U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA Serial Number:	209529
Drug Name:	Solifenacin Succinate 1 mg/mL Oral Suspension
Indication(s):	Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients
Applicant:	Astellas Pharma Global Development, INC.
Date(s):	Submission date: 02/28/2017
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Keywords: Change from Baseline, One-sample T-Test

Table of Contents

LIST OF TABLES

1. EXECUTIVE SUMMARY

Solifenacin succinate is currently approved under NDA 021518 VESIcare® 5 mg and 10 mg tablets for treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency in adults. A Written Request (WR) for the use of solifenacin succinate in treatment of neurogenic detrusor overactivity (NDO) in pediatric patients was issued under NDA 021518 on 27 Jul 2012 with subsequent amendments on 14 Sep 2012, 17 Apr 2014, and 12 Dec 2014.

In this submission, the Applicant submitted the safety and efficacy data from two Phase 3 open-label studies (905-cl-047 in patients 5 to less than 18 years old and 905-cl-074 in patients 6 months to less than 5 years old) to fulfill the WR and seek approval of solifenacin Succinate 1 mg/mL oral suspension for neurogenic detrusor overactivity (NDO) in pediatric patients. This review evaluates to determine from a statistical perspective if the submitted information supports this claim.

Both studies were multinational, multi-center, open-label, single arm Phase 3 studies with a 12-week dose titration period followed by 40 weeks of treatment with fixed dose.

The primary efficacy endpoint was the change from baseline in maximum cystometric capacity (MCC) during treatment period at week 24 (measured in mL). The secondary efficacy variables, based on urodynamic assessments and diaries, were change from baseline at week 24 in:

- the bladder compliance;
- the number of overactive detrusor contractions (> 15 cmH_2O) until leakage or end of bladder-filling;
- the bladder volume until first detrusor contraction (> 15 cmH_2O) as a percentage of expected bladder capacity (mL);
- the maximum catheterized volume per day; and
- the mean number of incontinence episodes per 24 hours.

The primary endpoint was analyzed using one-sample T-test to test that the change was equal to zero and the secondary endpoints were analyzed in a similar way. Due to lack of a control group, the interpretation of the results is descriptive in nature.

The efficacy results in subjects aged 2 to less than 5 years are:

- the MCC increased by 38.9 mL (SD: 35.5, 95% CI 20.6 to 57.2);
- the bladder compliance increased by 5.8 mL/cmH_2O (SD: 7.3; 95% CI: 2.1, 9.6);
- the number of overactive contractions > 15 cmH_2O decreased by -7.0 (SD: 9.3; 95% CI: -11.8, -2.2);
- the bladder volume until first detrusor contraction > 15 cmH_2O increased by 31.1% of expected bladder capacity for patients who had a detrusor contraction during the urodynamic assessment at Week 24;
- the maximum catheterized volume per day increased by 45.3 mL (SD: 54.7; 95% CI: 15.0, 75.6); and
- the mean number of incontinence episodes per 24 hours decreased by -1.6 (SD: 1.2; 95% CI: -2.3, -0.9).

The efficacy results in subjects aged 5 to less than 18 years are:

- the MCC increased by 57.2 mL (SD: 107.7, 95% CI 26.3 to 88.1);
- the bladder compliance increased by 9.1 mL/cmH_2O (SD: 28.6; 95% CI: 1.0, 17.2);

- the number of overactive contractions > 15 cmH_2O decreased by -2.3 (SD: 5.1; 95% CI: -3.7, -0.8);
- the bladder volume until first detrusor contraction > 15 cmH_2O increased by 13.3% of expected bladder capacity for patients who had a detrusor contraction during the urodynamic assessment at Week 24;
- the maximum catheterized volume per day increased by 67.5 mL (SD: 88.1; 95% CI: 42.7, 92.2); and
- the mean number of incontinence episodes per 24 hours decreased by -1.6 (SD: 2.0; 95% CI: -2.2, -1.0).

Both studies demonstrated that there is clinical benefit of solifenacin succinate in treatment of neurogenic detrusor overactivity (NDO) in pediatric patients.

2. INTRODUCTION

2.1 Overview

The Applicant, Astellas Pharma Global Development INC., submitted an original New Drug Application (NDA 209529) for solifenacin succinate1 mg/mL oral suspension for treatment of neurogenic detrusor overactivity (NDO) in pediatric patients.

According to the Applicant,

> "solifenacin succinate is a competitive muscarinic receptor antagonist with high affinity for M3-receptors. The muscarinic M3-receptor antagonist effect is considered the main mechanism of solifenacin-induced relaxation of the urinary bladder."

Solifenacin succinate is currently approved under NDA 021518 VESIcare® 5 mg and 10 mg tablets for treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency in adults. A Written Request (WR) for the use of solifenacin succinate in treatment of neurogenic detrusor overactivity (NDO) in pediatric patients was issued under NDA 021518 on 27 Jul 2012 with subsequent amendments on 14 Sep 2012, 17 Apr 2014, and 12 Dec 2014.

The statistical review for this NDA is based on two open-label, single arm phase 3 studies, 905-cl-047 and 905-cl-074, which are briefly summarized in Table 2.

Table 1: List of all Studies included in the Statistical Review

Study	Phase and Design	Treatment Period	# of Subjects per Arm	Study Population
905-CL-047	Phase 3, open label, baseline controlled, multicenter, sequential dose titration	Titration: 12 weeks Fixed dose: 40 weeks	Enrolled: 76 patients Completed: 58 patients	pediatric patients with NDO aged 5 years and older
905-CL-074	Phase 3, open label, baseline controlled, multicenter, sequential dose titration	Titration: 12 weeks Fixed dose: 40 weeks	Enrolled: 23 patients (4 patients aged 6 months to < 2 years; 19 patients aged 2 years to < 5 years) Completed: 21 (3 patients aged 6 months to < 2 years; 18 patients aged 2 years to < 5 years)	pediatric patients with NDO aged 6 months to < 5 years

Source: Statistical reviewer's summary.

2.2 Data Sources

The study protocols, reports, data and additional information were submitted electronically. These items are located in the Electronic Document Room at \\Cdsesub1\evsprod\NDA209529 under submission dates 2/28/2017, 4/10/2017, 4/21/2017, 5/16/2017, 6/19/2017, 6/22/2017 and 6/29/2017.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The Applicant submitted both tabulation data and analysis data for the two studies. Data sets were complete and documented. Statistical analysis programs were submitted per reviewer's request.

The statistical analyses of efficacy endpoints in each study were carried out following the pre-specified statistical analysis plan. It was noted that the Applicant erroneously included a patient in the full analysis data set for study 905-cl-074. All affected analyses by this error were re-conducted and updated results were submitted on 6/29/2017.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Both studies 905-cl-047 and 905-cl-074 (hereafter referred as 047 and 074) were phase 3, open-label, baseline-controlled, multicenter, sequential dose-titration studies to assess the pharmacokinetics, long-term efficacy and safety of solifenacin succinate suspension in children with neurogenic detrusor overactivity. Study 047 was conducted in children from 5 years old to less than 18 years old and study 074 was conducted in children from 6 months to less than 5 years old.

Each study contained a screening visit, a baseline visit (start of the 12-week titration period), four visits (Weeks 3, 6, 9, 12) during the titration period, and three visits during the fixed dose treatment period (Weeks 24, 36 and 52). Study 047 had an additional visit to start the washout period 2 weeks before baseline visit.

The primary and selected secondary variables (for labeling) were calculated based on (1) valid urodynamic assessments (baseline and post-baseline), (2) diary data (7-day diary for study 074 and 3-day diary for study 047).

For both studies, the primary efficacy endpoint was the change from baseline to Week 24 in maximum cystometric capacity (MCC) measured in mL. MCC was recorded in the "VOLUME" section of the "Urodynamic Testing" pages of the eCRF. When leakage occurred, the "Volume of fluid until leakage" was recorded. When filling stopped because the subject experienced pain or discomfort the "Volume of instilled fluid until Pain/Discomfort" field in the eCRF was used. When filling stopped because the bladder was filled to 135% of EBC (or MaxCV for children aged <2 years), the "Volume of instilled fluid until 135% of EBC" field in the eCRF was used.

The change from baseline to Week 24 in MCC is the MCC at the Week 24 visit minus the baseline MCC which was recorded at the baseline visit (Visit 3).

The selected secondary efficacy endpoints for the two studies were as follows.

Changes from baseline to Week 24 and Week 52 in:

- bladder compliance;
- bladder volume until first detrusor contraction (> 15 cmH_2O);
- number of overactive detrusor contractions (> 15 cmH_2O) until leakage or end of bladder-filling;
- maximum catheterized volume per day; and

- mean number of periods between the CICs with incontinence per 24 hours.

3.2.2 Statistical Methodologies

Changes from baseline in MCC at each visit were summarized (with and without last observation carried forward for missing data) for all subjects in the FAS. The following hypotheses were tested at the 2-sided significance level of 0.05:

H_0: Change from baseline to week 24 in MCC is equal to zero
H_1: Change from baseline to week 24 in MCC is not equal to zero

Mean change from baseline estimates, together with 95% CIs and the t-test p-value were provided. For study 047, in addition to the test of the null hypothesis, it would be assessed whether the lower bound of the two-sided 95% confidence interval lies above 16.9 mL.

All analyses of secondary endpoints were produced for subjects in the FAS. Each of the secondary efficacy endpoints were summarized by visit. The change from baseline for each secondary endpoint, based on urodynamics (except for the endpoint bladder volume as percentage of EBC) and for the average catheterized volume per catheterization and maximum catheterized volume per day based on the patient diary were summarized and analyzed using the same approach as for the primary efficacy endpoint.

For the analysis of bladder volume until first detrusor contraction (>15 cmH_2O) expressed as percentage of EBC, summary statistics were shown for all patients. If no detrusor contraction of at least 15 cmH_2O occurs, the bladder volume was imputed with MCC. A Wilcoxon Signed Rank Test was used to compare between baseline (Week 3) and end of treatment (Week 24). The Wilcoxon Signed Rank test p-value was provided.

Reviewer's comments: *For the bladder volume until first detrusor contraction (>15 cmH_2O) expressed as percentage of EBC, the reviewer analyzed it using the same approach as above for the subset of patients with detrusor contraction only per clinical team's request*

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

The disposition of study patients is summarized for each study (Table 2 and Table 3). In study 047, a total of 92 patients were screened and 76 received treatment. 10 out of 18 patients who discontinued the treatment were due to protocol violation. Study 074 screened 24 patients and 23 patients received treatment and only 2 patients discontinued early.

Table 2: Study 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 3: Study 074 - Summary of Subject Disposition

	6 months 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.

The applicant pre-defined the following analyses datasets in each study,

Safety Analysis Set (SAF): all subjects who took at least one dose of study drug. The SAF was used for summaries of demographic and baseline characteristics and all safety and tolerability related variables.

Full Analysis Set (FAS): all subjects who took at least one dose of study drug, and provided both valid baseline and at least one post-baseline value for the primary efficacy endpoint (MCC). The FAS was used for analyses of efficacy data, including the primary analysis of the primary efficacy variable, as well as for summaries of some demographic and baseline characteristics.

Per Protocol Set (PPS): all subjects of the FAS who fulfilled the protocol in terms of their eligibility, interventions and outcome assessments, and for whom MCC measurements at baseline/Visit 3 and at Visit 8 (Week 24) were observed.

Table 4: Analysis Sets

	Study 047	Study 074
SAF	76 (100%)	23 (100.0%)
FAS	55 (72.4%)	21 (91.3%)
PPS	39 (51.3%)	19 (82.6%)

Source: Table 12.1.1.2 in study 047 and 074 reports

SAF: safety analysis set. FAS: full analysis set; PPS: per protocol set.

Reviewer's comments: *In study 047, 21 out of 76 subjects who received treatment were not included in the full analysis set (FAS). Per reviewer's information request, dated 4/17/2017, the Applicant provided detailed explanation (dated 05/26/2017) why the 21 subjects were excluded from full analysis set. The clinical reviewer confirmed that the reasons for exclusion were acceptable.*

Demographics and Baseline Characteristics

The demographics and baseline characteristics by treatment groups are summarized in Table 24 and Table 25 for the two studies in the Appendix. In study 047, the population was predominantly White (59.2%) and Asian (30.3%). The mean age (SD) was 10.8 (3.3) years (between 5 and 17 years) and the median weight was 34.6 kg. In study 074, the population was White (54.2%) and Asian (45.8%). The mean age (SD) was 2.5 (1.0) years (between 13 months to 4 years) and the median weight was 13.0 kg.

3.2.4 Results and Conclusions

Study 047

Maximum Cystometric Capacity

The analysis results for the primary efficacy endpoints are shown in Table 5. At week 24, there was an increase (mean [SD]: 57.2 [107.7] mL) in MCC compared to baseline (95% CI: 26.3, 88.1) and the lower bound of the 95% CI for the change was greater than 16.9, the criteria for acceptable change. At week 52, the mean (SD) change from baseline in MCC was 51.0 (102.9) mL.

Table 5: Study 047 - Change from Baseline in Maximum Cystometric Capacity (mL) (FAS)

Statistic	Visit			
	Baseline	Week 24	Week 24 LOCF	Week 52
n	55	49	55	42
Mean (SD)	223.7 (132.9)	279.1 (126.8)	282.9 (127.1)	268.1 (104.1)
Change from baseline				
n†	-	49	55	
Mean (SD)		57.2 (107.7)	59.3 (107.5)	51.0 (102.9)
95% CI		26.3, 88.1	30.2, 88.3	
P-value‡		< 0.001	<0.001	

Source: Table 12.3.1.1.1 and 12.3.1.2.1 in study 047 report.
FAS: full analysis set; LOCF: last observation carried forward; n: number of patients; NA: not applicable.
† n is the number of patients with a nonmissing change from baseline at that week..
‡ From a 2-sided one sample t-test, testing the null hypothesis that change from baseline = 0.

Bladder Compliance

At week 24, there was an increase (mean [SD]: 9.1 [28.6] mL/cmH_2O) in bladder compliance compared to baseline (95% CI: 1.0, 17.2). At week 52, the mean (SD) change from baseline in bladder compliance was 1.6 (42.1) mL/cmH_2O.

Table 6: Study 047 - Change from Baseline in Bladder Compliance (mL/cmH_2O) (FAS)

Statistic	Visit			
	Baseline	Week 24	Week 24 LOCF	Week 52
n	54	50	53	42
Mean (SD)	14.6 (36.4)	24.4 (39.9)	23.4 (38.9)	17.6 (22.0)
Change from Baseline				
n†		50	53	42
Mean (SD)		9.1 (28.6)	8.8 (27.8)	1.6 (42.1)
95% CI		1.0, 17.2	1.1, 16.5	
P-value‡		0.029	0.026	

Source: Table 12.3.3.1 and Table 12.3.3.2 in study 047 report.
FAS: full analysis set; LOCF: last observation carried forward; n: number of patients; NA: not applicable.
† n is the number of patients with a nonmissing change from baseline at that week..
‡ From a 2-sided one sample t-test, testing the null hypothesis that change from baseline = 0.

Number of Overactive Detrusor Contractions (> 15 cmH_2O) Until End of Bladder Filling

At week 24, there was a decrease (mean [SD]: -2.3 [5.1]) in the number of overactive detrusor contractions (> 15 cmH_2O) compared to baseline (95% CI: -3.7, -0.8). At week 52, the mean (SD) change from baseline in the number of overactive detrusor contractions was -2.5 (4.7).

Table 7: Study 047 - Change from Baseline in Number of Overactive Detrusor Contractions (> 15 cmH_2O) Until End of Bladder Filling (FAS)

Statistic	Visit			
	Baseline	Week 24	Week 24 LOCF	Week 52
n	54	50	55	42
Mean (SD)	3.9 (4.7)	1.6 (2.2)	2.0 (4.5)	1.0 (2.0)
Change from Baseline				
n†		50	54	42
Mean (SD)		-2.3 (5.1)	-1.8 (6.0)	-2.5 (4.7)
95% CI		-3.7, -0.8	-3.5, -0.2	
P-value‡		0.003	0.028	

Source: Table 12.3.7.1 and Table 12.3.7.2 in study 047 report.
FAS: full analysis set; LOCF: last observation carried forward**;** n: number of patients; NA: not applicable.
† n is the number of patients with a nonmissing change from baseline at that week..
‡ From a 2-sided one sample t-test, testing the null hypothesis that change from baseline = 0.

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

In study 047, among the 55 patients, 25 had detrusor contraction at least > 15 cmH_2O at Week 24 assessment. For these 25 patients, there was an increase (median: 13.3%) in bladder volume until first detrusor contraction > 15 cmH_2O as a percentage of EBC compared with baseline. At week 52, the median change from baseline in bladder volume until first detrusor contraction > 15 cmH_2O as a percentage of EBC was 17.7%. If no detrusor contraction of at least 15 cmH_2O occurred, the bladder volume was imputed with MCC. For all patients, at week 24, there was an increase (median: 23.1%) in bladder volume until first detrusor contraction > 15 cmH_2O as a percentage of EBC compared with baseline.

Table 8 : Study 047 - Change from Baseline in Bladder Volume (mL) Until First Detrusor Contraction > 15 cmH2O as a Percentage of Expected Bladder Capacity (mL) (FAS)

	Statistic	Visit		
		Baseline	Week 24	Week 52
All Patients[1]	**N**	54	50	42
	Median	28.3	58.3	75.5
	Change from Baseline			
	n		50	42
	Median		23.1	37.3
	P-value†		<0.001	
Patients who had a Detrusor Contraction at Week 24	**n (%‡)**	25 (45.5%)	25 (45.5%)	
	Median	27.7	45.6	
	Change from Baseline			
	Median		13.3	
	P-value†		0.001	

Source: Reviewer's analysis; Table 12.3.4.1 and Table 12.3.4.2 in study 047 report.
1. If no detrusor contraction of at least 15 cmH2O occurs, the bladder volume was imputed with MCC.
† From a Wilcoxon Signed Rank testing the null hypothesis that the median at week 24 was equal to baseline median.
‡ The denominator for % is the number of patients in FAS set.
FAS: full analysis set; MCC: maximum cystometric capacity; n: number of patients; NA: not applicable.

Maximum Catheterized Volume (MCV) Per Day

At week 24, there was an increase (mean [SD]: 67.5 [88.1] mL) in MCV per day compared with baseline (95% CI: 42.7, 92.2). At week 52, the mean (SD) change from baseline in MCV per day was 61.0 (90.9) mL.

Table 9: Study 047 - Change from Baseline in Maximum Catheterized Volume (mL) (FAS)

Statistic	Visit			
	Baseline	Week 24	Week 24 LOCF	Week 52
n	54	52	55	50
Mean (SD)	203.5 (92.7)	272.6 (110.8)	274.8 (109.6)	263.6 (101.3)
Change from baseline				
n†		51	54	49
Mean (SD)		67.5 (88.1)	69.3 (88.8)	61.0 (90.9)
95% CI		42.7, 92.2	45.4, 93.9	
P-value‡		<0.001	<0.001	

Source: Table 12.3.10.1 and Table 12.3.10.2 in study 047 report.
FAS: full analysis set; LOCF: last observation carried forward; n: number of patients; NA: not applicable.
† n is the number of patients with a nonmissing change from baseline at that week..
‡ From a 2-sided one sample t-test, testing the null hypothesis that change from baseline = 0.

Mean Number of Incontinence Episodes per 24 Hours

At week 24, there was a decrease (mean [SD]: -1.6 [2.0]) in the mean number of incontinence episodes per 24 hours compared with baseline (95% CI: -2.2, -1.0). At week 52, the mean (SD) change from baseline in the mean number of incontinence episodes per 24 hours was -2.0 (2.3).

Table 10 : Study 047 - Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours (FAS)

Statistic	Visit			
	Baseline	Week 24	Week 24 LOCF	Week 52
n	54	52	55	50
Mean (SD)	3.4 (2.9)	1.8 (1.9)	1.7 (1.9)	1.5 (1.8)
Change from Baseline				
n†		51	54	49
Mean (SD)		-1.6 (2.0)	-1.6 (2.0)	-2.0 (2.3)
95% CI		-2.2, -1.0	-2.2, -1.1	
P-value‡		< 0.001	<0.001	

Source: Table 12.3.12.1 and Table 12.3.12.2 in study 047 report.
FAS: full analysis set; LOCF: last observation carried forward; n: number of patients; NA: not applicable.
† n is the number of patients with a nonmissing change from baseline at that week..
‡ From a 2-sided one sample t-test, testing the null hypothesis that change from baseline = 0.

Reviewer's comments: *The reviewer is able to replicate the Applicant's analysis results on primary and secondary efficacy endpoints for study 047.*

Study 074

It was noted that the Applicant erroneously included one more patient in the FAS set. All efficacy results were updated excluding one patient as per Division's request, dated 6/29/2017. The analysis results with or without LOCF at Week 24 are the same.

For the labeling, The Agency and the sponsor reached the agreement that only the results for patients who were at least 2 years in study 074 would be labeled. Therefore, this review presents the study results for all patients and 2 to 5 years old separately.

Maximum Cystometric Capacity

The analysis results for the primary efficacy endpoints are shown in Table 11. For patients between 2 to 5 year old, mean MCC (SD) at baseline was 97.8 (39.5) mL. At week 24, mean MCC (SD) was 136.7 (36.8) mL. The change from baseline to week 24 in mean MCC (SD) was 38.9 (35.5) mL. At week 52, the mean (SD) change from baseline in MCC was 60.3 (36.7) mL.

Table 11: Study 074 - Change from Baseline in Maximum Cystometric Capacity (mL) (FAS)

Statistic	Visit		
	Baseline	Week 24	Week 52
All Patients			
n	21	21	14
Mean (SD)	92.3 (38.2)	129.4 (40.2)	147.7 (45.8)
Change from baseline			
n†		21	14
Mean (SD)		37.0 (35.9)	58.6 (34.1)
95% CI		20.7, 53.4	
P-value‡		<0.001	
Patients Aged 2 to ≤ 5 Years			
n	17	17	12
Mean (SD)	97.8 (39.5)	136.7 (36.8)	151.3 (48.3)
Change from baseline			
n†		17	12
Mean (SD)		38.9 (35.5)	60.3 (36.7)
95% CI		20.6, 57.2	
P-value‡		<0.001	

Source: Table 12.3.1.1.1 and 12.3.1.2.1 in 6/29/2017 submission.

FAS: full analysis set; LOCF: last observation carried forward; n: number of patients; NA: not applicable.

† n is the number of patients with a nonmissing change from baseline at that week..

‡ From a 2-sided one sample t-test, testing the null hypothesis that change from baseline = 0.

Bladder Compliance

For patients between 2 to 5 years old, at week 24, there was an increase (mean [SD]: 5.8[7.3] mL/cmH_2O) in bladder compliance compared with baseline (95% CI: 2.1, 9.6). At week 52, the mean (SD) change from baseline in bladder compliance was 5.6 (4.2) mL/cmH_2O.

Table 12: Study 074 - Change from Baseline in Bladder Compliance (mL/cmH_2O) (FAS)

Statistic	Visit		
	Baseline	Week 24	Week 52
All Patients			
n	21	21	14
Mean (SD)	5.1 (4.6)	10.2 (10.3)	11.3 (7.2)
Change from baseline			
n†		21	14
Mean (SD)		5.1 (6.8)	5.9 (4.2)
95% CI		2.0, 8.2	
P-value‡		0.003	
Patients Aged 2 to ≤ 5 Years			
n	17	17	12
Mean (SD)	5.7 (4.9)	11.5 (11.0)	11.4 (7.7)
Change from baseline			
n†		17	12
Mean (SD)		5.8 (7.3)	5.6 (4.2)
95% CI		2.1, 9.6	
P-value‡		0.004	

Source: Table 12.3.2.1 and Table 12.3.2.2 in 6/29/2017 submission
FAS: full analysis set; LOCF: last observation carried forward; n: number of patients; NA: not applicable.
† n is the number of patients with a nonmissing change from baseline at that week..
‡ From a 2-sided one sample t-test, testing the null hypothesis that change from baseline = 0.

Number of Overactive Detrusor Contractions (> 15 cmH2O) Until End of Bladder Filling

For patients between 2 to 5 years old, there was a decrease (mean [SD]: -7.0 [9.3]) in the number of overactive detrusor contractions (> 15 cmH_2O) compared with baseline (95% CI: -11.8, -2.2) at week 24. At week 52, the mean (SD) change from baseline in the number of overactive detrusor contractions was -6.9 (10.6).

Table 13: **Study 074 - Change from Baseline in Number of Overactive Detrusor Contractions (> 15 cmH_2O) Until End of Bladder Filling (FAS)**

Statistic	Visit		
	Baseline	Week 24	Week 52
Overall			
n	21	21	14
Mean (SD)	9.5 (10.7)	2.5 (3.5)	2.4 (4.9)
Change from baseline			
n†		21	14
Mean (SD)		-7.0 (8.6)	-7.2 (10.2)
95% CI		-11.0, -3.1	
P-value‡		0.001	
Patients Aged 2 to ≤ 5 Years			
n	17	17	12
Mean (SD)	9.9 (11.6)	2.9 (3.8)	2.8 (5.2)
Change from baseline			
n†		17	12
Mean (SD)		-7.0 (9.3)	-6.9 (10.6)
95% CI		-11.8, -2.2	
P-value‡		0.007	

Source: Table 12.3.8.1 and Table 12.3.8.2 in 6/29/2017 submission
FAS: full analysis set; LOCF: last observation carried forward; n: number of patients; NA: not applicable.
*Primary analysis
† n is the number of patients with a nonmissing change from baseline at that week..
‡ From a 2-sided one sample t-test, testing the null hypothesis that change from baseline = 0.

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

In study 074, among 17 patients between 2 to 5 years old, 8 patients had detrusor contraction of at least 15 cmH_2O. For these 8 patients, the bladder volume until first detrusor contraction > 15 cmH_2O as a percentage of EBC increased by 31.1% compared with baseline at week 24. If no detrusor contraction of at least 15 cmH_2O occurred, the bladder volume was imputed with MCC. Under the imputation, the bladder volume until first detrusor contraction > 15 cmH_2O as a percentage of EBC increased by 53.3% compared with baseline.

Table 14: Study 074 - Change from Baseline in Bladder Volume (mL) Until First Detrusor Contraction > 15 cmH2O as a Percentage of Expected Bladder Capacity (mL) (FAS)

	Statistic	Visit		
		Baseline	Week 24	Week 52
All Patients				
Overall[1]	**N**	21	21	14
	Median	38.0	99.9	115.3
	Change from Baseline			
	n		21	14
	Median		53.3	82.3
	P-value†		0.001	
Patients who had a Detrusor Contraction at Week 24	**n (%‡)**	11 (52.4 %)	11(52.4%)	
	Median	37.3	43.3	
	Change from Baseline			
	n		11	
	Median		31.4	
	P-value†		0.2402	
Patients Aged 2 to ≤ 5 Years				
Overall[1]	**N**	17	17	12
	Median	37.3	88.3	107.9
	Change from Baseline			
	n		17	12
	Median		53.3	75.2
	P-value†		<0.001	
Patients who had a Detrusor Contraction at Week 24	**n (%‡)**	8 (47.1%)	8 (47.1%)	
	median	15.8	38.2	
	Change from Baseline			
	n		8	
	Median		31.1	
	P-value†		0.195	

Source: Reviewer's analysis.

1 If no detrusor contraction of at least 15 cmH_2O occurs, the bladder volume was imputed with MCC.

† From a Wilcoxon Signed Rank testing the null hypothesis that the median at week 24 was equal to baseline median.

‡ The denominator for the percentage is N at baseline.

FAS: full analysis set; MCC: maximum cystometric capacity; n: number of patients; NA: not applicable.

Maximum Catheterized Volume (MCV) Per Day

For patients between 2 to 5 years old, at week 24, there was an increase (mean [SD]: 45.3 [54.7] mL) in MCV per day compared with baseline (95% CI: 15.0, 66.1). At week 52, the mean (SD) change from baseline in MCV per day was 41.7(46.7) mL.

Table 15: Study 074 - Change from Baseline in Maximum Catheterized Volume (mL) (FAS)

Statistic	Visit		
	Baseline	Week 24	Week 52
Overall			
n	18	21	19
Mean (SD)	76.5 (40.6)	122.7(48.3)	124.7 (35.1)
Change from baseline			
n†		18	16
Mean (SD)		40.6 (51.5)	41.7 (46.7)
95% CI		15.0, 66.1	
P-value‡		0.004	
Patients Aged 2 to ≤ 5 Years			
n	15	17	16
Mean (SD)	76.7 (43.0)	125.9 (47.5)	121.3 (31.0)
Change from baseline			
n†		15	14
Mean (SD)		45.3 (54.7)	40.3 (49.5)
95% CI		15.0, 75.6	
P-value‡		0.006	

Source: Table 12.3.12.1.1 and Table 12.3.12.1.2 in 6/29/submission
FAS: full analysis set; LOCF: last observation carried forward; n: number of patients; NA: not applicable.
*Primary analysis
† n is the number of patients with a nonmissing change from baseline at that week..
‡ From a 2-sided one sample t-test, testing the null hypothesis that change from baseline = 0.

Mean Number of Incontinence Episodes per 24 Hours

For patients between 2 to 5 years old, there was a decrease (mean [SD]: -1.6 [1.2]) in the mean number of incontinence episodes per 24 hours compared with baseline at week 24 (95% CI: -2.3, -0.9). At week 52, the mean (SD) change from baseline in the mean number of incontinence episodes per 24 hours was -1.4 (1.5).

Table 16: Study 074 - Change from Baseline in Mean Number of Incontinence Episodes per 24 Hours (FAS)

Statistic	Visit		
	Baseline	Week 24	Week 52
Overall			
n	17	19	16
Mean (SD)	3.9 (0.8)	2.4 (1.5)	2.5 (1.5)
Change from baseline			
n†		17	14
Mean (SD)		-1.3 (1.4)	-1.3 (1.4)
95% CI		-2.0, -0.6	
P-value‡		0.001	
Patients Aged 2 to ≤ 5 Years			
n	14	15	13
Mean (SD)	3.9 (0.8)	2.2 (1.4)	2.4 (1.7)
Change from baseline			
n†		14	12
Mean (SD)		-1.6 (1.2)	-1.4 (1.5)
95% CI		-2.3, -0.9	
P-value‡		<0.001	

Source: Reviewer's analysis; Table 12.3.14.1 and Table 12.3.14.2 in 6/29/2017 submission.
FAS: full analysis set; LOCF: last observation carried forward; n: number of patients; NA: not applicable.
† n is the number of patients with a nonmissing change from baseline at that week.
‡ From a 2-sided one sample t-test, testing the null hypothesis that change from baseline = 0.

4. Evaluation of Safety

Refer to the clinical reviewer's report for evaluation of safety data.

5. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

5.1 Gender, Race, Age, and Geographic Region

Efficacy of solifenacin was also explored by subgroups defined by gender, age and race descriptively. The categories for each subgroup variable are defined in the following table.

Table 17: Subgroup categories defined in each study

Grouping variable	Subgroups
Gender	Female Male
Age group	Study 047: 5 years to < 12 years 12 years to < 18 years Study 074: 6 months to <2 years 2 years to <5 years
Race	White, Asian, Other

MCC and change from baseline in MCC are summarized by subgroups for all subjects in the FAS (see Tables 18 to 23). The changes from baseline in MCC are similar across the subgroups of gender and age numerically. In study 047, the change in MCC is smaller in white patients comparing to other racial groups. Due to the small sample size of the two studies, the subgroup analysis results are only for exploratory purpose and no definitive conclusion can be drawn.

Table 18: Study 047 - Change from Baseline in Maximum Cystometric Capacity (mL) by Gender (FAS)

Statistics	Male (n=28)		Female (n=27)	
	Baseline	Week 24	Baseline	Week 24
n	28	24	27	25
Mean (SD)	226.4 (134.5)	287.7 (133.8)	220.8 (133.7)	270.8 (133.8)
Change from baseline				
n		24		25
Mean (SD)		56.3 (102.7)		58.1 (114.3)

Source: Reviewer's analysis

Table 19: Study 074 - Change from Baseline in Maximum Cystometric Capacity (mL) by Gender (FAS)

Statistics	Male (n=8)		Female (n=13)	
	Baseline	Week 24	Baseline	Week 24
n	8	8	13	13
Mean (SD)	104.8 (40.3)	130.4 (41.2)	84.7 (36.2)	128.8 (41.3)
Change from baseline				
n		8		13
Mean (SD)		25.6 (34.8)		44.1 (36.0)

Source: Reviewer's analysis

Table 20: Study 047 - Change from Baseline in Maximum Cystometric Capacity (mL) by Age group (FAS)

Statistic	Aged 5 Years to < 12 Years		Aged 12 Years to < 18 Years	
	Baseline	Week 24	Baseline	Week 24
n	27	24	28	25
Mean (SD)	157 (92.0)	212 (104)	288 (136)	344 (114)
Change from baseline				
n†		24		25
Mean (SD)		59.9 (93.0)		54.6 (122)

Source: Reviewer's analysis

Table 21: Study 074 - Change from Baseline in Maximum Cystometric Capacity (mL) by Age group (FAS)

Statistic	Aged 6 months to <2 Years		Aged 2 Years to < 5 Years	
	Baseline	Week 24	Baseline	Week 24
n	4	4	17	17
Mean (SD)	69.0 (22.2)	98.3 (44.4)	97.8 (39.5)	136.7 (36.8)
Change from baseline				
n†		4		17
Mean (SD)		29.3 (41.7)		38.9 (35.5)

Source: Reviewer's analysis

Table 22: Study 047 - Change from Baseline in Maximum Cystometric Capacity (mL) by Race group (FAS)

Statistic	White (n=29)		Asian (n=18)		Other (n=8)	
	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24
n	29	24	18	18	8	7
Mean (SD)	242.6 (134.5)	271.4 (105.7)	181.9 (124.2)	262.5 (155.1)	248.9 (140.4)	348.1 (104.8)
Change from baseline						
n†		24		18		7
Mean (SD)		30.2 (117.2)		80.6 (86.3)		89.4 (114.8)

Source: Reviewer's analysis

Table 23: Study 074 - Change from Baseline in Maximum Cystometric Capacity (mL) by Race group (FAS)

Statistic	White		Asian	
	Baseline	Week 24	Baseline	Week 24
n	10	10	11	11
Mean (SD)	82 (22.2)	115.9 (33.8)	101.7 (47.6)	141.6 (43.1)
Change from baseline				
n†		10		11
Mean (SD)		33.9 (28.6)		39.9 (42.6)

Source: Reviewer's analysis

5.2 Other Special/Subgroup Populations

None.

6. SUMMARY AND CONCLUSIONS

6.1 Statistical Issues and Collective Evidence

The Applicant submitted two open-label single arm phase 3 studies (047 and 074) to evaluate the efficacy and safety of solifenacin succinate suspension in children and to fulfill the written request. These studies had limitations due to lack of control group for ethical reason. Therefore the evaluation of the treatment effect on efficacy is descriptive in nature.

The primary and secondary efficacy endpoints based on the urodynamic assessment and diaries demonstrated improvement at Week 24 compared to baseline.

6.2 Conclusions and Recommendations

The purpose of this review is to evaluate the efficacy data in support of solifenacin succinate suspension in the treatment of NDO in children. Based on reviewer's analyses, two studies demonstrated clinical benefit for this indication.

7. APPENDICES

Table 24: Study 047 - Summary of Demographics and Baseline Characteristics (SAF)

Parameter Category/Statistics	5 Years to < 12 Years n = 42	12 Years to < 18 Years n = 34	All Patients n = 76
Sex, n (%)			
Male	20 (47.6)	17 (50.0)	37 (48.7)
Female	22 (52.4)	17 (50.0)	39 (51.3)
Ethnicity, n (%)			
Hispanic or Latino	7 (16.7)	4 (11.8)	11 (14.5)
Not Hispanic or Latino	35 (83.3)	30 (88.2)	65 (85.5)
Race, n (%)			
White	22 (52.4)	23 (67.6)	45 (59.2)
Black/African American	1 (2.4)	1 (2.9)	2 (2.6)
Asian	17 (40.5)	6 (17.6)	23 (30.3)
American Indian/ Alaskan Native	0	1 (2.9)	1 (1.3)
Other	2 (4.8)	3 (8.8)	5 (6.6)
Age† (Years)			
Mean (SD)	8.3 (1.9)	13.9 (1.7)	10.8 (3.3)
Median	8.0	14.0	11.0
Min - Max	5 - 11	12 - 17	5 - 17
Weight† (kg)			
Mean (SD)	28.1 (8.46)	50.4 (13.3)	38.1 (15.5)
Median	26.2	48.5	34.6
Min - Max	15.0 - 53.7	32.0 - 83.2	15.0 - 83.2
Height† (cm)			
Mean (SD)	127 (11.0)	152 (9.31)	138 (16.3)
Median	126	154	140
Min - Max	107 - 154	131 - 171	107 - 171
BMI (kg/m^2)			
Mean (SD)	17.2 (3.32)	21.6 (5.01)	19.2 (4.69)
Median	16.1	20.0	18.2
Min - Max	11.8 - 27.7	15.2 - 34.7	11.8 - 34.7

† Age, weight and height at visit 1 (screening).
BMI: body mass index; Max: maximum; Min: minimum; n: number of patients; SAF: safety analysis set.

Table 25: Study 074 - Summary of Demographics and Baseline Characteristics (SAF)

Parameter Category/Statistics	All Children (6 Months to < 5 Years) n = 23
Sex, n (%)	
Male	9 (39.1)
Female	14 (60.9)
Ethnicity, n (%)	
Hispanic or Latino	2 (8.7)
Not Hispanic or Latino	21 (91.3)
Race, n (%)	
White	12 (52.2)
Black/African American	0
Asian	11 (47.8)
Age‡ (Months)	
Mean (SD)	35.3 (12.7)
Median	36.0
Min - Max	13.0 - 58.9
Weight‡ (kg)	
Mean (SD)	13.2 (2.87)
Median	13.0
Min - Max	8.8 - 20.3
Height‡ (cm)	
Mean (SD)	89.3 (9.21)
Median	92.3
Min - Max	67.0 - 104
BMI (kg/m^2)	
Mean (SD)	16.5 (2.23)
Median	16.2
Min - Max	13.3 - 20.9

‡ Age, Weight and Height at screening (visit 1).

BMI: body mass index; Max: maximum; Min: minimum; n: number of patients; SAF: safety analysis set.

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/s/

JIA GUO
08/18/2017

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08/18/2017