

A Pilot Dose Ranging Study of Dysport® (AbobotulinumtoxinA) in the Treatment of Oromandibular Dystonia

3 March 2015

NCT01921270

EXTERNALLY SPONSORED STUDY OUTLINE

<i>Enter ESS Title : A Pilot Dose Ranging Study of Dysport® (AbobotulinumtoxinA) in the treatment of Oromandibular Dystonia</i>	
EXTERNAL SPONSOR NAME, LOCATION :	PI: Stewart Factor, DO Professor and Director, Movement Disorders Program Emory University 12 Executive Park Drive Atlanta, GA 30329 E-mail: sfactor@emory.edu Tel: 404.712-7262
STUDY TITLE :	A Pilot Dose Ranging Study of Dysport® (AbobotulinumtoxinA) in the treatment of Oromandibular Dystonia
STUDY DESIGN :	<p>Study Rationale: Oromandibular dystonia (OMD) is an uncommon, disabling form of cranial dystonia, involving involuntary movements of the lower facial, masticatory, and lingual muscles. This can cause jaw movements including opening, closure, protrusion, retraction, or deviation. Common additional facial movements involve grimacing or lip pursing. When there is tongue involvement, it usually presents as tongue protrusion or curling [1, 2]. Such patients are impaired in relation to eating, speaking and swallowing. Most cases are idiopathic, followed by drug induced (tardive dystonia) [3].</p> <p>OMD comprises 3.1% of all focal dystonias [4] and its prevalence has been estimated in several studies to be 0.3 per 100,000 [5], 68.9 per million in the US [6] , 2.8 per 100,00 in Iceland [7] , and 0.8 per 100,000 in an Oslo, Norway based study[8]. When included as part of a segmental dystonia, which includes “cranial dystonia,” “Brueghel’s Syndrome,” or “Meige’s Syndrome,” the prevalence is increased.</p> <p>Botulinum toxin injection is considered the treatment of choice for most patients with focal dystonia, including OMD. Oral medications can also be used, including benzodiazepines (e.g., clonazepam, diazepam), anticholinergics (e.g., trihexyphenidyl, benztropine), and GABAergic drugs (e.g., baclofen, tizanidine). However, the impact of these medications is generally disappointing. For those patients with a tardive dystonia, tetrabenazine can be used [9].</p>

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Study Design:

Interventional , single site, prospective study with 2 parts:
1/ Dose raging (aim 1): 3 OMD groups undergoing 3 different Dysport® dosages with a step wise approach based on safety response. 6 weeks duration for the 3 groups.

2/ Efficacy & safety assessment of Dysport® selected dose from study part 1 (aim 2): 1 single arm with OMD subjects. 12 weeks duration.

Study Specific Aims:

Aim 1: To determine the best dose range for Dysport® for the treatment of oromandibular dystonia

In order to address Aim 1, patients with OMD who have been previously treated with any botulinum toxin Type A (abobotulinumtoxinA, onabotulinumtoxinA and incobotulinumtoxinA) and responded will be recruited into this study. The muscles to be injected will be tailored to the individual's presentation and up to the injector's discretion, but if a muscle is chosen it will be given a set amount of Dysport® (abobotulinumtoxinA)(see table 2). The subject will be injected with Dysport® only, with an unblinded open-label disclosure. There will be three dose levels and three subjects will be injected in each (OMD type for each group: 2 jaw opening + 1jaw closing). As there is no standard amount of Dysport® used for the treatment of OMD, we have estimated a dose range from cases in the literature [10, 11] [12] and discussion with Dr. Raymond Rosales of the Philippines who has a substantial experience injecting the jaw in Filipino patients with Lubag disease. There was some discrepancy in dosages between a review paper by Bhidayasiri [12] and Dr. Rosales' personal recommendations. We based our estimations on Dr. Rosales' recommendations since he has the largest personal experience in injecting Dysport® for OMD. The review in question gathered its data from several sources which would have variation in its technique. These various sources had limited experience regarding this particular medication in OMD.

As is the case in any type of dystonia, the dosing range of botulinum toxin is broad. We will separate subjects into three groups with a certain level of dosage: low, medium,

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and high. The study will start with a cohort of three subjects with OMD and inject using the low range of Dysport®. After efficacy and safety is assessed 6 weeks later, it will be determined if it is appropriate to increase the dosage to the next level. Safety alone, and not efficacy, will be the determinant on whether or not to proceed to the next dosing range although efficacy measure will be performed. If determined to be safe, three additional subjects with OMD will be injected with the medium range. These subjects will be assessed 6 weeks later, and if determined to be safe, three more subjects will be injected at the high range. This method will be utilized to assure safety at the particular dosages of Dysport®.

This optimal dosage will be the safest dosage that provides adequate efficacy. This will be based on the Clinical Global Impression Scale's Efficacy Index[13]. Subjects from Aim 1 will be offered enrollment into Aim 2.

Aim 2: To determine the efficacy and safety of Dysport® for the treatment of oromandibular dystonia

20 subjects will be included in the second part of the study and will be injected with the determined optimal dosage found at the end of the first study part. They would be injected for Aim 2 after at least 12 weeks have passed, given that the effect from the prior injection had either completely abated or at least declined significantly. The 9 subjects from Aim 1 will be offered to enter study part 2 unless they have severe adverse event (AE), ongoing AE or AE considered inappropriate for study continuation. Their previous injections with Dysport® should not confound the results of Aim 2 since botulinum toxins Type A and Dysport® should both have minimal clinical effect at 12 weeks out from injection. Since the local population suffering from OMD is small, the inclusion of the Aim 1 subjects into Aim 2 would lead to a much more rapid completion of recruitment.

Amendment 2 January 26, 2015: In the aim 1 protocol the result was that 2 of 3 of the first, lowest level, experienced adverse effects that were likely toxin related. It was determined that it was not safe to move to level 2. Since aim 2 will utilize the same dose as the completed aim 1 it is the plan to alter the number from 9 in part 1 and 20 in part

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2 (total 29) to 3 in part 1 and 17 in part 2 total being 20 subjects. This will not alter the power of the study since that was passed on the 20 subjects in part 2. In addition, for those in part 2, the option will be given to receive a second injection with an adjusted dose either up or down to their needs.

In both Aim 1 and Aim2, the safety and efficacy will be recorded for all subjects that undergo injection. All subjects will be examined and videotaped at the injection visit, then at 6 and 12 weeks after injection with a standardized protocol. The primary outcome will be blinded examination scores of the videos performed after the study is complete. The evaluators will be two different movement disorders experts, not otherwise involved in the study, who will review the videotaped examinations, presented in a random order, using the Global Dystonia Rating scale (GDS) [14]. They will rate the dystonia at baseline (injection visit) and 6 weeks after injection. The change in GDS score from baseline to 6 weeks after injection is the best objective measure of efficacy and will serve as the study's primary endpoint. We chose the GDS over other dystonia scales because of its ease of use, sensitivity to clinical changes because of its continuous rating system, internal consistency, and inter-rater reliability[14].

Secondary measures will include GDS scoring by blinded evaluation at 12 weeks after injection to assess duration of effect; GDS scoring by injecting practitioner at baseline, 6, and 12 weeks; Unified Dystonia Rating Scale (UDRS) [14] scoring of videos by the blinded evaluators, Clinical Global Impression at baseline and then along with the Efficacy Index at 6 and 12 weeks. We will also assess a score from a patient completed questionnaire regarding interference with eating, swallowing, drooling, speaking, pain, and quality of life.

Study Objectives:

Study subjects will be patients with symptoms of OMD seen in our practice who warrant therapy with botulinum toxin injection. This study plans for 9 patients to complete Aim 1 of the study and 20 patients (not necessarily different patients) to complete Aim 2.

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Amendment 2 January 26, 2015: the number is altered 3 in aim 1 and 17 in aim 2.

Primary: Standardized assessments (including the video) will be completed at baseline prior to injection and at weeks 6 and 12. The patient will be objectively evaluated by 2 blinded video raters as well as the injecting physician in face-to-face clinical examination. All raters will be movement disorder experts with experience in evaluating dystonias.

The standardized video protocol will be as follows:

- a. Subject looks at camera and rests with eyes open for 10 seconds
- b. Subject looks at camera and rests with eyes closed for 10 seconds
- c. Opening and closing mouth three times each from front view, lateral view from right, lateral view from left
- d. Subject opens mouth with tongue resting in floor of mouth for 10 seconds
- e. Subject opens mouth with tongue protruding for 10 seconds
- f. Reading the “Grandfather Passage”
- g. Having a conversation
- h. Eating two crackers without water, swallowing bolus of food
- i. Drinking water from a cup
- j. Subject has mouth closed and at rest, but performing tasks that may activate OMD: 5 seconds of tapping the thumbs to the index fingers and 5 seconds of opening and closing each hand

Rating will be evaluated by “Lower face” and “Jaw and tongue” sections in the Global Dystonia Severity Rating Scale (GDS) for a maximal severity score of 10 in each section and 20 total.

This assessment will be completed by the injector live and by the blinded raters viewing the video. The Ipsen reviewers had initially requested a change in the GDS that would be considered clinically significant. Based on our experience, a change of 2 or more points in a certain section marks a significant change in the patient’s condition. We will be able to further validate this by correlating it with all of the subjective measures we will be gathering.

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	<p>Subjects will also be rated by the Unified Dystonia Rating Scale by blinded raters via video and injectors live.</p> <p>Secondary: The patients will be evaluated <u>subjectively</u> by questionnaire. Evaluations will be performed at baseline (day of injection), 6, and 12 weeks after injection. Drooling and chewing/swallowing scales are not specifically designed for dystonia, but are well validated and are appropriate for quantifying symptom severity in OMD.</p> <ol style="list-style-type: none">1. Measure of jaw pain by visual analogue scale (0-100)2. Drooling (SCS-PD [19])3. Tendency for tongue biting (estimated number of tongue bites per day)4. Ease of chewing and swallowing (SDQ [20], modified to exclude questions 5, which is redundant since it regards drooling and question 15 which is not relevant to the study as it involves prior aspiration pneumonias)5. Ease of speaking: Fahn-Marsden Scale Part B “Speech” question [21]6. Quality of Life: Oromandibular dystonia questionnaire (OMDQ-25) [22]7. Global Clinical Impression Scale (CGI) with Efficacy Index [13] <p>Statistical analysis: This is a pilot study. Subjects will be their own controls. The primary end point will be the change in the GDS from baseline to week 6 based on the blinded video review. Analysis will be performed with a standard t-test.</p> <p>Secondary measures will also examine change of subjective symptoms from baseline to weeks 6 and 12 including questionnaire scores of pain, quality of life, drooling, tongue biting, chewing, swallowing and speaking as delineated above. GDS from the injecting practitioner at the injection visit, week 6, and week 12 will be measured as will the blinded video raters’ GDS score at 12 weeks. UDRS will also be rated at baseline, 6 weeks, and 12 weeks by blinded evaluators of the videos. CGI will be performed at baseline to determine the severity of the dystonia and then at weeks 6 and 12 to determine the safety and efficacy of the injections.</p> <p>Study Sites:</p>
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	<p>Emory University Movement Disorders Clinic only</p> <p>Timeline: This study will be completed within two years.</p> <p>References:</p> <ol style="list-style-type: none">1. Weiner, W.J. and E. Tolosa, <i>Hyperkinetic movement disorders</i>. Handbook of clinical neurology. 2011, Edinburgh: Elsevier. p.2. Stacy, M.A., <i>Handbook of dystonia</i>. Neurological disease and therapy. 2007, New York: Informa Healthcare. xvii, 412 p., 1 leaf of plates.3. Tan, E.K. and J. Jankovic, <i>Botulinum toxin A in patients with oromandibular dystonia: long-term follow-up</i>. Neurology, 1999. 53(9): p. 2102-7.4. Fahn, S., J. Jankovic, and M. Hallett, <i>Principles and practice of movement disorders</i>. 2nd ed. 2011, Edinburgh ; New York: Elsevier/Saunders. vii, 548 p.5. Nutt, J.G., et al., <i>Epidemiology of dystonia in Rochester, Minnesota</i>. Adv Neurol, 1988. 50: p. 361-5.6. Jankovic, J. and J. Orman, <i>Blepharospasm: demographic and clinical survey of 250 patients</i>. Ann Ophthalmol, 1984. 16(4): p. 371-6.7. Asgeirsson, H., et al., <i>Prevalence study of primary dystonia in Iceland</i>. Mov Disord, 2006. 21(3): p. 293-8.8. Le, K.D., B. Nilsen, and E. Dietrichs, <i>Prevalence of primary focal and segmental dystonia in Oslo</i>. Neurology, 2003. 61(9): p. 1294-6.9. Batla, A., M. Stamelou, and K.P. Bhatia, <i>Treatment of focal dystonia</i>. Curr Treat Options Neurol, 2012. 14(3): p. 213-29.10. Rosales, R.L., et al., <i>The broadening application of chemodenervation in X-linked dystonia-parkinsonism (Part II): an open-label experience with botulinum toxin-A (Dysport(R)) injections for oromandibular, lingual, and truncal-axial dystonias</i>. Int J Neurosci, 2011. 121 Suppl 1: p. 44-56.11. Van den Bergh, P., et al., <i>Five-year experience in the treatment of focal movement disorders with low-dose Dysport botulinum toxin</i>. Muscle Nerve, 1995. 18(7): p. 720-9.12. Bhidayasiri, R., F. Cardoso, and D.D. Truong, <i>Botulinum toxin in blepharospasm and oromandibular dystonia: comparing different botulinum toxin preparations</i>. Eur J Neurol, 2006. 13 Suppl 1: p. 21-9.13. Guy, W., ed. <i>Clinical global impression</i>. ECDEU Assessment Manual for Psychopharmacology, ed. W. Guy. 1976, DHEW: Rockville, Maryland: National
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	<p>Institute of Mental Health.</p> <p>14. Comella, C.L., et al., <i>Rating scales for dystonia: a multicenter assessment</i>. <i>Mov Disord</i>, 2003. 18(3): p. 303-12.</p> <p>19. Perez Lloret, S., et al., <i>Validation of a new scale for the evaluation of sialorrhea in patients with Parkinson's disease</i>. <i>Mov Disord</i>, 2007. 22(1): p. 107-11.</p> <p>20. Manor, Y., et al., <i>Validation of a swallowing disturbance questionnaire for detecting dysphagia in patients with Parkinson's disease</i>. <i>Mov Disord</i>, 2007. 22(13): p. 1917-21.</p> <p>21. Burke, R.E., et al., <i>Validity and reliability of a rating scale for the primary torsion dystonias</i>. <i>Neurology</i>, 1985. 35(1): p. 73-7.</p> <p>22. Merz, R.I., J. Deakin, and M.R. Hawthorne, <i>Oromandibular dystonia questionnaire (OMDQ-25): a valid and reliable instrument for measuring health-related quality of life</i>. <i>Clin Otolaryngol</i>, 2010. 35(5): p. 390-6.</p>
<p>STUDY POPULATION :</p>	<p>Sample size calculation: Power and Sample Size Analysis: This is a pilot study therefore does not require a power analysis</p> <p>Inclusion and exclusion criteria:</p> <p>Eligible OMD patients will be asked to join the study. If interested, they will be properly consented with an IRB approved consent form.</p> <p>Inclusion criteria: Patients will be included if they meet the following inclusion criteria: a diagnosis of primary or tardive OMD; moderate or severe severity, defined as GDS score ≥ 4 in either "lower face" or "jaw and tongue" section; age > 18 years; and capability of attending the scheduled visits. Candidates are only those who have been previously injected with any botulinum toxin type A and responded to that treatment, and are at least 12 weeks post last injection. Women of childbearing age need to use contraception in order to be included.</p> <p>Exclusion criteria: Existence of a systemic disease that could confound the evaluation; previous placement of Deep Brain Stimulation electrodes to treat dystonia; concomitant oral medications that could interfere with the action of BTX</p>

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	<p>Type A (e.g., aminoglycosides), on an unstable dosage of any medication prescribed to treat dystonia (e.g., benzodiazepines, baclofen or anticholinergics), any known hypersensitivity to any botulinum toxin preparation and allergy to cow’s milk protein, immunoresistance to other forms of botulinum toxin type A, existence of a concomitant neuromuscular disorder (e.g., Myasthenia Gravis or Lambert-Eaton syndrome, etc); infection at the proposed injection sites; pregnant women; women of childbearing age NOT on contraception, breastfeeding women, inability to comply with scheduled visits; and patients who had been previously injected but who did not respond.</p>						
<p>INVESTIGATIONAL MEDICINAL PRODUCT :</p>	<p>Dysport® (AbobotulinumtoxinA), provided by Ipsen: 1 injection cycle for each group and each study part.</p> <p>Location of injections will be determined by the clinician to treat the particular dystonic symptom and documented in the source document. Muscle choice will be at the discretion of the injector but will follow the injection technique from Table 1 and dosing guidelines from Table 2. There will be two expert practitioners performing the injections using EMG guidance. Each practitioner will stay with the patient for the duration of the study. Dysport® will be reconstituted at a concentration of 1.5 cc of normal saline/300 units.</p> <p>Table 1: Injection techniques that will be used in study:</p> <table border="1" data-bbox="662 1264 1430 1890"> <tr> <td data-bbox="662 1264 912 1522">Lateral Pterygoid</td> <td data-bbox="912 1264 1430 1522">Using the technique as described by Barbano, 2007 [15]. Under EMG guidance. The needle will be inserted into the notch inferior to the zygomatic arch and in between the condylar and coronoid processes in the mandibular ramus.</td> </tr> <tr> <td data-bbox="662 1522 912 1743">Medial Pterygoid</td> <td data-bbox="912 1522 1430 1743">Using technique by Brin et al [16]. Under EMG guidance. Needle is inserted beneath the angle of the mandible, angled superiorly and anteriorly to hug the inside of the mandible.</td> </tr> <tr> <td data-bbox="662 1743 912 1890">Anterior digastrics</td> <td data-bbox="912 1743 1430 1890">Using technique by Esper et al [17]. The patient is supine with the head tilted back. The placement of the needle is approximately two</td> </tr> </table>	Lateral Pterygoid	Using the technique as described by Barbano, 2007 [15]. Under EMG guidance. The needle will be inserted into the notch inferior to the zygomatic arch and in between the condylar and coronoid processes in the mandibular ramus.	Medial Pterygoid	Using technique by Brin et al [16]. Under EMG guidance. Needle is inserted beneath the angle of the mandible, angled superiorly and anteriorly to hug the inside of the mandible.	Anterior digastrics	Using technique by Esper et al [17]. The patient is supine with the head tilted back. The placement of the needle is approximately two
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		fingerbreadths back from the midline of the body of the mandible and 1-2 cm lateral. The needle is placed, with EMG guidance, into the digastric muscle.																						
	Masseter	Under EMG guidance. The needle is inserted where the muscle can be palpated over the inferior mandibular ramus. As in Cardoso et al [18].																						
	Genioglossus	Under EMG guidance. Needle is directed one finger breadth laterally from midline of mandible and one finger breadth posterior. As in Esper et al [17].																						
<p>References:</p> <p>15. Barbano, R.L., <i>Handbook of dystonia</i>. Neurological disease and therapy, ed. M.A. Stacy. 2007, New York: Informa Healthcare. xvii, 412 p., 1 leaf of plates.</p> <p>16. Brin, M.F., F. Danisi, and A. Blitzer, <i>Handbook of botulinum toxin treatment</i>. 2nd ed, ed. P. Moore and M. Naumann. 2003, Malden, Mass.: Blackwell Science. xii, 463 p.</p> <p>17. Esper, C.D., A. Freeman, and S.A. Factor, <i>Lingual protrusion dystonia: frequency, etiology and botulinum toxin therapy</i>. <i>Parkinsonism Relat Disord</i>, 2010. 16(7): p. 438-41.</p> <p>18. Cardoso, F., R. Bhidayasiri, and D. Truong, <i>Manual of botulinum toxin therapy</i>, ed. D. Truong, D. Dressler, and M. Hallett. 2009, Cambridge, UK ; New York: Cambridge University Press. xvi, 218 p.</p> <p>Table 2: Doses of Dysport® per muscle if selected for injection:</p> <p>Muscles that may be included for in injection for OMD with Jaw Closing:</p> <table border="1"> <thead> <tr> <th></th> <th>1st cohort of subjects</th> <th>2nd cohort of subjects</th> <th>3rd cohort of subjects</th> </tr> </thead> <tbody> <tr> <td>Medial Pterygoid</td> <td>50</td> <td>75</td> <td>100</td> </tr> <tr> <td>Masseter</td> <td>25</td> <td>50</td> <td>75</td> </tr> </tbody> </table> <p>Muscles that may be included in injection for OMD with Jaw Opening</p> <table border="1"> <thead> <tr> <th></th> <th>1st cohort of subjects</th> <th>2nd cohort of subjects</th> <th>3rd cohort of subjects</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>						1 st cohort of subjects	2 nd cohort of subjects	3 rd cohort of subjects	Medial Pterygoid	50	75	100	Masseter	25	50	75		1 st cohort of subjects	2 nd cohort of subjects	3 rd cohort of subjects				
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STUDY ENDPOINTS :												
PRIMARY EFFICACY ENDPOINT :	<p>For study Part 2: The primary end point will be the change in the GLOBAL DYSTONIA RATING SCALE (GDS) from baseline to week 6 based on the blinded video review.</p>											
SECONDARY EFFICACY ENDPOINT (IF APPLICABLE) :	<p>For study Part 2: Secondary measures will examine change of subjective symptoms from baseline to weeks 6 and 12 including questionnaire scores of pain, quality of life, drooling, tongue biting, chewing, swallowing and speaking as delineated above. GDS from the injecting practitioner at the injection visit, week 6, and week 12 will be measured as will the blinded video raters' GDS score at 12 weeks. UDRS will also be rated at baseline, 6 weeks, and 12 weeks by blinded evaluators of the videos. CGI will be performed at baseline to determine the severity of the dystonia and then at weeks 6 and 12 to determine the safety and efficacy of the injections.</p> <p>Exploratory endpoints: assessments (previous measures) for jaw opening and jaw closing groups.</p>											
SAFETY ENDPOINTS AND EVALUATIONS :	<p>Collection of AEs will be done throughout both study parts. These evaluations will be made by the study coordinator in-person at the injection visit, weeks 6, and 12 and also by phone conversation with the patient at weeks 2 and 4.</p> <p>Definition of some potential AEs:</p>											

Muscle that will be included in injection for OMD with Tongue Protrusion

	1 st cohort of subjects	2 nd cohort of subjects	3 rd cohort of subjects
Genioglossus	7.5*	25	35

*After 10 subjects were completed it appeared 15 units was too high as four developed dysphagia and dysarthria. Starting on subject 11 this will be cut to 7.5 units

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	<p>-Swallowing: any choking or aspiration. -Chewing: losing ability to chew something that subject could before the injections. -Soft palate incompetence: fluid leaking out from mouth through the nose. -Speaking: worse than baseline speech.</p>
PEC RECOMMENDATION ON STUDY	<input type="checkbox"/> NO OBJECTION
	<input type="checkbox"/> NO OBJECTION WITH RECOMMENDATIONS : <i>Please enter recommendations below :</i>
	<input type="checkbox"/> REJECTION <i>Please enter below justification for rejection :</i>
DEVELOPMENT COMMITTEE STATEMENT	<input type="checkbox"/> NO OBJECTION
	<input type="checkbox"/> NO OBJECTION WITH SUGGESTIONS : <i>Please enter suggestions below :</i>
	<input type="checkbox"/> REJECTION <i>Please enter below justification for rejection :</i>

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APPENDIX 1:

The Global Dystonia Severity Rating Scale (tailored for OMD)

The global score is an overall score for the body area. The investigator rates the patient in relationship to all patients. If the dystonia changes during the examination, the rating for the maximal dystonia is recorded.

Each body area is rated from 0 to 10:

- 0 No dystonia present in that body area
- 1 Minimal dystonia
- 5 Moderate dystonia
- 10 Most severe dystonia

Two body areas will be tested, each on a 0-10 scale: 1. lower face and 2. Jaw and tongue

Note: The aggregate score will be on a range from 0-20 (in order to meet inclusion criteria, subject must have at least a 4 in at least one of the affected body parts).

APPENDIX 2

The Unified Dystonia Rating Scale (UDRS) (tailored for OMD)

Factor/area Criteria

Duration

0 None

0.5 Occasional (< 25% of the time); predominantly submaximal

1.0 Occasional (< 25% of the time); predominantly maximal

1.5 Intermittent (25–50% of the time); predominantly submaximal

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- 2.0 Intermittent (25–50% of the time); predominantly maximal
 - 2.5 Frequent (50–75% of the time); predominantly submaximal
 - 3.0 Frequent (50–75% of the time); predominantly maximal
 - 3.5 Constant (75% of the time); predominantly submaximal
 - 4.0 Constant (75% of the time); predominantly maximal
- Motor severity

Lower face

0 None

1 Mild: grimacing of lower face with minimal distortion of mouth (25% maximal)

2 Moderate: grimacing of lower face with moderate distortion of mouth (25% but 50% Maximal)

3 Severe: marked grimacing with severe distortion of mouth (50% but 75% maximal)

4 Extreme: intense grimacing with extreme distortion of mouth (75% maximal)

Jaw and tongue

0 None

1 Mild: jaw opening or tongue protrusion 25% of possible range or forced jaw clenching
Without bruxism

2 Moderate: jaw opening or tongue protrusion 25% but 50% of possible range or forced jaw
Clenching with mild bruxism secondary to dystonia

3 Severe: jaw opening and/or tongue protrusion 50% but 75% of possible range or forced jaw
Clenching with pronounced bruxism secondary to dystonia

4 Extreme: jaw opening or tongue protrusion 75% of possible range or forced jaw clenching
with inability to open mouth

APPENDIX 3

Sialorrhea Clinical Scale for PD (SCS-PD) (from Perez et al. [19]):

Please read the following questions and try to answer them on the basis of how you felt during the past week.

A. During the day, when do you feel there is more saliva in your mouth?

1- Never.

2- At meal times.

3- Throughout the day, not related to meals.

3- All the time, even when I am asleep.

B. When you are asleep, how much saliva is there in your mouth?

0- I don't notice an increase in saliva.

1- I notice increased amounts of saliva in my mouth, but my pillow doesn't get wet.

2- My pillow gets wet.

3- My pillow and other bedclothes get wet.

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C. While you are awake,

- 0- I don't drool.
- 1- Saliva wets my lips.
- 2- Saliva accumulates on my lips, but I don't drool.
- 3- I drool.

D. Does accumulation of saliva in your mouth impair your speech?

- 0- No.
- 1- I must swallow frequently to avoid difficulties.
- 2- I have trouble speaking.
- 3- I can't speak at all.

E. Does accumulation of saliva in your mouth impair your eating ability?

- 1- No.
- 2- I must swallow frequently to avoid difficulties.
- 2- I have trouble eating.
- 3- I can't eat at all.

F. How many times do you drool during the daytime?

- 0- Never.
- 1- Not more than 3 times.
- 2- Often. I have to carry a handkerchief with me all the time.
- 3- Permanently.

G. When you go out or on social occasions, does saliva accumulation bother you?

- 1- No.
- 2- I notice an accumulation, but it does not bother me.
- 3- I realize other people notice it, but I can control the situation (for example, with a handkerchief).
- 4- I have stopped attending social meetings.

APPENDIX 4

Swallowing Disturbance Questionnaire [20] (without questions 5 and 15)

Questions	Never=0	Seldom (once a month or less)=1	Frequently (1-7 times per week)=2	Very frequently (more than 7 times a week)=3
1. Do you experience difficulty chewing solid				

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food like an apple, cookie or a cracker?				
2. Are there any food residues in your mouth, cheeks, under your tongue or stuck to your palate after swallowing?				
3. Does food or liquid come out of your nose when you eat or drink?				
4. Does chewed up food dribble from your mouth?				
6. Do you swallow chewed up food several times before it goes down your throat?				
7. Do you experience difficulty in swallowing solid food (i.e., do apples or crackers get stuck in your throat)?				
8. Do you experience difficulty in swallowing pureed food?				
9. While eating, do you feel as if a lump of food is stuck in your throat?				
10. Do you cough while swallowing liquids?				
11. Do you cough while swallowing solid foods?				
12. Immediately after eating or drinking, do you experience a change in your voice, such as hoarseness or reduced?				
13. Other than during meals, do you experience coughing or difficulty breathing as a result of saliva entering your windpipe?				
14. Do you experience difficulty in breathing during meals?				

APPENDIX 5:

From: Fahn-Marsden Dystonia Rating Scale [21]

Part B “Speech” question

0=Normal

1=Slightly involved, easily understood

2=Some difficulty understanding

3=Marked difficulty understanding

4=Complete or almost complete anarthria

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APPENDIX 6:

Oromandibular Dystonia Questionnaire (OMDQ-25)

Please answer the following questions according to your problems with oromandibular dystonia in the past two weeks. Mark or tick only one answer per question and ensure to complete all 25 questions.

1. How often has oromandibular dystonia affected your everyday life?

Never – Seldom – Sometimes – Often – Always

2. Has your work or housework been affected by the disease?

Never – Seldom – Sometimes – Often – Always

3. Have you felt lonely or isolated because of your dystonia?

Never – Seldom – Sometimes – Often – Always

4. Have you felt down and/ or depressed?

Never – Seldom – Sometimes – Often – Always

5. Have you felt angry or annoyed?

Never – Seldom – Sometimes – Often – Always

6. Have you avoided situations where many people are present?

Never – Seldom – Sometimes – Often – Always

7. Have you felt insecure while being in public?

Never – Seldom – Sometimes – Often – Always

8. Have you had problems with close friends or your family because of your dystonia?

Never – Seldom – Sometimes – Often – Always

9. How often has your dystonia affected your outer appearance?

Never – Seldom – Sometimes – Often – Always

10. How often have you complained about grimacing?

Never – Seldom – Sometimes – Often – Always

11. Have you felt embarrassed or ashamed because of your look/ outer appearance?

Never – Seldom – Sometimes – Often – Always

12. How often have you had problems keeping your tongue in your mouth?

Never – Seldom – Sometimes – Often – Always

13. Have you avoided going out for dinners, e.g. a restaurant or a pub?

Never – Seldom – Sometimes – Often – Always

14. Have you preferred to eat alone because of your dystonia?

Never – Seldom – Sometimes – Often – Always

15. How often have you dropped food or drink onto your clothes while eating?

Never – Seldom – Sometimes – Often – Always

16. Have you injured your tongue, lips or cheeks while eating?

Never – Seldom – Sometimes – Often – Always

17. Have you had pain in the face, head or neck?

Never – Seldom – Sometimes – Often – Always

18. Have you taken painkillers because of this?

Never – Seldom – Sometimes – Often – Always

19. Have you had problems getting understood when talking on the telephone?

Never – Seldom – Sometimes – Often – Always

20. Have you had problems getting understood when in quiet surroundings?

Never – Seldom – Sometimes – Often – Always

21. Have you had problems getting understood when talking in public or in loud surroundings?

Never – Seldom – Sometimes – Often – Always

22. Have you had problems with nasal regurgitation from your disease?

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Never – Seldom – Sometimes – Often – Always

23. Has it been difficult for you to keep food in your mouth while chewing or swallowing?

Never – Seldom – Sometimes – Often – Always

24. Have you had to watch the consistency of the food before eating it?

Never – Seldom – Sometimes – Often – Always

25. How often have you had to drink to enable swallowing?

Never – Seldom – Sometimes – Often – Always

APPENDIX 7:

Clinical Global Impression Scale [13]

CLINICAL GLOBAL IMPRESSION SCALE

1. Severity of Illness of Disease Under Study

Considering your total clinical experience with this particular population, how incapacitated has the subject been within the last week?

0=Not assessed

1=Normal, not at all incapacitated

2=Borderline incapacitated

3=Mildly incapacitated

4=Moderately incapacitated

5=Markedly incapacitated

6=Severely incapacitated

7=Among the most extremely incapacitated subjects

2. Global Improvement

Rate total improvement whether or not, in your judgment, it is due entirely to drug treatment.

Compared to baseline, how much has the subject changed?

0=Not assessed

1=Very much improved

2=Much improved

3=Minimally improved

4=No change

5=Minimally worse

6=Much worse

7=Very much worse

EXTERNALLY SPONSORED STUDY OUTLINE

3. Efficacy index-Rate this item on the basis of DRUG EFFECT ONLY

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect. This is scored as Therapeutic effect score divided by the side effect score.

Therapeutic effect	Side effects			
	None (1)	Do not significantly interfere with subject's functioning (2)	Significantly interferes with subject's functioning (3)	Outweighs therapeutic effect (4)
MARKED-Vast improvement. Complete or nearly complete remission of all symptoms (4)	4/1=4	4/2=2	4/3=1.33	4/4=1
MODERATE- Decided improvement. Partial remission of symptoms (3)	3/1=3	3/2=1.5	3/3=1	3/4=0.75
MINIMAL-Slight improvement which doesn't alter status of care of subject (2)	2/1=2	2/2=1	2/3=0.67	2/4=0.5
UNCHANGED OR WORSE (1)	1/1=1	1/2=0.5	1/3=0.33	1/4=0.25
NOT ASSESSED (0)	0	0	0	0