CLINICAL REVIEW

Application Type	NDA
Application Number(s)	209,529
Priority or Standard	Priority
Submit Date(s)	February 28, 2017
Received Date(s)	February 28, 2017
PDUFA Goal Date	August 28, 2017
Division / Office	DBRUP/ODE 3
Reviewer Name(s)	Guodong Fang
Review Completion Date	August 3, 2017
Established Name	Solifenacin Oral Suspension
(Proposed) Trade Name	VESIcare LS
Therapeutic Class	M_3 Muscarinic Receptor Antagonist
Applicant	Astellas Pharma Global Development, Inc.,
Formulation(s)	$C_{23}H_{26}N_2O_2 \cdot C_4H_6O_4$
Dosing Regimen	Aqueous suspension 1mg/mL
Indication(s)	(b) (4)
Intended Population(s)	

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

(b) (4)

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(b) (4)

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(b) (4)

2 Introduction and Regulatory Background

Solifenacin is a competitive muscarinic receptor antagonist with high affinity for M_3-receptors. Contractions of the detrusor muscle are mediated predominantly through stimulation of muscarinic M_3-receptors. The muscarinic M_3-receptor antagonistic effect is considered as the main mechanism of solifenacin-induced relaxation of the urinary bladder. Solifenacin succinate, 5 mg and 10 mg tablets, was approved on Nov. 19, 2004 under NDA 021518, in the United States for treatment of overactive bladder (OAB) in adults.

2.1 Product Information

The deferred pediatric studies for NDA 21,518 required under section 2 of the Pediatric Research Equity Act (PREA) were considered required postmarketing study commitments (PMCs) as "Pediatric studies under PREA for the treatment of overactive bladder in pediatric patients for ages five to 11 years old and adolescents for ages 12 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 (referred to as neurogenic detrusor overactivity, or NDO). A Written Request (WR) for the evaluation of solifenacin in pediatric NDO patients was issued on July 27,

2012, with subsequent amendments dated September 14, 2012, April 17, 2014, and December 12, 2014. Under the terms of the WR, clinical studies 905-CL-079 and 905-CL-047 were conducted: a pediatric pharmacokinetic study (Study 1) and a pediatric safety and efficacy study (Study 2), respectively. An oral suspension was developed to facilitate swallowing and accuracy of dosing. (b) (4)

(b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

(b) (4)

(b) (4)

2.3 Availability of Proposed Active Ingredient in the United States

The drug product, VESIcare LS (solifenacin oral suspension), is manufactured, packaged, tested and released by (b) (4) .

2.4 Important Safety Issues With Consideration to Related Drugs

The important safety issues with consideration to related drugs for the proposed product solifenacin oral suspension are not changed compared to the anticholinergic drug class, including solifenacin tablets.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

VESIcare® (solifenacin succinate), 5 and 10 mg tablets, were approved on November 19, 2004, under NDA 021518 for the treatment of overactive bladder in adult patients. The approval for NDA 021518 included a postmarketing commitment for pediatric studies under PREA for "the treatment of overactive bladder in pediatric patients aged 5 years to 11 years and adolescents aged 12 years to 17 years." On January 20, 2006, an agreement was reached to enroll only pediatric patients with detrusor overactivity due to known neurological disease (referred to as neurogenic detrusor overactivity, or NDO).

The pediatric study requirements established under PREA were aligned with the pediatric study requirements agreed in a Written Request (WR) for solifenacin. A WR for the evaluation of solifenacin in pediatric patients with neurogenic detrusor overactivity (NDO) was issued under NDA 021518 on July 27, 2012 with subsequent amendments on September 14, 2012, April 17, 2014 and December 12, 2014. The table below shows the dates of the original WR and subsequent WR amendments.

Date	Version	Description
07/27/2012	Original Written Request	Established the pediatric information needed on solifenacin succinate in children and adolescents with NDO. The studies submitted in response to the WR include Study 1 (905-CL-079) and Study 2 (905-CL-047). The timeline for submission of reports of the studies was established as 30 Jun 2015.
09/14/2012	Amendment 1	Updated the secondary efficacy variables for Study 2
04/17/2014	Amendment 2	Updated the study endpoints, dosage information, and statistical information for Study 2. In addition, the timeline for submission of reports of the studies was extended to June 30, 2016.
12/12/2014	Amendment 3	Updated the number of patients and statistical information for Study 2. In addition, the timeline for submission of the reports of the studies was extended to August 17, 2017

The two studies in children and adolescents with NDO submitted in response to the VESIcare PMCs, and WR, (b) (4) are the following:

Study 1	**905-CL-079**	A Multicenter, Open-label, Single-dose Study to Evaluate Pharmacokinetics, Safety, and Tolerability of Solifenacin Succinate Suspension in Pediatric Patients from 5 to < 18 years of Age with Neurogenic Detrusor Overactivity (NDO). This is a pediatric pharmacokinetic study in children and adolescents with NDO; the aim of this study is to confirm the comparability of the pharmacokinetic profiles in pediatric NDO and overactive bladder (OAB) patients.
Study 2	**905-CL-047**	A Phase 3, Open-Label, Baseline-controlled, Multicenter, Sequential Dose Titration Study to Assess the Long-Term Efficacy and Safety, and the Pharmacokinetics of Solifenacin Succinate Suspension in Patients from 5 to < 18 years of Age with Neurogenic Detrusor Overactivity (NDO). This is a long-term safety and efficacy study in children and adolescents with NDO.

Under the terms of the WR, Study 1 (a pharmacokinetic study) and Study 2 (a Phase 3 pediatric safety and efficacy study) have been conducted, respectively. An oral suspension was developed to facilitate swallowing and accuracy dosing.

(b) (4)

2.6 Other Relevant Background Information

In Europe, the pediatric clinical development program for solifenacin included both the use of solifenacin for treatment of NDO in patients aged 6 months to < 18 years as well as for treatment of idiopathic OAB (OAB) in patients aged 5 to < 18 years. The pediatric development program for solifenacin was agreed upon with the EMA Paediatric Committee and included 2 paediatric investigation plans (PIPs):

- The PIP for NDO (EMEA-00057-PIP02-13-M03) included studies for the treatment of NDO in the pediatric population aged 6 months to < 5 years (905-CL-074) in addition to the above-mentioned study in patients aged 5 years to < 18 years (905-CL-047);
- The PIP for OAB (EMEA-00057-PIP01-09-M05) included studies for the treatment of OAB in the pediatric population aged 5 years to < 18 years of age. A single ascending dose pharmacokinetic study was required (905-CL-075) along with a double-blind, placebo-controlled, dose-titration study for pharmacokinetics, efficacy and safety (905-CL-076) and a long-term open-label study for safety and efficacy (905-CL-077).

The results of the clinical studies in pediatric patients with NDO have been reviewed by the Paediatric Committee and a positive Compliance Statement has been issued. (b) (4)

3 Ethics and Good Clinical Practices

Through a thorough review of the clinical study protocols, protocol amendments, and informed consent forms, as well as the approval process by either central or local IRBs, and finally, clinical sites inspections conducted by CDER's Office of Scientific Investigations (OSI), no ethics or good clinical practice (GCP) issues have been identified.

3.1 Submission Quality and Integrity

The quality of the overall this resubmission was good with the information well organized and readily located.

3.2 Compliance with Good Clinical Practices

The primary studies 905-CL-047 and 905-CL-074 are the main clinical studies (b) (4) . And they studies were conducted in accordance with Good Clinical Practice as required by the guidelines of the Agency and the International Committee on Harmonization guidelines. DBRUP consulted the Office of Scientific Investigations (OSI) for clinical site inspections (b) (4)

3.3 Financial Disclosures

In compliance with 21 CFR Part 54, the Sponsor has adequately disclosed the absence of Investigator proprietary interest in this product or Investigator participation in financial arrangements with Sponsor.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

(b) (4)

4.2 Clinical Microbiology

(b) (4)

4.3 Preclinical Pharmacology/Toxicology

(b) (4)

4.4 Clinical Pharmacology

(b) (4)

4.4.1 Mechanism of Action

Solifenacin acts as competitive muscarinic receptor antagonist with high affinity for M_3-receptors.

4.4.2 Pharmacodynamics

Solifenacin induces relaxation of the urinary bladder through M_3 muscarinic receptors.

4.4.3 Pharmacokinetics

After oral administration of the solifenacin suspension in pediatric patients with NDO from 2 to <18 years old, at steady state the median C_{max} of solifenacin was 7.79 ng/mL/mg; the median T_{max} was 3 hours; the median AUC_{tau} was 146.42 ng·h/mL/mg; and the median $t_{1/2}$ was 26.4 hours.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 5.1 Clinical Studies Included in NDA 209,529

Type of Study	Study Identifier (Country)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route	Number of Subjects/ Patients	Subjects/ Patients	Duration of Treatment
Phase 1	**905-CL-066** (1 site in USA)	Primary: Determine relative BA and PK profile of 10 mg oral suspension (Formulation A) in comparison to the 10 mg tablet in the fasted state Secondary: Evaluate the food effect on the PK of a single dose 10 mg suspension	Open-label, single-dose, 3 period crossover study	solifenacin 10 mg tablet or 10 mg oral suspension (1 mg/mL) Treatmentgroups: Txt A: tablet (fasting); Txt B: oral suspension (fasting); Txt C: oral suspension (fed)	24 adult volunteers	Healthy adults	1 day (single doses)
Phase 1	**905-CL-080** (1 site in USA)	Determine relative BA & PK profile (primary) & safety and tolerability (secondary): 1) suspension Formulation B vs Formulation A; 2) Formulations A and B vs 10 mg tablet; after single doses of Formulations A and B, and 10 mg tablet	Open-label, single-dose, 3 treatment, 3 period crossover study	solifenacin 10 mg tablet; 10 mg oral suspension (1 mg/mL) Formulation A; or 10 mg Formulation B oral suspension (1 mg/mL) Treatment groups: Txt A: Formulation A Txt B: Formulation B Txt C: tablet	24 adult volunteers	Healthy adults	1 day (single dose)
Phase 1	**905-CL-075** (12 sites in Belgium Denmark, Norway, Poland, Sweden and UK)	Evaluate PK (Primary) and safety and tolerability (secondary) of oral suspension (Formulation A) after single-dose at different dose levels in pediatric patients with idiopathic OAB	Multicenter, open-label, single ascending dose study	oral suspension (1 mg/mL) at PED2.5, 5 & 10; single dose; 3 txt groups each in children and adolescents: CH-PED2.5; CH-PED5; CH-PED10; AD-PED2.5; AD-PED5; AD-PED10	Screened: 46 Treated: 42 (22 children and 20 adolescents) Completed: 42 (22 children and 20 adolescents)	Children & adolescents with idiopathic OAB (5 years to < 18 years)	1 day (single dose)
Phase 1	**905-CL-079** (4 sites in Belgium Denmark, Poland, and UK)	Evaluate PK (Primary) and safety and tolerability (secondary) of solifenacin oral suspension (Formulation B) after single-dose at different dose levels in pediatric patients with NDO	Multicenter, open-label, single dose study	solifenacin oral suspension at PED 5, single dose	Screened: 22 Treated: 14 (7 children and 7 adolescents) Completed: 14 (7 children and 7 adolescents)	Children & adolescents with NDO (5 years to < 18 years)	1 day (single dose)
Phase 3	**905-CL-047** (21 sites: Belgium, Brazil, Denmark, Hungary, Mexico, Philippines, Poland,	Evaluate the long-term efficacy, safety and PK of solifenacin oral suspension (Formulation B) after multiple dose in pediatric	Open-label, baseline-controlled, multicenter, sequential dose titration study	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)	Children & adolescents with NDO (aged 5 yrs to < 18 yrs)	52 wks: 12-wk dose titration period followed by a 40-wk fixed-dose period

	South Korea, Turkey & USA)	patients with NDO					
Phase 3	**905-CL-074** (8 sites in Belgium, UK, Poland, USA Philippines & South Korea)	Evaluate the long-term efficacy, safety and PK of solifenacin oral suspension (Formulation B) after multiple dose in pediatric patients with NDO	Open-label, baseline-controlled, multicenter, sequential dose titration study	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)	Children & adolescents with NDO (aged 6 months [M] to < 5 yrs [Y])	52 wks: 12-wk dose titration period followed by a 40-wk fixed-dose period
Phase 3	**905-CL-076** (50 sites: Belgium, Netherlands, Norway, Sweden, Denmark, UK, Poland, Serbia, Ukraine, Canada, USA, Brazil, Mexico, Philippines, South Africa, South Korea & Turkey)	Primary Evaluate efficacy & safety of solifenacin oral suspension (Formulation B) once daily in pediatric patients with idiopathic OAB; Secondary Perform population PK after multiple-dose in pediatric patients with idiopathic OAB	Multicenter, placebo-controlled sequential dose titration study: 1) single-blind 2-wk placebo run-in period combined with urotherapy; 2) double-blind, randomized, placebo-controlled 12-wk treatment period (urotherapy continued)	solifenacin suspension (1 mg/mL) once daily Doses: PED2.5, 5, 7.5 or 10	Screened: 278 Randomized: 189 (148 children [75 @placebo & 73 @solifenacin], 41 adolescents [19 @ placebo& 22 @ solifenacin])Completed:164 (131 children [66 @ placebo & 65 @ solifenacin], 33 adolescents [16 @ placebo & 17 @ solifenacin])	Children & adolescents with idiopathic OAB (aged 5 to < 18 yrs [Y])	Single-blind placebo run-in period: 2 wks; Double-blind treatment period: 12 wks
Phase 3	**905-CL-077** (39 sites: Belgium, Norway, Sweden, Denmark, UK, Poland, Serbia, Ukraine, Canada, USA, Brazil, Mexico, Philippines, South Africa, South Korea & Turkey)	Evaluate safety & efficacy, and PK of solifenacin oral suspension (Formulation B) once daily in pediatric patients with idiopathic OAB	Multicenter, open-label, sequential dose titration, long-term safety extension study	solifenacin suspension (1 mg/mL) once daily Doses: PED2.5, 5, 7.5 or 10	Pts completing 905-CL-076 could be included in the extension study Treated: 148 (119 children 29 adolescents) ; Completed: 122 (99 children, 23 adolescents)	Children & adolescents with idiopathic OAB (aged 5 to < 18 yrs [Y])	40-wk fixed-dose period following 12-wk dose titration period in prior Study 905-CL-076

5.2 Review Strategy

This review is based on the following information:

- The efficacy and safety data from two Phase 3 studies in patients with NDO: Phase 3 studies (905-CL-047 and 905-CL-074) for efficacy determination;
- 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) for safety determination;
- Additional clinical pharmacology studies including bioavailability studies in healthy adult volunteers (905-CL-066 and 080), and pharmacokinetic studies in patients with NDO (905-CL-079 and 075) to support the efficacy and safety.

5.3 Discussion of Individual Studies/Clinical Trials

The Sponsor's pediatric clinical development program comprises: 2 pharmacokinetic phase 1 studies (905-CL-079 in NDO and 905-CL-075 in OAB); 2 phase 3 studies in patients with NDO (905-CL-047 and 905-CL-074); and 2 phase 3 studies in patients with idiopathic OAB (905-CL-076 and 905-CL-077). (b) (4) . Bioavailability studies (905-CL-066 and 905-CL-080) were also performed in healthy adult volunteers. The clinical development program was conducted globally, including in Brazil, Europe, Turkey, the US, Mexico, South Africa, the Philippines and South Korea.

Two formulations of solifenacin oral suspension were evaluated during the pediatric development program. (b) (4) (Formulation B) was used in the single-dose pharmacokinetic safety and tolerability study in patients with the target condition, pediatric patients with NDO (905-CL-079), and in all subsequent pediatric phase 3 studies. Formulation A was used in the first phase 1 pharmacokinetic study (905-CL-075). Unless otherwise stated, when discussing the formulation development, solifenacin oral suspension refers to (b) (4) Formulation B.

Based on a clinical pharmacological study (Study 905-CL-080) that tested the relative bioavailability of final suspension Formulation B, it was concluded that suspension Formulations A and B and the tablet formulation of solifenacin are bioequivalent under fasted conditions. All 3 formulations of solifenacin were safe and well tolerated in this study.

6 Review of Efficacy

Efficacy Summary

- 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;
- Other urodynamic measurements from baseline to 24 weeks also demonstrated an improvement in both age groups, including: the mean bladder compliance increased, the mean number of overactive contractions > 15 cmH_2O decreased, bladder volume until first detrusor contraction > 15 cmH_2O increased;
- Additional measurements from baseline to 24 weeks demonstrated an increase in the maximum catheterized urine volumes, and a decrease in the number of incontinence episodes per 24 hours;
- The magnitude of the observed changes in both the primary and secondary endpoints in children (5 to < 12years of age) and in adolescents (12 to < 18 years of age) was comparable;
- The primary endpoint based on the long-term data showed generally similar efficacy but from a smaller sample size (n = 54 at week 52 vs. n = 66 at week 24).

Table 6.1 Summary Changes from Baseline to 24 Weeks for Solifenacin Suspension in Phase 3 NDO Population

Endpoint	Statistics	Change from Baseline at Week 24	
		Aged 2 to < 5 Years (N=17)	Aged 5 to < 18 Years (N=49)
Primary Endpoint			
Maximum Cystometric Capacity (mL)	Mean (SD)	38.9 (35.5)	57.2 (107.7)
Secondary Endpoints			
Bladder Compliance (mL/cmH_2O)	Mean (SD)	5.8 (7.3)	9.1 (28.6)
Number of Overactive Detrusor Contractions (> 15 cmH_2O) Until End of Bladder Filling	Mean (SD)	-7.0 (9.3)	-2.3 (5.1)
Bladder Volume Until First Detrusor Contraction > 15 cmH_2O as a Percentage of Expected Bladder Capacity (mL)†	Median	31.1%	13.3%
Maximum Catheterized Volume (MCV) / Day	Mean (SD)	45.3 (54.7)	67.5 (88.1)
Mean Number of Incontinence Episodes / 24 hrs	Mean (SD)	-1.6 (1.2)	-1.6 (2.0)

†For patients who showed a detrusor contraction during the urodynamic assessment at Week 24.
Source: Statistical Reviewer's analysis.

6.1 Indication

(b) (4)

6.1.1 Methods

(b) (4)

the sponsor provided data from the studies that addressed the requirements established by the Agency in the Written Request (WR) and post-approval requirements for VESIcare® tablets under NDA 021518. Together, these requirements included 2 phase 3 studies for the evaluation of solifenacin oral suspension:

- Study 905-CL-047 in pediatric patients aged 5 years and older
- Study 905-CL-074 in pediatric patients aged 6 months to < 5 years

The two Phase 3 primary studies were multi-center, open-label, baseline-controlled, sequential dose titration studies to assess the long-term efficacy and safety, and the pharmacokinetics of solifenacin succinate suspension in patients from 2 to < 18 years of age with NDO. Both are long-term safety and efficacy studies in children and adolescents with NDO. A total of 112 pediatric patients with NDO were enrolled in the Phase 3 studies that were conducted all over the world.

6.1.2 Demographics

The Phase 3 NDO population comprised male and female pediatric patients aged 2 years and older with NDO. A total of 112 patients were screened and 95 were enrolled. Overall, 17 Phase 3 NDO patients were screening or washout failures and 19 patients discontinued during the treatment.

Table 6.3 Summary of Demographics and Baseline Characteristics (SAF); Phase 3 NDO Population

Parameter Category/Statistics	905-CL-074 2 to < 5 Years n = 19	905-CL-047 5 to < 18 Years n = 76	Phase 3 NDO Population 2 to < 18 Years n = 95
Sex, n (%)			
Male	8 (42.1)	37 (48.7)	45 (47.4)
Female	11 (57.9)	39 (51.3)	50 (52.6)
Ethnicity, n (%)			
Hispanic or Latino	1 (5.3)	11 (14.5)	12 (12.6)
Not Hispanic or Latino	18 (94.7)	65 (85.5)	83 (87.4)
Race, n (%)			
White	10 (52.6)	45 (59.2)	55 (57.9)
Black/African American	0	2 (2.6)	2 (2.1)
Asian	9 (47.4)	23 (30.3)	32 (33.7)
Other	0	6 (7.89)	6 (6.3)
Age† (Years)			
Mean (SD)	2.9 (0.7)	10.8 (3.3)	9.2 (4.4)
Median	3.0	11.0	9.0
Min - Max	2 - 4	5 - 17	2 - 17
Weight† (kg)			
Mean (SD)	13.84 (2.65)	38.07 (15.51)	33.22 (16.98)
Median	13.3	34.60	29.00
Min - Max	10.3 – 20.3	15.0 - 83.2	10.3 – 83.2
Height† (cm)			
Mean (SD)	92.32 (6.56)	138.24 (16.31)	129.06 (23.70)
Median	93.30	140.25	130.00
Min - Max	77.5 – 104.0	107.0 – 171.0	77.5 – 171.0
BMI (kg/m^2)			
Mean (SD)	16.19 (2.15)	19.18 (4.69)	18.58 (4.46)
Median	15.283	18.18	17.86
Min - Max	13.3 – 19.3	11.8 - 34.7	4.46 – 34.7

† Age, weight and height at visit 1 (screening). American Indian or Alaska Native and Native Hawaiian or Other Pacific Islander were counted in the "Other" category. 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. BMI: body mass index; ISS: integrated summary of safety; Max: maximum; Min: minimum; n: number of patients; NDO: neurogenic detrusor overactivity; SAF: safety analysis set.
Source: 905-CL-074 Table 12.1.2.1.4; 905-CL-047 Table 12.1.2.1.1.4; ISS Table 13.3.1.1

Reviewer's Comment:

- **The largest enrollments (per Full Analysis Set, FAS) were from the study sites in Poland (n = 31, 31.5%) and the Philippines (n = 18, 24.7%), followed by South Korea (n = 8, 11.0%) and Belgium (n = 7, 9.6%). Only 5 patients from the US were included in the study population (6.8%, FAS). The global program is acceptable because there is no reason to believe that the study population or clinical treatment methods differ by region.**
- **A total of 2 Black/African American patients were enrolled in Study 905-CL-047, consisting of 2.6% population of Study 905-CL-047, and 2.1% of Phase 3 2 to < 18 years NDO population. This is acceptable because there is no reason to believe that the study population, clinical treatment methods, or efficacy or safety of solifenacin differ by race.**

The following tables provide an overview of the past medical history of the NDO study population

Table 6.4 Neurogenic Detrusor Overactivity Diagnosis and History (SAF); Phase 3 NDO Population

Parameter Category/Statistics	905-CL-074 2 Years to < 5 Years	905-CL-047 5 Years to < 18 Years
Duration of NDO Disease (Years) †		
n	19	76
Mean (SD)	2.303 (1.086)	8.13 (4.37)
Median	2.012	8.24
Min - Max	0.18 – 4.51	0.4 – 16.2
Surgery, n (%)		
Closure of Spina Bifida	19 (100)	64 (84.2)
Shunt for Hydrocephalus	9 (47.4)	28 (36.8)

† 905-CL-047: Time until first dose of study drug.
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.
ISE: integrated summary of efficacy; NDO: neurogenic detrusor overactivity; SAF: safety analysis set.
Source: 905-CL-074 Table 12.1.3.2; 904-CL-047 Table 12.1.3.2.1; ISE Table 8.2.2

Table 6.5 Overview of Therapies Current at Screening (FAS); Phase 3 NDO Population

Parameter Category/Statistics	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
Clean Intermittent Catheterization n (%)			
Yes	18 (100)	55 (100)	73 (100)
NDO Non-Medication Therapy n (%)			
Yes	1 (5.6)	0	
Any NDO Medication Therapy n (%)			
Yes	12 (66.7)	53 (96.4)	65 (89)
Alfuzosin	0	1 (1.8)	1 (1.4)
Oxybutynin	4 (22.2)	21 (38.2)	25 (34.2)
Propiverine	2 (11.1)	16 (29.1)	18 (24.7)

Solifenacin	6 (33.3)	16 (29.1)	22 (30.1)
Tolterodine	0	4 (7.3)	4 (5.5)

Patients not receiving a particular therapy at screening/start of washout were not included in the summary of duration of therapy. Patients from study 905-CL-047 that were taking > 1 NDO drug treatment at screening/start of washout were included in summaries for each treatment they received. 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.
FAS: full analysis set; ISE: integrated summary of efficacy; Source: 905-CL-074 Table 12.1.2.2.1; 905-CL-047 Table 12.1.2.2.2; ISE Table 8.2.3

Reviewer's comment: Prior to study enrollment, 100 % of the study population had been practicing clean intermittent catheterization (CIC) technique and the majority of patients (89%) had been under medication therapy.

6.1.3 Subject Disposition

Table 6.6 Disposition Prior to Treatment – All Subjects with Informed Consent (Phase 3 NDO Population

	Solifenacin oral suspension Open-Label (NDO) 52 Weeks (N=112)
Subjects with Informed Consent/Assent	112
Not Treated With Study Drug	17 (15.2%)
Received Study Drug Treatment	95 (84.8%)

Source: Study: YM905 (solifenacin succinate) ISE/SCE Table 8.1.1

Table 6.7 Number of Subjects in Each Analysis Set by Study Protocol: All Subjects with Informed Consent in Phase 3 NDO Population

Study	**905-CL-074**	**905-CL-047**	**Total**
Subjects with Informed Consent	20	92	112
Full Analysis Set [1]	17 (85.0%)	55 (59.8%)	72 (64.3%)
Per Protocol Set [2]	15 (75.0%)	39 (42.4%)	54 (48.2%)

Source: Study: YM905 (solifenacin succinate) ISE/SCE Table 8.1.2 submitted 06/29/2017
[1] The FAS consists of all subjects who took at least one dose of study drug, and provided both valid baseline and at least one postbaseline value for the primary efficacy endpoint (maximum cystometric capacity [MCC]).
[2] The PPS includes all subjects of the FAS who fulfill the protocol in terms of their eligibility, interventions and outcome assessments, and for whom MCC measurements at baseline and Week 24 Visits are observed.

Table 6.8 Study 905-CL-047 Summary of Subject Disposition

	5 to <12 years old n (%)	**12 to <18 years old n (%)**	**Total n (%)**
Screened	47	45	92
Received study drug[1]	42 (89.4%)	34 (75.6%)	76 (82.6%)
Treatment discontinuation[2]	11 (26.2%)	7 (20.6%)	18 (23.7%)
Primary reasons for discontinuation[2]			
Adverse event	2 (4.8%)	2 (5.9%)	4 (5.3%)
Withdrew by subject	2 (4.8%)	2 (5.9%)	4 (5.3%)
Protocol violation	7 (16.7%)	4 (8.8%)	10 (13.2%)

Source: Tables 12.1.1.3.1 and 12.1.1.4.3
[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.

Table 6.9 Study 905-CL-074 Summary of Subject Disposition

	6months to <2 years old n (%)	2 to >5 years old n (%)	Total n (%)
Screened	4	20	24
Received study drug[1]	4 (100%)	19 (95%)	23 (95.8%)
Treatment discontinuation[2]	1(25%)	1 (5.3%)	2 (8.7%)
Primary reasons for discontinuation[2]			
Lack of Efficacy	1 (25%)	0	1 (4.3%)
Protocol violation	0	1 (5.3%)	1(4.3%)

Source: Tables 12.1.1.3.1 and 12.1.1.4.3
[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.

Reviewer's comments: In study 905-CL-047, 55 out of 76 subjects who received treatment were included in FAS. Per IR from the Division, on 4/17/2017, the Sponsor submitted the detailed information on 05/26/2017 to explain why the 21 subjects were excluded from full analysis set. This Reviewer confirmed that the reasons for the 21 subjects being excluded were acceptable.

6.1.4 Analysis of Primary Endpoint(s)

The Phase 3 NDO population comprised male and female pediatric patients aged 2 years and older with NDO. A total of 112 patients were screened and 95 (84.8%) were enrolled and received study drug treatment. Overall, 17 Phase 3 NDO patients were screening or washout failures and 19 patients discontinued during the treatment

Table 6.10 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)

*From submission 06/29/2017. 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. IC: informed consent; FAS: full analysis set; NDO: neurogenic detrusor overactivity; PPS: per protocol set; SAF: safety analysis set. Source: ISE Table 8.1.2; ISS Table 13.1.1.1

The primary efficacy endpoint was the change from baseline in maximum cystometric capacity (MCC) after 24 weeks of treatment.

At week 24, pediatric patients aged 2 years to < 5 years and pediatric patients aged 5 years and older had a statistically significant increase in MCC compared with baseline. The increase in MCC in pediatric patients aged 2 years to < 5 years was numerically smaller than the increase in

pediatric patients aged 5 years and older. According to the Sponsor, this difference was expected due to the different age-related bladder volumes and baseline MCC between the 2 groups.

Table 6.11 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.
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. CI: confidence interval; FAS: full analysis set; ISE: integrated summary of efficacy; n: number of patients; NA: not applicable; NDO: neurogenic detrusor overactivity.
Source: 905-CL-074 Table 12.3.1.2.1; 905-CL-047 Table 12.3.1.2.1; ISE Table 8.3.2.1

Reviewer's comment: The primary endpoint is achieved.

MCC (for last possible titration step only): Secondary Analyses of the Primary Variable

The analysis of MCC expressed as a percentage of EBC or MCV support the results from the primary analysis at 24 weeks on the FAS. Due to the range of values, median data is also presented in addition to the mean data for change from baseline as a percentage of EBC in the following secondary endpoints analyses.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy endpoints based on urodynamics were change from baseline to the assessment for the last possible titration step (e.g., week 12 in protocol version 3.2, week 9 for patients enrolled under protocol version 1.0 or 2.0) and/or week 24 in:

- MCC (for last possible titration step only)
- Bladder compliance (Δvolume/Δdetrusor 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 end of bladder filling
- Detrusor pressure at leakage or end of bladder filling

There was an optional urodynamic investigation at week 52. When this was performed, the urodynamic parameters listed above were recorded and also evaluated as secondary efficacy endpoints.

The secondary efficacy endpoints based on diary were:

- Change from baseline to each postbaseline visit (week 3 up to week 52)
  - 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

- Change from baseline to visit 8 (week 24) and visit 10 (week 52) in:
  - Quality of life [QoL] (PinQ questionnaire score)

Other efficacy data were also collected in the study for comparisons with historical control data (published results from other studies).

Bladder Compliance (Δvolume/Δdetrusor pressure)

At week 24, there was an increase in bladder compliance (mean [SD]: 8.3 [25.0] mL/cmH_2O) compared with baseline (95% CI: 2.2, 14.4) in the Phase 3 NDO population. At week 24, pediatric patients aged 2 years to < 5 years and pediatric patients aged ≥ 5 years had an increase in bladder compliance compared with baseline. Of note, the pediatric patients aged 2 years to < 5 years had a lower baseline bladder compliance compared with those aged ≥ 5 years.

Table 6.12 Change from Baseline to Week 24 in Bladder Compliance (BC) (mL/cmH_2O) (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	54	50	71	67
Mean (SD)	5.7 (4.9)	11.5 (11.0)	14.6 (36.4)	24.4 (39.9)	12.5 (32.0)	21.1 (35.2)
Change from baseline						
n†	NA	17	NA	50	NA	67
Mean (SD)		5.8 (7.3)		9.1 (28.6)		8.3 (25.0)
95% CI		2.1, 9.6		1.0, 17.2		2.2, 14.4
P-value‡		0.004		0.029		0.008

† 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.
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.
CI: confidence interval; FAS: full analysis set; ISE: integrated summary of efficacy; n: number of patients;
NA: not applicable; NDO: neurogenic detrusor overactivity

Source: 905-CL-074 Table 12.3.2.2; 905-CL-047 Table 12.3.3.2; ISE Tables 8.4.1.2 and 8.5.2.1.2

Reviewer's comment: Bladder compliance was significantly improved from baseline in both phase 3 studies.

Bladder Volume Until First Detrusor Contraction > 15 cmH_2O as a Percentage of Expected Bladder Capacity

Table 6.13 Change from Baseline in Bladder Volume (mL) Until First Detrusor Contraction> 15 cmH_2O as a Percentage of Expected Bladder Capacity (mL) (FAS)

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	54	50	71	67
Median	37.3	88.3	28.3	58.3	30.0	61.9
Change from baseline						
n†	NA	17	NA	50	NA	67
Median		53.3		23.1		31.5
P-value‡		<0.001		<0.001		
Patients who had a detrusor contraction at Week 24						
n (%)§	8 (47.1%)	8 (47.1%)	25 (45.5%)	25 (45.5%)		
Median	15.8	38.2	27.7	45.6		
Change from baseline						
n§		8		25		NA
Median		31.1		13.3		NA
P-value‡		0.195		0.001		NA

Source: Statistical Reviewer's analysis. Table 12.3.4.1 and Table 12.3.4.2 in Studies 047 &074, Table 8.4.3.1 of ISE in 6/29/2017 submission; FAS: full analysis set; *Primary analysis; NA Not applicable;
† n is the number of patients with a nonmissing change from baseline at that week.
‡ From a Wilcoxon Signed Rank testing the null hypothesis that the median at week 24 was equal to baseline median.
§ n is the number of patients who had a Detrusor contraction at Week 24;
For patients without detrusor contraction > 15 cmH_2O, the MCC expressed as % of EBC was imputed at baseline/week 24, respectively, and was used as a censored value (open circles).
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. %: percentage; EBC: expected bladder capacity; FAS: full analysis set; ISE: integrated summary of efficacy; MCC: maximum cystometric capacity; NDO: neurogenic detrusor overactivity.

Reviewer's comment: Bladder volume until first detrusor contraction (>15 cmH_20) was significantly improved from baseline in both phase 3 studies.

Number of overactive detrusor contractions (> 15 cmH_2O) until leakage or end of bladder filling

At week 24, there was a decrease in the number of overactive detrusor contractions > 15 cmH_2O until end of bladder filling (mean [SD]: −3.5 [6.7]) compared with baseline (95% CI: −5.1, −1.9) in the Phase 3 NDO population. At week 24, both pediatric patients aged 2 years to < 5 years and pediatric patients aged ≥5 years had a decrease in the number of overactive detrusor contractions > 15 cmH_2O compared with baseline.

Table 6.14 Change from Baseline to Week 24 in Number of Overactive Detrusor Contractions > 15 cmH_2O Until End of Bladder Filling (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	54	50	71	67
Mean (SD)	9.9 (11.6)	2.9 (3.8)	3.9 (4.7)	1.6 (2.2)	5.3 (7.4)	1.9 (2.7)
Change from baseline						
n†	NA	17	NA	50	NA	67
Mean (SD)		−7.0 (9.3)		−2.3 (5.1)		−3.5 (6.7)
95% CI		−11.8, −2.2		−3.7, −0.8		−5.1, −1.9
P-value‡		0.007		0.003		<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.
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. CI: confidence interval; FAS: full analysis set; ISE: integrated summary of efficacy; n: number of patients; NA: not applicable; NDO: neurogenic detrusor overactivity.
Source: 905-CL-074 Table 12.3.8.2; 905-CL-047 Table 12.3.7.2; ISE Table 8.4.5.2

Maximum Catheterized Volume (MCV) in a Day

At week 24, there was an increase in MCV in a day (mean [SD]: 62.01 [81.29] mL) compared with baseline (95% CI: 42.18, 81.84) in the Phase 3 NDO population. The change in MCV is comparable to that observed for the primary endpoint (MCC). At week 24, both pediatric patients aged 2 years to < 5 years and pediatric patients aged ≥ 5 years had an increase in MCV per day compared with baseline.

Table 6.15 Change from Baseline to Week 24 in Maximum Catheterized Volume per Day (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	15	17	54	52	70	70
Mean (SD)	76.7 (43.0)	125.9 (47.5)	203.5 (92.7)	272.6 (110.8)	173.9 (100.00)	234.0 (118.3)
Change from baseline						
n†	NA	15	NA	51	NA	66
Mean (SD)		45.3 (54.7)		67.5 (88.1)		62.4 (81.8)
95% CI		15.0, 75.6		42.7, 92.2		42.2, 81.8
P-value‡		0.006		<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.
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. CI: confidence interval; FAS: full analysis set; ISE: integrated summary of efficacy; n: number of patients; NA: not applicable; NDO: neurogenic detrusor overactivity.
Source: 905-CL-074 Table 12.3.12.1.2; 905-CL-047 Table 12.3.710.1.2; ISE Table 8.4.7.1.2 in 6/29/submission

Incontinence

Although Studies 905-CL-074 and 905-CL-047 measured incontinence using different variables, the variables are related and can therefore be compared but not pooled.

At week 24, both pediatric patients aged 2 years to < 5 years and pediatric patients aged ≥ 5 years had a decrease in incontinence compared with baseline.

Table 6.16 Change from Baseline to Week 24 in Incontinence (FAS); Studies 905-CL-074 and 905-CL-047

Statistic	905-CL-074 2 Years to < 5 Years		905-CL-047 5 Years to < 18 Years	
	Mean number of periods between CICs with incontinence per 24 hours		Mean number of periods between CICs with incontinence per 24 hours	
	Baseline	Week 24	**Baseline**	**Week 24**
N	14	15	54	52
Mean (SD)	3.9 (0.8)	2.2 (1.4)	3.4 (2.9)	1.8 (1.9)
Change from baseline				
n†	NA	14	NA	51
Mean (SD)		–1.6 (1.2)		–1.6 (2.0)
95% CI		–2.3, –0.9		–2.2, –1.0
P-value‡		<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.
CI: confidence interval; CIC: clean intermittent catheterization; FAS: full analysis set; n: number of patients; NA: not applicable.
Source: Statistical Reviewer's analysis; 905-CL-047 Table 12.3.12.2; 905-CL-074 Table 12.3.14.1 and Table 12.3.14.2 in 6/29/2017 submission.

Comparison of Additional Secondary Efficacy Endpoints

After 24 weeks of treatment with solifenacin oral suspension, there was an increase from baseline in the following additional efficacy endpoints:

- Bladder volume at 30 cmH_2O detrusor pressure (mean±SD: 62.4±80.9 mL) in the Phase 3 NDO population (95% CI: 23.4, 101.4). At week 24, pediatric patients aged **≥ 5 years** had an **increase** in bladder volume at 30 cmH_2O detrusor pressure compared with baseline; there was no difference from baseline in this variable in pediatric patients aged 2 years to < 5 years.
- Average catheterized volume per catheterization (mean±SD: 43.82±45.28 mL) in the Phase 3 NDO population (95% CI: 32.77, 54.86). At week 24, pediatric patients aged **2 years to < 5 years** and pediatric patients **aged ≥ 5 years** had **increases** in this variable compared with baseline.
- Average first morning catheterized volume (mean±SD: 43.10±66.74 mL) in the Phase 3 NDO population (95% CI: 26.83, 59.38). At week 24, pediatric patients aged **2 years to < 5 years** and pediatric patients aged ≥ **5 years** had **increases** in this variable compared with baseline.

- Detrusor pressure at end of bladder filling: After 24 weeks of treatment with solifenacin oral suspension, there was a decrease from baseline in detrusor pressure at end of bladder filling (mean±SD: −7.5±29.7 cmH_2O) in the Phase 3 NDO population (95% CI: −14.9, 0.0). At week 24, there was **no relevant difference** from baseline in this variable in pediatric patients aged 2 years to < 5 years and pediatric patients aged ≥ 5 years and older.

Table 6.17 Decrease from Baseline in Detrusor Pressure at End of Bladder Filling

Detrusor pressure at the end of bladder filling	Change from Baseline (cmH_2O)							
	Week 24				Week 24 LOCF			
	n	mean±SD	95% CI	p	n	mean±SD	95% CI	p
074 2 to < 5 years)	17	−2.6±14.7	−10.2, 5.0	0.475	18	−2.4±14.3	−9.5, 4.8	0.495
047 5 to < 18 years)	46	−9.2±33.6	−19.2, 0.7	0.068	51	−8.2±32.2	−17.2, 0.9	0.075

Source: Reviewer's own table.

6.1.6 Other Endpoints

Results for all efficacy endpoints have been shown. No additional endpoints were designed to be evaluated.

6.1.7 Subpopulations

Efficacy: Gender Subgroup Analysis:

Table 6.18 Phase 3 NDO studies: Change from Baseline in Maximum Cystometric Capacity (mL) by Gender (FAS)

Statistics	Study 905-CL-047				Study 905-CL-074			
	Male (n=28)		Female (n=27)		Male (n=8)		Female (n=13)	
	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24
n	28	24	27	25	8	8	13	13
Mean (SD)	226.4 (134.5)	287.7 (133.8)	220.8 (133.7)	270.8 (133.8)	157 (92.0)	212 (104)	288 (136)	344 (114)
Change from baseline								
n		24		25		8		13
Mean (SD)		56.3 (102.7)		58.1 (114.3)		25.6 (34.8)		44.1 (36.0)

Age Subgroup Analysis:

Table 6.19 Phase 3 NDO studies: Change from Baseline in Maximum Cystometric Capacity (mL) by Age (FAS)

Statistics	Study 905-CL-047				Study 905-CL-074			
	5 to < 12 years		12 to < 18 years		6 months to < 2 years		2 to < 5 years	
	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24
n	27	24	28	25	4	4	17	17

Mean (SD)	157 (92.0)	212 (104)	288 (136)	344 (114)	69.0 (22.2)	98.3 (44.4)	97.8 (39.5)	136.7 (36.8)
Change from baseline								
n		24		25		4		17
Mean (SD)		59.9 (93.0)		56.4 (122)		29.3 (41.7)		38.9 (35.5)

Racial Subgroup Analysis:
Based on all pediatric subjects aged > 2 years who received at least 1 dose of study drug and who provided both a valid baseline and at least one valid postbaseline value for the primary efficacy endpoint maximum cystometric capacity (MCC) during the treatment period of either of the 2 Phase 3 studies for NDO patients:

Table 6.20 Results of Primary Analysis of Change from Baseline to Week 24 in Maximum Cystometric Capacity (MCC, mL) by Racial Subgroup

Statistic	Racial Subgroup							
	White N = 38		Asian N = 27		Black/African American N = 2		Other N = 6	
	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24
n	37	32	27	27	2	2	6	5
Mean (SD)	209.0 (135.5)	232.5 (115.0)	157.1 (110.3)	226.8 (136.7)	299.5 (326.0)	386.0 (65.1)	232.0 (70.7)	333.0 (120.0)
Change from baseline								
n		32		27		2		5
Mean (SD)		29.9 (101.9)		69.7 (74.9)		86.5 (260.9)		90.6 (52.3)

Source: Attachment 1, Table 8.5.1.9

Reviewer's comment: In comparison, MCC change from the baseline in White NDO children seemed less than Asian pediatric patients, (69.7±74.9 vs. 29.9±101.9), while the patient numbers in the group of Black/African American and group of Other were small. There is no known explanation for the observed differences.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The recommended dose of solifenacin oral suspension is determined based on patient weight. Treatment should be initiated at the recommended starting dose (PED5). Thereafter, the dose may be increased to the lowest effective dose. The maximum dose should not be exceeded (equivalent to 10 mg in adults [PED10]). The doses according to the patient's body weight are found in Table 12 Solifenacin Oral Suspension Recommended Doses by Weight Range for Pediatric Patients with NDO Aged 2 Years to Less than 18 Years.

According to study design for both pediatric phase 3 studies, each patient's dose of solifenacin oral suspension was up- or down-titrated to a minimum of PED2.5 and a maximum of PED10 for up to 12 weeks to determine the optimal dose. A minimum 40-week fixed-dose assessment period followed in which all patients were treated with their optimized dose.

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 PED 10:

At Week 12	PED 7.5	PED 10
Study 074 (2 to < 5 years)	6/18 patients	11/18 patients
Study 047 (5 to < 18 years)	11/61 patients	44/61 patients

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).

Efficacy was sustained over the 52 weeks of treatment and there was no apparent difference in optimal dose between the different age groups.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Based on the long-term data (week 52) for the Phase 3 NDO population that received solifenacin oral suspension for 52 weeks, the persistency of efficacy and tolerance are analyzed below. However, the size of the population for which measurements were available at week 52 was smaller (n = 54) than that at week 24 (n = 66).

Primary Efficacy Endpoint

Table 6.21 Change from Baseline in Maximum Cystometric Capacity (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	Week 52	Baseline	Week 24	Week 52	Baseline	Week 24	Week 52
Bladder Compliance (mL/cmH_2O)									
n	17	17	12	54	50	42	71	67	54
Mean (SD)	97.8 (39.5)	136.7 (36.8)	151.3 (48.3)	223.7 (132.9)	279.1 (126.8)	268.1 (104.1)	194.0 (129.1)	242.4 (127.1)	242.2 (106.2)
Change from baseline									
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)

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.
FAS: full analysis set; ISE: integrated summary efficacy; n: number of patients; NA: not applicable; NDO: neurogenic detrusor overactivity
Source: 905-CL-074 Table 12.3.1.1.1; 905-CL-047 Table 12.3.1.1.1; ISE Table 8.3.1.1

Secondary Efficacy Endpoints

Table 6.22 Change from Baseline in Secondary Variables (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	Week 52	Baseline	Week 24	Week 52	Baseline	Week 24	Week 52
Bladder Compliance (mL/cmH_2O)									

n	17	17	12	54	50	42	71	67	54
Mean (SD)	5.68 (4.93)	11.51 (10.99)	11.36 (7.68)	14.59 (36.39)	24.40 (39.87)	17.63 (21.99)	12.46 (31.98)	31.13 (35.24)	16.24 (19.83)
Change from baseline									
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 cmH_2O Until End of Bladder Filling									
n	17	17	12	54	50	42	71	67	54
Mean (SD)	9.9 (11.6)	2.9 (3.8)	2.8 (5.2)	3.9 (4.7)	1.6 (2.2)	1.0 (2.0)	5.3 (7.4)	1.9 (2.7)	1.4 (3.0)
Change from baseline									
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)	73.97 (42.92)	122.67 (48.02)	120.91 (30.05)	203.52 (92.68)	272.60 (110.76)	263.58 (101.29)	173.91 (100.00)	234.04 (118.29)	227.38 (108.39)
Change from baseline									
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. FAS: full analysis set; ISE: integrated summary of efficacy; n: number of patients; NA: not applicable; NDO: neurogenic detrusor overactivity; W: week. Source: 905-CL-074 Tables 12.3.2.1, 12.3.8.1 and 12.3.12.1.1; 905-CL-047 Tables 12.3.3.1, 12.3.7.1, and 12.3.10.1.1; ISE Tables 8.4.1.1, 8.4.5.1 and 8.4.7.1.1

Reviewer's comment: The efficacy of solifenacin suspension in the treatment of pediatric patients aged 2 to < 18 years old has been demonstrated through achievement of both the primary endpoint and secondary efficacy endpoints

6.1.10 Additional Efficacy Issues/Analyses

There are no additional efficacy issues/analyses.

7 Review of Safety

Safety Summary

There was sufficient exposure to solifenacin oral suspension to conduct a safety assessment. 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.

7.1 Methods

The focus of this safety review was the two Phase 3 studies in NDO patients (905-CL047 and 905-CL-074), and two Phase 3 studies in idiopathic OAB patients (905-CL-076 and 905-CL-077). Results from other Phase 1 studies of clinical pharmacokinetics (905-CL-079 in NDO patients, and 905-CL-075 in OAB patients) were also reviewed for safety.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The focus of this safety review was the two Phase 3 studies in NDO patients (905-CL-047 and 905-CL-074), and two Phase 3 studies in OAB patients (905-CL-076 and 905-CL-077), as well as the other Phase 1studies of clinical pharmacokinetics (905-CL-079 in NDO patients, and 905-CL-075 in OAB patients).

7.1.2 Categorization of Adverse Events

Adverse events were categorized using standard defined MedDRA terminology.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data from Phase 3 studies in patients with either NDO or idiopathic OAB as well as from Phase 1 clinical pharmacology studies were pooled for analysis. The Phase 3 trials were similarly designed so that pooling of safety data is appropriate and brings additional power to the analysis.

	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

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

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).

In total, 109 pediatric patients aged ≥ 2 years with NDO were treated with solifenacin oral suspension in the pediatric NDO development program (phase 1 and phase 3 studies).

The duration of treatment for the majority of Phase 3 NDO patients (65 [68.4%]) was ≥ 364 days and was similar across the relevant age group populations from both studies.

Table 7.1 Summary of Study Drug Compliance and Exposure over the Whole Treatment Period (SAF); Phase 3 NDO Population

Category Statistics	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
Duration† (Days)			
n	19	76	95
Mean (SD)	350.3 (84.6)	289.2 (143.6)	301.4 (135.8)
Median	370.0	364.0	365.0
Min - Max	2 – 388	1 – 413	1 – 413
n (%)			
< 21 days	ND	ND	11 (11.6)
≥ 21 to < 42 days			3 (3.2)
≥ 42 to < 63 days			1 (1.1)
≥62 to < 84 days			1 (1.1)
> 84 days	1 (5.3)	15 (19.7)	ND
≥84 to < 168 days	0	3 (3.9)	3 (3.2)
≥ 168 to < 252 days	0	0	0
≥ 252 to < 364 days	2 (10.5)	9 (11.8)	11 (11.6)
≥ 364 days	16 (84.2)	49 (64.5)	65 (68.4)
Treatment Compliance‡ (%)			
n	19	76	95
Mean (SD)	112.35 (35.27)	103.37 (23.67)	105.2 (26.4)
Median	106.90	99.80	102.80
Min - Max	87.8 – 256.2	53.1 - 214.8	53 - 256
n (%)			
< 70%	0	1 (1.3)	1 (1.1)
≥ 70% to < 80%	0	4 (5.3)	4 (4.2)
≥ 80% to < 120%	18 (94.7)	64 (84.2)	82 (86.3)
≥ 120% to < 130%	0	1 (1.3)	1 (1.1)
≥ 130%	1 (5.3)	6 (7.9)	7 (7.4)

† Duration is defined as (date of last dose – date of first dose + 1).
‡ Compliance = 100% * weight of suspension consumed/total weight of suspension planned or dispensed.
In case a patient's dose was titrated, the compliance was estimated according to assumptions described in the [ISS SAP Section 6.5.4]. For some patients this resulted in over- and underestimation of the compliance for that period. The overall compliance calculation has not been affected.
ISS: integrated summary of safety; Max: maximum; Min: minimum; n: number of patients; ND: not done;
NDO: neurogenic detrusor overactivity; SAF: safety analysis set.
Source: 905-CL-047 Table 12.2.1.4; 905-CL-074 Table 12.2.1.4; ISS Table 13.2.1.1

The overall extent of exposure for the individual phase 3 NDO studies, 905-CL-047 and 905-CL-074, is presented by dose and treatment duration in Table 7.2 and Table 7.3. In Study 905-CL-047 and Study 905-CL-074, the majority of patients' doses were up-titrated to pediatric equivalent dose (PED) 7.5 or PED10 during the treatment period. The majority of doses were up titrated by week 12 (905-CL-047) or by week 9 (905-CL-074) (Table 7.2 and Table 7.3). The optimized dose for most patients in all age groups was PED10.

Table 7.2 Summary of Study Drug Dosing During the Treatment Period (SAF); Study 905-CL-047

Period	Dose Group	Number of Patients (%)		
		Children (Aged 5 Years to < 12 Years) n = 42	Adolescents (Aged 12 Years to < 18 Years) n = 34	All Patients (Aged 5 Years to < 18 Years) n = 76
Baseline	PED5	42 (100)	34 (100)	76 (100)
Week 3	PED2.5	0	0	0
	PED5	8 (19.0)	8 (23.5)	16 (21.1)
	PED7.5	27 (64.3)	23 (67.6)	50 (65.8)
	PED10	0	0	0
Week 6	PED2.5	0	1 (2.9)	1 (1.3)
	PED5	6 (14.3)	4 (11.8)	10 (13.2)
	PED7.5	5 (11.9)	7 (20.6)	12 (15.8)
	PED10	22 (52.4)	18 (52.9)	40 (52.6)
Week 9	PED2.5	0	1 (2.9)	1 (1.3)
	PED5	5 (11.9)	4 (11.8)	9 (11.8)
	PED7.5	5 (11.9)	4 (11.8)	9 (11.8)
	PED10	23 (54.8)	21 (61.8)	44 (57.9)
Week 12	PED2.5	0	1 (2.9)	1 (1.3)
	PED5	3 (7.1)	2 (5.9)	5 (6.6)
	PED7.5	6 (14.3)	5 (14.7)	11 (14.5)
	PED10	23 (54.8)	21 (61.8)	44 (57.9)
Week 24	PED2.5	0	1 (2.9)	1 (1.3)
	PED5	3 (7.1)	2 (5.9)	5 (6.6)
	PED7.5	6 (14.3)	5 (14.7)	11 (14.5)
	PED10	23 (54.8)	19 (55.9)	42 (55.3)
Week 52	PED2.5	0	1 (2.9)	1 (1.3)
	PED5	3 (7.1)	2 (5.9)	5 (6.6)
	PED7.5	6 (14.3)	5 (14.7)	11 (14.5)
	PED10	22 (52.4)	19 (55.9)	41 (53.9)

n: number of patients; PED: pediatric oral suspension equivalent dose (mg); SAF: safety analysis set.

Source: 905-CL-047 Table 12.2.1.1

Table 7.3 Summary of Study Drug Dosing During the Treatment Period (SAF); Study 905-CL-074

Period	Dose Group	Number of Patients (%)		
		Aged 6 Months to < 2 Years) n = 4	Aged 2 Years to < 5 Years n = 19	All Patients (Aged 6 Months to < 5 Years) n = 23
Baseline	PED 2.5	4 (100)		4 (17.4)
	PED 5		19 (100)	19 (82.6)
Week 3	PED2.5	0	0	0
	PED5	4 (100.0)	4 (21.1)	8 (34.8)
	PED7.5	0	14 (73.7)	14 (60.9)
	PED10	0	0	0
Week 6	PED2.5	0	0	0
	PED5	1 (25.0)	3 (15.8)	4 (17.4)
	PED7.5	3 (75.0)	7 (36.8)	10 (43.5)
	PED10	0	8 (42.1)	8 (34.8)
Week 9	PED2.5	0	0	0
	PED5	0	1 (5.3)	1 (4.3)
	PED7.5	1 (25.0)	6 (31.6)	7 (30.4)
	PED10	3 (75.0)	11 (57.9)	14 (60.9)
Week 12	PED2.5	0	0	0
	PED5	0	1 (5.3)	1 (4.3)
	PED7.5	1 (25.0)	6 (31.6)	7 (30.4)
	PED10	3 (75.0)	11 (57.9)	14 (60.9)
Week 24	PED2.5	0	0	0
	PED5	0	1 (5.3)	1 (4.3)
	PED7.5	1 (25.0)	5 (26.3)	6 (26.1)
	PED10	2 (50.0)	12 (63.2)	14 (60.9)
Week 52	PED2.5	0	0	0
	PED5	0	1 (5.3)	1 (4.3)
	PED7.5	1 (25.0)	5 (26.3)	6 (26.1)
	PED10	2 (50.0)	12 (63.2)	14 (60.9)

n: number of patients; PED: pediatric oral suspension equivalent dose (mg); SAF: safety analysis set.
Source: 905-CL-074 Table 12.2.1.1

There is also supportive exposure data from Phase 3 studies (905-CL-076 and 905-CL-077) in pediatric population with idiopathic OAB. When combining the subpopulations with NDO and OAB (Table 7.4), 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), the daily dose used was 5.1±1.8 mg (Mean±SD).

Table 7.4 Study Drug Exposure, 52 Weeks of Treatment (SAF); Phase 3 Population

Category Statistics	ISS Pool / Study			
	Phase 3 NDO Population	905-CL-076 / 905-CL-077		Phase 3 Population
	Solifenacin Open-label (NDO)	Solifenacin Double-blind + Solifenacin Open-label (OAB)	Placebo Double-blind + Solifenacin Open-label (OAB)	Total† (OAB and NDO)
Duration (Days) ‡				
n	95	73	75	243
Mean (SD)	301.4 (135.8)	325.3 (80.6)	337.2 (68.3)	319.6 (103.7)
Median	365.0	364.0	364.0	364.0
Min - Max	1 - 413	107 - 378	91 - 391	1 - 413
n (%)				
< 21	11 (11.6)	0	0	11 (4.5)
≥ 21 to < 42 days	3 (3.2)	0	0	3 (1.2)
≥ 42 to < 63 days	1 (1.1)	0	0	1 (0.4)
≥ 63 to < 84 days	1 (1.1)	0	0	1 (0.4)
≥ 84 to < 168 days	3 (3.2)	6 (8.2)	5 (6.7)	14 (5.7)
≥ 168 to < 252	0	8 (11.0)	3 (4.0)	11 (4.5)
≥ 252 to < 364	11 (11.6)	13 (17.8)	24 (32.0)	48 (19.8)
≥ 364 days	65 (68.4)	46 (63.0)	43 (57.3)	154 (63.4)
Total Solifenacin Used (mg)				
n	95	72	75	242
Mean (SD)	1560.4 (967.3)	1711.3 (669.2)	1288.6 (574.6)	1521.1 (791.5)
Median	1628.9	1735.9	1290.5	1486.4
Min – Max	3 – 3812	341 – 3166	18 – 2820	3 – 3812
Average Daily Dose (mg)				
n	95	72	75	242
Mean (SD)	5.0 (1.9)	5.2 (1.5)	5.1 (1.8)	5.1 (1.8)
Median	4.9	5.1	4.9	5.0
Min – Max	2 – 10	2 – 9	2 – 10	2 – 10

† The Total (OAB and NDO) 52 weeks treatment group consists of results from all patients in the phase 3 population, including placebo-treated periods.
‡ Duration was defined as (the date of last dosing) - (the date of first dosing) + 1.
ISS: integrated summary of safety; Max: maximum; Min: minimum; n: number of patients; NDO: neurogenic detrusor overactivity; OAB: overactive bladder; SAF: safety analysis set.
Source: ISS Table 13.2.1.2

Reviewer's comment: Acrossed the Phase 3 studies, in both NDO and idiopathic OAB, the average daily dose level is similar.

Demographic and Other Characteristics of Study Population

Table 7.5 shows the demographic characteristics in the target indicated population, Phase 3 NDO patients, combined with the Phase 3 idiopathic OAB population. The patients were

predominantly White (72.0%), with some Asian (17.7%); the (mean±SD) age 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.

Table 7.5 Demographic Characteristics (Safety Analysis Set): Phase 3 Population

Parameter Category/Statistics	52 Weeks of Exposure			
	Solifenacin Open-Label (NDO) 52 Weeks (N = 95)	Solifenacin Double-Blind Solifenacin Open-Label (OAB) (N = 73)	Placebo DB + Solifenacin Open-Label (OAB) (N = 75)	Total (NDO and OAB) 52 Weeks (N = 243)
Sex, n (%)				
Male	45 (47.4)	27 (37.0)	35 (46.7)	107 (44.0)
Female	50 (52.6)	46 (63.0)	40 (53.3)	136 (56.0)
Ethnicity, n (%)				
Hispanic or Latino	12 (12.6)	8 (11.0)	9 (12.0)	29 (11.9)
Not Hispanic or Latino	83 (87.4)	65 (89.0)	66 (88.0)	214 (88.1)
Race, n (%)				
White	55 (57.9)	60 (82.2)	60 (80.0)	175 (72.0)
Black/African American	2 (2.1)	4 (5.5)	3 (4.0)	9 (3.7)
Asian	32 (33.7)	6 (8.2)	5 (6.7)	43 (17.7)
Other	6 (6.3)	3 (4.1)	7 (9.3)	16 (6.6)
Age† (Years)				
Mean (SD)	9.2 (4.4)	9.0 (3.3)	8.5 (3.1)	9.0 (3.7)
Median	9.0	8.0	8.0	8.0
Min - Max	2 – 17	5 – 17	5 – 17	2 – 17
Age Group				
≥ 2 to < 5	19 (20.0)	0	0	19 (7.8)
≥ 5 to < 12	42 (44.2)	58 (79.5)	61 (81.3)	161 (66.3)
≥ 12 to < 18	34 (35.8)	15 (20.5)	14 (18.7)	63 (25.9)
Weight† (kg)				
Mean (SD)	33.22 (16.98)	35.33 (15.33)	31.85 (13.90)	33.43 (15.98)
Median	13.329.00	29.90	26.50	28.50
Min - Max	10.3 – 83.2	17.0 – 80.8	15.8 – 73.5	10.3 – 83.2
Height† (cm)				
Mean (SD)	129.06 (23.7)	135.49 (16.35)	132.91 (16.01)	132.18 (19.58)
Median	130.0	131.0	129.0	130.0
Min - Max	77.5 – 171.0	107.0 – 175.0	108.0 – 168.0	77.5 – 175.0
BMI (kg/m^2)				
Mean (SD)	18.58 (4.46)	18.41 (3.79)	17.20 (3.41)	18.10 (3.99)
Median	17.86	17.10	16.28	16.81
Min - Max	11.8 – 34.7	12.7 – 29.7	12.8 – 28.4	11.8 – 34.7

Studies Included: 905-CL-076, 905-CL-077, 905-CL-047 and 905-CL-074.

The Total (NDO and OAB) 52 Weeks treatment group consists of results from all patients in the Phase 3 population, including Placebo-treated periods.

Reviewer's comment: There was a higher percentage of Asian patients (33.7%) in the phase 3 NDO population compared to in the idiopathic OAB population (10%).

7.2.2 Explorations for Dose Response

The design of the Phase 3 studies included multiple dose titrations either to increase or decrease dose to achieve the best dose response and optimal benefit/risk ratio.

7.2.3 Special Animal and/or In Vitro Testing

A juvenile mouse study was conducted prior to initiating trials in pediatric NDO patients. No clinically relevant findings were reported. The reader is referred to the Pharmcology/Toxicology review. No special animal and/or in vitro testing were conducted during the rest of the clinical development.

7.2.4 Routine Clinical Testing

Details of the routine clinical testing, including various clinical laboratory tests, are reviewed in the related sections of this review, and this testing was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

During the original solifenacin clinical development, the metabolism, clearance, and drug-drug interactions were extensively studied and the reader is referred to these reviews of the original NDA 21518.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Potential adverse reactions for drugs in the antimuscarinic class are well known and no exceptions have been observed for solifenacin. The adverse reaction profile for solifenacin is consistent with all marketed antimuscarinic drugs.

7.3 Major Safety Results

Phase 1 Study in Patients with NDO
Of the 14 pediatric patients (aged 5 years and older; 7 children and 7 adolescents) enrolled and treated in Study 905-CL-079, 2 (28.6%) experienced at least 1 TEAE. Overall, 5 TEAEs were reported. There were no serious TEAEs. Permanent discontinuation of study drug due to AEs did not apply as this was a single-dose study.

Phase 3 Studies in Patients with NDO

During 52 weeks of treatment, 61 of 95 (64.2%) Phase 3 NDO patients reported TEAEs [Table 7.6]. 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 drug-related. The proportions of patients reporting TEAEs was similar in pediatric patients aged 2 years to < 5 years and pediatric patients aged 5 years and older [Table 7.6].

In Study 905-CL-047, TEAEs were reported by 51 (67.1%) pediatric patients aged 5 years and older (28 children and 23 adolescents). Drug-related TEAEs were reported in 15 (19.7%) patients (9 children and 6 adolescents). Serious TEAEs were reported in 7 (9.2%) patients (2 children and 5 adolescents).

In study 905-CL-074 (in pediatric patients aged 2 years to < 5 years), fewer TEAEs (52.6%), drug-related TEAEs (15.8%) and serious TEAEs (1 patient; 5.3%) were reported. No discontinuations were reported in this age group.

Table 7.6 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.
ISS: integrated summary of safety; n: number of patients; NDO: neurogenic detrusor overactivity;
TEAE: treatment-emergent adverse event; SAF: safety analysis set.
Source: 905-CL-074 Table 12.6.1.1; 905-CL-047 Table 12.6.1.1, ISS Table 13.4.1.1

Reviewer's comment: The overall TEAE incidences and severities do not indicate a clinically relevant difference between the age groups.

Common Adverse Events

The most frequently reported TEAEs in Phase 3 NDO patients over the course of the studies were urinary tract infection (UTI) (30.5%; reported similarly across the age groups), constipation (7.4%), nasopharyngitis (6.3%), and upper respiratory tract infection (6.3%) [Table 7.7;].

The UTI-related preferred terms (PTs) Escherichia UTI, UTI, UTI bacterial, UTI enterococcal and UTI pseudomonal were analyzed both grouped and separately in the ISS. The most frequently reported UTI PTs in the Phase 3 NDO population were UTI bacterial (17.9%) and UTI (15.8%).

Nasopharyngitis was reported by a larger percentage of pediatric patients aged 2 years to < 5 years in Study 905-CL-074; however, the larger percentage should be interpreted with caution due to the small sample size of this population.

The most frequently reported TEAEs in Phase 3 NDO patients over the course of the studies were urinary tract infection (UTI) (30.5%; reported similarly across the age groups), constipation (7.4%), nasopharyngitis (6.3%) and upper respiratory tract infection (6.3%).

Table 7.7 Incidence (> 5% in Phase 3 NDO Patients) of TEAEs (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 TEAEs	**10 (52.6)**	**51 (67.1)**	**61 (64.2)**
Gastrointestinal Disorders			
Constipation	1 (5.3)	6 (7.9)	7 (7.4)
Infections and Infestations			
Urinary Tract Infection†	5 (26.3)	24 (31.6)	29 (30.5)
Nasopharyngitis	3 (15.8)	4 (5.3)	6 (6.3)
Upper Respiratory Tract Infection	2 (10.5)	4 (5.3)	6 (6.3)
Respiratory, Thoracic and Mediastinal Disorders			
Cough	1 (5.3)	4 (5.3)	5 (5.3)
Skin and Subcutaneous Tissue Disorders			
Decubitus ulcer	1 (5.3)	4 (5.3)	5 (5.3)

† In a post hoc analysis [905-CL-074 Table 12.6.1.2.1], 6 (26.1%) patients experienced UTIs.
TEAEs experienced at ≥ 5% in the total group include SAEs.
TEAEs were coded using MedDRA v19.0 for the ISS population (Phase 3 NDO) and using earlier versions (v13.0 and v16.0) for the individual studies. The number of patients experiencing TEAE of nasopharyngitis do not reconcile across the groups presented in this table due to the recoding. ISS: integrated summary of safety; NDO: neurogenic detrusor overactivity; SAF: safety analysis set. Source: 905-CL-074 Table 12.6.1.2.1 and 12.6.1.10.2; 905-CL-047 Table12.6.1.2.1 and 12.6.1.10.2; ISS Table 13.4.11.1

Drug-Related Adverse Events

The majority (45.3%) of TEAEs reported were not related (based on investigator judgment) to the study drug. Overall, 18 of 95 (18.9%) Phase 3 NDO patients reported drug-related TEAEs (Table 7.8), 3 of 19 (15.8%) pediatric patients aged 2 years to < 5 years in Study 905-CL-074, and 15 of 76 (19.7%) pediatric patients aged 5 years and older in Study 905-CL-047. All drug-related TEAEs were mild or moderate in intensity. The most frequently reported drug-related TEAEs in the Phase 3 NDO population during the first 12 weeks of treatment and over the course of the studies were constipation (1.1%, during 12 weeks and 7.4% during 52 weeks), dry mouth (2.1 % during 12 weeks and 3.2% during 52 weeks) and ECG QT prolonged (3.2%; 3

cases all experienced in the first 12 weeks and leading to discontinuation as per protocol). In regard to "ECG QT prolonged", the reader is referred to the Reviewer's comments that follow herein.

Table 7.8 Incidence of Drug-related TEAEs by SOC and PT (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 Drug-related	**3 (15.8)**	**15 (19.7)**	**18 (18.9)**
Gastrointestinal Disorders	**2 (10.5)**	**9 (11.8)**	**11 (11.6)**
Abdominal pain	0	1 (1.3)	1 (1.1)
Constipation	1 (5.3)	6 (7.9)	7 (7.4)
Dry mouth	1 (5.3)	2 (2.6)	3 (3.2)
Infections and Infestations	**1 (5.3)**	**2 (2.6)**	**3 (3.2)**
Pharyngotonsillitis	0	1 (1.3)	1 (1.1)
Urinary Tract Infection†	1 (5.3)	1 (1.3)	2 (2.1)
Viral Rash	0	1 (1.3)	1 (1.1)
Investigations	**1 (5.3)**	**3 (3.9)**	**4 (4.2)**
Bacterial Test Positive	1 (5.3)	0	1 (1.1)
ECG QT Prolonged	0	3 (3.9)	3 (3.2)
Nervous System Disorders	**0**	**1 (1.3)**	**1 (1.1)**
Somnolence	0	1 (1.3)	1 (1.1)

TEAEs were coded using MedDRA v19.0 for the ISS population (Phase 3 NDO) and using earlier versions (v13.0 and v16.0) for the individual studies. The number of patients experiencing TEAEs of dry mouth and some urinary tract infection categories do not reconcile across the groups presented in this table due to the recoding. ISS: integrated summary of safety;
Source: 905-CL-074 Table 12.6.1.3; 905-CL-047 Table 12.6.1.5 and 12.6.1.10.2; ISS Table 13.4.5.1.1

Reviewer's Comments:

1) **ECG QT prolonged was reported as a clinical AE in 3 patients as a consequence of pre-defined changes from baseline in ECG interval duration. When the protocol was revised to include repeated measurements of QT interval at baseline, no further AEs of ECG QT prolonged were reported. The IRT-QT concluded that these three AEs of ECG QT prolonged were artifact of high variability at baseline and were not clinically relevant (not real) prolongations of the QT interval.**
2) **Narratives for every case of UTI, constipation and somnolence were reviewed.**

Severity of TEAEs

The majority of TEAEs were mild or moderate in intensity. In Study 905-CL-047, 3 patients reported 1 severe TEAE each: megacolon, dengue fever and UTI bacterial, none were judged as drug-related. The only severe TEAE reported in Study 905-CL-074 was severe dental caries in a female child (aged 2 years to < 5 years), which was judged to be not drug related.

7.3.1 Deaths

No deaths were reported in the Phase 3 studies of 047 and 074, nor in the other supporting studies.

7.3.2 Nonfatal Serious Adverse Events

Overall, 8 of 95 (8.4%) Phase 3 NDO patients reported serious TEAEs. Serious TEAEs were reported by 7 (9.2%) pediatric patients aged 5 years and older in Study 905-CL-047 (2 children and 5 adolescents). Only one type of serious TEAE (UTI) was reported in either the study, and this was reported in 2 patients.

Table 7.9 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)

ISS: integrated summary of safety; n: number of patients; NDO: neurogenic detrusor overactivity; SAF: safety analysis set;
Source: 905-CL-047 Table 12.6.1.6; 905-CL-074 Table 12.6.1.6; ISS Table 13.4.7.1

Brief Narratives of SAEs (n = 8)

Study 905-CL-047				Study 905-CL-074
#3201800	#4501740	#3201701	#4801706	#4801916
#4801799	#5205763	#6301778		

Study 905-CL-047

#3201800

Patient 3201800 is a 5-year-old Caucasian male from Belgium who was screened on (b) (6) . The patient received the first dose of solifenacin PED5 (2.6 mg) on (b) (6) (day 1). Titrations were performed. On (b) (6) (day 236), the patient was hospitalized for elective surgery for mega rectosigmoid (SAE: hospitalization for mega recto-sigmoid). The study drug was interrupted on (b) (6) (day 236) due to the event. The patient underwent a laparoscopic rectosigmoid resection with appendicostomy on (b) (6) (day 237). Postoperatively, the patient was admitted to the pediatric intensive care. An AE of moderate colonic obstruction was reported on (b) (6) (day 242, postop day 5) which caused nausea, vomiting and increased stomach secretion. The patient was placed on 'nil by mouth' and his gastric tube was set to drainage. An abdominal overview image showed mild obstruction of underlying intestinal loops, for which rectal lavages were initiated. On (b) (6) (day 243), the patient experienced significant bladder spasms which were treated with oxybutynin and an AE of UTI with pseudomonas aeruginosa was reported the following day (b) (6) , day 244). Treatment with ciprofloxacin was initiated for the AE of UTI. The study drug was restarted on (b) (6) (day 244). On (b) (6) (day 246) the patient's feeding tube was removed and he was given ranitidine hydrochloride for gastric protection. The patient was transferred to the general pediatric ward with a patient controlled analgesia (PCA) pump and paracetamol. The AE of colonic obstruction (considered to be AE of special interest) resolved on (b) (6) (day 245). The SAE of megacolon was resolved on (b) (6) (day 247) and the patient was discharged from the hospital on the same day.

On (b) (6) (day 252, postop day 15), the patient experienced the SAE of severe toxic megacolon and was admitted to the pediatric intensive care unit on the same day. On admission, the patient experienced considerable tachycardia and lactate acidosis within the context of hypovolemic shock, and was administered fluids, plasma and oxygen support. The patient also developed fever. In view of the previous history and clinical picture, broad-spectrum antibiotic therapy (tazobactam, metronidazole and vancomycin) was started for a suspected toxic megacolon. The patient developed diarrhea and considerable abdominal cramps and morphine was administered for pain. On (b) (6) (day 258) the patient received Botox injections at the level of the anal sphincter, after which he recovered well with a decrease in the symptoms of abdominal pain and a better appetite. The patient was discharged from hospital on (b) (6) (b) (6) (day 261). The SAE of toxic megacolon was considered resolved on the same day , day 261). The study drug was interrupted due to the SAE of megacolon on (b) (6) (day 236) and was restarted on (b) (6) (day 244).

The investigator considered the event of colonic obstruction and both events of megacolon to be not related to study drug treatment. The sponsor's medical assessment was that a causal relationship between solifenacin and the surgery for megarectosigmoid, toxic megacolon and event of colonic obstruction is unlikely because of the patient's medical history.

Reviewer's comment: This Reviewer agrees with the investigator that the SAE of toxic megacolon in this patient was not related to the study drug, since the patient's medical history of megarectosigmoid, his complicated postsurgical course, and his rapid improvement with intra-anal Botox injection provide plausible alternative explanations for

the reported events. The patient's history of slow transit time poses a significant confounder for these events.

#4501740

Patient 4501740 is a 12-year-old Caucasian female from Denmark who was screened on 25-(b) (6) The patient received the first dose of solifenacin PED5 (3.4 mg) on (b) (6) (day 1). Titrations were performed. The patient was diagnosed with NDO in Sep-2001 and prior to this study, she received treatment with oxybutynin, loperamide and CIC 5 times daily. The patient experienced moderate constipation on (b) (6) (day 166) which was treated with laxavit and movicol. The event was resolved on (b) (6) (day 173). The patient experienced another episode of mild constipation on (b) (6) (day 251) which was treated with bisacodyl and sodium picosulfate. The event was not resolved. The events of constipation were considered to be adverse event of special interest. On (b) (6) (day 265) the patient was hospitalized for a spinal cord operation. The event was considered a serious adverse event due to the hospitalization. She received naproxen, morphine and paracetamol for postoperative pain, and ondansetron for postoperative nausea. She was discharged from the hospital on (b) (6) (day 267). The serious adverse event of spinal cord operation was considered resolved on the same day (day 267). The study drug dose was not changed. The investigator considered the adverse events of constipation to be possibly related to study drug. However, the spinal cord operation was considered to be not related to study drug. The sponsor's medical assessment was that a causal relationship between constipation and solifenacin cannot be ruled out as constipation is a known adverse drug reaction associated with solifenacin. However, constipation, just as NDO, is a condition related to the congenital malformation of the spinal cord, causing an absence of the defecation urge, while the recto-anal inhibitory reflex is maintained. In addition, many patients suffer from constipation secondary to immobility. As such, constipation can be considered a comorbidity associated with NDO. The sponsor's medial assessment was that a causal relationship between the serious event of spinal cord operation and solifenacin is unlikely, because the patient's operation was performed due to the underlying pathology of the spinal cord.

Reviewer's comment: This Reviewer agrees with the investigator that the serious event of spinal cord operation is unlikely related to solifenacin but rather, a consequence of underlying pathology of the spinal cord; and the relationship of constipation and solifenacin cannot be ruled out, but also could be a related comorbidity associated with NDO.

#3201701

Patient 3201701 was a 16-year-old Caucasian female from Belgium who was screened on (b) (6) . The patient received the first dose of solifenacin PED5 (4.6 mg) on (b) (6) (day 1). Titrations were performed. The patient's relevant medical history included spinal deformity (spinal dysraphism), spinal deformity correction (subtotal resection of sacral intrathecal lipoma; detethering of the medulla, laminecomy l5-s1) (in 2001 and 2009) and cystopexy (suburethral

sling). The patient was diagnosed with NDO on 08-Jul-1996 and received treatment prior to study entry with solifenacin, oxybutynin and CIC 4 times daily. On (b) (6) (day 48), the patient was diagnosed with moderate tethered cord syndrome (sensorimotor function loss and pain in relation to tethering of the spinal cord with extensive syringohydromyelie). The diagnosis was preceded by pain in the left leg and foot, loss of strength, loss of feeling in the left leg, falling, and difficulty walking up stairs and long distances. The patient was under evaluation for spinal cord deformities which were thought to have been the underlying cause for the worsening of symptoms. A magnetic resonance imaging (MRI) scan was conducted on the same day ((b) (6) day 48) and showed extensive perimedular (subpial) fluid collection from TH3 to TH9 with compression of the medulla. The patient was admitted to the general pediatric department on (b) (6) (day 101). On (b) (6) (day 103), the patient's tethered cord was surgically released. The procedure confirmed adhesion of the medullary cone and radices, but there was no compression of the nerve roots. Postoperatively, the patient was treated with analgesia. The event of tethered cord syndrome was assessed by the investigator as moderate in intensity and serious due to its medical significance and hospitalization. The event was considered resolved with sequelae on (b) (6) (day 214). Study medication was continued uninterrupted during hospitalization and the patient was discharged on (b) (6) (day 113). The study drug dose was not changed. The investigator considered the serious adverse event of tethered cord syndrome to be not related to study drug. The sponsor's medical assessment was that a causal relationship between the tethered cord syndrome and solifenacin is unlikely. The patient's underlying spinal deformity is considered to be a more plausible alternative etiology for the event.

Reviewer's comment: This Reviewer agrees with the investigator that the SAE of tethered cord syndrome was not related to study drug solifenacin.

#4801706

Patient 4801706 is a 16-year-old Caucasian female from Poland who was screened on 04-Jan-2013. The patient received the first dose of solifenacin PED5 (3.4 mg) on (b) (6) (day 1). Titrations were performed. The patient's relevant medical history included spinal deformity (spinal dysraphism and vertebral column deformation) and ventriculo-peritoneal shunt (insertion of ventriculoperitoneal shunt for hydrocephalus). The patient also had a family history of hypertension. The patient was diagnosed with NDO in Feb 2007 and received treatment prior to study entry with oxybutynin (2 dose levels) and CIC 6 times daily.

On (b) (6) (day 14), the patient experienced mild hypertension and mild tachycardia and was hospitalized on the same day. At the time of admission it was reported that the patient had grade 2 hypertension (137/92 mmHg). While hospitalized, the patient was treated with 5 mg amlodipine and 5 mg ramipril for the hypertension and 1.25 mg nebivolol for the tachycardia. With therapy, her SBP was reported to have dropped by approximately 10 mmHg during hospitalization. Urine cultures were also positive for *E.coli* and antibiotics (0.5 g ciprofloxacin) were prescribed. The study drug was not changed in response to these events. The serious adverse events of hypertension and tachycardia were resolved on (b) (6) (day 20) and the patient was discharged from the hospital on the same day. The study drug dose has not been

changed. The investigator considered the events of hypertension and tachycardia to be not related to the study drug. The sponsor's medical assessment was that both serious adverse events (hypertension and tachycardia) were unlikely to be related to solifenacin because of the positive family history of hypertension, concomitant UTI and resolution of the AEs while still taking study drug.

Reviewer's comment: The reviewer agrees with the investigator that the patient's hypertension and tachycardia were unlikely related to solifenacin suspension. The patient had a concomitant E. Coli UTI, a complicated past medical history, a family history of hypertension, and the hypertension and tachycardia resolved while the patient continued on study medication.

#4801799

Patient 4801799 is a 12-year-old Caucasian male from Poland who was screened on (b) (6) . The patient received the first dose of solifenacin PED5 (3.4 mg) on (b) (6) (day 1). Titrations were performed. The patient's relevant medical history included spinal deformity correction (closure of spina bifida), paresis (mild paresis) and spina bifida (spina bifida). The patient was diagnosed with NDO in Sep 2009 and received treatment prior to study entry with tamsulosin, solifenacin and CIC 5-6 times daily. On (b) (6) (day 220), the patient suffered pain and oedema of his testis, which was diagnosed as moderate orchitis. The patient was treated with augmentin (amoxicillin and clavulanate) 625 mg twice daily (1250 mg daily). The patient's orchitis persisted following treatment with the antibiotics and he was subsequently hospitalized on (b) (6) (day 221). An ultrasound was conducted on the same day, which revealed characteristics of inflammation of the scrotum considerably increased on the left side. The patient's scrotum was surgically explored on the following day (b) (6) (day 222) and antibiotics were discontinued ((b) (6) day 226). The patient was discharged from the hospital on (b) (6) (day 223). The serious adverse event of orchitis was considered resolved on (b) (6) (day 226). The study drug dose has not been changed. The investigator considered the orchitis to be not related to study drug. The sponsor's medical assessment was that a causal relationship between solifenacin and orchitis is unlikely, because the event occurred after 220 days of study drug treatment. Furthermore, infections of the lower urinary tract (testes included) are not unusual in patients who are treated with CIC.

Reviewer's comment: This Reviewer agrees with the investigator that the orchitis in this patient was unlikely related to study drug.

#5205763

Patient 5205763 is a 15-year-old male from Mexico who was screened on (b) (6) . The patient received the first dose of solifenacin PED5 (3.4 mg) on (b) (6) (day 1). Titrations were performed. The patient was withdrawn from the study on (b) (6) (day 168). The patient's relevant medical history included meningomyelocele (myelomeningocele), meningomyelocele repair (myelomeningocele repair), vesicoureteric reflux (mild ectasia of the

renal pelvis indicative of grade 2 vesicouretral reflux). The patient was diagnosed with NDO in 2000 and treatment included oxybutynin and CIC 4 times daily. On (b) (6) (day 21), the patient developed a moderate UTI with a positive urine culture for *E. coli*, which was reported as an adverse event that resolved on (b) (6) (day 41). On (b) (6) (day 132), the patient developed a severe UTI with *Klebsiella pneumoniae* and was hospitalized the same day. Study medication was stopped on this day ((b) (6) day 132). During hospitalization, a computed tomogram (CT) urography was performed, which showed obstructive pielocalyceal dilatation and chronic inflammation of the bladder. An excretory urography did not confirm obstructive uropathy. The patient was treated with meropenem 1 gm, nitrofurantoin 100 mg, sennoside (A+B) 187 g, trimethoprim/sulfamethoxazole tablets 80/400 mg and tamsulosin 0.4 g. The patient had a good response to antibiotic therapy, with a negative urine culture at 72 hours after initiation of treatment. The patient was discharged with advice to continue intermittent bladder catheterization every 4 hours without interruption. The serious adverse event of UTI was considered resolved on (b) (6) (day 142) and the patient was discharged from the hospital on the same day. The patient withdrew from the study on (b) (6) (day 168) because the parent and patient withdrew consent. The study drug treatment was stopped permanently in response to the serious adverse event of UTI and the patient withdrew from the study on (b) (6) (day 168). No rechallenge was performed. The investigator considered the urinary tract infection to be not related to study drug. The sponsor's medical assessment was that a causal relationship between solifenacin and the urinary tract infection was unlikely, because urinary tract infections are not unusual in patients who are treated with CIC.

Reviewer's comment: This Reviewer agrees with the investigator that the UTI in this patient was unlikely related to the study drug because episodes of UTI are not uncommon in patients who are treated with CIC.

#6301778

Patient 6301778 is a 7-year-old Asian female from the Philippines who was screened on (b) (6) The patient received the first dose of solifenacin PED2.5 (2.6 mg) on (b) (6) (day 1). Titrations were performed. The patient's relevant medical history included recurrent urinary tract infection (*E.coli*, *Enterobacter cloaca)*, episodes of constipation, vesicoureteric reflux, with hydronephrosis (bilateral grade 2 hydronephrosis). The patient was diagnosed with NDO in Jun 2010 and received treatment prior to study entry with propiverine and CIC 4 times daily. On (b) (6) (day 211) the patient suffered from fever that was treated with paracetamol and she experienced vomiting the next day. On (b) (6) (day 213), the patient was taken to a physician who diagnosed her of having tonsillitis due to redness of the tonsils and prescribed clarithromycin 4 mL BID from (b) (6) to (b) (6) On (b) (6) (day 215), the patient was hospitalized. The diagnosis of tonsillitis was rejected and Dengue fever, combined with a UTI was diagnosed. Both of these events were reported as adverse events. The patient's platelet count on (b) (6) (day 215) was 117 x $10^3/\mu L$. The patient was treated with clarithromycin and amyloid (doses unknown) and was administered fluids. The patient's platelet count on (b) (6) (day 218) was 155 x $10^3/\mu L$. The Dengue fever was reported to have been resolved on (b) (6) (day 219) and the patient was discharged from the hospital on the same

day. The study drug dose was not changed. The investigator considered the event of Dengue fever to be not related to the study drug. The sponsor's medical assessment was that a causal relationship between Dengue fever and solifenacin is unlikely because of the etiopathogenesis of the disease and the resolved Dengue fever without any interruption of the study drug.

Reviewer's comment: This Reviewer agrees with the investigator that the SAE of Dengue fever was not related to the study drug.

Study 905-CL-074

#4801916

Patient 4801916 was a 2-year-old Caucasian male from Poland who was screened on (b) (6) (day –21). The patient received the first dose of solifenacin PED 5 (1.2 mg) on (b) (6) (day 1). The study drug was taken for the study duration of 365 days. The final dose was PED10 (4.2 mg). The patient completed the study on (b) (6) (day 365) and the final study visit took place on (b) (6) (day 365). The patient was diagnosed with neurogenic detrusor overactivity (NDO) on (b) (6) (day –730). The underlying cause was a myelomeningocele that was surgically closed on (b) (6) (day -897). On the same day a ventriculoperitoneal shunt was implanted to treat hydrocephalus. The patient had been on a clean intermittent catheterization (CIC) regimen of 7-8 times daily since (b) (6) (day –893).
On (b) (6) (day 38), the patient developed a moderate pharyngitis and on (b) (6) (day 42) the patient developed a moderate urinary tract infection (UTI). The patient was admitted to the hospital on (b) (6) (day 42) because of a fever persisting since four days prior to admission, poorly responding to antibiotic medication (azithromycin and amoxiclavulanico). On admission, the patient was in general moderate condition with fever. He had a red throat with white coating on the tonsils. UTI was also diagnosed on admission, based on leucocyturia that was found in the urinalysis of (b) (6) (day 41). Treatment consisted of dextrose and sodium chloride, cefotaxime, fluconazole, ibuprofen, paracetamol and primadophilus (doses unknown) from (b) (6) (day 42) until (b) (6) (day 47). Because the patient had a fever until the third day of treatment, the result of a urine culture, ordered on (b) (6) (day 43), was awaited, prolonging the hospitalization. On (b) (6) (day 47), both the pharyngitis and the UTI were reported to be resolved and the patient was discharged in good condition. He was started on amoxicillin from (b) (6) (day 47) until (b) (6) (day 52) and lactobacillus from (b) (6) (day 48) until (b) (6) (day 52). The study drug dose was not changed in response to these adverse events. No other AEs have been reported for this subject. The investigator considered both serious adverse events (SAE) to be not related to the study drug. Pharyngitis was considered a serious adverse event because it required hospitalization. The UTI was considered a serious adverse event because it prolonged hospitalization. The sponsor's medical assessment was that a causal relationship between both SAEs (pharyngitis and UTI) and solifenacin seemed unlikely. The UTI could have been caused by the regimen of frequent (7-8 times daily) clean intermittent catheterizations.

Reviewer's comment: This Reviewer agrees with the investigator that the SAEs of pharyngitis and UTI in this patient were probably not related to the study drug, and the UTI is not uncommon in patients who are treated with CIC.

SAES from Supporting Studies 905-CL-076 and 905-CL-077 in idiopathic OAB patients

Table 7.10 Incidence of SAEs in Studies 905-CL-076 and 905-CL-077 (SAF)

Patient #	Age/Sex	SAEs MedDRA (V13.0) PT	Last Dose Day	Onset/Stop Day	Outcome	Relation to Study Drug
Study 905-CL-076						
Children						
Placebo						
4605080	6/F	Lymphadenitis	84	21/22	Recovered	Not Related
4801046	11/F	Hypertension	87	78/81	Recovered	Not Related
		Tachycardia	87	78/81	Recovered	Possible
Solifenacin						
3204009	6/M	Frontal lobe epilepsy	59	49/Ongoing	Not recovered	Not Related
4803144	8/F	Pyelonephritis	49	52/Ongoing	Recovering	Not Related
Adolescent						
Placebo						
1005198	17/F	Abdominal pain	35	17/19	Recovered	Not Related
Solifenacin						
4501079	12/F	Appendicitis	84	18/20	Recovered	Not Related
Study 905-CL-077						
Children						
4803134/ Placebo	7/F	Gastroenteritis	236	133/135	Recovered	Not Related
Adolescent						
4501079/ Solifenacin	12/F	Appendicitis	357	18/20	Recovered	Not Related

Placebo

#4605080

Patient 4605080 is a 6-year-old Caucasian female from Sweden who was screened on (b) (6) and randomized on (b) (6) to placebo. The patient was not exposed to solifenacin. The patient was diagnosed with OAB on (b) (6) (day -29). Patient never achieved daytime and nighttime continence. On (b) (6) (day 21), the patient experienced acute abdominal pain in the epigastric region with reduced appetite and mild nausea. She had a slight fever. Stools were normal and neither the patient nor her parents reported problems with micturition. Abdominal pain was mostly present when the patient needed to defecate. The patient was hospitalized for observation. UTI was excluded. Symptoms vanished after defecation and the event was reported to have recovered the next day, when she was discharged from hospital. No treatment was prescribed. The event was reported as an SAE of mild intensity. The investigator

indicated the symptom pattern to be without a confirmed diagnosis. Later however, the reported term was updated to "mesenteric lymphadenitis". Concurrent with the event, the patient suffered nausea at night that occurred about twice a week. Nausea was reported as an AE of mild intensity for which treatment was not required. The nausea did not recover and was ongoing at the final study visit. The investigator considered that the event was possibly related to treatment with study medication (placebo). Study medication was continued without interruption or dose adjustment.

Reviewer's comment: This Reviewer believes that the events of mesenteric lymphadenitis and nausea were not related to placebo.

#4801046

Patient 4801046 is an 11-year-old Caucasian female from Poland who was screened on (b) (6) and randomized on (b) (6) to placebo. The patient was not exposed to solifenacin. The patient was diagnosed with OAB on (b) (6) (day –39). Patient spontaneously achieved daytime and nighttime continence in 2002 and 2003 respectively. Both daytime and nighttime continence were lost in 2004 due to an unknown cause. The patient was hospitalized for observation of a suspected paroxysmal supraventricular tachycardia from (b) (6) (day 78) till (b) (6) (day 81) after the start of double blind study drug treatment. Two SAE's were reported, tachycardia and hypertension, both of mild intensity. The tachycardia was considered serious because of the hospitalization, the hypertension due to medical significance. Medical history revealed incidents of palpitations for about 3 years usually after physical exercise (PE lessons). At admission, the patient had a tachycardia approx. 120/min and an elevated blood pressure to 135/95 mmHg. No significant heart rhythm, SVT's or conduction disorders were detected during the 48-hour Holter ECG test, which revealed a sinus rhythm with an average heart rate of 95/min. Echocardiogram of the heart was normal. Thyroid function parameters were normal. A 24h Ambulatory BP Measurement (ABPM) was performed due to elevated blood pressure; mean daytime and night-time blood pressure was above the upper limit of normal for age, sex and height (mean blood pressure 127/71 mmHg). The Holter observations for HR and BP were in line with the observations at the scheduled pre- and post-baseline study visits, although the SBP was slightly higher during the Holter. No cause for the elevated blood pressure or tachycardia was identified during hospitalization and no treatment was initiated for the reported SAEs. The tachycardia was considered possibly related, the hypertension not related to study drug treatment. No treatment was introduced for any of the reported events. Both events were reported to have recovered at (b) (6) (day 81). Study drug was continued without interruption. The tachycardia was considered possibly related. The hypertension was considered not related. Sponsor considered that the patient was assigned to placebo, therefore these is no causal relation with study medication.

Reviewer's comment: This Reviewer considers the SAEs of hypertension and tachycardia were not related to placebo.

#1005198

Patient 1005198 is a 17-year-old Caucasian female from Canada who was screened on (b) (6) and randomized on (b) (6) to placebo in study 905-CL-076. The patient was not exposed to solifenacin. The patient was withdrawn from the study on (b) (6) (day 39). The patient was diagnosed with OAB on (b) (6) (day –38). Patient never achieved daytime continence. Patient achieved nighttime continence spontaneously on an unknown date. Patient was assigned to placebo. On (b) (6) (day 17), she experienced severe pain in stomach and back for which she was admitted to the hospital. Patient reported to have a history of repeated episodes of abdominal pain since about three years. This episode though, her complaints were more severe than usual. Patient was hospitalized for observation. During hospitalization, abdominal ultrasound and abdominal CT scan did rule out acute abdominal pathology. The abdominal CT-scan however revealed a minimal amount of free fluid in the right lower quadrant of the abdomen, in the same region where the pain was located. Patient was treated with morphine, dimenhydrinate and polyethylene glycol. Patient was hospitalized for one night after which pain improved. The hospital concluded the diagnosis to be mesenteric adenitis, although the event term was not updated accordingly. The event of severe abdominal (stomach and back) pain was reported to have recovered on (b) (6) (day 19). Treatment with study drug was interrupted for 2 days in relation to the events, but continued thereafter. On (b) (6) (day 35), a diagnosis of dysfunctional voiding was made . This event was reported as adverse of mild intensity, not related to study drug treatment. As prohibited therapy was required for the management of the event, treatment with study drug was permanently discontinued. The event was reported to be ongoing at the final study visit. The investigator considered the serious adverse event (SAE) of abdominal pain that required hospitalization to be not related to the study drug.

Reviewer's comment: This Reviewer agrees with the investigator that the event of abdominal pain was not related to placebo.

Solifenacin

#3204009

Patient 3204009 is a 6-year-old Caucasian male from Belgium who was screened on (b) (6) and randomized on (b) (6) to solifenacin in study 905-CL-076. The patient received the first dose of PED 5mg (1.8mL) on (b) (6) (day 1) and received solifenacin for the duration of 59 days. The patient was withdrawn from the study on (b) (6) (day 69). The patient was diagnosed with OAB on (b) (6) day –182). Patient never achieved daytime and nighttime continence. On (b) (6) (day 49), the patient was diagnosed with nocturnal frontal lobe epilepsy (NFLE), which meets the 'always serious' AE coding criteria as listed in protocol appendix 6. This was reported as an SAE of moderate intensity. The patient, as a result of construction work in the house he lives, shared a bedroom with his parents, who witnessed epileptiform tonic-clonic contractions that explained noises that the parents had been hearing for a long time prior to the start of the study. Patient was treated in the outpatient emergency department of the hospital with carbamazepine (a restricted medication) and was therefore

discontinued and withdrawn from the study. NFLE often presents as an autosomal dominantly inheriting disease (ADNFLE). In this case, this is probably an inherited disease as the patient's mother also suffers NFLE. The event was ongoing at the final study observation. The investigator judged the NFLE in the patient as not related to study drug. Sponsor believed that signs of the presence of epilepsy had already been present for a longer period of time and epileptiform seizures are not a previously observed ADR for solifenacin, therefore , the event of nocturnal frontal lobe epilepsy observed at day 49 after initiation of solifenacin is considered unrelated to treatment with solifenacin.

Reviewer's comment: The Reviewer agrees with the investigator that the event of nocturnal frontal lobe epilepsy was not related to the study drug.

#4501079

Patient 4501079 is a 12-year-old Caucasian female from Denmark who was screened on (b) (6) and randomized on (b) (6) to solifenacin in study 905-CL-076. The patient received the first dose of PED5 (3.4mL) on (b) (6) (day 1) and received solifenacin for the duration of 84 days. The patient was diagnosed with OAB on (b) (6) day -165). Patient never achieved daytime and nighttime continence. Patient was hospitalized and diagnosed an appendicitis acute on study (b) (6) (day 18). Patient underwent appendectomy and recovered without sequelea on (b) (6) (day 20). Study treatment was unaffected. The event was reported as SAE of severe intensity, not related to study drug treatment. Treatment with solifenacin did not change in relation to the event. The investigator considered that appendicitis is a coincidental adverse event, and despite the temporal relation with the start of solifenacin treatment, there is no reason to suspect a causal relation.

Reviewer's comment: The Reviewer agrees with the investigator that the SAE of appendicitis was not related to study drug

#4803134

Patient 4803134 is a 7-year-old Caucasian female from Poland who was screened for the 905-CL-076 study on (b) (6) (day –115) and randomized on (b) (6) (day –87) to placebo. On (b) (6) (day –1) the patient was enrolled in the 905-CL-077 study. The patient received the first dose of solifenacin PED5 (3.4mL) on (b) (6) (day 1) and received solifenacin for the duration of 236 days. The final dose level was PED2.5 (1.8mL). The patient completed the study on (b) (6) (day 236). The final study visit took place on (b) (6) (day 236). The patient was diagnosed with OAB on (b) (6) (day –1548). The patient achieved daytime and nighttime continence on (b) (6) (day -259) with support of treatment with anti-muscarinics. Daytime and nighttime continence were lost again on (b) (6) (day –158) because of discontinuation of the treatment after symptoms had improved. On (b) (6) (day 133) the patient was evaluated by a physician because of symptoms of vomiting and diarrhea. On physical examination the patient was reported to have a soft abdomen without an abnormal mass and negative signs of peritoneal irritation. She was diagnosed with gastroenteritis and was

hospitalized the same day due to signs of dehydration. The antigen tests on rotavirus and adenovirus in the faeces were negative. She required parenteral rehydration and the hospital course and treatment were without complications and the patient was discharged in a good general condition on (b) (6) (day 135). The event was reported as serious due to hospitalization. The study drug was continued without interruption and the study drug dose has not been changed as a result of the event. A mild urinary tract infection (from (b) (6) day 185 until (b) (6) day 190) was the only other TEAE that was reported for this patient. The investigator considered the SAE gastroenteritis not to be related to the study drug. The sponsor's medical assessment was that there is no causal relationship between the gastroenteritis and the use of solifenacin. The gastroenteritis was most probably caused by a viral or bacterial infection, which is very common in the pediatric population.

Reviewer's comment: This Reviewer considers that the event of gastroenteritis was unlikely to be related to study drug because the event resolved while treatment with study drug continued.

#4803144

Patient 4803144 is an 8-year-old Caucasian female from Poland who was screened on (b) (6) and randomized on (b) (6) to solifenacin in study 905-CL-076. The patient received the first dose of PED5 (2.6mL) on (b) (6) (day 1) and received solifenacin for the duration of 49 days. The patient was withdrawn from the study on (b) (6) (day 52). The patient was diagnosed with OAB on (b) (6) (day -306). Patient never achieved daytime and nighttime continence. At visit 5 on (b) (6) (day 42), the protocol defined triplicate measure of ECG's revealed a mean QTcB of 413.3msec. Compared to a baseline mean QTcB of 377.0msec (based on the visit 3 ECG's), this represented an increase of 36.3 msec, thereby meeting the discontinuation criterion specified in the protocol. The event was reported as an AE of mild intensity and was considered possibly related to treatment with solifenacin. The patient did not have any clinical signs or symptoms associated with the increase in QTcB. The AE was reported resolved at the End of Study (EoS) visit on (b) (6) (day 52), when the mean QTcB was 397.7 msec. Based on the (b) (6) ECG observation, the study drug was discontinued on (b) (6) (day 49). On that day, the patient reported fever for which the GP was consulted who treated the patient with amoxicillin/ clavulanic acid (Spektramox). The fever was reported as an AE of moderate intensity. On (b) (6) (day 52), the patient returned to the clinic for the End of Study visit. That day, the patient reported ongoing fever and flank-pain, which was suspected to be due to pylelonephritis. Further evaluation revealed a body temperature of 37.2°C. The patient was normotensive at that visit (Table 4). Based on the clinical suspicion of pyelonephritis, it was decided that the patient was to be hospitalized. The local laboratory results on admission revealed a CRP of 157 mg/L, a WBC of 13.700 x 10^6/L and a neutrophil fraction of 76%. At the last visit on study drug on (b) (6) (day 42), the PVR was 0 mL. At the EoS visit, the PVR again was 0mL.There were no signs of renal impairment associated with the event reported pyelonephritis. During hospitalization the patient was treated with intravenous piperacillin / tazobactam (Tazocin) and i.v. re-hydration. The patient recovered from the pyelonephritis and was discharged form hospital on (b) (6) (day 59). That day, the

event was considered recovering. The event was reported as SAE of severe intensity. The study drug solifenacin, and the pyelonephritis was considered not related.

Reviewer's comment: The role of solifenacin in the event of ECG QT prolonged cannot be ruled out. However, the case is confounded by a concurrent serious UTI. The event of pyelonephritis is considered unlikely to be related to study drug as the patient had no residual urine and had experienced multiple urinary tract infections in the past.

7.3.3 Dropouts and/or Discontinuations

The only reported TEAE that resulted in treatment discontinuation in Study 905-CL-047 was protocol-defined ECG QT prolonged; 4 of 76 (5.3%) patients aged ≥ 5 years (2 children and 2 adolescents) reported a TEAE of ECG QT prolonged that resulted in treatment discontinuation. The 3 of 4 TEAES leading to permanent discontinuation reported in 3 patients (2 children and 1 adolescent) were considered by the investigator to be related to the study drug [Section 2.1.1.3.2; ISS Table 13.4.10.1; Research Report: QTc]. There were no reported TEAEs that resulted in treatment discontinuation in Study 95-CL-074. Summary data for these cases are shown below in Table 3.3.3.9.

Table 7.11 Incidence of TEAEs Resulting in Discontinuation (SAF)

MedDRA v13.0 System Organ Class Preferred Term	Number of Patients (%)		
	Children (Aged 5 Years to < 12 Years) n = 42	Adolescents (Aged 12 Years to < 18 Years) n = 34	All Patients (Aged 5 Years to < 18 Years) n = 76
Overall	2 (4.8)	**2 (5.9)**	**4 (5.3)**
Investigations	2 (4.8)	2 (5.9)	4 (5.3)
ECG QT prolonged	2 (4.8)	2 (5.9)	4 (5.3)

Source: Section 2.1.3.1, Report of Study 905-CL-047 Table 36,

Table 7.12 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)
3201702	14	F	3.4 mg (PED 5)	423.0	456.0 (Day 59)
4801712	13	M	5.2 mg (PED 7.5)	387.7	429.0 (Day 22)
4801784	8	F	3.8 mg (PED 7.5)	427.3	461.7 (Day 21)
4801787	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

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

Reviewer's comment: During the conduct of the phase 3 pediatric program, a random effects analysis was performed on all ECG data to provide insight into the observed cases of patients meeting the discontinuation criterion for prolongation of QTcB, in the absence of changes of concern in the population means. This analysis demonstrated that the intra-patient variance in repeat QTcB measurements was sufficient to account for the observed

discontinuations. The pediatric protocols were subsequently amended to increase the accuracy of the baseline QTc measure by calculating the baseline QTcB over the 2 pre-randomization study visits. Following the implementation of the protocol amendment there were no further discontinuations due to QT prolongation and no new TEAEs of ECG QT prolonged. A consultation was obtained from the Interdisciplinary Review Team for QT studies (IRT-QT) in the Division of Cardiovascular and Renal Products (DCRP) and the IRT-QT agreed with the Sponsor that the cases of ECG QT prolonged reflected high variability in the QTcB interval at Baseline which was not accounted for by repeated baseline measures and averaging. Subsequent to the protocol change to increase the number of repeats at Baseline, there were no further reports of ECG QT prolonged. Therefore, the study discontinuation due to QT prolongation is not considered a clinically relevant finding of QT prolongation, but instead reflects an artfact of high variability at Baseline without repeat baseline measures as conducted early in the study.

In addition, none of the patients who were discontinued due to meeting the QTcB discontinuation criterion experienced any untoward clinical event in relation to the ECG observations (e.g., no arrhythmias, palpitations or other adverse events were reported).

Table 7.13 Drug Related TEAEs Leading to Permanent Discontinuation of Study Drug: Phase 3 Population

Parameter Category/Statistics n (%)	52 Weeks of Exposure			
	Solifenacin Open-Label (NDO) 52 Weeks (N = 95)	Solifenacin Double-Blind Solifenacin Open-Label (OAB) (N = 73)	Placebo DB + Solifenacin Open-Label (OAB) (N = 75)	Total (NDO and OAB) 52 Weeks (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 Total (NDO and OAB) 52 Weeks treatment group consists of results from all patients in the Phase 3 population, including Placebo-treated periods.

Reviewer's comment: Aside from "ECG QT prolonged" (the reader is referred to the previous Reviewer's comment for an explanation), the rest of the discontinuations due to AEs were reported in the supporting studies in patients with OAB, not with NDO.

7.3.4 Significant Adverse Events

There were no drug-related significant adverse events (AEs) reported from the Phase 3 studies in NDO patients. However, there were a few reported adverse events of special clinical interest. The AEs of special clinical interest were:

- Urinary tract infection (UTI) was a commonly reported TEAE, with 2 cases reported as SAEs. Neither of the two SAE UTIs were judged to be study drug-related. The Sponsor submitted brief narratives for all AEs of UTI (n = 24 in Study 905-CL-047 and n = 5 in Study CL-905-074).

- Constipation was reported in 6 patients in Study 905-CL-047 and 3 patients in Study 905-CL-074.

- ECG QT prolonged was reported in 4 patients in Study 905-CL-047.The reader is referred to previous Reviewer's comments for explanation of these cases.

- Hypertension was reported in 1 patient in Study 905-CL-047. The reader is referred to the previous brief narrative for this case.

- Somnolence was reported in 1 patient in Study 905-CL-047.

UTI: Urinary tract infection (UTI) was a commonly reported TEAE with 2 cases reported as serious AEs. In addition, 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 to be 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 047 and Case #3203918 in Study 074) were considered by the investigator to be "possibly related to study drug."

Reviewer's comment: The reported annual incidence of UTIs in pediatric patients with NDO practicing CICs is approximately 35% (Kaye IY, et al, 2016, Vigil HR et al, 2016). This Reviewer agrees that the majority of UTI AEs in Studies 905-CL-047 and 905-CL-074 were unlikely related to solifenacin oral suspension.

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

Hypertension: One SAE case of hypertension was reported and the reader is referred to the brief case narrative and Reviewer's comment in the previous section of this review for an explanation of this case.

Somnolence: One AE of somnolence was reported. Patient 1008714 is a 15-year-old Black or African American male from United States with a medical history of spinal deformity (spinal dysraphism), meningomyelocele repair, hydrocephalus, CSF shunt operation (right shunt placement), constipation (intermittent constipation), and UTI. NDO was diagnosed on (b) (6) and the patient received treatment prior to study entry with oxybutynin and CIC 3-4 times daily. He received the first dose of solifenacin PED5 (4.6 mg) on (b) (6) (day 1) and experienced moderate somnolence on the same day. The event was considered resolved on (b) (6) (day 4). On day 7 , the dose was down titrated to PED 2.5 (2.2 mg). On (b) (6) (day 23), the dose was up-titrated to PED 5[4.6 mg], and the patient experienced another episode of mild somnolence. The second event was considered resolved on (b) (6) (day 28). On day 30, the dose was down titrated back to PED2.5 (2.2 mg). Both events of somnolence were considered to be adverse events of interest. The investigator considered the adverse event of moderate somnolence to be possibly related and the mild somnolence probably related to the study drug.

Reviewer's comment: This Reviewer agrees with the investigator that a causal relationship between somnolence and solifenacin cannot be ruled out, because the onset date of the first event was on the day of solifenacin initiation, the second event was on the day after study drug up-titration and somnolence is a known adverse drug reaction associated with solifenacin.

Finally, the reader is referred to the previous section of this review for a brief narrative and a Reviewer's comment for an SAE case of toxic megacolon.

7.3.5 Submission Specific Primary Safety Concerns

No specific primary safety concerns were identified during the development of oral solifenacin suspension.

7.4 Supportive Safety Results

Treatment Emergent Adverse Events (TEAEs)

Supportive Phase 1 Study
Of the 42 patients (22 children and 20 adolescents) enrolled and treated in Study 905-CL-075, 9 (21.4%) experienced at least 1 TEAE. There were no serious TEAEs. Permanent discontinuation of study drug due to AEs did not apply as this was a single-dose study.

Phase 3 Pediatric Population (NDO and OAB) Supportive Analysis
During 52 weeks of treatment, 184 of 243 (75.7%) Phase 3 (NDO and OAB) patients reported TEAEs [Table 7.14]. Drug-related TEAEs were reported by 75 (30.9%) of Phase 3 patients. Serious TEAEs were reported by 12 (4.9%) Phase 3 patients. Differences between the NDO and

idiopathic OAB groups for TEAEs, drug-related TEAEs, drug-related TEAEs leading to discontinuation and serious TEAEs are detailed in the following Table.

Table7.14 Overview of TEAEs and Death, 52 Weeks of Treatment (SAF); Phase 3 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)		Total Open-label (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 Total (OAB and NDO) 52 weeks treatment group consists of results from all patients in the phase 3 population, including placebo-treated periods.
‡ Possible or probable, as assessed by the investigator, or records where relationship is missing.
§ Includes SAEs upgraded by the sponsor based on review of the sponsor's list of always serious terms, if any upgrade was done.
ISS: integrated summary of safety; n: number of patients; NDO: neurogenic detrusor overactivity; OAB: overactive bladder; SAF: safety analysis set; TEAE: treatment-emergent adverse event.
Source: ISS Table 13.4.1.2

The incidence of TEAEs, drug-related TEAEs, and TEAEs and drug-related TEAEs leading to withdrawal was higher in OAB patients than in Phase 3 NDO patients during the 52 weeks of treatment.

The incidence of SAEs is higher in OAB patients than Phase 3 NDO patients, and this may be related to the serious manifestations of the NDO background condition.

The most frequently reported TEAE resulting in treatment discontinuation in OAB patients was ECG QT prolonged. During the pediatric development program, an interim analysis of intrasubject variation on repeat QTc by Bazett's formula (QTcB) measurements demonstrated that the incidence of discontinuations (due to meeting the protocol specified discontinuation criterion of a change from baseline in QTcB > 30 ms) was equivalent to that estimated to be the case in the absence of any solifenacin treatment effect. After a protocol amendment was introduced to increase the precision of the reference QTcB value for calculating changes there were no further discontinuations or TEAEs associated with QTc prolongation. Based on this, the higher incidence of events leading to discontinuation in the OAB populations is likely to be due

to the larger extent of recruitment prior to the protocol amendment into Studies 905-CL-076 and 905-CL-077. The IRT-QT consult agreed with the Sponsor's explanation of this situation.

7.4.1 Common Adverse Events

Phase 1 Study in Patients with NDO

Two patients reported TEAEs in Study 905-CL-079. One (7.1%) adolescent reported mild micturition urgency and 1 (7.1%) adolescent reported moderate anxiety during the study.

Phase 3 Studies in Patients with NDO and Patients with OAB

The following table describes the incidence (> 5% incidence in total group) of TEAEs for 52 Weeks of Treatment (SAF) in the Phase 3 population.

Table 7.15 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 / 90CL-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 periods.
‡ 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.
ISS: integrated summary of safety; n: number of patients; NDO: neurogenic detrusor overactivity; OAB: overactive bladder; SAF: safety analysis set.

Source: ISS Table 13.4.11.2 and Table 13.4.2.2.1

Reviewer's comment: The reader is referred to previous Reviewer's comments for explanations of "ECG QT prolonged" and UTI.

Incidence of Drug-related TEAEs, 52 Weeks of Treatment (SAF); Phase 3Population

Table 7.16 Drug Related TEAEs Leading to Permanent Discontinuation of Study Drug: Phase 3 Population

Parameter Category/Statistics n (%)	52 Weeks of Exposure			
	Solifenacin Open-Label (NDO) 52 Weeks (N = 95)	Solifenacin Double-Blind Solifenacin Open-Label (OAB) (N = 73)	Placebo DB + Solifenacin Open-Label (OAB) (N = 75)	Total† (NDO and OAB) 52 Weeks (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)
Pharyngotonsilitis	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)

Weight Increased	0	1 (1.4)	0	1 (0.4)
Metabolism and Nutrition Disorders				
Iron Deficiency	0	1 (1.4)	0	1 (0.4)
Nervous System Disorders				
Dizziness	0	0	1 (1.3)	1 (0.4)
Headache	0	1 (1.4)	0	1 (0.4)
Somnolence	1 (1.1)	0	1 (1.3)	2 (0.8)
Psychiatric disorders				
Irritability	0	0	1 (1.3)	1 (0.4)
Mood Altered	0	1 (1.4)	0	1 (0.4)
Tic	0	1 (1.4)	0	1 (0.4)
Renal and Urinary Disorders				
Dysurea	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 periods.
‡ 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.
ISS: integrated summary of safety; n: number of patients; SAF: safety analysis set.
Source: ISS Table 13.4.5.2.1

Reviewer's comment: Constipation and dry mouth are known side effects of anticholinergic drugs, including solifenacin succinate, and these two AEs are still the two most common TEAEs leading to study discontinuation.

Severity of Adverse Events

Supportive Phase 1 Study: All TEAEs were mild in severity in Study 905-CL-075.

Phase 3 Pediatric Population (NDO and OAB) Supportive Analysis: TEAEs were mostly mild (124 [51.0%] patients) or moderate (53 [21.8%] patients) in severity in the Phase 3 pediatric population. Seven patients reported 1 severe TEAE each: 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.

Additional Adverse Event of Special Interest – Antimuscarinic side effects

During the 52 weeks of treatment, the most commonly reported antimuscarinic side effect was constipation in the Phase 3 NDO (7.4%) population. The incidence of constipation was higher in the idiopathic OAB study groups compared to the incidence in the Phase 3 NDO group during the 52 weeks of treatment.

Table 7.17 Overview of Common Antimuscarinic Side Effects, 52 Weeks of Treatment (SAF); Phase 3 Population

Preferred term	Phase 3 NDO Population		Phase 3 (NDO+OAB) Population	
	Solifenacin Open-label (NDO) n = 95		Total† (OAB and NDO) n = 243	
	n (%)	Events	n (%)	Events
Constipation	7 (7.4)	11	26 (10.7)	33
Dry Mouth	4 (4.2)	4	12 (4.9)	12
Blurred Vision	1 (1.1)	1	2 (0.8)	2
Dyspepsia	1 (1.1)	1	1 (0.4)	1

† The total solifenacin (OAB and NDO) 52 weeks treatment group consists of results from all patients in the phase 3 population, including placebo-treated periods.
Source: ISS Table 13.5.2 (modified by the Reviewer)

Reviewer's comment: Constipation is still the most common antimuscarinic TEAE.

7.4.2 Laboratory Findings

Overall, there were few changes of clinical relevance observed for biochemistry, hematology, and urinalysis variables throughout the studies.

Renal Function: Overall, monitoring of renal function variables in the Phase 3 NDO studies demonstrated that renal function was maintained. Renal function was assessed by monitoring *plasma cystatin C* and *creatinine levels* and the *estimated glomerular filtration rates (eGFRs)* derived from these variables using the Larsson and Schwartz formulas, respectively.

Urinalysis: In the urinalysis results from Phase 3 patients with NDO in Study 905-CL-047, shifts from normal levels at baseline to high levels at week 24 were observed in > 20% of the patients for the following parameters: urine bacteria quantitative (60.9%) and urine leukocytes quantitative (48.0%). The changes are consistent with the reported incidence of UTIs.

Reviewer's comment: Shifts from normal to high in bacteriuria and leukocytouria in urinalysis, along with clinical AEs of UTI, are not unexpected findings in the pediatric population with NDO and practicing CIC.

7.4.3 Vital Signs

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 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].

For the Phase 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) in Phase 3 NDO patients

- SBP – 5 (6.1%) Phase 3 NDO patients had a potentially clinically significant (PCS) SBP value above the reference range and an increase from baseline ≥ 20 mmHg while 2 (2.4%) patients had a PCS SBP value *below* the reference range and a *reduction* from baseline ≥ 20 mmHg.
- DBP – Five (6.1%) Phase 3 NDO patients had a PCS DBP value above the reference range and increase from baseline ≥ 15 mmHg.
- PR – Ten (12.2%) patients with NDO had a PCS pulse rate value above the reference range and an increase from baseline ≥ 15 beats/min, while 3 (3.7%) patients had a PCS pulse rate value *below* the reference range and a *reduction* from baseline ≥ 15 beats/min.

Table 7.18 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: 905-CL-047 Table 12.6.3.1; 905-CL-047 Table 12.6.3.1; ISS Table 13.6.1.1.1 (modified by the Reviewer)

Phase 3 pediatric population:

The changes reported for the Phase 3 pediatric population were generally expected over the time course of the phase 3 studies. Over 52 weeks, the vital signs profile of the solifenacin-treated patients with NDO was similar to that of the solifenacin-treated patients with OAB. Patients with NDO were enrolled in the open-label solifenacin oral suspension studies for 52 weeks; solifenacin-treated patients with OAB, however, were enrolled in a double-blind solifenacin oral suspension study for 12 weeks before the 40-week open-label solifenacin oral suspension treatment.

Table 7.19 Results of Change from Baseline to Week 52 in Vital Signs (SAF); Phase 3 Population

Statistic	ISS Pool / Study; Number of Patients (%)											
	Phase 3 NDO Population Solifenacin Open-label (NDO)			905-CL-076 / 905-CL-077						Phase 3 Population Total† (OAB and NDO)		
				Solifenacin Double-blind + Solifenacin Open-label (OAB)			Placebo Double-blind+ Solifenacin Open-Label (OAB)					
	B	W52	CFB	B	W52	CFB	B	W52	CFB	B	W52	CFB
SBP (mmHg)												
n	92	76	73	73	57	57	75	65	65	240	198	195
Mean	105.4	106.0	0.7	105.7	108.6	3.1	102.7	104.7	1.9	104.6	106.3	1.8
(SD)	(12.6)	(11.8)	(11.0)	(12.1)	(9.5)	(8.6)	(11.2)	(10.1)	(9.7)	(12.0)	(10.7)	(9.9)
DBP (mmHg)												
n	92	76	73	73	57	57	75	65	65	240	198	195
Mean	67.8	65.8	-1.6	65.4	66.5	1.1	63.2	64.6	1.2	65.6	65.6	0.1
(SD)	(10.6)	(10.2)	(9.9)	(8.6)	(7.9)	(8.9)	(8.2)	(8.3)	(8.5)	(9.5)	(8.9)	(9.2)
Pulse Rate (bpm)												
n	92	76	73	73	57	57	75	65	65	240	198	195
Mean	93.4	92.2	-2.9	83.7	83.1	-1.0	84.4	81.8	-3.1	87.6	86.2	-2.4
(SD)	(19.4)	(15.7)	(13.2)	(11.8)	(11.7)	(10.2)	(10.3)	(11.6)	(9.3)	(15.5)	(14.1)	(11.1)
Body Temperature (°C)												
n	92	76	73	73	57	57	75	65	65	240	198	195
Mean	36.4	36.4	0.0	36.4	36.3	-0.1	36.4	36.3	0	36.4	36.4	0
(SD)	(0.4)	(0.4)	(0.4)	(0.5)	(0.6)	(0.5)	(0.5)	(0.5)	(0.4)	(0.5)	(0.5)	(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 periods.
B: baseline; CFB: change from baseline; DBP: diastolic blood pressure; ISS: integrated summary of safety; n: number of patients; NDO: neurogenic detrusor overactivity; OAB: overactive bladder; SAF: safety analysis set; SBP: systolic blood pressure; W: week.
Source: ISS Table 13.6.1.2.1

Reviewer's comment: In the pooled analysis, only minor differences were observed between the 2 patient populations (NDO vs idiopathic OAB). The observed changes in vital signs may be related to the duration of the studies and patients' background conditions and maturation.

7.4.4 Electrocardiograms (ECGs)

According to the protocols, a 12-lead ECG was to be performed in triplicate at every visit; the mean of each triplicate of was used for each ECG variable at each visit. If fewer or > 3 results were recorded, the mean of all available values were used. The investigator assessed ECG traces and gave an overall interpretation. All ECGs were further evaluated by a cardiologist.

It is notable that four patients in Study 905-CL-047 experienced a TEAE of "ECG QT prolongation" that resulted in treatment discontinuation. QT data for these 4 patients has been previously discussed in this review and are summarized in Table 7.12.

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 or associated discontinuations in pediatric patients aged 2 years to < 5 years (Study 905-CL-074). Based on a random effect analysis on data of OAB pediatric patients, the Applicant found that there was absence of changes of concern in the population means of QT intervals and the intrapatient 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, there were no further discontinuations 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 7.20. The mean changes of QT intervals from baseline to week 52 were negligible.

Table 7.20 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

The incidence of patients with QTcB changes (at week 52) from baseline between 30 to 60 ms was lower in the phase 3 studies in pediatric patients with NDO (1.8% [1 patient] in Study 905-CL-047; 9.1% [2 patients] in Study 905-CL-074) than that in the phase 3 studies in adults with OAB (ranged from 7.2% to 13.2%: NDA 21518, Studies 905-CL-05 and 905-CL-018).

Reviewer's comment: Based on the observed overall findings for QT interval assessment in pediatric patients with NDO, as well as advice received by DBRUP from an IRT-QT consult, this reviewer concludes that there are no new findings of clinical concern in terms of QT prolongation following solifenacin treatments in pediatric patients. The Interdisciplinary Review Team for QT Studies (IRT-QT) also concluded that solifenacin is unlikely to have a clinically relevant effect on the QTc interval at the proposed doses in pediatric patients.

The mean changes from baseline in all ECG measurements in the Phase 3 NDO or Phase 3 pediatric population were negligible over 52 weeks of treatment; mean changes in QTcB and QTc by Fridericia's formula (QTcF) are presented in [Table 7.21].

Table 7.21 Overview of 12-Lead ECG QTcB and QTcF Results, 12 and 52 Weeks of Treatment; Phase 3 Population (SAF)

Criteria	ISS Pool / Study; Number of Patients (%)			
	Phase 3 NDO Population Solifenacin Open-Label (NDO)	905-CL-076 / 905-CL-077		Phase 3 Population Total† (NDO and OAB)
		Solifenacin Double-Blind Solifenacin Open-Label (OAB)	Placebo DB + Solifenacin Open-Label (OAB)	
QTcB (ms) Week 12 Analysis				
Baseline				
n	95	95	93	190
Mean (SD)	419 (16.9)	411 (15.8)	411 (15.9)	415 (16.7)
Week 12				
n	80	81	85	161
Mean (SD)	420 (17.6)	414 (15.6)	413 (16.2)	417 (16.9)
Mean change from baseline (SD)	3.3 (13.2)	1.0 (13.6)	0.9 (13.2)	2.1 (13.4)
QTcB (ms)Week 52 Analysis				
Baseline				
n	95	73	75	243
Mean (SD)	419 (16.9)	413 (15.4)	413 (14.3)	415 (15.9)
Week 52				
n	76	56	64	196
Mean (SD)	418 (17.3)	417 (14.5)	416 (14.2)	417 (15.5)
Mean change from baseline (SD)	1.5 (13.7)	3.3 (12.7)	1.1 (12.8)	1.9 (13.1)
QTcF (ms) Week 12 Analysis				
Baseline				
n	95	95	93	190
Mean (SD)	391 (16.3)	392 (14.9)	394 (15.7)	392 (15.6)
Week 52				
n	80	81	85	161
Mean (SD)	394 (15.8)	396 (15.1)	396 (14.5)	395 (15.4)
Mean change from baseline (SD)	4.3 (11.9)	2.2 (12.2)	1.5 (12.1)	3.2 (12.0)
QTcF (ms) Week 52 Analysis				
Baseline				
n	95	73	75	243
Mean (SD)	391 (16.3)	393 (14.6)	393 (13.9)	393 (15.0)
Week 52				
n	76	56	64	196
Mean (SD)	392 (16.6)	399 (13.5)	400 (14.1)	396 (15.3)
Mean change from baseline (SD)	3.6 (12.2)	4.3 (11.5)	5.1 (11.1)	4.3 (11.6)

† The total solifenacin (NDO and OAB) 12-week treatment group includes results from solifenacin treated patients only. The total (OAB and NDO) 52-week treatment group consists of results from all patients in the phase 3 population, including placebo-treated periods. For each patient, the mean value of triplicate readings at each time point was used. If a patient had more than 1 nonmissing value in a visit window, the nonmissing assessment which was closest to the target day within a window was used, with the exception of minimum/maximum after baseline time points.
The time points 'min/max after baseline are based on the smallest/largest mean value of all the visits of a subject after baseline.
ISS: integrated summary of safety; QTcB: QT interval corrected for heart rate by Bazett's formula; QTcF: QT interval corrected for heart rate by Fridericia's formula; SAF: safety analysis set.
Source: ISS Table 13.7.1.2.1

Most of the 12-lead ECGs that were collected in the pediatric population were assessed by the investigator as normal. No dose-dependent effect on ECGs was identified. Based on three broad categories of change (<0, 0-30msec and 30-<60 msec), the changes from baseline in QTcB and QTcF were between 0 and 30 ms for the majority of these patients; categorical analysis of QTcB and QTcF are presented in [Table 7.22].

Table 7.22 Categorized Change from Baseline to Week 12 and to Week 52 in QTcB and QTcF (ms); Phase 3 Population and Phase 3 NDO Population (SAF)

Criteria	ISS Pool / Study; Number of Patients (%)			
	Phase 3 NDO Population Solifenacin Open-Label (NDO)	905-CL-076 / 905-CL-077		Phase 3 Population Total† Solifenacin‡ (NDO and OAB)
		Solifenacin Double-Blind (OAB)	Placebo Double-Blind (OAB)	
QTcB (ms)				
Week 12				
n †	80	81	85	161
< 0	33 (41.3)	39 (48.1)	33 (38.8)	72 (44.7)
0 to < 30	47 (58.8)	42 (51.9)	52 (61.2)	89 (55.3)
30 to < 60	0	2 (2.5)	1 (1.2)	2 (1.2)
Week 52				
n †	76	56	64	196
< 0	35 (46.1)	20 (35.7)	32 (50.0)	87 (44.4)
0 to < 30	41 (53.9)	36 (64.3)	32 (50.0)	109 (55.6)
30 to < 60	4 (5.3)	1 (1.8)	2 (3.1)	7 (3.6)
QTcF (ms)				
Week 12				
n †	80	81	85	161
< 0	23 (28.8)	35 (43.2)	40 (47.1)	58 (36.0)
0 to < 30	57 (71.3)	46 (56.8)	45 (52.9)	103 (64.0)
30 to < 60	1 (1.3)	1 (1.2)	0	2 (1.2)
Week 52				
n †	76	56	64	196
< 0	33 (43.4)	17 (30.4)	21 (32.8)	71 (36.2)
0 to < 30	43 (56.6)	39 (69.6)	43 (67.2)	125 (63.8)
30 to < 60	1 (1.3)	2 (3.6)	2 (3.1)	5 (2.6)

† n means number of patients with a nonmissing value.

‡ The total solifenacin (NDO and OAB) 12-week treatment group includes results from solifenacin treated patients only. The total (OAB and NDO) 52-week treatment group consists of results from all patients in the phase 3 population, including placebo-treated periods. For each patient, the mean value of triplicate readings at each time point was used. If a patient had more than 1 nonmissing value in a visit window, the nonmissing assessment which was closest to the target day within a window was used, with the exception of the "any visit" category. Percentages were calculated as the total number of patients within each change from baseline category divided by the total number of patients with a nonmissing value. A patient could be classified into several categories. ISS: integrated summary of safety; n: number of patients;
QTcB: QT interval corrected for heart rate by Bazett's formula; QTcF: QT interval corrected for heart rate by Fridericia's formula; SAF: safety analysis set.
Source: ISS Table 13.7.4.2.1

Reviewer's comment: Increases from baseline in the ECG QT interval (QT prolongation) were reported as clinical TEAEs leading to study discontinuation in 4 subjects. These events may have reflected 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 increases required study discontinuations due to pre-defined per-protocol discontinuation criteria. The pediatric protocols were subsequently amended to increase the accuracy of the baseline QTcB by calculating the baseline QTcB over the 2 pre-randomization study visits. Following the implementation of this protocol amendment, there were no further discontinuations due to QT prolongation and no new TEAEs of ECG QT prolonged. A consult was obtained from the IRT-QT team in DCRP who concluded that the occurrence of those 4 events was likely related to inadequate baseline repeat testing and was not a true clinical safety signal.

In the following bullets, the Reviewer summarizes the consult review from the Interdisciplinary Review Team QT (IRT-QT):

- In study 905-CL-047, there were 4 discontinuations due to patients meeting a protocol specified discontinuation criteria for QTc (e.g., change from baseline of QTcB exceeding 30 ms). Following the amendment to increase the precision of the baseline QTcB estimate by averaging the 2 pretreatment values, there were no further discontinuations due to QTc prolongation and when the amendment was retrospectively applied to the data from the 4 subjects who discontinued, only 1 patient still met the criteria. Subsequent to these discontinuations the sponsor conducted an analysis of intrasubject variability and modified ongoing study protocols to define the baseline QTcB as an average of multiple pre-dose ECGs rather than a single ECG. After the implementation of this protocol change there were no new discontinuations due to QTc prolongation. We agree with the protocol amendment that the sponsor implemented.
- Evaluation of the QTc outlier data from the Phase 3 pediatric studies did not show any patients with QTcB intervals greater than 480 ms or change from QTcB interval greater than 60 ms. The applicability of these QTc prolongation thresholds in pediatrics is not known and the timing of ECG collection relative to dosing was not controlled, which limits the interpretation. However, the absence of cardiac adverse events related to QTc prolongation is reassuring and IRT-QT reached the following conclusion: 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.

- To better understand the potential for QTc prolongation in pediatrics due to solifenacin exposure with the proposed doses, IRT-QT reviewed a prior thorough QT study for solifenacin conducted in adults and developed a concentration-QTc model. This analysis showed a concentration-dependent increase in QTc for solifenacin, with a 90% upper bound of approximately 11 ms at expected supratherapeutic exposures in pediatric patients.

Reviewer's comment: 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."

7.4.5 Special Safety Studies/Clinical Trials

7.4.5.1 Ocular Accommodation

At the Division's request, ocular accommodation was assessed in Study 905-CL-047. Based on those assessments, it appeared that overall, accommodative accuracy was improved. According to the Sponsor, the 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.

Table 7.23 Analysis of Change from Baseline in Accommodative Error Index (Diopters); All Patients (Aged 5 Years to Less Than 18 Years) (SAF)

Statistic	Children (Aged 5 Years to < 12 Years)	Adolescents (Aged 12 Years to < 18 Years)	All Patients (Aged 5 Years to < 18 Years)
Baseline			
n	21	19	40
Mean (SD)	1.84 (2.49)	1.93 (2.45)	1.88 (2.44)
Week 12			
n	21	19	40
Mean (SD)	1.45 (0.96)	1.86 (1.45)	1.65 (1.22)
Change from baseline			
n	21	17	38
Mean (SD)	-0.39 (1.92)	-0.088 (1.84)	-0.25 (1.86)
95% CI	-1.26, 0.49	-1.03, 0.86	-0.87, 0.36
Week 52			
n	13	2	15
Mean (SD)	1.3 (0.52)	0.78 (0.022)	1.24 (0.52)

At each of the ocular accommodation time points (baseline, week 12 and week 52), 3 measures of the accommodative response (the mean spherical equivalent, MSE in diopters) were made for a range of different accommodative stimuli (0.5, 1.0, 2.0, 3.0, 4.0 and 4.5 diopters, in a random order) and their validity was determined by independent central review.
MSE: mean spherical equivalent; n: number of patients; SAF: safety analysis set.; Source: Table 12.6.5.2.1

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 ophthalmology consultant's comments are summarized herein:

- The procedure used in this study to evaluate accommodation is not a commonly used clinical measure. It is more common to evaluate individual's using accommodative amplitude. Accommodative amplitude is a measure of the maximum increase in diopter power that can be achieved at that time by the individual. Drug products which inhibit an individual's ability to accommodate will decrease the accommodative amplitude.

- In the consultant's opinion, the accommodative response curves measured in this study did not appear to be informative. In many of the cases, it does not appear that the true refractive error was accurately obtained. The patterns of many of the curves, even at baseline, were not as might have been expected.

- The values used to generate the curves were based on triplicate measurements. The triplicate measurements were often divergent, questioning the reliability of the measurement. In the opinion of the consultant, the averaging of these divergent values was not appropriate.

- The consultant states that in the applicant's analysis, "a large number of accommodative response curves were ignored without acknowledging that they were ignored or documenting the reason for ignoring them".

The Ophthalmology consultant provided the following overall consult opinion:

1) The application does not contain reliable information concerning the drug product's effect on accommodation.
    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: For purposes of the Written Request, the Division and the Pediatric Exclusivity Board 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. In regard to the clinical impact of the ophthalmology consultant's comments, we note that there were few vision AEs reported and no vision AE was reported as drug-related. (b) (4)

7.4.5.2 Cognitive Testing

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

- 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 should be 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.

7.4.6 Immunogenicity

No immunogenicity studies were planned or conducted.

7.5 Other Safety Explorations

Several clinical study investigative site inspections were undertaken to assure protocol and GCP compliance. Two large enrolling sites for both the Phase 3 NDO studies (one site in Poland [n=31] and one site in the Philippines [n=21]), were initially selected for inspection (see Table below). Based on political unrest in the Philippines, it was not possible for the inspector to visit Dr. Bolong's site. Instead, two sites in Belgium were chosen to replace the single Philipines sites (again, see Table below).

Study Sites	Principal Investigators	# of Subjects enrolled	
		905-CL-047	905-CL-074
Poland			
#4801: Pomnik-Centrum Zdrowia Dziecka	Malgorzata Baka-Ostrowska	24	7
Philippines			
#6301: Philippines Children's Medical Center	David T Bolong	15	6
Belgium			
#3201: Gent University Hospital #3203: Gent University Hospital	Piet Hoebeke Johan Vande Walle	6 0	0 1

Reviewer's comment: All clinical study site inspections have been conducted, and the Inspection Summary Report from OSI provides a final "NAI" recommendation.

7.5.1 Dose Dependency for Adverse Events

No dose dependency for adverse events was detected.

7.5.2 Time Dependency for Adverse Events

The only finding that appeared to show a time dependency was changes in urinalysis results in one Phase 3 NDO study, as follows:

Urinalysis: In urinalysis results from Phase 3 patients with NDO in Study 905-CL-047, shifts from normal levels at baseline to high levels at week 24 were observed in > 20% of the patients for the following parameters: urine bacteria quantitative (60.9%) and urine leukocytes quantitative (48.0%). The changes are consistent with reports of UTIs.

Reviewer's comment: Shifts from normal to high in bacteriuria and leukocytouria in urinalysis, along with clinical AEs of UTI, are not unexpected findings in this particular pediatric population with NDO and practicing CIC.

7.5.3 Drug-Demographic Interactions

No drug-demographic interactions were observed.

7.5.4 Drug-Disease Interactions

No drug-disease interactions were observed.

7.5.5 Drug-Drug Interactions

No drug-drug interactions were observed. No specific drug-drug interaction study was requested by the Division.

7.6 Additional Safety Evaluations

The Sponsor submitted the required 120-day Safety Update showing that no pediatric patients were undergoing long-term follow-up after the previous data-lock point (DLP) of 02-Sep-2016.

Both the original NDA and the 120-Safety Update contained information on the clinical use of solifenacin tablets in pediatric patient during the Postmarketing period for solifenacin tablets. Solifenacin oral solution is not yet approved in any country. The Sponsor provided Postmarketing data for both adult pediatric patients:

Adults: The cumulative adult exposure to solifenacin in the Postmarketing Experience was estimated to be (b) (4) patient-years at the DLP of 03 Feb 2017. No significant changes to the safety profile of solifenacin succinate were identified from the postmarketing data available since the previous DLP of 02 Sep 2016.

Reviewer's comment: Despite its widespread use in the postmarketing period, the safety profile of solifenacin in adults has not changed since the time of its approval.

Pediatric Patients: The Sponsor identified a total of 404 spontaneous AE reports in pediatric patients (6 neonates, 22 infants, 309 children and 67 adolescents) from a search of their global safety database at the time of the DLP (03 Feb 2017). For purposes of the 120-Day Safety Update, new information for 40 reports (37 initial and 3 follow-up reports) was identified and reviewed subsequent to the previous DLP of 02 Sep 2016. These 40 AE reports concerned 8 adolescents and 32 children. In total, there were 66 adverse events reported in 40 patients, of which 15 adverse events (in 5 patients) were coded as serious adverse events (SAEs). The Sponsor judged that only two of the 4 SAE cases in the 120-Day SU were possibly related to treatment with solifenacin and these two cases are summarized herein:

- #2016JP014099: A 10 y/o Japanese girl with "difficult to control" epilpepsy experienced "excitement" ("worsening of epileptic manifestation") while taking solifenacin 2.5 mg for the treatment of OAB, and within a day of initiating treatment with valproate for

worsening epilepsy. The "excitement" resolved after removing valproate from the child's epilepsy regimen and initiating Keppra for treatment of epilepsy while solifenacin treatment remained ongoing. (**Reviewer's comment: The child's excitement may have been related to uncontrolled epilepsy or to valproate, but is unlikely to have been related to solifenacin.**)

- #2016US039564: A 10 y/o UK boy experienced fibrous gingival hyperplasia and pain while eating and brushing teeth while taking solifenacin for the treatment of and unknown indication. The child was also taking azathioprine, prednisone, tacrolimus, and amlodipine as treatment to prevent post renal transplant rejection. (**Reviewer's comment: The immunosuppressive drugs that the child was taking to prevent renal transplant rejection have been associated with gingival hyperplasia. It is unlikely that solifenacin was related to the event**)

Reviewer's comment: The information provided in the 120-Day Safety Update, including the additional postmarketing pediatric adverse event cases from the Sponsor's global safety database (Period of 02-SEP-2016 through 03-FEB-2017), does not result in changes to the safety profile of solifenacin.

7.6.1 Human Carcinogenicity

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

7.6.2 Human Reproduction and Pregnancy Data

No human reproduction and pregnancy data were included in the NDA submission. The Sponsor conducted a literature search seeking potential human reproduction or pregnancy risks in the pediatric population, and retrieved 4 potentially relevant publications. 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.

7.6.3 Pediatrics and Assessment of Effects on Growth

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

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No issues with drug abuse potential, withdrawal or rebound have been reported. One overdose case in a pediatric patient was reported, in which a 2 y/o Japanese boy accidentally took 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.

7.7 Additional Submissions / Safety Issues

No additional submissions have been received and no new safety issues have been identified.

8 Postmarket Experience

Solifenacin oral suspension has not been approved for use in pediatric patients. However, there has been reports of off-label use of solifenacin tablets in pediatric patients for the treatment of voiding dysfunction disorders. As part of this NDA and with the Division's encouragement, the Sponsor conducted a search of their global postmarketing safety databases and from the launch of VESIcare tablets in 2004 up until 02 Sep 2016, the search identified a total of 369 postmarketing pediatric adverse event reports. Of these 369 reports, 349 were assessed by the reporter as non-serious AEs and 20 were assessed as serious AEs. A summary description of these reports is provided herein:

Table 7.24 Distribution of Solifenacin Postmarketing Adverse Event Reports in Pediatric Patients

Age Group	Number of Reports (Serious Reports)
Neonates (< 29 days)	6 (5)
Infants (29 days to < 2 years)	21 (0)
Child (2 years to < 12 years)	281 (11)
Aged 2 years to < 5 years	14 (1)
Aged 5 years to < 12 years	179 (9)
Age not specified (child)	88 (1)
Adolescent (12 years to < 16 years)	60 (4)
Pediatric (age not specified †)	1 (0)
Total	**369 (20)**

Of the 20 serious adverse event reports, only 3 had sufficient information for an assessment of relationship to solifenacin and were judged to be at least possibly related to solifenacin by the reporter and Sponsor:

- #YEHQ20051279: A 9 y/o Belgium boy with Down's Syndrome and a history of obstipation developed severe obstipation and was hospitalized for fecal disimpaction on the 1st day of treatment with solifenacin 5 mg once daily (in an uncontrolled study) for OAB. The patient required fecal impaction and recovered from the event without sequelae and solifenacin was stopped on Day 14. (**Reviewer's comment: The patient's pre-existing conditions, including chronic obstipation is a confounder factor. It is possibly that pre-existing obstipation contributed at least in part to the need for fecal disimpaction n the same day as initiating solifenacin.**)

- #2016US016128: A 14 y/o French boy with a history of hypermetropia (an accommodation disorder that results in visual-accommodation paralysis) experienced loss of near vision, blurred vision and loss of visual acuity during treatment with solifenacin 5 mg daily for nocturnal enuresis. The patient's solifenacin dose was further increased to 10 mg due to drug ineffectiveness. Treatment with solifenacin lasted for 2 months (daily dose 5 mg for one month and daily dose 10 mg for one month), then was discontinued. The outcomes of visual-accommodation paralysis, loss of near vision, blurred vision, and loss of visual acuity were reported as not recovered/not resolved 1 year following drug discontinuation. (**Reviewer's comment: The patient's underlying hypermetropia condition is an important confounder in this situation, and it is also notable that the patient's symptoms continued despite discontinuation of solifenacin.**)

- #2014US007659**:** One case of "aggression" was reported among 7 "aggression" cases in a published case series of one center's overall experience with solifenacin succinate in pediatric patients (*Nadeau G, et al., CUAJ 8:118-123;* 2014). The article provided no details concerning the "aggression cases", including no details provided for patient age, gender, symptoms severity, treatment and outcomes. (**Reviewer's comment: The published article contains insufficient information to conduct a reliable assessment of relatedness to solifenacin.**)

9 Appendices

9.1 Literature Review/References

There have been published reports of clinical trials of solifenacin in pediatric patients with idiopathic OAB (*J Urol. 2017 May 12. pii: S0022-5347(17)67189-1.* doi: 10.1016/ j.juro. 2017. 05. 038. [Epub ahead of print]); but there have been no published reports of solifenacin in pediatric patients with NDO.

9.2 Labeling Recommendations

(b) (4) .

9.3 Advisory Committee Meeting

It was determined that an Advisory Committee Meeting was not necessary for this application.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GUODONG FANG
08/02/2017

MARK S HIRSCH
08/02/2017
I concur.