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RESEARCH**

APPLICATION NUMBER:

125516Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	March 9, 2015
From	Patricia Keegan
Subject	Division Director Summary Review
BLA #	STN BL 125516
Applicant Name	United Therapeutic Corporation
Date of Submission	April 11, 2014
Date(s) of Major Amendment	November 14, 17, and 21, 2014
PDUFA Goal Date	March 10, 2015
Proprietary Name / Established (USAN) Name	Unituxin injection/ dinutuximab
Dosage Forms / Strength	Injection for intravenous use/ 17.5 mg/5 mL (3.5 mg/mL) solution in a single-use vial
Proposed Indication(s)	UNITUXIN (dinutuximab) is indicated for high-risk neuroblastoma (b) (4) treatment, in combination with granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin 2 (IL-2), and isotretinoin (RA)
Recommended Action for NME:	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Regulatory Project Manager Review	Gina Davis
Medical Officer Review	Martha Donoghue
Statistical Review	Sirisha Mushti
Pharmacology Toxicology Review	Dubravka Kufrin
OBP Reviews	Chikako Torigoe, & Jibril Abdus-Samad
CMC Microbiology Review	Lakshmi Narasimhan & Colleen Thomas,
Clinical Pharmacology Review	Jingyu Yu
OPDP	Carole Broadnax
OSI	Lauren Iacono-Connor
CDTL Review	Suzanne Demko
OSE/DMEPA	Otto Townsend
OSE/DRISK	Naomi Redd
ODE IV/ DPMH Consults	Erica Wynn & Carol H. Kastan

OND=Office of New Drugs
 OBP=Office of Biotechnology Product
 CDTL=Cross-Discipline Team Leader
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management
 ODE IV= Office of Drug Evaluation IVDPMH=Division of Pediatric and Maternal Health

Division Director Summary Review

1. Introduction

Unituxin (dinutuximab) is a chimeric monoclonal antibody composed of murine variable heavy and light chain regions and the human constant region for the heavy chain IgG1 and light chain kappa. Dinutuximab binds specifically to the GD2 disialoganglioside, which is expressed in both benign (neural tissues in the central nervous system tissues and peripheral nerves) and malignant tissues (neuroblastoma) of neuroectodermal origin.

The safety and efficacy of dinutuximab were evaluated in a randomized (1:1) cohort of a single, open-label, multicenter clinical trial conducted in pediatric patients with high risk neuroblastoma. Randomization was stratified by the protocol for initial therapy and, where purging of autologous cells was permitted, for administration of purged vs. unpurged autologous stem cells. Eligible patients were those who had achieved significant tumor reduction following a multi-agent chemotherapy regimen, including myeloablative chemotherapy but prior to autologous stem cell rescue on one of several protocols for first-line treatment of high-risk neuroblastoma conducted by the Children's Oncology Group (COG) or its predecessors (the Pediatric Oncology Group (POG) and the Children's Cancer Group (CCG)). In addition, all patients were required to have evidence of adequate pulmonary and cardiac function by appropriate physiologic testing as well as adequate renal and hepatic function. Within 50 to 100 days following myeloablative therapy with autologous stem cell rescue, with or without radiotherapy to sites of disease, patients were randomly assigned to investigational treatment [dinutuximab for five of six planned treatment cycles, in combination with retinoic acid and interleukin-2 (IL-2) in cycles 1, 3, and 5, with granulocyte-macrophage colony stimulating factor (GM-CSF) in cycles 2 and 4, and RA alone in the sixth cycle] or to control treatment with RA alone for six cycles. Patients with biopsy proven residual disease after myeloablative chemotherapy with autologous stem cell rescue were non-randomly assigned to the experimental regimen. The primary objective of the trial was to demonstrate superior event-free survival, defined as time from randomization to relapse or death, for those randomized to the dinutuximab-containing arm as compared retinoic acid alone. Overall survival was the key secondary objective.

A total of 226 patients with minimal residual disease were randomized; 113 patients to experimental therapy and 113 to the control arm. The study population had slight male predominance (60% male) with a median age of 3.8 years; 3% of patients were less than 18 months, 82% were White and 7% were Black. Most (80%) had International Neuroblastoma Staging System Stage 4 disease. Forty-six percent of patients had neuroblastoma that was not MYCN-amplified, 36% had tumors with known MYCN-amplification, and MYCN status was unknown or missing in 19% of patients. Forty-three percent of patients had hyperdiploid tumors, 36% had diploid tumors, and DNA ploidy status was unknown or missing in 21% of patients. The response to initial chemotherapy consisted of 35% complete response rate, 43% very good partial response, and 23% partial response.

The study was terminated prematurely, after accrual of 226 of the planned 386 patients, at the recommendation of the Data Safety Monitoring Board who determined that the boundary for EFS was crossed at the 7th interim analysis.

The trial demonstrated an improvement in EFS of 42% (HR 0.57 (0.37, 0.89), p=0.01]; the estimated median event free-survival had not been reached in the dinutuximab-containing arm and was estimated to be 1.9 years in the control arm. An interim analysis of overall survival was conducted at the time of the final analysis of EFS. In addition, an updated analysis of overall survival was conducted three years after the interim analysis, corresponding to the time when all patients would be evaluable for 3-year survival rates, which demonstrated an improvement in overall survival [HR 0.58 (0.37, 0.91)], favoring the dinutuximab arm.

Dinutuximab, when administered according to the package insert and with optimal medical management which includes intravenous hydration and concomitant medications (intravenous morphine infusion, antipyretics, and an antihistamines) administered prior to, during, and for up to several hours after completion of dinutuximab infusion over 20 hours, is a toxic regimen requiring administration in a hospital setting for management of dinutuximab-induced pain. In addition, careful patient selection based on adequate end-organ function and monitoring in a hospital/acute care setting are required to mitigate the risks and potential for death due to the potential serious risks of serious infusion reactions, capillary leak syndrome, and hypotension. Additional serious risks of dinutuximab, which require careful monitoring of vital signs and laboratory parameters, are the increased risk of infection, neurological disorders of the eye, bone marrow suppression, electrolyte abnormalities, and atypical hemolytic uremic syndrome. Approximately one-quarter of patients could not complete the planned treatment course.

Unituxin labeling includes a Boxed Warning for serious infusion reactions and for neuropathic pain and peripheral neuropathy as well as a Contraindication for use in patients with a history of anaphylaxis to dinutuximab. Since severe, and potentially irreversible, motor neuropathy was identified in adults with melanoma participating in dose-finding, safety and tolerability studies, the approved indication will be limited to pediatric patients. The most common severe and life-threatening (NCI CTCAE Grade 3 or 5) adverse reactions of dinutuximab are neuropathic pain (51%), pyrexia (40%), infusion-related reactions, which may include true hypersensitivity reactions (25%), capillary leak syndrome (23%), hypotension (16%), sepsis (16%), device-related infection (16%), diarrhea (13%), urticaria (13%) and hypoxia (12%).

All review disciplines have recommended approval of this application, given the serious nature of the disease and lack of effective alternative therapies. The need for a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use of dinutuximab was discussed by the review team and consultants. Since the medical management of patients with high-risk neuroblastoma is limited to pediatric oncologists at tertiary or specialized medical centers and these specialists are familiar with the risks of dinutuximab and there has been extensive experience gleaned through the expanded access program which enrolled more than 750 patients, the review team agreed that a REMS was not required.

Issues considered:

- The robustness of the results, in light of the multiple interim analyses, in a single trial supportive approval, which is discussed in greater detail in Section 7 of this review

- The limitations of the study design to isolate the contribution of IL-2 and GM-CSF, which is discussed in greater detail in Section 7 of this review
- The change in product characteristics (increased ADCC) in recent lots of UTC-manufactured dinutuximab, which is discussed in greater detail in Sections 3 and 8 of this review

2. Background

Proposed Indication and Available Therapy

Neuroblastoma is a cancer of the sympathetic nervous system, most commonly arising in neural tissue within the adrenal glands, but may also arise in the paraspinal ganglia in the abdomen, chest, and spinal cord. Neuroblastoma is slightly more common in boys, and occurs in approximately 1 out of 100,000 children. Approximately 90% of patients are diagnosed under age 5 years and the median age at diagnosis is 19 months.¹ There were an estimated 600 to 700 new cases of neuroblastoma in the United States in 2014.²

The prognosis of patients with advanced stage neuroblastoma (International Neuroblastoma Staging System (INSS) stage 4 disease) is dependent on age at diagnosis and other prognostic factors (e.g., MYCN amplification), with a 5-year disease-free survival rate of 50%–80% in children diagnosed before 18 months of age and 3% in children/young adult patients between 10 and 21 years of age.³

FDA-approved drugs for treatment of neuroblastoma

Cyclophosphamide, injection was approved on November 16, 1959. It is FDA-approved for the treatment of neuroblastoma. The basis for approval is not clearly stated in the labeling, which stated that neuroblastoma is one of several cancers that “are often susceptible to cyclophosphamide treatment.”

Doxorubicin Hydrochloride was approved on December 23, 1987. It is FDA-approved for the treatment of neuroblastoma. The basis for approval is not described in product labeling, which stated that “doxorubicin hydrochloride has been used successfully to produce regression in disseminated neoplastic conditions such as neuroblastoma.”

Vincasar PFS (vincristine sulfate PFS) was approved on July 17, 1987. It is FDA-approved for the treatment of neuroblastoma. The basis for approval is not described in product labeling, which states vincristine sulfate injection has been shown to be useful in combination with other oncolytic agents in neuroblastoma.

¹ London WB, Castleberry RP, Matthay KK, et al.: Evidence for an age cutoff greater than 365 days for neuroblastoma risk group stratification in the Children's Oncology Group. *J Clin Oncol* 23 (27): 6459-65, 2005.

² <http://www.cancer.org/cancer/neuroblastoma/detailedguide/neuroblastoma-key-statistics>. accessed February 28, 2015.

³ http://www.cancer.gov/cancertopics/pdq/treatment/neuroblastoma/HealthProfessional/page1#section_1.7. Accessed on February 29, 2015.

Clinical Practice Guidelines – Neuroblastoma Treatment (PDQ)⁴

- 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) supported by autologous stem cell rescue
- Radiation to the primary tumor site and metaiodobenzylguanidine (MIBG)-positive bony metastatic sites, either before, during or after myeloablative therapy
- For patients who achieve a partial, very good partial, or complete response to induction chemotherapy, six cycles of “maintenance therapy” with chimeric 14.18 in combination with GM-CSF, IL-2, and RA.

Pre-submission Regulatory History

December 4, 1991: IND 4308 submitted. The DCTD, NCI, has sponsored five phase 1 studies, one phase 2 study, and one phase 3 study with ch14.18 either as a single agent (B89-0005) or in combination with other agents/therapeutic modalities (Studies B90-0014, B93-0009, A0935A, B94-0002, POG-9347, ANBL0032).

October 2001: Initiation of Study ANBL0032, entitled “Phase III randomized study of chimeric anti-GD2 in high risk neuroblastoma following Myeloablative therapy and autologous stem cell rescue, a Children's Oncology Group Study”

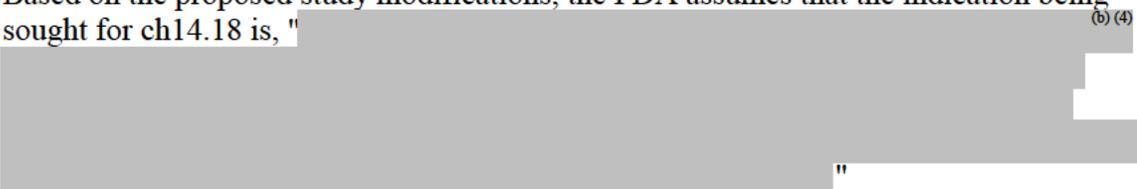
May 6, 2004, meeting:

- FDA recommended that once a new manufacturing facility (currently manufactured at SAIC) is identified, a biochemical comparability study should be performed comparing the SAIC material and material from the new facility.
- In response to an inquiry about toxicology data from animal models, NCI noted that there exists published data from syngeneic mice, although, in many cases, study drug was administered with cytokines. FDA requested that a list of published studies be provided.
- FDA stated, concerning assessment of the contribution of each component of the combination therapy (ch14.18, IL-2, and GM-CSF), that data establishing the contribution of each component need not be obtained in this protocol. Such data, however, must be provided in the license application. Nonclinical data may be used if compelling. FDA recommends that the plan for determination of the contribution of each component of this regimen be submitted to FDA for review.
- NCI proposed to explore ways of providing supportive evidence of efficacy. Possibilities include demonstration of significant treatment effects on secondary endpoints in this study and efficacy data from other studies.

⁴ Neuroblastoma Treatment (PDQ®), “Treatment Option Overview for Neuroblastoma” at <http://www.cancer.gov/cancertopics/pdq/treatment/neuroblastoma/HealthProfessional/page4#Reference4.8>. Accessed on May 23, 2014.

- The statistical analysis plan (SAP) would be revised to utilize two-sided tests for significance.

September 1, 2005 meeting with representatives from the NCI CTEP and COG

- Based on the proposed study modifications, the FDA assumes that the indication being sought for ch14.18 is, "" ^{(b) (4)}
- FDA stated that the inclusion of patients treated on the successor high risk neuroblastoma study, ANBL0532, is acceptable providing that the ANBL0032 study achieves the primary efficacy objective (increase in EFS), and that the treatment effect is robust and consistent across subgroups. Subgroup analyses of patients receiving purged and receiving unpurged stem cells, patients treated with A3973-type induction, patients treated with ANBL0532 induction, patients treated with one transplant, and patients treated with 2 transplants should have point estimates consistent with ITT analysis and the overall results should not be substantially impacted by a single subgroup. FDA clarified that the magnitude of effect [improvement in EFS (event-free survival)] may differ between with subgroups, defined by prior treatment, but the treatment effect should be in the same direction in each of the subgroups. FDA also advised that the study should not be powered on the groups, but should be powered on the study as a whole.
- NCI confirmed that they have not identified a commercial manufacturer for this product.
- With regard to published literature describing toxicology studies for ch14.18 administered with cytokines, FDA stated that studies supporting the application, especially those isolating the effect of ch14.18 are of particular interest. A separate meeting between NCI and FDA to discuss the toxicology data that are currently available and to identify which additional studies are needed to support an application.
- NCI agreed to provide the detailed methodology for the RT-PCR assay used to detect minimal residual disease (MRD) and planned analysis of the data. NCI noted that no data are yet available on MRD evaluations in ongoing trials.
- FDA noted that justification for use of EFS as a surrogate for overall survival would be needed to support a request for accelerated approval. Alternatively, a request for regular approval based on the contention that an improvement in EFS, by itself, is direct evidence of clinical benefit may be made. Since there is no precedent regarding EFS as a measure of clinical benefit, FDA would likely seek the advice of an Advisory Committee.
- With regard to a plan for assessing the contribution of each component of the combination therapy (ch14.18, IL-2, and GM-CSF), as discussed during the May 6, 2004 meeting, NCI stated that they have not established or provided such a plan to FDA. Once developed, the proposed approach would be submitted to FDA for comment. FDA stated determining the contribution of each component alone, constitute a very important part of a complete license application.
- FDA stated that data on the incidence and type of immune response to ch14.18 and its impact the safety, efficacy and pharmacokinetic profile of ch14.18 should be provided noting that NCI reported that "Human anti-chimeric antibody developed in 28% of patients" exposed to ch14.18 in association with GM-CSF" (JCO 2000; 18:4077). If drug is

present when samples are obtained, the assay should be validated to show that the presence of circulating ch14.18 will not interfere with the results of the assay. NCI confirmed that the last sampling time point for immune responses at day 55 occurred beyond 5 half-lives after the last dose. NCI agreed to submit a detailed description of the immunogenicity testing in study ANBL0032, a detailed description of the assay methods to detect binding and neutralizing antibodies directed against ch14.18 and assay qualification data to FDA to the IND.

April 3, 2009 letter advising the NCI to provide access via a new protocol; the specific objective of this protocol should be to obtain comprehensive safety information to support a license application for ch14.18 plus cytokines to replace Protocol ANBL0032. FDA further stated that, in support of a license application, complete safety data should be collected from a minimum of 100 patients. Safety data obtained should include the collection of all adverse events regardless of grade, and documentation of all concomitant medications the patient received. Adverse event collection should include: dosing at time of adverse event, dosing prior to event (if different), start and stop dates for adverse events, days on study drug at time of event, outcome of event (e.g. ongoing, resolved, led to discontinuation), whether or not the event occurred within 30 days of discontinuation of active treatment, identification of all serious adverse events, and collection of verbatim terms for adverse events.

December 20, 2010, letter granted Orphan Drug Designation for ch14.18 for the treatment of neuroblastoma.

January 27, 2011, pre-IND (pIND 110494)/pre-BLA meeting held. The objectives of the meeting were to discuss (1) the eventual transfer of manufacturing responsibility from NCI to United Therapeutics Corp (UTC) to support on-going and (2) UTC's intended approach to the manufacturing of ch14.18, including planned process changes and future plans to demonstrate material comparability between ch14.18 produced by NCI and ch14.18 produced by UTC.

- FDA generally agreed to the proposed approach to demonstrate analytical comparability for the technology transfer from NCI to UTC in support of an IND.
- FDA stated that the need for additional nonclinical bridging studies in a pharmacologically relevant species will be dependent on the assessment of the analytical comparability data. FDA asked that UTC provide information to justify that there is no relevant pharmacological animal species in which to conduct toxicology or DART testing. Alternative approaches to conducting DART testing for ch14.18 may be acceptable but would be based on information submitted.
- FDA agreed that Study ANBL0032 could serve as the single trial intended to demonstrate the safety and effectiveness of dinutuximab, in combination with IL-2, GM-CSF, and cis-RA, for the treatment of patients with high-risk neuroblastoma who had minimal residual disease following standard therapy (e.g., as in Study A3973).
- The BLA should contain the study reports for the proposed pharmacokinetic comparability protocol comparing NCI and UTD-sourced ch14.18 and study reports for all trials of dinutuximab under IND 4308.

- Since adequate evaluation of dinutuximab effects on QTc had not been obtained in completed or nearly completed clinical trials, this information should be collected in future trials.

March 9, 2012: IND 110494, sponsored by United Therapeutics, Corp. submitted

February 19, 2014 preBLA meeting held. Key discussion items included

- The need to provide data to establish the contribution of each therapeutic component (dinutuximab, IL-2, and GM-CSF). UTC agreed to provide published literature and clinical study data.
- FDA stated that consistency of efficacy across key patient subsets is an important factor in determining whether the single adequate and well-controlled study provides substantial evidence of effectiveness.

BLA Submission History

April 11, 2014: BLA submitted

December 7, 2014 letter, extending the review due to receipt of a major amendment received across multiple submissions (November 14, 17, and 21, 2014), responding to information requests for CMC and clinical safety information regarding recently manufactured lots of dinutuximab with high ADCC levels.

January 7, February 11, 12, and 23, 2015: Additional CMC data submitted to the BLA.

December 15, 2014, February 16 and 20, 2015: Additional clinical data submitted to the BLA.

3. Chemistry, Manufacturing, and Controls (CMC)

I concur with the conclusions reached by the quality review team regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 18 months from the date of manufacture when stored at 2°C to 8°C (36° - 46° F). There are no outstanding issues which preclude approval.

The protein content determination for dinutuximab manufactured by NCI/SAIC was measured using the wrong extinction coefficient for absorbance. Therefore the apparent differences in dosing in the clinical trials conducted with NCI-sourced material and UTC-sourced material are not true differences but reflect a change to a more accurate calculation of protein content in the UTC product.

Analytical comparability between the NCI-manufactured dinutuximab and the initial lots of UTC-manufactured dinutuximab supported extrapolation of safety and efficacy in Study ANBL0032 (DIV-NB-301 and DIV-NB-302) to the UTC product for commercial marketing.

However, during review of the BLA, it was noted the ADCC activity of dinutuximab manufactured by UTC had greater variability, with later lots having two-fold higher ADCC activity than earlier lots, which were used to establish the safety of dinutuximab in Study DIV-NB-303. Based on this observed difference, additional CMC and manufacturing information were requested during review. The submission of these additional data was deemed a major amendment, extending the review clock. Review of the CMC data did not identify additional analytical differences between the NCI- and UTC-sourced products. As discussed in Section 8 of this review, the adverse drug reaction profile with the “high-ADCC” lots of UTC-manufactured dinutuximab did not identify new safety signals.

As stated in the CMC review, based on the totality of the information in the BLA, “the data submitted in this Biologics License Application support the conclusion that the manufacture of Unituxin™ (dinutuximab) is well controlled, and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from the multiple production runs presented.”

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

The nonclinical pharmacology and toxicology information is supported by published literature references, tissue-cross reactivity studies with normal human, rat, and rabbit tissues, a limited safety pharmacology study, and a short-term (28-day) toxicology study in rats.

The mechanism of action of dinutuximab, through specific binding to the GD2 antigen on normal and malignant human cells which results in complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC), is adequately supported by published literature. This published literature describes *in vitro* and *in vivo*, non-clinical studies conducted with ch14.18 manufactured by the National Cancer Institute, and with the related products, murine 14.18 (m14.18, the parent compound from which the variable region of ch14.18 was derived) and the murine IgG2a isotype switch variant of m14.18 (14. G2a). The non-clinical information from these related molecules is relevant since the variable regions, binding affinity, and antibody-mediated cell cytotoxicity are very similar.

The data supporting the contribution of cytokines, specifically, with IL-2 (interleukin-2) or GM-CSF (granulocyte colony stimulating factor) to dinutuximab is based on *in vitro* experiments demonstrating that the addition of IL-2 or GM-CSF to dinutuximab resulted in an increase in antibody-dependent cellular cytotoxicity (ADCC) of dinutuximab against GD2-expressing cells. In dose-finding studies, ADCC appeared to be increased in adults with melanoma received GM-CSF or IL-2 in combination with dinutuximab. However the clinical relevance of these findings remains unclear.

The BLA contained the results of a single 28-day repeat-dose toxicology study in Sprague-Dawley rats. Animals in this study showed signs of developing a strong anti-drug antibody response, suggesting that longer term chronic toxicology studies in rats would be of limited value. The liver was identified as a potential target organ with increases in liver weight, mild increases in AST, ALT, and cholesterol along with minimal microscopic findings of hepatocellular necrosis, peri-central vein/interlobular fibrosis, and centri-lobular congestion. The majority of changes in the rats demonstrated evidence of reversibility within a 6 week recovery period. Though there were no histopathological indications of an effect of dinutuximab on peripheral nerves in this study, ch14.18 has been shown to bind to GD2 in rats. Literature reports of studies submitted to this BLA showed decreases in mechanical pain threshold in rats indicating that the rat was a relevant species for toxicology studies.

Normal tissue cross-reactivity studies demonstrated GD2-specific antibody binding to peripheral nerves across multiple species. Non-clinical studies confirmed evidence of neurologic effects. In rats treated with dinutuximab or related anti-GD2 antibodies, a decreased mechanical pain threshold was consistently demonstrated with persistence up to 48 hours after the last dose of an anti-GD2 antibody. A safety pharmacology study, limited to cardiovascular and respiratory parameters, was conducted in cynomolgus monkeys. Increased heart rate and blood pressure were observed, but no respiratory findings note and no evidence of prolongation of QTc.

Based on the median age of the proposed patient population (90% of patients less than 5 years of age), the Agency agreed that reproductive and developmental toxicology studies would not be required to support the BLA for dinutuximab for the treatment of high risk neuroblastoma. If, in the future, UTC wishes to pursue an additional indication for dinutuximab, reproductive toxicology studies may be required. Dinutuximab is not indicated for females of reproductive potential. Based on its mechanism of action, ADCC-mediated and CDC-mediated lysis of GD2-expressing cells, and the ability of IgG1 antibodies to cross the placental barrier, dinutuximab may cause fetal harm. Pregnancy Category D is recommended.

In order to gain a clearer understanding of dinutuximab toxicity, particularly of the potential for recovery of damage to peripheral nerves, UTC must conduct a 13-week GLP-compliant toxicology study to evaluate neurotoxicity under a 505(o) post-marketing requirement.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

The dose selected for study in DIV-NB-301 was based on the maximum tolerated dose of dinutuximab, when administered in combination with RA and GM-CSF RA and IL-2, in a single trial, Study CCG -0935A. Since pharmacokinetic samples were not obtained in StudyDIV-NB-301 or DIV-NB-302, exposure response relationships for efficacy or for toxicity could not be conducted to further investigate the optimal dose of dinutuximab.

In order to support extrapolation of the safety and efficacy data obtained with the NCI-sourced dinutuximab in Study DIV-NB-301 to the UTC-manufactured product, UTC conducted Study DIV-NB-201, entitled "A Comparative Pharmacokinetic and Safety Study of Chimeric Monoclonal Antibody ch14.18 with Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), Interleukin-2 (IL-2) and Isotretinoin in High Risk Neuroblastoma Patients Following Myeloablative Therapy," under their IND 110494. Study DIV-NB-201 was a multi-center, randomized, open-label, two-sequence, cross-over, comparative pharmacokinetic (PK) and safety study. The trial was conducted in 28 patients with high-risk neuroblastoma who met the eligibility criteria for Study DIV-NB-301 and who received the same treatment regimen as the experimental arm of Study DIV-NB-301. Following completion of induction chemotherapy and myeloablative therapy with autologous stem cell rescue, patients were randomly assigned to one of the two treatment sequences

- UTC-manufactured dinutuximab Cycles 1 & 2 → NCI-manufactured dinutuximab Cycles 3-5
- NCI-manufactured dinutuximab in Cycles 1 & 2 → UTC-manufactured dinutuximab Cycles 3-5

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).

The pharmacokinetic profile of dinutuximab was characterized in a population pharmacokinetic (popPK) analysis with data from 36 patients enrolled in Study DIV-NB-302 (n=9) and study DIV-NB-201 (n=27). Based on this analysis, the terminal half-life was estimated to be 10 days. There was insufficient data to allow an evaluation of the PK with chronic dosing; however treatment is limited to 5 cycles. There was insufficient data to evaluate the effect of intrinsic factors, such as age, gender, race, weight, underlying disease, and organ dysfunction, on exposure.

Mass balance and metabolism studies were not performed; such studies are not generally performed for proteins which are catabolized into amino acids. Drug interaction studies for dinutuximab and GM-CSF or IL-2 or RA were not performed, however the potential for interactions is considered to be low for dinutuximab, as with other monoclonal antibodies.

The incidence of anti-drug antibodies (ADA) to dinutuximab was evaluated in 414 patients enrolled in Studies DIV-NB-302, DIV-NB-303, and DIV-NB-201 using analytically validated assays, which demonstrated a 20% (83/414) incidence of binding antibodies and 4% (15/414) incidence of neutralizing antibodies to dinutuximab; these included 11 patients with evidence of ADA prior to dinutuximab dosing.

Based on the CMC reviewer's determination that the neutralizing antibody (NAb) assay was insensitive, and the risks of immunogenicity which is expected to be greater for this chimeric product than for a fully human monoclonal antibody, the clinical pharmacology team and CMC have required development of a new assay, with analysis of all available samples from Studies ANBL0032 [DIV-NB-301 or DIV-NB-302], DIV-NB-303, DIV-NB-201, and other

studies under IND4308 to accurately determine the risks of anti-product antibodies and their effects, if any, on safety and efficacy of dinutuximab in a post-marketing requirement under the provisions of 505(o).

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

October 28, 2001: COG Protocol ANBL0032 (later referred to as Study DIV-NB-301 during the two cohort/randomization phase and referred to as Study DIV-NB-302 after termination of randomization, when the study served as a single arm expanded access protocol) was activated. There were 14 amendments to the protocol between 2001 and 2009.

March 12, 2004:

- Increased the sample size from 322 to 386 patients and increase number of EFS events from 115 to 137 to allow for testing of EFS at an overall one-sided 0.025 significance level.
- Revised study endpoints from co-primary endpoints of EFS and OS to EFS as the sole primary endpoint and OS as a key secondary endpoint.

May 30, 2008 submission to IND 4308 containing protocol amendments, including

- Expanded eligibility to allowed patients who had achieved a response on the successor protocol to Study A3973 (ANBL0532)
- Number of required MRD determinations decreased from 3 to 2

September 24, 2008: NCI submitted a response to comments made during the May 6, 2004 meeting, the letters dated May 30, 2006 and August 8, 2006, that the primary analysis plan should have a one-sided type I error rate of at most 0.025, when ignoring futility boundary and to clarify how this requirement will be maintained in the interim analysis plan. NCI stated that monitoring of the EFS rate of randomized patients was conducted per the methods of O'Brien-Fleming, once 20% of the expected events were observed. NCI further stated that the last three interim monitoring looks (starting in the summer of 2007) were performed so the cumulative alpha level at the final analysis will be 0.025, two-sided. The protocol would be amended to state that the DSMB (Data Safety Monitoring Board) would recommend the action to be taken to the Group Chair if the efficacy boundary was crossed.

February 20, 2009: NCI contacted FDA to inform them the trial was reviewed by the DSMB after 61% of the planned patients were accrued with 83 (of the planned 137) EFS events. Based on this interim analysis, the DSMB recommended termination of randomization and release of study results.

April 16, 2009:

- Protocol was amended to terminate randomization and allowed patients in the RA arm to receive investigational therapy.
- Added new secondary objectives
- Expanded eligibility to patients with residual disease

Study Design

This was an open-label, multicenter, parallel cohort trial.

- The main cohort randomized and non-randomized trial evaluating the safety and effectiveness of ch14.18 in combination with GM-CSF, IL-2 and isotretinoin to isotretinoin alone for treatment of patients with high-risk neuroblastoma with minimal residual disease following cytoreductive, induction chemotherapy and myeloablative chemotherapy with a partial response or better prior to autologous stem cell support, and radiotherapy on either COG Study A3973, COG Study ANBL 0532, or COG Study ANBL00B1.
- Patients with biopsy-proven residual disease after autologous stem-cell transplantation were non-randomly assigned to receive the experimental regimen only.

The primary objective was to determine if ch14.18 (dinutuximab) administered in combination with cytokines and 13-cis-retinoic acid (RA) improves event-free survival (EFS) as compared to RA alone in patients with high-risk neuroblastoma who achieved a complete response (CR), very good partial response (VGPR), or partial response (PR) following induction chemotherapy and myeloablative therapy but prior to stem cell rescue.

Secondary objectives were to determine if ch14.18, in combination with cytokines and RA

- Improves overall survival (OS) in the intent-to-treat (ITT; all-randomized) population
- Improves EFS and OS in the subgroup of high risk INSS Stage 4 neuroblastoma patients who CR, VGPR, or PR prior to stem cell rescue for myeloablative chemotherapy
- Further reduces minimal residual disease in the ITT population
- The toxicities of the combination of ch14.18, cytokines, and RA
- The incidence of anti-drug antibody development

Exploratory endpoints include evaluation of the correlation between change in MRD and either OS or EFS; tumor biology and either OS or PFS; relationship between antibody-dependent cellular cytotoxicity (ADCC) and EFS; outcome data in the non-randomized subgroup with historical controls; evaluate the pharmacokinetics of RA; and evaluate for correlations between RA exposure or “genetic variations” and EFS.

For the randomized portion of the trial, the key eligibility criteria were: age <31 years; high-risk neuroblastoma at diagnosis or relapse (based on the International Neuroblastoma Staging System (INSS)); completion intensive induction chemotherapy followed by stem cell rescue and radiotherapy to the primary tumor site, if known and not fully resected, on any of the following studies: Protocols A3973, 9341/9342, CCG3891, NANT 2001-02, ANBL02P1, ANBL0532; POG 9640, COG ANBL00P1, or CHP 594; ≤ 12 months from initiation of intensive induction chemotherapy to myeloablative chemotherapy with stem cell rescue;

undergo registration and randomization for DIV-NB-301 between 50 and 100 days following myeloablative chemotherapy with stem cell rescue; achieve a CR, VGPR, or PR based on the International Neuroblastoma Response Criteria (INRC) with $\leq 10\%$ marrow involvement following induction chemotherapy and myeloablative chemotherapy but prior to stem cell rescue; no prior anti-GD2 therapy, and have a Lansky or KPS $\geq 50\%$.

Randomization was stratified by two factors: (1) the protocol followed for initial therapy and, in protocols where purging of autologous cells was permitted, for administration of purged vs. unpurged autologous stem cells which contained 13 potential choices and (2) best response to induction chemotherapy (CR vs. VGPR vs. PR); this resulted in total of 24 strata.

Treatment plan: Patients were randomly assigned to the experimental arm or the control arm in the major cohort of the trial. In both arms, patients were allowed to receive a maximum of 6 cycles of treatment as summarized in the table below

Cycle #	Experimental Arm	Cycle length (days)	Control Arm	Cycle length (days)
1	cis-RA ¹ , dinutuximab, and GM-CSF ²	24	cis-RA	28
2	cis-RA, dinutuximab, and IL-2 ³	32	cis-RA	28
3	cis-RA, dinutuximab, and GM-CSF	24	cis-RA	28
4	cis-RA, dinutuximab, and IL-2	32	cis-RA	28
5	cis-RA, dinutuximab, and GM-CSF	24	cis-RA	28
6	cis-RA	28	cis-RA	28

¹ cis-RA = cis-retinoic acid (isotretinoin)

² GM-CSF = granulocyte-macrophage colony stimulating factor (sargramostim)

³ IL-2 = interleukin-2 (aldesleukin)

Control arm:

- cis-RA 80 mg/m²/day (2.16 mg/kg/day if ≤ 12 kg), orally twice daily, days 1-14 of each 28-day cycle

Experimental arm

- Cycles 1, 3, and 5 (24 days in length):
 - GM-CSF 250 mcg/m²/d by subcutaneous injection (SC) or intravenous infusion (IV), days 0- 13
 - Dinutuximab (NCI-sourced) 25* mg/m²/d by intravenous infusion over 5-20 hrs, days 3-6
 - cis-RA 80 mg/m²/day (2.16 mg/kg/day if ≤ 12 kg) orally, twice daily, days 10-23
- Cycles 2 and 4 (32 days in length):
 - IL-2 .0 x 10⁶ IU/m²/d continuous intravenous infusion (CIVI) over 24 hrs, days 0-3; then 4.5 x 10⁶ IU/m²/d CIVI days 7-10
 - Dinutuximab (NCI-sourced) 25* mg/m²/d by intravenous infusion over 5-20 hrs, days 3-6
 - cis-RA 80 mg/m²/day (2.16 mg/kg/day if ≤ 12 kg) orally, twice daily, days 14-27

- Cycle 6 (28 days in length): cis-RA 80 mg/m²/day (2.16 mg/kg/day if ≤ 12 kg) orally, twice daily, days 1-14

*The dose of NCI-sourced dinutuximab was based on protein concentrations determined by an absorbance assay in which the extinction coefficient was not experimentally determined. The dose of “25 mg” is actually 17.5 mg dinutuximab, based on UTC’s validated absorbance assay using the correct extinction for this protein.

The primary endpoint of this study was event-free survival, defined as the time from randomization until the first occurrence of relapse, progressive disease, second primary cancer, or death or, if none of these events occurred, until the last contact with the patient. The primary efficacy analysis was an intention-to-treat comparison of event-free survival in the two treatment arms. The study was designed to enroll 386 randomly assigned patients, for a statistical power of 80% with a two-sided log-rank test at a level of 0.05 (or a one-sided test at a level of 0.025) at 137 EFS events to detect an absolute difference of 15 percentage points between the two groups in the 3-year estimate of event-free survival (50% in the standard-therapy group vs. 65% in the immunotherapy group).

The major efficacy outcome measure was investigator-assessed event-free survival (EFS), defined as the time from randomization to the first occurrence of relapse, progressive disease, secondary malignancy, or death. Overall survival (OS) was also to be evaluated, however a detailed plan for the analysis of overall survival was not provided in the protocol.

Results

The first patient was randomized October 26, 2001 and the last randomized patient enrolled November 3, 2008. As of January 13, 2009, the data cut-off date for the analysis by the DSMB which resulted in termination of the trial, a total of 226 eligible patients (58% of the 386 planned enrollment) had been randomly assigned to the experimental arm (n=113) or the control arm (n=113). The median duration of follow-up at the time of this analysis was 2.1 years. The trial was terminated based on the recommendation of the DSMB after an interim analysis of the randomized cohort, which was conducted with 83 (61%) of the 137 planned EFS events for the protocol-specified final analysis of EFS. Four patients in the control arm “crossed over” to receive the dinutuximab regimen following termination of randomization. There were also 25 patients with biopsy-proven residual disease who were enrolled in the non-randomized cohort. Neither the patients who “crossed over” nor the patients in the non-randomized cohort were included in efficacy analyses.

Across the randomized study population, 60% were male, the median age was 3.8 years (range 0.9 to 15.3 years), and 3.5% of patients were less than 1.5 years, 82% were White and 7% were Black. The majority (80%) of patients had International Neuroblastoma Staging System Stage 4 disease. Thirty-five percent of patients had a complete response, 43% had a very good partial response, and 23% had a partial response to therapy received prior to autologous stem cell transplant. Forty-six percent of patients had neuroblastoma that was not MYCN-amplified, 36% had tumors with known MYCN-amplification, and MYCN status was

unknown or missing in 19% of patients. Forty-three percent of patients had hyperdiploid tumors, 36% had diploid tumors, and DNA ploidy status was unknown or missing in 21% of patients.

The analyses of the primary and key secondary endpoints of the trial are summarized in the table below. Although the effects on EFS are not statistically robust as the Type I error boundary for the 7th interim analysis of 0.0115 approached but did not cross the pre-specified alpha boundary of 0.0108. As discussed more extensively in the statistical review of this BLA, these results were supported by additional exploratory analyses of EFS which also favored the experimental arm using alternative data cut-off dates of June 13, 2009 and of June 13, 2012 (which also included data from patients in the control arm who received investigational therapy under the expanded access trial following study termination), as well as exploratory subgroup analyses of EFS in subgroups defined by age (however insufficient numbers of patients less than 18 months or greater than 12 years were enrolled to evaluate treatment effects in these subgroups), gender, or response to initial induction therapy (CR vs. VGPR). In addition, the treatment effects of dinutuximab with IL-2 or GM-CSF are supported by effects on overall survival, favoring the dinutuximab-containing arm, in datasets using the data cut-off dates of January 13, 2009, June 13, 2009, and June 13, 2012.

Treatment effects also consistently favored the dinutuximab-containing arm in subgroups defined by demographic variables and prognostic factors. However, in patients with the poor prognostic factors of MYCN amplified tumors (HR 0.86 EFS/HR 0.80 OS), VGPR following induction therapy (HR 0.85 EFS/HR 0.70 OS), and hyperdiploid (HR 0.74 EFS/ HR 1.14 OS) tumors appeared smaller in magnitude than in those with good prognostic factors.

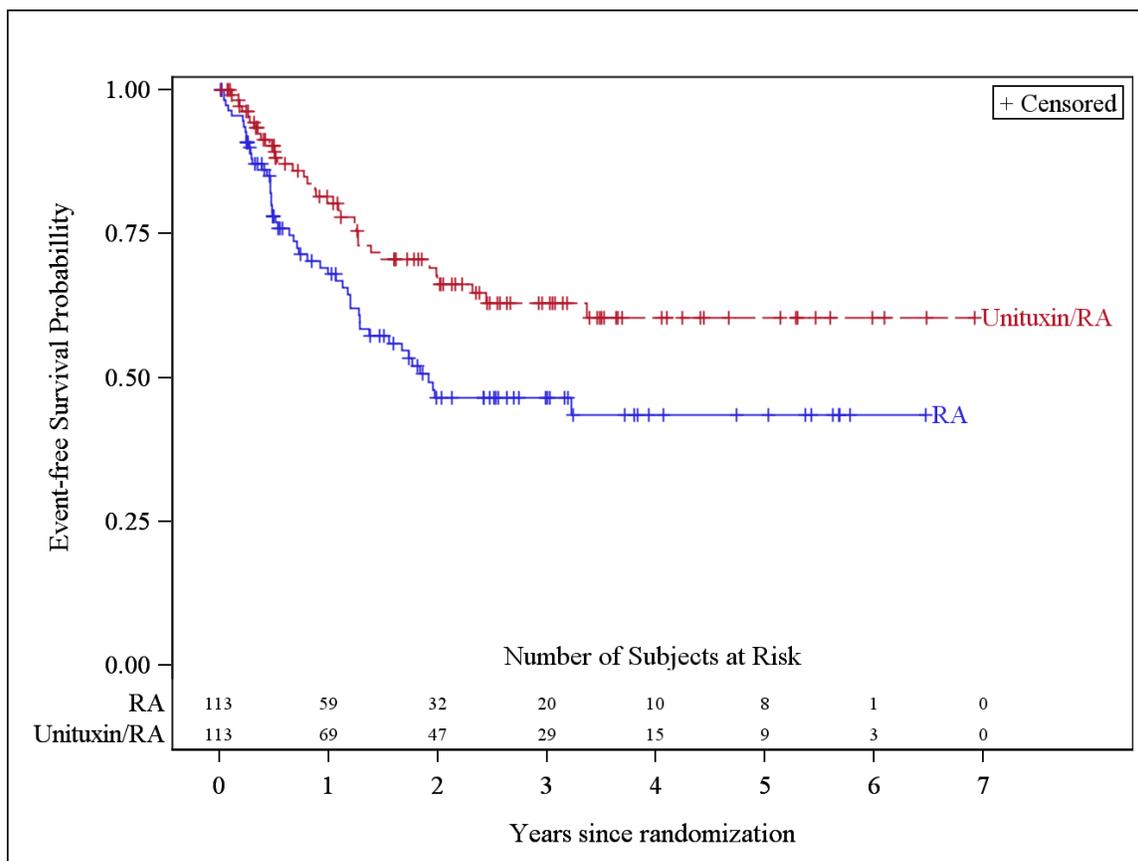
Efficacy Parameter		Unituxin/ RA arm n=113	RA arm n=113
EFS	No. of Events (%)	33 (29%)	50 (44%)
	Median (95% CI) (years)	NR (3.4 ,NR)	1.9 (1.3, NR)
	Hazard Ratio (95% CI)	0.57 (0.37, 0.89)	
	p-value (log-rank test) ¹	0.01	
OS ²	No. of Events (%)	31 (27%)	48 (42%)
	Median (95% CI) (years)	NR (7.5,NR)	NR (3.9,NR)
	Hazard Ratio (95% CI)	0.58 (0.37,0.91)	

NR = not reached

¹ Compared to the allocated alpha of 0.01 pre-specified for the seventh interim analysis of EFS

² Based on an additional three years of follow up after the seventh interim analysis of EFS

Kaplan-Meier Curves of Event-Free Survival in Study DIV-NB-301



In the FDA Guidance for Industry, entitled “*Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*” (May 1998), FDA’s considerations regarding when a single trial can provide substantial evidence of effectiveness are discussed. The single trial supporting this BLA meets some but not all of these criteria; those which are present are

- Demonstration of a clinically meaningful effect on potentially serious outcome (disease recurrence) in a multicenter trial; in this disease setting where patients had no evidence of residual disease after completing induction chemotherapy, myeloablative chemotherapy, and radiotherapy to sites of disease, EFS is more akin to relapse-free survival than to progression-free survival. Diagnosis of recurrence, given the implications to the patient, may require biopsy and are less likely to be subjective than progression-free survival.
- Consistent effects observed for both event-free survival and overall survival
- Consistent effects favoring the dinutuximab-containing arm in relevant subgroups based on demographics or on prognostic factors. ,

Based on the factors above, I concur that Study DIV-NB-301 demonstrates substantial evidence of effectiveness for patients receiving dinutuximab-containing chemotherapy.

With regard to the isolation of the treatment effect, the study design of DIV-NB-301 was adequate to isolate the effect of RA from that of dinutuximab and IL-2/GM-CSF. However, the study design was not adequate to “isolate” the contribution of IL-2 or GM-CSF to dinutuximab, or, conversely, the contribution of dinutuximab to either IL-2 or GM-CSF. The non-clinical data show that dinutuximab alone can induce tumor lysis; tumor lysis is enhanced with the addition of a cytokine in vitro, in some nonclinical studies, and potentially in patients. However, the importance of such enhance lysis to the clinical outcomes have not been established.

Neither GM-CSF nor IL-2 has been shown to have anti-tumor activity at the doses administered in Study DIV-NB-301. Administration of GM-CSF at the recommended dose and schedule, which is similar to that used in DIV-NB-301, has not been demonstrated to improve tumor outcomes in multiple, randomized clinical trials. Any survival advantage attributed to GM-CSF in randomized trials is confounded by its effects on reducing the risks of infection and cannot be attributed to anti-tumor activity.

Interleukin-2 has been shown to induce durable tumor shrinkage in highly selected patients when administered at substantially higher doses than in DIV-NB-301. However at doses similar to those used in DIV-NB-301, interleukin-2 appears to have minimal activity. The labeling for Proleukin contains the following information:

Lack of efficacy with low dose Proleukin regimens

Sixty-five patients with metastatic renal cell cancer were enrolled in a single center, open label, non-randomized trial that sequentially evaluated the safety and anti-tumor activity of two low dose Proleukin regimens. The regimens administered 18 million International Units Proleukin as a single subcutaneous injection, daily for 5 days during week 1; Proleukin was then administered at 9×10^6 International Units days 1-2 and 18×10^6 International Units days 3-5, weekly for an additional 3 weeks (n=40) followed by a 2 week rest or 5 weeks (n=25) followed by a 3 week rest, for a maximum of 3 or 2 treatment cycles, respectively.

These low dose regimens yielded substantially lower and less durable responses than those observed with the approved regimen. Based on the level of activity, these low dose regimens are not effective.

While this information does not exclude the possibility that IL-2 and GM-CSF may augment the efficacy of dinutuximab, they do not support a conclusion that either IL-2 or GM-CSF alone is likely to account for this treatment effect. Because all four drugs used in experimental arm carries the risk of adverse drug reactions, additional trials are warranted to evaluate the contribution, if any, to dinutuximab. Such data may be available from ongoing European trials where a willingness to explore the role of individual components appears to be greater than among the US pediatric oncology community.

8. Safety

Size of the database

The size of the safety database was adequate for assessment of serious adverse events occurring at an incidence of $\geq 0.3\%$ (3 in 1000) and included data from 1028 dinutuximab-treated patients receiving the proposed dosage regimen enrolled across four clinical trials, as outlined below. The major limitations of the safety database was that only one trial of modest size (DIV-NB-301) was internally controlled and the collection of important factors allowing description of the safety database (e.g., exposure data, duration of adverse events) were either collected in a non-standard manner (exposure data, dose modifications) or not collected (onset of and duration of adverse events, clinical laboratories) on case report forms for three of the four studies. The safety information collected in the safety database in the original application was derived from the following studies:

- Study ANBL0032 (also referred to as Study DIV-NB-301 prior to termination of randomization) was a randomized, open-label trial, in which 113 patients were randomized to receive dinutuximab-containing therapy and an additional 21 patients received dinutuximab-containing therapy in the non-randomized cohort of this study.
- Study ANBL0032 post-termination of randomization (also referred to as Study DIV-NB-302), entitled “A Comprehensive Safety Trial of Chimeric Antibody 14.18(ch14.18) with GM-CSF, IL-2 and Isotretinoin in High-Risk Neuroblastoma Patients Following Myeloablative Therapy”, was a single arm, multicenter, expanded access trial that enrolled 783 patients with high-risk neuroblastoma who would have met the eligibility criteria for Study DIV-NB-301 at the time of its closure. All patients received the dinutuximab-containing regimen administered in Study ANBL032.
- Study DIV-NB-303 was a multicenter, single arm safety study of dinutuximab manufactured by UTC in combination with GM-CSF, IL-2 and RA in 104 patients with high-risk neuroblastoma. This trial was initiated in early 2010 to further characterize the safety of SAIC-Frederick (NCI) manufactured ch14.18 administered with IL-2, GM-CSF, and isotretinoin as administered in Study DIV-NB-301. The primary study endpoint is to define the safety profile of ch14.18. Secondary endpoints include characterization of immunogenicity (anti-ch14.18 antibodies). In this trial, adverse events of all CTCAE grades and laboratory data were systematically and comprehensively collected.
- Study DIV-NB-201 was a multi-center, randomized, open-label, two-sequence, cross-over, comparative pharmacokinetic (PK) and safety study, conducted in 28 patients with high-risk neuroblastoma.

During review of the BLA, it was noted the ADCC activity of more recently manufactured lots was two-fold higher ADCC activity than earlier UTC-manufactured lots. Since there was little clinical experience with UTC-sourced product and all of that experience was with lots having lower ADCC activity, including those administered in Study DIV-NB-303, additional information were requested during review. This information consisted of analyses comparing

the per-patient incidence of severe and serious adverse events per cycle and overall for each UTC-manufactured dinutuximab lot with the information provided in the Integrated Summary of Safety (generated almost entirely with NCI-manufactured dinutuximab and narrative summaries for each new serious adverse event with UTC-manufactured lots, using a data cutoff date of January 31, 2015 or later. While the data are limited, containing data on 63 and 40 patients who received at least one dinutuximab dose from a “high-ADCC” lot, review of additional safety data did not suggest an increased risk or severity of previously identified adverse reactions and also did not identify new safety signals. Given the limited data presented, a post-marketing requirement has been generated under the provisions of 505(o) to obtain data in at least 220 patients who received and completed treatment with UTC-manufactured dinutuximab.

Major safety concerns related to labeling

Dinutuximab, when administered in accordance to the package insert and with optimal medical management which includes intravenous hydration and concomitant medications (intravenous morphine infusion, antipyretics, and an antihistamines) administered prior to, during, and for up to several hours after completion of dinutuximab infusion over 20 hours, is a toxic regimen requiring administration in a hospital setting for management of dinutuximab-induced pain. In addition, careful patient selection based on adequate end-organ function and monitoring in a hospital/acute care setting are required to mitigate the risks and potential for death due to the potential serious risks of serious infusion reactions, capillary leak syndrome, and hypotension. Additional serious risks of dinutuximab, which require careful monitoring of vital signs and laboratory parameters, are the increased risk of infection, neurological disorders of the eye, bone marrow suppression, electrolyte abnormalities, and atypical hemolytic uremic syndrome.

In the only study capable of characterizing tolerability of the recommended dinutuximab regimen, Study DIV-NB-303, only 77% of patients were able to complete planned treatment. The most common severe and life-threatening (NCI CTCAE Grade 3 or 5) adverse reactions of dinutuximab are neuropathic pain (51%), pyrexia (40%), infusion-related reactions (25%), capillary leak syndrome (23%), hypotension (16%), sepsis (16%), device-related infection (16%), diarrhea (13%), urticaria (13%) and hypoxia (12%).

Because of the serious nature of these findings, Unituxin labeling carries a Boxed Warning for serious infusion-related reactions and for severe neurologic toxicity. In addition, Unituxin is contraindicated in patients who have had a serious allergic reaction to dinutuximab.

UTC submitted publications characterizing the binding and activity profiles of dinutuximab, a human-murine chimeric monoclonal antibody (ch14.18), as well as pharmacodynamic information on m14.18 (a murine monoclonal antibody and 14.G2a (a murine monoclonal antibody); all three antibodies have the same murine variable regions with both 14.G2a and ch14.18 derived from the genetic sequence of m14.18. These publications summarized studies demonstrating that all three antibodies have similar binding affinity for GD2 and all three have the ability to mediate complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity. In addition, it was noted that the effector function of dinutuximab plays an important role in neurotoxicity, as discussed in Section 4 of this summary review.

In the limited clinical experience with dinutuximab, m14.18, and 14.G2a in adults, in which serious and potentially irreversible motor neuropathy was observed, dinutuximab is indicated only for use in pediatric patients. Off-label use in adults outside of carefully monitoring clinical trials is not recommended.

Adverse drug reactions of dinutuximab, based on a higher incidence as compared to patients receiving RA alone in Study DIV-NB-301, are listed in the following tables, abstracted from the package insert, for brevity.

**Selected Adverse Reactions Occurring in at Least 10% of Patients in Receiving
dinutuximab Study DIV-NB-301**

Adverse Reaction ^{1,2}	dinutuximab/RA (N=134)		RA (N=106)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General Disorders and Administration Site Conditions				
Pain ³	85	51	16	6
Pyrexia	72	40	27	6
Edema	17	0	0	0
Blood and Lymphatic System Disorders⁴				
Thrombocytopenia	66	39	43	25
Lymphopenia ⁴	62	51	36	20
Anemia	51	34	22	16
Neutropenia	39	34	16	13
Immune System Disorders				
Infusion reactions	60	25	9	1
Vascular Disorders				
Hypotension	60	16	3	0
Capillary leak syndrome ⁵	40	23	1	0
Hemorrhage ⁶	17	6	6	3
Hypertension	14	2	7	1
Metabolism and Nutrition Disorders				
Hyponatremia ⁴	58	23	12	4
Hypokalemia ⁴	43	37	4	2
Hypoalbuminemia ⁴	33	7	3	0
Hypocalcemia ⁴	27	7	0	0
Hypophosphatemia ⁴	20	8	3	0
Hyperglycemia ⁴	18	6	4	1
Hypertriglyceridemia ⁴	16	1	11	1
Decreased appetite	15	10	5	4
Hypomagnesemia ⁴	12	2	1	0
Investigations				

Adverse Reaction ^{1,2}	dinutuximab/RA (N=134)		RA (N=106)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased alanine aminotransferase ⁴	56	23	31	3
Increased aspartate aminotransferase ⁴	28	10	7	0
Increased serum creatinine ⁴	15	2	6	0
Increased weight	10	0	0	0
Gastrointestinal Disorders				
Vomiting	46	6	19	3
Diarrhea	43	13	15	1
Nausea	10	2	3	1
Skin and Subcutaneous Tissue Disorders				
Urticaria	37	13	3	0
Respiratory, Thoracic and Mediastinal Disorders				
Hypoxia	24	12	2	1
Cardiac Disorders				
Tachycardia ⁷	19	2	1	0
Infections and Infestations				
Sepsis	18	16	9	9
Device related infection	16	16	11	11
Renal and Urinary Disorders				
Proteinuria ⁴	16	0	3	1
Nervous System Disorders				
Peripheral neuropathy	13	3	6	0

¹ Adverse reactions occurring in $\geq 10\%$ of patients in the dinutuximab /RA group with at least a 5% (All Grades) or 2% (Grades 3-5) absolute higher incidence in the dinutuximab /RA group compared to the RA group.

² Adverse drug reactions were graded using CTCAE version 3.0.

³ Includes preferred terms abdominal pain, abdominal pain upper, arthralgia, back pain, bladder pain, bone pain, chest pain, facial pain, gingival pain, infusion related reaction, musculoskeletal chest pain, myalgia, neck pain, neuralgia, oropharyngeal pain, pain, pain in extremity, and proctalgia.

⁴ Based on investigator-reported adverse reactions rather than laboratory data.

⁵ One patient with Grade 5 capillary leak syndrome

⁶ Includes preferred terms gastrointestinal hemorrhage, hematochezia, rectal hemorrhage, hematemesis, upper gastrointestinal hemorrhage, hematuria, hemorrhage urinary tract, renal hemorrhage, epistaxis, respiratory tract hemorrhage, disseminated intravascular coagulation, catheter site hemorrhage, hemorrhage and hematoma.

⁷ Includes preferred terms tachycardia and sinus tachycardia.

Of 104 patients enrolled and treated in Study DIV-NB-303, 77% of patients completed planned treatment. The following adverse reactions not previously reported in Study DIV-NB-301 were reported in $\geq 10\%$ of patients in Study DIV-NB-303: nasal congestion (20%) and wheezing (15%).

The overall incidence of most adverse reactions of dinutuximab were generally similar in Study DIV-NB-301 regardless of the cytokine partner (IL-2 or GM-CSF), however the incidence of Grade 3-4 pain (43% vs. 35%) appeared to be higher during cycles with GM-CSF, while the incidence of Grade 3-4 pyrexia (37% vs. 10%), infusion-related reactions (20% vs. 10%), capillary leak syndrome (20% vs. 11%), hypotension (16% vs. 5%), and diarrhea (13% vs. 6%) appeared to be higher during cycles with IL-2.

**Per-Patient Incidence of Common ($\geq 5\%$) Grade 3-4 Laboratory Abnormalities
in Study DIV-NB-303**

Laboratory Test ¹	Grade ²	
	All Grades %	Grades 3-4 %
Hematology		
Anemia	100	46
Neutropenia	99	63
Thrombocytopenia	98	49
Chemistry		
Hypoalbuminemia	100	8
Hypocalcemia	97	7
Hyponatremia	93	36
Hyperglycemia	87	6
Aspartate Aminotransferase Increased	84	8
Alanine Aminotransferase Increased	83	13
Hypokalemia	82	41
Hypophosphatemia	78	6
Urinalysis³		
Urine protein	66	ND
Red blood cell casts	38	ND

ND = not determined

¹ Laboratory abnormalities with a per-patient incidence of at least 20% (all grades) and at least a 5% per-patient incidence of severe (Grade 3 or 4) laboratory abnormalities.

² Based on CTCAE version 4.0.

³ Urinalysis results were reported as positive or negative without assessment of grade.

REMS

I concur with the recommendations of the clinical and DRISK staff that a REMS is not required to ensure safe use. The rationale for this recommendation is that the treatment of patients with high-risk neuroblastoma is limited to pediatric oncologists at tertiary or specialized medical centers. These specialists are familiar with the risks of dinutuximab and there has been extensive experience gleaned through the expanded access program which enrolled more than 750 patients.

PMRs and PMCs

Based on serious risks of infusion reactions including anaphylaxis, development of anti-drug antibodies, and peripheral sensory and motor neuropathy, four post-marketing requirements were identified by the clinical review team (infusion reactions including anaphylaxis), CMC, clinical pharmacology, and clinical review teams (for characterization of immunogenicity and anti-drug antibodies); and nonclinical pharmacology/toxicology (for neurologic toxicity). These are described in greater detail in Section 13 of this review.

In addition, multiple post-marketing commitments were requested by the CMC review team.

9. Advisory Committee Meeting

This BLA for this new active moiety, first-in-class molecule was not referred for review to the Oncologic Drugs Advisory Committee (ODAC) for several reasons: the safety profile of dinutuximab is acceptable for the treatment of high-risk neuroblastoma, the evaluation of the safety data when used in the treatment of high-risk neuroblastoma did not raise significant safety or efficacy issues that were unexpected for a drug in this population, and the composition of the committee is predominantly adult oncologists who do not treat this disease. Instead, FDA sought advice from two pediatric oncologists and a patient representative as Special Government Employees, who concurred that substantial evidence of effectiveness had been demonstrated and the risk/benefit assessment was favorable in this life-threatening disease with no satisfactory alternative therapies.

10. Pediatrics

Orphan drug designation was granted for dinutuximab on December 20, 2010, for the treatment of neuroblastoma, therefore dinutuximab is exempt from the requirements of the Pediatric Research Equity Act (PREA).

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: The Division of Oncology Products 2 and the DMEPA concurred that the proposed proprietary name was not promotional or likely to result in medication errors. FDA issued a Proprietary Name-Conditionally Acceptable letter on July 10, 2014.
- Physician labeling
 - Boxed Warning: FDA requested a Boxed Warning for the serious adverse reactions of neuropathic pain/peripheral neuropathy and infusion reactions, which cannot always be distinguished from infusion reactions mediated by cytokine release. These serious

- adverse reactions carry sufficient risks of serious morbidity that they might affect a patients' (or parents') decision to take dinutuximab.
- Indications and Usage: The indication statement was modified to include specific details regarding the patient population (b) (4).
 - Dosage and Administration: Moved UTC's section (b) (4).
 - Dosage Forms and Strengths: no changes
 - Contraindications: (b) (4) (i.e., anaphylaxis) to dinutuximab and removed (b) (4).
 - Warnings and Precautions: Retitled subsections to indicate the serious risk included new subsections for bone marrow suppression, electrolyte abnormalities, atypical hemolytic uremic syndrome, and embryofetal toxicity. Management of serious adverse reactions as described in labeling revised where appropriate for consistency with the approach required by the Study DIV-NB-301.
 - Adverse Reactions: Tables limited to adverse reactions occurring at a higher incidence in the experimental arm at a threshold of $\geq 5\%$ difference overall or $\geq 2\%$ difference for Grade 3-4 adverse reactions, rather than (b) (4) as proposed by UTC. Included a table showing adverse reactions by cytokine partner (GM-CSF or IL-2) to illustrate the similarity across cycles and that toxicity was not driven by IL-2 administration as has been postulated in published literature. Included tabular listing of laboratory abnormalities in Study DIV-NB-303, as this is the only study for which laboratory results were supplied in the BLA. Included immunogenicity information observed across clinical trials obtained with an analytically validated binding assay.
 - Drug Interactions: No substantive changes
 - Use in Specific Populations: Section 8.1-8.3 revised to contain information, and in the format recommended by, the Pregnancy and Lactation Labeling Rule (PLLR) as recommended by the DPMH consultant, a "high-level" summary of Study DIV-NB-301 was presented in Section 8.4 with cross references to pediatric use information in the Sections 1, 2, 4, 5, 6, 12, 14, and 17. Added subsections on patients with renal and hepatic impairment.
 - (b) (4)
 - Description: No substantive changes
 - Clinical Pharmacology: Removed subsection (b) (4). Section 12.3 edited for brevity and essential information for safe use.
 - Nonclinical Pharmacology/Toxicology: Added information regarding lack of information regarding effects on fertility. Limited non-clinical studies information to those relevant to prescribers.
 - Clinical Studies: Included additional information describing the clinical protocol and dosage regimen in which efficacy was demonstrated and patient population studied.

Added table summarizing key efficacy endpoints and removed (b) (4)
(b) (4)
. Deleted (b) (4).

- How Supplied/Storage: No substantive changes
- Patient Counseling: Revised for consistency with December 2014 Guidance on this subsection of labeling.
- Carton and immediate container labels: UTC incorporated all recommendations for modification to the carton and immediate container labels made by DMEPA and the Division of Monoclonal Antibodies (DMA)
- Patient labeling/Medication guide: Patient labeling/medication guide was not proposed by UTC. These were not requested by FDA since all patients will receive this treatment in a hospital setting and by a medical subspecialty where informed consent is routinely obtained under the standard of care.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: I concur with the recommendations of all review disciplines that dinutuximab be approved.
- Risk Benefit Assessment: High-risk neuroblastoma is a life-threatening disease. The prognosis of patients with advanced stage neuroblastoma (International Neuroblastoma Staging System (INSS) stage 4 disease is heavily influenced by age at diagnosis and other prognostic factors (e.g., MYCN amplification), with a 5-year disease-free survival rate of 50%–80% in children diagnosed before 18 months of age and 3% in children/young adults patients between 10 and 21 years of age. In the patient population enrolled in Study DIV-NB-301, 80% had INSS Stage 4 disease and the median age was 3.8 years, with only 3% of patients less than 18 months of age; the anticipated 5-year survival rates would be less than 50% and in some patients, as low as 5%. There have been no drugs approved for treatment of this disease since 1987. Patients with high-risk neuroblastoma are typically treated on clinical protocols employing sequential multimodality that includes combination chemotherapy, myeloablative therapy with stem cell support, surgical debulking, and radiation to sites of disease, followed by retinoic acid for up to 6 months. Thus background therapy in this disease is also toxic and considered acceptable in light of the life-threatening nature of the disease.

Study DIV-NB-301 demonstrated a 42% improvement in event-free survival (median EFS in the control arm 1.9 years) with a trend in improved overall survival; these findings were present at multiple time-points as the study results matured and were present across relevant subgroups. Together, these findings demonstrate substantial benefit for dinutuximab-treated patients. While the study design of DIV-NB-301 isolated the effects of retinoic acid, it did not isolate the treatment effects of concomitant cytokines (GM-CSF and IL-2) administered to enhance ADCC. At the doses administered, these agents alone are unlikely to account for these improvements in EFS and OS, based on external data described in product labeling for each of these drugs.

When administered in accordance to the package insert and with optimal medical management which includes intravenous hydration and concomitant medications (intravenous morphine infusion, antipyretics, and an antihistamines) administered prior to, during, and for up to several hours after completion of dinutuximab infusion over 20 hours, is a toxic regimen requiring administration in a hospital setting for management of dinutuximab-induced pain. In addition, careful patient selection based on adequate end-organ function and monitoring in a hospital/acute care setting are required to mitigate the risks and potential for death due to the potential serious risks of serious infusion reactions, capillary leak syndrome, and hypotension. The risks of dinutuximab are substantial and require Study DIV-NB-303, only 77% of patients were able to complete planned treatment. The most common severe and life-threatening (NCI CTCAE Grade 3 or 5) adverse reactions of dinutuximab are neuropathic pain (51%), pyrexia (40%), infusion-related reactions (25%), capillary leak syndrome (23%), hypotension (16%), sepsis (16%), device-related infection (16%), diarrhea (13%), urticaria (13%) and hypoxia (12%).

The benefits of dinutuximab outweigh these serious and sometimes fatal risks, which are commonly accepted in the pediatric oncology community by both healthcare providers, patients, and their parents, as the price of improvement in overall survival and delaying time to relapse. However, additional studies to confirm or rule out the role of GM-CSF, IL-2, and retinoic acid to determine if toxicity can be reduced with removal of ineffective drugs from this complex and toxic treatment regimen.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
I concur with the recommendations of the clinical and DRISK staff that a REMS is not required to ensure safe use. The rationale for this recommendation is that the treatment of patients with high-risk neuroblastoma is limited to pediatric oncologists at tertiary or specialized medical centers. These specialists are familiar with the risks of dinutuximab and there has been extensive experience gleaned through the expanded access program which enrolled more than 750 patients.
- Recommendation for other Postmarketing Requirements and Commitments
The following post-marketing requirements under 505(o) will be conducted to assess the known serious risks of serious infusion reactions; hypersensitivity, including anaphylaxis; and neurologic toxicity, including sensory and motor neuropathy.
 - Conduct a study to compare exposure and safety data from approximately 220 patients who complete treatment with dinutuximab, pooling across dinutuximab lots and by individual lot, with the historical experience observed in approximately 1100 patients treated with ch14.18 (manufactured by SAIC for the National Cancer Institute). Based on these data, provide thoughtful analyses of the risk of serious infusion reactions, pain, and neuropathy, and the overall safety and tolerability of the marketed product, Unituxin. In addition, assess whether variations in antibody-dependent cell-mediated toxicity across dinutuximab lots alter the safety and tolerability of dinutuximab.
 - Conduct a study to analyze laboratory data including serum complement, IgE, tryptase, histamine, and human anti-chimeric antibody levels obtained in patients with

documented Grade 4 allergic reactions or anaphylaxis from a sufficient number of patients with neuroblastoma to allow for improved characterization of these adverse reactions to better inform product labeling. For each case identified, provide a narrative description that includes a summary of the allergic reaction or anaphylaxis adverse reaction, rechallenge information, and an assessment of whether the clinical presentation and laboratory data obtained were consistent with an allergic reaction or an infusion reaction. In addition, submit the datasets used for safety analyses of the laboratory data.

- 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 submitted in a Prior Approval Supplement.
- Conduct a study to assess the neutralizing anti-drug antibody responses to dinutuximab with a validated assay capable of sensitively detecting neutralizing antibody responses in the presence of dinutuximab levels that are expected to be present in the blood at the time of patient sampling. The clinical impact of the neutralizing antibody response should be evaluated in at least 300 patients.
- Conduct a study to compare exposure and safety data from approximately 220 patients who complete treatment with dinutuximab, pooling across dinutuximab lots and by individual lot, with the historical experience observed in approximately 1100 patients treated with ch14.18 (manufactured by SAIC for the National Cancer Institute). Based on these data, provide thoughtful analyses of the risk of serious infusion reactions, pain, and neuropathy, and the overall safety and tolerability of the marketed product, Unituxin. In addition, assess whether variations in antibody-dependent cell-mediated toxicity across dinutuximab lots alter the safety and tolerability of dinutuximab.

Post-marketing commitments

Approximately two dozen post-marketing commitments were identified by the quality review team, which included requests for modification of release specifications based on additional manufacturing experience, validation of multiple assay methods, detection of leachables and extractables, and shipping validation.

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PATRICIA KEEGAN
03/09/2015