CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125516Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review-Addendum	
BLA	125516
Submission Dates Submission Type	April 11, 2014 Original BLA
Brand Name	Unituxin™
Generic Name	Dinutuximab; Chimeric Monoclonal Antibody (mAb) 14.18 (Ch14.18);
Dosage Form / Strength	17.5 mg in 5 ml (3.5 mg/mL) solution in single-use vial for intravenous infusion
Dosing Regimen	Administer intravenously after dilution at a dose of 17.5 mg/m^2/day for 4 days during each of 5 courses of treatment
Proposed Indication	used in combination with granulocyte macrophage colony stimulating factor (GM-CSF), interleukin-2 (IL-2) and isotretinoin (RA) for (b) (4) patients with high-risk neuroblastoma (b) (4)
Applicant	United Therapeutics Corp.
Clinical Pharmacology Reviewer	Jingyu Yu, Ph.D.
Clinical Pharmacology Team Leader	Hong Zhao, Ph.D.
OCP Division	Division of Clinical Pharmacology V
OND Division	Division of Oncology Products 2

This review addendum is for the primary clinical pharmacology review logged in DARRTS on September 12, 2014 for original BLA 125516. The addendum is focused on: (1) update the long term stability of PK samples as discussed in section 2.6.4.4 of the primary clinical pharmacology review. (2) a PMR study to test neutralizing antibody in clinical studies using a sensitive neutralizing antibody assay.

(1) Long-term stability of PK samples

Based on the stability data submitted on September 19th, 2014, PK samples of dinutuximab were considered stable to storage at [(b) (4)]°C and [(b) (4)]°C for up to 12 months with recoveries ranging from 81.7 -116.6%, with CVs from 1.1- 3.3% (Table 1 and Table 2). These results can adequately support the validity of the PK assessment as all PK samples for DIV-NB-201 (PK comparability study) were stored at [(b) (4)]°C and analyzed within the confirmed 12-month stability window.

Table 1: Long-Term Stability of dinutuximab at High and Low Concentration in Pooled Human Sodium Heparin Plasma Stored at [(b) (4)]°C

Stability Sample	Time Period	Replicate Concentration (ng/mL) of Samples Stored at [(b) (4)]°C						Mean (ng/mL)	CV (%)	% Recovery
		1	2	3	4	5	6			
High Control	Day 0	103	101	101	102	104	98.8	102	1.7	100.0
	1 month	109	111	114	113	105	108	110	3.1	108.3
	6 month	119	117	121	113	116	115	117	2.5	114.8
	12 month	107	106	107	105	102	103	105	1.9	103.3
Low Control	Day 0	20.7	20.5	20.6	20.7	20.6	19.7	20.5	1.9	100.0
	1 month	19.9	19.5	18.6	19.3	20.1	19.3	19.5	2.7	95.2
	6 month	21.0	21.1	21.6	21.1	21.2	20.7	21.1	1.5	103.2
	12 month	19.9	19.3	19.6	19.4	19.3	19.1	19.4	1.5	94.8

Table 2: Long-Term Stability of dinutuximab at High and Low Concentration in Pooled Human Sodium Heparin Plasma Stored at [(b) (4)]°C

Stability Sample	Time Period	Replicate Concentration (ng/mL) of Samples Stored at [(b) (4)]°C						Mean (ng/mL)	CV (%)	% Recovery
		1	2	3	4	5	6			
High Control	Day 0	103	101	101	102	104	98.8	102	1.7	100.0
	1 month	90.7	86.0	91.1	89.6	84.7	88.8	88.5	2.9	87.0
	6 month	120	114	123	122	120	114	119	3.3	116.6
	12 month	104	104	107	105	103	104	105	1.2	103.0
Low Control	Day 0	20.7	20.5	20.6	20.7	20.6	19.7	20.5	1.9	100.0
	1 month	16.7	16.7	16.5	16.7	17.2	16.5	16.7	1.6	81.7
	6 month	22.1	21.7	22.5	22.2	22.2	21.2	22.0	2.2	107.4
	12 month	20.0	19.9	19.9	19.8	19.6	19.4	19.8	1.1	96.6

(2) PMR study associated with neutralizing antibody response

As presented in section 5.3.1.4 of the primary CMC review logged in DARRTS on September 13, 2014, the performance of neutralizing antibody (Nab) assay, particularly with regard to sensitivity, is poor. Given that this particular concern on immunogenicity is related to the safety, a PMR study is recommended as following from clinical pharmacology perspective.

PMR: To conduct an assessment of neutralizing antibodies response to dinutuximab with a validated assay (under CMC PMC) capable of sensitively detecting neutralizing antibody responses in the presence of dinutuximab levels that are expected to be present at the time of patient sampling. The clinical impact of the neutralizing antibody response should be evaluated in all available samples from ANBL0032 (b) (4) DIV-NB-303, DIV-NB-201 studies and other studies under IND4308 (b) (4) NANT2011-04].

Signatures:

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Division Director: Nam Atiqur Rahman Division of Clinical Pharmacology V	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JINGYU YU
02/08/2015

HONG ZHAO
02/08/2015
I concur.

NAM ATIQUR RAHMAN
02/08/2015
I support the recommendation

Clinical Pharmacology Review	
BLA	125516
Submission Dates Submission Type	April 11, 2014 Original BLA
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Generic Name	Dinutuximab; Chimeric Monoclonal Antibody (mAb) 14.18 (Ch14.18);
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Applicant	United Therapeutics Corp.
Clinical Pharmacology Reviewer	Jingyu Yu, Ph.D.
Pharmacometrics Reviewer	Jingyu Yu, Ph.D.
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1. EXECUTIVE SUMMARY

Dinutuximab is a chimeric (human-murine) IgG1κ monoclonal antibody which binds to cell surface GD2 and induces lysis of the GD2-expressing cells. The proposed indication is for the treatment of high-risk neuroblastoma (b) (4) in combination with granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin 2 (IL-2), and isotretinoin (RA).

The DIV-NB-301 study provides the primary evidence for safety and effectiveness of dinutuximab in combination with GM-CSF, IL-2, and RA to patients with high-risk neuroblastoma in comparison with RA alone. Efficacy and safety was also evaluated in the DIV-NB-302 study (on-going) after the close of randomization. Comparable pharmacokinetic (PK) exposure between the to-be-marketed dinutuximab manufactured by United Therapeutics Corporation (UTC) and the clinical trial dinutuximab manufactured by the National Cancer Institute (NCI) was demonstrated based on both the population PK model-based assessment and non-compartmental analysis (NCA).

1.1 Recommendations

BLA 125516 is acceptable for approval from a clinical pharmacology perspective, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the labeling language. The adequacy of the clinical pharmacology program in the overall development plan of dinutuximab is summarized in the table below.

Decision	Acceptable?			Comment
Overall	Yes ×	No	NA	
Pivotal PK comparability	Yes ×	No	NA	Refer to **Section 4.1**

1.2 Post Marketing Commitments and Requirements

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Dinutuximab is a chimeric (human-murine) IgG1κ monoclonal anti-GD2 antibody. Its molecular weight is approximately 148 kDa.

Mechanism of Action: Dinutuximab binds to cell surface glycolipid GD2 expressed on many neuroblastoma cells as well as on many normal cells in the central nervous system and peripheral nerves and induces lysis of the GD2-expressing cells. The possible mechanisms of cell lysis are antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

Efficacy: The DIV-NB-301 study provides the primary evidence for safety and effectiveness of dinutuximab in combination with GM-CSF, IL-2, and RA as compared to RA alone in patients with high-risk neuroblastoma. This was an open-label, randomized, Phase III trial where patients were randomized (1:1) to receive standard therapy with RA alone or dinutuximab in combination with GM-CSF, IL-2, and RA. The primary intent-to-treat (ITT) analysis (n=226) concluded that there was a statistically significant improvement (p = 0.0115) in event free survival (EFS) in the dinutuximab and RA arm as compared to RA alone arm. The two-year point estimate of EFS (95% CI) was 66% (56%, 75%) for the dinutuximab and RA arm and 46% (36%, 57%) for the RA alone arm.

PK comparability between NCI product and UTC product: Results of the PK comparability study DIV-NB-201 (n=28, crossover) demonstrate comparable PK exposure between the NCI clinical trial dinutuximab and UTC to-be-marketed dinutuximab based on the population PK assessment as well as the non-compartmental analysis (NCA).

Pharmacokinetics*:* The PK profile of dinutuximab has been characterized by population PK analysis based on the data from study DIV-NB-302 (n=9) and study DIV-NB-201 (n=27). The volume of distribution of dinutuximab at steady state is 5.37 L (CV%= 27%); the systemic clearance is 0.21 L/day (CV %=62%) and the terminal half-live is estimated to be 10 days.

Exposure/Dose-Response Relationship for Efficacy and Safety*:* Exposure/dose response relationship for efficacy and safety cannot be characterized due to the lack of PK data as no PK samples were collected in study DIV-NB-301.

Immunogenicity: Preliminary data from study DIV-NB-301 using an academic non-validated ELISA assay found that 8 of 118 patients (7%) receiving dinutuximab and RA tested positive for human anti-chimeric antibody (HACA). Of 414 patients evaluated for HACA by validated assay across studies DIV-NB-302, DIV-NB-303, and DIV-NB-201, 83 patients (20%) tested positive for HACA with 15 patients (4%) testing positive for neutralizing antibody (Nab). Notably, 11 patients had confirmed HACA responses prior to dosing with dinutuximab in study DIV-NB-302 (n=8) and study DIV-NB-303 (n=3). Data from study DIV-NB-301 (pivotal study) is not sufficient to allow for assessment of the impact of immunogenicity on PK and/or PD. The clinical impact of immunogenicity will be assessed by applicant after the ongoing studies are complete.

Signatures:

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2. QUESTION-BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Dinutuximab (ch14.18) is an anti- disialoganglioside (GD2) antibody composed of the variable region heavy and light chains of the murine monoclonal antibody (mAb) 14.18 and the human constant region genes for heavy chain immunoglobulin (IgG)1 and light chain kappa. Its molecular weight is approximately 148 kDa.

Unituxin (Dinutuximab) is supplied as a 17.5 mg/5 mL (3.5 mg/mL) single-use vial for intravenous infusion.

2.1.2 What are proposed mechanism(s) of action and therapeutic indication(s)?

Dinutuximab binds to the glycolipid GD2. This glycolipid is expressed on most neuroblastoma cells as well as on many normal cells in the central nervous system and peripheral nerves. Dinutuximab binds to cell surface GD2 and induces lysis of the GD2-expressing cells through antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

The proposed indication of Dinutuximab is to be used as a component of a multi-agent, multi-modality regimen, for high-risk neuroblastoma (b) (4) in combination with granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin 2 (IL-2), and isotretinoin (RA).

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The treatment regimen consists of Unituxin, GM-CSF, IL-2 and RA (Table 1 and Table 2). Unituxin is to be administered intravenously after dilution at a dose of 17.5 mg/m^2/day for 4 days per course for 5 courses, on Days 4-7 during courses 1, 3, and 5 (24 days per course) and on Days 8-11 during courses 2 and 4 (32 days per course).

Table 1: Courses 1, 3, and 5 Dosing Regimen for Dinutuximab, (b) (4)

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-24
(b) (4)															
Unituxin [2]				X	X	X	X								
(b) (4)															

Sources: Sponsor's proposed label

Table 2: Courses 2 and 4 Dosing Regimen for Dinutuximab (b) (4)

Day	1	2	3	4	5	6	7	8	9	10	11	12-14	15-28[4]
(b) (4)													
Unituxin [2]								X	X	X	X		
(b) (4)													

Sources: Sponsor's proposed label

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

2.2.1.1 Major clinical trials

The maximum tolerated dose (MTD) of dinutuximab in combination with GM-CSF, IL-2, and RA was found to be 25 mg/m^2/day (equivalent to 17.5 mg/m^2/day dinutuximab manufactured by UTC based on extinction factor of 1.4) with dose limiting toxicities (DLTs) in the CCG-0935A study. The DIV-NB-301 study provides the primary evidence for the evaluation of safety and efficacy of dinutuximab in combination with GM-CSF, IL-2, and RA to patients with high-risk neuroblastoma in comparison with RA alone. Efficacy was also evaluated in DIV-NB-302 after the close of randomization. The design feature of these two trials is provided in Table 3.

Table 3: Design features of major clinical studies

Study Number	Patient Population	Study Design and Status
DIV-NB-301	• Patients with high risk NB (0.9-15.3 years old) • N=226 (randomized) plus 25 non-randomly assigned to treatment • Enrolled 10/26/01-11/3/08	Open label multicenter randomized study • RA alone vs ch14.18+GM-CSF/IL-2+RA • Primary endpoint EFS • Secondary endpoint: OS • Randomization stopped after interim analysis of EFS and OS using 1/13/09 data cutoff date • Updated EFS and OS analysis performed using data cutoff date of 6/30/2012 • Follow-up ongoing
DIV-NB-302	• Same patient population • N=737 • Patients enrolled 1/13/09-6/13/13	Single arm study • Primary endpoint: EFS • Secondary endpoint: OS

2.2.1.2 Clinical pharmacology studies

Study DIV-NB-201 was a multi-center, randomized, open-label, two-sequence, cross-over, comparative pharmacokinetic (PK) and safety study in patients with high-risk neuroblastoma following successful completion of myeloablative therapy and autologous stem cell rescue. Patients were randomly assigned to one of the two treatment sequences such that all patients would receive dinutuximab manufactured by UTC or NCI during Courses 1 and 2 followed by dinutuximab manufactured by the other manufacturer during Courses 3, 4, and 5. All patients received isotretinoin (RA) for six courses. For the first five of those courses, patients also received dinutuximab with cytokines. Specifically, in Courses 1, 3, and 5, dinutuximab was administered with granulocyte macrophage colony-stimulating factor (GM-CSF). In Courses 2 and 4, dinutuximab was administered with aldesleukin (IL-2).

The population PK model-based assessment and non-compartmental analysis (NCA) was conducted by applicant to assess the PK comparability of dinutuximab manufactured by NCI and UTC.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints and how are they measured in clinical pharmacology and clinical studies? What is the clinical outcome in terms of efficacy and safety?

The primary efficacy endpoint is the EFS (Event-free survival), which was calculated as the time from study enrollment until the first occurrence of relapse, progressive disease,

secondary malignancy, death, or date of last contact (if no event occurred). Progressive disease was defined according to International Neuroblastoma Response Criteria (INRC) and included the development of any new lesion, the increase of a measurable lesion by > 25%, previously negative bone marrow testing positive for tumor, or an increase from ≤ 10% tumor in marrow to > 10% tumor. Overall Survival (OS) was the secondary endpoint defined as the time from enrollment until death (or time of last contact in the absence of death).

The primary intent-to-treat (ITT) analysis (n=226 with age of 0.9-15.3 years old) concluded that there was a statistically significant improvement (p = 0.0115) in EFS in dinutuximab and RA arm as compared to RA alone arm in study DIV-NB-301. The two-year point estimate of EFS (95% CI) was 66% (56%, 75%) for the dinutuximab and RA arm and 46% (36%, 57%) for the RA alone arm. The two-year estimate of EFS (95% CI) reported in the non-randomized DIV-NB-302 study was 66% (62%, 70%) which was consistent with DIV-NB-301 study.

In addition, there was a clinically and statistically significant improvement in OS with dinutuximab and RA as compared to RA alone for the primary ITT analysis (p = 0.0223). Specifically, the two-year point estimate of OS (95% CI) with the dinutuximab and RA arm was 86% (79%, 94%) as compared to 75% (65%, 84%) in the RA alone arm.

A greater number of patients receiving dinutuximab and RA reported AEs as compared to patients receiving RA alone in study DIV-NB-301. This was expected given the use of multiple medications (i.e., dinutuximab, GM-CSF, IL-2, and RA) and the known AE profiles of each of the components of therapy.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Human plasma samples were analyzed for dinutuximab by (b) (4) using a GLP-validated Meso Scale Discovery (MSD) electrochemiluminescence sandwich-based immunoassay. Refer to Section 2.6 for description of the bioanalytical methodology.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Exposure/dose response relationship for efficacy could not be characterized due to the lack of PK data (e.g., no PK samples were collected in study DIV-NB-301) and only one dose level of dinutuximab was studied in clinical trials that provided efficacy and safety data.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

See 2.4.2.1.

2.2.4.3 Does this drug prolong the QT/QTc interval?

The DIV-NB-302 and DIV-NB-201 studies are currently evaluating electrocardiogram (ECG) parameters. ECGs are being obtained in triplicate at the following five time points: Baseline (prior to GM-CSF), Day 6 (end of dinutuximab infusion), Day 80 (prior to IL-2), Day 90 (end of dinutuximab infusion) and Study End (within two weeks of Day 163 [last dose of RA]). No notable changes have been observed in ECG parameters (HR, PR interval, QRS interval, QT interval, QTcB interval, QTcF interval, and RR interval), N=65 per a 31 January 2014 data cut. See the review performed by the QT-Interdisciplinary Review Team for details.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The dosing regimen selected by the applicant is identified as MTD of dinutuximab in combination with GM-CSF, IL-2, and RA in study CCG-0935A. Exposure/dose response relationship for efficacy and safety could not be characterized due to the lack of PK data (e.g., no PK samples were collected in study DIV-NB-301) and only one dose level of dinutuximab was studied in major clinical studies. There appeared no unresolved dosing or administration issues for the indicated population.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

The PK profile of dinutuximab has been characterized by population PK analysis based on the data from study DIV-NB-302 (n=9) and study DIV-NB-201 (n=27). The volume of distribution of dinutuximab at steady state is 5.37 L (CV%= 27%); the systemic clearance is 0.21 L/day (CV %=62%) and the terminal half-live is estimated to be 10 days.

2.2.5.1 What are the single dose and multiple dose PK parameters?

Dinutuximab is administered as i.v. infusion for 4 consecutive days in each course. The PK parameters are based on studies with multiple dose. There is no sufficient data to determine the single dose PK parameters.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Not applicable. Dinutuximab has not been administered to healthy volunteers.

2.2.5.3 What are the characteristics of drug absorption?

Not applicable. Dinutuximab is administered via IV infusion.

2.2.5.4 What are the characteristics of drug distribution?

The volume of distribution of dinutuximab at steady state is 5.37 L (CV%=27%).

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Mass balance studies are not generally performed for biological products such as dinutuximab, because they are proteins which are degraded into amino acids that are then recycled into other proteins.

2.2.5.6 What are the characteristics of drug metabolism?

Dinutuximab is expected to be catabolized into amino acids by general protein degradation process. Metabolism studies are generally not performed for biologic products like dinutuximab, because they are proteins which are degraded into amino acids that are then recycled into other proteins.

2.2.5.7 What are the characteristics of drug excretion and elimination?

The clearance of dinutuximab is 0.21 L/day (CV %=62%) and the terminal half-live is estimated to be 10 days.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The PK linearity could not be assessed given the PK data is only available for one dose level of dinutuximab.

2.2.5.9 How do the PK parameters change with time following chronic dosing?

There is no sufficient PK information to determine change of PK parameters with time following chronic dosing.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

A formal exploration of significant covariates was not conduced in the population PK analysis due to the data limitation. A fixed allometric relationship of body weight vs clearance and volume parameters was included in the final population PK model. The unexplained inter-individual variability (CV%) in CL or V1 was 62% and 36%, respectively. PK of dinutuximab has not been evaluated in healthy volunteers.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence -exposure and/or -response and what is the impact of any differences in exposure on efficacy or safety responses?

No dedicated studies and population PK analysis were conducted to evaluate the effect of intrinsic factors on exposure. Allometric body weight scaling of PK parameters (0.75 for clearance term and 1 for volume term) was included as a pre-determined covariate in the final population PK model. E-R analysis was not performed due to the data limitation.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dose regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

No dedicated studies or population PK analysis were conducted to evaluate the effect of intrinsic factors on exposure. E-R analysis was not performed due to the data limitation. Body-surface based dosing is generally acceptable considering the dinutuximab is a monoclonal antibody to be administered to pediatric patients.

2.3.2.1 Elderly Patients

No dedicated studies or population PK analysis were conducted to evaluate the effect of age on dinutuximab exposure. PK data in elderly patients is not available given the proposed pediatric indication and the clinical trials only included pediatric patients.

2.3.2.3 Sex

No dedicated studies or population PK analysis were conducted to evaluate the effect of sex on dinutuximab exposure due to data limitation.

2.3.2.4 Body weight

Allometric body weight scaling of PK parameters (0.75 for clearance term and 1 for volume term) was included as a pre-determined covariate in the final population PK model. Clearance of dinutuximab increased with body weight.

2.3.2.5 Race

No dedicated studies or population PK analysis were conducted to evaluate the effect of race on dinutuximab exposure due to data limitation.

2.3.2.5 Renal Impairment

No dedicated studies or population PK analysis were conducted to evaluate the effect of renal impairment on dinutuximab exposure.

2.3.2.6 Hepatic Impairment

No dedicated studies and population PK analysis were conducted to evaluate the effect of hepatic impairment on dinutuximab exposure.

2.3.2.7 What pregnancy and lactation use information is in the application?

Dedicated studies examining the effects of dinutuximab in animals have not been conducted. No clear effects on reproductive organs were observed in general toxicology studies conducted in rats

2.3.3 Immunogenicity

2.3.3.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

Immunogenicity of dinutuximab was evaluated in DIV-NB-301, DIV-NB-302, DIV-NB-303 and DIV-NB-201 trials. Specifically, plasma samples for the determination of HACA were obtained at the following time points: day -1 (prior to starting GM-CSF or dinutuximab in Course 1), day 6 (in the morning on fourth day of dinutuximab administration), day 80 (trough sample prior to IL-2 dosing in Course 4), day 90 (in the morning on fourth day of dinutuximab administration), day 111 (trough sample prior to GM-CSF dosing in Course 5), and day 118 (in the morning on fourth day of dinutuximab administration).

Preliminary data from study DIV-NB-301 using an academic non-validated ELISA assay found that 8 of 118 patients (7%) receiving dinutuximab immunotherapy and RA tested positive for HACA with 7 of these patients reporting positive HACA responses after study start between day 80 and day 118. One patient had a positive HACA value prior to the

treatment. Of 414 patients evaluated for HACA across studies DIV-NB-302, DIV-NB-303, and DIV-NB-201, 83 patients (20%) tested positive for HACA with 15 patients (4%) testing positive for neutralizing antibody (Nab). Notably, 11 patients had confirmed HACA responses prior to dosing with dinutuximab in studies DIV-NB-302 (8 patients) and DIV-NB-303 (3 patients). While the mechanism of this positive response prior to dosing is not fully understood, it is expected to be related to cross-reactivity within the assay with underlying murine antigens.

2.3.3.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

Data from study DIV-NB-301 (pivotal study) is not sufficient to allow for assessment of the impact of immunogenicity on PK and/or PD. The clinical impact of immunogenicity will be assessed by applicant after the ongoing studies are complete.

2.3.3.3 Do the anti-product antibodies have neutralizing activity?

Of 414 patients evaluated for HACA across DIV-NB-302, DIV-NB-303, and DIV-NB-201 studies, 83 patients (20%) tested positive for HACA and 15 patients (4%) tested positive for NAb.

2.3.3.4 What is the impact of anti-product antibodies on clinical efficacy?

The impact of HACA response on clinical efficacy could not be assessed at this time due to the data limitation from DIV-NB-301 study (pivotal study). The clinical relevance of immunogenicity will be assessed by the applicant after the ongoing studies are complete.

2.3.3.5 What is the impact of anti-product antibodies on clinical safety? (e.g., infusion-related reactions, hypersensitivity reactions, cross-reactivity to endogenous counterparts, etc.)?

The impact of HACA response on clinical safety could not be assessed at this time due to the data limitation from study DIV-NB-301 (pivotal study). The clinical relevance of immunogenicity will be assessed by the applicant after the ongoing studies are complete.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or –response and what is the impact of any differences in exposure on response?

No dedicated studies or population PK analysis were conducted to evaluate the effect of extrinsic factors on dinutuximab exposure. Allometric body weight scaling of PK parameters (0.75 for clearance term and 1 for volume term) was included as a pre-determined covariate in the final population PK model. E-R analysis was not performed due to the data limitation.

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

No, given dinutuximab is a biologic protein. It is expected to be catabolized into amino acids by general protein degradation process, not to be metabolized by phase I and II metabolizing enzymes (CYP450 enzymes or UGTs). As dinutuximab is not considered a cytokine modulator, it is unlikely to have an effect on CYPs or UGTs in terms of inhibition or induction.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

No. See response in Section 2.4.2.1.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

No. See response in Section 2.4.2.1.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

No. See response in Section 2.4.2.1.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

No, as dinutuximab is expected to be degraded into amino acids and recycle into other proteins syntheses pathway.

2.4.2.6 Does the label specify co-administration of another drug (e.g. combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Dinutuximab is proposed to be used in combination with GM-CSF, IL-2, and RA for (b) (4) patients with high-risk neuroblastoma. The interaction potential between these drugs has not been evaluated, but is considered to be low.

2.5 General Biopharmaceutics

2.5.1 What are the manufacturing differences between the to-be-marketed formulation and the formulation used in the pivotal clinical trial?

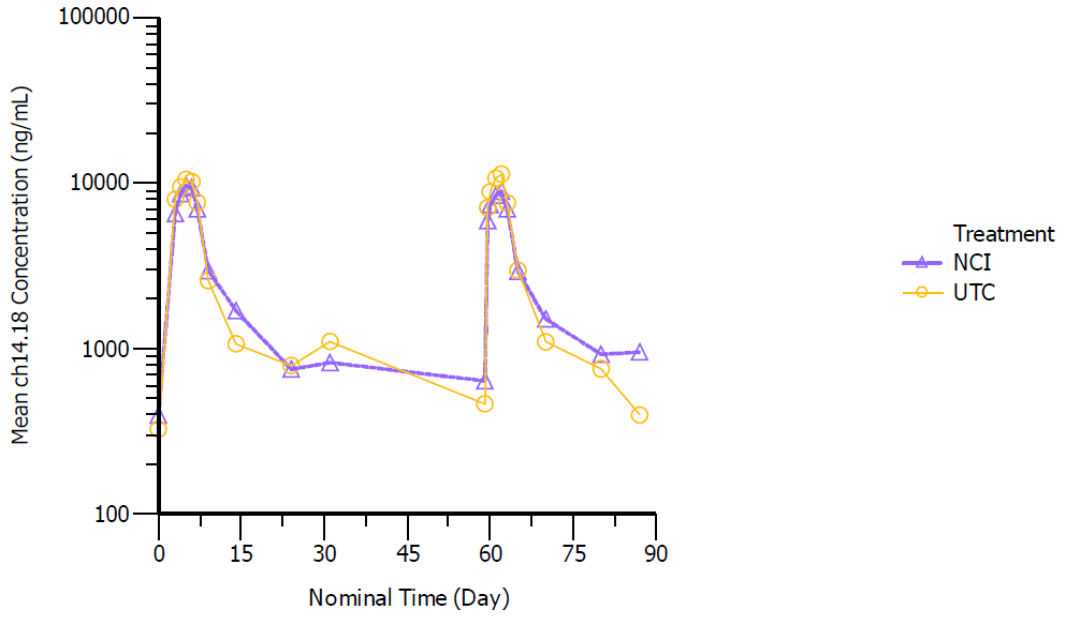
The materials used in the clinical development are manufactured by NCI. The to-be-marketed product is manufactured by UTC. The NCI production process required various (b) (4) modifications to achieve full-scale commercial production capacity at UTC. There are multiple differences in manufacturing process (b) (4)

2.5.2 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

Study DIV-NB-201 is a multi-center, randomized, open-label, two-sequence, cross-over study in patients with neuroblastoma (n=28) were randomly assigned to one of two treatment sequences such that all subjects will receive dinutuximab manufactured by UTC or NCI during Courses 1 and 2 followed by dinutuximab manufactured by the other manufacturer (UTC or NCI) during Courses 3, 4, and 5. The to-be-marketed product by UTC is comparable in PK exposure to the NCI product used in clinical trials based on the population PK analysis and NCA analysis with the data from the dedicated PK comparability study (DIV-NB-201). The results based on population PK model indicate that UTC manufactured dinutuximab and NCI manufactured dinutuximab provide comparable systemic exposure with the 90% confidence intervals for exposure ratios (AUCinf ratio: (0.98, 1.11); Cmax ratio (0.88, 1.04) contained within the standard bioequivalence bounds (0.80 – 1.25). The results from NCA also demonstrate the PK comparability of these two products with 90% confidence intervals for dose-normalized AUClast ratio of (0.91, 1.20) contained within the standard bioequivalence (BE) bounds.

The mean concentration-time profiles of two products are presented in Figure 1. Details are further discussed in pharmacometrics review in section 4.1.

Figure 1: Mean Concentration-Time Profiles of Dinutuximab (NCI Product vs UTC product)



Sources: Sponsor's Addendum to DIV-NB-201 Population PK Report, Page68

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

In study DIV-NB-301, study DIV-NB-302 and study DIV-NB-201, dinutuximab was measured by a validated sandwich immunoassay, employing the Meso Scale Discovery (MSD) electrochemiluminescence (ECL) platform that utilizes a biotinylated monoclonal capture antibody and a SULFO-TAG- (ruthenium) labeled IgG(Fc) detection antibody which binds to dinutuximab. The method description hereafter will focus on this validated assay.

2.6.2 What bioanalytical methods are used to assess therapeutic protein concentrations?

See question 2.6.1

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The standard curve was generated using a five-parameter logistic curve fit of log10-transformed data (Gen5 Secure software, BioTek Instruments). The calibration curve generated from eight dinutuximab standards at final nominal concentrations of 200, 125, 78.1, 48.8, 30.5, 19.1, 11.9, and 7.45 ng/mL, which are equivalent to plasma concentrations

of 20,000, 12,500, 7810, 4880, 3050, 1910, 1190 and 745 ng/mL before dilution. The concentration range of the standard curves is adequate for the purposes of determining plasma concentrations of dinutuximab collected in clinical studies (Figure 1).

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The LLOQ is 1,000 ng/mL and the ULOQ is 18, 000 ng/mL.

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

Accuracy and Precision

Most part of the bioanalytical assays fulfilled the regulatory criterion (refer to the FDA guidance for industry "Bioanalytical Method Validation) for precision and accuracy of inter-assay and intra-assay. A summary of the intra-assay and inter-assay accuracy and precision from six runs is shown in Table 4.

Table 4: Summary of Accuracy and Precision at LLOQ and ULOQ

	LLOQ	ULOQ
Nominal Concentration	10 ng/mL in sodium heparin plasma diluted 100-fold in Assay Diluent	180 ng/mL in sodium heparin plasma diluted 100-fold in Assay Diluent
Mean Concentration Found	10.7 ng/mL	190 ng/mL
Inter-run SD	1.1	17.3
Inter-run %CV	10.7	9.1
Inter-run % RE	7.0	5.5
Intra-assay %CV (range)	4.9 - 10.8	2.7 - 17.1
Intra-assay %RE (range)	5.3-20.0	-1.1 - 12.7
Note: SD=standard deviation=$\sqrt{\sum}$(yi-ymean)2/(N-1) %CV=coefficient of variation=(SD/mean)*100 %RE=relative error=[(Measured value-Nominal value)/Nominal value]*100		

Assay selectivity (matrix variability) was assessed using ten individual preparations of human sodium heparin plasma. The matrix was run un-spiked and spiked with dinutuximab at approximately 2 times the anticipated LLOQ. Selectivity samples were run one time in duplicate. Results are shown in Table 5. All ten of the sodium heparin plasma samples tested met acceptance criteria for selectivity, with recoveries between 84.3-108.0% of the nominal concentration and CVs between 0.4 - 4.0%.

Table 5: Assay Selectivity

Individual Sodium Heparin Plasma	Selectivity Sample	Nominal Concentration (ng/mL)	Mean Concentration (ng/mL)	CV (%)	% Nominal
1	Unspiked	N/A	BLQ	N/A	N/A
	Spiked	20.0	16.9	0.4	84.4
2	Unspiked	N/A	BLQ	N/A	N/A
	Spiked	20.0	18.4	0.5	92.0
3	Unspiked	N/A	BLQ	N/A	N/A
	Spiked	20.0	18.0	2.1	90.0
4	Unspiked	N/A	BLQ	N/A	N/A
	Spiked	20.0	19.1	4.0	95.7
5	Unspiked	N/A	BLQ	N/A	N/A
	Spiked	20.0	17.2	2.3	86.0
6	Unspiked	N/A	BLQ	N/A	N/A
	Spiked	20.0	16.9	1.9	84.3
7	Unspiked	N/A	BLQ	N/A	N/A
	Spiked	20.0	21.8	1.2	108.9
8	Unspiked	N/A	BLQ	N/A	N/A
	Spiked	20.0	18.5	1.6	92.4
9	Unspiked	N/A	BLQ	N/A	N/A
	Spiked	20.0	18.9	0.8	94.7
10	Unspiked	N/A	BLQ	N/A	N/A
	Spiked	20.0	18.7	1.1	93.5
	Buffer + Spike	20.0	18.6	3.0	93.0

Sources: Sponsor's Summary of Biopharmaceutic Studies, Page 12

Specificity was assessed in matrix spiked with dinutuximab at a concentration approximating the midpoint of the dose response curve, in the presence of human IgG at approximately 1X and 5X molar excess. Specificity samples were tested a minimum of one time in duplicate. Results are shown in Table 6. The assay met acceptance criteria for specificity for dinutuximab in the presence of human IgG at an equal concentration and at 5-fold excess, with recoveries of 93.9% and 92.8% of the nominal concentration, respectively, and CVs equal to or less than 3.1%.

Table 6: Assay Specificity

Spiked Concentration (ng/mL)		Expected Concentration (ng/mL)	Mean Measured Concentration (ng/mL)	CV (%)	% Recovery
ch14.18	IgG				
40.0	200	40.0	37.1	0.8	92.8
40.0	40.0	40.0	37.6	3.1	93.9
40.0	0	40.0	37.1	2.7	92.7

Sources: Sponsor's Summary of Biopharmaceutic Studies, Page 13

2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

A summary of the sample stability for dinutuximab is shown in Table 7.

Table 7: Summary of Sample Stability in Pooled Human Sodium Heparin Plasma for Dinutuximab

Stability Conditions	Description
Short term stability	Stable up to 17 hours at (b) (4)
Short term stability	Stable up to 4 hours (b) (4)
Long term stability*	Stable up to 12 months hours (b) (4)
Freeze-thaw stability	Stable up to five freeze-thaw cycles

** Data of the 12-month stability will be documented as an addendum to this review.*

Two additional time points at 18 and 24 months to evaluate the long term storage stability of PK samples are planned. The final method validation report will be amended upon completion of the long-term stability study.

2.6.4.5 What is the QC sample plan?

A summary of the accuracy and precision of QC samples from six run days is shown in Table 8.

Table 8: Summary of Accuracy and Precision for QC Samples

Nominal Concentration (ng/mL) in 1% matrix	180 (ULOQ)	150	80	40	25	12.5	10 (LLOQ)
Mean Concentration Found (ng/mL)	190	164	76.6	38.4	25	13.4	10.7
Inter-run SD	17.3	16.9	6.1	3.6	2.1	1.4	1.2
Inter-run %CV	9.1	10.3	8	9.3	8.5	10.7	10.7
Inter-run % RE	5.6	9.4	-4.3	-4.1	0	7.4	6.7

3. DETAILED LABELING RECOMMENDATIONS

Section 6.2:

a. Deleted [redacted (b) (4)].

b. Revised for consistency with other biologics.

c. Deleted the statement "[redacted (b) (4)]"

Section 7:

Revised for clarity

Section 8:

Add sections regarding the status of renal and hepatic impairment studies

Section 12.3:

a. Deleted [redacted (b) (4)].

b. Revised for clarity

4. APPENDICES

4.1 Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

Summary of Findings

Efficacy and safety data for this application were mainly based on NCI sponsored clinical studies, Study DIV-NB-301. Following the completion of study DIV-NB-301, in July 2010, UTC entered into a Cooperative Research and Development Agreement (CRADA) with the NCI to collaborate on the late-stage development and commercialization of dinutuximab. As part of this agreement, UTC took over the manufacturing of dituxuximab. Study DIV-NB-201 study was subsequently conducted to evaluate the PK comparability of UTC manufactured dinutuximab as compared to NCI manufactured dinutuximab.

Results from the population PK model-based assessment and non-compartmental analysis (NCA) based on study DIV-NB-201 indicate that UTC manufactured dinutuximab and NCI manufactured dinutuximab provide comparable systemic exposure.

Key Review Questions

The purpose of this review is to address the following key questions.

1. Is the UTC product comparable in PK to NCI product?

Yes. The results based on population PK model indicate that UTC manufactured dinutuximab and NCI manufactured dinutuximab provide comparable systemic exposure with the 90% confidence intervals for exposure ratios (AUCinf ratio: (0.98, 1.11); Cmax ratio (0.88, 1.04) contained within the standard bioequivalence bounds (0.80 – 1.25).

The results from NCA also demonstrate the PK comparability of these two products with 90% confidence intervals for dose-normalized AUClast ratio of (0.91, 1.20) contained within the standard BE bounds. Similar assessment was performed for Cmax values as well, suggesting 90% confidence intervals for dose-normalized Cmax ratio is not contained within the standard BE bounds. However, given the variability in infusion rate and infusion interruptions in this PK comparability study DIV-NB-201, the observed Cmax values at the end of infusion is not considered reliable indicators of PK comparability for this study.

Recommendations

- This application is acceptable from pharmacometrics perspective. See Clinical Pharmacology QBR for final recommendations.

Label Statements

- See section 3 of Clinical Pharmacology QBR

Pertinent regulatory background

Dinutuximab was submitted as a new molecular entity (NME) BLA. The proposed indication is for the treatment of high-risk neuroblastoma (b) (4) in combination with granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin 2 (IL-2), and isotretinoin (RA).

2. **Results of Sponsor's Analysis**

Background: Study DIV-NB-201 is a multi-center, randomized, open-label, two-sequence, cross-over study in patients with high-risk neuroblastoma following successful completion of myeloablative therapy and autologous stem cell rescue. Patients (n=28) were randomly assigned to one of two treatment sequences such that all subjects will receive dinutuximab manufactured by UTC or NCI during Courses 1 and 2 followed by dinutuximab manufactured by the other manufacturer (UTC or NCI) during Courses 3, 4, and 5. All subjects will receive isotretinoin (RA) for six courses. For the first five of those courses, subjects will also receive dinutuximab with cytokines. Specifically, in Courses 1, 3, and 5, dinutuximab will be administered with granulocyte macrophage colony-stimulating factor (GM-CSF). In Courses 2 and 4, dinutuximab will be administered with aldesleukin (IL-2).

A non-compartmental analysis (NCA) comparability/bioequivalence approach is typical for a richly-sampled study with strictly controlled dosing regimens. However, in DIV-NB-201 study, dinutuximab was administered to children with neuroblastoma. As necessitated when treating a pediatric oncology population, this study was associated with limited PK sampling, differences in infusion duration and interruption/re-initiation of infusions in certain patients based on safety/tolerability considerations. These factors could limit the feasibility of a standard NCA comparability analysis. As such, sponsor used a population PK model based approach, which can account for the complexities of the study while providing a quantitative assessment of comparability for dinutuximab manufactured by NCI and UTC. A standard NCA analysis was also performed to supplement the population PK model-based analysis.

Study material manufactured by NCI employed a theoretical extinction coefficient of 1.00 to calculate the concentration of antibody; whereas, UTC material employed an actual extinction coefficient of 1.41 to determine the concentration of antibody. 25 mg/m^2 dose of NCI manufactured dinutuximab and 17.5 mg/m^2 dose of UTC manufactured dinutuximab are equivalent in amount of antibody content (dinutuximab). To account for this during the population PK analysis and NCA, NCI doses were multiplied by 0.7 (Corrected Doses).

Population Pharmacokinetic Analysis

-Methods:

The PK Data from an independent study CHP1002 (n=9) using NCI manufactured dinutuximab was used to develop a structural PK model. Allometric body weight scaling of PK parameters (0.75 for clearance terms and 1 for volume terms) was included as a pre-determined covariate in the final population PK model, which was applied to data from study DIV-NB-201. The impact of other covariates on PK was not evaluated.

After fitting the final model to data from study DIV-NB-201 (n=27, age: 3.9±1.9 years old), the Bayesian approach (MCMC method and empirical bayesian (post hoc) method) in

NONMEM was used to generate the distribution of PK parameters, which were then used to derive typical PK parameters (i.e., AUCinf and Cmax) for assessment of comparability based on a standardized dosing regimen.

- Results:

The PK of dinutuximab is well-described by a two-compartment PK model with first-order distributional and elimination clearance. The final model was parameterized as following:

CL = CL coefficient*(Body Weight) $^{0.75}$*Formulation Effect

Q = Q coefficient*(Body Weight) $^{0.75}$*Formulation Effect

V1 = V1 coefficient*(Body Weight)$^{1.0}$*Formulation Effect

V2 = V2 coefficient*(Body Weight)$^{1.0}$*Formulation Effect

F1 was fixed to 0.7 and 1.0 for NCI and UTC, respectively to normalize doses.

Parameters estimates of the final covariate model are presented in Table 9.

Table 9: Final Model Parameters Estimates

Parameter	Estimate	Standard Error (From NONMEM)
CL allometric coefficient (L/h)	0.000361	0.000430
V1 allometric coefficient (L)	0.0875	0.00883
V2 allometric coefficient (L)	0.243	0.0143
Q allometric coefficient (L/h)	0.00515	0.000564
Additive Residual Error	146	26.1
Proportional Residual Error	0.308	0.0141
Effect of UTC manufacturer on CL	0.960	0.0348
Effect of UTC manufacturer on V1 and V2	1.10	0.0773
Effect of UTC manufacturer on Q	0.831	0.117
Variance term on CL (Exponential)	0.386	0.115
Variance term on V1 (Exponential)	0.131	0.042
Covariance term CL:V1	0.0313	0.0523

Sources: Sponsor's Population PK report DIV-NB-201, Page 27

The 90% CIs of exposure (AUCinf and Cmax) ratios were contained within the standard bioequivalence limits (0.80 – 1.25), indicating that dinutuximab manufactured by UTC and NCI provide comparable PK exposure.

Table 10: Results of PK Comparability Analysis (Population PK-based Approach)

PK Parameter	Geometric Mean UTC (Comparator)	Geometric Mean NCI (Reference)	Ratio	90% CI of Ratio	
				Lower	Upper
AUC_{inf} (µg*h/mL)	431.2	413.5	1.04	0.98	1.11
Cmax (ng/mL)	6568.2	6876.9	0.96	0.88	1.04

Sources: Sponsor's Population PK report DIV-NB-201, Page 32

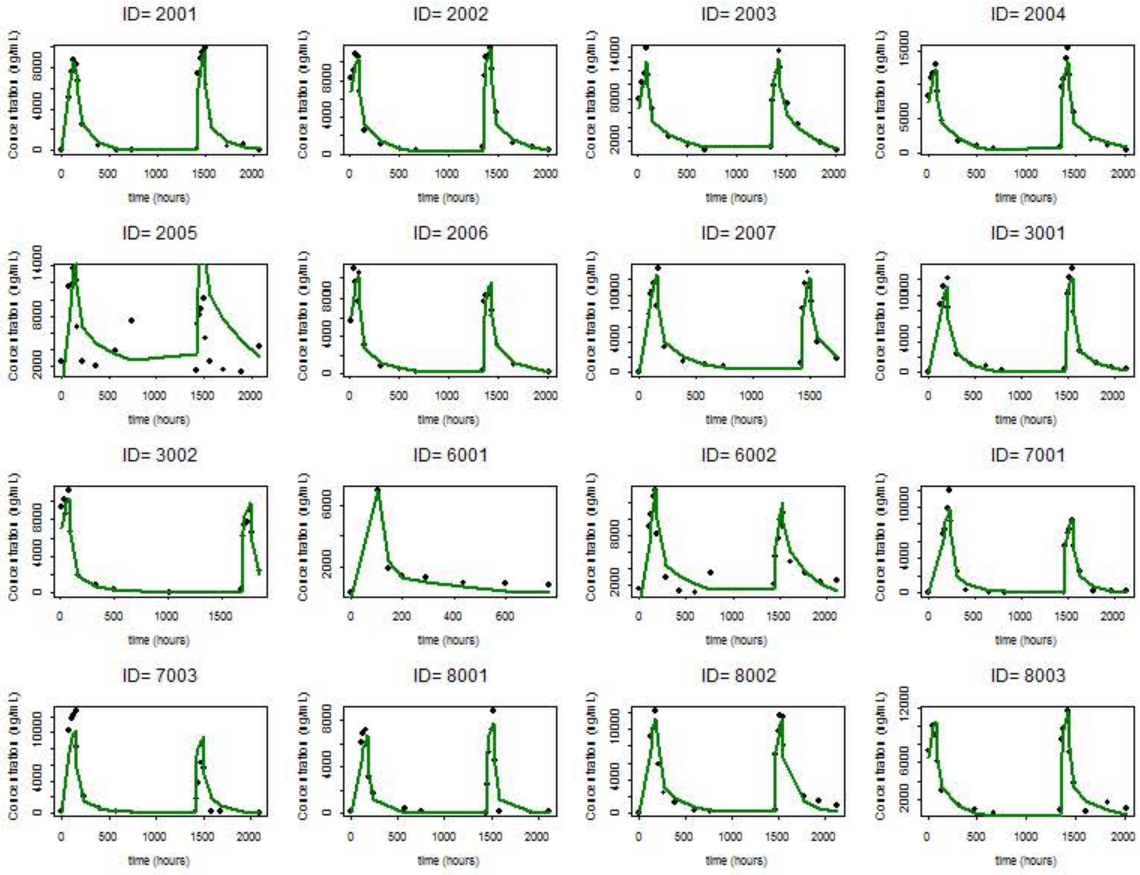
Reviewer's comments:

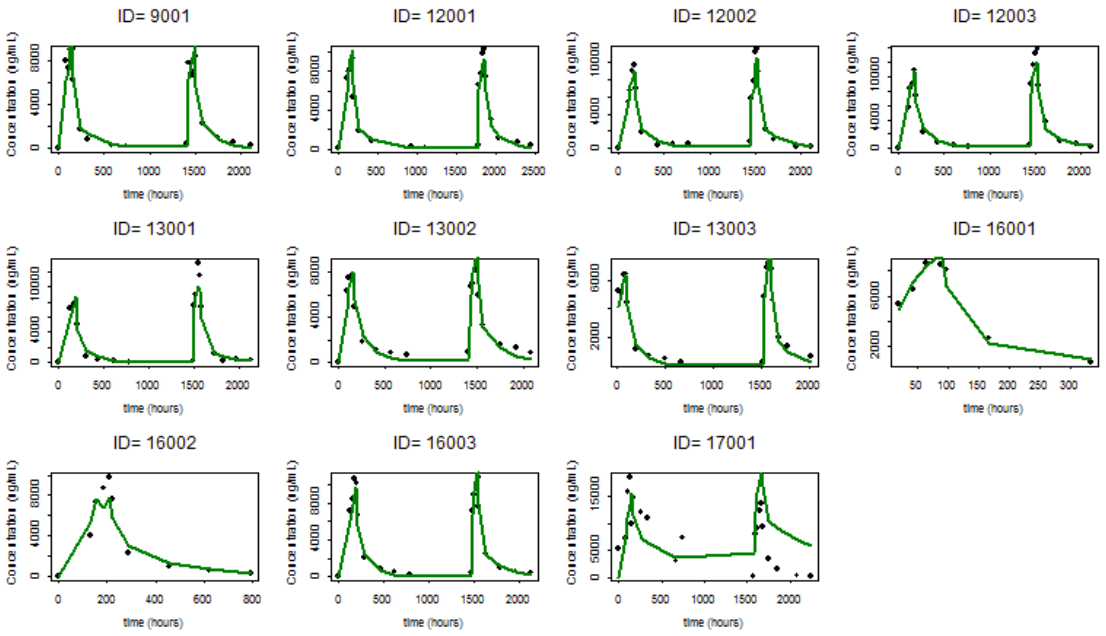
*1. The population PK model can adequately describe the observed PK data (*Figure 2*).*

2. The PK exposures of the two products appear to be comparable. However, uncertainty on whether the population PK approach is sufficient for BE/PK comparability assessment for two biological products still remains.

3. The only objective of this population PK analysis was to assess the PK comparability of two products manufactured by UTC and NCI. No exploration of covariate effect was performed due to the data limitation.

Figure 2: Individual Prediction vs Observed Concentration





X axis is the time (hours), y axis is the dinutuximab concentration (ng/mL). Solid dots and lines represent observation and prediction, respectively.

Sources: Reviewer's analysis

Non-compartmental Analysis

-Method: The PK parameters for this NCA analysis were AUClast and AUC0-216. A 90% confidence interval (CI) of ratio of dose-normalized PK parameters was calculated for UTC vs NCI products.

-Results: As shown in Table 11**,** 90% confidence intervals of ratios of dose-normalized AUClast and AUC0-216 were contained within the BE bounds, indicating that dinutuximab manufactured by UTC and NCI provide comparable PK exposure.

Similar assessment was performed for Cmax values as well, suggesting 90% confidence intervals for dose-normalized Cmax ratio is not contained within the standard BE bounds. However, given the variability in infusion rate and infusion interruptions in this PK comparability study DIV-NB-201, the observed Cmax values at the end of infusion is not considered reliable indicators of PK comparability for this study.

Table 11: Results of PK Comparability Analysis (NCA)

PK Parameter	N	Geometric Mean Ratio (%)	90% Confidence Interval
Absolute			
AUClast	23	104.62	(90.88, 120.44)
AUC0-216	23	108.02	(97.40, 119.80)
Dose-Normalized			
AUClast	23	104.58	(90.75, 120.53)
AUC0-216	23	107.98	(97.12, 120.05)

Sources: Addendum to DIV-NB-201 Population PK Report, Page 64

Reviewer's Comments: It should be noted observed exposures (AUCs, Cmax) do not represent values associated with a single dose as there was not sufficient wash out period between each treatment. However, the small amount of drug carried over from last treatment during product cross over cannot significantly influence the NCA analysis results.

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/s/

JINGYU YU
09/12/2014

HONG ZHAO
09/12/2014
I concur.

LIANG ZHAO
09/12/2014