AI137709 and F32; the Fulbright Scholar Program; the Natural Sciences and Engineering Research Council of Canada PGSD3-502274; and the Skaggs Institute for Chemical Biology.
Keywords: Bifunctional; Botulinum neurotoxin A; Covalent; Reactivity

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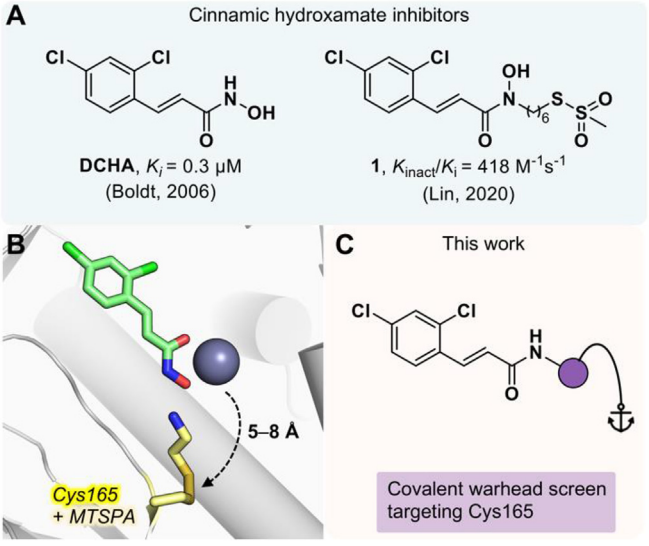

Fig. 1(A). BoNT/A inhibitors based on the cinnamic hydroxamate scaffold. (B) X-ray co-crystal structures outlining the basis for a bifunctional approach, overlaying DCHA (green; PDB 2IMA) and MTSEA (yellow; PDB 4ELC) bound to Cys165 near the active site Zn^{2+} (purple sphere). (C) Overview of research explored.

ECONOMIC OUTCOMES IN REAL-WORLD USE OF BOTULINUM TOXIN-A PRODUCTS FOR ADULT PATIENTS WITH UPPER LIMB SPASTICITY: A UK PERSPECTIVE

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Introduction: Clinical trials show that botulinum toxin A (BoNT-A) can be effective in the treatment of upper limb spasticity (ULS). However, comparative data on effectiveness and economic outcomes are limited. Based on real-world data from an observational study, this analysis aimed to compare outcomes of treatment with abobotulinumtoxinA (aboBoNT-A), onabotulinumtoxinA (onaBoNT-A) and incobotulinumtoxinA (incoBoNT-A), from a UK perspective.
Methods: ULIS III (NCT02454803) is an international, multicenter, non-interventional, prospective, longitudinal (2-year) study of adult patients with ULS treated with aboBoNT-A, onaBoNT-A, or incoBoNT-A. Patients were excluded from analysis of response and injection interval if they changed BoNT-A during follow-up. Response was defined as a ≥10-point increase in the cumulated Goal Attainment Scaling (GAS) T score, vs baseline. Toxin costs were estimated by applying unit costs (from the British National Formulary) to the annualized mean dose for each product.
Results: Overall, 832 patients contributed data for injection interval (N=555 for aboBoNT-A, 198 for onaBoNT-A, and 79 for incoBoNT-A), and 830 for response. Response rates for the three BoNT-As were 78.2%, 61.6%, and 75.6%, respectively. The mean (SD) dose per injection was 843 (353), 256 (136), and 278 (129) units, with mean (SD) days between injections of 222.8 (167.2), 204.4 (173.6), and 166.9 (105.1). This corresponds to annualized toxin costs of £464 (aboBoNT-A), £707 (onaBoNT-A), and £872 (incoBoNT-A).
Conclusion: These real-life data indicate that aboBoNT-A injections may be a cost-effective treatment for ULS, due to lower injection costs and longer intervals between treatments. However, additional comparative data from larger patient cohorts would be valuable to confirm these findings.
Funding: This study was funded by Ipsen.
Keywords: Botulinum neurotoxin type A; Cost-effectiveness analysis; Quality of life; Spasticity costs

THE SPASTICITY-RELATED QUALITY OF LIFE 6-DIMENSIONS TOOL (SQOL-6D) IN UPPER LIMB SPASTICITY: A FIRST PSYCHOMETRIC EVALUATION

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Introduction: To describe the psychometric properties (validity, reliability, responsiveness) of SQoL-6D, a tool designed to assess disease burden and change after focal upper limb spasticity (ULS) therapy.
Methods: Multicentre prospective study in adults (aged ≥18 years) with ULS. Patients completed the SQoL-6D at enrolment (Visit [V]1), 8 (±2) weeks (V2) and 1–4 days after V2 (re-test). SQoL-6D covers 6 dimensions (pain/discomfort, involuntary movements/spasms, restricted range of movement, caring for the affected limb, using the affected limb, mobility) each rated from 0-4 (4=worse outcome) and a total score (TS) calculated from 0-100 (100=better outcome). Standard ULS measures (Modified Ashworth Scale, Arm Activity Measure, Goal Attainment Scaling, EuroQoL 5 Dimensions 5 Levels questionnaire, global assessment of benefit) were also recorded.
Results: The SQoL-6D was shown to be unidimensional and demonstrated adequate construct validity. The internal reliability of the SQoL-6D was supported by Cronbach's alpha (>0.70), while the intraclass correlation coefficient supported the test-retest reliability (0.82). Correlation coefficients with established instruments supported convergent validity, while significant differences between known-groups (of differing clinical severity of weakness) in SQoL-6D TS confirmed its sensitivity. Significant

differences in mean SQoL-6D TS change and effect sizes across patients rating "some benefit" and "great benefit" (0.51 and 0.88 respectively, Table) supported its sensitivity to clinical change.
Conclusions: SQoL-6D is a promising new measure of patient-reported disease burden and health status in ULS.
Funding: Ipsen
Keywords: Patient-reported disease burden; Spasticity, Quality of life; Spasticity-related Quality of Life 6-Dimensions tool; SQoL-6D

Table. Change in SQoL-6D Total Score Between V1 and V2 by Subgroups of Clinical Benefit*.

Subgroups of clinical benefit	N	Change in SQoL-6D total score	
		Mean (95%CI)	Effect size
Patient global assessment of benefit scale			
No benefit	5	2.5 (-10.5, 15.5)	0.19
Some benefit	51	9.5 (6.6, 12.4)	0.51
Great benefit	31	17.6 (13.1, 22.1)	0.88
Clinician global assessment of benefit scale			
No benefit	5	-0.8 (-14.2, 12.6)	-0.04
Some benefit	56	10.1 (7.1, 13.1)	0.52
Great benefit	29	17.5 (13.3, 21.8)	0.98

* Defined by change in clinical severity by Visit 2. CI, confidence interval; SQoL-6D, spasticity-related quality of life 6-dimensions; V, visit.

LONGITUDINAL GOAL ATTAINMENT WITH INTEGRATED UPPER LIMB SPASTICITY MANAGEMENT INCLUDING BOTULINUM TOXIN A: PRIMARY RESULTS FROM THE ULIS-III STUDY

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Introduction: The primary aim of the ULIS-III study was to assess the longitudinal effects of integrated spasticity management incorporating repeated cycles of botulinum toxin A (BoNT-A) over 2 years.
Methods: ULIS-III (NCT02454803) was a prospective, observational study following adult (≥18 years) patients living with spasticity over 2 years of integrated upper limb spasticity (ULS) management including repeat BoNT-A treatment. The study was the first to use the Upper Limb Spasticity Index (ULS Index), an assessment battery including a structured approach to goal attainment scaling (GAS) alongside a set of standardized measures. Participants continued with their usual concomitant therapies, which were recorded in the Upper Limb Focal Spasticity Therapy Recording Schedule (ULSTR) to document the number/duration/type of therapies related to specific goals.
Results: A total of 1004 participants from 14 countries were enrolled, of which 953 underwent ≥1 BoNT-A injection cycle and had ≥1 GAS assessment. Overall, participants underwent a median [range] of 4 [1-9] BoNT-A injection cycles. A majority of participants (55.9-64.6% across cycles 1-6) saw a therapist after BoNT-A treatment; the most frequent therapy intervention was passive stretch (70.1-79.8% across cycles 1-6). Patients achieved their goals as expected over repeated cycles; mean [95% CI] GAS T scores at baseline were 36.7 [36.5, 36.9] and mean cumulated GAS T scores at 2 years was 49.5 [49.1, 49.9]. Higher rates of goal achievement were seen for primary goals related to passive vs. active function (86.6% vs 71.4% achievement) [Figure]. Standardised measures of spasticity, pain, involuntary movements, active and passive function improved over each treatment cycle.
Conclusions: This large, international study provides evidence for the benefit of repeated cycles of BoNT-A, sustained over 2 years and captured through goal attainment scaling and standardised measures.
Keywords: Botulinum toxin; Goal attainment scaling; Observational study; Spasticity; Upper-limb

Fig. Percentage achievement of primary goal set by area.

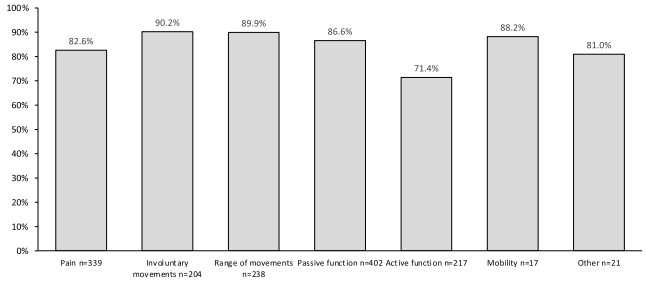

Fig. Percentage achievement of primary goal by goal area.

NOVEL SECRETION INHIBITORS OF PAIN-RELATED MEDIATORS WITH POTENTIAL FOR RELIEVING CHRONIC PAIN

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Targeted delivery of a potent inhibitor of pain-related mediators into inflammatory or pain-sensing cells is a promising avenue for treating chronic pain, a major, world-wide healthcare problem. There is an unmet need for a specific and effective delivery strategy. Herein, we developed a novel approach using a sortase to site-specifically ligate a non-toxic botulinum neurotoxin type D (BoNT/D) core therapeutic (synaptobrevin-cleaving protease and translocation domains) to cell-specific targeting ligands. A recombinantly-engineered core therapeutic was efficiently ligated to IL-1β ligand within minutes. The resultant conjugate specifically entered into cultured murine primary macrophages, cleaved synaptobrevin isoform 3 and inhibited LPS/IFN-γ–evoked IL-6 release. Likewise, a CGRP receptor antagonist ligand delivered BoNT/D protease into sensory neurons and inhibited K^+-evoked substance P release. As cytokines and neuropeptides are major regulators of inflammation and pain, blocking their release using novel engineered inhibitors highlights the therapeutic potential of these inhibitors. Our study provides a new platform with broad applicability for developing targeted biotherapeutics for safer treatments of chronic diseases.
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Keywords: Cytokine; Neuropeptides; Neurotoxin; Protein conjugation; Targeting; Therapeutics

CHARACTERIZATION OF THE PROTOSPACER TARGETS OF *Clostridium botulinum* CRISPR-CAS SPACER ARRAYS

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