Safety and efficacy of repeated NT 201 (Botulinum neurotoxin type A free from complexing proteins) injections of patients with blepharospasm

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Background

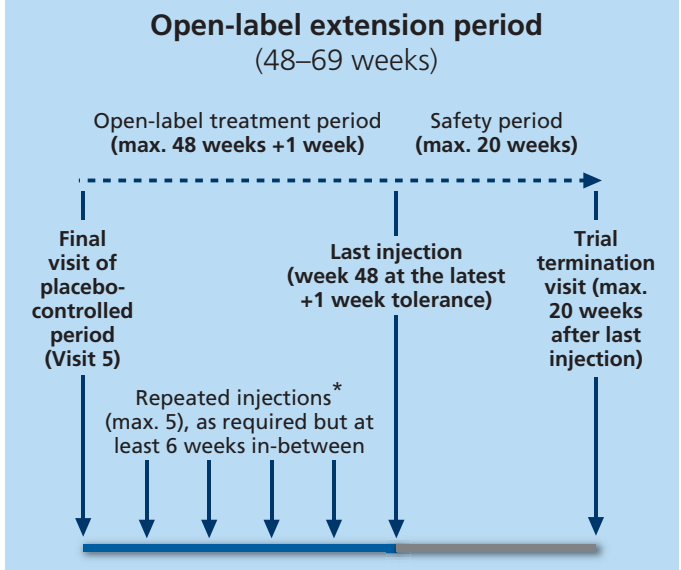
- Blepharospasm is a form of focal dystonia that is characterized by excessive muscle tone in the orbicularis oculi muscle of the eyelid. This leads to a sporadic or permanent involuntary closure of the eyelid, and can result in functional blindness.[1]
- The visual impairment caused by blepharospasm is associated with significant disability that can impact on many aspects of daily life. For example, people with blepharospasm may find it difficult, or impossible, to read, watch television or perform household tasks. Frequently, they are unable to leave the house without a companion.
- NT 201 (Xeomin®, Merz Pharmaceuticals, Germany) is a preparation of Botulinum neurotoxin type A (BoNT/A) that is free from complexing proteins, and is indicated for the symptomatic treatment of blepharospasm.[2]
- In a previous double-blind, randomized, clinical study of ~300 patients with blepharospasm, NT 201 demonstrated comparable efficacy and safety to onabotulinumtoxinA (Botox®, Allergan, USA) when used in a 1:1 dosing.[3]
- In another study, a single injection session with NT 201 produced significant efficacy versus placebo, improving the symptoms and disability associated with blepharospasm.[4] The aim of the investigation presented here, is to assess the long-term safety and efficacy of repeated injections with NT 201 in an open-label extension of this placebo-controlled study over a 1-year period.

Methods

Study design

- The study was an open-label extension (OLEX) of a ≤20-week placebo-controlled, double-blind study of NT 201 in patients with blepharospasm.[4]
- In the double-blind study, patients received a single treatment with NT 201 or placebo and were followed for up to 20 weeks. At week 20, or if a new injection was required between weeks 6 and 20 and the Jankovic Rating Scale (JRS) severity subscore was ≥2, the final visit was performed, and patients entered the OLEX period (re-injection was included in the OLEX period).
- In the OLEX period, all patients (from 29 centers in the US and Canada) received active treatment with NT 201. Patients were followed for up to 48 weeks, receiving up to five injections of NT 201 (≤50 U per eye per session), with an injection interval of at least 6 weeks (**Figure 1**). Mandatory study visits took place at 6 weeks after each injection.
- Injection intervals were chosen at the patient's and physician's discretion, and dosing was tailored to the individual patient, based on the severity and frequency of spasms, patient response, duration of effect, and occurrence of adverse events (AEs).
- After the last injection of the OLEX period, there was a safety follow-up until a new injection was required (maximum of 20 weeks) = study termination visit.

Figure 1: OLEX study design



Outcome measures

Efficacy

- Efficacy measures included:
  - change in the JRS severity and frequency subscores, and in the JRS sumscore (blinded Investigator-rated), at 6 weeks after each injection, and at study termination (versus first OLEX injection visit). The JRS includes two categories: severity and frequency, each with 5 rating classes of 0–4 points (0=absent, 4=most severe)[5]
  - change in Blepharospasm Disability Index (BSDI) at 6 weeks after each injection, and at study termination (versus first OLEX injection visit)[6]
  - change in JRS severity, frequency, and sumscores, rated by subject diary, at 6 weeks after the first injection. Values were calculated as the median score of the 7 days prior to the study visit
  - patient evaluation of global response at 6 weeks after each injection, and at the study termination visit
  - duration of treatment effect (= interval between two injection sessions).

Safety

- Safety was assessed via the frequency of AEs, and the Investigator's global assessment of tolerability.

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.
- In the OLEX period, only observed case (OC) analyses were performed.
- Descriptive summary statistics (mean ± standard deviation, SD) were calculated for all efficacy variables. The mean change in JRS and BSDI scores were analyzed using one-sample t-tests, with differences considered significant if $p<0.05$.
- Patient and Investigator global assessments, and safety data, were analyzed descriptively.
- All analyses of the OLEX period can be regarded as descriptive only.

Results

Population characteristics

- In total, 102/109 patients completed the double-blind study and entered the OLEX period.
- The baseline demographics of the OLEX population are shown in **Table 1**. The ITT and EFS populations both included all 102 patients.

Table 1: Patient baseline demographics (ITT population)

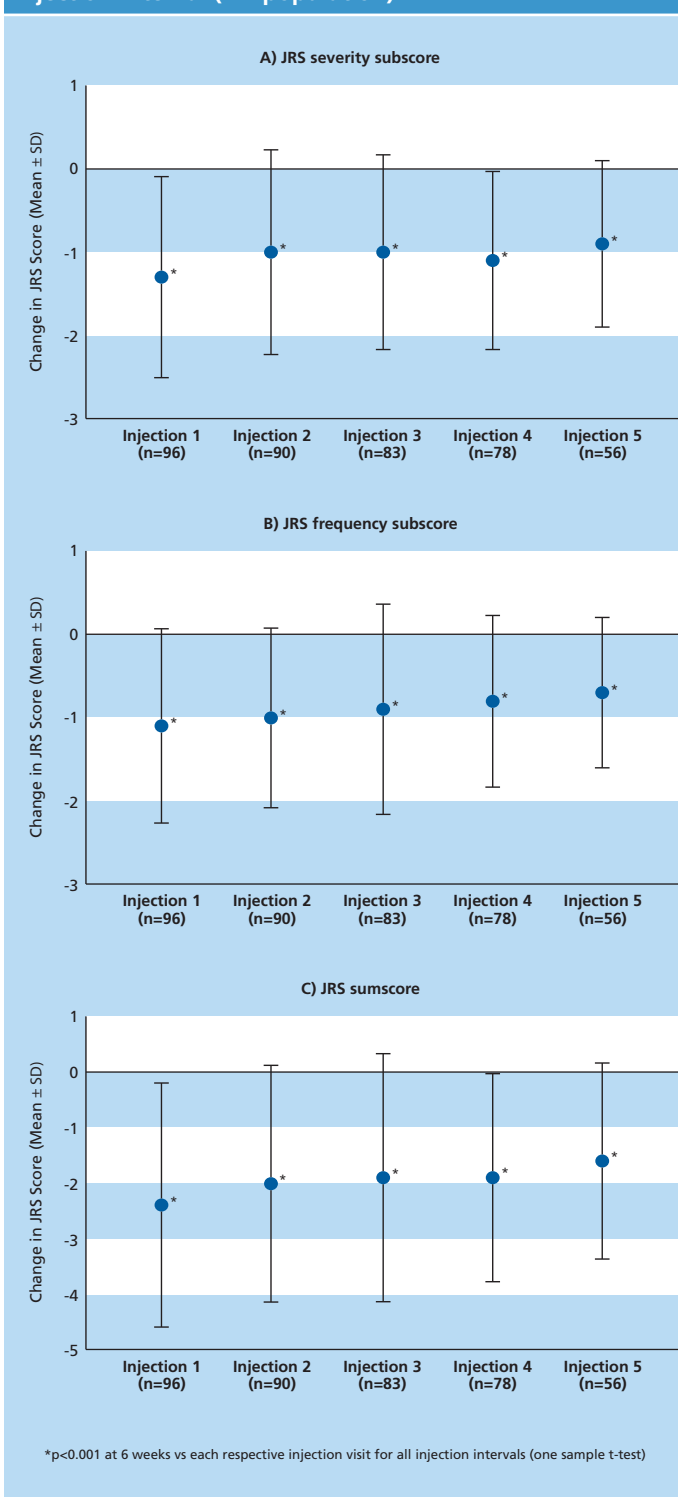
	Patients receiving NT 201 in OLEX phase (n=102)
Gender, n (% male)	36 (35.3)
Mean age, years (±SD)	62.2 (±10.3)
Mean BMI, kg/m² (±SD)	28.4 (±5.3)

- The mean dose of NT 201 per injection session ranged from 64.7 ± 22.4 U to 72.7 ± 22.0 U, with a maximum dose of 100 U.
- The mean cumulative dose was 276.7 ± 135.6 U, with a maximum cumulative dose of 500 U.
- Overall, 82 patients (80.4%) completed the OLEX period. The most frequent reasons for study withdrawal were 'informed consent withdrawn' (6 patients; 5.9%), 'withdrawal criteria', 'insufficient efficacy', and 'other' (4 patients each; 3.9%).

Efficacy outcomes

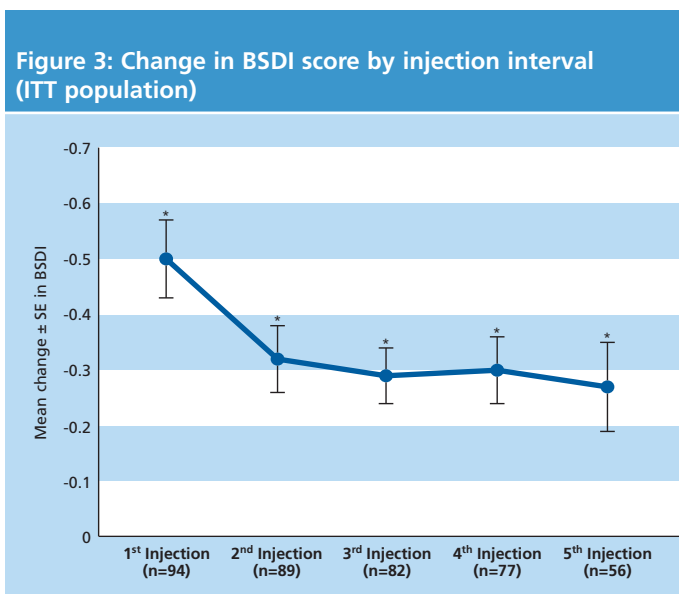
- In terms of symptomatic outcomes, the JRS frequency and severity subscores, and the JRS sumscore (Investigator-rated), were significantly improved at 6 weeks after each injection visit ($p<0.001$) (**Figure 2**).
- JRS scores (frequency, severity, and sumscore) were also improved across the whole OLEX phase, with a significant change in score at the study termination visit as compared with the baseline OLEX visit prior to the first injection ($p<0.001$).

Figure 2: Change in JRS scores (Investigator-rated) by injection interval (ITT population)



- JRS ratings from subject diaries (first injection interval only) were consistent with these findings. Based on the subject diaries, the JRS sumscore was significantly improved at 6 weeks after the first injection ($p<0.001$).
- As shown in **Figure 3**, patient disability (BSDI score) was also significantly improved at 6 weeks after each injection interval ($p\leq0.001$).

Figure 3: Change in BSDI score by injection interval (ITT population)



Patient global response

- Across the OLEX period, the range of patients who rated their global response to NT 201 treatment as 'improved' varied between 83.9% and 90.8% of cases. This included ratings of 'marked improvement' (34.5%–48.1%) and 'complete abolishment of all signs and symptoms' (5.4%–11.8%).
- Viewed by injection interval, these positive patient ratings did not diminish with repeated injections.

Duration of treatment effect

- The mean duration of treatment effect after each injection ranged from 9.1 ± 5.1 weeks to 10.9 ± 5.8 weeks.

Safety outcomes

- Over the whole OLEX period, AEs were experienced by 81/102 patients (79.4%).
- The incidence of AEs decreased from the first to the fifth injection, indicating no cumulative effect with repeated doses (**Table 2**).
- The AEs with the highest reported incidence rates were eyelid ptosis (32 patients; 31.4%), dry eye (18 patients; 17.6%), nasopharyngitis (9 patients; 8.8%), visual disturbance, and upper respiratory tract infection (both 8 patients; 7.8%).
- A total of 10 patients reported serious AEs, but none were considered as related to treatment with NT 201.
- No patient withdrew from the study due to AEs.

Table 2: Patients experiencing at least one AE by injection interval (EFS population)

Injection interval	Total number of patients	Number (%) of patients with at least one AE
Total (1–5)	**102**	**81 (79.4)**
1	102	52 (51.0)
2	93	45 (48.4)
3	87	35 (40.2)
4	81	35 (43.2)
5	56	24 (42.9)

- Investigators rated the global tolerability of NT 201 injections as 'very good' or 'good' in the large majority of cases (93.9%–100%).

Conclusions

- Repeated injections with NT 201 were effective in improving symptoms (JRS scores) and disability (BSDI scores) in patients with blepharospasm.
- The efficacy of NT 201 was maintained across up to five injection intervals over a period of >48 weeks.
- NT 201 was also well tolerated in the long-term, with no safety concerns associated with repeated dosing.
- Overall, Investigators rated the global tolerability of NT 201 as 'good/very good' in 93.9% to 100% of cases.

References

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