

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125360

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

BLA:	125360
Brand Name:	Xeomin [®]
Generic Name:	NT201 (Botulinum neurotoxin Type A)
Sponsor:	Merz Pharmaceuticals
Type of Dosage Form:	Parental solution for intramuscular injection
Strengths:	Powder for solution; reconstituted for injection (50 or 100 LD ₅₀ units/vial)
Indications:	Treatment of Cervical Dystonia (Spasmodic Torticollis) and Blepharospasm
OCP Reviewer:	Ta-Chen Wu, Ph.D.
OCP Team Leader:	Angela Yuxin Men, M.D., Ph.D.
OCP Division:	DCP-1 HFD-860
OND Division:	Neurology Drug Products HFD-120
Submission Dates:	July 01, 2009; September 25, 2009
Type of Submission:	Standard BLA Review

1. EXECUTIVE SUMMARY

The sponsor seeks approval of Xeomin[®] (NT 201) for the treatment of Cervical Dystonia (CD) (Spasmodic Torticollis), and Benign Essential Blepharospasm (BEB) with this BLA 125360, originally submitted on July 01, 2009. The proposed dosing regimen for CD is listed in the Table below.

(b) (4)

For BEB, the total Xeomin dose is up to (b) (4) per eye. The initial recommended dose is 1.25-2.5 U at each site. The initial dose should not exceed (b) (4) per eye. Subsequent dosing per muscle should be tailored to the individual patient's need.

NT 201 (Xeomin[®]) is an injectable form of a highly purified fermentation-derived botulinum neurotoxin type A (150 kDa) that is free of clostridial non-toxin complexing proteins and is derived from a strain of Clostridium botulinum bacteria. The mechanism of action of the neurotoxin initially involves high affinity, specific and saturable binding to cell surface receptors on the presynaptic membrane. Clostridium botulinum neurotoxin type A blocks the presynaptic release of acetylcholine from the neuromuscular endplates of peripheral nerves, and thus prevents the cholinergic transmission of nerve impulses to the muscle. The resultant muscle relaxation exerts the therapeutic effect of NT 201 in treating CD and BEB.

According to the sponsor, NT 201 is expected to be less immunogenic based on nonclinical study results compared to other botulinum toxins (i.e., Botox[®], Dysport[®], and Myobloc[®]), and with better safety profile after oral administration in animal models. As proposed by the sponsor, NT 201 will be injected directly into the skeletal muscle in patients with CD, and injected subcutaneously in the area of the affected muscles of patients with blepharospasm. The subcutaneous injection in patients with blepharospasm will result in intramuscular application since the targeted small muscles around the eyes are located directly under the skin and have very thin fascia. As provided by the sponsor, most of the Botulinum toxin type A, whether in free or complexed form, does not diffuse from the injection site. The extent of diffusion is dependent on local anatomy, the injection volume, and the dose. The distribution into systemic circulation is limited. After systemic absorption in animals, the neurotoxin is rapidly metabolized by proteases to smaller molecular structures, with no specific organ for elimination. White blood cells (e. g. macrophages, lymphocytes) play a role in the disposal of circulating Botulinum toxin type A as shown for other proteins. The neurotoxin is then degraded intracellularly.

This submission included 6 randomized, double-blind, placebo-controlled Phase 3 studies for the proposed indications, as well as active comparator studies and open-label extensions studies, one Phase 2 dose-finding study, and three Phase 1 studies. The Phase 2 dose-ranging study was performed (9801 [CD]) to compare the efficacy of NT 201 with Botox for the decreasing muscle dystonia in the sternocleidomastoid muscle assessed by surface electromyography. Three Phase 1 pharmacodynamic (PD) studies (9901, 0113 and 0709) were performed in healthy subjects to evaluate the time course, degree of muscle paralysis, and local diffusion into adjacent muscles, compared to other botulinum toxin products (i.e., Botox[®], Vistabel[®] or Dysport[®]). These studies are reviewed by the medical officers.

The chemical complexity of NT 201 combined with its extreme potency limits the opportunity to study its pharmacokinetic (PK) profile in humans. Therefore, no Clinical Pharmacology or human PK studies have been conducted for the proposed new indication.

2. RECOMMENDATION:

There are no clinical pharmacology studies and data are being submitted in this application. Therefore, reference will be made to studies in animals (literature information) that are considered to resemble the humans. The recommended labeling language had been conveyed to the sponsor.

2.1 Labeling Languages relevant to Clinical Pharmacology

Ta-Chen Wu, Ph.D. 
Reviewer, Neurology Drug Products, DCP-1, OCP

Concurrence: 
Angela Yuxin Men, M.D., Ph.D.
Team Leader, Neurology Drug Products, DCP-1, OCP

Cc: HFD-120 CSO/VN Kishore
HFD-860 /ATL Clin Pharm/A. Men
/DDD Clin Pharm/R. Uppoor
/DD DCP-1/M. Mehta

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	125360	Brand Name	Xeomin [®]
OCP Division (I, II, III, IV, V)	DCP-I	Generic Name	NT201 (Botulinum neurotoxin Type A)
Medical Division	HFD-120	Drug Class	Neurotoxin
OCP Reviewer	Ta-Chen Wu, Ph.D.	Indication(s)	(b) (4) Cervical Dystonia (CD; Spasmodic Torticollis), and Benign Essential Blepharospasm (BEB)
OCP Team Leader	Angela Yuxin Men, M.D., Ph.D.	Dosage Form	Powder for solution; reconstituted for injection (50 or 100 LD ₅₀ units/vial)
Pharmacometrics Reviewer		Dosing Regimen	(b) (4) <ul style="list-style-type: none"> • CD: total dose from 120 (b) (4) U per treatment session • BEB: no more than (b) (4) (b) (4) per eye per treatment session
Date of Submission	07/01/2009	Route of Administration	Intramuscular injection
Estimated Due Date of OCP Review	03/02/2010	Sponsor	Merz Pharmaceuticals GmbH
Medical Division Due Date	03/17/2010	Priority Classification	S
PDUFA Due Date	05/02/2010		

Summary:

The sponsor seeks approval of Xeomin[®] (NT 201) as treatment for (b) (4), (2) Cervical Dystonia (CD) (Spasmodic Torticollis), and (3) Benign Essential Blepharospasm (BEB) with this BLA 125360, submitted on July 01, 2009. NT 201 (Xeomin[®]) is an injectable form of fermentation-derived botulinum neurotoxin type A (150 kDa) that is free of clostridial non-toxin complexing proteins and is derived from a strain of Clostridium botulinum bacteria.

(b) (4)

Clostridium botulinum neurotoxin type A blocks the presynaptic release of acetylcholine from the neuromuscular endplates of peripheral nerves, and thus prevents the cholinergic transmission of nerve impulses to the muscle. The mechanism of action of the neurotoxin initially involves high affinity, specific and saturable binding to cell surface receptors on the presynaptic membrane.

According to the sponsor, NT 201 is expected to be less immunogenic based on nonclinical study results compared to other botulinum toxins (i.e., Botox[®], Dysport[®], and Myobloc[®]), and with better safety profile after oral administration in animal models. NT 201 is injected directly into the skeletal muscle in patients with cervical dystonia (b) (4). In patients with blepharospasm NT 201 is injected subcutaneously in the area of the affected muscles. Since the targeted small muscles around the eyes are located directly under the skin and have very thin fascia, subcutaneous injection will result in intramuscular application. The recommended doses for the proposed indications are shown in Appendix 1.

The clinical development program included 10 randomized, double-blind, placebo-controlled Phase 3 studies for the proposed indications, as well as active comparator studies and open-label extensions studies, one Phase 2 dose-finding study, and three Phase 1 studies. The Phase 2 dose-ranging study was performed (9801 [CD]) to compare the efficacy of NT 201 with Botox for the decreasing muscle dystonia in the sternocleidomastoid muscle assessed by surface electromyography. Tabular listing of all clinical studies is shown in Appendix 2.

The chemical complexity of NT 201 combined with its extreme potency limits the opportunity to study its PK profile in humans. No traditional PK or biopharmaceutical studies were performed. Reference will be made to studies in animals (literature information) that are considered to resemble the humans. Three Phase 1 PD studies (9901, 0113 and 0709) were performed in healthy subjects to evaluate the time course, degree of muscle paralysis, and local diffusion into adjacent muscles, compared to other botulinum toxin products (i.e., Botox[®], Vistabel[®] or Dysport[®]). Highlights of these 3 studies are provided below:

Study 9901: Neurophysiological study of different intramuscular botulinum-A toxins in human extensor digitorum brevis (EDB) muscle

Study 0113: Dose-response profile of NT 201 (Botulinum neurotoxin type A free of complexing proteins) in human EDB muscles and comparison of systemic diffusion of different Botulinum neurotoxins type A in healthy male volunteers

Study 0709: Double-blind, randomized, single-dose, single-center study with healthy female subjects to evaluate the migration potential of Xeomin (NT 201) as compared to two other Botulinum toxin type A products, Vistabel and Dysport

Trial Countries (Study report location)	Phase, Population and Design	Study Treatment	Primary Endpoint
9901 (HV) Germany (Section 5.3.4.1)	Phase 1 14 healthy male volunteers Open-label, within-treatment comparison	4 UNT 201 or Botox intramuscular	Change in maximal amplitude of CMAP
0113 (HV) Germany (Section 5.3.4.1)	Phase 1b 32 healthy male volunteers Double-blind, within-treatment comparison examining dose response profile, systemic diffusion and duration of effect	2, 4, 16, or 32 U of NT 201 or Botox intramuscular	Reduction in CMAP M-wave at Week 4. Follow up for 52 weeks
0709 (HV) Germany (Section 5.3.4.1)	Phase 1 29 healthy female volunteers Double-blind, randomized, single-dose, single-center study	5 UNT 201 or 5 U Vistabel or 12.5 U Dysport intramuscular	Maximal area of anhidrosis

CMAP: Compound muscle action potential; HV: healthy volunteer (subject); U: Units

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			Inadequate hyperlinking for TOC and body of the study reports
Tabular Listing of All Human Studies	X			
HPK Summary	X			Reference to nonclinical information
Labeling	X			Sponsor provided annotated PDF file, but not annotated Word file for labeling
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				

Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -	X (Phase 1)			3 Phase 1 PD studies (9901, 0113 and 0709): <ul style="list-style-type: none"> • 9901: no hyperlink (TOC and study report) • 0113: no hyperlink (TOC and study report; seprate TOC for Tables/Figures has hyperlinks) • 0709: hyperlinks provided
Phase 2:	X			Phase 2 dose-finding (9801): no hyperlink (TOC and entire report)
Phase 3:	X			10 Phase 3 efficacy trials, including extension
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability	-			
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	-			
replicate design; single / multi dose:	-			
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics	-			
Pediatric development plan	-			
Literature References	X	28		
Total Number of Studies		4 (14 studies submitted)	0	No Clin Pharm, human PK, or biopharm study was conducted for the proposed new indications

On **initial** review of the NDA/BLA application for filing:

Content Parameter	Yes	No	N/A	Comment
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Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			N/A	
2	Has the applicant provided metabolism and drug-drug interaction information?			N/A	(label information)
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			N/A	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			N/A	
5	Has a rationale for dose selection been submitted?	Yes			Phase 2 dose-finding study
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	Yes			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	Yes			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?		No		Insufficient hyperlinks in some study reports
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	Yes			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			N/A	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?			N/A	(label information)
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	Yes			Phase 2 dose-finding study
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			N/A	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			N/A	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug			N/A	

	is indeed effective?				
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			N/A	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			N/A	Most information seems to be available in label, but also a matter of review issue
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?				Review issue
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			N/A	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Provide adequate hyperlinks in TOC and study reports to data/Tables/Figures/References
2. Please provide annotated Word file for labeling.

Reviewing Clinical Pharmacologist

Date

Team Leader/Supervisor

Date

Appendix 1. Recommended intramuscular dose ranges of Xeomin



Benign Essential Blepharospasm (BEB):

The total Xeomin dose is up to (b) (4) per eye. The initial recommended dose is 1.25-2.5 U at each site. The initial dose should not exceed (b) (4) per eye. Subsequent dosing per muscle should be tailored to the individual patient's need.

Appendix 2. Tabular listing of all clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 1	BTC 60201-9901	5.3.4.1	Neurophysiological study of different intramuscular Botulinum-A toxins in human extensor digitorum brevis (EDB)-muscle	Open-label single centre intra-individual controlled, single centre	4 U NT 201 vs. 4 U Botox single intramuscular injection in each foot	n=14	Healthy male volunteers with ages 20 - 45 years	up to 90 days	Finalized ICH
Phase 1b	MRZ 60201-0113	5.3.4.1	Dose-response profile of NT 201 in human EDB muscles and comparison of systemic diffusion of NT 201 and Botox	Double-blind, intra-individual controlled, randomized by feet and dose group, mono-centre trial	2.4, 16.32 U of NT 201 or Botox intramuscular injection at baseline	n=32 EFS n=26 IIT n=20 IIT ARV	Healthy male volunteers with ages 18 - 45 years	32 weeks (16 weeks observation period and 36 weeks extension period)	Finalized ICH
Phase 1	MRZ 60201-0709/1	5.3.4.1	Migration potential of NT 201 as compared to Vistabel® and Dysport®	Double-blind, randomized, single-dose, mono-centre trial	5 U NT 201 or 5 U Vistabel® or 12.5 U Dysport®	n=29	Healthy female volunteers with ages 18 - 45 years	6 months (first blinded analysis after 6 weeks)	Finalized ICH
Phase 3	MRZ 60201-0410/1	5.3.5.1 (SP)	Superiority of NT 201 compared to Placebo in terms of efficacy and safety in patients with post-stroke spasticity of the upper limb	Randomized double-blind placebo-controlled, parallel group multicenter trial to test superiority	170 - 400 U NT 201 or placebo intramuscular injection at baseline	n=148 IIT n=140 TPP n=148 EFS	Naïve and pre-treated patients with post-stroke spasticity of the upper limb	Up to 20 weeks	Finalized ICH
Phase 3	MRZ 60201-0410/2	5.3.5.1 (SP)	Efficacy and safety of individually dosed, repeated injections of NT 201 over one year in patients with post-stroke spasticity of the upper limb	Open-label, non-controlled, multicenter trial	Up to 400 U NT 201 - repeated treatments with up to 5 injection sessions	n=143 IIT n=143 TPP n=143 EFS	Patients with post-stroke spasticity of the upper limb who participated in the placebo-controlled study MRZ 60201-0410/1	Up to 49 weeks	Finalized ICH
Phase 3	MRZ 60201-0607/1	5.3.5.1 (SP)	Efficacy and safety of two dilutions of NT 201 (20 or 50 U/mL) in subjects with chronic upper limb spasticity of various etiologies	Phase 3, prospective, observer-blind, randomized, multicenter, controlled study	Up to 400 U NT 201 (20 or 50 U/mL) intramuscular injection at baseline	n=192 IIT n=165 TPP n=192 EFS	Pre-treated or treatment-naïve subjects with spasticity of the upper limb of various etiologies	Up to 20 weeks	Finalized ICH
Phase 2	BTC 60201-9801	5.3.5.1 (CD)	Dose-finding study to determine the therapeutically relevant dose in comparison to the therapeutically effective dose of Botox	Randomized open-label active control multicenter with stepwise inclusion of patients	Patients received either: NT 201 10/20 U NT 201 20/40 U NT 201 30/60 U Botox 30/60 U Intramuscular injection into Sternocleidomastoid/Splenius capitis muscle	n=53 IIT n=41 TPP	Patients with cervical dystonia (rotational form with hypertrophied Sternocleidomastoid muscle)	14 days controlled dose-finding period and 106 days follow-up	Finalized ICH
Phase 3	MRZ 60201-0408/1	5.3.5.1 (CD)	Safety and Efficacy of two doses of NT 201 compared with placebo in pre-treated and treatment-naïve subjects with Cervical Dystonia	Randomized, double-blind, placebo-controlled, multicenter study	120 U or 240 U NT 201 or placebo in a 1:1:1 ratio	n=109 IIT	Pre-treated and treatment-naïve patients with Cervical Dystonia	Up to 20 weeks	Finalized ICH

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3	MRZ 60201-0013	5.3.5.1 (CD)	Non-inferiority of NT 201 compared to Botox in terms of efficacy and safety in patients with Blepharospasm	Randomized double-blind active-controlled (Botox) parallel group multicenter trial to test non-inferiority	70-300 U NT 201 70-300 U Botox intramuscular injection at baseline	n=463 ITT n=420 TPP n=463 EFS	Patients with cervical dystonia Previous successful treatment with Botox in two consecutive sessions directly before trial entry	Up to 16 weeks	Finalized ICH
Phase 3	MRZ 60201-0433/1	5.3.5.1 (BEB)	Safety and Efficacy of NT 201 compared with placebo in pre-treated subjects with Blepharospasm	Randomized, double-blind, placebo-controlled, multicenter study	Up to 50 U NT 201 per eye vs. placebo in a 2:1 ratio	n=109 ITT	Pre-treated patients with Blepharospasm Previous successful treatment with Botox in two consecutive sessions before trial entry	Up to 20 weeks	Finalized ICH
Phase 3	MRZ 60201-0003	5.3.5.1 (BEB)	Non-inferiority of NT 201 compared to Botox in terms of efficacy and safety in patients with Blepharospasm	Randomized double-blind active-controlled (Botox) parallel group multicenter trial to test non-inferiority	≤35 U per eye NT 201 ≤35 U per eye BOTOX* intramuscular injection at baseline	n=300 ITT n=256 TPP n=303 EFS	Patients with Blepharospasm Previous successful treatment with Botox in two consecutive sessions before trial entry	Up to 16 weeks	Finalized ICH