Real-world Safety and Effectiveness of OnabotulinumtoxinA in Patients with Overactive Bladder or Neurogenic Bladder

Results from a 48-week, Multicenter post-marketing Surveillance

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ABSTRACT

Objectives: To evaluate the safety and effectiveness of intradetrusor onabotulinumtoxinA in patients with overactive bladder (OAB) or neurogenic bladder (NB) who have an inadequate response to existing therapies or for whom existing therapies are inappropriate, in Japanese clinical practice.

Methods: This prospective, multicenter, post-marketing surveillance enrolled patients who initiated onabotulinumtoxinA between March 2020 and June 2022, with follow-up of up to 48 weeks. Safety endpoints included adverse drug reactions (ADRs) related to urinary tract infections (UTIs) and urinary retention (UR). Effectiveness endpoints included investigator-rated global assessment; Overactive Bladder Symptom Score (OABSS) in OAB, as well as urinary incontinence (UI) frequency and urodynamics in NB.

Results: The safety analysis set included 532 patients (OAB, $n=503$; NB, $n=29$; mean age, 70.1 years; female, 74.8%). ADRs occurred in 14.1%, most often residual urine volume increased (5.5%) and dysuria (3.6%). Serious ADRs occurred in 2.8%. ADRs related to UTIs and those related to UR occurred in 4.5% and 10.7%, respectively. Non-spontaneous voiding at baseline independently predicted UTI risk (adjusted odds ratio, 7.548; 95% confidence interval, 1.378-41.359). In the effectiveness analysis set ($n=495$), treatment was rated "effective" in 82.2% of patients (OAB, 81.2%; NB, 100%). OABSS improved by Week 12 in OAB, and patients with NB showed reduced UI and improved urodynamics.

Conclusions: OnabotulinumtoxinA demonstrated a favorable benefit-risk profile in OAB and NB in routine Japanese practice, with no new safety concerns.

Key words: Botulinum toxin type A, Neurogenic bladder, Overactive bladder, Postmarketing surveillance

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INTRODUCTION

Overactive bladder (OAB) is a syndrome characterized by urgency (a sudden compelling desire to void that is difficult to defer), typically accompanied by frequency and nocturia, with or without urgency urinary incontinence (urgency UI)[1,2]. OAB is highly prevalent, potentially affecting approximately 24% of people worldwide and significantly impairs quality of life and burdens healthcare systems[3,4]. In Japan, approximately 12.4% of individuals aged 40 years or older are affected, with prevalence rising steeply with age[5,6].

Neurogenic bladder (NB) is a related but distinct entity, referring to lower urinary tract dysfunction caused by a neurologic condition and often associated with involuntary detrusor contractions (IDCs)[7]. It increases the risk of urinary retention (UR), recurrent urinary tract infections (UTIs), and long-term upper tract damage, necessitating complex management. NB most commonly arises from spinal cord injury, multiple sclerosis, spina bifida, stroke, and Parkinson's disease[8].

The management of OAB and NB typically follows a stepwise approach, beginning with behavioral therapy, progressing to pharmacological treatment (anticholinergics or β_3-adrenergic receptor agonists), and, when necessary, device- or procedure-based interventions[9]. Intradetrusor injection of botulinum toxin type A is a treatment option for OAB and NB when pharmacological treatment is limited by suboptimal effectiveness, adverse events (AEs), or contraindications[9].

OnabotulinumtoxinA (BOTOX), a botulinum toxin type A formulation, inhibits acetylcholine release from presynaptic nerve terminals at the neuromuscular junction, resulting in local muscle relaxation[10,11]. In the bladder, intradetrusor injection of onabotulinumtoxinA reduces IDCs and increases capacity, alleviating urgency and UI[12]. OnabotulinumtoxinA was first approved in Japan in 1996 for blepharospasm and subsequently for other neurological and movement disorders, as well as hyperhidrosis, before receiving approval in December 2019 for OAB and NB in patients who have an inadequate response to existing therapies or for whom existing therapies are inappropriate[13]. Clinical trials have demonstrated significant efficacy of onabotulinumtoxinA in patients with OAB and NB in Japan[14-16].

UTIs and UR have been defined in the risk management plan (RMP) for onabotulinumtoxinA as important identified risks[17]. Mechanistically, these AEs/adverse drug reactions (ADRs) are thought to result both from reduced detrusor contractility and from treatment-related procedural factors such as cystoscopic injection and the need for catheterization. In line with the RMP, this post-marketing surveillance (PMS) was conducted to characterize the incidence and risk factors of UTIs and UR, in addition to overall safety and effectiveness of onabotulinumtoxinA in routine clinical practice in Japan.

PATIENTS AND METHODS

1 Study design

This was a multicenter, prospective, observational PMS of patients with OAB or NB who received onabotulinumtoxinA under routine clinical practice conditions in Japan. The study was conducted primarily in urology departments across Japan. Patients were observed for up to 48 weeks after the first administration. In accordance with the package insert, patients could receive additional administrations of onabotulinumtoxinA with intervals at least 12 weeks if its effect diminished, at the physician's discretion.

2 Study population

Eligible patients were those initiating onabotulinumtoxinA for the treatment of OAB or NB following regulatory approval of these indications. OAB and NB diagnoses were recorded per the treating physician's judgment in routine practice. Patients with a history of using personally imported botulinum toxin type A preparations and those with a history of using onabotulinumtoxinA for indications other than OAB or NB were not excluded from this PMS.

3 Data collection

Data were prospectively collected using paper case report forms (CRFs) completed by investigators at baseline and throughout the observation period, within the scope of routine clinical practice and when such information was available. The following data were collected: patient demographics, baseline clinical characteristics, urination status, history of UTIs/UR, comorbidities, and (for females) pelvic organ prolapse (POP) stage; prior and concomitant therapies for OAB/NB, including clean intermittent catheterization (CIC); and onabotulinumtoxinA administration details, including date, dose, and any subsequent administrations. Effectiveness data included Overactive Bladder Symptom Score (OABSS) for OAB, number of UI episodes and urodynamic parameters for NB, and investigators' global assessment of effectiveness for both OAB and NB. Safety data included AEs, recorded by diagnosis or symptoms, onset date, severity, seriousness and the investigator's reason for classifying an AE as serious, outcome, causal relationship to onabotulinumtoxinA, and suspected contributing factors other than onabotulinumtoxinA. AEs were classified according to the system organ class and preferred terms in the Medical Dictionary for Regulatory Activities/Japanese version (MedDRA/J) version 27.0. AEs for which a causal relationship to onabotulinumtoxinA could not be excluded were classified as ADRs.

4 Endpoints

The primary endpoints were the incidence of ADRs in the safety analysis set (SAS), with special emphasis on AEs/ADRs related to UTIs and UR, which were defined as AEs/ADRs of special interest.

The secondary endpoints focused on effectiveness. In the effectiveness analysis set (EAS), investigators rated global effectiveness at the end of the observation period as effective, not effective, or indeterminable, and the proportion of patients for whom onabotulinumtoxinA was rated as effective was reported. In patients with OAB, effectiveness was assessed by the course of OABSS[18] immediately before and at Weeks 2, 6, and 12 after onabotulinumtoxinA administration. In patients with NB, effectiveness was assessed by the course of daily UI frequency and changes in urodynamic parameters immediately before and after the first administration, including maximum cystometric capacity (MCC), maximum detrusor pressure during the first IDC (P_{maxIDC}), volume at the first IDC ($V_{PmaxIDC}$), and maximum detrusor pressure during the storage phase (P_{detMAX}).

AEs/ADRs related to UTIs were defined as events coded to the MedDRA/J preferred terms under the high-level terms "genitourinary tract infections and inflammations not elsewhere classified (NEC)," "bladder infections and inflammations," and "renal infections and inflammations (except nephritis)." AEs/ADRs related to UR were defined as events coded to the MedDRA/J preferred terms "urinary retention," "micturition disorder," "dysuria," "strangury," "urinary hesitation," "urine flow decreased," "micturition frequency decreased," "residual urine volume increased," and "hypourocrisia."

5 Statistical analysis

The planned sample size was 500 patients with OAB or NB, which was determined to ensure adequate power to evaluate ADR incidence, specifically UTIs and UR, and to explore potential risk factors. The power of Fisher's exact test (two-sided 5%) was calculated under the null hypothesis that the risk ratio of developing AEs with versus without a risk factor is 1, for total sample sizes of 450–500 patients and a female subgroup proportion of 70% (300–350 patients). Under these assumptions, the power to detect associations for ADRs related to UTIs and UR was estimated to be ≧80%.

The SAS included all patients who received at least one dose of onabotulinumtoxinA and had available safety data. Patients were excluded from the SAS for out-of-period registration or treatment, contract violations, registration errors, withdrawal of consent, no administration of onabotulinumtoxinA reported after registration, having no visits after onabotulinumtoxinA treatment, having no available AE data or for being judged ineligible by the patient review committee. The type, severity, outcome, and timing of ADRs were summarized.

The EAS included patients who met the criteria for the SAS and had evaluable effectiveness data. Patients were excluded from the EAS for use of onabotulinumtoxinA for indications other than OAB or NB, indeterminable effectiveness assessment, an ineligible indication reported after registration, or for being judged to be ineligible by the patient review committee. Although some dose-indication combinations (e.g., 200 units for OAB, 100 units for NB) may be considered off-label in clinical practice, dose was not an exclusion criterion and patients were not excluded based on administered dose. For effectiveness analyses, the proportion of patients for whom onabotulinumtoxinA was rated as "effective" by the investigator was calculated with 95% confidence intervals (CIs). In patients with OAB, the course of OABSS over time was summarized descriptively. In patients with NB, the course of daily UI frequency and urodynamic parameters were also summarized descriptively.

No statistical testing was performed to calculate P values for any effectiveness outcomes. Exploratory multivariable logistic regression analyses were performed to identify baseline covariates associated with the incidence of ADRs. Odds ratios (ORs) and corresponding 95% CIs were estimated and presented descriptively.

All statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

6 Compliance with ministerial ordinances

This study was conducted in accordance with the Declaration of Helsinki and in compliance with the Good Post-marketing Study Practice (GPSP; Ministry of Health, Labour and Welfare [MHLW] Ordinance No. 171, December 20, 2004; and MHLW Pharmaceutical Safety and Environmental Health Bureau [PSEHB] Notification No. 1026-1, October 26, 2017). The study protocol was reviewed and approved by the Ethics Review Committee at Kitamachi Clinic (approval No. GSK07007). Written informed consent was obtained from all patients or their representatives.

RESULTS

1 Patient disposition and characteristics

A total of 547 patients were enrolled in this study between March 2020 and June 2022 (**Fig. 1**). Of these, 532 patients from 79 institutions were included in the SAS. The EAS comprised 495 patients.

Most patients included in the SAS were female (74.8%), and the mean (standard devia-

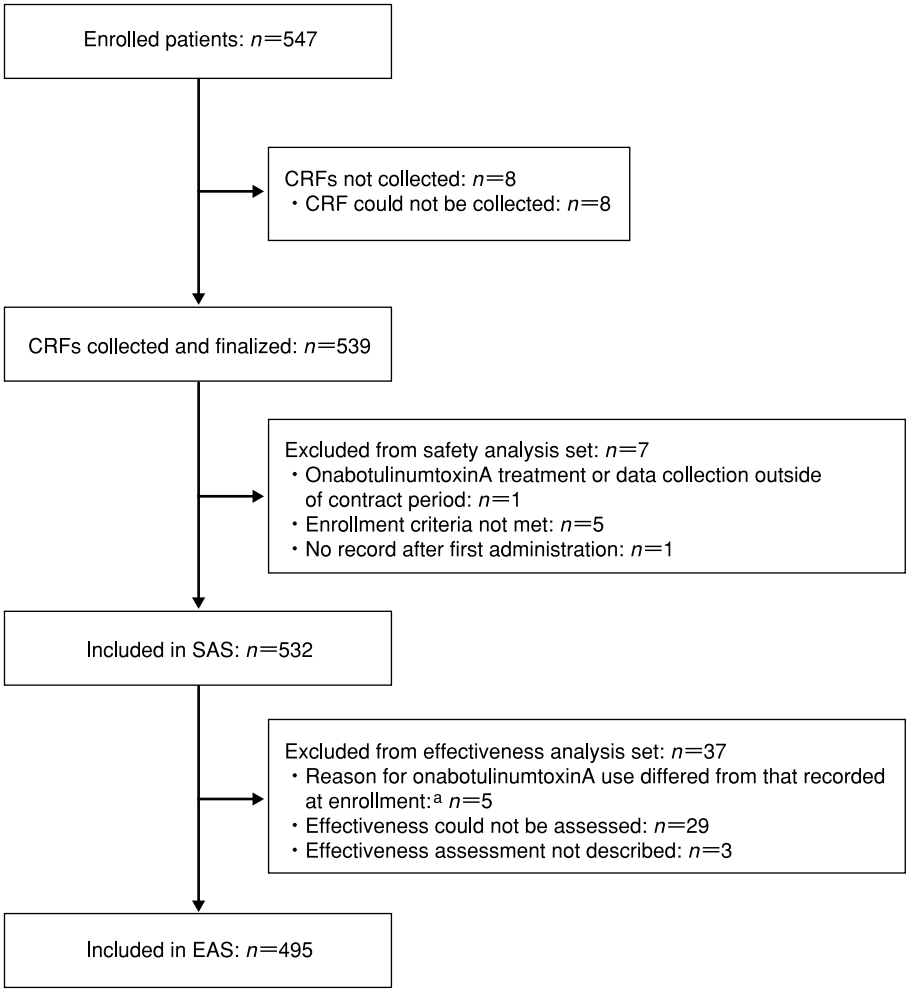

Fig. 1 Patient disposition

[a]Excluded from the effectiveness analysis set because, after enrollment, the reason for use was changed from OAB to NB or from NB to OAB at the physician's discretion. As a result, the information required to evaluate effectiveness for the original indication could not be collected.
CRF: case report form, EAS: effectiveness analysis set, NB: neurogenic bladder, OAB: overactive bladder, SAS: safety analysis set

tion [SD]) age was 70.1 (13.2) years; nearly half (45.9%) were aged ≧75 years (**Table 1**). The majority of patients were treated for OAB (94.5%), while 5.5% had NB. Among patients with NB (n=29), the most frequent underlying causes were spinal cord injury (n=14) and Parkinson's disease (n=3). Most patients (97.2%) were able to void spontaneously, while 3.0% used CIC and 0.6% had indwelling urethral or balloon catheters. A history of UTIs was present in 16.5% of patients and UR in 3.4%. More than half of the population (52.4%) had at least one comorbidity, most commonly prostatic hyperplasia (55.2% of males). Pretreatment with anticholinergics or β_3-adrenergic receptor agonists was reported in 95.6% of patients with OAB and

Table 1　Patient characteristics

Patient characteristic	SAS（*n*＝532）	EAS（*n*＝495）
Sex		
Female	398（74.8）	374（75.6）
Male	134（25.2）	121（24.4）
Pregnancy[a]		
Yes	0	0
Age, years		
Mean（SD）	70.1（13.2）	69.9（13.2）
Median（range）	73.5（16–97）	73.0（16–91）
Age category		
＜65 years	136（25.6）	129（26.1）
≧65 to＜75 years	152（28.6）	145（29.3）
≧75 years	244（45.9）	221（44.6）
Reason for use		
OAB	503（94.5）	468（94.5）
NB	29（5.5）	27（5.5）
Causative disease in patients with NB[b]		
Spinal cord injury	14（48.3）	14（51.9）
Multiple sclerosis	1（3.4）	1（3.7）
Other[c]	14（48.3）	12（44.4）
Age at onset, years		
Mean（SD）	61.8（16.7）	61.2（17.0）
Median（range）	66.0（0–87）	65.0（0–87）
Disease duration		
＜2 years	94（17.7）	89（18.0）
≧2 to＜4 years	48（9.0）	43（8.7）
≧4 to＜6 years	38（7.1）	36（7.3）
≧6 to＜8 years	23（4.3）	22（4.4）
≧8 to＜10 years	21（3.9）	19（3.8）
≥10 years	56（10.5）	52（10.5）
Unknown	252（47.4）	234（47.3）
Urination status[b]		
Spontaneous voiding	517（97.2）	480（97.0）
CIC	16（3.0）	16（3.2）
Placement of catheter, use of balloon catheter	3（0.6）	2（0.4）
Setting at first administration		
Outpatient	317（59.6）	296（59.8）
Inpatient	213（40.0）	197（39.8）
During hospitalization for another reason	2（0.4）	2（0.4）
History of surgery for intrapelvic organs potentially affecting urination	83（15.6）	71（14.3）
History of surgical treatment for UI	41（49.4）	34（47.9）
History of UTI or UR[b]	96（18.0）	85（17.2）
UTI	88（16.5）	79（16.0）
UR	18（3.4）	16（3.2）

Table 1　Patient characteristics（continued）

Patient characteristic	SAS（n=532）	EAS（n=495）
Comorbidity[b]	279（52.4）	255（51.5）
Prostatic hyperplasia[d]	74（55.2）	67（55.4）
Renal impairment	8（1.5）	8（1.6）
Hepatic impairment	6（1.1）	4（0.8）
Other	239（44.9）	218（44.0）
Pelvic organ prolapse of stage Ⅱ or higher[a,e]	6（1.5）	6（1.6）
Pre-therapy intended for OAB[b]	485（96.4）	453（96.8）
Drug therapy with anticholinergics or β_3 agonists	481（95.6）	449（95.9）
Behavioral therapy	108（21.5）	99（21.2）
Surgical treatment	4（0.8）	3（0.6）
Neuromodulation therapy	3（0.6）	3（0.6）
Pre-therapy intended for NB[b]	27（93.1）	25（92.6）
Drug therapy with anticholinergics or β_3 agonists	27（93.1）	25（92.6）
Behavioral therapy	3（10.3）	3（11.1）
Surgical treatment	1（3.4）	1（3.7）
Neuromodulation therapy	0	0

Data are shown as n（%）, unless otherwise specified.
[a]Female patients only.
[b]Subcategories are not mutually exclusive—individuals may appear in more than one subcategory.
[c]Parkinson's disease（3 patients）, spina bifida（2 patients）, brain contusion, traumatic epilepsy, essential tremor, ossification of the ligamentum flavum, dementia, acute disseminated encephalomyelitis, cerebral infarction, lumbar spondylolisthesis, lumbar spinal stenosis, chronic rheumatoid arthritis, status post pelvic surgery（surgery for prostate cancer）, diabetes mellitus, and unknown（1 patient each）.
[d]Male patients only.
[e]According to stage classification using the POP-Q method.
CIC: clean intermittent catheterization, EAS: effectiveness analysis set, NB: neurogenic bladder, OAB: overactive bladder, POP-Q: pelvic organ prolapse quantification, SAS: safety analysis set, SD: standard deviation, UI: urinary incontinence, UR: urinary retention, UTI: urinary tract infection

93.1% of patients with NB.

2　Treatments

At the first administration, most patients with OAB received 100 units of onabotulinumtoxinA（99.8%）and most patients with NB received 200 units（93.1%）, consistent with the approved dosing（**Table 2**）. Overall, 408（81.1%）, 88（17.5%）, and seven（1.4%）of 503 patients with OAB and 23（79.3%）, six（20.7%）, and 0 of 29 patients with NB received one, two, or three administrations of onabotulinumtoxinA, respectively, during the observation period. No fourth administration was reported. In the SAS, the mean interval between administrations of onabotulinumtoxinA was 221.7（58.9）days from the first to second administration（range 112-335; n=101）and 151.0（16.9）days from the second to third administration（range 126-170; n=7）.

At the first administration, most patients received onabotulinumtoxinA under anesthesia（99.6%; n=530/532）, with local bladder muco-

Table 2　Treatment details for patients in the SAS（*n*＝532）

Item/category	OAB（*n*＝503）	NB（*n*＝29）
Dose at first administration		
100 units	502（99.8）	2（6.9）
200 units	1（0.2）	27（93.1）
Total number of administrations		
1	408（81.1）	23（79.3）
2	88（17.5）	6（20.7）
3	7（1.4）	0
Concomitant medications	503（100.0）	29（100.0）
Concomitant therapy[a]	82（16.3）	4（13.8）
Behavioral therapy	78（15.5）	3（10.3）
Neuromodulation therapy	3（0.6）	0
Surgical treatment	2（0.4）	1（3.4）
Status of onabotulinumtoxinA treatment		
Treatment withdrawal/termination[b]	293（58.3）	13（44.8）
Treatment continuation[c]	210（41.7）	16（55.2）

Data are shown as n（%）.
[a]Subcategories are not mutually exclusive—individuals may appear in more than one subcategory.
[b]Defined as patients who discontinued onabotulinumtoxinA treatment before the end of the observation period（48 weeks from the first administration of onabotulinumtoxinA）.
[c]Defined as patients continuing onabotulinumtoxinA treatment after the end of the observation period（48 weeks from the first administration of onabotulinumtoxinA）.
NB: neurogenic bladder, OAB: overactive bladder, SAS: safety analysis set

sal anesthesia being the most common method（63.2%; *n*＝336）（**Table 3**）.

By study end, 42.5% of patients remained on treatment（*n*＝226）, while 57.5% had discontinued（n＝306）. The most frequent reasons for discontinuation of onabotulinumtoxinA were effectiveness-related, including sufficient or insufficient effectiveness（46.1%; *n*＝141）, premature termination of visits（29.4%; *n*＝90）, patient convenience（17.6%; *n*＝54）, and occurrence of AEs（6.2%; *n*＝19）. Among patients discontinuing for effectiveness-related reasons, the result of the global assessment of effectiveness was "effective" in 51.8%（*n*＝73）,"not effective" in 46.8%（n＝66）, and "indeterminable" in 1.4%（*n*＝2）.

3　Safety

ADRs occurred in 14.1% of patients（n＝75/532）（**Table 4**）. The frequency of ADRs according to the number of administrations was 13.2%, 4.0%, and 14.3% after the first, second, and third administrations, respectively. The most common ADRs by preferred term were residual urine volume increased（*n*＝29, 5.5%）, dysuria（*n*＝19, 3.6%）, and cystitis（*n*＝15, 2.8%）. The majority of ADRs had resolved or were resolving by study end, while the outcome was "Not resolved" in four patients and "Unknown" in five. Serious ADRs were reported in 2.8%（*n*＝15）, most often UR（2.4%）; fungal cystitis, pyelonephritis, bacterial prostatitis, and autonomic dysreflexia were each reported in one patient（0.2%）. All serious

Table 3 Actions taken for onabotulinumtoxinA administration

	1st administration (*n*=532)	2nd administration (*n*=101)	3rd administration (*n*=7)
Presence or absence of anesthesia procedure			
Present	530 (99.6)	100 (99.0)	7 (100.0)
Absent	2 (0.4)	1 (1.0)	0
Category of anesthesia procedure[a,b]			
Local anesthesia	478 (89.8)	86 (85.1)	7 (100.0)
General anesthesia	72 (13.5)	18 (17.8)	0
Type of local anesthesia[b]			
Bladder mucosal anesthesia	336 (63.2)	74 (73.3)	6 (85.7)
Spinal anesthesia	100 (18.8)	7 (6.9)	0
Urethral anesthesia	91 (17.1)	20 (19.8)	1 (14.3)
Epidural anesthesia	35 (6.6)	3 (3.0)	1 (14.3)
Other	10 (1.9)	0	0
Sedatives			
Absent	415 (78.0)	76 (75.2)	5 (71.4)
Present	117 (22.0)	25 (24.8)	2 (28.6)
Antibiotics			
Present	506 (95.1)	95 (94.1)	6 (85.7)
Absent	26 (4.9)	6 (5.9)	1 (14.3)

Data are shown as *n* (%).
[a]General anesthesia: intravenous anesthesia and inhalation anesthesia. Local anesthesia: urethral anesthesia, bladder mucosal anesthesia, spinal anesthesia, epidural anesthesia, and other.
[b]Subcategories are not mutually exclusive—individuals may appear in more than one subcategory.

ADRs were reported after the first administration; none occurred with repeat doses. Two deaths (cerebral hemorrhage and cardiac failure acute) were reported as serious AEs, and in both cases the investigators considered there to be no causal relationship to onabotulinumtoxinA.

ADRs were observed in 13.7% (*n*=69) of patients with OAB and 20.7% (*n*=6) of patients with NB (**Table 5**). In OAB, the most frequent events were residual urine volume increased (5.4%), dysuria (3.8%), and cystitis (2.8%). In NB, residual urine volume increased and UTIs occurred in 6.9% of patients each.

There were no reports of ADRs suggesting effects of onabotulinumtoxinA at distant sites.

4 AEs/ADRs of special interest

AEs related to UTIs (i.e., AEs assigned to the UTI category) occurred in 8.3% of patients (*n*=44) and AEs related to UR (i.e., AEs assigned to the UR category) occurred in 11.5% of patients (*n*=61). Twenty-four patients (4.5%) had ADRs related to UTIs, with cystitis being the most frequent (2.8%, *n*=15) (**Table 6**). Of the two serious ADRs related to UTIs (fungal cystitis and pyelonephritis), one had resolved and the other was resolving. ADRs related to UR occurred in 57 patients (10.7%), with residual urine volume increased being the most frequent (5.5%, *n*=29) (**Table 6**). Among 13 patients with serious ADRs related to UR, all had a MedDRA/J preferred term of "urinary retention"; the

Table 4　Incidence of ADRs during repeated administrations[a,b]

System organ class/preferred term	Overall (*n*=532)	1st administration (*n*=532)	2nd administration (*n*=101)	3rd administration (*n*=7)
Any ADR	75 (14.1)	70 (13.2)	4 (4.0)	1 (14.3)
Renal and urinary disorders	36 (6.8)	35 (6.6)	0	1 (14.3)
Dysuria	19 (3.6)	18 (3.4)	0	1 (14.3)
UR	13 (2.4)	13 (2.4)	0	0
Haematuria	2 (0.4)	2 (0.4)	0	0
Pollakiuria	2 (0.4)	2 (0.4)	0	0
Hypertonic bladder	1 (0.2)	1 (0.2)	0	0
Nocturia	1 (0.2)	1 (0.2)	0	0
Urethral pain	1 (0.2)	1 (0.2)	0	0
UI	1 (0.2)	1 (0.2)	0	0
Investigations	29 (5.5)	25 (4.7)	4 (4.0)	0
Residual urine volume increased	29 (5.5)	25 (4.7)	4 (4.0)	0
Infections and infestations	24 (4.5)	23 (4.3)	1 (1.0)	0
Cystitis	15 (2.8)	15 (2.8)	0	0
UTI	6 (1.1)	5 (0.9)	1 (1.0)	0
Fungal cystitis	1 (0.2)	1 (0.2)	0	0
Pyelonephritis	1 (0.2)	1 (0.2)	0	0
Cystitis bacterial	1 (0.2)	1 (0.2)	0	0
Bacterial prostatitis	1 (0.2)	1 (0.2)	0	0
General disorders and administration site conditions	2 (0.4)	2 (0.4)	0	0
Condition aggravated	1 (0.2)	1 (0.2)	0	0
Injection site pain	1 (0.2)	1 (0.2)	0	0
Nervous system disorders	1 (0.2)	1 (0.2)	0	0
Autonomic dysreflexia	1 (0.2)	1 (0.2)	0	0
Skin and subcutaneous tissue disorders	1 (0.2)	1 (0.2)	0	0
Urticaria	1 (0.2)	1 (0.2)	0	0

Data are shown as *n* (%).

[a]Events that occurred from each administration up to the day before the next administration.

[b]No fourth administration was reported. ADRs were coded using MedDRA/J version 27.0.

ADR: adverse drug reaction, MedDRA/J: Medical Dictionary for Regulatory Activities/Japanese version, UI: urinary incontinence, UR: urinary retention, UTI: urinary tract infection

outcome was "Resolved" or "Resolving" in nine and "Not resolved" or "Unknown" in four.

Multivariable analyses identified urination status other than spontaneous voiding (e.g., catheterization) at baseline (at first administration of onabotulinumtoxinA) as the only independent predictor of risk of ADRs related to UTIs (adjusted OR, 7.548; 95% CI, 1.378–41.359) (**Table 7**). No baseline factors independently predicted ADRs related to UR in either males (**Table 8**) or females (**Table 9**).

5　Effectiveness

In the investigator-rated global assessment of effectiveness, onabotulinumtoxinA was rated as "effective" in 82.2% of patients in the EAS (*n*=407/495), including 81.2% of those with OAB (*n*=380/468) and all patients with NB (*n*=27/27).

Table 5 Occurrence of ADRs according to the indication for onabotulinumtoxinA

System organ class/preferred term	OAB (n=503)	NB (n=29)
Patients with ADRs	69 (13.7)	6 (20.7)
Renal and urinary disorders	35 (7.0)	1 (3.4)
Dysuria	19 (3.8)	0
UR	12 (2.4)	1 (3.4)
Haematuria	2 (0.4)	0
Pollakiuria	2 (0.4)	0
Hypertonic bladder	1 (0.2)	0
Nocturia	1 (0.2)	0
Urethral pain	1 (0.2)	0
UI	1 (0.2)	0
Investigations	27 (5.4)	2 (6.9)
Residual urine volume increased	27 (5.4)	2 (6.9)
Infections and infestations	21 (4.2)	3 (10.3)
Cystitis	14 (2.8)	1 (3.4)
UTI	4 (0.8)	2 (6.9)
Fungal cystitis	1 (0.2)	0
Pyelonephritis	1 (0.2)	0
Cystitis bacterial	1 (0.2)	0
Bacterial prostatitis	1 (0.2)	0
General disorders and administration site conditions	2 (0.4)	0
Condition aggravated	1 (0.2)	0
Injection site pain	1 (0.2)	0
Nervous system disorders	0	1 (3.4)
Autonomic dysreflexia	0	1 (3.4)
Skin and subcutaneous tissue disorders	1 (0.2)	0
Urticaria	1 (0.2)	0

Data are shown as n (%).
ADR: adverse drug reaction, NB: neurogenic bladder, OAB: overactive bladder, UI: urinary incontinence, UR: urinary retention, UTI: urinary tract infection

In patients with OAB, the mean baseline OABSS was 9.8 (**Fig. 2**). By subgroup, baseline scores were 9.5 in patients aged ＜75 years, 10.0 in those aged ≧75 years, 9.6 in males, and 9.8 in females. By Week 12, the mean OABSS decreased to 6.2 in the overall OAB population. The subgroup scores at Week 12 were 5.3 in patients aged ＜75 years, 7.0 in those aged ≧75 years, 6.5 in males, and 6.1 in females. Total OABSS declined through Week 12 after the first administration, with similar trends after subsequent doses, although numbers were small (**Fig. 3**).

In patients with NB, onabotulinumtoxinA treatment led to improvements in UI frequency (**Fig. 4**). At baseline (before the first administration), none of the 20 evaluable patients were continent, whereas 60.0% (n=9/15) reported no UI at Week 2. This proportion decreased to 40.0% (n=6/15) at Week 6 and 30.0% at Week 12 (n=3/10), though numbers were small. Six patients received a second administration, four of whom had evaluable data; all four had UI at the pre-administration assessment. By Week 2, all four

Table 6 Incidence of ADRs of special interest related to UTIs or UR

ADR of special interest/preferred term	Total (n=532)
ADRs related to UTIs[a]	24 (4.5)
Cystitis	15 (2.8)
UTI	6 (1.1)
Cystitis bacterial	1 (0.2)
Fungal cystitis	1 (0.2)
Pyelonephritis	1 (0.2)
ADRs related to UR[b]	57 (10.7)
Residual urine volume increased	29 (5.5)
Dysuria	19 (3.6)
UR	13 (2.4)

Data are shown as n (%).
[a]Defined as events coded using the preferred terms under the high level terms "genitourinary tract infections and inflammations NEC," "bladder infections and inflammations," and "renal infections and inflammations (except nephritis)."
[b]Defined as events coded using the preferred terms "urinary retention," "micturition disorder," "dysuria," "strangury," "urinary hesitation," "urine flow decreased," "micturition frequency decreased," "residual urine volume increased," and "hypourocrisia."
ADRs were coded using MedDRA/J version 27.0.
ADR: adverse drug reaction, MedDRA/J: Medical Dictionary for Regulatory Activities/Japanese version, NEC: not elsewhere classified, UR: urinary retention, UTI: urinary tract infection

evaluable patients were continent, and this was maintained in 50% of patients at Week 6 (n=1/2) and in the single evaluable patient at Week 12.

Urodynamic assessments in patients with NB with available data (n=9) indicated numerical improvement in several parameters (**Table 10**). Following treatment, the mean MCC increased from 254.8 mL to 324.9 mL, and the mean P_{detMAX} decreased from 48.0 cmH_2O to 43.6 cmH_2O. The $V_{PmaxIDC}$ also increased and P_{maxIDC} decreased.

DISCUSSION

In this PMS of Japanese clinical practice, onabotulinumtoxinA, at doses approved in Japan, demonstrated a favorable safety and effectiveness profile in patients with OAB or NB who have an inadequate response to existing therapies or for whom existing therapies are inappropriate. The incidence and nature of ADRs were consistent with those observed in clinical trials, and no new safety signals were identified. Effectiveness outcomes, including reductions in OABSS in OAB and decreased UI frequency in NB, and a high proportion of patients rated as "effective," confirmed the clinical utility of onabotulinumtoxinA.

The safety profile observed in this study aligns with prior reports from randomized trials and observational cohorts. UTIs and UR remain the most clinically significant adverse outcomes associated with botulinum toxin injection[19,20]. The incidence of ADRs was within the expected range, and the types of events mirrored those reported in pre-approval studies[14–16], indicating that no new safety concerns were identified in

Table 7 Multivariable analysis of risk factors for ADRs related to UTIs[a]

Item	Category	Patients with ADRs, *n/N* (%)	Adjusted OR (95% CI)
All patients with ADRs related to UTIs	All patients	24/532 (4.5)	
Sex	Male	4/134 (3.0)	
	Female	20/398 (5.0)	2.325 (0.734–7.363)
Age category	＜65 years	5/136 (3.7)	
	≧65 years	19/396 (4.8)	2.173 (0.639–7.388)
Urination status at the first administration	Spontaneous voiding only	21/514 (4.1)	
	Other than spontaneous voiding	3/18 (16.7)	7.548 (1.378–41.359)
History of UTI	Absent	16/444 (3.6)	
	Present	8/88 (9.1)	1.897 (0.735–4.897)
Comorbidity	Absent	8/253 (3.2)	
	Present	16/279 (5.7)	1.973 (0.811–4.800)

[a]The incidence of ADRs related to UTIs was calculated as the proportion and the two-sided 95% CI of patients experiencing at least one ADR.
ADR: adverse drug reaction, CI: confidence interval, OR: odds ratio, UTI: urinary tract infection

routine clinical practice.

Regarding UTIs, baseline urinary status, particularly catheterization, was identified as a major determinant of risk. This observation is consistent with findings in spinal cord injury populations, in which bladder management methods strongly influence infection rates[21]. The incidence of UTIs was lower than that reported in pre-approval Japanese studies[14], suggesting that the real-world risk remains within the expected range but warrants attention in patients managed with catheters.

In contrast, with respect to UR, no clear baseline predictors were identified in this PMS. A systematic review of intradetrusor onabotulinumtoxinA for refractory idiopathic OAB suggested that male sex and impaired baseline voiding function may be associated with an increased risk of voiding dysfunction or UR requiring CIC in some cohorts, although definitions, effect estimates, and overall certainty of evidence were heterogeneous and generally low[22]. Prior evidence suggests that the risk of large post-void residuals or UR is not universal but concentrated in susceptible subgroups. Liao and Kuo[23] reported numerically higher post-void residual urine and less favorable long-term success rates in frail elderly patients compared with non-frail patients, although the difference in UR did not achieve statistical significance. Similarly, real-world data indicate that individual patient factors, including age, comorbidity burden, and bladder

Table 8　Multivariable analysis of risk factors for ADRs related to UR in males

Item	Category	Patients with ADRs, *n/N* (%)	Adjusted OR (95% CI)
Patients with ADRs related to UR, males[a]	All patients	21/134 (15.7)	
Age category	＜65 years	3/31 (9.7)	
	≧65 years	18/103 (17.5)	1.715 (0.432–6.805)
History of surgery for intrapelvic organs potentially affecting urination	Absent	17/117 (14.5)	
	Present	4/17 (23.5)	1.932 (0.495–7.549)
History of UR	Absent	19/123 (15.4)	
	Present	2/11 (18.2)	1.495 (0.249–8.990)
Comorbid prostatic hyperplasia	Absent	7/60 (11.7)	
	Present	14/74 (18.9)	1.908 (0.671–5.425)

[a]UR was analyzed separately in males and females because some of the potential risk factors are sex-specific, including comorbid prostatic hyperplasia in males and POP-Q stage Ⅱ or higher in females.
ADR: adverse drug reaction, CI: confidence interval, OR: odds ratio, POP-Q: pelvic organ prolapse quantification, UR: urinary retention

management strategies, may influence the risk of complications[24]. The present findings therefore support previous observations that UR after onabotulinumtoxinA treatment is multifactorial, and generally manageable.

The effectiveness outcomes of this PMS were favorable, and treatment was rated as "effective" in over 80% of patients. The improvements in OABSS among patients with OAB are consistent with the reductions reported in randomized controlled trials and post hoc analyses, which have established the durability of symptom control across diverse populations[25,26]. These results are also consistent with those of Japanese phase III trials, where OABSS and patient satisfaction showed sustained improvements following onabotulinumtoxinA 100 units treatment[14,15]. Similarly, in NB, decreases in UI frequency and favorable urodynamic changes support onabotulinumtoxinA as an effective option, echoing prior reports in both trial and real-world settings[27–29]. As this PMS mostly comprised older adults (aged ≧65 years), these findings further support the effectiveness of onabotulinumtoxinA in this population.

As this was a single-arm, observational study without a non-treated comparator, direct comparisons with untreated patients or alternative therapies were not possible. Effectiveness evaluations, particularly for OAB, relied mainly on subjective measures, including patient-reported symptom scores (OABSS) and investigator-rated global assessments, and no formal statistical testing was performed. These factors may have influenced the interpretation of treatment effectiveness. The sample, while large, included relatively few patients with NB, limiting generalizability to this subgroup. In addition,

Table 9 Multivariable analysis of risk factors for ADRs related to UR in females

Item	Category	Patients with ADRs, *n/N* (%)	Adjusted OR (95% CI)
Patients with ADRs related to UR, females[a]	All patients	36/398 (9.0)	
Age category	＜65 years	7/105 (6.7)	
	≧65 years	29/293 (9.9)	1.706 (0.689–4.229)
History of surgery for intrapelvic organs potentially affecting urination	Absent	28/332 (8.4)	
	Present	8/66 (12.1)	1.442 (0.617–3.366)
Pelvic organ prolapse of stage Ⅱ or higher[b]	Absent	35/392 (8.9)	
	Present	1/6 (16.7)	2.354 (0.259–21.361)
History of UR	Absent	34/391 (8.7)	
	Present	2/7 (28.6)	5.280 (0.899–31.008)
Comorbidity	Absent	14/218 (6.4)	
	Present	22/180 (12.2)	1.998 (0.983–4.057)

[a]UR was analyzed separately in males and females because some of the potential risk factors are sex-specific, including comorbid prostatic hyperplasia in males and POP-Q stage Ⅱ or higher in females.
[b]According to stage classification using the POP-Q method.
ADR: adverse drug reaction, CI: confidence interval, OR: odds ratio, POP-Q: pelvic organ prolapse quantification, UR: urinary retention

subgroup analyses involved small numbers of patients, resulting in wide CIs and limiting the robustness of these findings.

CONCLUSIONS

This PMS indicated that intradetrusor onabotulinumtoxinA has a favorable benefit-risk profile in patients with OAB and NB in routine Japanese clinical practice. No new safety signals were detected. The analyses suggested that patients who were not spontaneously voiding at the time of first administration may have a higher risk of UTIs, although this finding should be interpreted with caution given the limited number of cases and the absence of data on post-treatment changes in urination status. Overall, these results support the role of onabotulinumtoxinA as a well-tolerated and clinically beneficial treatment option for OAB and NB in real-world practice.

CONFLICT OF INTEREST

All authors are employees of GlaxoSmithKline K. K. Yasuyo Nose and Yoriko Morioka hold shares in the company.

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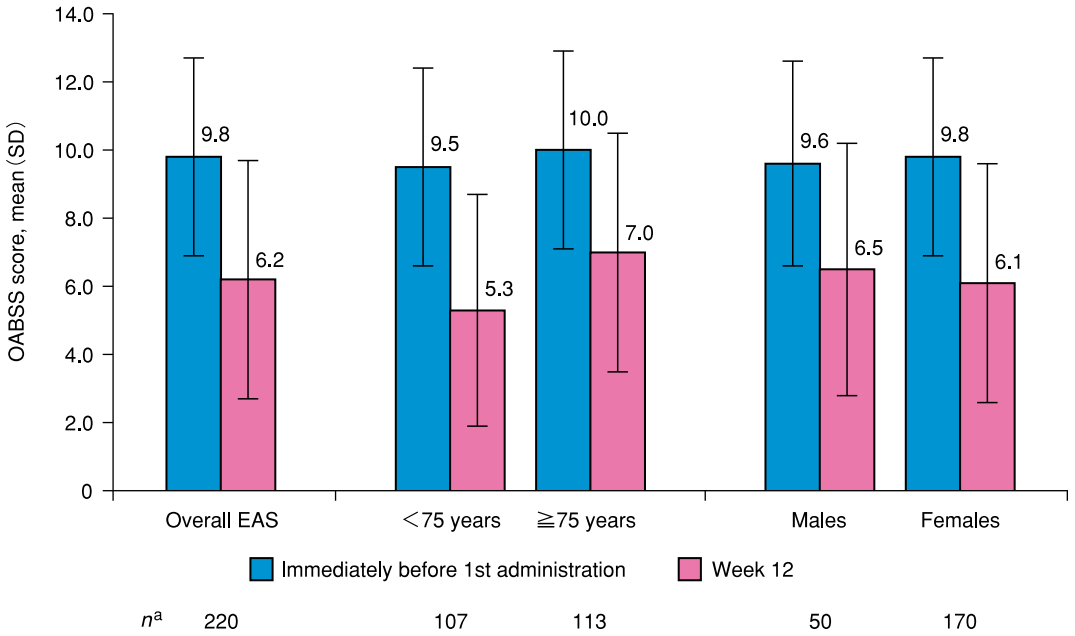

Fig. 2 Total OABSS immediately before the first administration and at Week 12 after the first administration in patients with OAB

[a]Includes only patients with available data both immediately before the first administration and 12 weeks after the first administration; therefore, the numbers of patients before and after treatment are identical.

EAS: effectiveness analysis set, OAB: overactive bladder, OABSS: Overactive Bladder Symptom Score, SD: standard deviation

tion, analysis, interpretation of results, manuscript preparation, and the decision to submit the manuscript for publication.

AUTHOR CONTRIBUTIONS

Conceptualization, Y. N. and Y. Y.; formal analysis, Y. M.; investigation, T. D.; writing—original draft preparation, Y. N.; writing—review and editing, Y. N., T. D., Y. M., and Y. Y.; project administration, Y. N. All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

The pseudonymized individual participant data of this study are not publicly available because data sharing with third parties, excluding health authorities, was not included in the contracts with study sites. The associated documents of this study can be found at www.gsk-studyregister.com/en.

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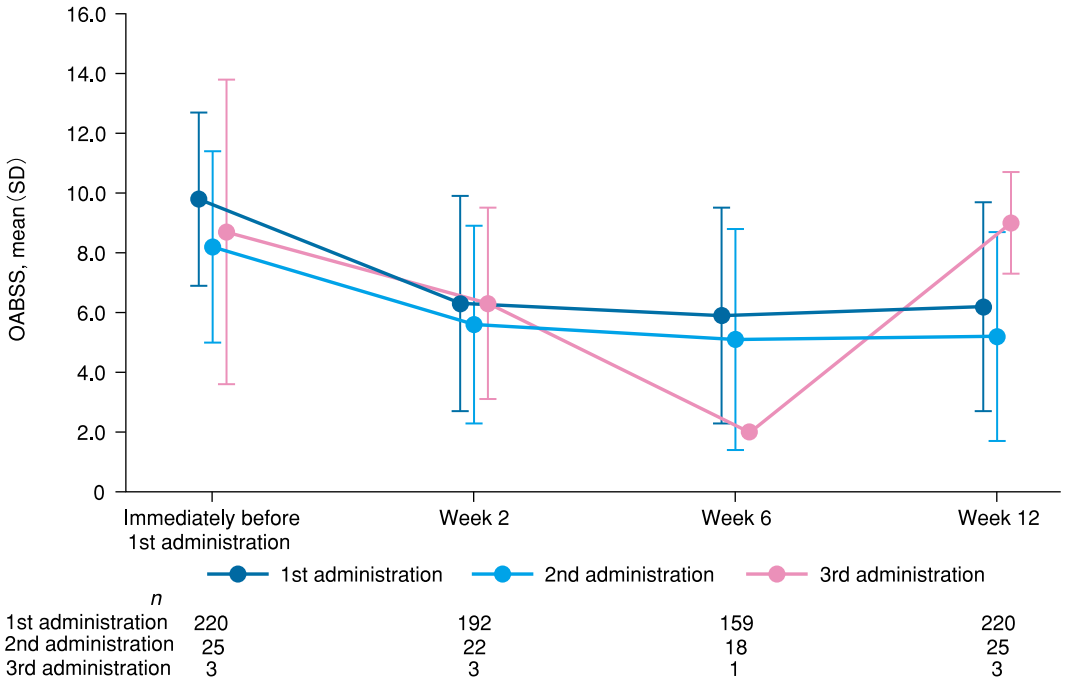

Fig. 3 Changes in the total score of OABSS for each onabotulinumtoxinA administration in OAB patients

OAB: overactive bladder, OABSS: Overactive Bladder Symptom Score, SD: standard deviation

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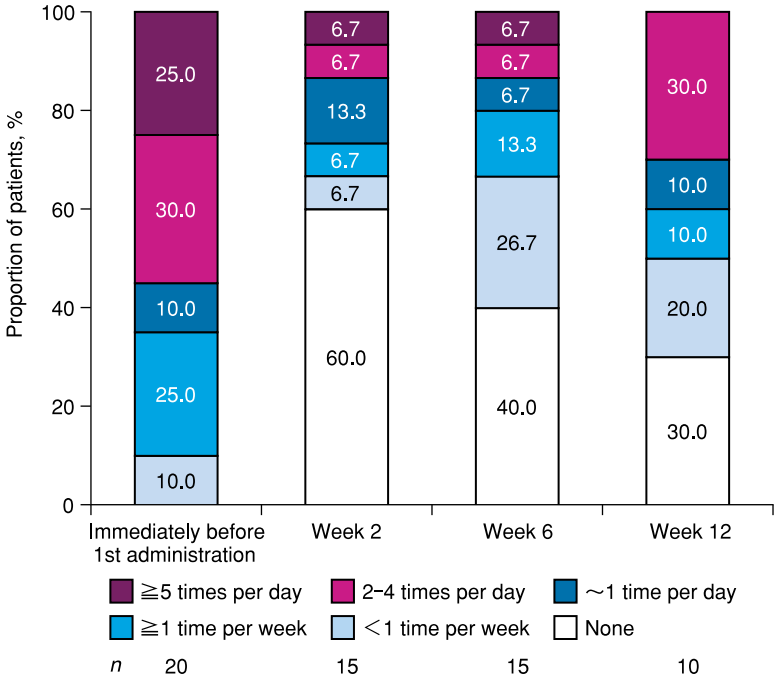

Fig. 4 Changes in the frequency of UI in patients with NB after the first administration of onabotulinumtoxinA

NB: neurogenic bladder, UI: urinary incontinence

Table 10 Urodynamic tests in patients with NB

	Immediately before the 1st administration	After the 1st administration
MCC, mL (n=9)[a]		
Mean (SD)	254.8 (127.3)	324.9 (77.3)
Median (range)	229.0 (86–404)	359.0 (187–402)
P_{detMAX}, cmH_2O (n=9)[a]		
Mean (SD)	48.0 (32.4)	43.6 (23.8)
Median (range)	49.0 (4–111)	44.0 (7–88)
$V_{PmaxIDC}$, mL (n=7)[a,b]		
Mean (SD)	161.0 (102.4)	214.4 (86.4)
Median (range)	113.0 (70–361)	190.0 (95–313)
P_{maxIDC}, cmH_2O (n=7)[a,b]		
Mean (SD)	57.1 (27.3)	52.1 (18.8)
Median (range)	53.0 (31–111)	53.0 (31–88)

[a]Includes only patients with available data both immediately before and after the first administration.

[b]Data were available only for patients in whom involuntary detrusor contraction was present.

MCC: maximum cystometric capacity, NB: neurogenic bladder, P_{detMAX}: maximum detrusor pressure during the storage phase, P_{maxIDC}: maximum detrusor pressure during the first involuntary detrusor contraction, SD: standard deviation, $V_{PmaxIDC}$: volume at the first involuntary detrusor contraction

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