INCOBOTULINUMTOXINA (NT-201) INJECTIONS ARE SAFE AND EFFECTIVE IN ADULT SUBJECTS WITH BLEPHAROSPASM ACROSS DOSING INTERVALS IN A REPEATED DOSE STUDY

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Background

- IncobotulinumtoxinA (XEOMIN®, formerly also called NT 201), a purified botulinum toxin type A free from accessory proteins with a low immunogenic potential, has shown comparable efficacy and safety to onabotulinumtoxinA in the treatment of blepharopasm and cervical dystonia when used in a 1:1 dosing ratio.[1-5]

- In the previously presented prospective, placebo-controlled, double-blind main period (MP) of this study, subjects with blepharospasm were randomized 2:1 to receive incobotulinumtoxinA (≤50 U per eye) or placebo.[6]

  o IncobotulinumtoxinA was well tolerated and provided significant improvements

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in clinical scores compared with placebo.

- There is a lack of studies reporting the long-term treatment of blepharospasm with repeated injections of botulinum toxin type A.

Objective

- To compare safety and efficacy across flexible dosing intervals in a repeated-dose study of incobotulinumtoxinA injections in subjects with blepharospasm.

Methods

Open-label extension (OLEX) study design

- Subjects with blepharospasm who had completed the MP[6] received incobotulinumtoxinA (Figure 1):

  - ≤5 injection sessions

  - ≤50 U per eye per session

  - ≥6-week intervals according to:

    - physician and subject discretion

    - requirement of a Jankovic Rating Scale (JRS)[7] severity subscore ≥2.

Subjects

- Male or female, aged 18-80 years.

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- Previously treated with ≥2 injection sessions of OnabotulinumtoxinA (Botox[®])

    o had treatment ≥10 weeks prior to baseline assessment for the MP (was there an upper limit as to the latency from last Botox injection?) What about if the patient has not been treated for >2 years?

    o had a stable therapeutic response prior to study entry

    o had received doses ≤50 U per eye.

Outcome measures

- Change in JRS Sumscore from each injection session to a control visit 6 weeks later

    o JRS includes two sub-categories: severity and frequency, each with five rating classes of 0-4 points (0 = absent, 4 = most severe).

- Post-hoc analysis:

    o Each subject receiving ≥2 OLEX injection sessions was classified into an injection group according to their median injection interval:

        ▪ ≤10 weeks

        ▪ >10 to ≤12 weeks

        ▪ >12 to ≤14 weeks or >14 weeks.

    o Mean change in JRS Sumscore, across all injection sessions, was then analyzed by injection group.

- Safety outcomes included a post-hoc analysis of the frequency of treatment-emergent adverse events (TEAEs) across injection groups. Patients were actively asked by direct questioning about the occurrence of certain adverse events.

Statistical analyses

- One-sample t-tests were used to evaluate the mean change in JRS Sumscore between each injection session and the control visit 6 weeks later.

- Paired t-tests were used to evaluate the mean change in JRS Sumscore across all injection sessions for each of the injection groups.

- Chi-square test was used to evaluate differences in the overall occurrence of TEAEs between injection groups.

Results

Subjects

- 102/109 (93.6%) subjects completed the MP and entered the OLEX period.

  - The baseline demographics of the OLEX population are shown in Table 1.

- The mean (standard deviation [SD]) dose of incobotulinumtoxinA per OLEX injection session ranged from 64.7 (22.4) U to 72.7 (22.0) U, with a maximum overall dose of 100 U.

- Of the 93 subjects receiving ≥2 OLEX injection sessions, the numbers of subjects in each injection group are shown in Table 2.

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JRS Sumscore

- In the overall OLEX population, JRS Sumscores were significantly improved across the whole OLEX period between each injection session and the respective control visit 6 weeks later (p<0.001; Figure 2).

- Mean changes in JRS Sumscores across all injections sessions indicated statistically significant improvements in all injection groups (p<0.001; Table 2).

Safety and tolerability outcomes

- TEAEs were experienced by 81/102 (79.4%) subjects.

- The TEAEs with the highest reported incidence rates during individual injection cycles were eyelid ptosis, dry eye, visual disturbance, nasopharyngitis, visual disturbance, and upper respiratory tract infection.

- There were no statistically significant differences in the overall occurrence of TEAEs between injection groups (p=0.1229; Table 2).

Conclusions

- Repeated injections of incobotulinumtoxinA provided a sustained efficacy for up to 89 weeks and were well tolerated in the treatment of blepharospasm when administered according to a flexible dosing regimen, even when injected more frequently than every 12 weeks. There were no statistically significant differences in the frequencies of TEAEs between the groups with different injection intervals.

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References (please provide at least the 3 first names of authors and the title of the papers)

1. Kenney C, Jankovic J. Botulinum toxin in the treatment of blepharospasm and hemifacial spasm. J Neural Transm 2008;115:585-591.

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Table 1: Demographics and characteristics at OLEX baseline <mark>[Table to be redrawn]</mark>

	Subjects in OLEX period (n=102)
Female gender, n (%)	66 (64.7)
Mean age, years (SD)	62.2 (10.3)
Mean JRS Sumscore (SD)	5.9 (1.38)

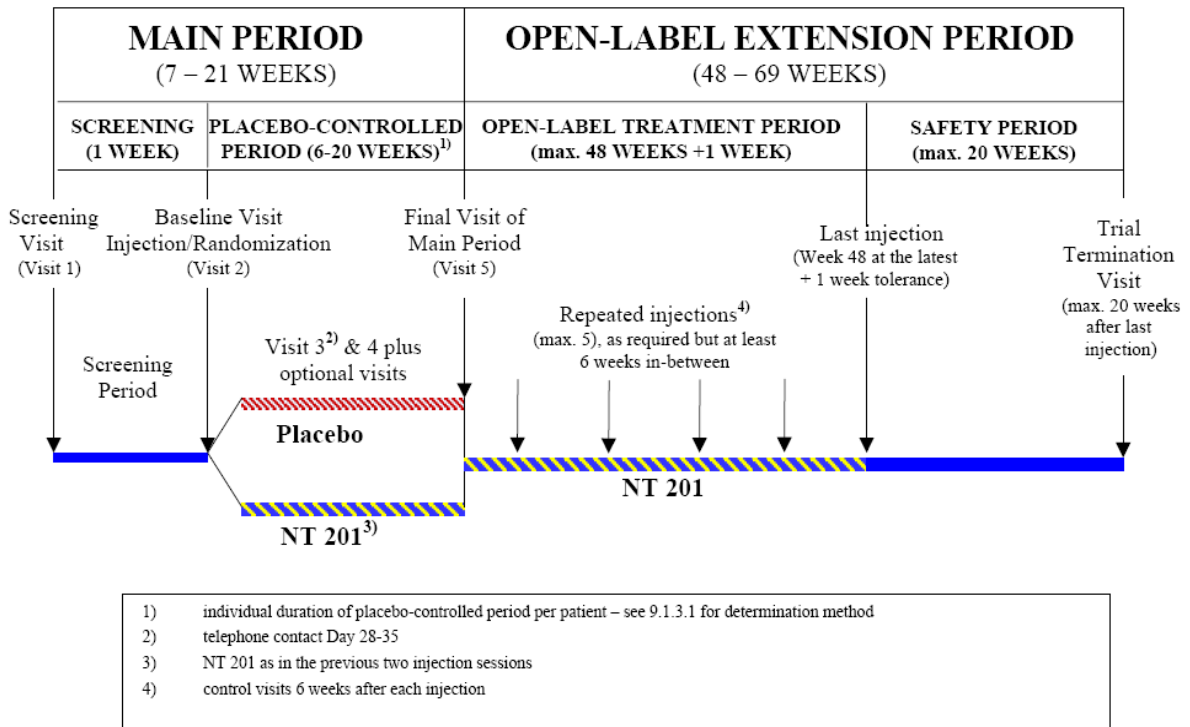JRS, Jankovic Rating Scale; OLEX, open-label extension period; SD, standard deviation.

Table 2: Incidence of TEAEs by injection group. Subjects had to accomplish ≥2 injection sessions in the OLEX period. [Table to be redrawn]

Injection group	Number of subjects (%) N=93	Incidence of TEAEs, n (%) N=76	Comparison of frequency of TEAEs between injection groups
≤10 weeks	22 (23.7)	18 (81.8)	n.s.
>10 to ≤12 weeks	30 (32.3)	24 (80.0)	n.s.
>12 to ≤14 weeks	23 (24.7)	22 (95.7)	n.s.
>14 weeks	18 (19.4)	12 (66.7)	n.s.

JRS, Jankovic Rating Scale; n.s., not significant; SD, standard deviation; TEAEs, treatment-emergent adverse events.

Figure 1: Study design [To be redrawn]

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1) individual duration of placebo-controlled period per patient – see 9.1.3.1 for determination method
2) telephone contact Day 28-35
3) NT 201 as in the previous two injection sessions
4) control visits 6 weeks after each injection

Figure 2: Mean changes in JRS Sumscores between each injection session and the respective control visit 6 weeks later (ITT; N=102) <mark>[Bar chart to be developed from data below]</mark>

Text Table 1:   Descriptive Statistics for Mean JRS Severity Subscore, JRS Frequency Subscore, and JRS Sumscore by Visit (Rated by Investigator, ITT population, OLEX Period)

Visit		JRS Sumscore
	N	
		Mean (SD)
1st Injection Visit (V6)	102	5.9 (1.38)
Control Visit after 1st Injection (V7)	96	3.4 (2.28)
2nd Injection Visit (V8)	93	5.3 (1.34)
Control Visit after 2nd Injection (V9)	90	3.3 (2.13)
3rd Injection Visit (V10)	87	5.0 (1.40)
Control Visit after 3rd Injection (V11)	83	3.1 (2.21)
4th Injection Visit (V12)	81	5.0 (1.23)
Control Visit after 4th Injection (V13)	78	3.1 (2.03)
5th Injection Visit (V14)	56	4.9 (1.16)
Control Visit after 5th Injection (V15)	56	3.4 (2.04)

ITT, intent-to-treat population; JRS, Jankovic Rating Scale; SD, standard deviation.

*p<0.001 at 6 weeks vs each respective injection visit for all injection intervals (two-sided t-test)