Summary Review

Date	12/17/2020
From	Gerald D. Podskalny, DO, MPHS Eric Bastings, MD
Subject	Summary Review
BLA # Supplement#	BLA 125360 Supplement 86
Applicant	Merz Pharmaceuticals LLC
Date of Submission	06/18/2020
PDUFA Goal Date	12/18/2020 (Priority Review)
Proprietary Name / Established (USAN) names	Xeomin / incobotulinumtoxinA
Dosage forms / Strength	Single-dose vials for injection / 50-, 100-, and 200-Unit vials
Proposed Indication(s)	Treatment of chronic sialorrhea in patients ages 2 to 17 years
Recommended:	Approval

1. Introduction

Xeomin (incobotulinumtoxinA) is a type A botulinum toxin. All botulinum toxins block the fusion of cholinergic vesicles with the presynaptic membrane and prevent the release of acetylcholine (Ach) into the synapse. The production and secretion of saliva can be reduced by inhibiting the release of ACh from the parasympathetic postganglionic neurons that supply the salivary glands.

Merz (the applicant) submitted this supplemental Biologic License Application (sBLA) seeking approval of Xeomin (referred to as NT 201 in the applicant's submission) for the treatment of chronic sialorrhea in patients ages 2 to 17 years. Sialorrhea (excess salivation) can contribute to difficulty speaking, cause skin irritation, aspiration and pneumonia. Glycopyrrolate (Cuvposa) is the only marketed oral medication for the treatment of chronic severe drooling in patients aged 3-16 years. The adverse effects of glycopyrrolate (e.g., dry mouth, constipation, and urinary retention) are generally caused by its systemic anticholinergic effects.

The Xeomin clinical development program for the treatment of chronic sialorrhea in pediatric patients includes a single prospective, randomized, double-blind, placebo-controlled, parallel-group multicenter study, with an open-label extension.

2. Background

Xeomin is approved for the treatment of cervical dystonia, blepharospasm, the temporary improvement in the appearance of moderate to severe glabellar lines in adult patients, and upper limb spasticity in adult and pediatric patients ages 2 to 17 years (excluding spasticity caused by cerebral palsy). Xeomin was also approved for

the treatment of chronic sialorrhea in adult patients on July 3, 2018. The approval for the treatment of chronic sialorrhea in adults triggered the requirement for pediatric studies under the Pediatric Research Equity Act (PREA). The Applicant received a waiver for the age group birth to 2 years, and a deferral for pediatric patients ages 2 to 17 years. The PREA postmarketing requirement (PMR) for a pediatric study was included in the approval letter for supplement 73 for the treatment of chronic sialorrhea in adults. Submission of the final report for Study MRZ60201_3091_1, included in this supplement, is intended to fulfill the PREA requirement for pediatric studies.

The application was assigned Priority Review status because Xeomin is an improvement over existing therapy. Xeomin treats a broader population of pediatric patients (ages 2-17 years) with chronic sialorrhea, compared with glycopyrrolate (existing therapy), which is approved in patients ages 3-16 years.

Reviews for this supplemental application were completed by the clinical review team in the Division of Neurology 1 (DN 1), the Division of Biometrics I, the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) (see table 1).

Table 1. Review Team Members

Reviewer	Role	Office or Division
Kenneth Bergmann, MD Gerald David Podskalny, DO, MPHS	Primary clinical review CDTL, secondary clinical review	Division of Neurology 1
Minjeong Park, PhD Kun Jin, PhD H.M. James Hung, PhD	Primary statistical review Biometrics supervisory concurrence	Division of Biometrics I
Maria Nguyen, MSHS, BSN, RN Sharon Williams, MSN, BSN, RN LaShawn Griffiths, MSHS-PH, BSN, RN	Patient labeling review Supervisory concurrence	Division of Medical Policy Programs (DMPP)
Dhara Shah Aline Moukhtara,	Regulatory Review Officer Team Leader	Office of Prescription Drug Promotion (OPDP)

3. CMC/Device

The marketed Xeomin (incobotulinumtoxinA) product was used in this development program. No new CMC information was submitted.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical information was submitted.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology information was submitted in this supplement.

6. Clinical/Statistical- Efficacy

Dr. Minjeong Park, PhD, was the primary statistical reviewer for this application, and Drs. Kun Jin, PhD, and H.M. James Hung, PhD, provided supervisory concurrence. Ken Bergmann, MD, was the primary clinical reviewer.

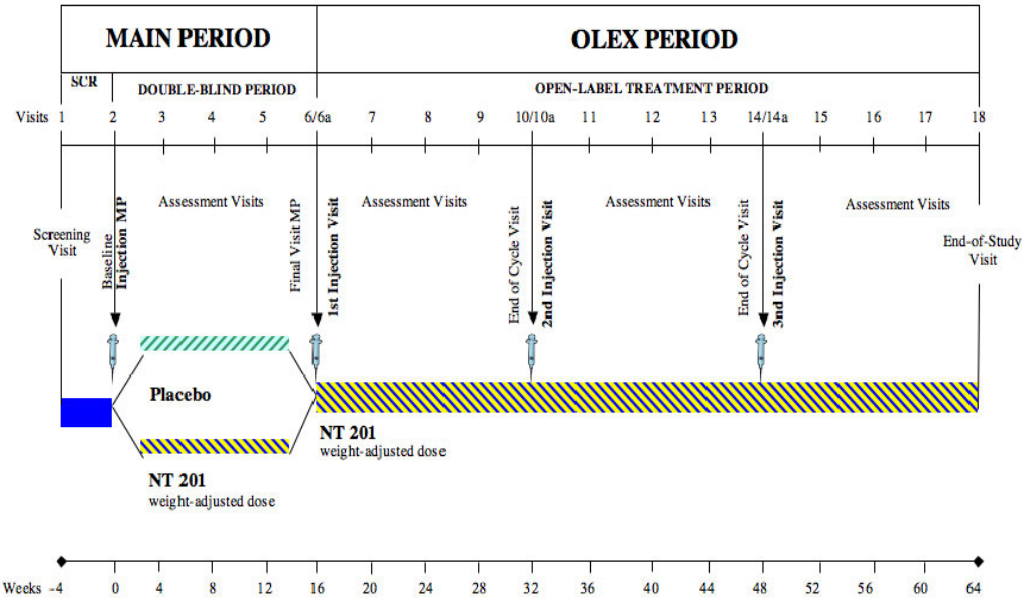
The efficacy and safety of Xeomin for the treatment of chronic sialorrhea was studied in children and adolescents with chronic troublesome sialorrhea associated with neurological disorders, and/or intellectual disability.

In support of this new population, the Applicant conducted a single controlled efficacy study with an open-label extension phase (Study MRZ60201_3091_1). The study recruited patients with cerebral palsy, genetic disorders causing developmental disability, or traumatic brain injury. The inclusion and exclusion criteria were acceptable, and the enrolled pediatric patients adequately represent likely users of Xeomin for the treatment of sialorrhea.

The Main Phase (MP) of Study MRZ60201_3091_1 was randomized, double-blind, placebo-controlled, and parallel-group for patients ages 6 to 17 years, while patients ages 2-5 years were treated only with open-label Xeomin (Figure 1).

In the open-label extension (OLEX) phase, enrolled patients could receive up to 3 additional open-label Xeomin treatments 16 ± 2 weeks apart.

Figure 1. Study MRZ60201-3091 Design Schematic



Source Complete study report

In the MP, patients weighing 12 kg to < 30 kg received a single treatment of 2 U/kg according to their weight category (see table 2), while patients weighing 30 kg or more

received a fixed total dose of 75 U of Xeomin, or placebo (Table 2). Ultrasound was used to guide injections into the submandibular and parotid glands bilaterally in all patients during the main and OLEX phases of the study.

Table 2. Study 3091 Dosing scheme

Body weight [kg]	Parotid gland, each side		Submandibular gland, each side	
	Total dose per gland [units]	Volume per injection [ml]	Total dose per gland [units]	Volume per injection [ml]
≥12 and <15	6	0.24	4	0.16
≥15 and <19	9	0.36	6	0.24
≥19 and <23	12	0.48	8	0.32
≥23 and <27	15	0.60	10	0.40
≥27 and <30	18	0.72	12	0.48
≥30	22.5	0.90	15	0.60

Source: Clinical review

One dose reduction was permitted only for the third or fourth OLEX treatment, if patients reported a treatment emergent adverse event (TEAE). Patients who experienced a TEAE at the lowest dose did not receive additional open-label treatment. In patients reporting a TEAE after previous treatment with at least 9 U in the Parotid glands and 6 U in the Submandibular glands, the dose was reduced one dose level.

Study Endpoints

The co-primary endpoints were the change from baseline (Visit 2) to Week 4 (Visit 3). in the mean uSFR and the parent or caregiver Global Impression of Change Scale (GICS) at Week 4 (Visit 3).

The prespecified analyses of the primary and co-primary endpoints in patients ages 6-17 years of age specified an MMRM model at a 2-sided, significance level with alpha=0.05 for comparison of the Least Square Means (LS-Means) between Xeomin-treated and placebo-treated patients. The MMRM model for the uSFR included treatment, pooled site, and age group as factors, and the uSFR at baseline as a covariate. The MMRM model for the GCIS included pooled site, age group, and modified Teachers Drooling Scale (mTDS) at baseline as variables.

The secondary endpoints in patients ages 6-17 years included the change in uSFR from baseline to Week 8 (Visit 4) and 12 (Visit 5) and the change for the caregiver/patient GICS at Weeks 8 and 12.

Unstimulated Salivary Flow Rate (uSFR)
Standard dry swabs (with safety threads) were weighed before placing them into the patient's mouth. The mean uSFR was measured by weighing the absorbent swabs that were placed between the cheek and gum over the openings of the salivary ducts on each side of the mouth. The moist swabs were re-weighed after remaining in the patients mouth for 5 minutes. The investigator or other site staff were trained in how to perform the measurement. The Salivary Flow Rate (SFR) was calculated according to the formula below.

$$\text{Salivary flow rate [mg/min]} = \frac{\text{Weight increase of swabs [mg]}}{\text{Time of collection [min]}}$$

The procedure was to be repeated after 30 minutes (± 5 minutes), and the average of the two results for flow rate was calculated to determine the mean uSFR.

Global Impression of Change Scale (GICS)
The caregiver/parent GICS used in the study was a 7-point scale, with -3 = "very much worse", 0 = "no change" and +3 = "very much improved".

Analysis Populations and Disposition
A total of 255 patients ages 6-17 years were randomized and treated in the MP (148 patients in the Xeomin group, and 72 patients in the placebo group), and 35 patients ages 2-5 years were treated with open-label Xeomin. Patients were recruited from 28 sites in the Ukraine 7 sites (n-121, 47.5 %); Poland 4 sites (n=51, 20 %); Russia 7 sites (n=44, 17.3 %); Georgia 3 sites (n=25, 9.8 %); Hungary 6 sites (n=13, 5.1 %) and; Serbia 1 site (n=1, 0.4 %). Most patients completed the Main Phase of the study (see Table 3).

Table 3. Study 3091 Analysis Populations (Main Phase)

	Placebo (6-17 years)		NT 201 (6-17 years)		NT 201 (2-5 years)	
	n	**(%)**	**n**	**(%)**	**n**	**%**
Randomized/assigned	72	(100.0)	148	(100.0)	36	(100.0)
Randomized/assigned and treated in MP as randomized/assigned	72	(100.0)	148	(100.0)	35	(97.2)
SES MP	72	(100.0)	148	(100.0)	35	(97.2)
FAS MP	72	(100.0)	148	(100.0)	35	(97.2)
PPS MP	65	(90.3)	138	(93.2)		
Completed MP	70	(97.2)	146	(98.6)	34	(94.4)
Discontinued MP	2	(2.8)	2	(1.4)	2	(5.6)
Reason for discontinuation of MP [a]						
AE(s)	0	(0.0)	1	(0.7)	1	(2.8)
Withdrawal by subject	2	(2.8)	0	(0.0)	1	(2.8)
Physician decision	0	(0.0)	0	(0.0)	1	(2.8)
Lost to follow-up	0	(0.0)	1	(0.7)	0	(0.0)

	Placebo (6-17 years)		NT 201 (6-17 years)		NT 201 (2-5 years)	
Main reason for discontinuation of MP [b]						
AE(s)	0	(0.0)	1	(0.7)	1	(2.8)
Withdrawal by subject	2	(2.8)	0	(0.0)	1	(2.8)
Lost to follow-up	0	(0.0)	1	(0.7)	0	(0.0)

100% base = N = number of subjects randomized/assigned to respective treatment group.
a: Multiple entries possible.
b: Main reason derived from multiple entries according to the above given order of reasons, e.g., AE(s) plus, Lack of efficacy leads to main reason AE(s).
FAS: full analysis set; MP: main period; n: number of subjects; PPS: per protocol set; SES: safety evaluation set.
AE: adverse event; MP: main period; n: number of subjects.
Source: Clinical review

Three patients (one in each group) did not continue in the OLEX phase after completing the MP. "Withdrawal by Subject" was the most common reason for discontinuation among patients ages 6-17 years during the OLEX period. Four patients discontinued from the OLEX phase because of an adverse event. No patient ages 2-5 years withdrew from the OLEX phase (see Table 4).

Table 4. Study 3091 OLEX Discontinuations

	NT 201 (MP=Placebo, 6-17 years)		NT 201 (MP=NT 201, 6-17 years)		NT 201 (MP=NT 201, 2-5 years)	
	n	(%)	n	(%)	n	(%)
Completed OLEX	60	(87.0)	129	(89.0)	33	(100.0)
Discontinued OLEX	9	(13.0)	16	(11.0)	0	(0.0)
Reason for discontinuation*						
AE(s)	0	(0.0)	4	(2.8)	0	(0.0)
Lack of efficacy	1	(1.4)	1	(0.7)	0	(0.0)
Withdrawal by subject	7	(10.1)	11	(7.6)	0	(0.0)
Physician decision	0	(0.0)	3	(2.1)	0	(0.0)
Lost to follow-up	2	(2.9)	1	(0.7)	0	(0.0)
Other	0	(0.0)	4	(2.8)	0	(0.0)
Main reason for discontinuation**						
AE(s)	0	(0.0)	4	(2.8)	0	(0.0)
Lack of efficacy	1	(1.4)	1	(0.7)	0	(0.0)
Withdrawal by subject	7	(10.1)	9	(6.2)	0	(0.0)
Physician decision	0	(0.0)	1	(0.7)	0	(0.0)
Lost to follow-up	1	(1.4)	1	(0.7)	0	(0.0)

100% base = N = number of subjects randomized/assigned to respective treatment group and treated in OLEX (overall period)/in the respective cycle
** Multiple entries possible*
*** Main reason derived from multiple entries according to the above given order of reasons, e.g., AE(s) plus Lack of efficacy leads to main reason AE(s)*
Source: Clinical Review

Demographics and Medical History

Dr. Park (Biometrics reviewer) found that patient demographic features were similar across all treatment arms. All patients in the MP of the study were White. The mean age in the MP population was 10 years in both treatment groups. The mean age in the subgroup of 2-5-year-old patients was 3.9 years. Approximately 63 % of the trial

participants were male in each of the treatment arms (see Table 5). Cerebral palsy was the most frequent cause of chronic sialorrhea (see Table 6) in each age group.

Table 5. Study 3091 Patient Demographic Characteristics at Baseline

	Placebo (6-17 years) (N = 72)	NT 201 (6-17 years) (N = 148)	NT 201 (2-5 years) (N = 35)
Sex (n (%))			
Male	45 (62.5)	93 (62.8)	22 (62.9)
Female	27 (37.5)	55 (37.2)	13 (37.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Age [years]			
n	72	148	35
Mean (SD)	10.3 (3.25)	10.4 (3.17)	3.9 (0.91)
Median	10.0	10.0	4.0
Min, max	6, 17	6, 17	2, 5
Ethnic origin/race (n (%))			
White	72 (100.0)	148 (100.0)	35 (100.0)
Height [cm]			
n	72	148	35
Mean (SD)	135.3 (16.92)	132.8 (17.15)	101.1 (8.09)
Median	132.5	131.5	101.0
Min, max	99, 170	93, 170	81, 124
Weight [kg]			
n	72	148	35
Mean (SD)	30.8 (11.67)	28.8 (11.48)	15.7 (3.00)
Median	27.5	26.5	15.2
Min, max	15, 69	12, 74	12, 25
BMI [kg/m^2]			
n	72	148	35
Mean (SD)	16.4 (3.65)	15.8 (3.25)	15.3 (1.85)
Median	16.1	15.1	15.1
Min, max	10, 32	10, 28	12, 19

Source: Statistical review

Table 6. Study 3091 Patient Medical History of Sialorrhea at Baseline

	Placebo (6-17 years) (N = 72)	NT 201 (6-17 years) (N = 148)	NT 201 (2-5 years) (N = 35)
Primary reason for sialorrhea (n (%))			
Cerebral palsy	43 (59.7)	102 (68.9)	20 (57.1)
Traumatic brain injury	1 (1.4)	9 (6.1)	0 (0.0)
Other	28 (38.9)	37 (25.0)	15 (42.9)
Time since first diagnosis of sialorrhea at screening [months]			
n	41	103	32
Mean (SD)	97.4 (47.96)	85.8 (46.15)	28.8 (15.45)
Median	94.9	80.9	28.1
IQR	71.3, 123.1	42.8, 125.5	17.8, 34.4
Min, max	2, 208	7, 210	7, 62
Intellectual disability (n (%))			
Yes	64 (88.9)	130 (87.8)	33 (94.3)
No	8 (11.1)	18 (12.2)	2 (5.7)

Source: Statistical review

Efficacy Results

Primary Efficacy Analysis (patients 6 to 17 years of age)
As confirmed by Dr. Park, the Change in uSFR from baseline to Week 4 was significantly greater for Xeomin-treated patients than for placebo-treated patients (p=0.0012, see Table 7).

Table 7. Change in uSFR from baseline to Week 4 – MP

		Placebo (6-17 years) (N = 72)	NT 201 (6-17 years) (N = 148)
Baseline	Mean (SD)	0.60 (0.25)	0.57 (0.25)
	Median (IQR)	0.55 (0.45; 0.73)	0.57 (0.40; 0.70)
Week 4	Mean (SD)	0.52 (0.21)	0.45 (0.21)
	Median (IQR)	0.49 (0.38; 0.60)	0.43 (0.32; 0.54)
Change	Mean (SD)	-0.07 (0.15)	-0.13 (0.17)
	Median (IQR)	-0.05 (-0.14; 0.01)	-0.10 (-0.22; -0.01)
	LS-Mean (SE) (95% CI)	-0.07 (0.015) (-0.10; -0.04)	-0.14 (0.012) (-0.16; -0.11)
LS-Mean difference versus placebo			-0.06 (0.019) (-0.10; -0.03)
	p-value		0.0012

uSFR is given in g/min
*LS-Means are from model with treatment, pooled site, and age group included as (fixed) factors and uSFR at baseline included as covariate. visit*treatment is interaction term and visit is repeated factor.*
CI: confidence interval; FAS: full analysis set; IQR: interquartile range; LS: least square; MMRM: mixed model repeated measurement; MP: main period; N: number of subjects in the respective group and analysis set; SD: standard deviation; SE: standard error; uSFR: unstimulated salivary flow rate
Source: Statistical review

Source: Statistical review

Similarly, the GICS rating was significantly greater for Xeomin-treated patients than for placebo-treated patients (p=0.0320; see Table 8).

Table 8. Study 3091 Caregivers GICS ratings at Week 4 – MP

		Placebo (6-17 years) (N = 72)	NT 201 (6-17 years) (N = 148)
Week 4	Mean (SD)	0.7 (0.9)	0.9 (0.9)
	LS-Mean (SE) (95% CI)	0.63 (0.104) (0.43; 0.84)	0.91 (0.075) (0.76; 1.06)
LS-Mean difference versus placebo			0.28 (0.127) (0.02; 0.53)
	p-value		0.0320

*LS-Means are from model with treatment, pooled site, and age group included as (fixed) factors and mTDS at baseline included as covariate. visit*treatment is interaction term and visit is repeated factor.*
Carer: caregiver/parent(s); CI: confidence interval; FAS: full analysis set; GICS: global impression of change scale; LS: least square; MMRM: mixed model repeated measurement; MP: main period; mTDS: modified Teacher's Drooling Scale; N: number of subjects in the respective group and analysis set; SD: standard deviation; SE: standard error
Source: Statistical review

The proportion of responders, defined as patients with a CGIS score of at least +1 (minimally improved) at Week 4 following treatment, was 71% for Xeomin-treated patients, vs. 46% for placebo-treated patients (see Table 9). The proportion of non-responders (0=No change) was about 26% in Xeomin-treated patients, vs. 53% in placebo-treated patients.

Table 9. Study 3091 Frequency of Caregivers / Parent GICS Ratings at Week 4 – MP (FAS)

	Placebo (6-17 years) (N = 72)	NT 201 (6-17 years) (N = 148)
n (%)		
-3 = Very much worse	0 (0.0)	1 (0.7)
-2 = Much worse	0 (0.0)	0 (0.0)
-1 = Minimally worse	1 (1.4)	3 (2.0)
0 = No change	38 (52.8)	39 (26.4)
+1 = Minimally improved	21 (29.2)	72 (48.6)
+2 = Much improved	9 (12.5)	27 (18.2)
+3 = Very much improved	3 (4.2)	6 (4.1)

Carer: caregiver/parent(s); FAS: full analysis set; GICS: global impression of change scale; MP: main period; n: number of subjects with respective rating; N: number of subjects in the respective group and analysis set.

Source: Statistical review

Dr. Park also noted that the results of various sensitivity analyses were generally consistent with those of the primary analysis.

Efficacy in Subgroups

The efficacy of Xeomin in patients age 6-17 years was similar in subgroup analyses by region, age, and gender (see Table 10). The consistent effects across subgroups support the overall efficacy of Xeomin for the treatment of chronic sialorrhea in pediatric patients.

Table 10. Study 3091 Subgroup analysis for uSFR

Subgroup		Treatment Arm	Sample Size (N)	Baseline Mean (SD)	LS Mean Difference from Baseline to Week 4 (SE)	LS Mean Difference from Placebo (95% CI)
Pooled site	Georgia	NT 201	42	0.53 (0.21)	-0.14 (0.02)	-0.056 (-0.128, 0.017)
	/Russia	Placebo	20	0.54 (0.20)	-0.08 (0.03)	--
	Hungary	NT 201	38	0.66 (0.38)	-0.17 (0.02)	-0.080 (-0.153, -0.007)
	/Poland /Serbia	Placebo	21	0.61 (0.36)	-0.09 (0.03)	--
	Ukraine	NT 201	68	0.55 (0.16)	-0.11 (0.02)	-0.057 (-0.115, 0.000)
		Placebo	31	0.63 (0.18)	-0.05 (0.02)	--
Age group	6-9 years	NT 201	60	0.57 (0.16)	-0.15 (0.02)	-0.062 (-0.122, -0.002)
		Placebo	30	0.56 (0.21)	-0.09 (0.02)	--
	10-12	NT 201	50	0.59 (0.31)	-0.13 (0.02)	-0.064 (-0.130, 0.002)

Subgroup		Treatment Arm	Sample Size (N)	Baseline Mean (SD)	LS Mean Difference from Baseline to Week 4 (SE)	LS Mean Difference from Placebo (95% CI)
	years					
		Placebo	24	0.59 (0.20)	-0.07 (0.03)	--
	13-17 years	NT 201	38	0.56 (0.29)	-0.12 (0.02)	-0.067 (-0.143, 0.009)
		Placebo	18	0.67 (0.36)	-0.06 (0.03)	--
Gender	Female	NT 201	55	0.63 (0.22)	-0.14 (0.02)	-0.082 (-0.145, -0.020)
		Placebo	27	0.56 (0.23)	-0.06 (0.02)	--
	Male	NT 201	93	0.54 (0.26)	-0.13 (0.02)	-0.052 (-0.10, -0.004)
		Placebo	45	0.62 (0.26)	-0.08 (0.02)	

uSFR: unstimulated salivary flow rate, MP: main period, FAS: full analysis set, MMRM: mixed model with repeated measurement, N: number, SD: standard deviation, SE: standard error, CI: confidence interval, LS: least square.
Source: Statistical review

The effect of Xeomin on the GICS is more variable across subgroups, but in the direction supporting meaningful benefit over placebo in all groupings (see Table 11).

Table 11. Study 3091 Subgroup analysis for Caregiver GICS – summary statistics by subgroup and MMRM with subgroup interaction term – MP

Subgroup		Treatment Arm	Sample Size (N)	LS Mean at Week 4 (SE)	LS Mean Difference from Placebo (95% CI)
Pooled site	Georgia/Russia	NT 201	42	0.80 (0.14)	0.064 (-0.413, 0.541)
		Placebo	20	0.73 (0.20)	--
	Hungary/Poland	NT 201	38	0.99 (0.15)	0.283 (-0.195, 0.761)
	/Serbia	Placebo	21	0.71 (0.19)	--
	Ukraine	NT 201	68	0.98 (0.11)	0.416 (0.036, 0.797)
		Placebo	31	0.56 (0.16)	--
Age group	6-9 years	NT 201	60	0.91 (0.12)	0.189 (-0.205, 0.583)
		Placebo	30	0.72 (0.16)	--
	10-12 years	NT 201	50	1.05 (0.13)	0.579 (0.143, 1.015)
		Placebo	24	0.47 (0.18)	--
	13-17 years	NT 201	38	0.76 (0.15)	0.012 (-0.491, 0.515)
		Placebo	18	0.75 (0.21)	--
Gender	Female	NT 201	55	0.98 (0.12)	0.422 (0.008, 0.835)
		Placebo	27	0.56 (0.17)	--
	Male	NT 201	93	0.86 (0.10)	0.188 (-0.132, 0.507)
		Placebo	45	0.67 (0.13)	

GICS: global impression of change scale, MP: main period, FAS: full analysis set, MMRM: mixed model with repeated measurement, N: number, SE: standard error, CI: confidence interval, LS: least square.
Source: Statistical review

Efficacy Conclusion

The results from the MP of Study 3091 support a clinically meaningful benefit of Xeomin 2 U/kg (to a total dose of 75 U) administered by injection into the salivary glands for treatment of chronic troublesome sialorrhea in pediatric patients ages 6-17 years. The overall effectiveness is also supported by the mechanism of action of Xeomin, which interferes with release of Ach from the presynaptic nerve terminals and

FDA's finding of safety and efficacy for Xeomin for the treatment of chronic sialorrhea in adults.

As there are no clinically meaningful differences in the syndrome or expected response to Xeomin between patients with chronic sialorrhea 2 to 5 years of age and older pediatric patients (6 to 17 years of age), it is reasonable to extrapolate the efficacy observed in the older age group to the former.

7. Safety

Exposure

Long-term patient exposure in Study 3091 is presented in Table 12. Dr. Bergmann, clinical reviewer, considers the exposure and the information included in the study report sufficient to assess safety.

Table 12. Study 3091 Repeat Exposure (n) by treatment- MP and OLEX Phases

Cohort	MP Treatment	MP	OLEX Treatment	OLEX 1	OLEX 2	OLEX 3		
Age 6-17 y.	Placebo	72	Xeomin	69	64	62	62	Total 3 sessions
	Xeomin	148		145	141	131	164	Total 4 sessions
Age 2-5 y.	Xeomin	35		33	33	33		
Total by epoch (N)		255		247	238	226		

Source: Clinical review

Serious Adverse Events

Deaths

There were no patient deaths during the MP or OLEX phases of the study.

Non-Fatal Serious Adverse Events

There were 20 serious adverse events (SAEs) reported in 12 (4%) patients in all phases of the study.

Two patients reported a SAE in the Main Phase of the study. One patient had been randomized to placebo. The other patient (age 4 years), who was treated with open-label Xeomin, withdrew because of a seizure and staphylococcal bacteremia on study day 28.

Two patients discontinued because of a SAE during the OLEX. One patient suffered a joint dislocation, and the other developed pneumonia 122 days after the second open-label Xeomin treatment. Eight patients continued in the study after experiencing a SAE; these events included respiratory tract infections (3), gastroenteritis (1), or gastrointestinal disorders (4). None of the events appeared related to treatment with Xeomin.

Discontinuations

During the course of the entire study, 13% of patients randomized in the MP did not complete the study, and 24% of patients who entered the OLEX discontinued during the OLEX, for the reasons listed in table 13. All 33 patients age 2-5 years who entered the OLEX completed the study.

Table 13. Study 3091 Discontinuations During OLEX

	NT 201 (MP=Placebo, 6-17 years)		NT 201 (MP=NT 201, 6-17 years)		NT 201 (MP=NT 201, 2-5 years)	
	n	(%)	n	(%)	n	(%)
Completed OLEX	60	(87.0)	129	(89.0)	33	(100.0)
Discontinued OLEX	9	(13.0)	16	(11.0)	0	(0.0)
Reason for discontinuation*						
AE(s)	0	(0.0)	4	(2.8)	0	(0.0)
Lack of efficacy	1	(1.4)	1	(0.7)	0	(0.0)
Withdrawal by subject	7	(10.1)	11	(7.6)	0	(0.0)
Physician decision	0	(0.0)	3	(2.1)	0	(0.0)
Lost to follow-up	2	(2.9)	1	(0.7)	0	(0.0)
Other	0	(0.0)	4	(2.8)	0	(0.0)

Source: Clinical review

Adverse Reactions-Main Phase

The adverse reactions in the MP of the study that were reported in at least 1% of patients and were more common than on placebo are shown in table 14.

Table 14. Study 3091 Adverse Reactions with Incidence ≥ 1% and Greater than Placebo in Patients 6-17 years (MP)

Adverse Reaction	XEOMIN (6-17 years) (N = 148) %	Placebo (6-17 years) (N = 72) %
Bronchitis	1	0
Headache	1	0
Vomiting	1	0

Source: Clinical review

In the 2 to 5 years of age group, nasopharyngitis was the only adverse event reported in more than one patient treated with open-label Xeomin in the MP. Local injection site reactions (i.e., one each for bruising, erythema, hematoma and induration) were the next most commonly reported adverse events.

Adverse Reactions in the Open-label Phase

Adverse events observed in patients during the OLEX phase of the study were generally similar to those observed in the MP. The frequency of adverse reactions were similar across age groups (see table 15).

Table 15. Study 3091 Adverse Events Observed in ≥ 3% of Patients during OLEX

SOC / PT	NT 201 (6-17 years) (N = 214)			NT 201 (2-5 years) (N = 33)			NT 201 (2-17 years) (N = 247)		
	n	(%)	m	n	(%)	m	n	(%)	m
Infections and infestations	50	(23.4)	81	13	(39.4)	23	63	(25.5)	104
Pharyngitis	12	(5.6)	13	3	(9.1)	3	15	(6.1)	16
Nasopharyngitis	13	(6.1)	16	1	(3.0)	1	14	(5.7)	17
Respiratory tract infection	7	(3.3)	7	3	(9.1)	4	10	(4.0)	11
Upper respiratory tract infection	7	(3.3)	7	1	(3.0)	1	8	(3.2)	8
Viral infection	4	(1.9)	7	2	(6.1)	3	6	(2.4)	10
Respiratory tract infection viral	1	(0.5)	2	4	(12.1)	5	5	(2.0)	7
Rhinitis	2	(0.9)	2	3	(9.1)	4	5	(2.0)	6
Respiratory, thoracic and mediastinal disorders	20	(9.3)	28	2	(6.1)	3	22	(8.9)	31
Cough	7	(3.3)	7	0	(0.0)	0	7	(2.8)	7
Gastrointestinal disorders	21	(9.8)	30	0	(0.0)	0	21	(8.5)	30
General disorders and administration site conditions	13	(6.1)	13	1	(3.0)	2	14	(5.7)	15
Pyrexia	10	(4.7)	10	1	(3.0)	2	11	(4.5)	12
Nervous system disorders	10	(4.7)	14	1	(3.0)	1	11	(4.5)	15
Headache	7	(3.3)	8	1	(3.0)	1	8	(3.2)	9

Source: Clinical review

Adverse Events in Select Subgroups (in patients ages 6-17 years - Main Period)

Age and Gender subgroups

The number of patients in each age category (6-9 years, 10-12 years and 13-17 years) in each treatment arm (Xeomin vs placebo) was too small for meaningful comparison. The number of patients in each gender group and treatment arm were also too small for meaningful comparison.

Race

All patients randomized in the study were White, thus comparisons of adverse reactions by racial groups was not possible.

Vital Signs

There were slight fluctuations in parameter means and outlying values, mainly for temperature (i.e., fever) and temporary weight loss. There were no meaningful trends for changes in vital signs in Xeomin-treated patients.

Clinical Laboratory

Clinical laboratory samples were drawn at screening, at the end of cycle Week 16 ± 2 weeks (Visit 6), and at the end of the OLEX (End of Study) visit. There were no meaningful changes in group mean or individual hematology or chemistry values. Seven patients had isolated, transient adverse events of abnormal values that did not appear related to treatment with Xeomin.

Botulinum Toxin A antibodies
In patients weighing at least 30 kg, fluorescent immune assay antibody (FIA-AB) screening tests were performed at the screening visit (Visit 1) and at the end of study visit (Visit 18). Positive FIA-AB assays results were followed up by an ex-vivo hemidiaphragm antibody assay (HAD-AB). Three patients who had positive HAD-AB at screening remained positive at Visit 18 (end of the OLEX study). All patients in the study, including the 3 patients with a positive HAD-AB, continued to respond to treatment with Xeomin.

Adverse Events of Special Interest (AESI)

Dental Adverse Events
Dental and oral cavity examinations were performed at screening, the final visit of the MP (week 16), the final visit of the second injection cycle (week 32), and the end-of-study visit (week 64). During the MP, there were no dental adverse events reported.

Distant Spread of Toxin Events
Dr. Bergmann noted 5 patients who had dysphagia during the entire study. The severity of 4 of the 5 cases was mild, with the last one moderate. All cases resolved without treatment.

Suicidality Assessment
The applicant amended the protocol to include the Columbia-Suicide Severity Rating Scale (C-SSRS) where feasible. The applicant used the suicidality Standardized MedDRA Query to search the adverse events for suicidality related events and found that no patient in the MP or OLEX showed suicidal or self-injurious behavior.

Safety Conclusions
Treatment of patients with Xeomin based on body weight at 2 U/kg, up to a recommended dose of 75 U, in the population 6-17 years of age has acceptable safety. The frequency of adverse events observe in this population, compared to placebo, was relatively low. The type and severity of adverse events were similar to those observed in pediatric patients treated with Xeomin for upper limb spasticity.

Adverse events in children ages 2-5 years were similar to those seen in older children.

8. Pediatrics

Study 3091 fulfills the PREA post-marketing requirement to evaluate the efficacy and safety, and to investigate the safety of repeat dosing of Xeomin in patients (2-17 years) treated for chronic troublesome sialorrhea.

9. Other Relevant Regulatory Issues

Clinical site inspections by the Office of Scientific Investigation were not requested for this supplement. No single center or country seemed to drive the efficacy results for

both co-primary endpoints. A risk assessment of the individual sites in the MP of the study did not reveal a pattern suggesting investigator misconduct.

10. Labeling

Incorporated in this document is the review of Supplement 92, a Changes Being Effected supplement that corrects a typographical error in Table 3 of the Xeomin label under Section 2.3, describing the treatment of pediatric upper limb spasticity. The revision shows the correct number of recommended injections, two in the pronator teres muscle, and one in the pronator quadratus muscle. The revision matches the information in the Study MRZ60201-3072-1 protocol and the final study report.

11. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

Approval.

Risk Benefit Assessment

The efficacy and safety of Xeomin for the treatment of chronic sialorrhea was previously demonstrated in adult patients. The persuasive efficacy results from the Main Phase of the applicant's placebo-controlled Study 3091 on reducing uSFR and on the co-primary GCIS are evidence that Xeomin provided a clinically meaningful reduction of sialorrhea caused by a variety of neurologic conditions in children and adolescents age 6-17 years. The safety and efficacy of weight-based dosing at 2 U/kg to 75 U of Xeomin in Study 3091 support the safety and efficacy of Xeomin using this approach. Information from the Study 3019 open-label extension support the safety of repeat dosing of Xeomin for the treatment of chronic sialorrhea using weight adjusted dosing.

Spread of toxin events do not appear to occur in pediatric patients following intraglandular administration of Xeomin at 2 U/kg of body weight to 75 U. The degree of reduced saliva production caused by treatment does not appear to increase the frequency of dental or oral mucosal adverse events, based on the available information. The use of ultrasound to locate and deliver Xeomin to the Parotid and Submandibular glands is recommended.

As there are no clinically meaningful differences in the syndrome or expected response to Xeomin between patients with chronic sialorrhea 2 to 5 years of age and older pediatric patients (6 to 17 years of age), it is reasonable to extrapolate the efficacy observed in the older age group to the former. Safety of that age group is acceptable.

The PREA post-marketing requirement to study Xeomin for the treatment of chronic sialorrhea in pediatric patients age 2-17 years is fulfilled.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

None.

Recommendation for other Postmarketing Requirements and Commitments

None.

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/s/

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