CLINICAL REVIEW

Application Type	NDA Resubmission
Application Number(s)	**NDA** 209529
Priority or Standard	Standard (Complete Response to August 28, 2017, Action Letter)
Submit Date(s)	November 27, 2019
Received Date(s)	November 27, 2019
PDUFA Goal Date	May 27, 2020
Division/Office	DUOG/ODE 3
Reviewer Name(s)	Elena Boley
Review Completion Date	May 15, 2020
Established/Proper Name	Solifenacin Oral Suspension
(Proposed) Trade Name	VESIcare LS
Applicant	Astellas Pharma Global Development, Inc.
Dosage Form(s)	Aqueous suspension 1 mg/mL
Applicant Proposed Dosing Regimen(s)	The recommended dose of VESIcare LS is determined based on patient weight. Treatment should be initiated at the recommended starting dose. Thereafter, the dose may be increased to the lowest effective dose. The maximum dose should not be exceeded.
Applicant Proposed Indication(s)/Population(s)	Neurogenic detrusor overactivity (NDO) in pediatric patients aged 2 years (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Neurogenic detrusor overactivity (NDO) in pediatric patients aged 2 years and older.

Weight range (kg)	Starting dose (mL)	Maximum dose (mL)
9 to 15	2	4
> 15 to 30	3	5
> 30 to 45	3	6
> 45 to 60	4	8
> 60	5	10

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CIC	Clean intermittent catheterization
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DEPI	Division of Epidemiology
DMC	data monitoring committee
DMEPA	Division of Medical Error Preventions and Analysis
DMPP	Division of Medical Policy Programs
DPV	Division of Pharmacovigilance
DRISK	Division of Risk Management
DUOG	Division of Urology, Obstetrics, and Gynecology
EBC	estimated bladder capacity
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
IC	informed consent
ICH	International Council for Harmonization

IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITQoL SF-47	Infant and Toddler Quality of Life Short Form-47
ITT	intent to treat
MCV	mean catheterized volume
MCC	mean cystometric capacity
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OAB	overactive bladder
OCS	Office of Computational Science
OPDP	Office of Prescription Drug Promotion
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PinQ	Pediatric Incontinence Questionnaire
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PPS	per protocol set
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
QoL	quality of life
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
WR	written request

1. Executive Summary

1.1. Product Introduction

Solifenacin (VESIcare LS®) is a competitive muscarinic receptor antagonist with high affinity for M3-receptors. Antagonism of the M3-receptors, which blocks contractions of the detrusor muscle that are typically mediated through stimulation of these receptors, is considered the main mechanism of solifenacin-induced relaxation of the bladder. Solifenacin succinate, 5 mg and 10 mg tablets, was originally approved on November 19, 2004 under NDA 021518 for the treatment of overactive bladder (OAB), with symptoms of urge urinary incontinence, urgency and urinary frequency. In this NDA, additional data for the pediatric population is presented to support the safety and efficacy of solifenacin (tablet and oral suspension) for the treatment of neurogenic bladder overactivity (NDO) in pediatric patients aged 2 years to less than 18 years.

The recommended starting dose for solifenacin oral suspension in children is determined based on patient weight. Treatment should be initiated at the recommended starting dose appropriate for the patient's weight. Thereafter, the dose may be increased to the lowest effective dose. The maximum dose in the dose range for each weight range should not be exceeded.

Solifenacin oral suspension is a white to off-white colored, aqueous, homogenous suspension containing 1 mg/mL solifenacin succinate. One (1) mg solifenacin succinate is equivalent to 0.75 mg solifenacin.

1.2. Conclusions on the Substantial Evidence of Effectiveness

From the Clinical perspective, the evidence presented in the original submission for this NDA is adequate to support the effectiveness of this product in the treatment of pediatric patients with NDO. No new clinical data to support efficacy was provided in this resubmission.

1.3. Benefit-Risk Assessment

VESIcare LS (solifenacin) oral suspension will be indicated for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients. Neurogenic detrusor overactivity is defined as detrusor overactivity that develops as a result of a neurologic lesion. An oral suspension, which facilitates swallowing for younger children and allows accurate dose titration, is intended to provide another treatment option for pediatric patients with NDO. The goal of treatment is to preserve renal function and minimize symptoms of incontinence by increasing bladder capacity and the duration of time between incontinence episodes.

At this time, the Clinical review team recommends that this NDA should be APPROVED.

NDO results from neurological lesions often related to congenital anomaly and injury to the spinal cord. In this special pediatric patient population, NDO poses a meaningful burden both physically and socially/emotionally. Physical consequences of untreated NDO are bladder wall injury and renal damage. Interference in social and emotional development results from the limited lifestyle and decreased level of engagement caused by frequent incontinence episodes.

Current oral pharmacologic treatment options for NDO are limited and include oxybutynin - the only approved pharmacologic agent for this condition - in combination with clean intermittent catherization (CIC). Oxybutynin's side effect profile includes central nervous system adverse effects which may affect learning and school performance, as well as more typical side effects associated with anticholinergic medications such as headaches, blurred vision, constipation, altered behavior, dry mouth, and flushed cheeks. There is a need for alternative options for treatment of this patient population that are safe and effective.

Solifenacin works by blocking M3-receptors, which in turn blocks involuntary contractions of the bladder's detrusor muscle and induces relaxation of the bladder smooth muscle. The efficacy of solifenacin oral suspension has been demonstrated through clinically meaningful increases in maximum cystometric capacity and supported by improvement in many urodynamic parameters and voiding diary measurements. The magnitude of treatment effect was similar across age groups. The efficacy of solifenacin oral suspension does not appear to be associated with any new safety issues.

The safety profile of solifenacin oral suspension is consistent with the known risks of solifenacin tablets for the treatment of OAB in adults and of anticholinergics in general. There were no deaths in the development program, and none of the SAEs appeared to be drug-related. Discontinuations (n=4) were all due to "ECG QT prolonged", which was an artifact of high intrapatient variance in sparse baseline QT assessments as revealed by a random effects model analysis and corrected by simple protocol amendment. The most commonly reported (>5%) treatment emergent adverse events (TEAEs) in the clinical trials were primarily the typical antimuscarinic effects of constipation and dry mouth. UTI TEAEs were also common but were thought to reflect, at least in part, the high annual incidence of UTI in pediatric patients with NDO

practicing CIC and not all associated with solifenacin treatment. Other TEAEs of special interest included hypertension, tachycardia, somnolence, and toxic megacolon, each reported in a single patient, and only somnolence could not be ruled out as being causally related to solifenacin treatment. Vital signs data showed a small increase from baseline in mean systolic blood pressure (SBP) (0.7 mmHg), a decrease from baseline in mean diastolic blood pressure (DBP) (-1.6 mmHg) and a decrease from baseline in mean pulse rate (-2.9 beats/min). These changes were considered likely to be related to normal growth and maturation, not drug-related change. Overall, TEAEs were reported with similar frequency in the pediatric NDO patients as they were in clinical trials of adults with OAB, except for the two most common drug-related TEAEs, constipation and dry mouth, for which the reported incidence in NDO patients was less than in adult OAB patients. Postmarket experience SAE cases were also consistent with the known side effect profile of solifenacin.

The benefit-risk analysis takes into account that NDO in the pediatric population a serious condition that is associated with bladder wall changes and renal damage, as well as social and emotional distress that greatly interferes with the development of these children. Solifenacin oral suspension provides an alternative treatment to the single approved option, is efficacious, and has a similar side effect profile. Additionally, solifenacin oral suspension offers a more convenient once daily dosing regimen and data to support safety and efficacy for pediatric patients as young as 2 years old.

These benefits compare favorably against the safety profile which reflects the known risks apparent in the premarket and postmarket experience with solifenacin tablets to date. The clinical trials of solifenacin oral suspension provided no safety signals beyond those known for solifenacin tablets. Labelling is adequate to address the known risks of solifenacin. The safety data submitted supports the use of solifenacin oral suspension as an additional first line therapy, coupled with CIC, for the treatment of pediatric patients aged 2 to < 18 years with NDO.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• NDO is defined by the International Children's Continence Society (ICCS) as detrusor overactivity when there is a relevant neurological condition. NDO is a urodynamic observation characterized by involuntary detrusor contractions that are spontaneous or provoked during the filling phase, involving a detrusor pressure increase of greater than 15 cm H_2O above baseline. • NDO can develop as a result of a lesion at any level in the nervous system.	This condition is important because of the irreversible kidney damage it can cause without treatment as well as the severe limitations on daily living and the resulting social and emotional harm it causes during the critical childhood developmental life stage.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	The most prevalent cause of NDO in children is myelodysplasia, which includes such conditions as myelomeningocele, meningocele, and occult spinal dysraphism/spina bifida occulta, and results from neural tube closure defects during fetal development. The most common acquired cause for NDO is cerebral palsy. An injury in the perinatal period (e.g. perinatal infection, anoxia) can produce a neuromuscular disability or a specific cerebral dysfunction. Less common acquired causes include spinal tumors, trauma, or sequalae of transverse myelitis. Because NDO results from a number of different conditions, prevalence is not easily quantifiable. • If untreated, NDO can cause bladder wall changes and renal damage due to hydronephrosis. • Chronic incontinence in children with NDO leads to limited social participation, embarrassment and shame, and decreased independence. These consequences adversely affect the social and emotional development of children and also of adolescents transitioning into adulthood.	
Current Treatment Options	• The current first line treatment option is antimuscarinics coupled with CIC (4-5 times a day). The only approved medication is oxybutynin, which comes in tablets or syrup, is approved for patients with NDO age 5 years and older and is dosed 2-3 times a day. Off label therapies include oral β_3 agonist mirabegron and intravesical Botox injections. More invasive treatment options for those who fail treatment with medication and CIC include incontinent urinary diversion or reconstructive bladder surgery with augmentation cystoplasty. • Current approved pharmacotherapy decreases mean MCC at 24 weeks by 49 mL compared to baseline. • The safety profile for oxybutynin includes typical anticholinergic side effects such as headaches, blurred vision, constipation, altered behavior, dry mouth, and flushed cheeks. There are also potential CNS adverse effects	There is a need for an additional pharmacotherapy option for a wider pediatric age group (includes children younger than 5), with less frequent dosing, and with a similar safety profile. Such an alternative may improve patient adherence (and be more convenient for caregivers), may wind up being more effective and well tolerated than current therapy in some patients, and may delay or obviate the use of invasive therapies in the future.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	that raise concerns for cognitive effects that could affect learning and school performance in the pediatric demographic.	
Benefit	• The Phase 3 "pivotal" trials that supported this application were two, open-label, baseline-controlled, multicenter, sequential dose titration studies performed in pediatric patients with NDO who had been practicing CIC technique. One study (905-CL-074) was performed in patients aged 6 months to < 5 years; the other study (905-CL-047) was performed in patients aged 5 years to < 18 years. Both studies were 52 weeks in total and were composed of a 12-week dose titration period followed by a 40-week fixed dose period. • The primary endpoint for the pivotal studies was change from baseline to 24 weeks in mean maximum cystometric capacity (MCC). The secondary endpoints were based on urodynamics, patient voiding diary responses, and PROs and included: ◦ Change from baseline to the assessment for the last possible titration step and/or week 24 in: MCC (for the last possible titration step only), bladder compliance (change in volume/change in detrusor pressure), bladder volume until first detrusor contraction (> 15 cmH_2O) as percentage of expected bladder capacity, number of overactive detrusor contractions (> 15 cmH_2O) until leakage or until end of bladder filling, detrusor pressure at leakage or until end of bladder filling ◦ Change from baseline to each postbaseline visit (week 3 up to week 52) in: average catheterized volume per catheterization, maximum catheterized volume (MCV) per day, average first morning catheterized volume, mean number of incontinence episodes per 24	Baseline-controlled, open label studies have demonstrated the efficacy of solifenacin oral suspension in pediatric patients with NDO, ages 2 to < 18 years old. Overall, the magnitude of the benefit in children (5 to < 12 years of age) and in adolescents (12 to < 18 years of age) was comparable. The duration of this efficacy was present at one year. The clinical meaningfulness of the changes in the primary endpoint is supported by secondary endpoint analyses. • The evidence provided meets the evidentiary standard for benefit. • The quality of the evidence is supported by analysis of secondary endpoints which also demonstrate the clinical relevance of the findings. Solifenacin oral suspension may provide benefit to patients in ways that the one current option does not by providing more convenient dosing and treating patients as young as 2 years old while possessing a similar side effect profile. In addition, aside from one report of somnolence, no cognitive effects were observed

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	hours, incidence of incontinence per 24 hours, incidence of catheterization per 24 hours ◦ Change from baseline to visit 8 (week 24) and visit 10 (week 52) in the PinQ questionnaire score (Study 905-CL-047) and change from baseline to Visit 7 (week 24) and visit 9 (week 52/EoS) for each of the derived Infant and Toddler Quality of Life Short Form-47 (ITQoL SF-47) questionnaire ITQoL scale scores. • In the pivotal studies, the overall mean change from baseline to week 24 was 52.5 mL (95% CI 29.2 mL, 75.7 mL, $p < 0.001$). While the mean increase in MCC for pediatric patients aged 2 to < 5 years (38.9 mL [95% CI 20.6mL, 57.2mL, $p < 0.001$]) was smaller than the increase in pediatric patients aged 5 years and older (57.2 mL [95% CI 26.3mL, 88.1mL, $p < 0.001$]), the difference was expected to be due to the different age-related bladder volumes and baseline MCC between the 2 groups. This endpoint is deemed appropriate based on prior use as a primary efficacy endpoint in the clinical studies that supported approval of oxybutynin for the same indication and its routine use in clinical practice as a marker of bladder filling capacity. • Secondary endpoints support the primary efficacy results with improved urodynamic measurements and improvement in diary reported clinical measurements that reflect clinical meaningfulness. There were statistically significant increases in bladder compliance, maximum catheterized volume, and bladder volume until first detrusor contraction > 15 cmH_2O as a percentage of expected bladder capacity (in 905-CL-047 only) and decreases in number of overactive detrusor contractions (>15 cmH_2O) until end of bladder filling and mean number of incontinence episodes/24 hours.	in NDO patients in these clinical studies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• While the PRO data did not show significant mean changes from baseline, for a number of reasons, the PROs may not have been capable of showing the clinical meaningfulness of the urodynamic and incontinence data. • The Sponsor worked hard to achieve the recruitment numbers that were needed to show improvement in the primary and secondary endpoints. Inclusion of patients < 5 years old provided data to support a wider target patient population. • The treatment effect measured at 24 weeks appeared to be similar to the treatment effect over the longer-term (52 weeks), demonstrating persistence of efficacy. • The magnitude of treatment effect was similar across age groups, with qualitative differences in effect explained by the anatomical changes that occur with physical growth during maturation in the age group of the patient population studied. • Solifenacin oral suspension provides an option in a wide pediatric age group (includes children younger than 5), requires convenient once daily dosing, and showed no signal for cognitive effects. • The study drug was not studied in all races and ethnicities, though there is no reason to expect differences in efficacy based on race or ethnicity.	
Risk and Risk Management	• The extent of exposure and overall safety assessment in this application includes pediatric NDO patients and pediatric OAB patients. The product's safety profile is informed by two Phase 3 trials in pediatric NDO patients, two Phase 3 trials in pediatric OAB patients, and two pharmacokinetic Phase 1 studies (one each in pediatric OAB and NDO patients). The overall understanding of this product's safety profile is also based on years of post-approval experience with solifenacin and other members of the anticholinergic drug class. • The safety database population consisted of mainly White and Asian	The safety results from the two Phase 3 studies demonstrated the expected adverse reactions to solifenacin, with no new safety signals identified. Solifenacin oral suspension was generally well tolerated in pediatric NDO patients. The safety profile of solifenacin oral suspension in the pediatric NDO population was fully consistent with the safety profile of approved

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	pediatric patients. While an overall diverse population is expected to use the product, there is no reason to presume differences in efficacy or safety based on race or ethnicity. Unexplained differences in efficacy between White and Asian pediatric NDO patients observed in exploratory subgroup analyses may be related to the pooling of variable data from different age groups and the small demographic subgroup sizes. The study populations for other racial groups were too small to assess for differences in drug effect. • The medication is intended for chronic use, which was reflected in the 52-week study duration. • Safety concerns were investigated extensively, and aside from common expected safety concerns of constipation and dry mouth, there were no signals for drug-related increases in ECG QT prolonged, UTI, changes in vital signs, cognition AEs, or vision/accommodation AEs. No SAEs in the clinical trials were drug-related. • The product quality issues (biopharmaceutics and microbiology) that were responsible for the deficiencies that led to the CR of the original NDA submission were resolved. • There are no specific concerns for solifenacin oral suspension in the post-market setting in the indicated pediatric NDO population. If solifenacin oral suspension were to be used off-label in geriatric patients unable to swallow solifenacin tablets, potential risk is mitigated by comparable solifenacin doses and exposures.	solifenacin tablets in adults with OAB. There were no new or unresolved safety issues.

1.4. Patient Experience Data

The efficacy and safety data that support this NDA were derived primarily from two adequate and baseline-controlled Phase 3 trials in pediatric patients with NDO. Several additional trials in pediatric patients with NDO and OAB contributed to the safety database. Safety and efficacy data collected from the patients in these studies comprise the substantial evidence that supports this NDA. In addition to the primary efficacy endpoint data obtained from urodynamic studies and daily urinary diaries, a single patient reported outcome (PRO) instrument was examined as an exploratory secondary endpoint in 905-CL-047: the PinQ. A different exploratory PRO was examined in 905-CL-074: the Infant and Toddler Quality of Life Short Form-47 (ITQoL SF-47).

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		X	Patient reported outcome (PRO)	6.1.1. and 7.1.1.
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

NDO is defined by the International Children's Continence Society (ICCS) as detrusor overactivity when there is a relevant neurological condition. NDO is a urodynamic observation characterized by involuntary detrusor contractions that are spontaneous or provoked during the filling phase, involving a detrusor pressure increase of greater than 15 cm H_2O above baseline.

NDO can develop as a result of a lesion at any level in the nervous system, including the cerebral cortex, spinal cord, or peripheral nervous system. The most prevalent cause of NDO in children is myelodysplasia, a group of developmental abnormalities that results from defects that occur during neural tube closure such as myelomeningocele, meningocele, and occult spinal dysraphism (spina bifida occulta). The most common acquired cause for NDO is cerebral palsy. An injury in the perinatal period (e.g. perinatal infection, anoxia) can produce a neuromuscular disability or a specific cerebral dysfunction. Less common acquired causes include spinal tumors, trauma, or sequalae of transverse myelitis.

Early management of NDO is focused on optimizing bladder function to prevent hydronephrotic renal damage and secondary bladder wall changes that result from high-pressure detrusor contractions and elevated bladder pressure during filling. The most common pharmacologic treatment for NDO is the antimuscarinic oxybutynin (oral or intravesical), which suppresses detrusor overactivity. Clean intermittent catheterization (CIC), typically performed 4-5 times per day, improves bladder drainage and reduces bladder pressure during filling. To date, the vast majority of patients are treated successfully with oxybutynin treatment coupled with CIC. Experience with pharmacologic therapies other than oxybutynin is still limited in children with NDO.

NDO is a condition that significantly impacts a child's social participation due to the frequency of CIC and the occurrence of incontinence episodes. Optimizing quality of life throughout early childhood and in the adolescent years improves social and emotional health and physical development and contributes to a successful transition to adulthood. Better management of incontinence related to neurogenic bladder dysfunction improves quality of life by allowing greater independence and opportunities for social participation.

2.2. Analysis of Current Treatment Options

The first-line treatment for pediatric NDO is the combination of continuous intermittent catheterization (CIC) and anti-muscarinic drugs. The only currently approved oral drug for NDO in pediatric patients is oxybutynin chloride, available as immediate-release tablets, extended-release tablets, and syrup. Oxybutynin used in the pediatric population has been associated with side effects such as headaches, blurred vision, constipation, altered behavior, dry mouth, flushed cheeks, and effects on the CNS, which are of particular concern as they can lead to impaired school performance. Intravesical oxybutynin, which has a reduced first pass metabolism in the liver compared to oral anticholinergic therapy and has high systemic efficacy and bioavailability, has been evaluated for its potential to be effective with a more tolerable side effect profile. Currently available alternatives to anticholinergic therapy, such as the β_3 agonist mirabegron, have not yet been approved for the indication of NDO in pediatric patients. VESIcare LS (solifenacin oral suspension) was developed to provide another oral medication option to use in combination with CIC for pediatric patients with NDO aged 2 and older.

Table 1 Currently Available Treatments for Pediatric Neurogenic Detrusor Overactivity (NDO)

Oral antimuscarinic drugs (mainstay)	Intravesical antimuscarinic drugs	Alternatives to anticholinergic drugs
Ditropan (oxybutynin chloride) Syrup (5 mg/5 mL); tablets (immediate release and extended release)	Oxybutynin	β_3 agonist: mirabegron
Detrol, Detrol LA (tolterodine)		
Trosec (trospium)		
VESIcare (solifenacin tablets)		
Enablex (darifenacin tablets)		

Source: Adapted from Dr. Fang's Clinical Review, Table 1.2, p. 10.

In addition, intravesical botulinum toxin A is approved for the treatment of NDO in adults with multiple sclerosis (MS) and spinal cord injury (SCI), and one day it may prove beneficial in the treatment of pediatric patients with NDO. Patients who fail treatment with anticholinergic medications coupled with CIC may be candidates for more invasive procedures such as incontinent urinary diversion or reconstructive bladder surgery with augmentation cystoplasty.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The reader is referred to Section 3.2 of this review for the specific regulatory history and activity for this submission. The reader is referred to the original NDA Clinical review for a more exhaustive summary of regulatory history.

3.2. Summary of Presubmission/Submission Regulatory Activity

On November 19, 2004, solifenacin succinate (VESIcare), 5 mg and 10 mg tablets, were approved under NDA 021518 for the treatment of overactive bladder in adults. The approval included a postmarketing commitment (PMC) for pediatric studies under Pediatric Research Equity Act (PREA) for "the treatment of overactive bladder in pediatric patients ages 5 years to 11 years and adolescents ages 12 years to 17 years old."

On January 20, 2006, an agreement was reached to enroll only pediatric patients with detrusor overactivity due to known neurological disease (neurogenic detrusor overactivity, or NDO).

On July 27, 2012, a Written Request (WR) for the evaluation of solifenacin in pediatric NDO patients was issued, with subsequent amendments dated September 14, 2012, April 17, 2014, and December 12, 2014. Under the terms of the WR, two clinical studies were conducted: Study 1 was the Phase 1 PK study 905-CL-079 and Study 2 was the Phase 3 safety and efficacy study 905-CL-047. An oral suspension was developed for easy swallowing and accuracy of dosing.

On October 14, 2016, a Pre-NDA meeting was held under IND 058135 at the request of the Sponsor to discuss the adequacy of their clinical and nonclinical programs to support a new NDA for the oral suspension, a supplemental NDA for VESIcare tablets, and a path toward pediatric exclusivity.

On February 28, 2017, the Sponsor submitted a new NDA for review to market the oral suspension, to fulfill the PREA-related PMCs and to be granted pediatric exclusivity.

Pediatric exclusivity was granted for VESIcare and was published under Section 505A of the Federal Food, Drug, and Cosmetic Act on August 10, 2017.

On August 28, 2017, a Complete Response (CR) letter was issued for NDA 209529 with reference to three deficiencies for Chemistry, Manufacturing, and Controls (CMC).

A Type B Pre-NDA meeting (IND 058135) was scheduled for April 10, 2019, to discuss the CMC deficiencies specified in the CR letter: the conditions at (b) (4) that required correction, the determination of a root cause for viscosity failures of the scaled-up commercial batches, the strategy to adapt the drug product formulation to minor changes in the carbomer homopolymer B excipient, and the batch analysis and stability data. After receiving the Division's preliminary written comments on April 9, 2019, the Sponsor determined that further discussion was not required and decided to cancel the Pre-NDA meeting. The reader is referred to the final Type B meeting minutes dated April 9, 2019.

On November 27, 2019, the Sponsor submitted this resubmission in response to the CR letter.

3.3. Foreign Regulatory Actions and Marketing History

On March 9, 2018, solifenacin oral suspension received approval in Europe for the treatment of NDO in pediatric patients aged 2 to 18 years.

According to the Periodic Safety Update Report for solifenacin succinate (film-coated tablets, orodispersible tablets, and oral suspension) for the time period June 9, 2018 to July 26, 2019, no actions were taken for safety reasons by the Sponsor, acting as both Marketing Authorization Holder (MAH) in Europe and the Sponsor of clinical trials intended to support U.S. approval. In addition, no actions were taken by regulatory authorities, data and safety monitoring boards, or independent ethics committees. There were no restrictions on distribution, no clinical study suspensions, no dosage modifications, and no changes in target population, indications, or formulation.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An OSI audit was not requested for this re-submission. Audits were completed in the first cycle of this submission. In his Clinical Inspection Summary dated August 2, 2017, Roy Blay reported that the clinical sites of three investigators were inspected, and some discrepancies in the secondary efficacy endpoint of bladder compliance and recordkeeping were noted. However, overall, the studies appeared to have been conducted adequately, and the data generated by these sites and submitted by the Sponsor appeared acceptable for purpose of regulatory decision-making. The classification of all three inspections was "NAI", No Action Indicated.

4.2. Office of Product Quality (OPQ)

4.2.1. Division of Microbiology

From the Microbiology perspective, in the CR letter, the product quality Microbiology review team indicated that inadequate controls were in place to ensure the absence of (b) (4) (b) (4) in the drug product at release and on stability.

To address this deficiency, the Sponsor was asked to revise the release specification for the microbial limit to include test methods and acceptance criteria to demonstrate the product is free

of (b) (4). Additionally, the Sponsor was asked to similarly revise the post approval stability program so that stability testing would be capable of showing absence of (b) (4)

At the Mid-Cycle and Wrap-Up meetings for this NDA, the Microbiology review team stated that the (b) (4) review issue had been successfully resolved.

4.2.2. Division of Biopharmaceutics

From the Quality perspective, in the CR letter, the Chemistry review team identified deficiencies related to inspection findings that the product viscosity for two batches intended for marketing (commercial batches) was below the specification limit. This (b) (4) was thought to be a result of changes in the manufacturing process of the excipient carbomer homopolymer Type B by its supplier. And (b) (4) (b) (4) the Chemistry review team noted that the application could not be approved without the establishment of adequate controls for carbomer homopolymer type B and demonstration that the Sponsor could consistently manufacture drug product of the requisite quality.

To address the deficiencies, the Sponsor was asked to provide batch release data from 3 drug product batches that were manufactured with the new carbomer homopolymer type B and
1) Propose an extra control of the carbomer homopolymer type B that would ensure the drug product meets the viscosity specification, or
2) Include a dispersibility test in the drug product specification to assure the homogeneity of the drug product. (b) (4) (b) (4). If this pathway was selected, the dispersibility test would need to be performed at the drug product release and during the stability testing.

In his review of the Sponsor's resubmission, the Biopharmaceutics reviewer noted that the Sponsor addressed the deficiency related to carbomer homopolymer (b) (4) (b) (4) (b) (4) in the to-be-marketed pediatric formulation. To demonstrate comparability of the clinical trial and commercial formulations, FDA requested that the Sponsor provide *in vitro* dissolution data (specifically, multi-point profiles in multiple media) to support the proposed change (the reader is referred again to the Pre-NDA meeting minutes dated April 9, 2019). In this resubmission, the Applicant addressed the deficiency by submitting comparative dissolution data for formulation B (the clinical trial formulation) and the pediatric commercial formulation (the currently proposed to-be-marketed formulation) in various dissolution media as recommended. The submitted dissolution data were determined to be adequate, and the data showed that all batches had a similar dissolution profile.

In their final review dated April 1, 2020, the Biopharmaceutics review team made the following recommendation:

"*Approval of this NDA is recommended by the Division of Biopharmaceutics*."

Finally, in regard to manufacturing site facility inspections, especially the (b) (4) drug product manufacturing site, Mark Seggel of OPQ, in a May 9, 2020, email informed the Clinical review team that:

"*OPMA and ORA have completed their 'paper' inspection of the* (b) (4) *drug product manufacturing site conducted under Sec. 704 (a)(4) (FDASIA Sec. 706). After several rounds of requests for documentation and review, OPMA and ORA are now recommending APPROVAL for this site*".

4.1. Clinical Microbiology

There were no clinical Microbiology issues – see the OPQ section of this review for comments on the routine product quality microbiology issues.

4.2. Pharmacology/Toxicology

No new nonclinical studies were requested, and none was conducted in support of this efficacy supplement.

4.3. Clinical Pharmacology

There were no new Clinical Pharmacology issues for this re-submission. The reader is referred to the Clinical Pharmacology review of the original NDA for issues related to clinical pharmacology, including systemic exposure (absorption, distribution, metabolism and excretion [ADME]), drug interactions, use in specific populations, and dose selection.

4.4. Devices and Companion Diagnostic Issues

There were no devices and no companion diagnostics included in this application.

4.5. Consumer Study Reviews

Solifenacin is available only by prescription. Therefore, over-the-counter, pre-marketing consumer behavior studies are not relevant to this application.

4.6. Office of Prescription Drug Promotion (OPDP)

At the Mid-Cycle meeting, OPDP had no additional comments or concerns. The final OPDP consult received on May 4, 2020 included one comment pertaining to the Contraindications section of VESIcare LS labeling relevant to the potential need for a urinary retention Contraindication. The Clinical review team acknowledged this OPDP comment, including the existence of a urinary retention Contraindication in labeling for VESIcare Tablets and Ditropan Tablets and Syrup, both approved in adults. However, the Clinical review team concluded that a urinary retention Contraindication was not needed for VESIcare LS labeling because the pediatric NDO patient population indicated for VESIcare LS would largely, if not exclusively, be maintained on clean intermittent catheterization (CIC). OPDP deferred to DUOG on this issue.

4.7. Division of Medication Error Prevention and Analysis (DMEPA)

DMEPA evaluated the proposed container and carton labels, as well as the PI, for any potential vulnerabilities to medication errors.

DMEPA initially concluded that the revised carton labeling was unacceptable from a medication error perspective because the principal display panel appeared cluttered, which hindered readability of critical information. They recommended that the Sponsor consider relocating the equivalency and recommended dosage statements to another panel on the carton labeling to improve the readability of other critical information or address this concern by other means.

On April 6, 2020, the Sponsor resubmitted a revised carton labeling to address the concerns stated by DMEPA. DMEPA reviewed the revised carton labeling and concluded that the labels were acceptable from a medication errors perspective.

DMEPA also participated fully in the labeling review process that led to final agreed-upon labeling for the prescriber and patient. Finally, DMEPA's review raised no concerns and no objections to the tradename VESIcare LS.

4.8. Division of Medical Policy Programs (DMPP)

At the midcycle meeting, DMPP had no additional comments or concerns. The final DMPP review, dated May 8, 2020, provided proposed edits to the proposed Patient Information (PPI) labeling. The DMPP edits to the PPI were all either instituted by discussion with the Sponsor negotiations or resolved by discussion among the FDA review team.

4.8.1. Division of Epidemiology (DEPI)

There were no issues and no comments from the Epidemiology (DEPI) perspective.

4.8.2. Division of Risk Management (DRISK)

There were no issues and no comments from the Risk Management (DRISK) perspective.

4.8.3. Division of Pharmacovigilance (DPV)

There were no issues and no comments from the Pharmacovigilance (DPV) perspective.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Reviewer's Comment: For a detailed review of the efficacy and safety data, the reader is referred to the Medical Officer's Review of the original NDA submission. As no new efficacy data was submitted in this cycle, this review contains a summary of previously reviewed efficacy and safety data. The only sections that contain a review of newly submitted safety data, which was submitted in the re-submission Safety Update and in the 120-Day Safety Update, are Section 8.9.1 and Section 8.10.

Table 2 summarizes the two Phase 3 studies in pediatric patients with NDO.

Table 2 Phase 3 NDO Studies supporting NDA 209529

Study Identifier (Country)	Study Design and Type of Control	Study Population	Test Product(s); Dosage Regimen	Number of Subjects/	Duration of Treatment
905-CL-074 (8 sites in Belgium, UK, Poland, USA Philippines & South Korea)	Phase 3, open-label, baseline- controlled, multicenter, sequential dose titration study	Children & adolescents with NDO (aged 6 months [M] to < 5 years [Y])	solifenacin suspension (1 mg/mL) once daily Doses: PED2.5, 5, 7.5 or 10	Screened: 24 Enrolled: 23 (4 @ 6M to <2 Y; 19 @ 2 to < 5 Y) Completed: 21 (3 @ 6M to <2 Y; 18 @ 2 to < 5 Y)	52 wks: 12-wk dose titration period followed by a 40-wk fixed- dose period

905-CL-047 (21 sites: Belgium, Brazil, Denmark, Hungary, Mexico, Philippines, Poland, South Korea, Turkey & USA)	Phase 3, open-label, baseline- controlled, multicenter, sequential dose titration study	Children & adolescents with NDO (aged 5 years to < 18 years)	solifenacin suspension (1 mg/mL) once daily Doses: PED2.5, 5, 7.5 or 10	Screened: 92 Enrolled: 76 (42 children; 34 adolescents) Completed: 58 (31 children; 27 adolescents)	52 wks: 12-wk dose titration period followed by a 40-wk fixed- dose period

Pediatric patients aged 6 months to < 2 years (n=4) were excluded from calculations of Study 905-CL-074 because they were not part of the proposed indication for solifenacin oral suspension.
Source: Adapted from Dr. Fang's Clinical Review, Table 5.1, p. 15.

5.2. Review Strategy

The clinical data presented in the original NDA were derived from the following sources:

- The efficacy data from the two Phase 3 studies in patients with NDO as listed in Table 2 above: Phase 3 studies 905-CL-047 and 905-CL-074
- The safety data from the above two Phase 3 studies in NDO patients, combined with another two Phase 3 studies in patients with idiopathic OAB (905-CL-076 and 905-CL-077)
- Additional clinical pharmacology studies including bioavailability studies in healthy adult volunteers (905-CL-066 and 080), and pharmacokinetic studies in pediatric patients with NDO and OAB (905-CL-079 and 075, respectively)

Of note, two formulations of solifenacin oral suspension were evaluated over the course of the drug development. The first formation, Formulation A, was used in the initial Phase 1 PK study (905-CL-075 in OAB patients). Formulation B was used in the single-dose PK safety and tolerability study in pediatric patients with NDO (905-CL-079) and in all subsequent Phase 3 pediatric studies. The results of the Phase 1, bioequivalence study in adults (Study 905-CL-080), as per the Clinical Pharmacology review team, showed that the suspension (Formulations A and B) and the tablet formulations of solifenacin were bioequivalent under fasting conditions and that all formulations were safe and well tolerated.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 905-CL-074 and Study 905-CL-047

6.1.1. Study Design

Overview, Objective and Trial Design
The two Phase 3 primary studies were both multi-center, multi-national, open-label, baseline-controlled, sequential dose-titration studies to assess the long-term efficacy and safety and pharmacokinetics of solifenacin oral suspension in pediatric patients with NDO who had been practicing CIC technique.

Study 905-CL-047 enrolled pediatric patients aged 5 years to < 18 years, and study 905-CL-074 enrolled pediatric patients aged 6 months to < 5 years.

In each study, pediatric patients completed a 12-week dose-titration period followed by a 40-week fixed-dose period. Each subject's starting dose was determined by weight (the dose for each weight range was equivalent to a 5 mg daily dose in adults [referred to as PED5]) and was up- or down-titrated every three weeks to a minimum dose of PED2.5 (equivalent to a 2.5 mg daily dose in adults), an intermediate dose (PED7.5, equivalent to a 7.5 mg daily dose in adults), or a maximum dose of PED10 (equivalent to a 10 mg daily dose in adults) for up to 12 weeks to determine the optimal final titration dose. The determination of an optimal final dose was based on efficacy; however, the dose was not to exceed the maximum dose based on weight range (see Table 3 below). All subjects were administered solifenacin (1mg/mL) once daily at final titrated doses equivalent to steady state exposure of 2.5 mg, 5 mg, 7.5 mg, or 10 mg in adults. A minimum 40-week fixed-dose assessment period followed in which all patients were treated with their optimized dose.

Table 3 Solifenacin Oral Suspension Recommended Daily Doses by Weight Range for Pediatric Patients with NDO Aged ≥ 2 Years

Weight Range (kg)	Starting Dose (mL) †	Maximum Dose (mL) †
9 to 15	2	4
> 15 to 30	3	5
> 30 to 45	3	6
> 45 to 60	4	8
>60	5	10

† Solifenacin oral suspension is provided as a 1 mg/mL oral suspension. Starting dose is equivalent to steady-state exposure after a 5 mg daily dose in adults. Maximum dose is equivalent to steady-state exposure after a 10 mg daily dose in adults. Two additional intermediate dose titration levels were allowed: the dose equivalent to steady-state exposure after 2.5 mg daily dose in adults and after 7.5 mg daily dose in adults.
NDO: neurogenic detrusor overactivity
Source: Dr. Fang's Clinical Review, Table 1.1, p. 9.

A total of 95 pediatric patients with NDO were enrolled in the Phase 3 studies that were conducted at clinical investigative sites all over the world.

Study Endpoints
These two Phase 3 studies had identical primary and similar secondary efficacy endpoints.

The primary efficacy endpoint for both studies was change from baseline to week 24 of treatment in maximum cystometric capacity (MCC).

The common secondary efficacy endpoints (based on urodynamics) were change from baseline to endpoint, defined as the assessment conducted at the last possible titration step (the week number of the last possible titration step depended on the study and the protocol version) and/or last week in:

- MCC (for last possible titration step only)
- Bladder compliance (change in volume/change in detrusor pressure)
- Bladder volume until first detrusor contraction (> 15 cmH_2O) as a percentage of expected bladder capacity (EBC)
- Number of overactive detrusor contractions (> 15 cmH_2O) until leakage or until end of bladder filling
- Detrusor pressure at leakage or until end of bladder filling

Additional secondary efficacy endpoints (based on patient voiding diary) in both studies were change from baseline to each postbaseline visit (week 3 up to week 52) in:

- Average catheterized volume per catheterization
- Maximum catheterized volume (MCV) per day
- Average first morning catheterized volume
- Mean number of incontinence episodes per 24 hours
- Incidence of incontinence per 24 hours
- Incidence of catheterization per 24 hours

Additional exploratory secondary endpoints based on PRO responses included:

In 905-CL-047:

- Change from baseline to visit 8 (week 24) and visit 10 (week 52) in Quality of life (QoL) as measured by the PinQ questionnaire score.

In 905-CL-074:

- Change from baseline to Visit 7 (week 24) and visit 9 (week 52/EoS) for the scale scores on the Infant and Toddler Quality of Life Short Form -47 (ITQoL SF-47) questionnaire.

For purposes of evaluating the duration of effect, additional secondary endpoints based on

urodynamic parameters were measured at 52 weeks.

Statistical Analysis Plan
According to the Statistical review of the original application, the analysis plans for the efficacy endpoints were the same in all four pediatric protocols. The planned analysis was an ANOVA model with factors for treatment, site, and the interaction term. The statistical analysis plan stated that a check for the required normality assumptions would be conducted, and if the normality assumptions were not met, the van Elteren test (a non-parametric method for controlling for site) would be used instead of the ANOVA model. An ANCOVA model with baseline as the covariate was also planned as a secondary analysis. The Full Analysis Set (FAS), which the Sponsor used for the efficacy analysis for the two studies in pediatric NDO, included all subjects who received drug, had baseline data, and had at least one on-treatment observation.

Protocol Amendments
The reader is referred to the original NDA reviews and NDA submission for a complete accounting of protocol amendments. Here, we will discuss the protocol amendment most important to the original Clinical review.

Global substantial Amendment 2 (version 2.0 of study 905-CL-047, dated September 30, 2013) concerned a notable number of discontinuations (n=4) related to increases from baseline in QT interval. These discontinuations were required by pre-defined per-protocol discontinuation criteria. These events were thought to potentially reflect high intra-patient variance in the QTcB assessments, and the unaccounted variance may have been sufficient to account for the observed increases from baseline in QT interval. The amendment made changes to the protocol to increase the accuracy of the baseline QTcB calculation by ensuring a higher number of measurements would be considered in the calculation of the baseline QTcB for the eligibility check and the discontinuation criterion. The revised baseline QTcB calculation was based on the average of the QTcB mean from the 2 pre-randomization study visits instead of using the QTcB mean from a single visit only. Following the implementation of this protocol amendment, there were no further discontinuations due to QT prolongation and no new TEAEs of ECG QT prolonged.

Reviewer's Comment: In support of this protocol amendment, the Sponsor submitted a QTc Research Report in which the Sponsor described the random effects model analysis they had conducted of pre-treatment QTcB measurements obtained in Study 905-CL-076 in pediatric patients with idiopathic OAB. As a result of this analysis and its findings (which were reviewed in depth and confirmed by the Interdisciplinary Review Team for QT Studies (IRT-QT) in their June 23, 2017, final consult), the Sponsor amended the protocol and no further reports of QTc prolongation were received. This resolved the safety concerns over the earlier discontinuations and TEAEs that had been reported as QTc prolonged. Thus, this protocol amendment was critical to proper evaluation of ECGs in pediatric patients receiving solifenacin oral suspension.

6.1.2. Study Results

Reviewer's Comment: Compliance with Good Clinical Practice (GCP), financial disclosure, patient disposition, baseline characteristics, and data quality are addressed here. For the remainder of the summary of efficacy, the reader is referred to Section 7 (the Integrated Review of Effectiveness section) of this review.

Compliance with Good Clinical Practices and Financial Disclosure
According to the original NDA Clinical Review, the primary studies were conducted in accordance with Good Clinical Practice as required by the guidelines of the Agency and the International Committee on Harmonization guidelines. In the first review cycle, the Division consulted the Office of Scientific Investigations (OSI) to conduct clinical site inspections in Poland and in the Philippines (later switched to Poland and Belgium due to political turmoil in the Philippines).

It was concluded in the original Clinical Review that the Sponsor had adequately disclosed the absence of Investigator proprietary interest in this product or Investigator participation in financial arrangements with the Sponsor, in compliance with 21 CFR Part 54.

Patient Disposition
In the combined Phase 3 NDO population, of the 112 patients who were screened, 95 (84.4%) were enrolled in the studies, took at least 1 dose of the study drug, and were included in the safety analysis set. Of those who were treated with the study drug, a total of 72 (64.3%) patients were included in the full analysis set (FAS) and 54 (48.2%) patients were included in the per-protocol set (PPS). Table 4 below provides the contributions to each analysis set by study.

Table 4 Analysis Sets, Phase 3 NDO Population

Analysis Set	Number of Patients (%)		
	905-CL-074 2 Years to < 5 Years	905-CL-047 5 Years to < 18 Years	Phase 3 NDO Population 2 Years to < 18 Years
Patients with IC	20	92	112
SAF	19 (95.0)	76 (82.6)	95 (84.8)
FAS*	17 (85.0%)	55 (59.8)	72 (654.3)
PPS	15 (75.0)	39 (42.4)	54 (48.2)

IC: informed consent; FAS: full analysis set; NDO: neurogenic detrusor overactivity; PPS: per protocol set; SAF: safety analysis set.
Source: Dr. Fang's Clinical Review, Table 6.10, p. 23.

Table 5 summarizes the subject disposition in the two Phase 3 NDO studies. Twenty (21%) of the 95 subjects ≥ 2 years of age who received the study drug discontinued prematurely. A large

majority of these 21 discontinued subjects were pediatric patients aged 5 to <18 years who participated in the larger study 905-CL-047 and had reported the following primary reasons for discontinuation: adverse event, withdrawal by subject, and protocol violation.

Table 5 Summary of Subject Disposition for Phase 3 NDO Population

	Study 905-CL-047			Study 905-CL-074		
	5 to <12 yrs n (%)	12 to <18 yrs n (%)	Total n (%)	6 mos to <2 yrs n (%)	2 to >5 yrs n (%)	Total n (%)
Screened	47	45	92	4	20	24
Received study drug[1]	42 (89.4%)	34 (75.6%)	76 (82.6%)	4 (100%)	19 (95%)	23 (95.8%)
Treatment discontinuation[2]	11 (26.2%)	7 (20.6%)	18 (23.7%)	1(25%)	1 (5.3%)	2 (8.7%)
Primary reasons for discontinuation[2]						
Adverse event	2 (4.8%)	2 (5.9%)	4 (5.3%)	0	0	0
Withdrawal by subject	2 (4.8%)	2 (5.9%)	4 (5.3%)	0	0	0
Protocol violation	7 (16.7%)	4 (8.8%)	10 (13.2%)	0	1 (5.3%)	1(4.3%)
Lack of efficacy	0	0	0	1 (25%)	0	1 (4.3%)

1 The percentage is calculated using number of screen patients as the denominator.

2 The percentage is calculated using number of treated patients as the denominator.

Source: CDTL Review, compiled from Tables 2 and 3, p. 12.

Demographic and Baseline Characteristics

For demographics and other baseline subject characteristics, the reader is referred to the tables summarizing demographic characteristics in the original NDA Clinical Review (Table 7.5 on p.38). Overall, of the 95 total patients aged 2 years and above, 47% were male and 53% were female; the mean patient age was 9.2 years (with 19 patients aged 2 to < 5 years and 76 patients aged 5 to < 18 years); and 58% of patients were White, 33% were Asian, 2% were Black/African American, and 6% were of Other ethnicity.

The average length of time that the patient had previously experienced NDO was 8.1 years in Study 905-CL-047 and 2.3 years in Study 905-CL-074. The majority of patients had undergone surgery for closure of spina bifida (84% in Study 047, and 100% in Study 905-CL-074). In addition, many patients had also undergone a shunting procedure for hydrocephalus (37% in Study 905-CL-047, and 47% in Study 905-CL-074). All 95 patients were practicing CIC, and 89% had previously taken a medication for the treatment of NDO, including oxybutynin (34%), propiverine (25%), solifenacin (30%), tolterodine (6%) and alfuzosin (1.4%).

Data Quality and Integrity

The quality of the overall submission was considered by the original Clinical and Statistical reviewers to be good.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary and Secondary Endpoints

The results for the primary endpoint and secondary endpoints are presented here.

The primary endpoint results are summarized in Table 6 below.

Table 6 Change from Baseline to Week 24 in Maximum Cystometric Capacity (MCC) (mL) (FAS); Phase 3 NDO Population

Statistic	905-CL-074 2 Years to < 5 Years		905-CL-047 5 Years to < 18 Years		Phase 3 NDO Population 2 Years to < 18 Years	
	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24
n	17	17	55	49	72	66
Mean (SD)	97.8 (39.5)	136.7 (36.8)	223.7 (132.9)	279.1 (126.8)	194.0 (129.1)	242.4 (127.1)
Change from baseline						
n†	NA	17	NA	49	NA	66
Mean (SD)		38.9 (35.5)		57.2 (107.7)		52.5 (94.5)
95% CI		20.6, 57.2		26.3, 88.1		29.2, 75.7
P-value‡		<0.001		<0.001		<0.001

†n is the number of patients with a nonmissing change from baseline to week 24.
‡From a 2-sided one sample t-test, testing the null hypothesis that change from baseline = 0.
Source: Dr. Fang's Clinical Review, Table 6.11, p. 24.

For the primary endpoint (change from baseline in maximum cystometric capacity [MCC]), after 24 weeks of solifenacin oral suspension treatment, a statistically significant improvement in MCC was observed both in subjects aged 2 to < 5 years and in subjects aged 5 to < 18 years. The numerically smaller increase in MCC in the younger pediatric patients was expected due to age-related bladder volumes and baseline MCC values.

To investigate the smaller increase in MCC in the younger patients, two analyses of MCC for the last possible titration step only were performed. In these analyses, change from baseline in MCC was expressed as a percentage of expected bladder capacity (EBC) or relative to individual bladder capacity estimated from maximum catheterized volume (MCV). These analyses supported the primary analysis and provided evidence of comparable efficacy across age groups.

The secondary endpoints, whose results are summarized in Table 7 below, are also considered as informative to the prescribing physician and for the characterization of the overall treatment

effect. Three of these endpoints are based on urodynamics, and two are based on the diary responses.

Table 7 Summary Changes from Baseline to 24 Weeks for Solifenacin Suspension in Phase 3 NDO Population, Secondary Endpoints

Endpoint	Statistics	905-CL-074 2 Years to < 5 Years (N= 17)	905-CL-047 5 Years to < 18 Years (N=49)	Phase 3 NDO Population 2 Years to < 18 Years (N=66)
		Change from Baseline to Week 24		
Bladder Compliance (mL/cmH_2O)	Mean (SD) P-value	5.8 (7.3) P = 0.004	9.1 (28.6) P = 0.029	8.3 (25.0) P = 0.008
Number of Overactive Detrusor Contractions (>15 cmH_2O) Until End of Bladder Filling	Mean (SD)	-7.0 (9.3) P = 0.007	-2.3 (5.1) P = 0.003	-3.5 (6.7) P < 0.001
Bladder Volume Until First Detrusor Contraction > 15 cmH_2O as a Percentage of Expected Bladder Capacity (mL)†	Median	31.1% P = 0.195	13.3% P = 0.001	N/A
Maximum Catheterized Volume (MCV) / Day (mL)	Mean (SD)	45.3 (54.7) P = 0.006	67.5 (88.1) P < 0.001	62.4 (81.8) P < 0.001
Mean Number of Incontinence Episodes / 24 hrs OR Mean Number of Periods Between CICs with Incontinence per 24 hours *	Mean (SD)	-1.6 (1.2) P < 0.001	-1.6 (2.0) P < 0.001	N/A

N is the number of patients who took at least one dose and provided valid values for MCC at baseline and Week 24.
†For patients who showed a detrusor contraction during the urodynamic assessment at Week 24.
*Study 905-CL-074 measured incontinence using Mean Number of Periods Between CICs with Incontinence per 24 hours and Study 905-CL-047 measured incontinence using Mean Number of Incontinence Episodes / 24 hrs. These two variables are related but they are not the same, so they cannot be pooled. These two variables are referred to overall as incidence of incontinence per 24 hours.
Source: Dr. Fang's Clinical Review, compiled from Tables 6.1, 6.12, 6.13, 6.14, 6.15, and 6.16, pp. 18-28.

Secondary endpoints were supportive of the primary efficacy findings and showed, in both age groups, improvement in the following urodynamic measurements of change from baseline to 24 weeks: the mean bladder compliance (increases of 5.8 mL/cmH_2O and 9.1 mL/cmH_2O for patients aged 2 to < 5 years and patients aged 5 to < 18 years, respectively) and the mean number of overactive detrusor contractions > 15 cmH_2O (decreases of 7.0 overactive detrusor contractions and 2.3 overactive detrusor contractions for patients 2 to < 5 years and patients aged 5 to < 18 years, respectively). Improvements based on diary responses were demonstrated in change from baseline to 24 weeks in maximum catheterized urine volumes (increases of 45.3 mL and 67.5 mL for patients aged 2 to < 5 years and patients aged 5 to < 18 years, respectively). The change in MCV was comparable to that observed for the primary endpoint, MCC. For diary-recorded

incontinence episodes, because the two trials measured incontinence using different variables, the results were not pooled. However, in each of the two studies, the results showed a decrease of 1.6 incontinence episodes at week 24 compared with baseline for each age group. For bladder volume until first detrusor contraction > 15 cmH_2O, improvements were noted in both age groups but statistical significance was achieved only for the older group (13.3% improvement for patients aged 5 to < 18 years).

Overall, the magnitude of the observed changes in the above primary and secondary endpoints in children (5 to < 12 years of age) and in adolescents (12 to < 18 years of age) was comparable.

Analysis of additional secondary efficacy endpoints provided further support for the primary efficacy endpoint results. In the Phase 3 NDO population, there were increases from baseline to 24 weeks in the following additional secondary endpoints:

- Bladder volume at 30 cmH_2O detrusor pressure: mean ± SD: 62.4 ± 80.9 mL (95% CI: 23.4, 101.4).
- Average catheterized volume per catheterization: mean ± SD: 43.82 ± 45.28 mL (95% CI: 32.8, 54.9).
- Average first morning catheterized volume: mean ± SD: 43.1 ± 66.74 mL (95% CI: 26.8, 59.4).

After 24 weeks of treatment with solifenacin oral suspension in the Phase 3 NDO population, there as a decrease from baseline in the following additional efficacy endpoint:

- Detrusor pressure at end of bladder filling: mean ± SD: -7.5 ± 29.7 cmH_2O (95% CI: -14.9, 0.0).

In regard to longer-term efficacy data, the primary endpoint showed generally similar efficacy at Week 52 but from a smaller sample size (n = 54 at week 52 vs. n = 66 at week 24).

For each of the Phase 3 studies in pediatric patients with NDO, there was a single, different, exploratory secondary endpoint based on a PRO, as follows:

- In study 905-CL-074, the patient's parent/legal guardian completed the ITQoL SF-47 questionnaire, a 47-item validated questionnaire that measures overall health, physical activities, development, discomfort, moods and temperaments, perceptions or current past and future health and perception of changes. After 24 weeks of treatment, there was no statistically significant difference in ITQoL SF-47 scores in solifenacin-treated patients compared with baseline, except for the Parent Time impact.

- In study 905-CL-047, the patient's parent/legal guardian completed the PinQ which was chosen as the most appropriate cross-cultural, disease-specific QoL measurement tool available at this time in this population. At week 24, there was no statistically significant difference in PinQ score compared with baseline.

Reviewer's Comment: While the results of these two PROs did not demonstrate a detectable change in quality of life, both of these PROs were completed by the patient's parent/legal guardian and so may not be an accurate reflection of the patient's perceived quality of life. Furthermore, these PROs are not known to be validated in the pediatric NDO population specifically and for a number of reasons, may not have been capable of showing clinical meaningfulness of the urodynamic and urinary diary endpoint data.

7.1.2. Subpopulations

Table 8 below shows the change from baseline to week 24 in MCC by gender and age. The change from baseline at week 24 in MCC for each of the subgroup categories appear similar for patients in study 905-CL-047. For the younger age group in study 905-CL-074, which included fewer patients, the changes-from-baseline appear to differ between subgroup categories but it is not possible to conclude true differences between subgroup categories because the sample sizes are very small, and the standard deviations are large and they overlap.

Table 8 Phase 3 NDO studies: Change from Baseline to week 24 in Maximum Cystometric Capacity (mL) by Gender and Age (FAS)

Subgroup	Statistics	Study 905-CL-047			Study 905-CL-074		
		Baseline	Week 24	Change from Baseline to Week 24	Baseline	Week 24	Change from Baseline to Week 24
Gender							
Male	n	28	24		8	8	
	Mean (SD)	226.4 (134.5)	287.7 (133.8)	56.3 (102.7)	157 (92.0)	212 (104)	25.6 (34.8)
Female	n	27	25		13	13	
	Mean (SD)	220.8 (133.7)	270.8 (133.8)	58.1 (114.3)	288 (136)	344 (114)	44.1(36.0)
Age							
Younger†	n	27	24		4	4	
	Mean (SD)	157 (92.0)	212 (104)	59.9 (93.0)	69.0 (22.2)	98.3 (44.4)	29.3 (41.7)
Older *	n	28	25		17	17	
	Mean (SD)	288 (136)	344 (114)	56.4 (122)	97.8 (39.5)	136.7 (36.8)	38.9 (35.5)

†Younger group for study 905-CL-047 is 5 to < 12 years, for study 905-CL-074 is 6 months to < 2 years
*Older group for study 905-CL-047 is 12 to < 18 years, for study 905-CL-074 is 2 to < 5 years
Source: Dr. Fang's Clinical Review, compiled from Tables 6.18 and 6.19, p. 29.

Table 9 Phase 3 NDO studies: Change from Baseline to week 24 in Maximum Cystometric Capacity (mL) by Racial Subgroup (FAS)

Race	Statistics	Study 905-CL-047 and Study 905-CL-074		
		Baseline	Week 24	Change from Baseline to Week 24
White	n	37	32	
	Mean (SD)	209.0 (135.5)	232.5 (115.0)	29.9 (101.9)
Asian	n	27	27	
	Mean (SD)	157.1 (110.3)	226.8 (136.7)	69.7 (74.9)
Black/AA	n	2	2	
	Mean (SD)	299.5 (326.0)	386.0 (65.1)	86.5 (260.9)
Other	n	6	5	
	Mean	232.0 (70.7)	333.0 (120.0)	90.6 (52.3)

Source: Dr. Fang's Clinical Review, compiled from Tables 6.18 and 6.19, p. 29.

In this pooled analysis of the two pediatric NDO studies, there was no apparent explanation for the observed difference between the changes from baseline in MCC at 24 weeks in the White NDO patient subgroup vs. the Asian NDO patient subgroup; however, the sample sizes in this exploratory subgroup analysis are small, the standard deviations are large, and the effect of pooling data across all ages into this single exploratory analysis is unclear. In addition, the Black NDO patient subgroup and the Other NDO patient subgroup had very small numbers of subjects.

7.1.3. Dose and Dose-Response

The design of the Phase 3 studies included multiple dose titrations either to increase or decrease the dose to achieve the best dose response and the optimal benefit/risk ratio. During the treatment period, most of the Phase 3 NDO patients' doses were up-titrated to a fixed dose at week 12 of either PED7.5 or PED10. The optimal dose for most Phase 3 NDO patients was PED10 (12 out of 19 [63.2%] pediatric patients aged 2 years to < 5 years; 41 out of 76 [53.9%] pediatric patients aged ≥ 5 years).

7.1.4. Onset, Duration, and Durability of Efficacy Effects

The persistence of efficacy and tolerance was based on the Phase 3 population who completed treatment for 52 weeks (n=54, compared to n=66 for the population who completed 24 weeks). The primary endpoint for study 905-CL-074 and 905-CL-047 and for the Phase 3 NDO population remained stable at week 52. Table 10 below compares the change from baseline to week 24 and week 52 for the primary endpoint and 3 secondary endpoints in the two Phase 3 studies and in the overall Phase 3 population. For these endpoints, efficacy appears to be similar at 24 and 52 weeks.

Table 10 Comparison of Change from Baseline to 24 weeks vs 52 weeks in Primary and Secondary Endpoints

Statistic	905-CL-074 2 Years to < 5 Years			905-CL-047 5 Years to < 18 Years			Phase 3 NDO Population 2 Years to < 18 Years		
	Baseline	Week 24	Week 52	Baseline	Week 24	Week 52	Baseline	Week 24	Week 52
Maximum Cystometric Capacity (mL)									
n	17	17	12	54	50	42	71	67	54
Mean (SD)	NA	38.9 (35.5)	60.3 (36.7)	NA	57.2 (107.7)	51.0 (102.9)	NA	52.5 (94.5)	53.1 (92.1)
Bladder Compliance (mL/cmH2O)									
n	17	17	12	54	50	42	71	67	54
Mean (SD)	NA	5.83 (7.28)	5.61 (4.16)	NA	9.11 (28.62)	1.63 (42.12)	NA	8.28 (24.96)	2.52 (37.13)
Number of Overactive Detrusor Contractions > 15 cmH2O Until End of Bladder Filling									
n	17	17	12	54	50	42	71	67	54
Mean (SD)	NA	-7.0 (9.3)	-6.9 (10.6)	NA	-2.3 (5.1)	-2.5 (4.7)	NA	-3.5 (6.7)	-3.5 (6.6)
Maximum Catheterized Volume in a Day (mL)†									
n	16	16	17	54	51	50	70	70	67
Mean (SD)	NA	44.66 (52.93)	43.13 (48.90)	NA	67.45 (88.07)	60.95 (90.86)	NA	62.01 (81.29)	56.77 (82.94)

† Mean of daily maximum in each diary day. Phase 3 NDO population includes all patients from Study 905-CL-047 and the pediatric patients aged 2 years to < 5 years from Study 905-CL-074.
Source: Dr. Fang's Clinical Review, compiled from Tables 6.21 and 6.22, p. 31.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Because the overall study population was small (n=95) and included very small numbers of subjects from different racial subgroups, efficacy in various racial subgroups of pediatric patients with NDO is unknown.

7.2.2. Other Relevant Benefits

Solifenacin oral suspension is a once daily medication for NDO that has shown efficacy in clinical trials in pediatric patients as young as 2 years old. Oxybutyin treatment for neurogenic bladder is dosed 2-3 times a day and is approved for patients age 5 years and older. Solifenacin oral suspension provides the opportunity to extend treatment to a younger group of patients, and its once a day dosing is a useful benefit to patients and caregivers and may improve adherence and efficacy in the postmarket setting.

In addition, while not an efficacy benefit, the results of cognitive testing in the pediatric NDO studies, described in subsequent sections of this review (see section 8.7.2.), did not appear to reflect deterioration in cognition in these patients, and the expected improvements in cognition in children aged 5 to < 18 years were not precluded by treatment with solifenacin succinate. In light of concerns that oxybutynin may be associated with adverse CNS effects, the results of this study could provide additional support for solifenacin oral suspension for treatment of NDO in pediatric patients.

7.3. Integrated Assessment of Efficacy

Through the achievement of both the primary and secondary efficacy endpoints, substantial evidence of effectiveness has been demonstrated for solifenacin oral suspension in the treatment of pediatric patients with NDO ages 2 to <18 years.

Study 905-CL-074 (patients ages 2 to <5) and 905-CL-047 (patients ages 5 to <18) studied patients with NDO who had been practicing CIC technique. In these patients, a statistically significant overall mean change in MCC of 52.5 mL was shown at 24 weeks of treatment with solifenacin oral suspension. The clinical meaningfulness of these results is supported by the secondary efficacy analyses, which showed improvements in urodynamic parameters (such as bladder compliance, the number of overactive detrusor contractions until end of bladder filling, bladder volume until first detrusor contractions (> 15 cmH2O) as a percentage of EBC, and detrusor pressure at leakage or end of bladder filling) and diary reported clinical measures (such as maximum catheterized volume/day, and incidence of incontinence per 24 hours, average catheterized volume per catheterization, average first morning catheterized volume).

These findings appeared to be durable for over the fixed dose period out to 52 weeks of treatment. No gender or age differences in efficacy were noted. In regard to subgroup analysis, the change from baseline to 24 weeks in MCC appeared to be greater in Asian pediatric NDO patients than in White NDO patients, although this finding was observed in an exploratory subgroup analysis that pooled data from all ages, was conducted in a generally small overall population (n=95), included small number of subjects in each subgroup category (n=32 vs n=27), and included data which had wide variability as demonstrated by large standard deviations on the means. For these reasons, the clinical meaningfulness of this finding is unclear.

Solifenacin oral suspension has an effect on important clinical endpoints similar to the current approved therapy, oxybutynin. Oxybutynin syrup is approved for patients with NDO ages 5 and older. While many of the secondary efficacy endpoints in the oxybutynin studies were slightly different from the secondary efficacy endpoints in the Phase 3 studies for solifenacin oral suspension in pediatric NDO patients, the increase from baseline to 24 weeks in MCC was used as a measure of efficacy also for oxybutynin syrup. For oxybutynin syrup, the mean change

from baseline (230 mL) to 24 weeks (279 mL) was 49 mL. This mean change is on par with the findings for similarly aged patients in study 905-CL-047, in which the increase in MCC from baseline to 24 weeks was 224 mL to 279 mL, or 57 mL.

8. Review of Safety

8.1. Safety Review Approach

The Clinical safety review conducted when the original NDA was submitted focused mainly on the two Phase 3 studies in pediatric NDO patients (905-CL047 and 905-CL-074) and the two Phase 3 studies in pediatric patients with idiopathic OAB (the randomized, double-blind, placebo-controlled efficacy and safety Study 905-CL-076 [n=189; 12 weeks] and the open-label, sequential dose-titration, long-term extension Study 905-CL- 077 [n=148; 40 week long-term extension study]). These Phase 3 studies were similarly designed making it possible to pool data from studies for some safety analyses. Results from other Phase 1 studies of clinical pharmacokinetics (905-CL-079 in pediatric NDO patients, and 905-CL-075 in pediatric OAB patients) were also reviewed to confirm conclusions regarding safety demonstrated in the Phase 3 studies as provided in the original NDA Clinical review.

Table 11 Studies Included in the Safety Review by Study Phase and Study Population

	In NDO patients	In OAB patients
Phase 3 Studies	905-CL-047	905-CL-076
	905-CL-074	905-CL-077
Phase 1 Clinical Pharmacology Studies	905-CL-079	905-CL-075

Source: Dr. Fang's Clinical Review, p. 33.

The safety findings from the original NDA, focusing on the Phase 3 NDO patients for which the drug will be indicated, are summarized here. The reader is referred to the original Clinical review for a more detailed analysis and associated tables. The focus of the current review is on the new safety data included in the resubmission Safety Update and in the 120-Day Safety Update to the resubmission (see section 8.9).

8.2. Review of the Safety Database

8.2.1. Overall Exposure

In total, 299 pediatric patients aged ≥ 2 years (with NDO or with idiopathic OAB) were treated with solifenacin oral suspension in clinical trials (Phase 1 and Phase 3 studies). Of those, 109 patients had NDO.

In the Phase 3 studies in patients with NDO, the duration of treatment for the majority of patients (65 [68.4%]) was ≥ 364 days and was similar across the relevant age group populations from both studies. For a majority of the patients in these studies, the treatment doses were up-titrated to pediatric equivalent dose (PED)7.5 or PED10 during the treatment period (by week 12 in 905-CL-047 or by week 9 in 905-CL-074). The optimized dose for most patients in all age groups was PED10.

The exposure data from Phase 3 studies (905-CL-076 and 905-CL-077) in pediatric population with idiopathic OAB, while not from the specifically indicated population, is considered as supportive. When data from the subpopulations with NDO and OAB were combined, the duration of treatment for the majority of all Phase 3 pediatric patients (63.4%) was ≥ 364 days, the duration of treatment for all Phase 3 pediatric patients was 319.6±103.7 days (Mean±SD), and the daily dose used was 5.1±1.8 mg (Mean±SD).

8.2.2. Relevant Characteristics of the Safety Population

The demographic characteristics in the target indicated population, Phase 3 NDO patients, combined with the Phase 3 idiopathic OAB population are described as predominantly White (72.0%), with some Asian (17.7%); the age (mean±SD) of the population was 9.0±3.7 years (2 to < 18 years); the majority of patients (66.3%) were aged 5 years to < 12 years, with 19 (7.8%) patients being aged 2 years to < 5 years, and 63 (25.9%) patients were adolescents aged 12 years to < 18 years. Overall, demographic characteristics such as gender, ethnicity, mean weight, and mean age were similar across the Phase 3 study populations. It was noted in the original Clinical review that Asian patients made up a higher percentage of patients (33.7%) in the Phase 3 NDO population compared to in the idiopathic OAB population (10%).

8.2.3. Adequacy of the Safety Database

The extent of the safety database was determined in part by the specific terms the Written Request (WR) taking into consideration the postmarketing studies (PMRs) required under the Pediatric Research Equity Act (PREA). Because there is no reason to expect race-based differences in drug exposure or pharmacology for solifenacin oral suspension in the pediatric NDO or OAB population, the relatively larger percentage of Asian patients in the NDO population does not raise concerns regarding the adequacy of the safety database.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The overall quality of the resubmission was good, as was the original submission. The information was well organized and readily located.

8.3.2. Categorization of Adverse Events

Adverse events were categorized using standard defined MedDRA terminology.

8.3.3. Routine Clinical Tests

Details of the routine clinical testing, including various clinical laboratory tests, were reviewed in the original submission, and this testing was adequate.

8.4. Safety Results

Table 12 and Table 13 below provide an overview of the TEAEs, including serious TEAEs, in the Phase 3 pooled safety population (pooled NDO and OAB) and in the indicated Phase 3 NDO population, respectively.

Table 12 Overview of TEAEs and Death, 52 Weeks of Treatment (SAF); Phase 3 Pooled NDO and OAB Population

Category	ISS Pool / Study; Number of Patients (%)							
	Solifenacin Open-label (NDO)		Solifenacin Double-blind + Solifenacin Open-label (OAB)		Placebo Double-blind + Solifenacin Open-label (OAB)		Phase 3 Population (NDO and OAB)	
	n = 95		n = 73		n = 75		n = 243	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
TEAEs	61 (64.2)	206	58 (79.5)	214	65 (86.7)	245	184 (75.7)	665
Drug-related TEAEs ‡	18 (18.9)	27	29 (39.7)	52	28 (37.3)	45	75 (30.9)	124
Serious TEAEs §	8 (8.4)	11	1 (1.4)	1	3 (4.0)	4	12 (4.9)	16
Drug-related Serious TEAEs ‡§	0	0	0	0	1 (1.3)	1	1 (0.4)	1
TEAEs Leading to Withdrawal	4 (4.2)	4	10 (13.7)	10	8 (10.7)	8	22 (9.1)	22
Drug-related TEAEs Leading to Withdrawal ‡	3 (3.2)	3	9 (12.3)	9	8 (10.7)	8	20 (8.2)	20
Deaths	0	0	0	0	0	0	0	0

† The Phase 3 Pooled Safety Population (OAB and NDO) 52 weeks treatment group consists of results from all patients in the Phase 3 population, including placebo-treated patients.
‡ Drug-related defined as possibly or probably related, as assessed by the Investigator, or records where causal relationship is missing.
§ Includes SAEs upgraded by the Sponsor based on review of the Sponsor's list of always serious AE terms, if any upgrade was done.

ISS: integrated summary of safety; n: number of patients; SAF: safety analysis set; TEAE: treatment-emergent adverse event.
Source: Dr. Fang's Clinical Review, Table 7.14, p. 59.

Table 13 Overview of TEAEs and Serious AEs (SAF); Phase 3 NDO Population

Category	905-CL-074 2 Years to < 5 Years n = 19		905-CL-047 5 Years to < 18 N = 76		Phase 3 NDO Population 2 Years to < 18 Years n = 95	
	n (%)	Events	n (%)	Events	n (%)	Events
TEAEs	10 (52.6)	30	51 (67.1)	176	61 (64.2)	206
Drug-related TEAEs†	3 (15.8)	6	15 (19.7)	21	18 (18.9)	27
Serious TEAEs	1 (5.3)	2	7 (9.2)	9	8 (8.4)	11
Drug-related Serious TEAEs†	0	0	0	0	0	0
TEAEs Leading to Withdrawal	0	0	4 (5.3)	4	4 (4.2)	4
Drug-related TEAEs Leading to Withdrawal†	0	0	3 (3.9)	3	3 (3.2)	3
Deaths	0	0	0	0	0	0

† Possible or probable, as assessed by the investigator, or records where relationship is missing.
Source: Dr. Fang's Clinical Review, Table 7.6, p. 40.

During 52 weeks of treatment, 61 of 95 (64.2%) Phase 3 NDO patients reported treatment emergent AEs (TEAEs). Drug-related TEAEs were reported by 18 (18.9%) patients and serious TEAEs were reported by 8 (8.4%) patients. None of the serious TEAEs were determined by the investigator to be drug-related. The proportions of patients reporting TEAEs were similar in pediatric NDO patients aged 2 years to < 5 years and pediatric NDO patients aged 5 years and older.

The single Phase 1 study in patients with NDO, Study 905-CL-079, included a total of only 14 patients (aged 5 years and older; 7 children and 7 adolescents). Overall, 5 TEAEs were reported and two patients (28.6%) experienced at least 1 TEAE. There were no serious TEAEs reported. There were not discontinuations of study drug due to AEs because this was a single-dose study.

8.4.1. Deaths and Serious Adverse Events

No deaths were reported in the Phase 3 NDO studies or in any other studies included in the safety analysis.

Serious adverse events (SAE) were reported by 8 of 95 (8.4%) Phase 3 NDO patients, seven of which were reported by patients in Study 047 (in 2 children and in 5 adolescents). Table 14 below

summarizes the SAEs in the Phase 3 NDO population. SAEs included: UTI (n=2, reported once in each study), tachycardia, megacolon, dengue fever, orchitis, pharyngitis, tethered cord syndrome, spinal cord operation, and hypertension (n=1 each). None of these SAEs was determined by the investigator to be drug-related.

Table 14 Incidence of Serious TEAEs, 52 Weeks of Treatment (SAF); Phase 3 NDO Population

SOC Preferred Term	905-CL-074 2 Years to < 5 Years n = 19	905-CL-047 5 Years to < 18 N = 76	Phase 3 NDO Population 2 Years to < 18 Years n = 95
Overall	**1 (5.3)**	**7 (9.2)**	**8 (8.4)**
Cardiac Disorders	**0**	**1 (1.3)**	**1 (1.1)**
Tachycardia	0	1 (1.3)	1 (1.1)
Gastrointestinal Disorders	**0**	**1 (1.3)**	**1 (1.1)**
Megacolon	0	1 (1.3)	1 (1.1)
Infections and Infestations	**1 (5.3)**	**3 (3.9)**	**4 (4.2)**
Dengue Fever	0	1 (1.3)	1 (1.1)
Orchitis	0	1 (1.3)	1 (1.1)
Pharyngitis	1 (5.3)	0	1 (1.1)
Urinary Tract Infection	1 (5.3)	1 (1.3)	2 (2.1)
Nervous System Disorders	**0**	**1 (1.3)**	**1 (1.1)**
Tethered Cord Syndrome	0	1 (1.3)	1 (1.1)
Surgical and Medical Procedures	**0**	**1 (1.3)**	**1 (1.1)**
Spinal Cord Operation	0	1 (1.3)	1 (1.1)
Vascular Disorders	**0**	**1 (1.3)**	**1 (1.1)**
Hypertension	0	1 (1.3)	1 (1.1)

Source: Dr. Fang's Clinical Review, Table 7.9, p. 43.

Reviewer's Comment: Narratives for each of the SAEs (n=8) in the Phase 3 NDO population can be found in Dr. Fang's Clinical Review of the original NDA. In summary, Dr. Fang concluded three SAEs were not related to the study drug (toxic megacolon, tethered cord syndrome, Dengue fever), three SAEs were unlikely to be related to the study drug (spinal cord operation, hypertension and tachycardia, orchitis, UTI), and two were probably not related to the study drug (pharyngitis and UTI).

In pediatric OAB patients, nine (9) SAEs were reported in 8 patients. Serous AEs in this group included: appendicitis (n=2); lymphadenitis, hypertension and tachycardia (n=1 each in placebo); and frontal lobe epilepsy, pyelonephritis, abdominal pain, and gastroenteritis (n=1 each). Table 15 below summarizes the SAEs in the Phase 3 OAB population. There was one report of QT prolongation (change from baseline of 36 milliseconds in corrected QTcB), but this case was determined by the investigator (and by the Clinical review team) to be confounded by tachycardia associated with pyelonephritis.

Table 15 Incidence of SAEs in Studies 905-CL-076 and 905-CL-077 (SAF), Phase 3 OAB Population

Patient #	Treatment group	Age/Sex	SAEs MedDRA (V13.0) PT	Last Dose Day	Onset/Stop Day	Outcome	Relation to Study Drug†
Study 905-CL-076							
Child							
(b) (6)	Placebo	6/F	Lymphadenitis	84	21/22	Recovered	Not Related
	Placebo	11/F	Hypertension	87	78/81	Recovered	Not Related
			Tachycardia	87	78/81	Recovered	Possible
	Solifenacin	6/M	Frontal lobe epilepsy	59	49/Ongoing	Not recovered	Not Related
	Solifenacin	8/F	Pyelonephritis	49	52/Ongoing	Recovering	Not Related
Adolescent							
(b) (6)	Placebo	17/F	Abdominal pain	35	17/19	Recovered	Not Related
	Solifenacin	12/F	Appendicitis	84	18/20	Recovered	Not Related
Study 905-CL-077							
Child							
(b) (6)	Solifenacin	7/F	Gastroenteritis	236	133/135	Recovered	Not Related
Adolescent							
(b) (6)	Solifenacin	12/F	Appendicitis	357	18/20	Recovered	Not Related

†as determined by the investigator
Yellow shading identifies the same patient listed twice.
Source: Adapted from Dr. Fang's Clinical Review, Table 7.10, p. 50.

Reviewer's Comment: The reader is referred to Dr. Fang's Clinical Review of the original NDA for individual case narratives and an analysis of each SAE in the Phase 3 OAB population. Of the 4 SAEs noted in the patients treated with solifenacin, two were considered not related to the study drug (frontal epilepsy and appendicitis) and one unlikely to be related to the study drug (pyelonephritis and gastroenteritis). While the role of solifenacin in the TEAE of ECG QT prolonged (reported in the pyelonephritis SAE case), cannot be ruled out, the Investigator and the Clinical review team determined that the case was confounded by a concurrent serious UTI/pyelonephritis.

8.4.2. Dropouts and/or Discontinuations Due to Adverse Effects

In Study 905-CL-047, all 4 of the 76 (5.3%) patients who discontinued treatment due to TEAE reported ECG QT prolonged. Of these patients aged ≥ 5 years, 2 were children and 2 were adolescents. The data for the cases is summarized in Table 16 below.

Table 16 : Summary of QTcB from 4 Patients with NDO Discontinued from Phase 3 Study 905- CL-047

Patient #	Age	Gender	Dose	Baseline (ms) QTcB	Maximum QTcB change (ms)
(b) (6)	14	F	3.4 mg (PED 5)	423.0	456.0 (Day 59)
	13	M	5.2 mg (PED 7.5)	387.7	429.0 (Day 22)
	8	F	3.8 mg (PED 7.5)	427.3	461.7 (Day 21)
	9	F	3.4 mg (PED 5)	419.3	440.7 (Day 22)

PED: pediatric equivalent dose; QTcB: QT interval corrected using Bazett's formula
Source: CDTL review of original NDA submission, Table 11, p. 20.

To further investigate these 4 patients who met the discontinuation criterion for prolongation of QTcB despite no concerning changes in the population means, the Sponsor performed a random effects analysis on all ECG data from the pediatric OAB studies. The analysis was performed using the data from the pediatric OAB studies because these studies were further along with regard to recruitment than the pediatric NDO studies and thus provided a larger dataset for the analysis. The findings were considered to be equally applicable to studies in pediatric NDO patients. The analysis suggested that the intra-patient variance in repeat QTcB measurements could explain the 4 discontinued patients' prolonged QTcB measurements. The Interdisciplinary Review Team for QT studies (IRT-QT) was consulted and agreed with the Sponsor. The Sponsor amended the protocols to require calculation of the baseline QTcB based on 2 pre-randomization study visits. This increased the accuracy of the baseline QTc measurements. After the protocol amendment was implemented, no new TEAEs of ECG prolonged were reported. In light of this, the study discontinuations due to QT prolongation were not considered a clinically relevant finding indicative of QT prolongation, but instead reflected an artifact of high variability at Baseline without repeat baseline measures as conducted early in the study. Furthermore, none of these patients experienced any clinical adverse events related to the ECG observations of QT prolongation.

There were no reported TEAEs that resulted in treatment discontinuation in Study 905-CL-074.

All other discontinuations due to study drug were reported in the supporting studies conducted in pediatric patients with OAB. Table 17 summarizes drug-related TEAEs leading to discontinuation of study drug for the entire Phase 3 study population, which largely reflects experience in the pediatric OAB population.

Table 17 Drug-related TEAEs Leading to Permanent Discontinuation of Study Drug: Phase 3 Population

	52 Weeks of Exposure

SOC Preferred Term	Solifenacin Open-Label (NDO) 52 Weeks	Solifenacin Double-Blind Solifenacin Open-Label (OAB)	Placebo DB + Solifenacin Open-Label (OAB)	Phase 3 Population (NDO and OAB) 52 Weeks
	(N = 95)	(N = 73)	(N = 75)	(N = 243)
Overall n (%)	**3 (3.2)**	**9 (12.3)**	**8 (10.7)**	**20 (8.2)**
Gastrointestinal disorders	**0**	**2 (2.7)**	**0**	**2 (0.8)**
Constipation	0	2 (2.7)	0	2 (0.8)
Investigations	**3 (3.2)**	**6 (8.2)**	**8 (10.7)**	**17 (7.0)**
ECG QT prolonged	3 (3.2)	6 (8.2)	8 (10.7)	17 (7.0)
Psychiatric disorders	**0**	**1 (1.4)**	**0**	**1 (0.4)**
Tic	0	1 (1.4)	0	1 (0.4)

Studies Included: 905-CL-076, 905-CL-077, 905-CL-047 and 905-CL-074.
The Phase 3 Population (NDO and OAB) 52 Weeks treatment group consists of results from all patients in the Phase 3 population, including Placebo-treated patients.
Source: Dr. Fang's Clinical Review, Table 7.13, p. 56.

Reviewer's Comment: With only 4 discontinuations for drug-related TEAEs in Phase 3 NDO population (all from Study 905-CL-047), which were not considered to be clinically relevant for reasons explained above, the remaining TEAEs leading to discontinuation occurred in pediatric patients with OAB.

8.4.3. Significant Adverse Events

No drug-related significant AEs were reported in the Phase 3 pediatric NDO patients. However, adverse events of special interest, which included UTI, constipation, ECG QT prolonged, hypertension, and somnolence, did occur. Of these AEs of special interest, only AEs of constipation (5 possibly related and one probably related; 5 of those mild and one moderate in severity) and somnolence (1 moderate severity case possibly related to treatment and 1 mild case probably related to treatment) were considered possibly or probably related to the study drug. AEs of special interest are discussed below in section 8.4.4 of this review.

Reviewer's Comment: Of the 8 AEs of special interest that were possibly or probably related, most (6) were mild in severity.

8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

Commonly Reported TEAEs
Table 18 below shows the incidence (for TEAEs reported in >5% of patients in the Phase 3 Population Total Group) of TEAEs during 52 weeks of treatment for the Phase 3 population. The reader is referred to previous sections of this review for an explanation as to the clinical relevance of the TEAE "ECG prolonged". Regarding UTI, the original Clinical review

concluded that a majority of UTI AEs in the Phase 3 NDO studies were unlikely to be related to the study drug, based on the Investigators' determinations that only 2 of the UTI cases were possibly related to the study drug and the high annual incidence (~35%) of UTIs in pediatric patients with NDO practicing CIC.

Table 18 Incidence (> 5% Incidence in Total Group) of TEAEs, 52 Weeks of Treatment (SAF); Phase 3 Population

MedDRA v19.0 SOC Preferred Term	ISS Pool / Study; Number of Patients (%)			
	Phase 3 NDO Population Solifenacin Open-label (NDO) n = 95	905-CL-076 / 905-CL-077		Phase 3 Population Total† (NDO and OAB) n = 243
		Solifenacin Double-blind + Solifenacin Open-label (OAB) n = 73	Placebo Double-blind + Solifenacin Open-label (OAB) n = 75	
Overall	**61 (64.2)**	**58 (79.5)**	**65 (86.7)**	**184 (75.7)**
Gastrointestinal Disorders				
Constipation	7 (7.4)	11 (15.1)	8 (10.7)	26 (10.7)
Diarrhea	4 (4.2)	8 (11.0)	4 (5.3)	16 (6.6)
General Disorders and Administration Site Conditions				
Pyrexia	4 (4.2)	3 (4.1)	8 (10.7)	15 (6.2)
Infections and Infestations				
Gastroenteritis	3 (3.2)	6 (8.2)	8 (10.7)	17 (7.0)
Nasopharyngitis	6 (6.3)	8 (11.0)	16 (21.3)	30 (12.3)
Upper Respiratory Tract Infection	6 (6.3)	2 (2.7)	7 (9.3)	15 (6.2)
Urinary Tract Infection ‡	29 (30.5)	9 (12.3)	10 (13.3)	48 (19.8)
Investigations				
ECG QT Prolonged	4 (4.2)	7 (9.6)	9 (12.0)	20 (8.2)
Nervous System Disorders				
Headache	4 (4.2)	10 (13.7)	8 (10.7)	22 (9.1)

† The Total (OAB and NDO) 52 weeks treatment group consists of results from all patients in the Phase 3 population, including placebo-treated patients.
‡ The category urinary tract infection gathers MedDRA preferred terms of Escherichia urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal and urinary tract infection pseudomonal.
SOCs and preferred terms within each SOC are organized by ascending alphabetical order.
Source: Dr. Fang's Clinical Review, Table 7.15, p. 60.

Reviewer's Comment: It is notable that the TEAE of "ECG QT prolonged" was reported in 7/73 (9.6%) actively-treated pediatric OAB patients compared to 9/75 (12.0%) placebo-treated pediatric OAB patients in studies 905-CL-076 and 905-CL-077. This finding, from a comparison of controlled safety data, would appear to support the conclusion that the early cases reported as "ECG QT prolonged" do not actually reflect a drug effect, but instead are an artifact of

insufficient QT assessments at baseline and narrowly-defined clinical AE reporting criteria in the original protocols.

In the Phase 1 Study in patients with pediatric NDO, Study 905-CL-079, only two patients (both adolescent) reported TEAEs: 1 (7.1%) reported mild micturition urgency and 1 (7.1%) reported moderate anxiety.

Drug-related AEs (as determined by the Investigator's judgment and over 52 weeks of treatment, shown in Table 19 below, were reported in 18 patients with pediatric NDO (18.9%). They included constipation (7.4%), dry mouth (3.2%), ECG QT prolonged (3.2%), UTI (2.1%), and abdominal pain, urinalysis bacterial test positive, viral rash, and pharyngotonsillitis (1.1% each).

Table 19 Drug-related TEAEs: Phase 3 Population, Including NDO and OAB Patients

SOC Preferred Term	52 Weeks of Exposure			
	Phase 3 NDO Population Solifenacin Open-Label (NDO) (N = 95)	Solifenacin Double-Blind + Solifenacin Open-Label (OAB) (N = 73)	Placebo Double-blind + Solifenacin Open-label (OAB) (N = 75)	Phase 3 Population Total† (NDO and OAB) (N = 243)
Overall n (%)	**18 (18.9)**	**29 (39.7)**	**28 (37.3)**	**75 (30.9)**
Cardiac Disorders				
Tachycardia	0	0	1 (1.3)	1 (0.4)
Eye Disorders				
Conjunctivitis Allergic	0	1 (1.4)	0	1 (0.4)
Dry Eye	0	2 (2.7)	0	2 (0.8)
Vision Blurred	0	0	1 (1.3)	1 (0.4)
Gastrointestinal disorders				
Abdominal Pain	1 (1.1)	1 (1.4)	2 (2.7)	4 (1.6)
Abdominal Pain Upper	0	2 (2.7)	0	2 (0.8)
Constipation	7 (7.4)	9 (12.3)	8 (10.7)	24 (9.9)
Dry Mouth	3 (3.2)	4 (5.5)	4 (5.3)	11 (4.5)
Faeces Hard	0	0	1 (1.3)	1 (0.4)
Nausea	0	1 (1.4)	1 (1.3)	2 (0.8)
Rectal Fissure	0	1 (1.4)	0	1 (0.4)
General Disorders and Administration Site Conditions				
Fatigue	0	1 (1.4)	2 (2.7)	3 (1.2)
Influenza-like Illness	0	1 (1.4)	0	1 (0.4)
Infections and Infestations				
Conjunctivitis	0	1 (1.4)	0	1 (0.4)

Cystitis	0	1 (1.4)	1 (1.3)	2 (0.8)
Nasopharyngitis	0	1 (1.4)	0	1 (0.4)
Pharyngotonsillitis	1 (1.1)	0	0	1 (0.4)
Urinary Tract Infection‡	2 (2.1)	2 (2.7)	2 (2.7)	6 (2.5)
Viral Rash	1 (1.1)	0	0	1 (0.4)
Investigations				
Bacterial Test Positive	1 (1.1)	0	0	1 (0.4)
Cardiac Murmur	0	0	1 (1.3)	1 (0.4)
ECG QT Prolonged	3 (3.2)	6 (8.2)	8 (10.7)	17 (7.0)
Residual Urine Volume Increased	0	0	1 (1.3)	1 (0.4)

† The Total (OAB and NDO) 52 weeks treatment group consists of results from all patients in the phase 3 population, including placebo-treated patients.
‡ The category urinary tract infection gathers MedDRA preferred terms of Escherichia urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal and urinary tract infection pseudomonal.
SOCs and preferred terms within each SOC are organized by ascending alphabetical order.
Source: Dr. Fang's Clinical Review, Table 7.16, p. 61.

Reviewer's Comment: The most common drug-related side effects were constipation and dry mouth, which are consistent with the safety profile for anticholinergic drugs. Drug-related AEs were similar for pediatric patients with NDO and idiopathic OAB. The reader is referred to previous sections of this review for explanation of the events coded as ECG QT prolonged. These do not appear to be drug-related but instead appear to reflect lack of sufficient baseline QT assessment and high baseline variability.

In regard to AE severity, in the overall Phase 3 pediatric population, most TEAEs were reported as mild (124 [51.0%] patients) or moderate (53 [21.8%] patients). Each of the following 7 severe TEAEs was reported by an individual patient: gastroenteritis, appendicitis, maternal exposure with timing unspecified (reported as drug exposure during pregnancy under MedDRA v13.0: a patient became pregnant during the study in Study 905-CL-077), dental caries, megacolon, dengue fever, and UTI.

TEAEs of Special Interest

TEAEs of special interest included: UTI, constipation (anticholinergic effects), ECG QT prolonged, hypertension, tachycardia, somnolence (CNS effects), and megacolon.

- UTI was a commonly reported TEAE (30.5%, n=24 in Study 905-CL-047 and n=5 in Study 905-CL-074). As noted earlier, the high incidence of UTI was thought to reflect the high background incidence of UTI in the patient population. The two SAEs due to UTI were considered by the investigator to be possibly related to study drug. In Dr. Fang's Clinical Review, he concluded of the two UTI SAEs, one was probably not related to the study drug and one was unlikely to be related to the study drug.

- Constipation was commonly reported (n=6 in Study 905-CL-047 and n=3 in Study 905-CL-074), all cases were considered possibly (5) or probably (1) related to study drug, and reports of constipation were expected given solifenacin's known safety profile.

- ECG QT prolonged was reported in 4 patients in Study 905-CL-047 though, as noted earlier, this was determined to not be clinically relevant because this incidence was accounted for by intra-patient variability resulting from inadequate sampling used for baseline QT interval measurement and calculation.

- Hypertension and tachycardia (both TEAEs of special interest), which were reported SAEs in one patient in Study 905-CL-047, the original Clinical reviewer agreed with the investigator that solifenacin was unlikely to be causally related.

- Only one patient in the Phase 3 NDO population reported special events of interest related to CNS effects. That patient (in 905-CL-047) reported somnolence, for which a causal relationship could not be ruled out given the temporal association of the events.

- For toxic megacolon, the reader is referred to the original NDA Clinical review for a brief narrative and the Reviewer's comment pertaining to the single case reported. The Clinical reviewer agreed with the investigator that the SAE of toxic megacolon was not related to the study drug.

Common Antimuscarinic Side Effects
The incidence of constipation (7.4% vs 10.7%), dry mouth (4.2% vs 4.9%), blurred vision (1.1% vs 0.8%), and dyspepsia (1.1% vs 0.4%) were comparable in the Phase 3 NDO population and the total Phase 3 population inclusive of pediatric NDO and pediatric OAB patients. As is the case with antimuscarinics in general, constipation and dry mouth were the most commonly reported antimuscarinic TEAEs.

Reviewer's Comment: Each of the most common antimuscarinic side effects, constipation and dry mouth, occurred at a higher frequency in pediatric patients with OAB than in pediatric NDO patients.

8.4.5. Laboratory Findings and Vital Signs

Clinically relevant changes were infrequently observed for chemistry, hematology, and urinalysis parameters across the studies. The original Clinical review noted that shifts from normal levels at baseline to high levels at week 24 were observed in >20% of the patients in Study 905-CL-047 for urine bacteria quantitative (60.9%) and urine leukocytes quantitative (48.0%). It was further

noted that these changes are consistent with the reported incidence of UTI. And finally, it was noted that these are not unexpected findings for a pediatric population with NDO and practicing CIC.

Overall, vital signs did not indicate any safety concerns in the Phase 3 NDO population studies, and changes from baseline to end of treatment were similar between the age groups across the studies. The small changes that were observed were likely the result of expected changes based on the annual age-related changes for patients in the age groups in these studies [National Institute of Health Blood Pressure Tables for Children and Adolescents, 2005; Fleming et al, 2011]. Table 20 below summarizes vital signs in the Phase 3 NDO population.

Table 20 Summary of Vital Signs (SAF); Phase 3 NDO Population

Vital Signs	Mean (SD)								
	905-CL-074 2 Years to < 5 Years n = 19			905-CL-047 5 Years to < 18 Years n = 76			Phase 3 NDO Population 2 Years to < 18 Years n= 95		
	Baseline	EoT	Change From Baseline	Baseline	EoT	Change From Baseline	Baseline	EoT	Change From Baseline
SBP (mmHg)	97.05 (10.01)	100.31 (10.10)	3.42 (10.68)	108 (12.34)	108 (11.9)	–0.03 (11.1)	105.4 (12.6)	106.0 (11.8)	0.7 (11.0)
DBP (mmHg)	62.83 (6.52)	63.25 (7.85)	0.53 (7.30)	69.1 (11.1)	67.1 (10.3)	–1.67 (9.88)	67.8 (10.6)	65.8 (10.2)	–1.6 (9.9)
Pulse Rate (beats/min)	109.46 (16.30)	105.22 (12.39)	–4.33 (14.57)	89.3 (18.0)	87.9 (14.3)	–2.15 (12.3)	93.4 (19.4)	92.2 (15.7)	–2.9 (13.2)

The value at the Final Visit (EoT) is the most recent non-missing postbaseline value at or prior to Visit 9. DBP: diastolic blood pressure; EoT: end of treatment; ISS: integrated summary of safety; n: maximum number of patients with data; NDO: neurogenic detrusor overactivity; SAF: safety analysis set; SBP: systolic blood pressure.
Source: Dr. Fang's Clinical Review, Table 7.18, p. 64.

For the Phase 3 pediatric NDO population (Studies 905-CL-047 and 905-CL-074), after 52 weeks of treatment, there was a small increase from baseline in mean systolic blood pressure (SBP) (0.7 mmHg), a decrease from baseline in mean diastolic blood pressure (DBP) (-1.6 mmHg) and a decrease from baseline in mean pulse rate (-2.9 beats/min).

Overall, the Phase 3 pediatric NDO and OAB populations had similar vital sign profiles. When the vital sign data from the two studies were pooled, the analysis showed minor differences. It was proposed that these differences may have been related to differences in the duration of the studies and the patients' background conditions and level of maturation.

Reviewer's Comment: Solifenacin oral suspension shows no clinically concerning effect on laboratory parameters or vital signs.

8.4.6. Electrocardiograms and QT

12-lead ECGs were performed in triplicate at every visit. The mean of each triplicate was used for each ECG variable at each visit. ECGs were assessed by the investigator and interpreted. Additionally, a cardiologist evaluated each ECG.

An explanation for the 4 patients from Study 905-CL-047 with the TEAE ECG QT prolonged that resulted in discontinuation can be found in Section 8.4.2.

In short, these 4 subjects were discontinued from the study based on the pre-defined, per-protocol criteria (an increase from baseline in QTcB of > 30 ms or a QTcB of > 460 ms). There were no AEs of QT prolongation in pediatric patients aged 2 to < 5 years (Study 905-CL-074). Based on a random effect analysis of ECG data of pediatric patients in the OAB studies, the Sponsor found that there were no changes of concern in the population means of QT intervals and the intra-patient variance in repeat QTcB measurements; however, in these 4 patients, baseline measurements were from single assessments, not an average of triplicates. In order to increase the accuracy of the baseline QTc measure, the calculating method was amended from one-time to two-time measure over 2 visits. Subsequent to implementing this change, no patients were discontinued due to ECG QT prolongation in the two phase 3 trials.

QT data observed before and after 52 weeks treatments in all subjects enrolled in phase 3 trial 905-CL-047 are summarized in Table 21. The group mean changes in corrected QT intervals from baseline to week 52 were negligible. Furthermore, the incidence of patients with QTcB changes from baseline at week 52 between 30 and 60 ms was lower in the Phase 3 studies of pediatric NDO patients (ranging from 1.8% to 9.1%) than in the phase 3 studies in adults with OAB (ranging from 7.2% to 13.2%).

Table 21 Summary of QTcB and QTcF at Baseline and Week 52 (Study 905-CL-047)

	Children (5 to < 12 years) n = 42	Adolescents (12 to < 18 years) n = 34	All Patients n = 76
Mean QTcB (ms)			
Mean baseline	424 (14.5)	412 (16.9)	419 (16.7)
Mean week 52	423 (15.6)	412 (20.8)	418 (18.9)
Mean Change from baseline	1.93 (12.3)	-1.45 (12.8)	0.33 (12.5)
Mean QTcF (ms)			
Mean baseline	396 (14.4)	391 (15.6)	394 (15.1)
Mean week 52	397 (14.9)	394 (20.0)	395 (17.4)
Mean Change from baseline	3.09 (12.0)	3.21 (11.9)	3.15 (11.8)

QTcB and QTcF: QT interval corrected using Bazett's and Fridericia's formula, respectively.
Source: Dr. Fang's Clinical Review, Table 7.20, p. 66.

A consult was provided by the IRT-QT review team. The reader is referred to the original NDA review for a detailed summary of the IRT-QT consultation, the highlights of which have been included in related sections of this review. In their consult, the IRT-QT concluded that "Overall, based on the data collected in this program and the predicted QTc effect using the concentration-QTc relationship developed from the TQT study in adults, it does not appear likely that solifenacin will have a clinically relevant effect on the QTc interval at the proposed doses in pediatric patients."

Reviewer's Comment: The QT interval assessment in pediatric patients with NDO as well as the IRT-QT consult advice led the Clinical review team to conclude that there were no new findings of clinical concern regarding QT prolongation following solifenacin oral suspension treatments in pediatric patients. The IRT-QT similarly concluded that solifenacin was unlikely to have a clinically relevant effect on the QTc interval at the proposed doses in pediatric patients.

The reader is referred to the original NDA Clinical review for detailed reviews of the following:

- ECG QTcB and QTcF results at 12 and 52 weeks of treatment for the Phase 3 pediatric NDO population, the pediatric OAB population, as well as the total Phase 3 pediatric population (NDO and OAB patients).
- A detailed summary of the consult review from the Interdisciplinary Review Team QT (IRT-QT).

8.4.7. Immunogenicity

No immunogenicity studies were planned or conducted.

8.5. Analysis of Submission-Specific Safety Issues

Based upon the known safety profile of solifenacin succinate in adults, several safety issues were specially targeted by the Sponsor and carefully reviewed by the medical officer in the original NDA Clinical review. These included: UTI, constipation, changes in vital signs, ECG changes, attention/cognition, and ocular accommodation. Special tests for ocular accommodation and cognition were conducted during the pediatric clinical studies.

UTI

Urinary tract infection (UTI) was a commonly reported TEAE with 2 cases reported as serious TEAEs. In addition, as noted earlier in this review, shifts from normal levels at baseline to high levels at week 24 were observed in > 20% of the patients for urine bacteria and urine leukocytes. UTI, bacteriuria and leukocyturia are common in this population and the majority of UTI cases (27/29, 93%) were considered not related to study drug by the investigator. It is well known that patients performing clean intermittent catheterization (CIC) have a high incidence of UTIs. Only

2 UTI cases (Case #3201701 in Study 905-CL-047 and Case #3203918 in Study 905-CL-074) were considered by the investigator to be possibly related to study drug.

Constipation
All constipation cases in Study 905-CL-047 were considered possibly (5) or probably (1) related to study drug by the investigator, with 5 of 6 cases described as mild in severity, the other as moderate in severity.

Changes in Vital Signs
For the Phase 3 pediatric NDO population, after 52 weeks of treatment, there was a small increase from baseline in mean systolic blood pressure (SBP) (0.7 mmHg), a decrease from baseline in mean diastolic blood pressure (DBP) (-1.6 mmHg) and a decrease from baseline in mean pulse rate (-2.9 beats/min). These were not considered as likely drug-related changes but were more likely related to normal growth and maturation over the 52 weeks of study treatment. One SAE of hypertension was reported in an actively treated patient, but that patient had a serious UTI requiring hospitalization and his blood pressure returned to normal while remaining on solifenacin. The reader is referred to the original NDA Clinical review for the narrative of this SAE.

ECG Changes
Mean changes from baseline in all ECG measurements were negligible over 52 weeks of treatment. Most of the 12-lead ECGs that were collected in the pediatric population were assessed by the investigator as normal. The occurrence of 4 events of QT prolongation in the pediatric NDO population was determined to be related to inadequate baseline repeat testing and is not considered to be a true clinical safety signal.

Ocular Accommodation
Ocular accommodation was assessed in Study 905-CL-047. Based on those assessments, the Sponsor concluded that overall, accommodative accuracy was improved. According to the Sponsor, the small changes from baseline to Week 12 (-0.25 diopters [95% CI: -0.87, 0.36]) and to week 52 were expected based on the annual age-related changes for patients in this study's age group, demonstrating that solifenacin did not have an effect on ocular accommodation. Dr. Chambers of DTOP was of the opinion that the accommodation testing was not conducted properly, thus definitive conclusions are premature (see Section 8.7.1 of this review). Nonetheless, no significant ocular AEs were reported in the pediatric NDO and OAB population.

Attention / Cognition
At the Division's request, cognitive testing was conducted in Study 905-CL-047, and the results of those tests appeared to show improvement, not decline, in cognitive function after treatment with solifenacin oral suspension. Improvements in cognition are expected in patients of this age

due to the rapid developmental maturation that occurs during late childhood and adolescence. There was one case of somnolence in a 15-year old male with NDO in which the role of solifenacin could not be excluded. A more detailed summary of the cognitive testing in study 905-CL-047 is provided in Section 8.7.2.

8.6. Safety Analyses by Demographic Subgroups

For the Phase 3 pediatric NDO population and in Phase 3 pediatric OAB Study 905-CL-076, analyses were performed to assess the influence of intrinsic factors (age and gender) on vital signs and ECG (including changes in QTcB and QTcF). TEAEs were analyzed by age group and treatment group by gender.

In the original submission ISS, TEAEs, vital signs, and ECG were presented by age. There were no clinically relevant differences in TEAE incidence, vital signs, or ECG measurements across the Phase 3 pediatric NDO population age groups.

Pharmacokinetics were analyzed by age and gender in the Phase 1 study 905-CL-079 and exposure was not affected by age or gender.

*Reviewer's Comment: Overall, no clear trends for clinically meaningful differences between subgroups of age and gender within the popul*ation *were observed. However, in this small pediatric study population, it is not possible to discern differences in safety (or efficacy) due to the small sizes of the demographic subgroups.*

8.7. Specific Safety Studies/Clinical Trials

8.7.1. Ocular Accommodation

The Division requested an assessment of ocular accommodation in Study 905-CL-047. Based on those assessments, it appeared that overall, accommodative accuracy actually improved. The Sponsor noted that the observed changes from baseline to week 12 and week 52 were similar to the expected annual age-related changes for pediatric patients in the study's age group. They concluded that solifenacin did not have any effect on ocular accommodation. The reader is referred to the original NDA Clinical review Table 7.23 for a detailed comparison of changes in baseline to 12 and 52 weeks for accommodative error index in patients of each age range.

In addition, solifenacin also did not appear to have an effect on the slope of the mean spherical equivalent (MSE) versus diopter stimulus. Vision related TEAEs were infrequent and no drug-related vision TEAEs were reported. Ocular accommodation results were similar between age groups.

A consult was requested from the Division of Ophthalmology and Transplant Products (DOTP) to review the accommodation study results. The consultant made a number of observations about the procedures, measurements, and calculations that questioned the utility of the results from the ophthalmologic assessment.

The Ophthalmology consultant made the following overall consult statements at the time of the original NDA submission:

1) The application does not contain reliable information concerning the drug product's effect on accommodation (for the following reasons):
    a. The choice of an accommodation response-stimulus curve instead of measuring the accommodative amplitude to measure a drug product's effect on accommodation is not supported. There is no evidence that this measure is capable of detecting a change in accommodation.
    b. The choice to represent the accommodation response-stimulus curve with a calculated accommodative error index (AEI) is not supported. There is no evidence that this index will be reflective of a change in accommodative ability.
    c. The variability of triplicate measurements used to construct the accommodation response-stimulus curve suggests that the collected values are not reliable measures of accommodation.
2) The analyses of accommodation failed to utilize all of the data collected on accommodation. Approximately one third of the accommodation data collected was not used in the analysis and there was no explanation given for the exclusion of that data.
3) The Applicant's claim that Study 905-CL-047 demonstrated improvement in "accommodative accuracy" is not supported, because the data is inconsistent. The claim that solifenacin also did not have an effect on the slope of the MSE versus diopter stimulus is not supported because the data is inconsistent and there is no evidence to support the capability of this methodology to detect a difference if a true difference was to be present.

Reviewer's Comment: During the first cycle, for purposes of the Written Request, the Division and the Pediatric Exclusivity Board (including Dr. Chambers) concluded that the Sponsor's assessment of ocular accommodation met the basic request in the WR to conduct ocular accommodation testing, although the Sponsor used a method that was different from the one advocated by Dr. Chambers, our Ophthalmology consultant. In regard to the clinical impact of the Ophthalmology consultant's comments, there were few vision AEs reported and no vision AE was reported as drug-related. While the ophthalmologic testing and analysis methods preclude definitive conclusions from that data, there is no current evidence of an adverse effect on vision.

8.7.2. Cognitive Testing

At the Division's request, cognitive testing was conducted in Study 905-CL-047, and the results of those tests are summarized below:

- Detection Test: There was a statistically significant decrease from baseline in detection test score after 24 weeks (-0.04; P < 0.001) and 52 weeks (-0.05; P < 0.001) of solifenacin oral suspension treatment, indicating an improvement in reaction time and thus an improvement in psychomotor function.
- Identification Test: There was a statistically significant decrease from baseline in identification test score after 24 weeks (-0.03; P = 0.012) and 52 weeks (-0.05; P < 0.001) of solifenacin oral suspension treatment, indicating an improvement in reaction time and thus an improvement in attention.
- One Card Learning Test: There was a statistically significant increase from baseline in one card learning test score after 52 weeks (0.05; P = 0.007) but not after 24 weeks (0.02; P = 0.268) of solifenacin oral suspension treatment, indicating an improvement in accuracy of performance and thus an improvement in visual learning.
- One Back Test: There was a statistically significant decrease from baseline in one back test scores after 24 weeks (-0.03; P = 0.005) and 52 weeks (-0.04; P < 0.001) of solifenacin oral suspension treatment, indicating an improvement in reaction time and thus an improvement in working memory.

Reviewer's Comment: Although the results from all 4 cognitive tests appear to show improvement in cognitive function after treatment with solifenacin oral suspension, it was noted in the original Clinical Review noted that improvements in cognition are expected in patients of this age due to the rapid developmental maturation that occurs during late childhood and adolescence. Still, aside from one case of somnolence, no adverse effects on cognition were observed in NDO patients in these clinical studies.

8.7.3. Interdisciplinary Review Team for QT Studies Consult

A consultation was requested from the IRT-QT team for a QTc evaluation. The most salient IRT-QT observations, with respect to the analysis of prolonged ECG QT interval TEAEs which occurred in the pediatric OAB and NDO studies, have been noted several times in this review. In summary, IRT-QT concluded that an effect of solifenacin on the QT interval at the recommended doses in the target pediatric population was unlikely. For a complete summary of the IRT-QT consultation, the reader is referred to the Clinical review of the original NDA submission.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

No human carcinogenicity studies were requested, and none was conducted. There are no concerns regarding human carcinogenicity for solifenacin.

8.8.2. Human Reproduction and Pregnancy

No human reproduction and pregnancy data were included in the original NDA submission. In the original NDA submission, the Sponsor retrieved 4 potentially relevant publications as a result of a literature search they conducted seeking potential human reproduction or pregnancy risks in the pediatric population. An association between the use of solifenacin succinate in pregnant or lactating women, paternal exposure, and/or adverse effects on male or female fertility were not identified in any of these publications.

8.8.3. Pediatrics and Assessment of Effects on Growth

No adverse effects on growth were detected in the 52-week Phase 3 studies.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No issues with drug abuse potential, withdrawal or rebound were reported in the original NDA submission. One overdose case in a pediatric patient was reported, in which a 2 y/o Japanese boy accidentally took nineteen (19) solifenacin 5 mg tablets and required hospitalization for anticholinergic overdose toxicity, including constipation, dry mouth, accommodation disorder, dry skin and urinary retention. Following routine resuscitative measures, the child recovered completely and was discharged without sequalae.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

The Sponsor submitted two safety updates containing postmarketing safety data for solifenacin, for both solifenacin tablets and solifenacin oral suspension in both adults and pediatric patients treated for NDO or OAB, as follows: a Safety Update (including safety data received after the February 3, 2017 data lock point (DLP) through July 31, 2019) and a 120-Day Safety Update (including safety data received between August 1, 2019 through December 31, 2019). Each safety update submission was comprised of the following components:

- An analysis of adverse event case reports received during the specified time periods. The Sponsor reports that after the DLP, they conducted no new clinical studies for the oral suspension and there were no pediatric clinical study patients undergoing long-term follow-up.

- Cumulative postmarketing safety data
- Review of the published literature

During the Safety Update reporting period, for all age groups, 5423 initial postmarketing cases were received with a total of 9636 events reported, and 34.2% of those were from the US. Of these, pediatric initial case reports numbered 291 (5.4%) and contained 406 reported AEs, and 11% of those were from the US. During the 120-Day Safety Update reporting period, for all age groups, an additional 623 initial postmarketing cases were received with a total of 1075 adverse events reported, and 11.6% of those were from the US. Cumulatively, 31818 cases with 57689 events were reported; 42.2% of those were from the US and 2.3% were reported in children.

During the Safety Update reporting period, of the 291 initial case reports for pediatric patients, 211 were for preferred terms (PTs) related to off-label use (the reader is reminded that solifenacin oral suspension was approved in the EU and first marketed in Germany on October 11, 2018), and the remaining cases were related to lack of efficacy (11), accidental intake (16), medication errors only (13), and at least one AE (40).

Of the 40 reported cases of pediatric patients who experienced at least one AE, a total of 70 AEs (including 7 SAEs) were experienced, and a total of 61 AEs (87%) were reported in patients aged 2 to 11 years old. Most AEs were reported only once, but the following AEs were reported more than once: insomnia, dry mouth (n=5 each), fatigue, pyrexia, somnolence, thirst (n=3 each), dizziness, dysuria, flushing, visual acuity reduced, and vomiting (n=2 each).

The CIOMS reports for the 7 cases that reported serious AEs received by Sponsor during the Safety Update period, are summarized in Table 22 below and are subsequently reviewed in detail. These SAEs included: abdominal pain, faecaloma, alopecia, hallucination, neutropenia and sialoadenitis, dysphagia, and sinus tachycardia and hypertension.

Table 22 SAEs included in the Re-submission Safety Update (February 4, 2017 through July 31, 2019)

#	**MFR. Control # Country/Source**	**Dose**	**Adverse Events** Preferred Term	**Reviewer's assessment of causality**
Child: 2 to11 years				
1	(b) (6) Spain, HP	5 mg, 2.5 mg	**Abdominal discomfort** acne, hirsutism (upper lip), hirsutism (perianal), off-label use	**Probably related**
2	(b) (6) Belgium, HP	5 mg	**Faecaloma** off-label use	**Unassessable**
3	(b) (6) France, HP	5 mg	**Alopecia** vomiting, off-label use	**Possibly related but confounded by concomitant medication**
4	(b) (6) Netherlands, Auth	5 mg	**Hallucination** diarrhea, vomiting projectile, fatigue	**Probably related**

5	(b) (6) Australia, C	5 mg	**Neutropenia (*Comment: Probably Osteopenia*), Sialoadenitis**	**Refer to Case #2 in the 120-Day Safety Update section below**
Adolescent: 12 to < 16 years				
6	(b) (6) US, HP	5 mg	**Dysphagia** off-label use	**Unassessable**
7	(b) (6) Poland, C	5 mg (10 mg split)	**Sinus tachycardia** **Hypertension** off-label use, wrong technique in product usage process, drug ineffective	**Unassessable** **Unassessable**

HP = health professional; C = consumer; Auth = authority

Mfr. Control No. (b) (6) **(Spain):** This is a spontaneous report by a physician in Spain via a company representative received on 10-FEB-2017 concerning a 7-year old, 29 kg female patient from Spain who took solifenacin once daily for treatment of overactive bladder. The patient took oral solifenacin 5 mg, switched to oral solifenacin 2.5 mg, and then restarted solifenacin 5 mg. Start and stop dates of each dose are unknown. The patient developed mild hirsutism on her upper lip (unspecified date in (b) (6)), mild hypogastric discomfort ((b) (6) (b) (6)), moderate hirsutism in the perianal area (unspecified date in (b) (6)), and mild pimples (unspecified date in (b) (6)). Finally, an AE of "use of Vesicare in paediatric patient" [off label use] was also reported. After mild hypogastric discomfort (the SAE) was experienced, the initial 5 mg dose of solifenacin was reduced to 2.5 mg. As a result of this dose reduction, the hypogastric discomfort resolved and AEs of mild hirsutism both on the upper lip and perianal area improved (but were not resolved). Once the solifenacin dose was increased to 5 mg daily, the hirsutism increased again, and pimples appeared on the patient's cheeks. Whether hypogastric discomfort returned after the dose was increased to 5 mg was not noted.
No medical history, concomitant medication, or lab test information was provided.
The action with solifenacin treatment in response to the event was no change.
The reporting physician assessed the hypogastric discomfort as serious (though the patient was not hospitalized and did not appear to experience permanent damage) and probably causally related to solifenacin, the hirsutism (both upper lip and perianal) as non-serious and probably causally related to solifenacin, and the pimples as non-serious and probably causally related to solifenacin.

Reviewer's Comment: This appears to be a relatively complete case reported by a physician from Spain. The report contains a positive "dechallenge" because the dose of solifenacin was lowered, and the reported AEs either resolved (hypogastric discomfort) or improved (hirsutism). The report also contains a positive "rechallenge" when the increased dose worsened the hirsutism. The outcome with respect to the hypogastric discomfort when solifenacin was increased from 2.5 mg to 5 mg was not reported. Additionally, it is unclear why the reporting physician assessed hypogastric discomfort as serious. Overall, we assess the event in this case – hypogastric discomfort – as probably causally related to solifenacin treatment due to positive

dechallenge. We assess the other non-serious adverse events of hirsutism (upper lip and perianal) as probably causally related due to positive dechallenge and rechallenge, and pimples (occurred only on rechallenge) as possibly causally related to solifenacin treatment.

Mfr. Control No. (b) (6) **(Belgium):** This report was received on 17-MAR-2017 from a health professional from Belgium who provided information about a patient from Belgium enrolled in an unsponsored open label study (SOL_Unspon_Op_Study) who took solifenacin 5 mg for the indication of overactive bladder. The patient's age and sex were unknown/not provided. On an unspecified date, the patient experienced a serious adverse event of fecal impaction [faecaloma], which required hospitalization. An adverse event of "solifenacin used in a child" [off label use] was also reported. The dates of solifenacin treatment were not provided. The outcome of fecal impaction and "solifenacin used in a child" were not provided. The patient's concomitant therapies and medical history were not provided. The health professional assessed fecal impaction as possibly causally related to solifenacin. The reporter provided the following citation as part of this case report:

Hoebeke P, De Pooter J, De Caestecker K, Raes A, Dehoorne J, Van Laecke E et al. Solifenacin for therapy resistant overactive bladder. The Journal of Urology. 2009; vol. 182; pp. 2040-4.

Reviewer's Comment: The information in this case is limited. The report only indicates that solifenacin use occurred, and the patient experienced fecal impaction requiring hospitalization. The date of reaction onset or dates of solifenacin treatment are unknown. No further details are provided. The cited article describes a retrospective chart review study of charts from patients treated with solifenacin between August 2005 and 2008. If this patient was indeed eligible for the chart review, that suggests the adverse event was temporally related to solifenacin use. However, the article contains no details of this patient's case. Furthermore, it is not clear whether this citation was intended to provide an example of past reports of fecal impaction or if the patient with fecal impaction is the same patient described in this case. For these reasons, this case is considered Unassessable.

Mfr. Control No. (b) (6) **(France):** This is a spontaneous report received on 15-MAY-2018 from a pharmacist in France concerning an 8-year old female patient (DOB (b) (6)) from France who took solifenacin 5 mg daily for an unspecified duration with unspecified start and stop dates (however, a course of medication was delivered to the patient by the reporter on (b) (6)) to treat "urinary disorders". At an unspecified timepoint after solifenacin was initiated, the patient experienced a reported SAE of "loss of hair" [alopecia] ("by clump"), in addition to AEs of vomiting and "Vesicare used for a child" [off label use]. The severity of each AE was unknown. The patient's concomitant therapies included Dotarem (meglumine gadoterate), benzylpenicillin, and a cephalosporin, each to treat an unknown indication with

unknown start and stop dates. The only medical history provided was recurrent urinary disorders. No lab test information was provided. In response to the event of loss of hair, solifenacin was discontinued. Action with respect to meglumine gadoterate, a co-suspect drug, was unknown. No actions with respect to the two other drugs were noted. The outcomes for loss of hair and vomiting were unknown.

The reporter assessed loss of hair as serious due to medically significance and did not assess seriousness of vomiting. Both AEs were considered by the reporter to be probably causally related to solifenacin. The reporter did not assess the causal relationship of the events with meglumine gadoterate.

Reviewer's Comment: This case provides some useful information, but it lacks important information. It does appear that the patient was taking solifenacin at the time of the hair loss. However, the patient was also taking a co-suspect medication – meglumine gadoterate – which may be a confounder. The report provides no details on start or stop dates for either of these medications, or outcomes after solifenacin was withdrawn. Based on the incomplete information presented in this case, we consider solifenacin as Possibly related, with the caveat that important case details are missing, and this case may be confounded by concomitant medications.

Mfr. Control No. 2019US019246 (Netherlands): Originally reported by a consumer to Lareb Health Authority, this case was received from the European Medicines Agency (EMA) on 02-MAY-2019 and concerns a 4-year old, 16 kg male patient from the Netherlands who took solifenacin 5 mg orally for two days starting on (b) (6) to treat overactive bladder. On (b) (6) the patient experienced hallucinations (SAE) as well as projectile vomiting, substantial diarrhea for hours, and fatigue. Solifenacin was withdrawn. The reported adverse events resolved on an unknown date. No concomitant medications or lab test information was provided. The patient's medical history included food intolerance NOS.

The consumer did not report the seriousness of any AE or assess causal relationship of the drug to any AE.

Reviewer's Comment: This is a relatively complete report, and while brief, it contains identifying information about the patient, clear dates of solifenacin treatment, onset of the adverse events, and documentation of a positive dechallenge. Two of the events – hallucinations (the SAE) and fatigue – are known, labeled adverse reactions to solifenacin and in this case, are considered probably related to solifenacin treatment. Based on the information as presented in this case, we also consider projectile vomiting and substantial diarrhea as Probably related to solifenacin. Of note, the patient's weight was not provided in the report – a dose of 5 mg may have been too large for this patient's weight.

Case #5 in Table 23, Mfr. Control No. (b) (6) (Australia), is reviewed in the subsequent section that summarizes the 120-Day Update.

Mfr. Control No. (b) (6) **(U.S.):** This is a spontaneous report received on 09-JAN-2018 from a U.S. pharmacist concerning a 12-year old female patient from the United States who experienced dysphagia requiring a nasojejeunal feeding tube during off label use of Vesicare 5 mg daily. The events that were reported were "now requires an NJ tube" [Dysphagia](SAE) and "12-year old female patient taking Vesicare 5 mg once daily" [Off label use]. The date on which the NJ tube was required and the rationale for the NJ tube was not provided. Although the pharmacist inquired about crushing solifenacin tablets for administration, it was confirmed that the tablets had not been crushed. Action taken with solifenacin and outcome were not provided. Additionally, indication for use, therapy start and stop dates, concomitant medications, and lab test information were not provided. Medical history included only unspecified physical disabilities.
The reporter (pharmacist) neither assessed the seriousness nor the causality of the two adverse events.

Reviewer's Comment: This report includes few details. Causality is considered Unassessable.

Mfr. Control No. (b) (6) **(Poland):** This spontaneous report received on 05-DEC-2018 from a patient's mother about her daughter from Poland who, at age 12 years old (two years prior to the report) weighing 32 kg, experienced sinus tachycardia and hypertension during treatment with Vesicare 5 mg daily treatment and Betigma (mirabegron) 25 mg daily treatment for neurogenic bladder. Adverse events included sinus tachycardia (SAE), hypertension (SAE), off label use, wrong technique in product usage process (because the patient was splitting 10 mg tablets), and drug ineffective. Medical history included myelomeningocele, hydrocephalus, and fluid in pericardium; and under "Other", wheelchair use and presence of ventricular valve. The report states "medical history of underlying diseases was too extensive." Concomitant medications included Uroflow (tolterodine L-tartrate), ascorbic acid, calcium, and Uro-Vaxom (Escherichia coli), and Betigma.

The patient took solifenacin 5 mg daily from 2013 to an unspecified date, 10 mg from an unspecified date to (b) (6), and 5 mg from (b) (6) to an unspecified date. It was noted that the patient split the 10 mg tablets in order to administer a 5 mg dose. At an unspecified date, solifenacin was deemed ineffective, was discontinued, and mirabegron was started. However, the report also states that the patient took mirabegron 25 mg starting in 2012 through an unknown stop date and mirabegron 50 mg starting on1 (b) (6) and ongoing at the time of the report, suggesting possible overlap between solifenacin and mirabegron therapies.

On (b) (6) the patient developed moderate sinus tachycardia above 100 beats/min and moderate hypertension at 150/100 mmHg and was treated with Nedal (nebivolol hydrochloride)

¼ tablet of 5 mg daily starting on [redacted]. One week before the information was reported [redacted], Metocard (metoprolol) was added.

Medical consultation and ascending pyelography was planned on [redacted]. A Holter monitor was planned for [redacted]

The patient remained on mirabegron, and the action taken with solifenacin was unknown. The outcome of the events sinus tachycardia above 100 beats/min and hypertension -- 150/100 mmHg was reported a not recovered/not resolved.

The lab data provided in the report included the following: On [redacted] blood pressure of 150/100 mmHg and sinus tachycardia of > 100 beats/min was recorded on [redacted]; on unknown dates, blood morphology and urine tests were performed and were normal; on [redacted], echocardiography was normal; and on unknown dates blood pressure of 120/80 mmHg, height of 140 cm, body weight of 35 kg; one week before the information was reported ([redacted]), BP was 140/87, pulse was 120 beats/min and pupils were dilated.

The consumer assessed the causal relationship of the reported events of sinus tachycardia above 100 beats/min and hypertension (150/100 mmHg) to mirabegron as Possible. The consumer did not assess the causal relationship with those events to solifenacin.

Reviewer's Comment: This report appears to have extensive details, but key information regarding temporal association of solifenacin to the adverse events is lacking. It is not clear whether the patient was taking solifenacin at the time of the adverse events. The consumer did not include solifenacin in their assessment of event causality. However, the patient was taking mirabegron - which could be a confounder - and causality with respect to mirabegron was assessed by the consumer as Possible. Additionally, "medical history of underlying diseases was too extensive" suggests that a full history was not provided, which may have included unmentioned potentially confounding underlying conditions. Finally, there is no outcome information to document a positive dechallenge. In light of the uncertain temporal relationship between solifenacin administration and the adverse events, we consider this report Unassessable.

During the 120-Day Safety Update reporting period for the resubmission, 10 of the 22 initial case reports for pediatric patients were for PTs of "off-label use" (solifenacin oral suspension was approved in the EU and first marketed in Germany on October 11, 2018), and the remaining cases were attributed to lack of efficacy (1), medication errors only (3), and at least one AE (8).

Of the 8 reported cases in pediatric patients who experienced at least one AE, 15 AEs (including 4 SAEs) were experienced, and 14 (93%) were reported in patients aged 2 to 11 years old. Most

AEs were reported only once, but the following AEs occurred more than once: pyuria, tooth discoloration, and urinary incontinence (n=2 each). The following AEs occurred once: epilepsy, hydronephrosis, tachycardia, vision blurred, constipation, visual impairment, eye pain, memory impairment, and tic.

The CIOMS initial reports for the 3 cases that reported SAEs and were included in the 120-Day Safety Update period are reviewed below. The SAEs reported in these 3 cases were: hydronephrosis, tachycardia and vision blurred, and epilepsy. A fourth case that reported SAEs (neutropenia and sialoadenitis), that was initially submitted with the resubmission Safety Update, will be reviewed here as important update information about this case was submitted in the 120-Day Safety Update.

Table 24 summarizes the 4 serious cases initially reported (3) or updated (1) during the 120-Day Safety Update period.

Table 23 120-Day Safety Update (August 1, 2019 through December 31, 2019)

#	**MFR. Control # Country/Source**	**Dose**	**Adverse Events** Preferred Term	**Reviewer's assessment of causality**
Child: 2 to 11 years				
1	(b) (6) Japan, HP	unknown	**Hydronephrosis** urinary incontinence, pyuria, off-label use	**Possibly related but confounded by underlying disease**
2	(b) (6) Australia, C	5 mg (1/2 10 mg tab)	**Neutropenia (*Note: Likely to mean Osteopenia*)** **Sialoadenitis** salivary gland calculus, salivary gland pain, salivary gland enlargement, arthralgia (knee), arthralgia (elbow), wrong technique in product usage process	**Unassessable** **Probably related**
3	(b) (6) Spain, C/HP	4 mg/mL dose unknown	**Tachycardia** **Vision blurred** constipation, product use in unapproved indication	**Probably related** **Probably related**
4	(b) (6) China, C	1.25 mg (1/4 tab)	**Epilepsy- (or Tic-like) Symptom** tic, product use in unapproved indication, product use issue, wrong technique in product usage process,	**Unassessable**

HP = health professional; C = consumer

Below are summaries of the 4 serious cases:

Mfr. Control No. (b) (6) **(Japan):** This literature case, received on 19-DEC-2019 and reported by a physician from Japan, concerns a 10-year old male patient from Japan who took solifenacin (unknown dose and formulation, with unknown start and stop dates and for an unknown duration) to treat neurogenic bladder related to spina bifida. On an unknown date, the patient experienced the SAE of hydronephrosis with bladder compliance of 4.1mL/cm H_2O and

detrusor leak point pressure (DLPP) of 60 cm H_2O [PT: hydronephrosis], as well as adverse events of urinary incontinence, intermittent pyuria [PT: pyuria], and solifenacin was administered to child with neurogenic bladder [PT: off label use]. The action with respect to solifenacin was not provided. Additional treatment with mirabegron 50 mg was started, and one month later, the AEs hydronephrosis, urinary incontinence, and intermittent pyuria had resolved. Six months after mirabegron administration, bladder compliance was 10.5 mL/cm H_20. The outcome with respect to these events was reported as resolved.

The reporting physician did not comment on the seriousness of the AE hydronephrosis, but considered causality with solifenacin as Possible, although "small" because patients with spina bifida often develop similar symptoms due to their condition. The reporting physician did not report the seriousness of the events urinary incontinence and intermittent pyuria but assessed causality with solifenacin as Possible. Mirabegron was not considered by the reporting physician to be related to any of the reported events.

Reviewer's Comment: This case lacks important information. Not only is there no information provided about the duration of solifenacin treatment prior to the occurrence of the adverse events, it is not clear if treatment was ever stopped. Additionally, the assessment of causality is confounded by the patient's medical condition, which could also be responsible for the reported adverse events. In light of the lack of key information and the important confounding variable, we assess causality of the events to solifernacin as Possibly related.

Mfr. Control No. (b) (6) **(Spain):** This spontaneous case report, received on 10-DEC-2019 from a pharmacist (mother of the patient) in Spain, concerns a 7-year old female patient from Spain who took Vesicare oral suspension 4 mg/mL to treat overactive bladder and experienced reported SAEs of tachycardia and blurred vision, as well as constipation.
No concomitant medications, medical history, or lab test information was provided.
The patient was started on solifenacin in the first week of November as prescribed by the treating urologist. Four (4) days after starting solifenacin, the patient experienced tachycardia, blurred vision, and constipation. The patient's pediatrician discontinued the treatment due to the events and the patient recovered from all the events "as soon as the treatment with solifenacin was withdrawn." Although the pediatrician recommended restarting the treatment 15 days later at a lower dose (2 mg/day), the mother decided to discuss with the urologist at a future appointment.

The reporting pharmacist/mother did not provide a reason for assessing the reported events as serious, though she did consider causality with solifenacin therapy as Possible for tachycardia, blurred vision, and constipation.

Reviewer's Comment: This case is quite complete and contains strong support for a causal relationship. Based on the temporal relationship, the known drug safety profile, and the positive

dechallenge, we consider solifenacin as "Probably" related to the events of tachycardia, blurred vision, and constipation.

Mfr. Control No. (b) (6) **(China):** This spontaneous report was received on 29-NOV-2019 from a consumer (the patient's relative) and physician in China and concerned a 32-month old female patient from China who took Vesicare 1.25 mg (¼ of a tablet daily, with unspecified start and stop dates were not provided) for treatment of neurocystitis [PT: cystitis]. After three months of treatment, the patient experienced "a symptom like epilepsy and tic." The report notes that the physician mentioned the symptom would be relieved if solifenacin was stopped. Four (4) additional AEs (all non-serious) were reported: "Vesicare use for neurocystitis", "Vesicare used in 32-month old", "the patient took a quarter of a tab a day", and "misuse".

No concomitant medication information was provided. No lab test information was provided. The action with respect to solifenacin therapy was unknown, as was the outcome of the symptom described as "like epilepsy and tic".

Neither the consumer nor the physician assessed the seriousness of the symptom described as "like epilepsy and tic" or the possible causal relationship of the events to solifenacin.

Reviewer's Comment: This case appears to be reported by a reliable source but it contains very little information. Although it provides adequate information to conclude a temporal relationship between the intake of solifenacin and the reported events, it is unclear what is meant by "a symptom like epilepsy or tic." Based on the information provided, we consider this case Unassessable.

Mfr. Control No. (b) (6) **(Australia):** This spontaneous report was received on 06-AUG-2019 from a consumer's mother and physician in Australia concerning an 11-year old male patient of African descent from Australia who took solifenacin 5 mg treatment for overactive bladder and bed wetting. The report noted the patient took solifenacin for "4 months" (from (b) (6) (b) (6)). The events he experienced were: moderate neutropenia [PT: neutropenia], sialoadenitis [PT: sialoadenitis], painful and swollen glands/pain of submandibular glands [PT: salivary gland pain], painful and swollen glands/swelling of submandibular glands [PT: salivary gland enlargement], joint pain on knee [PT: arthralgia], joint pain on elbow [PT: arthralgia], suspected stones in glands/multiple calcifications in the parotid glands [PT: salivary gland calculus], and "patient only taking half" [PT: wrong technique in product usage process].

The patient had been taking solifenacin for 1-2 months prior to the onset of "painful and swollen glands", which lasted for 3 months. His symptoms worsened such that he could no longer eat and on (b) (6), he presented to the emergency department where he was evaluated over 4 hours, blood tests were normal, and he was discharged home with a diagnosis of suspected

stones in his salivary glands. A sonogram was apparently scheduled for (b) (6) though it was performed on (b) (6). The patient consulted his physician again on (b) (6) for "pain and swelling of submandibular glands with sialadenitis and multiple calcifications." The report states that "it was observed that the calcifications will take some time to resolve. It is possible that calcification could have occurred over five months, but not likely. There is no treatment for the swollen lymph glands and the management of sialadenitis and multiple parotid calcifications is ceasing medication that causes the saliva to be too concentrated and encouraging production of saliva with treatment such as chewing gum." At some time after this, solifenacin was stopped, and the pain and swelling in the glands improved.

Additionally, the patient experienced events of "joint pain on knee" for more than one month prior to the emergency department visit. Then, two weeks prior to the emergency department visit, the patient experienced "joint pain in the elbow". He underwent an elbow x-ray which showed "moderate neutropenia." Solifenacin treatment was stopped per the advice of the patient's general practitioner.

The patient's past medical history included sleep apnea, adenotonsillectomy, and adenoidectomy. Concomitant medications included half strength Betnovate (betamethasone valerate) cream to be applied to the penis for six weeks.

The consumer did not assess the seriousness or causality of any of the reported events. The patient did not assess the causality of "moderate neutropenia" but assessed the suspected "stones in glands/multiple calcifications in parotid glands" as possibly related to solifenacin.

Reviewer's Comment: This case provides a good amount of information from a consumer, but the chronology and details of many of the events are confusing. For example, the report clearly states that solifencin was stopped on the same day as the ED visit, (b) (6). *However, the report mentions that solifenacin was stopped by the general practitioner after details of the elbow pain evaluation were described. It is not clear that the elbow evaluation occurred around the time of the ED visit. Regarding the serious event of "moderate neutropenia": this event cannot reasonably be concluded by an x-ray, may actually reflect "Ospeopenia", and we consider this the causal relationship with solifenacin as Unassessable. Regarding the SAE suspected stones in glands/multiple calcifications in parotid glands: based on the clear temporal relationship, the positive dechallenge, and the biological plausibility of anticholinergics decreasing salivary secretions, we consider solifenacin as Probably causally related to this SAE.*

Pregnancy, Lactation, and Fertility

Any available postmarketing data related to pregnancy, lactation, and fertility was provided in the resubmission Safety Update. During the 120-Day Safety Update reporting period, no cases

reporting pregnancy, exposure resulting from lactation, or AEs related to male or female fertility were received.

In the Safety Update, the Sponsor provided a table to describe 15 individual cases with 11 reported pregnancies during the current reporting period. Of the 11 reported pregnancy reports, 7 contained inadequate information for assessment and lacked pregnancy outcome data, two were normal live births (exposure duration was unclear or unknown), one showed morbidities in the infant (and was confounded by concomitant medications) and one was terminated (due to unilateral cleft lip and palate in a patient with many medical conditions). Four reported cases were duplicates of previously reported cases.

Thus, there were a total of 12 pregnancy reports in the Safety Update reporting period: 9 with PT of Exposures during pregnancy and 3 with PT Maternal exposure during pregnancy. These PTs were the top two PTs for pregnancy reports for the cumulative time period.

Case reports of exposure resulting from lactation totaled 3 during the Safety Update reporting period. No adverse events were associated with these reports.

The Sponsor provided a table comparing the AEs relating to male or female fertility in the Safety Update reporting period and cumulatively. In the Safety Update reporting period, only three AEs were reported in females (amenorrhea [n=1], menstruation delayed [n=2], and menstruation irregular [n=1]) and males (haematospermia [n=2], semen volume decreased [n=1], and sperm concentration decreased [n=1]. In the cumulative time period, all of these AEs had been reported before, except haematospermia and semen volume decreased. The following AEs were reported cumulatively but were absent from reports during the Safety Update reporting period: blood testosterone abnormal, fallopian tube disorder, hypogonadism, infertility male, oligomenorrhoea, semen discoloration, and sperm concentration zero.

Reviewer's Comment: The data presented by the Sponsor does not indicate a new safety signal concerning fetal exposure to solifenacin during pregnancy or infant exposure during lactation. Furthermore, the data did not suggest increased incidence or variety of AEs related to infertility.

Literature Search
The Sponsor performed a search of using Embase, Medline, and BIOSIS Previews for Safety Update and 120-Day Safety Update reporting periods. According to the Sponsor, the 41 publications on the use of solifenacin that were retrieved did not identify any new safety or efficacy issues, any associations between safety problems and the use of solifenacin succinate in pregnancy or in lactating women (or due to paternal exposure), or any issues related to male and female fertility.

Reviewer's Comment: In summary, the new clinical data contained in the two safety update submissions from this cycle are comprised of 10 serious cases with 13 SAEs in pediatric patients with NDO treated with solifenacin oral suspension. Six (6) SAEs were Unassessable (faecaloma, dysphagia, sinus tachycardia, hypertension, neutropenia and symptoms like epilepsy or tic), two (2) were Possibly related but confounded by concomitant medication or underlying disease (alopecia and hydronephrosis, respectively), and five (5) were Probably related (abdominal discomfort, hallucination, sialoadenitis, tachycardia, and blurred vision) to treatment with solifenacin. With the exception of a single case of sialoadenitis, SAEs considered Probably related to solifenacin are consistent with the known side effect profile of solifenacin. Sialoadenitis is an AE that could reasonably result from the known drying effect/decreased salivation of anticholinergic drugs in general. Sialadenitis will be added under "Gastrointestinal Disorders" in the ADVERSE REACTIONS, Postmarketing Experience *subsection. Additionally, these two safety updates identified no new clinical issues or changes in the safety profile of solifenacin tablet in the adult population with OAB.*

8.9.2. Expectations on Safety in the Postmarket Setting

There is substantial previous postmarket experience with the tablet dosage form of solifenacin. Solifenacin oral suspension for pediatric NDO patients has been marketed in Germany since October 11, 2018. Based on the limited, ex-U.S., postmarket experience with the oral suspension in pediatric patients with NDO, the extensive experience with the solifenacin tablets in adults with OAB, and the comparability of solifenacin systemic exposure between adult and pediatric patients, we anticipate no additional potential safety issues in the postmarket setting for solifenacin oral suspension in pediatric patients.

8.10. Integrated Assessment of Safety

The two (2) Phase 3 clinical studies conducted by the Sponsor in support of solifenacin oral suspension for the treatment of NDO in pediatric patients provided a comprehensive safety assessment in the indicated population. The safety findings were further supported by safety data from two Phase 3 studies in pediatric patients with OAB as well as two Phase 1 clinical pharmacology studies (one in NDO patients, one in OAB patients). This re-submission review as well as the original NDA Clinical review provide details regarding the extent of exposure, demographics, and safety results. The reader is referred to the original review and to earlier sections of this review for those details.

In regard to patient exposure and demographics in the major clinical studies provided in this submission:

- 299 pediatric patients aged ≥ 2 years (with NDO or with idiopathic OAB) received solifenacin oral suspension in clinical trials (Phase 1 and Phase 3 studies). Of those, 109 patients had NDO.

- In the Phase 3 studies in patients with NDO, the duration of treatment for the majority of patients (65 [68.4%]) was ≥ 364 days and was similar across the relevant age group populations from both studies.
- For a majority of the patients in these studies, the treatment doses were up-titrated to pediatric equivalent dose (PED) PED7.5 or PED10 during the treatment period (by week 12 in 905-CL-047 or by week 9 in 905-CL-074). The optimized dose for most patients in all age groups was PED10.
- The mean duration of treatment for all Phase 3 pediatric patients was 319.6±103.7 days (Mean±SD), and the mean daily dose used was 5.1±1.8 mg (Mean±SD).

In regard to deaths, SAEs, and TEAEs leading to discontinuations in the major clinical studies:

- There were no deaths reported in the development program.
- In the Phase 3 pediatric NDO population, SAEs were reported by 8 of 95 (8.4%) patients, seven of which were reported by patients in Study 047 (2 children and 5 adolescents). SAEs included UTI (n=2, reported once in each study), tachycardia, toxic megacolon, dengue fever, orchitis, pharyngitis, tethered cord syndrome, spinal cord operation, and hypertension (n=1 each). None of these SAEs appeared to be drug-related.
- In pediatric OAB patients, nine (9) SAEs were reported in 8 patients. Of the 9 SAEs in this group, only 4 occurred in patients treated with solifenacin: frontal lobe epilepsy, pyelonephritis, gastroenteritis, and appendicitis. None of these four were determined to be drug-related. There was a single report of QT prolongation but it was confounded by a concomitant serious UTI causing tachycardia and pyelonephritis.
- In the Phase 3 NDO population, TEAEs leading to discontinuation occurred only in Study 905-CL-047, and in all 4 of these cases (4/76 [5.3%]), the patients were discontinued from treatment due to the per-protocol discontinuation criterion for "ECG QT prolonged". Of these 4 patients aged ≥ 5 years, 2 were children and 2 were adolescents. Based on a random effect analysis performed on the phase 3 OAB pediatric patient ECG data, the Sponsor found that there were no changes of concern in the population means of QT intervals. However, the intra-patient variance in repeat QTcB measurements, when applied to the Phase 3 pediatric NDO studies, appeared to account for the discontinuations of 4 NDO patients from Study 905-CL-047 in whom baseline measurements were derived from single assessments, not an average of triplicates. In order to increase the accuracy of the baseline QTc measure, the protocols were amended to require calculations of QTcB to incorporate multiple measurements from two pre-randomization study visits instead of one. Subsequent to implementing this change, no patients were discontinued due to ECG QT prolongation in the phase 3 trials. The IRT-QT team was consulted, who agreed with the Sponsor's determination, and ultimately concluded that the QT prolongations responsible for the study discontinuations were not considered clinically relevant findings.

In regard to commonly reported TEAEs in the major clinical studies:

- In the Phase 3 pediatric NDO population, TEAEs reported by > 5% of patients were UTI 29/95 (30.5%); constipation 7/95 (7.4%); and nasopharyngitis and upper respiratory infection 6/95 (6.3%) for each. UTI TEAEs were thought to reflect the high annual incidence of UTI in pediatric patients with NDO practicing CIC.
- The most commonly reported drug-related TEAEs in the Phase 3 pediatric NDO population were: constipation (7/95 [7.4%]), dry mouth (3/95 [3.2%]), ECG QT prolonged (3/95 [3.2%]), UTI (2/95 [2.1%]), and abdominal pain, pharyngotonsillitis, viral rash, bacterial test positive, and somnolence (each 1/95 [1/1%]).

In regard to TEAEs of special interest and special safety issues:

- UTI was a commonly reported TEAE (30.5%, n=24 in Study 905-CL-047 and n=5 in Study 905-CL-074). The high incidence was thought to reflect the high background incidence in the patient population. The two SAEs due to UTI were considered by the investigator to be "possibly related to study drug."
- Constipation was commonly reported (n=6 in Study 905-CL-047 and n=3 in Study 905-CL-074), all cases of constipation were considered possibly (5) or probably (1) related to study drug, and reports of constipation were expected given solifenacin's known safety profile.
- "ECG QT prolonged" was reported in 4 patients in Study 905-CL-047 and was determined to not be clinically relevant for reasons explained previously in this review.
- Hypertension and tachycardia (n=1 each, reported as SAEs) was determined by the investigator and agreed by the original Clinical reviewer to be unlikely casually related.
- For somnolence (n=1), a causal relationship could not be ruled out given the temporal association of the events.
- For toxic megacolon, the original Clinical reviewer agreed with the investigator that this TEAE was not related to the study drug.

In regard to Postmarket experience:

- We reviewed the 10 serious cases reporting 13 SAEs.
- Six (6) SAEs were considered as Unassessable (faecaloma, dysphagia, sinus tachycardia, hypertension, neutropenia and symptoms like epilepsy or tic), two (2) were considered as Possibly related but confounded by concomitant medication or underlying disease (alopecia and hydronephrosis, respectively), and five (5) were considered as Probably related (abdominal discomfort, hallucination, sialoadenitis, tachycardia, and blurred vision) to treatment with solifenacin.
- With the exception of a single case of sialoadenitis, the SAEs considered as Probably related to solifenacin are consistent with the known side effect profile of solifenacin. Sialadenitis will be added to "*Gastrointestinal Disorders*" in the ADVERSE

REACTIONS, Postmarketing Experience subsection of the solifenacin oral suspension label.

Overall, solifenacin oral suspension was generally well tolerated in pediatric patients. The safety profile of solifenacin oral suspension in pediatric patients with NDO is consistent with the safety profile of approved solifenacin tablets. There are no new or unresolved safety issues.

9. Advisory Committee Meeting and Other External Consultations

There were no issues that required advice from an FDA Advisory Committee and an Advisory Committee meeting was not held for this efficacy supplement.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Labeling discussions were initiated during the first review cycle for the original NDA. FDA provided the Sponsor with labeling edits on August 7, 2017 and August 21, 2017. The Sponsor included with this resubmission that label with annotations in response to FDA edits from 2017 and to support additional content revisions proposed by the Sponsor. The Sponsor also proposed additional editorial revisions for document maintenance.

In FDA's comments to the Sponsor from 2017, a note was made that revisions to labeling related to narrow angle glaucoma may be considered given that practice standards had evolved since the current language had been created. Narrow angle glaucoma no longer goes untreated (it is treated surgically); therefore, a Contraindication or Warning related to untreated narrow angle glaucoma is no longer relevant. To address this revision across the anticholinergic OAB drug, we plan to issue a class Prior Approval Supplement request subsequent to the regulatory action on this NDA.

For the resubmission, the only adverse event to be added to labeling that resulted from the safety review was sialoadenitis, which will be added under "*Gastrointestinal Disorders*" in the ADVERSE REACTIONS, Postmarketing Experience subsection.

Labeling discussions were held with the entire review team on April 23, 2020, April 28,2020 and April 30, 2020. The Division's edited labels (PI and PPI) were conveyed to the Sponsor on May 1, 2020 and May 12, 2020, respectively. The Sponsor accepted all of the Division PI edits and

returned the PI document with minor revisions on May 8, 2020. Several minor Division edits were conveyed to the Sponsor on May 12, 2020.

In parallel with labelling for VESicare LS oral suspension under NDA 209529, the Sponsor had also submitted a prior approval supplement to NDA 021518 for VESIcare Tablets to update the Pediatric Use section of that label. In addition to several editorial revisions proposed for document maintenance, the Sponsor included updated content related to Pregnancy and Lactation to comply with PLLR. Also, in Section 6.2 Post-Marketing Experience, the following adverse events were added: dizziness, urinary retention, and vomiting. To support these additions, the Sponsor provided a link to the post marketing safety report index with the cumulative summary tabulation through December 2016 which showed urinary retention with 799 reports cumulatively, vomiting with 136 reports, and dizziness with 921 reports. Labeling discussions for this supplement (SLR017) were held with the entire review team on May 4, 2020 and May 6, 2020 and the FDA-edited labeling for SLR017 was conveyed to the Sponsor on May 7, 2020. The Sponsor accepted all of the Division edits and returned the label with minor revisions on May 13, 2020.

10.2. Nonprescription Drug Labeling

Solifenacin is available by prescription only.

11. Risk Evaluation and Mitigation Strategies (REMS)

There was no reason to require a REMS for this product, and none was requested.

12. Postmarketing Requirements and Commitments

Neither a postmarketing requirement nor commitment is needed for this product.

13. Appendices

13.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): 905-CL-074

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from

		Applicant)
Total number of investigators identified: 33		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0*		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ N/A

Covered Clinical Study (Name and/or Number): 905-CL-047

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 116		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0*		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ N/A

Covered Clinical Study (Name and/or Number): 905-CL-076

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 135		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0*		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ N/A

Covered Clinical Study (Name and/or Number): 905-CL-077

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 119		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0*		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____		

Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ N/A

Covered Clinical Study (Name and/or Number): 905-CL-066

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 6		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0*		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial	Yes ☐	No ☐ (Request details from Applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ N/A

Covered Clinical Study (Name and/or Number): 905-CL-080

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 7		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0*		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		

Is an attachment provided with the reason:	Yes ☐	No ☒ N/A

Covered Clinical Study (Name and/or Number): 905-CL-075

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 22		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0*		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ N/A

Covered Clinical Study (Name and/or Number): 905-CL-079

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from

		Applicant)
Total number of investigators identified: 5		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0*		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ N/A

* Based on the information submitted, in which no investigator in any of these clinical studies had a disclosable financial interest, we conclude that no investigator was a Sponsor employee.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ELENA N BOLEY
05/15/2020 05:59:08 PM

MARK S HIRSCH
05/18/2020 11:11:00 AM
I concur.