Before intradetrusor injections, body weight and diuresis of SCI rats were similar among rats. This is the first preclinical dose-ranging study with Minimal effective dose (MED) of onabotulinumtoxinA (onaBoNT-A) and abobotulinumtoxinA (aboBoNT-A) in a rat model of neurogenic detrusor overactivity (NDO).

### OBJECTIVES

- Spinal cord injury (SCI) induces plasticity within neural pathways innervating the lower urinary tract (LUT), with the recruitment of nociceptive “silent” C-fibers leading to the development of an abnormal automatic micturition reflex and emergence of neurogenic detrusor overactivity (NDO), thereby greatly compromising bladder filling during the micturition cycle.

- In SCI patients, intradetrusor injections of both onabotulinumtoxin A (BOTOX®) and abobotulinumtoxin A (DYSPORT®) have been evaluated for the treatment of refractory NDO and have been reported to decrease urinary incontinence frequency and maximum intravesical pressure while increasing bladder capacity and compliance. However, these two distinct commercialized products have different potency units and are therefore not interchangesable.

The main objective of this study was to determine the dose-response and the minimal effective dose (MED) of each product in the SCI rat, a relevant experimental model for human NDO after SCI.

### MATERIALS & METHODS

#### Experimental design

A total of six adult female Sprague-Dawley rats weighing 250-350 g (Stallwedge Janvier, France) were used. The protocol for the study complied with the animal protection legislation for animal studies in experimentation and all other applicable laws and regulations in force in France (Ministry of Agriculture - Agreement No. A91-471-109, May 2009).

#### Animal preparation

- A spinal midline incision was made through the dorsal muscles to the T7–T8 vertebrae. The dura and the muscle in front of T7–T8 were peeled away and a T7–T8 laminectomy was then performed. The duro and spinal cord were then protected by the laminectomy using a microscope to ensure that the transection was complete. A sterile wire spring (0.5 x 2 mm) was placed between the cut ends of the cord. The covering muscle and skin were then sutured. Postoperatively, the animals were treated with antibiotics to prevent urinary tract infection and bladder was manually emptied by Credé maneuver until the abnormal micturition reflex was totally established.

#### Intradetrusor injection and cystometry

At 19 days post-spinalization, bladders were exposed under isoflurane anesthesia (1.5-2.0%) and emptied by catheterization through the urethra. Using a microsyringe, aboBoNT-A, onaBoNT-A or Vehicle (V) was injected into the bladder using 2 ml 30-gauge needle connected to a microliter pump (Sensirion, Switzerland). Then, a P2-PU ureter was implanted within the bladder dome and submitted subcutaneously anteriorized at the level of the neck and sutured between the scapulae. Postoperatively, rats were treated with gentamicin (Gentetil®, 1 mg/kg, Schering-Plough, USA).

#### Cystometry experiments

Fourteen days after intradetrusor injections, cystometry was performed in conscious rat. Bladder pressure was recorded using a pressure transducer (Statham BM 70, UK) and direct measurements of instillation volumes were performed by means of a weighing device (Sartorius BPU21S, France). After 30 minutes of accumulation, the bladder was continuously perfused with saline until 3 or 4 reproducible micturition cycles were obtained. Then, an evaluation period was recorded (60 min) in order to determine the effect of aboBoNT-A, onaBoNT-A or Vehicle on the micturition reflexes.

#### Data and statistical analysis

The following parameters were analyzed: maximal pressure (Pm), mean pressure (Pmean), voiding pressure (PV), bladder compliance (Cv), pressure threshold (Pth), pressure frequency (PF), rate of increase of pressure (ΔP), duration of non-voiding contractions (NVC), duration of首创期 voiding contractions (CPV), interval (ICV), initial pressure (IPV), and percentage of micturition responses (MRR) between successive injections. All data were expressed as means ± SEM and averaged per treatment group. A Grubbs test was used for exclusion of outliers. A one-way ANOVA test followed by Dunnett’s post-test was used for pharmacological parameters (GraphPad Prism® 6.0). An ANCOVA (Step Down Trend Test) (ASDTT) was performed for non-voiding and voiding contractions (NVC, CPV) and interval (ICV) if the assumptions were not satisfied. A Spearman correlation was performed to determine if there was a linear relationship between the parameters. All statistical analyses were performed using GraphPad Prism® 6.0. *p < 0.05, **p < 0.01, ***p < 0.001 were considered significant.

### RESULTS

#### Effect on baseline pressure

Baseline Pressure vs. Volume threshold NVC

#### Effect on amplitude of NVC

Effect on volume threshold to elicit NVC

### CONCLUSIONS

- The MED which decreased significantly intravesical BP was 10U for aboBoNT-A and 7.5U for onaBoNT-A (vs Vehicle). Moreover, both aboBoNT-A 10U and onaBoNT-A 7.5U, modulated significantly all NVC parameters vs Vehicle by decreasing i) amplitude and ii) frequency of NVC, and iii) by increasing the volume threshold to elicit NVC.

- This is the first preclinical dose-ranging study with aboBoNT-A and onaBoNT-A in standardized conditions showing similar inhibiting effects on NDO, albeit at different MED.

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