Efficacy and Safety of NT 201 (neurotoxin free from complexing proteins) in Cervical Dystonia

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Abstract

Objective: To evaluate the safety and efficacy of two dose groups of NT 201 (Botulinum neurotoxin A (BoNT A) free from complexing proteins, Merz Pharmaceuticals, Germany) compared to placebo in subjects with cervical dystonia (CD).

Background: NT 201 differs from available formulations of BoNT because it has no complexing proteins. NT 201 has shown non-inferiority to one other BoNT for the treatment of CD.

Design/Methods: This is a prospective, double-blind, placebo-controlled, multi-center study of two doses of NT 201 compared to placebo. CD patients were randomized to placebo, 120 U NT 201, or 240 U NT 201. Following injection, patients were evaluated at 4 weeks using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), adverse events (AEs) were also collected. The primary outcome was the change from Baseline to week 4 for the TWSTRS-Total score analyzed using an ANCOVA model.

Results: There were 233 CD patients (66% women, mean age 52.8 years, mean CD duration 51.9 months), 39% not previously treated with BoNT. Patients were randomized to placebo (N= 74), 120 U NT 201 (N= 78), and 240U NT 201 (N= 81). The change in total TWSTRS from baseline to week 4 was -2.2 ± 7.3 points (placebo group); -9.9 ± 10.4 points (120 U group) and -10.9 ± 11.7 points (240 U group) (p < 0.001 compared to placebo). AEs occurred in 41.9% of the placebo group, 56.4% of the 120 U group and 55.6% of the 240 U group. AEs reported most frequently for each group respectively were dysphagia (2.7% vs 12.8% vs 18.5%), neck pain (4.1% vs 6.4%, vs 14.8%), and muscular weakness (1.4% vs 6.4% vs 11.1%).

Conclusions/Relevance: NT 201 (BoNT free from complexing proteins) is a safe and effective treatment for CD.

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Specific Aims

1. To evaluate two dose groups of NT 201, (Merz Pharmaceuticals, Germany) compared to placebo in subjects with cervical dystonia (CD) for:
   - Efficacy
   - Adverse effects

Inclusion criteria

Primary Cervical dystonia
- > TWSTRS Total ≥ 20
  - TWSTRS Motor Severity ≥ 10
  - TWSTRS Disability ≥ 3
  - TWSTRS Pain ≥ 1
- > Stable doses of medication for 3 months

For previously treated subjects
- > 2 prior injections with stable response
- > At least 10 weeks from previous injection
- > Maximal dose: 300 U BoNT A (BOTOX®)
- > Maximal dose: 12,000 U BoNT B (Myobloc®)

Exclusion criteria

- •Secondary cervical dystonia (e.g. tardive, traumatic)
- •Predominant anterocollis
  - •TWSTRS Motor Severity anterocollis ≥ 2
- •Predominant retrocollis
  - •TWSTRS Motor Severity retrocollis ≥ 2
- •Previous surgery for cervical dystonia
- •Marked limitation on passive range of motion
- •Treatment with BoNT for any indication other than CD within 4 months of entry
- •Hypersensitivity to HSA, sucrose or BoNT A
- •History of neuromuscular disease
- •Uncontrolled medical problem
- •Current clinically significant dysphagia

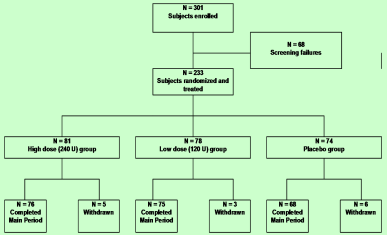
Methods

Prospective, double blind, randomized, placebo controlled design

Subjects randomized to 1 of 3 groups in a 1:1:1 ratio
- – Higher dose (240U NT 201)
- – Lower dose (120U NT 201)
- – Placebo (vehicle: sucrose, human serum albumin)

Study Drug
- – NT 201 vial with 100U BoNT A free of complexing proteins
- – Reconstituted each vial with 2 mL sterile saline solution
- – 240U: 4 vials NT 201
- – 120U: 2 vials NT 201 and 2 vials Placebo
- – Placebo: 4 vials placebo
- – Pooled in a collection vial to total volume of 8 mL
- – Drawn up 4.8 mL for administration

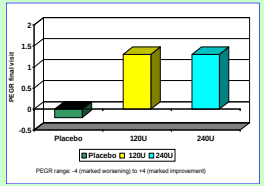
Patient disposition



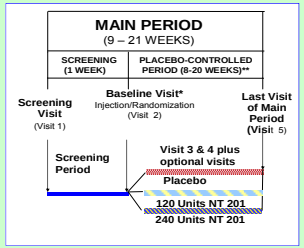
Outcomes: ITT group

Change from Baseline to Week 4	Placebo	120 Units NT-201	240 Units NT 201	p-values 240 U vs plc; 120 U vs. plc
ΔTWSTRS Total	**-2.2 (7.3)**	**-9.9 (10.4)**	**-10.9 (11.7)**	p<0.001; p<0.001
ΔTWSTRS Severity	-1.9 (3.96)	-3.9 (4.34)	-5.5 (5.99)	p<0.001; p=0.003
ΔTWSTRS Disability	0.0 (3.41)	-3.3 (4.72)	-3.0 (4.35)	p<0.001; p<0.001
ΔTWSTRS Pain	-0.3 (2.97)	-2.7 (4.55)	-2.4 (4.36)	p<0.001; p<0.001

Patient global response



Study Design



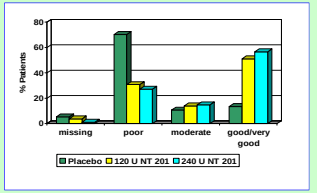
Patients: ITT group

	Placebo N=74	120 Units NT 201 N=78	240 Units NT 201 N=81
Mean age years (SD)	52.4 (10.8)	52.8 (11.5)	53.2 (12.2)
% female	66%	65%	67%
Mean duration CD (months)	53.9 (72.2)	52.4 (66.5)	49.4 (67.2)
Without prior BTX	28 (38%)	31 (40%)	31 (38%)

Adverse events

	Placebo	120 Units NT 201	240 Units NT 201
At least 1 TEAE	31 (41.9%)	44 (56.4%)	45 (55.6%)
Dysphagia	2 (2.7%)	10 (12.8%)	15 (18.5%)
Neck pain	3 (4.1%)	5 (6.4%)	12 (14.8%)
Muscular weakness	1 (1.4%)	5 (6.4%)	9 (11.1%)
Injection site pain	5 (6.8%)	7 (9.0%)	3 (3.7%)

Investigator: global assessment of efficacy



Conclusions

> NT 201 free of complexing proteins is a safe and effective treatment for Cervical dystonia

> Following injection, there is an improvement in TWSTRS total score for both the 120U and 240U groups of NT 201

> AE's that are more common include dysphagia, neck pain and weakness are more frequent with 240U

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