Efficacy and Safety of IncobotulinumtoxinA in the Treatment of Children and Adolescents with Chronic Troublesome Sialorrhea Associated with Neurological Disorders and/or Intellectual Disability

Steffen Berweck,[1,2] Birgit Flatau-Baque,[3] Michael Althaus,[3] on behalf of the SIPEXI study group

The SIPEXI study

SIPEXI (Sialorrhea Pediatric Xeomin Investigation, NCT02270736) was a Phase III, prospective, multicentre study with a randomized, double-blind, placebo-controlled, parallel-group main phase (MP) and an open-label extension period (OLEX), conducted at 28 sites in Europe and Russia, in 2015 to 2019.

Objective: To investigate efficacy and safety of incobotulinumtoxinA (incoBoNT/A) compared with placebo for the treatment of chronic troublesome sialorrhea (drooling) in children and adolescents. Outcomes of repeated intraglandular incoBoNT/A injections were assessed regarding efficacy, impact on quality of life, and side effects.

Methods

Subjects: Children/adolescents (2–17 years) with chronic troublesome sialorrhea and/or intellectual disability associated with neurological disorders, and severe drooling (investigator's Modified Teacher's Drooling Scale rating ≥6), were recruited with a stepwise approach, enrolling older subjects first for safety reasons.

Treatments: IncoBoNT/A (Botulinum neurotoxin type A, free from complexing proteins) was administered into the submandibular and parotid salivary glands. Subjects aged 6-17 years were randomized (2:1) to receive ~2 U/kg body weight (BW) of incoBoNT/A (fixed total dose 75 U for subjects ≥30kg BW; Table 1) or matching placebo in the MP. Subjects aged 2–5 years were treated only with incoBoNT/A. All subjects received up to 3 further incoBoNT/A injection cycles during the OLEX. Each injection was followed by 16 weeks of observation.

Endpoints: The co-primary efficacy endpoints were the unstimulated Salivary Flow Rate (uSFR) change from baseline to Week 4 and the carers' Global Impression of Change Scale (GICS) score at Week 4, both in 6-17-year-old patients. The change in uSFR and the GICS score were also assessed at later time points of the MP and the OLEX. Treatment-emergent adverse events (AEs) overall and by injection cycle were documented.

Statistics: The analysis of the co-primary efficacy endpoints was a mixed model repeated measures (MMRM) approach with comparison of least squares (LS) means between incoBoNT/A and placebo (for subjects aged 6-17 years). All results for the cohort of 2-5-year-olds were descriptive only.

Dosing

All patients were treated according to the pre-defined, weight-dependent dosing scheme (Table 1).

Table 1: IncoBoNT/A dosing scheme

Body weight	Parotid gland, each side		Submandibular gland, each side		Total
	Total dose per gland [units]	Volume per injection [mL]	Total dose per gland [units]	Volume per injection [mL]	[units]
≥12 to <15 kg	6	0.24	4	0.16	20
≥15 to <19 kg	9	0.36	6	0.24	30
≥19 to <23 kg	12	0.48	8	0.32	40
≥23 to <27 kg	15	0.60	10	0.40	50
≥27 to <30 kg	18	0.72	12	0.48	60
≥30 kg	22.5	0.90	15	0.60	75

Study population

In the MP, 256 subjects were randomized, 255 were treated, and 250 (97.7%) completed the phase. Of those, 247 subjects entered the OLEX and 222 (89.9%) of them completed the study (Fig. 1).
The majority of subjects had cerebral palsy (>57%), and intellectual disability (>85%). The treatment groups were comparable regarding demographics and baseline disease status.

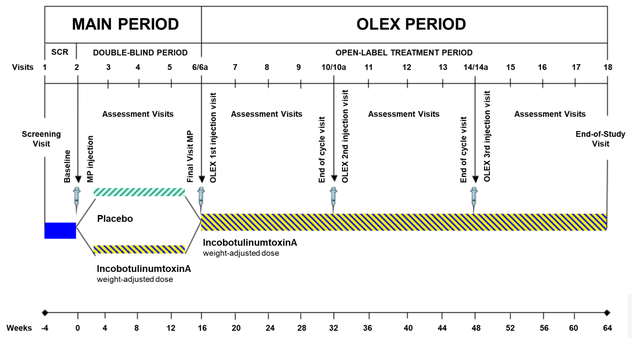

Figure 1: Study flow chart

Efficacy Results

Unstimulated Salivary Flow Rate

The incoBoNT/A group showed superiority over placebo in the mean uSFR change from baseline to Week 4 of the MP, and at the later MP time points (Fig. 2). Repeated treatments during the OLEX showed a prolonged and sustained effect. Slightly larger mean uSFR decreases from baseline to Week 4 were observed with each cycle.

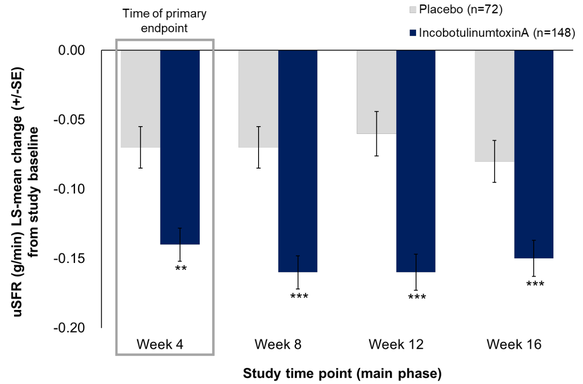

Figure 2: Mean change in mean salivary flow rate from baseline during MP. Comparison of incoBoNT/A vs placebo, with *: p<0.05, **: p<0.01, ***: p≤0.001.

Efficacy Results

Global Impression of Change

The carers' GICS score showed higher improvements in the incoBoNT/A group compared to placebo at MP Week 4, and at the later MP time points (Fig. 3). The GICS ratings were also consistently positive over the course of the OLEX, showing an increasing effect over time. Similarly good and sustained results were seen for the 2-5-year-olds during MP and OLEX.

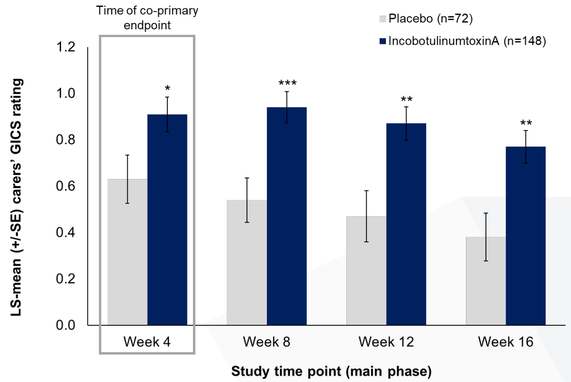

Figure 3: Mean GICS ratings during MP (6-17-year-olds). Comparison of incoBoNT/A vs placebo, with *: p<0.05, **: p<0.01, ***: p≤0.001.

Safety Results

Table 2: Adverse events during main phase and OLEX

Number of subjects (%) with	Main phase			OLEX	
	Placebo (6-17 years) N=72 n (%)	IncoBoNT/A (6-17 years) N=148 n (%)	IncoBoNT/A (2-5 years) N=35 n (%)	IncoBoNT/A (6-17 years) N=145 n (%)	IncoBoNT/A (2-5 years) N=33 n (%)
AE(s)	11 (15.3%)	27 (18.2%)	5 (14.3%)	63 (43.4)	15 (45.5%)
Related AE(s)	0 (0.0%)	2 (1.4%)	1 (2.9%)	8 (5.5)	0 (0.0%)
AESI(s)	0 (0.0%)	1 (0.7%)	0 (0.0%)	4 (2.8)	0 (0.0%)
Related AESI(s)	0 (0.0%)	1 (0.7%)	0 (0.0%)	4 (2.8)	0 (0.0%)
SAE(s)	1 (1.4%)	0 (0.0%)	1 (2.9%)	8 (5.5)	0 (0.0%)
Related SAE(s)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0)	0 (0.0%)
AE(s) leading to discont.	1 (1.4%)	1 (0.7%)	1 (2.9%)	4 (2.8)	0 (0.0%)
Related AE(s) leading to discont.	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7)	0 (0.0%)

No fatal AEs occurred in this study.
OLEX data for 6-17-year-olds are from subset of subjects who had received incoBoNT/A already in the MP.

Both MP and OLEX had good overall safety profiles. No major differences were observed in AE incidence between incoBoNT/A and placebo in the MP and AEs did not increase notably with increasing number of injections. Rates of serious AEs, related AEs, AEs of special interest and AEs leading to discontinuation were low (Table 2). The most frequent AEs were respiratory infections. Only few dental/periodontal AEs were reported. No subject newly developed neutralizing antibodies under therapy.

Conclusion

IncoBoNT/A is effective and well tolerated for the treatment of children/adolescents with chronic sialorrhea. A conservative, weight dependent approach to dosing can minimize side effects while providing clinically relevant and sustained improvements of sialorrhea.

[1] Schoen Klinik Vogtareuth, Germany and [2] Dr. von Hauner Children's Hospital, Munich University, Munich, Germany; [3] Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany
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