the EDC system to attest to its accuracy, authenticity, and completeness.

Data contained in the eCRFs are the sole property of BeiGene and should not be made available in any form to third parties without written permission from BeiGene, except for authorized representatives of BeiGene or appropriate regulatory authorities.

15.1.3. Data Management/Coding

All final patient data, both eCRF and external data (eg, laboratory data), collected according to the protocol will be stored by BeiGene at the end of the study.

Standard procedures (including following data review guidelines, computerized validation to produce queries, and maintenance of an audit file that includes all database modifications) will be followed to support accurate data collection. Data will be reviewed for outliers, logic, data inconsistencies, and completeness.

During the study, a study monitor will make site visits to review protocol compliance, compare eCRFs against individual patient's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements.

The eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Checking the eCRFs for completeness, clarity, and cross-checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits, and will be carried out with due consideration to data protection and medical confidentiality.

The AE verbatim descriptions (the investigator's description from the eCRF) will be coded using MedDRA. AEs will be coded to MedDRA by lowest level term, preferred term, and primary system organ class. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using MedDRA.

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15.2. Study Records Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least 1 of the following 2 categories: 1) investigator's study file and/or 2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/IEC and governmental approval with correspondence, ICFs, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include but not be limited to documents such as the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, x-ray, pathology and special assessment reports, consultant letters, screening and enrollment logs, etc.

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (eg, audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable backup of these reproductions and that an acceptable quality control process exists for making these reproductions.

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements, local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify the sponsor of any changes in the archival arrangements including but not limited to the following: archival at an off-site facility or transfer of ownership of or responsibility for the records in the event the investigator leaves the study center.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and BeiGene to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

Biological samples at the conclusion of this study may be retained as outlined in the agreement with the Contract Research Organization (CRO) managing the biological samples, for the shorter of: a period of up to 10 years or as allowed by your IRB/IEC.

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15.3. Protocol Deviations

The investigator is responsible for ensuring that the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators assert they will apply due diligence to avoid protocol deviations and shall report all protocol deviations to the sponsor.

The investigator is to document and explain any deviations from the approved protocol. The investigator must promptly report any major deviations that might impact patient safety and/or data integrity to the sponsor and to the IRB/IEC, in accordance with established IRB/IEC policies and procedures. Notwithstanding, in China, unless otherwise provided by China GCP, investigator shall not deviate from this protocol without IRB/IEC and BeiGene's approval.

15.4. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). BeiGene will ensure that the report meets the standards set out in the International Council for Harmonisation Guideline for Structure and Content of Clinical Study Reports (ICH E3). An abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance, and the need to protect the intellectual property of the sponsor, regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. For a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication, or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors 2016).

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor for review before submission or presentation in accordance with the clinical study agreement. This allows the sponsor to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be presented in the investigator's clinical study agreement. Each investigator agrees that, in accordance with the terms of the clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings and/or protection in advance of the publication/presentation.

15.5. Study and Study Center Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or study center personnel, as appropriate:

- Return/provide all study data to the sponsor
- Resolution and closure of all data queries

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- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Collection of all study documents for the trial master file filing according to GCP and local regulation
- Shipment of samples (including but not limited to those for PK) to the assay laboratory for central laboratory analysis according to protocol and laboratory manual requirements

In addition, the sponsor reserves the right to suspend the enrollment or prematurely discontinue this study either at a single study center or at all study centers at any time for any reason. Potential reasons for suspension or discontinuation include but are not limited to: safety or ethical issues or noncompliance with this protocol, GCP, the sponsor's written instructions, the clinical study agreement, or applicable laws and regulations. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action before it takes effect.

The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons. The sponsor will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must still be provided to the sponsor. In addition, arrangements will be made for the return of all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

Financial compensation to the investigators and/or institutions will be in accordance with the clinical study agreement established between the investigator and/or institutions and the sponsor.

15.6. Information Disclosure and Inventions

All rights, title, and interests in any inventions, know-how, or other intellectual or industrial property rights that are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the sponsor and are hereby assigned to the sponsor.

If a written contract for the conduct of the study, which includes ownership provisions inconsistent with this statement, is executed between the sponsor and the study center, that contract's ownership provisions shall apply rather than this statement.

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) are the sole property of the sponsor and will be kept confidential by the investigator and other study center personnel.

This information and data will not be used, by the investigator or other study center personnel for any purpose other than conducting the study, without the prior written consent of the sponsor.

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These restrictions do not apply to:

- Information that becomes publicly available through no fault of the investigator or study center personnel
- Information that is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information that is necessary to disclose to provide appropriate medical care to a patient
- Study results that may be published as described in Section 15.4

If a written contract for the conduct of the study, which includes provisions inconsistent with this statement is executed, that contract's provisions shall apply rather than this statement.

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17. APPENDICES

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

	Screening (Day −28 to Day −1)	**Cycles 1 to 5**																	**EOT/early termination [b]**	**Safety follow-up [c]**
Visit day		Day 1[a]	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11[a]	Day 12	Day 15	Day 22	Day 25	Day 29	Day 35	-7 to 7 days or 0 to 7 days	+ 40 days
Visit window		± 3																		**± 7**
Informed consent	X																			
Inclusion/exclusion criteria	X																			
Demography	X																			
Medical history	X																			
Oxygen saturation on room air	X	X																		X
Pregnancy test in WOCBP[d]	X	X																		
HBsAg/HCV-Ab[e]	X																			
Ophthalmologic examination	X																		X	X
Height/weight	X	X																		
Physical examinations [f]	X	X----------X																	X	X
Vital signs	X	X----------X																	X	X
Performance status	X	X----------X																	X	X
ECHO or MUGA scan	X	As clinically indicated																	X	X
12-Lead ECG [g]	X	X										X							X	X
Chest X-Ray [h]		X	As clinically indicated																	
Complete blood count (including differential count)/biochemistry [i, j]	X	X							X			X		X	X		X		X	X
Urinalysis [i, j]	X	X																	X	X
Coagulation [i, j]	X	X																	X	X
Dinutuximab beta infusion [k]		X----------Continuous infusion----------X																		
13-cis-RA													X----------X							
PK sampling in Cycle 1[l]		X		X					X			X		X[m]	X[m]		X			

PK sampling in Cycle 2-4 [l]		X									X								
Tumor assessments [n]	X																	X	
Adverse events	X----------X																		
Concomitant medications [o]	X----------X																		

Abbreviations: AE, adverse event; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiography; EOT, end of treatment; HBsAg, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; INRC, international neuroblastoma response criteria; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; MUGA, multigated acquisition scan; PK, pharmacokinetic(s); QTcF, QT interval corrected for heart rate using Fridericia's formula; WOCBP, woman of childbearing potential; ^{123}I, iodone-123.

[a] Day 1 evaluations must be done before the start of the dinutuximab beta infusion. Day 11 evaluations must be done just before the end of the dinutuximab beta infusion.

[b] The EOT Visit is conducted within ± 1 week of the end of Cycle 5. For early termination, the EOT Visit is conducted ≤ 7 days after the investigator determines that the patient must permanently discontinue the study drug or the patient decides to withdraw from the study before the end of Cycle 5.

[c] Safety Follow-up Visit: within 40 days [± 7 days] after last dose of study drug; initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever comes first.

[d] Pregnancy test in WOCBP is described in Appendix 4.

[e] If HCV-Ab positive, HCV-RNA test will be required for eligibility check.

[f] Physical examinations is presented in Section 8.2.2.

[g] At each timepoint, 3 consecutive 12-lead ECGs should be performed approximately 2 minutes apart to determine the mean QTcF interval.

[h] Chest X-ray should be performed within 7 days before the start of dinutuximab beta infusion in each cycle. It can be skipped if chest MRI or CT scan has been performed already before administration per investigator's discretion.

[i] If clinical chemistry, hematology, coagulation and urinalysis at screening are not performed ≤ 7 days before study drug administration on Day 1 of Cycle 1, these tests should be repeated and reviewed before study drug administration. After Day 1 of Cycle 1, results are to be reviewed within 72 hours before study drug administration (Section 8.2.5).

[j] The test for clinical chemistry, hematology, coagulation, and urinalysis, excluding PK sampling, will be performed within 72 hours before study drug administration on Day 1 of each cycle. All laboratory tests with values considered clinically abnormal during participation in the study or within 40 days after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor (Section 8.2.5).

[k] The recommended dose of dinutuximab beta depends on the patient's body surface area (BSA) and the actual dose is calculated on every Day 1 of Cycle 1 to 5 (BSA = SQRT [weight (kg) x height (cm)/ 3600]).

[l] PK sampling time refers to Table 4 provided in Section 8.3.

[m] PK sampling on Day 15 and Day 22 in Cycle 1 is optional.

[n] Tumor assessments will be performed by the investigators at Screening Visit, end of treatment Cycle 3 and end of treatment Visit per their clinical practice. The INRC (Brodeur et al 1993) is recommended as a reference for response evaluation in patients evaluable for response. Tumor assessments may include MRI and/or CT scan and/or ^{123}I-MIBG scan and/or ^{18}F-FDG-PET and/or bone marrow assessment.

[o] Concomitant medications will be defined as medications that started before the first dose of study drug(s) and were continuing at the time of the first dose of study drug(s), or started on or after the date of the first dose of study drug(s) up to 40 days after the patient's last dose (as of the Safety Follow-up Visit) in Section 10.1.5.

X: evaluations must be regularly repeated during the timepoints indicated according to routine medical care to ensure safe treatment of the patient.

APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS

Table 8: Protocol-Required Safety Laboratory Assessments

Clinical chemistry	Hematology	Coagulation	Urinalysis[a]
Alanine aminotransferase Aspartate aminotransferase Total bilirubin Potassium Sodium Total calcium Creatinine Chloride C-reactive protein Gamma-glutamyl transferase	Hemoglobin Platelet count White blood cell count Lymphocyte count Neutrophil count Basophils	Prothrombin time Activated partial thromboplastin time International normalized ratio	Glucose Protein Blood Ketones

In case of abnormal result: urinary sediment assessment (red blood cells per high-power field, white blood cells per high-power field, cellular casts)

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APPENDIX 3. PERFORMANCE STATUS

Lansky Play-Performance Scale (for patients ≤ 16 years)

100 - Fully active, normal

90 - Minor restrictions in physically strenuous activity

80 - Active but tires more quickly

70 - Both greater restriction of and less time spent in play activity

60 - Up and around but minimal active play; keeps busy with quieter activities

50 - Gets dressed but lies around much of the day; no active play but able to participate in all quiet play and activities

40 - Mostly in bed; participates in quiet activities

30 - In bed; needs assistance even for quiet play

20 - Often sleeping; play entirely limited to very passive activities

10 - No play; does not get out of bed

0 - Unresponsive

Karnofsky Performance Scale (for patients > 16 years)

100 - Normal, no complaints, no evidence of disease

90 - Able to carry on normal activity; minor signs or symptoms of disease

80 - Normal activity with effort; some signs or symptoms of disease

70 - Cares for self; Unable to carry on normal activity or do active work

60 - Requires occasional assistance but is able to care for most of own needs

50 - Requires considerable assistance and frequent medical care

40 - Disabled; requires special care and assistance

30 - Severely disabled; hospitalization hospitalisation is indicated although death is not imminent

20 - HospitalizationHospitalisation necessary; very sick, active supportive treatment necessary

10 – Moribund; fatal processes progressing rapidly

0 - Dead

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APPENDIX 4. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

The Clinical Trials Facilitation Group's recommendations related to contraception and pregnancy testing in clinical trials include the use of highly effective forms of birth control (Clinical Trials Facilitation Group 2014). These methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation
  - Oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with the inhibition of ovulation:
  - Oral, injectable, or implantable
    Note: Oral birth control pills are not considered a highly effective form of birth control, and if they are selected, they must be used with a second, barrier method of contraception such as condoms with or without spermicide.
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized male partner
  Note: This is only considered a highly effective form of birth control when the vasectomized partner is the sole partner of the study participant and there has been a medical assessment confirming surgical success.
  - A sterile male is one for azoospermia has been demonstrated in a semen sample examination as definitive evidence of infertility.
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study drug).
  NOTE: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patient's usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods), declaration of abstinence for the duration of exposure to study drug(s), and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception and if used, this method must be combined with another acceptable method listed above.

Definitions of "Women of Childbearing Potential," "Women of No Childbearing Potential"

As defined in this protocol, "women of childbearing potential" are female patients who are physiologically capable of becoming pregnant.

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Conversely, "women of no childbearing potential" are defined as female patients meeting any of the following criteria:

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
  - ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR
  - < 55 years of age with no spontaneous menses for ≥ 12 months AND with a postmenopausal follicle-stimulating hormone concentration > 30 IU/mL and all alternative medical causes for the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.

If an FSH measurement is required to confirm postmenopausal state, concomitant use of hormonal contraception or hormonal replacement therapy should be excluded.

Adapted from Clinical Trials Facilitation Group 2014.

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