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*APPLICATION NUMBER:*

**125516Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	March 6, 2015
<b>From</b>	Suzanne G. Demko
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>BLA # /Supp#</b>	125516/0
<b>Applicant</b>	United Therapeutics Corporation
<b>Date of Submission</b>	April 11, 2014
<b>PDUFA Goal Date</b>	December 10, 2014/extended to March 10, 2015 after major amendment
<b>Proprietary Name / Established (USAN) names</b>	Unituxin/dinutuximab
<b>Dosage forms / Strength</b>	Injection for intravenous infusion/3.5 mg/mL
<b>Proposed Indication(s)</b>	High risk neuroblastoma
<b>Recommended:</b>	BLA Approval and Issuance of Rare Pediatric Disease Priority Review Voucher

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**Acronyms used throughout this review (not inclusive):**

OND=	Office of New Drugs
DOP2=	Division of Oncology Products 2
CMC=	Chemistry, Manufacturing, and Controls
COG=	Children's Oncology Group
ONDQA=	Office of New Drug Quality Assessment
OSI=	Office of Scientific Investigations
OPDP=	Office of Prescription Drug Promotion (formerly DDMAC)
OSE=	Office of Surveillance and Epidemiology
DRISK=	Division of Risk Management
DHOT=	Division of Hematology Oncology Toxicology
DARRTS=	Document Archiving, Reporting & Regulatory Tracking System
UTC=	United Therapeutics Corporation
DMA=	Division of Monoclonal Antibodies
CTEP=	National Cancer Institute's Clinical Therapy Evaluation Program

NDA 125516  
Cross Discipline Team Leader Review

## 1. Introduction

United Therapeutics Corporation (UTC) submitted the current application for dinutuximab (Unituxin) on April 11, 2014. Dinutuximab is a first-in-class monoclonal antibody that binds to GD2, a glycolipid expressed on neuroblastoma cells and normal cells of neuroectodermal origin. The mechanism of action for dinutuximab is induction of cell lysis of GD2-expressing cells through antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). The indication proposed by the applicant is for the treatment of patients with high risk neuroblastoma. Late in the original review cycle, on November 14 and 17, the applicant submitted two separate amendments that were declared a major amendment by the CMC and clinical review teams. As a result, the goal date for review and action on the application was extended by three months to March 10, 2015.

High risk neuroblastoma is a rare, life threatening cancer diagnosed in approximately 650 pediatric patients each year in the United States. The median age at diagnosis is 19 months, with 90% of patients diagnosed at less than 5 years of age. Dinutuximab has been designated by FDA as a drug for a “rare pediatric disease” (neuroblastoma) and as such is a candidate for the Rare Pediatric Disease Priority Review Voucher Program.

The clinical development of dinutuximab was conducted by the Children’s Oncology Group (COG) using an investigational product (chimeric monoclonal antibody to GD2 antigen, or ch14.18) provided by the National Cancer Institute (NCI) Cancer Therapy and Evaluation Program (CTEP). The data submitted to support the application were reported from a multicenter, open-label randomized trial conducted in 226 patients with high risk neuroblastoma. Prior to enrollment, patients were required to have achieved at least a partial response to prior therapy for their disease, consisting of induction combination chemotherapy, maximum feasible surgical resection, myeloablative consolidation chemotherapy followed by autologous stem cell transplant, and radiation therapy. The trial randomized patients to ch14.18 and 13-cis- retinoic acid (RA) in combination with granulocyte macrophage-colony stimulating factor and RA (Cycles 1, 3, and 5), interleukin-2 and RA (Cycles 2 and 4), RA (Cycle 6) or six cycles of RA alone. Pre-planned interim analyses of event-free survival (EFS) were conducted approximately every six months. In 2009 the seventh interim analysis led to cessation of randomization in the trial when a numerical improvement in EFS favoring the ch14.18 combination arm was observed. Analyses of EFS performed based on data cut-offs for later time points were supportive of the primary EFS analysis. In addition, analyses of overall

survival confirmed an improvement in overall survival in the ch14.18 combination arm and were also supportive.

Dinutuximab, the to-be-marketed product, is already the standard of care in the United States (US) for first-line treatment of patients with high-risk neuroblastoma.

There were a number of issues arising during the review of the application that will be discussed during the course of this review. Of specific note are the following:

- Data-related issues.
- The results of the seventh interim analysis of EFS are not statistically significant; the results approached but did not meet the pre-specified stopping boundary.
- The OS analyses were not prespecified and the trial was not powered for OS.
- The efficacy trial was not designed to isolate the treatment effect of ch14.18 from that of GM-CSF and IL-2. These components, particularly IL-2, confer substantial additive toxicity but their contribution to efficacy is unknown. Additionally, neither RA, GM-CSF, or IL-2 is approved for the treatment of neuroblastoma.
- There are limited safety data from use of the to-be-marketed product (dinutuximab).
- Recent lots of dinutuximab (sent to clinical sites starting in the summer of 2014) have twice the ADCC activity compared to prior lots. The impact, if any, on the safety of dinutuximab is unknown.
- The applicant has limited experience with the manufacture of biologics; therefore, there are numerous CMC issues some of which will be addressed by planned post marketing commitments.

## 2. Background

*The information in this section was largely derived from the primary review of Martha Donoghue, M.D., and revisions were made.*

### *Disease*

Neuroblastomas represent a heterogeneous group of neuroblastic tumors originating from primitive sympathetic ganglion cells in the adrenal medulla or paraspinal sites and having the

capacity to synthesize and secrete catecholamines. A hallmark of these tumors is diversity in that the clinical presentation and prognosis of patients are influenced by a number of factors, including patient age, tumor location and stage, tumor histology, and tumor molecular characteristics.

With approximately 650 new cases diagnosed each year in the United States, neuroblastoma is the most common extracranial solid tumor occurring in pediatric patients. It rarely occurs in adults. The median age at diagnosis is 19 months, and 90% of patients are diagnosed at less than five years of age.

In North America, treatment for children with neuroblastoma is based upon risk assignment according to a schema developed by the Children's Oncology Group (COG). Children are determined to have low-risk, intermediate-risk, or high-risk neuroblastoma based upon the following characteristics:

- International Neuroblastoma Staging System (INSS) stage
- Age
- International Neuroblastoma Pathologic Classification (INPC)
- Ploidy (tumor DNA index)
- Amplification of the MYCN oncogene

Additional tumor molecular characteristics, such as chromosome 1p and 11q deletions, confer increased risk and also influence treatment.

The approach to risk stratification in neuroblastoma is evolving, and current COG trials classify neuroblastoma as high-risk if it meets one of the following criteria:

- Stage II, III, IV, or IV-S disease with amplified MYCN
- Stage III disease in patients > 18 months with unfavorable histology
- Stage IV disease in patients 12-18 months with non-amplified MYCN, unfavorable histology, or DNA index of 1
- Stage IV disease in patients > 18 months

The five year survival rates of children with neuroblastoma range from 87% for children less than one year of age to 65% in children 1 to 14 years of age. The prognosis for this disease is highly variable. Children of any age with localized neuroblastoma and infants 18 months of age and younger with advanced neuroblastoma who have a favorable histology and molecular characteristics have a high likelihood of long term survival. Older children, however, with advanced-stage disease have a much lower chance of being cured despite treatment with intensive multimodality therapy. Approximately half of the patients diagnosed with

neuroblastoma have disease that is categorized as high-risk. Patients with high-risk neuroblastoma, including patients greater than 18 months of age with metastases or unresectable disease with high-risk genetic features (including amplification of the MYCN oncogene), have a 40% to 50% chance of long term survival. Patients with low-risk tumors have a greater than 98% chance of survival with treatment limited to observation or tumor resection. Patients with intermediate-risk neuroblastoma typically receive a chemotherapy regimen that varies in duration and intensity depending upon clinical and biological risk factors prior to surgical resection. The survival rate for intermediate risk patients approaches 95%.

In the US, standard treatment for patients with high-risk neuroblastoma includes the following:

- Induction chemotherapy consisting of cisplatin and etoposide alternating with vincristine, cyclophosphamide and doxorubicin
- Maximum feasible surgical resection
- Consolidation chemotherapy consisting of myeloablative chemotherapy (either carboplatin/etoposide/melphalan or busulfan/melphalan) followed by autologous stem cell transplant
- Radiation to the primary tumor site and metaiodobenzylguanidine (MIBG)-positive bony metastatic sites, before, during or after myeloablative therapy
- For patients who achieve a partial, very good partial, or complete response to therapy, six months of “maintenance therapy” consisting of anti-GD2 antibody chimeric 14.18 combined with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid [isotretinoin (RA)] .

### *Regulatory*

The table below, copied from the Primary Clinical Review, summarizes key regulatory interactions, advice, and decisions related to this BLA. The majority of clinical data submitted to support the BLA was derived from clinical trials studying ch14.18 and conducted by the NCI CTEP in conjunction with COG. On July 1, 2010, United Therapeutics Corporation (UTC) and the NCI executed a Cooperative Research and Development Agreement (CRADA) to collaborate on the clinical and commercial development of ch14.18 for the treatment of patients with neuroblastoma following myeloablative therapy and autologous stem cell transplant in combination with granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-2 (IL-2) and isotretinoin (RA). The CRADA permitted UTC to have exclusive access to the clinical study data from all studies of ch14.18 sponsored by NCI under IND 4308 and the technical information required to support commercial manufacturing of ch14.18 (hereafter referred to as dinutuximab when specifically discussing the ch14.18 product produced by UTC).

Date	Nature of Regulatory Activity	Issues
12/4/1991	IND submission	<ul style="list-style-type: none"> <li>Application for IND 4308 submitted by CTEP</li> </ul>
10/2/2002	FDA placed IND 4308 on partial clinical hold	<ul style="list-style-type: none"> <li>IND placed on partial hold to prevent treatment of patients under Study ANBL0032 (DIV-NB-301) at the Children’s Hospital of Eastern Ontario (CHEO) investigational site, where two patients received an overdose of IL-2 (one overdose caused a death). Formal letter issued 11/1/2002.</li> </ul>
4/9/2003	FDA removed partial hold	<ul style="list-style-type: none"> <li>Action plan developed by the Special Protocol Review Committee of CHEO was provided that instituted safety precautions to mitigate the risk of medication errors.</li> </ul>
4/30/2003	FDA placed IND 4308 on partial clinical hold	<ul style="list-style-type: none"> <li>IND placed on partial hold to prevent enrollment of new patients at any site into Study ANBL0032. Deficiencies included inadequate dose modification rules for IL-2 and ch14.18 (ANBL0032 protocol permitted toxicities that would be acceptable for high dose IL-2 therapy, which typically requires intensive care support, but were not considered reasonable for patients receiving low dose IL-2 therapy), lack of on-site training at COG sites, inadequate trial oversight by the principal investigator, and lack of criteria for screening clinical sites for their ability to administer toxic biologic therapies. Additionally, pre-printed orders at the CHEO site appeared to be the cause of the IL-2 overdose; therefore, incorporation of sample orders into the protocol and a requirement that modifications to pre-printed orders be reviewed and submitted by COG was deemed necessary. Formal letter issued 5/9/2003.</li> </ul>

Date	Nature of Regulatory Activity	Issues
7/18/2003	FDA removed partial hold	<ul style="list-style-type: none"><li>• CTEP adequately responded to deficiencies outlined in the partial hold letter and agreed to revise the dose modification and stopping criteria for Study ANBL0032 to permanently discontinue IL-2 for any Grade IV toxicity and include stopping criteria for hyponatremia and Grade 4 skin toxicity.</li><li>• The remove hold letter contained a non-hold comment informing CTEP that as designed, Study ANBL0032 will not provide sufficient data to meet the regulatory standards for a licensing study. FDA described the following flaws in study design and requested a response explaining how these flaws will be corrected:<ul style="list-style-type: none"><li>– A one-sided log-rank test comparing the two arms with an alpha of 0.05 would not support licensure</li><li>– Lack of clarity regarding whether there were co-primary endpoints or one primary endpoint. A single primary endpoint of overall survival (OS) was recommended.</li><li>– The analysis of event-free survival did not address the post-randomization loss of patients due to missing data, toxicity, and refusal of future treatment, and the necessary adjustment in sample size and analyses for these events.</li><li>– The statistical plan to conduct interim analyses for futility and efficacy every six months following occurrence of 20% of deaths (possibly up to 10 such analyses during the estimated trial course of seven years) presented potential concern and there was lack of clarity on how trial integrity and lack of bias would be maintained in this open label trial over a long period of time. FDA requested clarification regarding the degree to which the Data Monitoring Committee deliberations are closed, how interim efficacy data are reported, and a plan to for alpha adjustment for multiple analyses.</li></ul></li></ul>

<b>Date</b>	<b>Nature of Regulatory Activity</b>	<b>Issues</b>
9/1/2005	Type C meeting held between FDA and CTEP	<ul style="list-style-type: none"><li>• Meeting held to review the progress of Study ANBL0032 and preview the proposed ANBL0532 induction and consolidation regimen and determine whether all patients from this new regimen who meet ANBL0032 response criteria could be included as evaluable patients in the ANBL0032 study.</li><li>• FDA stated that inclusion of patients treated on the successor high-risk neuroblastoma study, Study ANBL0532, is acceptable provided that Study ANBL0032 achieves the primary efficacy event-free survival (EFS) endpoint and the treatment effect is robust, consistent across subgroups, and not substantially impacted by a single subgroup.</li><li>• FDA stated that CTEP needs to provide a plan for isolating the effect of IL-2 and GM-CSF in the treatment regimen, and that this is a critical component of an application. CTEP acknowledged this comment and agreed to submit a plan to establish the contribution of cytokines to the treatment effect.</li><li>• FDA stated that the primary statistical analysis should have a one-sided type 1 error rate no greater than 0.025.</li><li>• FDA stated that if NCI plans to request accelerated approval based on a claim of improvement in EFS, they needed to provide evidence to support their contention that a change in EFS is predictive of a change in OS.</li></ul>

<b>Date</b>	<b>Nature of Regulatory Activity</b>	<b>Issues</b>
5/30/2006	FDA issued advice letter and request for information	<ul style="list-style-type: none"><li>• FDA informed CTEP that for regulatory purposes, an appropriate primary analysis plan should have a one-sided type 1 error rate at most 0.025, when ignoring the futility boundary. FDA requested clarification regarding how this requirement would be maintained taking into account interim analyses and whether the trial would be continued if early boundaries are crossed.</li><li>• FDA requested adequate justification for the use of EFS as a surrogate for OS based on analyses of the correlation between EFS with OS.</li></ul>
8/8/2008	FDA reiterated advice and request for information previously communicated on 5/30/2006.	
1/15/2009	IND 4308 placed on partial clinical hold	<ul style="list-style-type: none"><li>• IND placed on partial clinical hold preventing enrollment of new patients onto Study ANBL0032 (DIV-NB-301) after being informed of six cases of Grade 3/4 allergic reactions linked to ch14.18 lot L0512003 (formal letter issued 1/27/2009).</li></ul>

Date	Nature of Regulatory Activity	Issues
4/3/2009	FDA removed partial hold	<ul style="list-style-type: none"><li>• CTEP adequately addressed the concerns regarding lot L0512003. Based on the information provided, FDA concluded that the apparent increase in severe allergic/hypersensitivity reactions was related to a change in categorization of reporting adverse events, not a true increase in incidence. The remove hold letter included the following non-hold comments and requests for information:<ul style="list-style-type: none"><li>– The amended ANBL0032 protocol should include the requirement that lot numbers of IL-2 and GM-CSF be recorded and be revised to ensure collection of information about targeted adverse events including allergic reaction/hypersensitivity, hypotension, urticaria, adult respiratory distress syndrome, dyspnea, cytokine release syndrome/acute infusion reaction, and acute vascular release syndrome.</li><li>– FDA reminded CTEP that in light of COG’s decision to stop randomization (information submitted to FDA on March 5, 2009), it is critical to diligently pursue commercial development of ch14.18, and that the single arm extension portion of the study is only a temporary measure to provide access to ch14.18 to patients.</li><li>– FDA requested that CTEP submit a new protocol with the specific objective of obtaining comprehensive safety information from a minimum of 100 patients to support a licensing application for ch14.18 plus cytokines within the next six months.</li></ul></li></ul>
12/20/2010	FDA granted orphan drug status to ch14.18 for the treatment of neuroblastoma	

Date	Nature of Regulatory Activity	Issues
1/27/2011	Type B Pre-IND meeting with United Therapeutics (pIND 110494)	<ul style="list-style-type: none"> <li>FDA stated that if UTC provides data to demonstrate that UTC-manufactured ch14.18 (dinutuximab) is comparable to NCI-derived ch14.18, data from Study ANBL0032 can be submitted as the single trial supporting efficacy of ch14.18 in combination with GM-CSF and IL-2 as a component of standard treatment of patients with high-risk neuroblastoma who have minimal residual disease after autologous stem cell transplant.</li> <li>DOP2 emphasized that UTC was responsible for the content and quality of the application.</li> </ul>
3/9/2012	IND application submission	<ul style="list-style-type: none"> <li>UTC submitted IND 110494 for dinutuximab.</li> </ul>
4/9/2012	Teleconference between DOP2, CMC, and UTC	<ul style="list-style-type: none"> <li>Teleconference held to discuss UTC's plans for addressing results that were out of specification for drug product lot P110602 at the 3-month stability testing time point and reach agreement regarding the use of lot S110601 for Study DIV-NB-201. UTC agreed not to use Lot S11601, not the failed lot, in Study DIV-NB-201. UTC agreed to provide 3-month and 6-month stability data for Lot S110601 as a formal IND amendment when it becomes available.</li> </ul>
4/11/2012	FDA issued may proceed letter for IND 110494	
12/11/2012	Type C meeting	<ul style="list-style-type: none"> <li>UTC, DOP2, and CMC Division of Monoclonal Antibodies met to discuss status of commercial manufacturing for dinutuximab, planned validation efforts, and reach agreement on CMC requirements for the filing of a future BLA.</li> </ul>
8/28/2013	Informal teleconference between UTC and DOP2	<ul style="list-style-type: none"> <li>Teleconference held to discuss the status of commercial development of dinutuximab and the potential timing of a BLA application.</li> </ul>
12/20/2013	Office of Orphan Products Development (OOPD) designated dinutuximab as a drug for a "rare pediatric disease" for the treatment of neuroblastoma	

Date	Nature of Regulatory Activity	Issues
1/14/2014	Type B pre-BLA CMC meeting	<ul style="list-style-type: none"><li>Multiple issues were discussed, including the need to include polysorbate 20 in the specifications, lower the bioburden specification for the (b) (4) (b) (4) justify the use o (b) (4) for bioburden studies, and perform hold time studies to determine the reliability of the endotoxin test results.</li></ul>
2/19/2014	Type B pre-BLA meeting	<ul style="list-style-type: none"><li>FDA reminded UTC of the need to provide data in the BLA establishing the contribution of each therapeutic component (dinutuximab, IL-2, and GM-CSF).<ul style="list-style-type: none"><li>UTC stated that they will address this requirement in the ISE by referencing published literature and clinical study data.</li><li>FDA stated that the adequacy of the information to isolate the effects of ch14.18 will be determined during the BLA review.</li><li>FDA stated that consistency of efficacy across key patient subsets is an important factor in determining whether a single adequate and well controlled study provides sufficient evidence to support an effectiveness claim.</li></ul></li></ul>

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The European Union (EU) granted orphan drug status to dinutuximab for the treatment of high-risk neuroblastoma on June 21, 2011. (b) (4)

(b) (4)

UTC submitted a Marketing Authorization Application for dinutuximab to the EMA on December 5, 2013. A decision on this application is still pending as of the filing date for this review.

### 3. CMC/Device

*The information in this section was derived from the reviews of the CMC review teams including those of Chikako Torigoe, Ph.D., Jibril Abdus-Samad, Pharm.D., Lakshmi Narasimhan, Ph.D., Patricia Hughes, Ph.D. and Laurie Graham, Ph.D.*

The CMC review and manufacturing site inspection teams recommend approval of this BLA with a number of postmarketing commitments (PMCs). I agree with their recommendations.

As noted above, the data to support the findings of safety and effectiveness of ch14.18/dinutuximab were derived from clinical trials conducted using material manufactured by NCI, i.e., ch14.18. The first Phase I trial was initiated in 2001. As previously noted, in 2010, NCI entered into a CRADA with UTC. There were extensive manufacturing changes between the NCI and UTC processes, including:

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As discussed above, there has been limited clinical experience with the product manufactured by UTC, i.e., dinutuximab.

Late in the review cycle for this BLA there remained a number of questions with regard to the UTC product and its manufacture. Many of the issues were grounded in safety concerns regarding the comparability of the original clinical trial material manufactured by NCI (ch14.18) and the current to-be-marketed material manufactured by UTC (dinutuximab). As noted previously, as a result of the late submission of additional data to address some of the CMC questions still outstanding, a major amendment was declared and the review cycle was lengthened by three months.

To support the changes in drug substance (DS) and drug product (DP) manufacturing, UTC performed an analytical comparability assessment of ch14.18 vs. the first three batches of dinutuximab DP manufactured by UTC. The comparability assessment included release, characterization, and stability testing. The interpretation of the results was confounded by the

age of the lots of ch14.18, which were demonstrating degradation. The available data support the finding that the differences observed between the UTC and NCI lots could be the result of the observed degradation. In addition to analytical testing, a clinical PK comparability study of NCI vs. UTC product was performed. Dr. Jingyu Yu, the clinical pharmacology reviewer, concluded that the NCI and UTC materials were comparable in terms of PK. It is noted that NCI has been using UTC lots in on-going clinical trials since January 2014. Dr. Donoghue, the clinical reviewer, specifically assessed the safety data from clinical trials using UTC-manufactured dinutuximab and concluded that there were no obvious new safety concerns. Cumulatively, the data provided in the BLA are considered adequate by the CMC review teams to support the comparability of the NCI and UTC products.

Even at the date of this review, CMC issues regarding the manufacture of dinutuximab remain; however, the benefit/risk assessments conducted by multidisciplinary FDA reviewer teams indicate that the CMC issues identified do not preclude approval. The remaining issues will be addressed as post-marketing commitments (PMCs) as follows:

- To verify (b) (4) lifetimes at commercial scale using a validation protocol to evaluate (b) (4) capability and cleaning procedures throughout the intended lifetime of the (b) (4).
- To further investigate the root cause for the (b) (4) observed in drug product stored under recommended conditions and to perform a risk assessment based on the root cause, the levels of (b) (4) observed, and the potential effects on safety and efficacy of dinutuximab. Appropriate corrective and preventative actions will be implemented based on the results of the root cause investigation and risk assessment. The root cause investigation and risk assessment reports and proposed corrective and preventive actions will be provided as a prior approval supplement.
- To confirm validation of the SEC-HPLC assay. Validation reports will be updated to include evaluations of accuracy, precision, specificity, quantitation limit, linearity and range with respect to the purity and the product related impurities included in the final drug substance and drug product release and stability specifications. The validation reports will be provided.
- To confirm validation of the cSDS reduced assay. Validation reports will be updated to include evaluations of accuracy, precision, specificity, quantitation limit, linearity and range with respect to the purity and the product related impurities included in the

final drug substance and drug product release and stability specifications. The validation reports will be provided.

- To confirm validation of the cSDS non-reduced assay. Validation reports will be updated to include evaluations of accuracy, precision, specificity, quantitation limit, linearity and range with respect to the purity and the product related impurities included in the final drug substance and drug product release and stability specifications. The validation reports will be provided.
- To develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against dinutuximab in the presence of dinutuximab levels that are expected to be present in samples at the time of patient sampling. The validation report will be submitted as a Prior Approval Supplement.
- To develop, validate/qualify and implement an osmolality assay for the drug product release specifications. The analytical procedure, qualification report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be provided as a CBE-30.
- To confirm compatibility of drug product with IV bags and IV administration sets of different materials of construction. The compatibility study will include monitoring samples for protein concentration, purity by SEC-HPLC, cIEF, sub-visible particulates, and potency. The final report will be submitted as a Prior Approval Supplement.
- To confirm compatibility of the drug product with the use of an in-line filter during administration. These studies will include monitoring samples for protein concentration, purity by SEC-HPLC, cIEF, sub-visible particulates, and potency. The final report will be submitted as a Prior Approval Supplement.
- To re-evaluate dinutuximab drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis, and the statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final report.
- To re-evaluate dinutuximab drug product lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The

corresponding data, the analysis, and the statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final report.

#### *Product Quality Microbiology Evaluation*

The UTC-manufactured drug product, dinutuximab was reviewed for sterility assurance. The review team recommends approval for the application with three PMCs as follows:

- Conduct a comparison study between the LAL kinetic chromogenic test and the rabbit pyrogen test for drug product that has been spiked with endotoxin and then held prior to testing.
- Conduct studies to understand the mechanism of endotoxin masking in the drug product. Explore alternative test methods and develop a more suitable endotoxin release test for the drug product.
- Validate the dye ingress test using dinutuximab drug product vials. The validation study should identify the range of breach sizes detectable by the assay. The positive control used for the dye ingress test should be based on the validation study data.

#### *Facilities Inspection*

From June 9, 2014 to June 13, 2014 an inspection was performed of the commercial manufacturing facilities for dinutuximab drug substance and drug product at United Therapeutics, Corp. in Silver Spring, MD. Please see the specific observations made during the inspection in Dr. Torigoe's (DMA) primary review. It was determined that none of the observations made would preclude the approval of this application.

There are no other notable issues outstanding for this application from a CMC and quality perspective.

## **4. Nonclinical Pharmacology/Toxicology**

*The information in this section was derived from the reviews of Dubravka Kufrin, Ph.D. and Whitney Helms, Ph.D. and minimally revised.*

The nonclinical review team has determined that the BLA for dinutuximab is approvable. I agree with this determination.

Dinutuximab is a chimeric mouse/human IgG1 monoclonal antibody produced in SP2/0 hybridoma cells derived from a murine precursor, Mab 14.18. The chimeric antibody is composed of the variable region heavy and light chains of the parent murine monoclonal

antibody (Mab) 14.18 and a constant region consisting of the human IgG1 heavy chain and kappa light chain. The antibody binds to the disialo ganglioside, GD2, which is expressed on tissues from the central nervous system and peripheral nerves as well as on many tumors of neuroectodermal origin, including neuroblastoma. The chimeric antibody has been studied clinically over the last 20 years. Dinutuximab is the ch14.18 antibody produced by UTC's manufacturing process.

The pharmacologic characterization of dinutuximab is based on published literature describing experiments using ch14.18 and surrogate antibodies with the same variable domain but with alternative murine constant regions. The published results demonstrate that the antibody is able to bind GD2 and potentiate antibody-dependent cellular cytotoxicity (ADCC), mediated primarily by neutrophils and NK cells, as well as complement dependent cytotoxicity (CDC). In separate experiments, both GM-CSF and IL-2 were each shown to have some capacity for enhancing ADCC mediated by anti-GD2 antibodies. In the absence of complement or effector cells there was no evidence of tumor inhibition following anti-GD2 binding, though early studies did suggest that the ganglioside may play a role in cellular attachment to the extracellular matrix.

Animal safety studies of dinutuximab were conducted in Sprague Dawley rats and cynomolgus monkeys. Rats were administered dinutuximab at doses significantly higher than the clinically recommended dose with a 6-week recovery period. The liver was identified as a target organ, though only minimal histopathological and clinical chemistry changes were observed. Increases in lymphocytes, neutrophils, and NK cells were also noted in rats. The rats appeared to develop an anti-drug antibody response which affected the pharmacokinetics of dinutuximab, particularly at the lowest dose level. Dinutuximab was also administered to cynomolgus monkeys in a single-dose cardiovascular safety study. In this study, increases in heart rate were observed, however, no changes in QTc, respiratory rate, or blood gas parameters were noted.

The major toxicity associated with administration of dinutuximab clinically is severe neuropathic pain. UTC submitted multiple publications investigating the mechanism of ch14.18-mediated pain. These publications suggest that the pain is related to the pharmacologic activity of the drug: binding of the antibody to GD2 expressed on peripheral nerves and subsequent Fc domain-mediated ADCC and CDC activity. Clinical signs of toxicity in monkeys administered a single dose of dinutuximab included vomiting and reduced food consumption; these findings along with the increases in heart rate suggest that the monkey is a relevant model for longer term studies of GD-2 mediated neuropathic pain and recovery.

Because there are approximately 20 years of clinical experience with the use of anti-GD2 antibodies in the treatment of patients with neuroblastoma, no long term toxicology studies were conducted to support the use of dinutuximab for this indication. The majority of clinical experience with anti-GD2 therapy for neuroblastoma is, however, in combination with other therapies, including GM-CSF and IL-2. For this reason, questions remain about the potential toxicity of dinutuximab as a single agent and whether there is a potential for longer term neuropathic effects or neuropathy following treatment. Because the clinical experience with ch14.18 has not resulted in a signal suggesting that long term neuropathic damage is likely, this concern will be addressed as a nonclinical post-marketing requirement.

Consistent with ICH S6 guidance, genetic toxicology studies were not conducted or required for dinutuximab. Carcinogenicity studies were not required to support the application for a product intended to treat advanced human cancer and are neither planned nor expected as post-marketing requirements. The requirement for reproductive toxicity studies was discussed prior to submission of the BLA. Because the median age of the proposed patient population is 18 months and 90% of the cases occur in children under the age of 5, reproductive toxicology studies of dinutuximab were not required. Dinutuximab is not indicated for females of reproductive potential. If UTC explores additional indications in the future, nonclinical studies investigating the effects of dinutuximab on embryofetal development may be required. Pregnancy Category D was recommended by the nonclinical review team.

A post-marketing requirement to further investigate the toxicologic effects of dinutuximab as a single agent following chronic administration of the antibody, particularly its effects on the nerves and neuropathic pain, has been agreed to by UTC.

## **5. Clinical Pharmacology/Biopharmaceutics**

*The information in this section was derived from the review of Jingyu Yu, Ph.D. and minimally revised.*

The Clinical Pharmacology review team has recommended approval for this BLA. I agree with this recommendation.

Following is a list and summary of the significant review issues noted by Dr. Yu during the original six month review cycle:

- **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).
- **PK comparability between NCI product (ch14.18) and UTC product (dinutuximab):** 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-life 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.

During the major amendment-lengthened review cycle, Dr. Yu filed a primary review addendum focusing on an update to the long term stability of the PK samples from the original PK studies. Based on the additional data reviewed by Dr. Yu, the validity of the PK assessment was supported. In addition, the review addendum noted that a PMR would be imposed to study neutralizing antibodies in ongoing clinical studies using a sensitive neutralizing antibody assay.

## **6. Clinical Microbiology**

*Not applicable to this BLA*

## **7. Clinical/Statistical- Efficacy**

*The information in this section was derived from the primary reviews of Sirishi Mushti, Ph.D. and Martha Donoghue, M.D. as well as parts of the clinical study report submitted by the applicant.*

The primary statistical and clinical reviewers have recommended approval for this BLA. I concur with their recommendations.

The evidence supporting the approval of this application was largely from a single controlled trial, DIV-NB-301 (Study 301), an international, multicenter open-label randomized (1:1) trial comparing the ch14.18 antibody (provided by the National Cancer Institute) in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid [isotretinoin (RA)] to RA alone in 226 patients with newly diagnosed neuroblastoma. Eligible patients had completed intensive induction chemotherapy followed by autologous stem cell transplantation (ASCT) and radiation therapy, and achieved at least a partial response (PR). Patients were required to have adequate hematologic, hepatic, renal, cardiac, and pulmonary function and not be reliant on systemic corticosteroids or other immune suppressing agents in order to be enrolled.

Randomization was stratified based upon objective response status (complete response vs. very good partial response vs. partial response) using the International Neuroblastoma Staging System (INSS) Response Evaluation Criteria and the treatment regimen received prior to enrollment. The first patient was randomized on October 26, 2001 and the last patient was enrolled on November 03, 2008.

The primary efficacy outcome measure was investigator-assessed event-free survival (EFS), defined as the first occurrence of relapse, disease progression, secondary malignancy, or death. The primary analysis of EFS was a stratified log-rank test of the intent-to-treat (ITT) population. Overall survival (OS) was the key secondary endpoint; however, the study was not powered to detect a statistical difference in overall survival between the study arms. The primary analysis of OS was also a stratified log-rank test of the intent-to-treat (ITT) population. The demographic and disease characteristics of the patients in the intent to treat population are included in the tables below copied from the primary review of Dr. Donoghue.

**Baseline Demographic Characteristics of Randomized Patients in Study 301**

Patient Characteristics	Ch14.18 (n = 113)	RA (n=113)	Total (N=226)
<b>Age at Enrollment (years)</b>			
Mean (sd)	4.3 (2.5)	4.0 (2.1)	4.1 (2.3)
Median (range)	3.9 (0.9 - 15.3)	3.5 (0.9 - 13.3)	3.8 (0.9 - 15.3)
<1.5 years, n (%)	4 (4)	4 (4)	8 (3)
<b>Gender, n (%)</b>			
Male	71 (63)	64 (57)	135 (60)
Female	42 (37)	49 (43)	91 (40)

<b>Patient Characteristics</b>	<b>Ch14.18 (n = 113)</b>	<b>RA (n=113)</b>	<b>Total (N=226)</b>
<b>Race, n (%)</b>			
White	95 (84)	90 (80)	185 (82)
Black	8 (7)	8 (7)	16 (7)
Asian/Pacific Islander	2 (2)	6 (6)	8 (4)
Other/Unknown	8 (7)	9 (8)	17 (8)
<b>Ethnicity</b>			
Not Hispanic or Latino	100 (89)	96 (85)	196 (87)
Hispanic or Latino	11 (10)	11 (10)	22 (10)
Unknown	2 (2)	6 (5)	8 (4)
<b>Country of Enrollment, n (%)</b>			
United States	101 (89)	97 (86)	198 (88)
Canada	11 (10)	13 (12)	24 (11)
Australia	1 (1)	3 (3)	4 (2)

**Baseline Disease Characteristics of Randomized Patients in Study 301**

<b>Patient Characteristics</b>	<b>Ch14.18 (n = 113)</b>	<b>RA (n=113)</b>	<b>Total (N=226)</b>
<b>INSS Stage, n (%)</b>			
Stage 2A	4 (4)	0 (0)	4 (2)
Stage 3	10 (9)	16 (14)	26 (12)
Stage 4	89 (79)	92 (81)	181 (80)
Stage 4s	2 (2)	0 (0)	2 (1)
Unknown	8 (7)	5 (4)	13 (6)
<b>MYCN status, n (%)</b>			
Amplified	36 (32)	45 (40)	81 (36)
Non-amplified	52 (46)	51 (45)	103 (46)
Missing	25 (22)	17 (15)	42 (19)
<b>DNA Ploidy, n (%)</b>			
Diploid	35 (31)	46 (41)	81 (36)
Hyperdiploid	49 (43)	48 (43)	97 (43)
Missing	29 (26)	19 (17)	48 (21)
<b>Tumor Histology, n (%)</b>			
Favorable	4 (4)	5 (4)	9 (4)

<b>Patient Characteristics</b>	<b>Ch14.18 (n = 113)</b>	<b>RA (n=113)</b>	<b>Total (N=226)</b>
Unfavorable	68 (60)	81 (72)	149 (66)
Missing	41 (36)	27 (24)	68 (30)
<b>Pre-ASCT Response, n (%)</b>			
CR	40 (35)	38 (34)	78 (35)
VGPR	47 (42)	49 (43)	96 (43)
PR	26 (23)	26 (23)	52 (23)

Interim analyses were planned and performed approximately every six months. At the seventh interim analysis with a data cut-off date of January 13, 2009, a numerical improvement in EFS [HR 0.57 (95% CI: 0.37, 0.89); p = 0.0115, unstratified log-rank test] was demonstrated. Median EFS was not reached in the ch14.18/RA arm and was 1.9 years in the RA arm. The 2-year survival rate (95% CI) in the ch14.18/RA arm was 66.3% (56.3, 76.3) and in the RA alone arm was 46.4% (35.8, 57.1) indicating a higher 2-year EFS rate in the treatment arm compared to the control arm. The primary EFS analysis results are summarized in the following table and figure copied from the reviews of Drs. Donoghue and Mushti respectively.

#### Study 301: Primary Efficacy Analysis

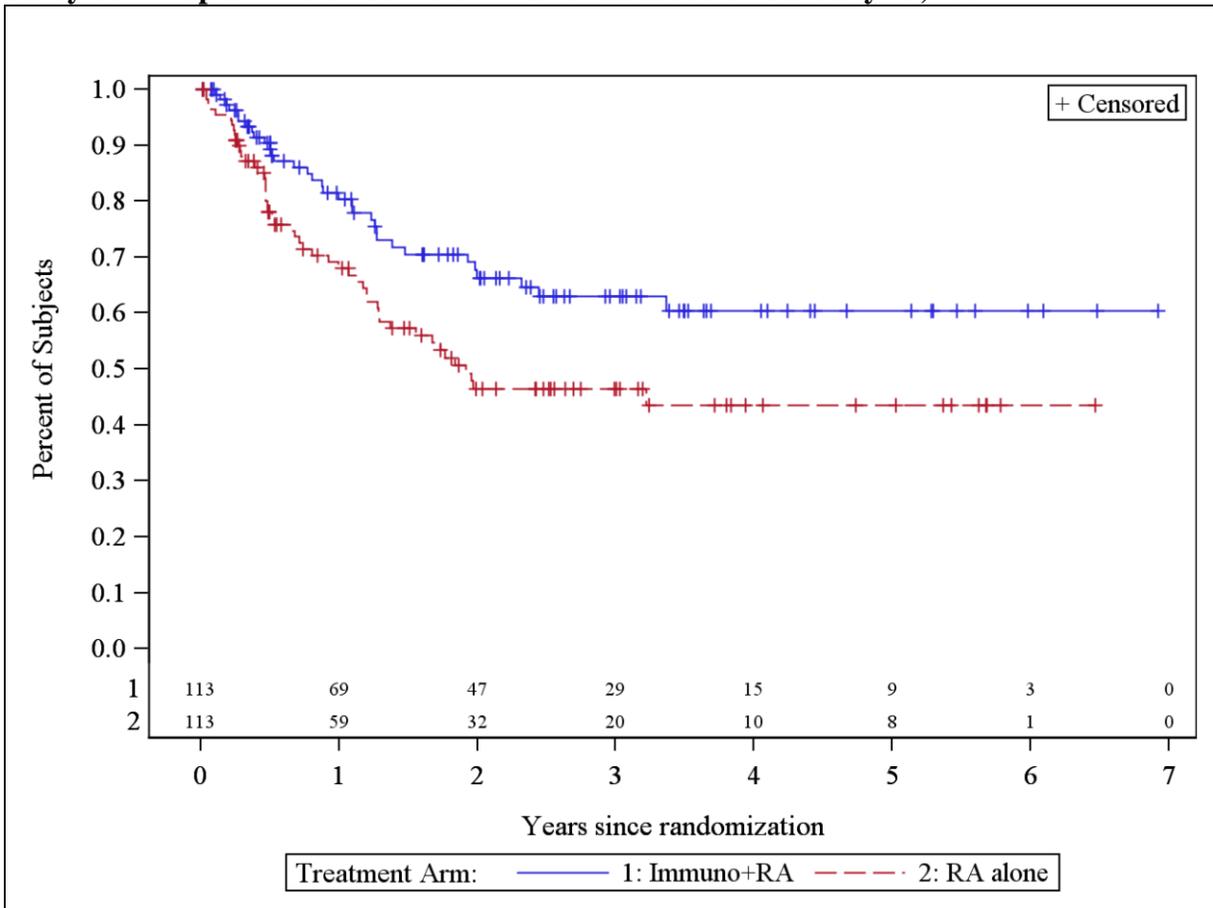
	<b>Ch14.18 combination n=113</b>	<b>RA alone n=113</b>
No. of EFS events (%)	33 (29.2)	50 (44.25)
2-yr EFS rate (%) (95% CI)	66.29 (56.25, 76.33)	46.44 (35.82, 57.06)
Median EFS (years) (95% CI)	NR(3.36,NR)	1.92 (1.29,NR)
Hazard ratio (95% CI)	0.57 (0.37,0.89)	
p-value <sup>a</sup> (Unstratified log-rank test)	0.0115	

\* Using a data cutoff date of January 13, 2009 (corresponding to the seventh interim analysis)

Abbreviations: CI: confidence interval; EFS: event-free survival; No.: number

<sup>a</sup>This p-value approaches but is marginally above the pre-specified p-value of 0.0108 that was required under the statistical plan for stopping randomization for efficacy.

**Study 301: Kaplan-Meier Curve of EFS for data cut-off January 13, 2009**



Results for EFS from using data cut-off dates of June 30, 2009 (2-year data) and June 30, 2012 (3-year data) were supportive of the primary analysis of EFS. The 2-year EFS rates for the ch14.18/RA arm and RA arm respectively were 65.6% (56.1, 75.2) and 48.1% (38.0, 59.2). The 3-year EFS rates for the ch14.18/RA arm and RA arm respectively were 62.9% (53.9, 71.7) and 50.9% (41.6, 60.2).

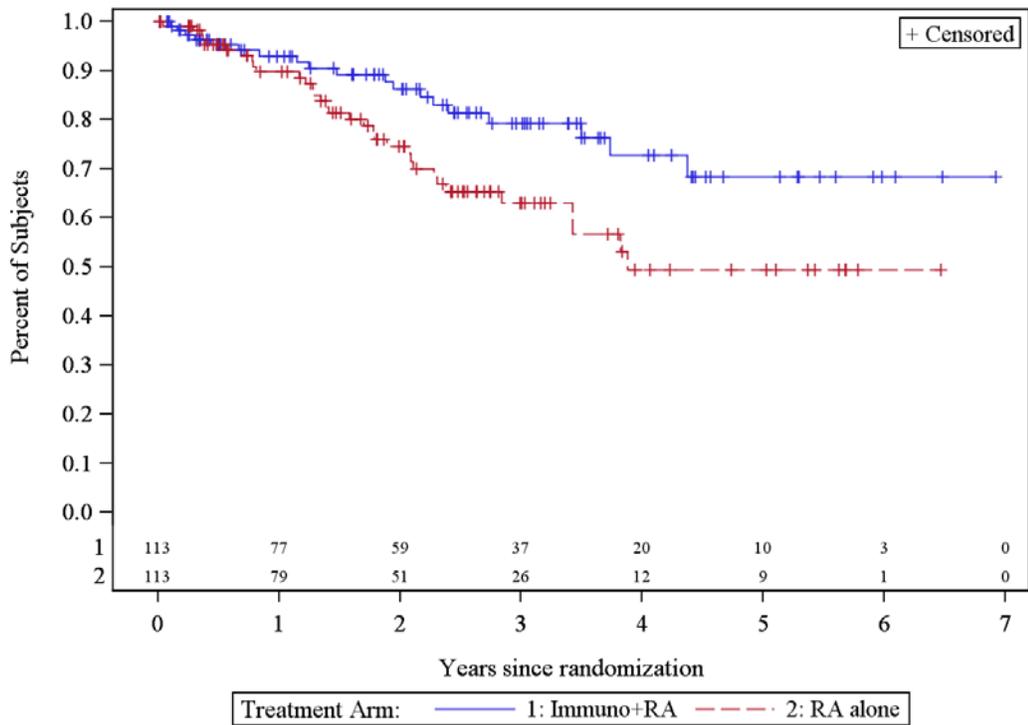
The primary OS analysis results are depicted in the following table and figure copied from the reviews of Drs. Donoghue and Mushti respectively. These analyses were consistent with the numerical improvement observed for EFS and documented a strong trend toward improvement in overall survival in patients randomized to the ch14.18 combination arm.

**Study 301: Primary OS Analysis**

	<b>Ch14.18 combination n=113</b>	<b>RA alone n=113</b>
No. of OS events (%)	19 (16.81)	33 (29.2)
2-yr survival rate (%) (95% CI)	86.17 (78.76,93.58)	74.53 (65.18,83.88)
Median (years) (95% CI)	NR (NR,NR)	3.88 (3.43,NR)
Unadjusted Hazard Ratio (95% CI)	0.52 (0.30,0.92)	
Nominal p-value (Unstratified log-rank test)	0.0223	

Abbreviations: CI: confidence interval; No.: number; NR: not reached; OS: overall survival

**Study 301: Kaplan-Meier Curve of OS for data cut-off January 13, 2009**



Both the two year and three year OS analyses were supportive of the primary OS analysis documenting an improvement in OS in the dinutuximab/RA arm compared to the RA arm with HR 0.58 (0.37, 0.91) observed for both analyses. At the time of all OS analyses, median OS had not been reached for either arm.

The main issue from this study, identified by both the statistician and the clinical reviewer, is termination of randomization to the RA alone arm based on the seventh interim analysis despite the fact that the observed p-value of 0.0115 did not cross the pre-specified alpha boundary of 0.0108. In addition, the primary OS analysis was not powered for the OS endpoint. Having identified these issues, both reviewers performed numerous analyses and investigations into the data contained in the application as well as into FDA guidance and controlling legislation and regulations to make their determinations on the approvability of the

application. Additionally, the applicant was asked to perform analyses and submit additional data to respond to multiple information requests (IR) made by both reviewers.

During her review, Dr. Donoghue considered whether data from the single adequate and well-controlled trial supporting the effectiveness of dinutuximab provided adequate scientific and legal bases for approval. Reviewed were relevant guidance and controlling regulations. While the results from this trial were not statistically robust, Dr. Donoghue concluded that the primary EFS results supported by updated analyses of both the primary efficacy outcome and the OS analyses (using data collected through June 30, 2009 and June 30, 2012) were persuasive and both corroborate the efficacy findings and strengthen the application overall. In reviewing Dr. Donoghue's argument, I find it well researched, well-formed and credible.

Another shortcoming of the BLA considered by Dr. Donoghue was the lack of clinical data to isolate the treatment effect of dinutuximab from that of GM-CSF and IL-2. During interactions with CTEP and UTC throughout the development of ch14.18 and dinutuximab, FDA had emphasized the importance of characterizing the contributions of each component of ch14.18 combination therapy (GM-CSF, IL-2, and ch14.18/dinutuximab) to the overall treatment effect observed in patients with high risk neuroblastoma. Ultimately, the application contained insufficient clinical data to assess the relative contributions of GM-CSF and IL-2 to the observed results.

Similarly, the safety review of dinutuximab was hampered by a relative lack of clinical data from use of dinutuximab as monotherapy because IL-2 and GM-CSF are administered concurrently with dinutuximab in the relevant major supporting trials.

The application includes information from published literature to support the rationale for use of ch14.18 in combination with IL-2 and GM-CSF for the treatment of patients with high risk neuroblastoma. To date, there are no data from controlled trials comparing the efficacy of ch14.18 administered as monotherapy with the efficacy of ch14.18 administered with IL-2 or GM-CSF (or both) in the patient population studied. In Europe, an ongoing randomized study is evaluating the efficacy of a related ch14.18 antibody administered with or without IL-2 in patients with newly diagnosed neuroblastoma.

## **8. Safety**

*The information in this section was derived from the primary review and addendum of Martha Donoghue, M.D. and minor revisions were made.*

Chimeric 14.18 (the NCI product) and dinutuximab (the UTC-manufactured product) have been evaluated in 16 clinical trials in patients with melanoma and neuroblastoma including 11 studies sponsored by the National Cancer Institute (NCI), one study sponsored by United Therapeutics Corporation (UTC), and four additional studies conducted outside of the NCI and UTC. United Therapeutics Corporation has also sponsored one clinical trial in patients with neuroblastoma which was completed in February 2014 (DIV-NB-201) for which the safety data analyses are currently ongoing. Four additional studies have been conducted in patients with neuroblastoma outside of the NCI and UTC. Dr. Donoghue's summary and review of safety focuses on the NCI and UTC sponsored studies of ch14.18 in patients with neuroblastoma. The two primary studies relied upon to support the finding of safety were Studies DIV-NB-301(Study 301) and DIV-NB-302 (Study 302).

It is the primary clinical reviewer's conclusion that patients receiving dinutuximab are at risk for developing serious and potentially life-threatening adverse reactions, such as infusion reactions, capillary leak syndrome, hypotension, anaphylaxis, infection, and neuropathy. Dr. Donoghue has recommended that patients receive dinutuximab in an inpatient setting in hospitals capable of providing intensive care unit support. Additionally, it is recommended that treatment with dinutuximab occur only under the oversight of pediatric oncologists who are skilled in the identification and management of the observed toxicities. During and following treatment with dinutuximab, careful monitoring of patients for signs and symptoms of adverse reactions is also recommended to ensure prompt intervention, including dose interruption, dose modification, dose discontinuation, and institution of supportive care when necessary. I concur with Dr. Donoghue's analyses and conclusions.

Late in the original review cycle, UTC provided additional data on antibody-dependent cell-mediated (ADCC) cytotoxicity indicating that recent UTC-manufactured drug substance and drug product lots had consistently higher ADCC activity compared to early drug product lots of UTC material that were used in the analytical comparability assessment. This information prompted concern among the clinical, nonclinical, and quality review teams that the differences in ADCC activity could adversely affect the safety and tolerability of dinutuximab. In particular, there was a concern that increased ADCC activity could result in increased neuropathic effects such as severe pain, sensory neuropathy, and motor neuropathy. The wide variability in ADCC activity also raised concerns regarding process consistency. Review of the updated safety information submitted to the BLA did not result in identification of additional safety signals from use of dinutuximab provided by UTC to patients enrolled in Study 302 over the approximately one year time period covered by the information request. Overall, the toxicity profile of dinutuximab appears comparable to the toxicity profile of NCI-provided ch14.18. Additionally, analyses of these data did not uncover a trend for increased toxicity in

the dinutuximab lots with higher ADCC activity compared to the lots with lower ADCC activity. It is noted that these results, while supportive of the original safety analyses, are from a small number of patients exposed to a given lot of the antibody; therefore a PMR addressing this issue will be required.

The primary safety risks of dinutuximab identified during the safety review are infusion-related or allergic reactions, capillary leak syndrome, hypotension, systemic infection, neuropathy (that can manifest as severe pain or motor weakness), or neurological disorders of the eye such as impaired pupillary light reflex, photophobia, or visual impairment.

Deaths within 30 days of ch14.18 were relatively infrequent in light of the severity of the underlying disease and comorbidities of patients enrolled in the studies. The majority of deaths that occurred within 30 days of receipt of ch14.18 combination treatment (9/15 or 60%) were attributed to progressive disease, and it appears that attribution of deaths to progressive disease were unbiased and accurate. Of the deaths unrelated to disease progression, one death was due to inadvertent IL-2 overdose, and the remaining deaths appeared to be multifactorial in nature and confounded by other causes, including concomitant use of GM-CSF or IL-2, prior cytotoxic and myeloablative treatment, and underlying neuroblastoma. There were two deaths related to cardiac arrest: in the first case the patient died of cardiac arrest less than 24 hours following the first infusion of ch14.18. This case is potentially compatible with a severe infusion reaction or anaphylaxis, but there are insufficient details regarding the case to conclusively identify the cause of this patient's cardiac arrest. The second case of cardiac arrest is not compatible with an infusion reaction or anaphylaxis due to the long latency period from the patient's last treatment but there are insufficient details provided to enable a determination of causality.

In Study 301, all patients who received ch14.18 combination therapy (N=134) received premedication with acetaminophen, hydroxyzine or diphenhydramine, and morphine sulfate prior to the ch14.18 infusion. Severe [ $\geq$ Grade 3 using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)] hypersensitivity reactions occurred in 35 (26%) patients in the ch14.18 combination therapy group compared to one (1%) patient in the RA monotherapy group. In addition, anaphylaxis was reported as a serious adverse event in nine (7%) patients in the ch14.18 combination therapy group.

Severe capillary leak syndrome occurred in 31 (23%) patients in the ch14.18 combination therapy group, and in no patients in the RA group. Capillary leak syndrome was reported for Cycles 1 through 5, but occurred more commonly during the cycles containing IL-2 compared to the cycles containing GM-CSF. In Study 301, 22 (16%) patients treated with ch14.18 had

severe hypotension compared to no patients in the RA group. Sepsis was reported in 24 (18%) patients in the ch14.18 group, compared to 10 (9%) patients in the RA group. Additionally, severe bacteremia occurred in 17 (13%) patients in the ch14.18 combination group compared to five (5%) patients in the RA group.

In Study 301, for prevention and management of pain, all patients randomized to the ch14.18 combination arm received acetaminophen and morphine sulfate immediately prior to and during the ch14.18 infusion. Additional pain medications were administered as necessary. Despite use of analgesics, the majority (84%) of patients treated with ch14.18 experienced pain compared to 16% of patients in the control group. Severe pain occurred in 51% of patients in the ch14.18 combination treatment group compared to 5% of patients in the RA group.

Additionally, 3% of patients in the ch14.18 combination therapy group experienced severe peripheral neuropathy compared to no patients treated with RA alone. A total of 5% of patients in the ch14.18 combination group experienced neurological disorders of the eye (all graded as mild) compared to 3% of patients in the RA group.

Serious adverse events were common in the ch14.18 investigational treatment group; 51% of patients in the ch14.18 combination therapy group experienced at least one serious adverse event. The most common (per-patient incidence  $\geq 5\%$ ) serious adverse reactions were infections, pain, hypokalemia, hypotension, anaphylaxis, capillary leak syndrome, catheter-related infection, and fever.

The most common ( $\geq 10\%$  PPI) laboratory-related adverse events in the ch14.18 combination group were platelet disorder (i.e., decreased platelet count), lymphopenia, hyponatremia, increased alanine aminotransferase, decreased hemoglobin, hypokalemia, abnormal granulocytes, hypoalbuminemia, increased aspartate aminotransferase, hypocalcemia, hypophosphatemia, hyperglycemia, and hypertriglyceridemia and hypomagnesemia.

#### *Immunogenicity*

Preliminary data from Study 301 using an academic non-validated ELISA assay demonstrated 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, 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 two studies. These reported data are 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 UTC in the postmarketing period as a PMR.

## **9. Advisory Committee Meeting**

No advisory committee meeting was held to discuss this application because the application did not raise significant public health questions on the role of treatment with a biologic product for patients with high-risk neuroblastoma.

Two Special Government Employees (SGE) with expertise in pediatric oncology and one patient representative with oncology expertise were consulted for their opinions on this application. The consultants were cleared through the FDA clearance process. All consultants expressed definitive opinions that dinutuximab appeared to provide a treatment benefit to patients with high risk neuroblastoma, and that the risk/benefit assessment favors treatment of patients with high risk neuroblastoma with dinutuximab. Each of the consultants also indicated that the risks of dinutuximab treatment appeared to be acceptable for this patient population, given the life-threatening nature of the disease.

## **10. Pediatrics**

The development of dinutuximab for patients with high risk neuroblastoma was conducted entirely in a pediatric population. High risk neuroblastoma is a rare, life threatening cancer diagnosed in approximately 650 pediatric patients each year in the United States. The median age at diagnosis is 19 months, with 90% of patients diagnosed at less than 5 years of age. Dinutuximab has received an FDA designation as a drug for a “rare pediatric disease” (neuroblastoma) and has been granted the third priority review voucher issued by FDA under its Rare Pediatric Disease Priority Review Voucher Program. In addition, since ch14.18 has orphan drug status, it is exempt from the requirements of PREA and an appropriate waiver request is included in the application.

## **11. Other Relevant Regulatory Issues**

### *Debarment Certification*

The applicant and the National Cancer Institute provided certification that it did not and will not use in any capacity the services of any person debarred under sections 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act as related to the current application.

### *Financial Disclosures*

The Clinical Investigator Financial Disclosure Review Template was included in Dr. Donoghue’s primary clinical review. Her conclusions are as follows: “The applicant has

adequately disclosed financial interests/arrangements with clinical investigators, as recommended in FDA's February 2013 Guidance for Clinical Investigators, Industry, and FDA Staff, entitled Financial Disclosure by Clinical Investigators. In Form 3454, the applicant attests that the applicant has not entered into any financial arrangement with any of the listed clinical investigators for Study 201. In a subsequent submission to the BLA (May 19, 2014), the applicant clarified that this list comprised all clinical investigators and subinvestigators currently directly involved in the treatment or evaluation of research subjects in Study 201. The applicant also provided a comprehensive list of all the investigators either actively or previously involved in Study 201, who had no disclosable financial interests."

*Patent Exclusivity/Orphan Drug Exclusivity*

Chimeric monoclonal antibody 14.18 was granted orphan-drug status on December 20, 2010 (#10-3242) for the treatment of neuroblastoma. The applicant has certified that the requested indication for marketing authorization is consistent with the orphan-designation indication and claims that they qualify for a seven year period of market exclusivity.

*DSI audits*

The final classification for the primary site inspected, NCI/CTEP, was Voluntary Action Indicated (VAI) because while regulatory violations existed, they do not have a significant impact on data integrity or the rights, safety or welfare of subjects. A meeting will take place with NCI/CTEP to discuss the findings from the inspection prior to a final letter containing the findings is issued.

NCI/CTEP was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program. The inspectional findings suggest that NCI/CTEP has not maintained adequate oversight and control of their specific study over time. The violations are largely procedural, albeit required under 21 Title 312/314. Although the sponsor has not fully complied with the regulations, data submitted by the sponsor in support of this application appear reliable for use in support of the respective indication.

In addition to the above, four clinical sites were chosen for inspection based upon the number of patients enrolled in the randomized and non-randomized portions of the primary study supporting the application. Because of the large number of sites involved in the conduct of the trial, no single site was deemed likely to have influenced the efficacy results. A review of protocol deviations, study discontinuations, and incidence of serious adverse events did not uncover a signal to facilitate site selection.

*Letters of Authorization*

Appropriate letters of authorization were filed for DMFs [REDACTED] (b) (4) [REDACTED] as well as NCI IND 4308.

## **12. Labeling**

*Proprietary Name*

The proprietary name “Unituxin” was deemed acceptable by FDA on July 10, 2014.

*Physician Labeling*

As of the date of this review, labeling negotiations are being finalized. The most recent version of the working label was received by the applicant on February 12, 2015. A copy of that label is included with this review in Appendix A.

Of note since the label was received from the applicant, a case of hemolytic uremic syndrome (HUS) was received by Dr. Donoghue as an initial safety report. Based on this case and another known case that occurred in 2011 where a re-challenge and recurrence of HUS was documented, HUS will be added to the label with a recommendation that dinutuximab be discontinued if HUS develops. A full discussion of the cases can be found in the clinical review addendum filed by Dr. Donoghue.

*Carton and Container Labeling*

The carton and container labels for Unituxin™ (dinutuximab) were reviewed and found to comply with: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia, USP 37/NF 32 [12/1/14 – 4/30/15]. Initial labeling deficiencies were identified, mitigated, and resolved. The labels are acceptable.

## **13. Recommendations/Risk Benefit Assessment**

*Recommended Regulatory Actions*

1. Approval
2. Issuance of a Rare Pediatric Disease Priority Review Voucher

*Risk Benefit Assessment*

High-risk neuroblastoma is a serious and rare disease affecting pediatric patients. The median age at diagnosis is 19 months and 90% of patients are diagnosed with this disease at less than 5 years of age. There are no FDA-approved treatments for high-risk neuroblastoma and few for

neuroblastoma overall. About 50% of patients with high-risk disease eventually die as a result of their disease after initial treatment and relapse.

Dinutuximab is a first-in-class monoclonal antibody which binds to GD2, a glycolipid expressed on normal cells of neuroectodermal origin and neuroblastoma cells. The mechanism of action for the antibody is induction of cell lysis of GD2-expressing cells through antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

All review teams have recommended approval for BLA 125516 for dinutuximab (Unituxin) for the treatment of pediatric patients with high-risk neuroblastoma and I concur with their decisions. The recommendations for approval are based primarily upon the results of a single study, DIV-NB-301 (Study 301) demonstrating improvements in event-free survival and overall survival for patients who had achieved at least a partial response to prior standard multi-agent, multi-modality treatment.

Study 301 was an international, multicenter open-label randomized (1:1) trial comparing the ch14.18 antibody in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid (RA) to RA alone in 226 patients with newly diagnosed, high risk neuroblastoma. Eligible patients had completed intensive induction chemotherapy followed by autologous stem cell transplantation (ASCT) and radiation therapy, and achieved at least a partial response (PR). Patients were required to have adequate hematologic, hepatic, renal, cardiac, and pulmonary function and not be reliant on systemic corticosteroids or other immunosuppressants in order to be enrolled.

Randomization for Study 301 was stratified based upon objective response status (complete response vs. very good partial response vs. partial response) using the International Neuroblastoma Staging System (INSS) Response Evaluation Criteria and the treatment regimen received prior to enrollment. Randomization was balanced between the treatment arms for both demographics and baseline disease characteristics.

The primary efficacy outcome measure was EFS, defined as the first occurrence of relapse, disease progression, secondary malignancy, or death. Overall survival was the key secondary endpoint; however, the study was not powered to detect a statistical difference in overall survival between the study arms.

Interim analyses were planned and performed approximately every six months. At the seventh interim analysis, a numerical improvement in EFS [HR 0.57 (95% CI: 0.37, 0.89);  $p = 0.0115$ ,

unstratified log-rank test] was demonstrated. Median EFS was not reached in the ch14.18/RA arm and was 1.9 years in the RA arm.

Results for EFS using 2-year and 3-year data were supportive of the primary analysis of EFS. The 2 year EFS rates for the ch14.18/RA arm and RA arm respectively were 65.6% (56.1, 75.2) and 48.1% (38.0, 59.2), and the 3 year EFS rates for the ch14.18/RA arm and RA arm respectively were 62.9% (53.9, 71.7) and 50.9% (41.6, 60.2).

The primary OS analysis results were consistent with the numerical improvement in EFS with a HR of 0.52 (0.30, 0.92). Subsequent OS results at 2-years and 3-years were nearly identical to the primary analysis documenting a strong trend toward improvement in overall survival in patients randomized to the ch14.18 combination arm.

The main statistical/efficacy issue with this study is the termination of randomization to the RA alone arm based on the seventh interim analysis despite the fact that the observed p-value of 0.0115 did not cross the pre-specified alpha boundary of 0.0108. In addition, the OS analysis was not pre-specified and the trial was not powered for the OS endpoint.

Another shortcoming of the application was the lack of clinical data to isolate the treatment effect of dinutuximab from that of GM-CSF and IL-2. Though unfortunate, ultimately, the application contained insufficient clinical data to assess the relative contributions of GM-CSF and IL-2 to the observed results. This alone, however, is not a compelling reason for rejecting the approval of this application.

In considering whether the data from a single adequate and well-controlled trial support a finding of effectiveness for dinutuximab in this population of patients, one must determine if both the results of the trial are persuasive and if there are adequate scientific and legal bases for approval. The clinical reviewer investigated these questions thoroughly and concluded that while the results from this trial were not statistically robust, the primary EFS results supported by updated analyses and the OS analyses at similar time points were persuasive from both clinical and scientific perspectives. All of the aforementioned results corroborated the findings from the primary analysis of efficacy, thus strengthening the application overall. This argument is well-considered and sound and I am in full agreement with it. Additionally, when considering the evidence of effectiveness in this application as measured against controlling FDA statutes and regulations, the results appear to meet all such standards lending even further weight to the argument for approval. It must also be noted here that therapy with this antibody is already regarded as standard of care for this population of patients in the United States.

The risk evaluation for this product includes significant serious risks for patients treated with the multi-modality regimen in which dinutuximab is included. The primary safety risks identified are infusion-related or allergic reactions, capillary leak syndrome, hypotension, systemic infection, neuropathy, manifesting as severe pain or motor weakness or neurological disorders of the eye such as impaired pupillary light reflex, photophobia, or visual impairment. All patients who were treated with the antibody received premedication in an attempt to mitigate some of the known severe reactions associated with therapy. In spite of this, infusion reactions, capillary leak syndrome, hypotension and pain still occurred with relative frequency with pain reported in 84% and severe pain reported in 51% of patients treated. It is notable that some of these symptoms occurred more commonly during cycles of therapy containing IL2 as compared to cycles containing GM-CSF which may indicate a greater role for IL2 than dinutuximab as the causal agent for some of these symptoms. Serious adverse events were also common in patients treated with the antibody with 51% experiencing at least one serious adverse event during the trial. Deaths within 30 days of receiving the antibody were infrequent in light of the severity of the underlying disease and comorbidities of patients enrolled.

Given that high-risk neuroblastoma is a serious and rare pediatric cancer for which there is no FDA-approved treatment to date, that dinutuximab is regarded by the pediatric oncology community as standard of care when administered as part of a multi-modality treatment regimen, that primary efficacy results from an adequate and well-controlled trial support a finding of effectiveness (albeit of a numerical nature) for dinutuximab in this population of patients, that updated analyses from the clinical trials are supportive of the primary efficacy findings, that the clinical trial findings represent a clinically meaningful result for patients, and that the risks patients face, while serious, are well known to prescribers and are capable of being mitigated or managed, there is a favorable benefit: risk assessment for dinutuximab for the treatment of patients with high risk neuroblastoma.

*Recommendation for Postmarketing Risk Evaluation and Management Strategies*

No REMS is being recommended for dinutuximab in the postmarketing setting.

*Recommendation for other Postmarketing Requirements and Commitments*

*PMRs*

Postmarketing Requirements (PMR) are being imposed with the approval of Unituxin. Please see the action letter for this application for a complete list of the PMRs and the dates agreed to by the applicant for their completion. The issues for which PMRs are being imposed are discussed briefly below.

Because of the serious risk of neurologic toxicity, including sensory and motor neuropathy, and the differences in antibody dependent cell mediated cytotoxicity observed between ch14.18, the antibody utilized for the majority of patients in the clinical trials, and dinutuximab, the applicant will be required to evaluate any overall differences in safety between the products as well as assess and characterize the neurotoxicity observed.

In addition, because of the serious risk of hypersensitivity, including anaphylaxis, and the poor characterization of this toxicity in the data from clinical trials to date, a more thorough safety analysis to better characterize this adverse event will be required.

Lastly, to better characterize the immunogenicity associated with dinutuximab, an assessment of neutralizing antibodies response to dinutuximab and the clinical impact of the neutralizing antibody response will be required.

*PMCs*

In addition to the above PMRs, the following Postmarketing Commitments (PMCs) were made by the applicant:

1. To re-assess drug substance and drug product specifications based on additional clinical experience with material manufactured using the commercial process and/or additional characterization data on product critical quality attributes. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided.
2. To manufacture, qualify, and implement a new reference standard and enter the reference standard into a requalification program. The reference standard qualification and requalification protocols and the qualification report for the new reference standard will be submitted in a prior approval supplement.
3. To develop and validate a process-specific host cell protein (HCP) assay that has improved sensitivity and capability to detect a greater range of potential HCPs compared to the current assay and to implement this assay in the dinutuximab drug substance release program. The anti-HCP antiserum will be evaluated using two-dimensional SDS-PAGE and western blot analysis of proteins from the production cell line or a representative cell line for the determination of the percent of potential HCP impurities that are recognized by this antiserum. The analytical procedure, validation report, reproductions of an appropriately stained two-dimensional gel and the corresponding western blot, the analysis of the approximate percent of HCP coverage,

the proposed specification acceptance criterion, and the data used to set the acceptance criterion will be provided in a prior approval supplement.

4. To validate an assay for the detection of dinutuximab (b) (4) and implement this assay in the drug substance and drug product release and stability specifications. The analytical procedure, validation report, the proposed specification acceptance criterion, and the data used to set the acceptance criterion will be provided in a prior approval supplement.
5. To establish and qualify a Working Cell Bank (WCB) to be used for production of dinutuximab. Qualification of the WCB will include safety testing, an evaluation of the growth of WCB cultures relative to the growth of Master Cell Bank (MCB) cultures, testing of end of production cells generated from the commercial scale process, and a comparability assessment that includes the first three lots manufactured from the WCB using the commercial process. One lot manufactured using the commercial process will be placed on a stability protocol, and the data will be provided in the subsequent BLA annual reports. The WCB qualification report will be provided in a prior approval supplement.
6. To provide additional studies to confirm the monoclonality of the Master Cell Bank.
7. To perform validation studies to confirm acceptable product quality and shipper performance during shipping of dinutuximab drug product. This should include consideration for worst case shipping routes, including routes to testing sites. The study will include monitoring of temperature during the shipment, testing of pre- and post-shipment samples for drug product quality [e.g., opalescence, protein concentration, purity by SEC-HPLC, cSDS (reduced and non-reduced), cIEF, WCX, sub-visible particulates, and potency of dinutuximab], and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.
8. To perform a leachable study of drug product through the end of shelf-life under recommended storage conditions. Testing will be performed at 0, 3, 6, 12, 24, and 36 month time points. This should include consideration for the detection of extractables observed in drug substance and drug product extractable studies. The analysis of leachables should include organic nonvolatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semivolatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Study results will be updated annually in the BLA Annual Report.

9. To verify (b) (4) lifetimes at commercial scale using a validation protocol to evaluate (b) (4) capability and cleaning procedures throughout the intended lifetime of the (b) (4).
10. To further investigate the root cause for the (b) (4) observed in drug product stored under recommended conditions and to perform a risk assessment based on the root cause, the levels of (b) (4) observed, and the potential effects on safety and efficacy of dinutuximab. Appropriate corrective and preventative actions will be implemented based on the results of the root cause investigation and risk assessment. The root cause investigation and risk assessment reports and proposed corrective and preventive actions will be provided as a prior approval supplement.
11. To confirm validation of the SEC-HPLC assay. Validation reports will be updated to include evaluations of accuracy, precision, specificity, quantitation limit, linearity and range with respect to the purity and the product related impurities included in the final drug substance and drug product release and stability specifications.
12. To confirm validation of the cSDS reduced assay. Validation reports will be updated to include evaluations of accuracy, precision, specificity, quantitation limit, linearity and range with respect to the purity and the product related impurities included in the final DS and DP release and stability specifications.
13. To confirm validation of the cSDS non-reduced assay. Validation reports will be updated to include evaluations of accuracy, precision, specificity, quantitation limit, linearity and range with respect to the purity and the product related impurities included in the final DS and DP release and stability specifications.
14. To confirm validation of the cIEF assay. Validation reports will be updated to include evaluations of accuracy, precision, specificity, quantitation limit, linearity and range with respect to the purity and the product related impurities included in the final drug substance and drug product release and stability specifications.
15. To develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against dinutuximab in the presence of dinutuximab levels that are expected to be present in samples at the time of patient sampling. The validation report should be provided in a Prior Approval Supplement.
16. To develop, validate/qualify and implement an osmolality assay for the drug product release specifications. The analytical procedure, qualification report, proposed

- acceptance criterion, and data used to set the proposed acceptance criterion should be provided as a Changes Being Effected in 30 Days (CBE-30) supplement.
17. To confirm compatibility of drug product with IV bags and IV administration sets of different materials of construction. The compatibility study will include monitoring samples for protein concentration, purity by SEC-HPLC, cIEF, sub-visible particulates, and potency. The final report will be submitted as a Prior Approval Supplement.
  18. To confirm compatibility of the drug product with the use of an in-line filter during administration. These studies will include monitoring samples for protein concentration, purity by SEC-HPLC, cIEF, sub-visible particulates, and potency. The final report will be submitted as a Prior Approval Supplement.
  19. To re-evaluate dinutuximab drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis, and the statistical plan used to evaluate the specifications, and any proposed changes to the specifications.
  20. To re-evaluate dinutuximab drug product lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis, and the statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final report
  21. To determine whether endotoxin masking occurs in vivo, conduct a comparison study between the LAL kinetic chromogenic test and the rabbit pyrogen test for drug product that has been spiked with an endotoxin standard and then held prior to testing.
  22. Conduct studies to understand the mechanism of endotoxin masking in the drug product. Explore alternative test methods and develop a more suitable endotoxin release test for the drug product.
  23. Validate the dye ingress test using dinutuximab drug product vials. The validation study should identify the range of breach sizes detectable by the assay. The positive control used for the dye ingress test should be based on the validation study data.

24. Conduct the bioburden method qualification studies for the [REDACTED] (b) (4) [REDACTED] using 2 additional batches and for the bulk drug substance using 3 different drug substance lots and submit the results.
25. Submit the final established [REDACTED] (b) (4) [REDACTED] after trending the data from 10 drug substance batches.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUZANNE G DEMKO  
03/06/2015