Use of an Interactive Voice Response System by patients with blepharospasm receiving repeated injections of NT 201 (Botulinum neurotoxin type A free from complexing proteins)

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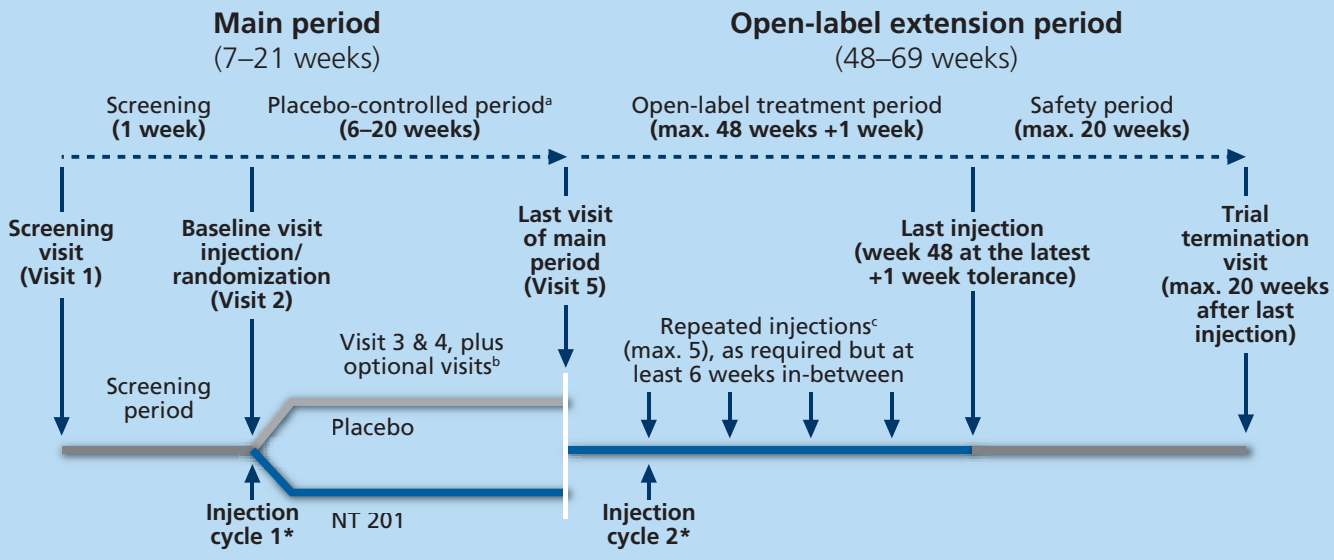
Background

- Blepharospasm is characterized by spontaneous, spasmodic, bilateral, intermittent or persistent involuntary contractions of the orbicularis oculi muscles. It is a type of focal dystonia. Blepharospasm can cause visual impairment, and can have a significant impact on the daily life of patients, producing functional blindness in some cases.
- Botulinum neurotoxin Type A (BoNT/A) acts selectively on peripheral cholinergic nerve endings, inhibiting the release of acetylcholine and thereby reducing muscle contraction. Given as a local injection, BoNT/A has been shown to be a highly effective and well tolerated symptomatic treatment of blepharospasm.[1]
- NT 201 (Xeomin®, Merz Pharmaceuticals, Germany) is the only available preparation of BoNT/A that is free from complexing proteins.[2]
- The efficacy and safety of NT 201 in the treatment of blepharospasm is supported by data from two clinical studies. In one double-blind, comparator-controlled study, NT 201 treatment showed comparable efficacy and safety to onabotulinumtoxinA (Botox®, Allergan, USA) when used in a 1:1 dosing.[3]
- In a second study (described here), the efficacy and safety of repeated injections with NT 201 was investigated in a placebo-controlled investigation with an open-label extension.[4] Importantly, this study included a patient rating of symptomatic efficacy (in addition to physician assessment) using an Interactive Voice Response System (IVRS).

Figure 1: Study design



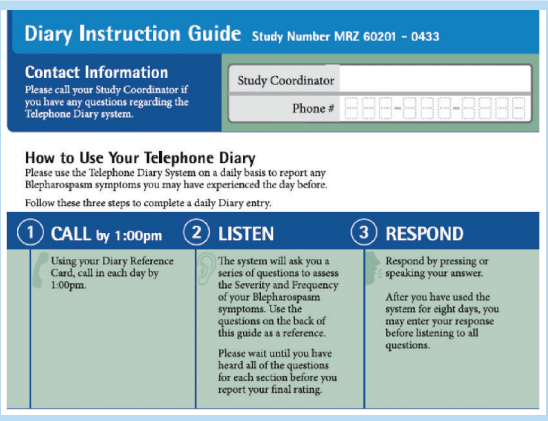
a) Individual duration of placebo-controlled period per patient b) Telephone contact Day 28–35 c) Control visits 6 weeks after each injection *IVRS recorded daily

Methods

Study design

- The study was a multicenter (US and Canada), prospective investigation, involving a ≤20-week placebo-controlled, double-blind period, followed by a 48–69-week open-label extension (OLEX) period (**Figure 1**).
- Eligible patients were aged 18–80 years, with a clinical diagnosis of bilateral benign essential blepharospasm, and a stable response to pre-treatment with at least two injections of onabotulinumtoxinA.
- Patients entering the placebo-controlled period were randomized (2:1) to receive a single cycle of treatment with NT 201 (≤50 U per eye; '**injection cycle 1**') or placebo. The injection with NT 201 in injection cycle 1 had to be similar to the two previous injections with onabotulinumtoxinA.
- Jankovic Rating Scale [JRS] rating was performed by an independent rater, not involved in any other study procedures, during the placebo-controlled period and at the 1st injection visit of the OLEX period.
- Upon entering the OLEX period, patients received immediate re-injection with NT 201 (termed '**injection cycle 2**'). Patients were followed for up to 48 weeks, receiving up to five injections of NT 201 (≤50 U per eye per session), with an interval between injections of at least 6 weeks. Dosing in the OLEX period was tailored to the individual patient. However the JRS severity subscore had also to be ≥2 prior to injection.
- Mandatory study visits took place 3 weeks (Visit 3) and 6 weeks (Visit 4) after the injection during the placebo-controlled period, and 6 weeks after each injection during the OLEX period.
- Patient diary ratings of the JRS scores were recorded daily during injection cycles 1 and 2 using an Interactive Voice Response System (IVRS), which was available in all relevant languages. Patients were required to call a toll-free number every day, preferably in the morning, and the IVRS guided them through the assessment of JRS scores. If the call was not made during the expected time frame, the IVRS diary system contacted the patient to evaluate the outstanding data (**Figure 2**).

Figure 2: Interactive Voice Response System (IVRS) telephone diary instructions



Outcome measures

Efficacy

- Efficacy measures included change from baseline in the JRS severity and frequency subscores, and in the JRS sumscore:
  - at 3 and 6 weeks after injection in the placebo-controlled period (injection cycle 1) – scores determined by independent rater assessment
  - at 6 weeks after each injection in the OLEX period – scores determined by investigator
  - at 3 and 6 weeks after injection in the placebo-controlled period (injection cycle 1), and at 6 weeks after the first injection in the OLEX period (injection cycle 2) – scores determined by patient diaries.

Safety

- Safety assessments included the frequency of AEs.

Statistical analyses

- Efficacy analyses were performed on the intent-to-treat (ITT) population, which included all randomized subjects. Safety was assessed in the evaluable for safety (EFS) population, which included all subjects who received study medication.
- At each study visit, IVRS scores were computed as the median of the previous 7 days, and were calculated if at least 3 of the previous 7 days were available. Baseline scores were calculated as the median value of all IVRS values collected before injection. If IVRS data for less than 3 of the previous 7 days were available, the median value was defined as missing.
- Confirmatory analysis examining the difference between treatment groups (placebo-controlled period) was based on the comparison of least squares (LS) means from an analysis of covariance (ANCOVA) model. Change from baseline in JRS scores was assessed using a one-sample t-test (OLEX period). Missing data were replaced by the last observation carried forward (LOCF) strategy during injection cycle 1. No replacement of missing values took place during injection cycle 2.
- Correlations between independent/investigator rated and patient diary (IVRS) rated JRS scores were calculated using Pearson's correlation coefficient of observed case (OC) data.
- Safety data were analyzed descriptively.

Results

Population characteristics

- Overall, 109 patients were randomized, and 102 patients continued into the OLEX period (ITT population). The EFS population consisted of 108 patients in the placebo-controlled period (1 patient did not receive study medication), and of 102 patients in the 1st injection of the OLEX.
- The baseline demographics of the placebo-controlled population are shown in **Table 1**.
- IVRS data were available for 99 patients in the placebo-controlled period and for 100 patients in the OLEX period.
- In the placebo-controlled period, 75 patients were randomized to NT 201 and 34 patients were randomized to placebo.

Table 1: Patient baseline demographics in placebo-controlled period (ITT population)

	NT 201 (n=75)	Placebo (n=34)	Total (n=109)
Male, n (%)	26 (34.7)	12 (35.3)	38 (34.9)
Female, n (%)	49 (65.3)	22 (64.7)	71 (65.1)
Mean age, years (±SD)	61.5 (±11.0)	62.6 (±8.7)	61.9 (±10.3)
Mean BMI, kg/m² (±SD)	28.6 (±5.5)	28.1 (±6.1)	28.5 (±5.7)

- The mean dose of NT 201 received during injection cycle 1 was 66.9 ± 22.3 U, and the mean dose of placebo during injection cycle 1 was 60.2 ± 21.7 U.
- The mean dose of NT 201 received during injection cycle 2 was 64.7 ± 22.4 U.

Efficacy outcomes

JRS scores: Interactive Voice Response System (IVRS)

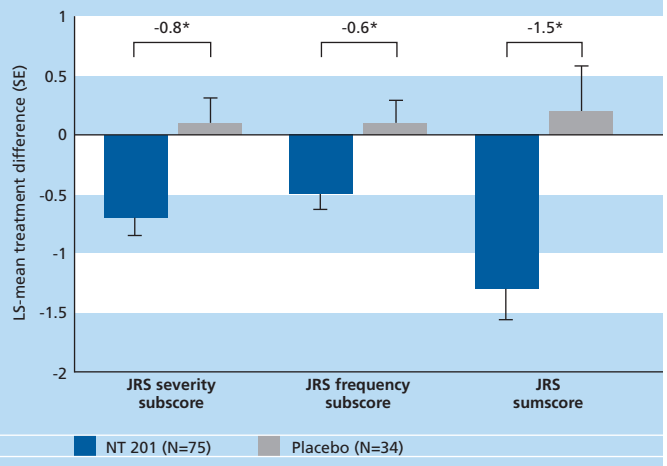
- JRS severity subscore, JRS frequency subscore, and JRS sumscore were markedly reduced 3 and 6 weeks after injection during the placebo-controlled period (**Table 2**), as well as 6 weeks after injection during the OLEX period. As shown in the second injection cycle (OLEX period), these reductions were significant versus baseline (p<0.001, one-sample t-test; **Table 3**).
- Comparison of LS means during the placebo-controlled period (injection cycle 1) also revealed that the changes from baseline in JRS scores were significant for NT 201 treatment versus placebo (p<0.05 at 3 weeks for JRS severity subscore and JRS sumscore, and p≤0.009 at 6 weeks for all JRS scores, ANCOVA) (**Figure 3**).

Table 2: JRS scores rated by IVRS in placebo-controlled period (ITT population)

	Injection cycle 1					
	JRS severity subscore		JRS frequency subscore		JRS sumscore	
Visit	NT 201 (N=67)	Placebo (N=32)	NT 201 (N=67)	Placebo (N=32)	NT 201 (N=67)	Placebo (N=32)
Baseline Mean (SD)	2.6 (0.98)	2.5 (1.17)	2.5 (1.00)	2.4 (1.15)	5.1 (1.86)	4.9 (2.21)
Week 3 Mean (SD) change	-0.8 (1.15)	-0.2 (0.93)	-0.6 (1.20)	-0.2 (1.01)	-1.4 (2.18)	-0.36 (1.87)
Week 6 Mean (SD) change	-0.8 (1.24)	0.2 (1.07)	-0.5 (1.13)	0.2 (1.05)	-1.3 (2.19)	0.3 (2.00)

N=number of subjects with assessments; JRS=Jankovic Rating Scale; ITT=intent-to-treat; Missing Values Replaced by last observation carried forward (LOCF); SD=standard deviation

Figure 3: LS mean treatment difference in JRS scores rated by IVRS at 6 weeks post-injection in the placebo-controlled period (ITT population)



* adjusted treatment difference (95% Confidence Interval), p≤0.01
JRS=Jankovic Rating Scale; ITT=intent-to-treat;
Missing Values Replaced by last observation carried forward (LOCF); LS=least squares

Table 3: JRS scores rated by IVRS and investigators in the OLEX period (injection cycle 2) (ITT population)

	IVRS				Investigator rating			
Visit	N	JRS severity subscore	JRS frequency subscore	JRS sumscore	N	JRS severity subscore	JRS frequency subscore	JRS sumscore
1st Injection OLEX Period Mean (SD)	100	2.6 (1.07)	2.6 (0.96)	5.2 (1.96)	102	3.1 (0.76)	2.8 (0.79)	5.9 (1.38)
Week 6 Mean (SD) change	92	-1.0 (1.01)*	-0.9 (1.00)*	-1.8 (1.93)*	96	-1.3 (1.20)*	-1.1 (1.17)*	-2.4 (2.20)*
p-value		<0.001	<0.001	<0.001		<0.001	<0.001	<0.001

* p<0.001 one sample t-test
N=number of subjects; JRS=Jankovic Rating Scale; ITT=intent-to-treat; SD=standard deviation; IVRS=interactive voice response system

Table 4: JRS scores rated by independent raters in placebo-controlled period (ITT population)

	Injection cycle 1					
	JRS severity subscore		JRS frequency subscore		JRS sumscore	
Visit	NT 201 (N=75)	Placebo (N=34)	NT 201 (N=75)	Placebo (N=34)	NT 201 (N=75)	Placebo (N=34)
Baseline Mean (SD)	3.1 (0.73)	2.9 (0.81)	2.8 (0.90)	2.8 (0.76)	5.9 (1.49)	5.8 (1.42)
Week 3 Mean (SD) change from Baseline	-1.0 (1.20)	-0.3 (1.02)	-0.9 (0.98)	-0.3 (0.86)	-1.9 (1.93)	-0.5 (1.78)
Week 6 Mean (SD) change from Baseline	-0.8 (1.18)	0.2 (0.91)	-0.6 (1.03)	-0.03 (0.90)	-1.4 (1.98)	0.2 (1.68)

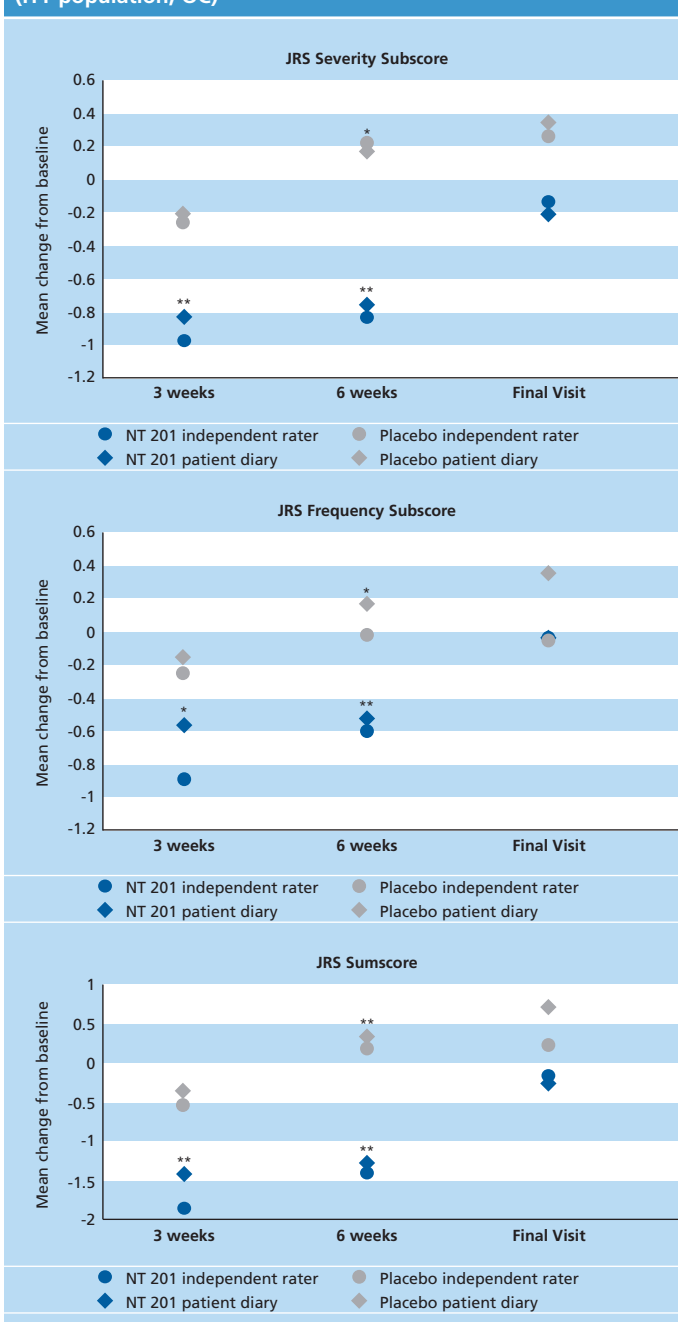
N=number of subjects, JRS=Jankovic Rating Scale; ITT=intent-to-treat; Missing Values Replaced by last observation carried forward (LOCF), SD=standard deviation

- Therapeutic effect (reflected by the difference between results in the NT 201 group and the placebo group at corresponding visits) was more clearly demonstrated with the JRS severity subscore than with the JRS frequency subscore and was most evident at Week 6 (**Table 2**).

JRS scores: independent/investigator rated

- According to independent ratings, JRS severity and frequency subscore, and sumscores were markedly reduced at 3 and 6 weeks after injection in injection cycle 1 (**Table 4**).
- In the placebo-controlled period (injection cycle 1), comparison of LS means revealed that the changes from baseline in JRS scores were significant for NT 201 treatment versus placebo (p≤0.006 at 3 weeks for JRS scores, and p≤0.006 at 6 weeks, ANCOVA).
- In the second injection cycle (OLEX period), the investigator rated JRS severity, and frequency subscores, and the JRS sumscore were significantly reduced versus baseline (p<0.001, one-sample t-test) (**Table 3**).
- Independent rater and IVRS ratings of JRS scores correlated positively at all study visits during the placebo-controlled period. Correlation was only assessed during injection cycle 1.
- Correlations were significant in the NT 201 group at 3 and 6 weeks post-injection, and for the placebo group at 6 weeks post-injection (**Figure 4**).

Figure 4: Correlation of independent rater and IVRS ratings of JRS scores post-injection during the placebo-controlled period (ITT population; OC)



*p<0.05; **p<0.001 for correlation between rater assessments (Pearson's correlation coefficient); JRS=Jankovic Rating Scale; ITT=intent-to-treat; OC=observed cases

Safety outcomes

- Repeated injections with NT 201 were generally well tolerated.
- Slightly more subjects reported AEs under treatment with NT 201 (70.3%) than under treatment with placebo (58.8%).
- In the 1st injection cycle of the OLEX period, 51.0% of patients treated with NT 201 reported at least one AE.
- The most common AEs in both injection cycles were eyelid ptosis and dry eye under treatment with NT 201; the most common AEs for the placebo group in the placebo-controlled period were dry eye and upper respiratory tract infection.
- No serious or unexpected AEs were reported in patients receiving treatment with NT 201.

Conclusions

- NT 201 produced significant improvements in the symptoms of blepharospasm as assessed by JRS scores in comparison to placebo.
- Consistent significant improvements were also seen during injection cycle 2. Changes in the respective JRS scores 6 weeks after injection were even slightly higher both by IVRS and investigator assessments than in the placebo-controlled period.
- Patient ratings (via the IVRS system) indicated the favorable therapeutic efficacy of repeated NT 201 treatments in blepharospasm.
- Correlation between IVRS and independent rater scores were significant under treatment with NT 201 at 3 and 6 weeks post-injection in the placebo-controlled period.
- Repeated injections with NT 201 were safe and well tolerated.

References

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