CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209529Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader (CDTL) Brief Memo Update

Date	May 26, 2020
From	Mark S. Hirsch, M.D.
Subject	Cross-Discipline Team Leader Brief Update
NDA/BLA# /Supplement#	209529
Applicant	Astellas Pharma US, Inc.
Date of Submission	November 27, 2019
PDUFA Goal Date	May 27, 2020
Proprietary Name / Established (USAN) names	VESIcare LS solifenacin succinate
Dosage forms / Strengths	2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 8 mg, 10 mg oral suspension
Indication(s)	Treatment of neurogenic detrusor overactivity in pediatric patients aged 2 years and older
Recommended:	***Approval***

The purpose of this CDTL Brief Memo Update is:

1) To confirm my agreement with the review team's recommendation for Approval of this application, which is a resubmission in response to the August 28, 2017, Complete Response Letter describing Chemistry, Manufacturing, and Controls (CMC) deficiencies,

2) To provide brief summaries of the recently completed discipline-specific and consultative FDA reviews, and

3) To confirm my agreement with the final labeling for this NDA.

1. Confirm CDTL Recommendation for Approval

CDTL Note: For full CDTL conclusions on benefits and risks of VESIcare LS for the indication, the reader is referred to the final Clinical Review dated May 18, 2020, under "Benefit-Risk Assessment" (Section 1.3) and to my August 28, 2017, CDTL review of the February 28, 2017, original NDA. Herein, I briefly summarize conclusions on the product's benefits and risks, and I confirm my agreement with the team's regulatory decision.

In brief, VESIcare LS (solifenacin) oral suspension will be indicated for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients. NDO is defined as detrusor overactivity that develops as a result of a neurologic lesion. An oral suspension will facilitate dosing in young children and will allow for accurate dose titration. The goal of treatment is to preserve renal function by increasing bladder capacity and bladder compliance, and to minimize the negative consequences of NDO by improving voiding indices such as reducing the number of incontinence episodes.

The efficacy of VESIcare LS oral suspension was demonstrated in two adequate and well-controlled studies (Studies 905-CL-074 and 905-CL-047) through clinically meaningful increases in maximum cystometric capacity (MCC) and was supported by 1) improvements in other urodynamic parameters, such as bladder compliance and number of overactive detrusor contractions, and 2) improvements in voiding diary measurements, such as maximum catheterized urine volume and incontinence episode frequency. The magnitude of the treatment effect was similar across age groups.

The safety of VESicare LS oral suspension was assessed in 95 pediatric patients with NDO in the two pivotal Phase 3 studies and their long-term extensions. The safety profile of VESicare LS in pediatric patients with NDO was shown to be consistent with the known safety profile of VESIcare tablets for the treatment of overactive bladder (OAB) in adults. As expected, the most commonly reported adverse reactions to VESIcare LS in pediatric NDO patients were constipation, dry mouth and urinary tract infection (UTI). Aside from one report of somnolence, there were no CNS adverse effects observed in the pediatric clinical studies of VESIcare LS.

Based on the benefits and risks reported in the pediatric NDO clinical studies, I confirm my agreement with the review team that the prior CMC deficiencies have been resolved and this application for VESIcare LS for the treatment of NDO in patients 2 years of age and older may now be Approved.

2. Brief Summaries of the Recently Completed Discipline-Specific and Consultative FDA Reviews

CDTL Note: For details on the discipline-specific and consultative reviews completed for this NDA through May 18,2020, the reader is referred to the final Clinical Review dated May 18, 2020, under "Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety" and to my August 28, 2017, CDTL review of the February 28, 2017, original NDA. The reader is also referred to the final discipline-specific reviews themselves. Herein, I briefly summarize the recently completed discipline-specific and consultative reviews.

2.1 Chemistry

In their final Integrated Quality Assessment #2 (IQA), conveyed by email on May 25, 2020, the Chemistry (OPQ) team of Mark Seggel and Moo Jong Rhee had the following Quality Assessment Team Recommendation and Conclusion:

"Astellas Pharma's resubmission of 505(b)(1) New Drug Application 209529, for VESIcare LS (solifenacin succinate) oral suspension, 1 mg/mL, is recommended for APPROVAL from the OPQ perspective.

Sufficient chemistry, manufacturing and controls information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality,

purity, and bioavailability of the drug product. The previously identified product quality microbiology issues have been adequately resolved. To ensure that the requisite product viscosity is maintained throughout the shelf life and in-use period, the acceptance tests for (b) (4) *have been revised* (b) (4) (b) (4)

The drug product labels (container / carton) as submitted on May 15, 2020, and the labeling (prescribing information, PPI) as submitted on May 19, 2020, is accurate, complete and complies with the requirements under 21 CFR 201.

The drug substance manufacturing, packaging and testing facility has acceptable CGMP status. The (b) (4) *drug product manufacturing site, which was cited as deficient in the August 28, 2017 Complete Response Letter, was recently found acceptable via the Sec. 704 (a)(4) (FDASIA Sec. 706) Records Request process. The associated product packaging and testing facilities also have acceptable drug CGMP status. An overall manufacturing inspection recommendation of APPROVE was issued on May 8, 2020.*

An expiration dating period of 24 months for product packaged in amber PET bottles and stored at 20°C to 25°C is granted.

The claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) is acceptable."

2.1.1 Chemistry: Biopharmaceutics

In their final review dated April 1, 2020, the ***Biopharmaceutics*** review team of Assadollah Noory and Vidula Kolhatkar had the following Conclusion:

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

The original NDA received a Complete Response due to three Chemistry deficiencies. The first Chemistry deficiency was related to an inspection finding that the product viscosity for two batches intended for marketing (commercial batches) was below the specification limit. (b) (4) thought to be a result of changes in the manufacturing process (b) (4) (b) (4) by its supplier. (b) (4) (b) (4) (b) (4) the Chemistry review team noted that the original application could not be approved without the establishment of adequate controls (b) (4) (b) (4) and demonstration that the Sponsor could consistently manufacture drug product of the requisite quality.

In their review of this resubmission, the Biopharmaceutics review team noted that the Sponsor addressed this deficiency (b) (4) (b) (4) in the to-be-marketed product. To demonstrate comparability of the commercial and clinical trial formulations, the Sponsor provided FDA-requested in vitro dissolution data from multi-point profiles using multiple, physiologic pH media that showed similar release profiles from the two formulations.

2.1.2 Chemistry: Manufacturing

In a May 9, 2020, email, Mark Seggel stated:

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

The May 25, 2020, OPQ IQA concluded:

- "*As described in the attached Integrated Manufacturing Assessment (Chapter V), a "paper' inspection (of the* (b) (4) *site) was conducted in accordance with the Sec. 704 (a)(4) (FDASIA Sec. 706) Records Request process. Documents were requested and reviewed by ORA and OPMA. After three rounds of this inspection process, ORA and OPMA now recommend approval of the* (b) (4) *site".*

- *An overall manufacturing inspection recommendation of APPROVE was issued on May 8, 2020*".

The May 25, 2020, OPQ IQA also stated that the Applicant had successfully demonstrated that (b) (4) (b) (4) finished product that meets the previously established viscosity requirements. In this regard, the IQA concluded:

- "*The Applicant has demonstrated that the drug product with the requisite quality can be manufactured consistently*".

2.1.3 Chemistry: Product Quality Microbiology

At the milestone review team meetings for this resubmission, the ***Product Quality Microbiology*** review team of Andrew Brown and Nandini Bhattacharya stated that the prior deficiency related to inadequate manufacturing controls to ensure the absence of (b) (4) (b) (4) in the drug product had been successfully resolved.

Concerning the (b) (4) NDA deficiency, the May 25, 2020, OPQ IQA concluded:

> "*Although the drug product contains* (b) (4) (b) (4) *, because this is an aqueous formulation it is susceptible to contamination* (b) (4) (b) (4) *. As documented in the November 27, 2019 NDA resubmission and the January 12, 2020 resubmission amendment, controls for ensuring that the absence of* (b) (4) *have been established. The Applicant has added a test and suitably validated analytical procedure for confirming the absence of* (b) (4) *in the finished product to the regulatory specification. The Microbiology deficiencies identified in the Complete Response letter have been adequately resolved*".

2.2 Division of Biometrics III (DB3)

In their final ***Statistical*** review dated May 19, 2020, Jia Guo and Mahboob Sobhan had the following Conclusion:

> "*…This submission did not contain new efficacy data. For efficacy evaluation from statistical perspective, please refer to the Statistical review dated 18 August 2017 for the original submission, which concluded that both studies demonstrated that there is clinical benefit of solifenacin succinate in treatment of neurogenic detrusor overactivity (NDO) in pediatric patients"*.

2.3 Clinical

In our final ***Clinical*** review dated May 18, 2020, Elena Boley and I had the following Conclusion:

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

In regard to efficacy, safety and benefit-risk analysis, the Clinical team concluded:

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

- "*The safety profile of solifenacin oral suspension is consistent with the known risks of solifenacin tablets for the treatment of OAB in adults and of anticholinergics in general*".

- "*Solifenacin oral suspension provides an alternative treatment to the single approved option, is efficacious, and has a similar side effect profile. Additionally, solifenacin oral suspension offers a more convenient once daily dosing regimen and data to support safety and efficacy for pediatric patients as young as 2 years old*".

2.4 Division of Medical Policy Program (DMPP)

In their final ***Patient Labeling*** review dated May 8, 2020, Kelly Jackson, Elvy Varghese and LaShawn Griffiths had the following Conclusion:

> "*…The PPI is acceptable with our recommended changes."*

All of the PPI changes recommended by DMPP were successfully instituted.

2.5 Office of Prescription Drug Promotion (OPDP)

In their final ***OPDP*** review dated May 4, 2020, Elvy Varghese and Matthew Falter stated:

> *"OPDP's comments on the proposed labeling are based on the draft PI*

downloaded from the DUOG Vesicare LS SharePoint on May 1, 2020 and are provided below."

All of OPDP's labeling comments were successfully addressed, either through internal discussion or by instituting labeling changes.

2.6 Office of Clinical Pharmacology (OCP)

In their final ***Clinical Pharmacology*** review dated May 1, 2020, Jihong Shon and Yanhui Lu of had the following Conclusions:

"(For the original application)….The Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology III, the Division where the clinical pharmacology review team resided prior to formation of Division of Cardiometabolic and Endocrine Pharmacology (DCEP), and the Division of Pharmacometrics…concluded that the application was acceptable and recommended approval from the clinical pharmacology standpoint (refer to) the original Clinical Pharmacology review for NDA 209529 dated August 8, 2017)…. The NDA is still approvable from the Clinical Pharmacology standpoint provided that the CMC review team determines that CMC deficiencies have been resolved and an agreement on the language in the package insert is reached between the Applicant and the Agency".

The CMC review team determined that the CMC deficiencies have been resolved and agreement has been reached between the Sponsor and the Agency on all labeling.

2.7 Pharmacology/Toxicology

In their final ***Pharmacology/Toxicology*** review dated April 27, 2020, Laurie McLeod-Flynn and Kim Hatfield had the following Conclusion:

"*No additional nonclinical studies were submitted with the 27 November 2019 resubmission. Reference is made to the Pharmacology/Toxicology review submitted to DARRTS for NDA 209529 on 28 July 2017 by Laurie McLeod-Flynn, which recommended approval of this product from a nonclinical perspective…. At this time, there is no impediment to Approval of this drug from a Pharmacology/Toxicology perspective".*

2.8 Division of Medication Errors Prevention and Analysis (DMEPA

In their final ***DMEPA*** labeling reviews dated April 9, 2020, March 23, 2020 and March 2, 2020, Justine Kalonia and Briana Rider had the following Conclusions:

In regard to carton and container labeling

"*The Applicant submitted revised carton labeling received on April 6, 2020 for VESIcare LS…The (Applicant's) revisions are in response to recommendations that we made during a previous labeling review… The Applicant implemented all of our recommendations and we have no additional recommendations at this time*".

In regard to the Prescribing Information labeling

"*Our evaluation of the proposed VESIcare LS prescribing information (PI), container label, and carton labeling identified areas of vulnerability that may lead to medication*

errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Astellas Pharma US, Inc. so that recommendations are implemented prior to approval of this NDA".

All of DMEPA's recommendations for changes to the PI and container and carton labeling were successfully instituted.

In their final ***DMEPA*** tradename review dated February 21, 2020, Denise Baugh and Briana Rider had the following Conclusion:

"We have completed our review of the proposed proprietary name, Vesicare LS, and have concluded that this name is acceptable".

3. Confirm CDTL Agreement with Final Labeling

3.1 VESIcare LS Labeling

Labeling discussions were held with the entire FDA review team on April 23, 2020, April 28,2020 and April 30, 2020.

The Division's edits to the PI were conveyed to the Sponsor on May 1, 2020. The Sponsor accepted all of the Division edits and returned the PI with minor revisions on May 8, 2020. Several additional minor Division edits to the PI were conveyed to the Sponsor on May 12, 2020 and May 18, 2020. A final, agreed-upon PI was received from Sponsor on May 19, 2020.

For the PPI, the Division's edits were conveyed to the Sponsor on May 12, 2020. The Sponsor accepted all of the Division edits and returned the PPI with minor revisions on May 15, 2020. Several additional minor Division edits to the PPI were conveyed to the Sponsor on May 18, 2020. A final, agreed-upon PPI was received on May 19, 2020.

I confirm that I agree with the final agreed-upon VESIcare LS PI and PPI received from Sponsor on May 19, 2020.

3.2 VESicare Tablets Labeling

In parallel with labelling for VESicare LS oral suspension under NDA 209529, the Sponsor also submitted prior approval supplement (PAS) 017 to NDA 021518 for VESIcare Tablets to update the Pediatric Use section of that label. In addition to changes to the Pediatric Use section, SLR017 included:

- Updated content in Section 8 related to Pregnancy and Lactation to comply with the Pregnancy and Lactation Labeling Rule (PLLR).
- Additions to Section 6.2 Post-Marketing Experience, of the following adverse event terms: "dizziness", "urinary retention", and "vomiting".
- Minor changes in other sections for document maintenance and internal consistency.

To support the addition of the three new postmarketing event terms, the Sponsor provided a link to a post marketing safety report index showing, through December 2016, a total of 799 cumulative reports of urinary retention, 136 cumulative reports of vomiting, and 921 cumulative reports of dizziness.

Labeling discussions for SLR017 were held with the entire review team on May 4, 2020 and May 6, 2020. The FDA-edited labeling for SLR017 was conveyed to the Sponsor on May 7, 2020. The Sponsor accepted all of the Division edits and returned the label with minor revisions on May 13, 2020. Several minor edits were returned to Sponsor on May 18, 2019 and the final agreed-upon PI and PPI for VESIcare Tablets was received on May 19, 2020.

I confirm that I agree with the final agreed-upon VESIcare Tablets PI and PPI received from Sponsor on May 19, 2020.

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

/s/

MARK S HIRSCH
05/26/2020 09:07:49 AM

CHRISTINE P NGUYEN
05/26/2020 11:18:51 AM

Cross-Discipline Team Leader Memo

Date	August 27, 2017
From	Mark S. Hirsch, M.D.
Subject	Cross-Discipline Team Leader Memo
NDA/BLA# /Supplement#	209529
Applicant	Astellas Pharma Global Development
Date of Submission	February 28, 2017
PDUFA Goal Date	August 28, 2017
Proprietary Name / Established (USAN) names	VESIcare LS solifenacin oral suspension
Dosage forms / Strength	1 mg/mL
Proposed Indication(s)	Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 2 years and older
Recommended:	***Complete Response***

1. Introduction/Executive Summary

Solifenacin is a competitive antagonist of muscarinic receptors with high affinity for M3-muscarinic receptors. Contractions of the detrusor muscle are mediated predominantly through stimulation of the M3 receptors. The antagonistic effect of solifenacin on M-3 receptors is considered to be the main mechanism of solifenacin-induced relaxation of the urinary bladder. On November 18, 2004, solifenacin succinate was approved in the United States under NDA 021518 as VESIcare 5 mg and 10 mg tablets for treatment of overactive bladder (OAB) in adults.

The approval of VESIcare tablets under NDA 021518 in November 2004 included a requirement to conduct postmarketing pediatric studies 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 between the Sponsor and the Division to focus the pediatric studies on patients with detrusor overactivity due to known neurological disease (referred to as neurogenic detrusor overactivity, or NDO), not on pediatric patients with idiopathic OAB (OAB).

The current first-line, mainstay treatment for pediatric NDO is the combination of continuous intermittent catheterization (CIC) and anti-muscarinic drugs, including oxybytynin chloride. Oxybutynin chloride is currently the only FDA-approved drug for the NDO indication in pediatric patients. Oxybutynin is available as immediate-release tablets, extended-release tablets and syrup.

VESIcare LS (solifenacin oral solution) was developed to be another child-friendly anti-muscarinic drug formulation intended for use in conjunction with CIC for NDO in pediatric patients aged 2 years and older.

This NDA is supported by two main Phase 1 studies (Study 905-CL-079 in pediatric NDO patients, and Study 905-CL-075 in pediatric OAB patients) and two main Phase 3 studies (Studies 905-CL-047 and 905-CL-074 conducted in children and adolescents with NDO), as follows:

Phase 1 Study	**905-CL-075**	*A Multicenter, Open-label, Single Ascending Dose Study to Evaluate Pharmacokinetics, Safety, and Tolerability of Solifenacin Succinate Suspension in Pediatric Patients from 5 to 17 Y ears (Inclusive) with Overactive Bladder (OAB).* This was a pediatric pharmacokinetic (PK) study in children and adolescents with idiopathic OAB; the aim of this study was to evaluate PK (primary objective) and safety and tolerability (secondary objective) of solifenacin oral suspension in pediatric patients with idiopathic OAB
Phase 1 Study	**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 was a pediatric pharmacokinetic (PK) study in children and adolescents with NDO; the aim of this study was to confirm the comparability of the pharmacokinetic profiles in pediatric NDO and OAB patients.
Phase 3 Study	**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 Less than 18 years of Age with Neurogenic Detrusor Overactivity (NDO).* This was an open-label, baseline-controlled, multicenter, sequential dose titration study to evaluate long-term (52 weeks) safety and efficacy of solifenacin oral suspension in children and adolescents 5 years to < 18 years of age with NDO.
Phase 3 Study	**905-CL-074**	*A Phase 3, Open-Label, Baseline-controlled, Multicenter, Sequential Dose-titration Study to Assess the Pharmacokinetics, Long-term Efficacy and Safety of Solifenacin Succinate Suspension in Children from 6 Months to 5 years of Age with Neurogenic Detrusor Overactivity (NDO).* This was an open-label, baseline-controlled, multicenter, sequential dose titration study to evaluate long-term (52 weeks) safety and efficacy of solifenacin oral suspension in children 6 months to 5 years of age with NDO

A total of 95 pediatric NDO patients aged 2 years and above were enrolled in the two Phase 3 NDO studies. These studies enrolled NDO patients at investigative sites all over the world.

Both Phase 3 studies demonstrated the expected clinical efficacy benefit of an antimuscarinic in patients with NDO. For the primary endpoint (change from baseline in maximum cystometric capacity [MCC]), after 24 weeks of solifenacin oral suspension treatment, statistically significant and clinically meaningful improvements in MCC were observed in subjects aged 2 to < 5 years as well as in subjects aged 5 to < 18 years. Clinically meaningful improvements in other urodynamic measurements in both patient age groups included: increases in mean bladder compliance, decreases in mean number of overactive contractions > 15 cmH_2O, and increases in bladder volume until first detrusor contraction > 15 cmH_2O. In addition, increases were observed in the maximum catheterized urine volumes and decreases were observed in the number of incontinence episodes per 24 hours. Finally, the primary

endpoint showed generally similar efficacy over the longer-term (52 weeks) compared to the shorter-term (24 weeks), but from a smaller sample size (n = 54 at week 52 vs. n = 66 at week 24).

Safety results from the two Phase 3 studies demonstrated the expected adverse reactions to solifenacin, with no new safety signals identified. Solifenacin oral suspension was generally well tolerated in pediatric NDO patients. The safety profile of solifenacin oral suspension in the pediatric NDO population was fully consistent with the safety profile of approved solifenacin tablets in adults with OAB. There were no new or unresolved safety issues.

Based on these clinical efficacy and safety data from pediatric NDO patients, and consistent safety results from two additional Phase 3 studies in pediatric patients with idiopathic OAB, we have identified no Clinical deficiencies and no Clinical issues that would preclude approval of the NDA. There are no Clinical Pharmacology, Statistical or Nonclinical deficiencies or issues that would preclude approval.

However, based on an FDA inspection of the manufacturing facilities that revealed a deficiency in the drug product itself (for details, refer to the section of this memo entitled "CMC"), as well as an unresolved drug product microbiology issue, the NDA cannot be approved at this time. Based on these Chemistry deficiencies (again, refer to the "CMC" section below), I agree that the application should receive a ***Complete Response (CR)*** regulatory action.

2. Background

2.1 DESCRIPTION OF PRODUCT

The recommended starting dose for VESIcare (solifenacin succinate tablets) for the treatment OAB in adults is 5 mg once daily. If the starting dose is tolerated, the solifenacin dose may be increased to 10 mg once daily.

An oral suspension was developed to facilitate swallowing and accuracy of dosing in pediatric patients with NDO. The solifenacin oral suspension is dosed as 1 mg/mL, with 5 mg in 5 mL.

The recommended dose of solifenacin oral suspension is determined based on patient weight. Treatment should be initiated at the recommended starting dose that is shown in Table 1. Thereafter, the dose may be increased to the lowest effective dose up to the maximum dose.

Table 1: Solifenacin Oral Suspension Recommended Daily Doses by Weight Range for Pediatric Patients with NDO Aged ≥ 2 Years

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

† Solifenacin oral suspension is provided as a 1 mg/mL oral suspension.

It is notable that the starting dose provides steady-state exposure that is equivalent to steady-state exposure after a 5 mg daily dose in adults with OAB. In addition, the maximum dose provides steady-state exposure that is equivalent to steady-state exposure after a 10 mg daily dose in adults with OAB.

2.2 REGULATORY HISTORY

On November 19, 2004, 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 requirement for the Sponsor to conduct studies in pediatric patients 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 between Sponsor and the Division to enroll only pediatric patients with detrusor overactivity due to known neurological disease (referred to as neurogenic detrusor overactivity or NDO).

Formal discussions and communications between the Sponsor and the Division concerning the pediatric formulation and pediatric studies took place periodically from 2005 until 2012. Meetings between Sponsor and FDA concerning solifenacin pediatric drug development took place on November 2, 2005, May 30, 2005 and August 31, 2010.

The pediatric study requirements established under PREA were aligned with the study requirements under an FDA Written Request (WR) for Pediatric Studies. On July 27, 2012, the official WR was issued. Subsequent WR amendments were found acceptable on September 14, 2012, April 17, 2014 and December 12, 2014.

On July 20, 2017, the Pediatric Exclusivity Board determined that the Sponsor had met the terms of the WR and for this reason, the Board agreed to grant the Sponsor an additional 6 months market exclusivity on solifenacin succinate.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary Clinical reviewer, Guodong Fang, stated in his final review, dated August 2, 2017:

> *"Recommendation on Regulatory Action: From the Clinical perspective, the evidence presented in the current submission is adequate to support the effectiveness and safety of this product. Therefore, Clinical recommends an Approval action for the indication of the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 2 years and older."*

The major issues from the medical officer's review are highlighted here:

Regarding Efficacy

- *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).*

Regarding Safety

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.

3. CMC

The Chemistry Review team, including Debasis Ghosh, Zhengfang Ge, James Norman, Jean Tang, Andre Brown, Krishnakali Ghosh, Ho-pi Lin and Mark Seggel, had the following recommendation in their final review dated August 21, 2017:

"*In its present form, Astellas Pharma's 505(b)(1) New Drug Application #209529, for VESIcare LS (solifenacin succinate) oral suspension, 1 mg/mL, is not ready for approval.*

As observed during the inspection of the drug product manufacturing facility, and as described in amendments to the NDA, drug product that meets the proposed drug product specification, and in particular the requirements for product viscosity, currently cannot be manufactured. As a result of changes in the manufacture of (b) (4) *drug product viscosity now falls below the established lower limit. The applicant is evaluating* (b) (4) *controls that will identify* (b) (4) *suitable for use in the manufacture of VESIcare LS.*

(b) (4)

Nevertheless, from both the drug product and facilities review perspectives, this application cannot be recommended for approval until adequate controls (b) (4) *are established, and the applicant has demonstrated that drug product with the requisite quality can be manufactured consistently.*

(In addition) The product quality microbiology review team has determined that there are inadequate controls to ensure the absence of (b) (4) *in the drug product at release and on stability. The application cannot be approved until this issue is addressed by the applicant.*

Attachment II of the CMC review contains a list of specific Chemistry deficiencies that should be conveyed to the Sponsor in the Complete Response regulatory action letter. The Chemistry deficiency items are shown here:

Drug Product Deficiencies

The quality of (b) (4) *is not sufficiently controlled. Therefore, the recent drug product batches, manufactured with* (b) (4) *after the supplier changed the manufacturing process, failed the product specification.*

Not sufficient drug product batch data are provided to assure the homogeneity of the drug product manufactured with the new (b) (4) *to ensure the dosing accuracy*

To address these deficiencies, the applicant should meet the following requirement and provide batch release data from three drug product batches manufactured with the new (b) (4)*:*

- *Propose an extra control* (b) (4) *in addition to NF monograph to assure that the drug product meets the specification*

Or

- *Include a dispersibility test in the drug product specification to assure the homogeneity of the drug product* (b) (4) (b) (4) *This test should be performed at the drug product release and during the stability testing*

Microbiology Deficiencies

For release specifications in P.5.1, it is acknowledged that acceptable microbiological test methods and release specifications (TAMC microbial limit and Escherichia coli) are provided. (However), revise the microbial limit release specification to include the test methods and acceptance criteria to demonstrate that the product is free of the (b) (4)*. Additionally, in Quality Overall Summary Table 12 it still states "Microbial limit test will be performed as a skip lot test on every tenth batch or once a year whichever comes first." Provide an explanation and update the relevant sections of the submission as applicable.*

(Also), revise the post approval stability program to include testing and specifications to confirm the absence of (b) (4).

(Finally), during stability studies the results of the microbial limit test should comply with the acceptance criteria which include the absence of (b) (4).

The Chemistry review team had the following additional comment:

"Adequate drug substance and product manufacturing process information has been provided. And, from the biopharmaceutics perspective, suitable controls for in vitro dissolution have been established. In its present form the labeling (package insert, container/carton) is acceptable from the CMC perspective. However, because labeling negotiations have not been completed, the adequacy of the labeling will need to be confirmed when the NDA is resubmitted."

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review team, Laurie McLeod-Flynn and Mukesh Summan, had the following Recommendation in their final review dated July 28, 2017:

"*Approvability:*
There is no impediment to approval of this product from a Pharmacology/Toxicology perspective.

Dr Summan specifically concluded: "*Nonclinical Recommends AP*".

The PharmTox team had the following main comments about the toxicology study that was conducted in juvenile mice:

In juvenile mice dosed beginning on post-natal day (PND) 10, a no-observed-adverse-effect-level was 10 mg/kg/day (AUC at that dose was 0.3- to 1.7-fold the AUC observed with the 10 mg maximum recommended human dose). At 30 mg/kg/day (0.5- to 5.5-fold), and 60 mg/kg/day (1.3- to 8.3 fold), some increase in lethality and effects on triglyceride levels were reported.

In juvenile mice dosed beginning PND21, solifenacin succinate was well tolerated at 10 mg/kg/day (with an AUC 0.2 to 0.7-fold) and 30 mg/kg/day (AUC 0.9- to 3-fold). No unique target organs were identified. Fertility was reduced to 75% at 100 mg/kg/day (AUC 3- to 10-fold). Slightly decreased food consumption and/or reduced body weight gains were also observed at this dose. No effects on learning and memory, passive avoidance behavior, motor activity, performance in an open field, or mating performance were observed.

In addition to the observed differences in metabolism between juvenile mice, adult mice, and humans, general differences in the brain development of mice compared to humans are considered to be explanations for the sensitivity of juvenile mice to solifenacin. The juvenile mice studies also showed the increased sensitivity of juvenile mice to solifenacin exposure at PND10 compared to the older and more developed PND21 mice. While development of the blood-brain barrier may continue to 28 days in mice, it is complete at birth in humans. Data from a lactation study in mice showed distribution of drug to neonatal brains at 24 hours post-dose, while distribution was below the limit of detection in brains of adult mice at that time period.

(In addition) cholinergic receptors mature postnatally in rodents. In rats, it has been reported that development of muscarinic receptors and enzyme activities associated with cholinergic neurons in the brain occurs during the first 3 to 4 weeks after birth. After post-natal Day 20, rat cholinergic function is comparable to that of a newborn human baby. Rats and mice are reported to have similar patterns of neurogenesis. (The cholinergic system in humans is complete at birth.)

In conclusion, the findings in juvenile mice appear to be related to the timing of dosing in the post-natal period and the delayed maturation of the mouse central nervous system resulting in increased sensitivity to solifenacin's antimuscarinic effect compared to humans.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review team, including Jihong Shon, Yuching Yang, Yanning Wang, Simbarashe Zvada, Jeffry Florian, Donny Tran, and Dennis Bashaw, had the following recommendation in their final review dated August 8, 2017:

> *"The Office of Clinical Pharmacology/Division of Clinical Pharmacology III and Division of Pharmacometrics have reviewed the information in NDA 209529 of solifenacin succinate oral suspension for the treatment of NDO in pediatric patients. The review team recommends approval of this NDA from a clinical pharmacology perspective, provided that an agreement on the language in the package insert is reached between the Applicant and review team."*

The Clinical Pharmacology review team had the following comments of note:

In regard to the evidence for effectiveness in the pediatric NDO population:

- "*In the two phase 3 trials of pediatric patients with NDO aged 2 years and < 18 years, the efficacy data using urodynamic and patient diary endpoints provided supportive evidence of effectiveness of solifenacin succinate oral suspension".*

In regard to the dosing regimen for the pediatric NDO population:

- "*The dosing table was developed based on simulations of AUC using a PBPK model to achieve the exposure to solifenacin in pediatric patients equivalent to that in adults at once daily doses of 5 mg and 10 mg. Prediction of solifenacin PK in pediatric patients using the developed PBPK model was verified with PK observations from multiple clinical studies performed in pediatric patients with NDO or OAB. The proposed recommended dosing table is also generally consistent with those administered in the two phase 3 studies. Provided that safety and efficacy reported in the phase 3 trials are acceptable* (Note from CDTL: Safety and efficacy are acceptable)*, the proposed dosing recommendation is appropriate for pediatric patients with NDO up to 60 kg. For patients with body weight > 60 kg, we recommend using a starting dose of 5 mg with maximal dose of 10 mg.*

  Notes from CDTL: Labeling was revised as recommended by Clinical Pharmacology; specifically, in patients with body weight > 60 kg, the Division requested that the label state a starting dose of 5 mg and a maximal dose > 60 kg.

In regard to dosing in patient subgroups:

- "*The proposed dosing recommendations for pediatric patients with renal or hepatic impairment or taking concomitant medications that may lead to a clinically relevant drug-drug interaction (DDI) are the same as those for adult patients. Given that the clearance of solifenacin in pediatric population, including hepatic metabolism and renal excretion, is unlikely to be different from that in adults, the currently proposed dosing guidance is acceptable.*"

In regard to dosing in food effect:

- "*While food intake does not significantly affect the bioavailability of solifenacin, the Applicant proposes to avoid simultaneous intake of food and/or drinks due to a potential for a bitter taste. When considering pediatric patients' compliance issue in relation to the bitter taste, the proposed recommendation is acceptable*".

6. Clinical Microbiology

The main Microbiology issue for the NDA was whether the Sponsor agreed to adjust the drug product release specifications to confirm the absence of (b) (4) (b) (4) in the drug product. The Sponsor was also asked to add testing for (b) (4) to the stability studies program. The reader is referred to the "CMC" section of this review for this specific Microbiology deficiency and how it should be resolved.

7. Clinical/Statistical – Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

To support the efficacy of solifenacin oral suspension in the treatment of NDO in pediatric patients, the Sponsor provided data from two Phase 3 studies that addressed the requirements established by the Agency in the Written Request (WR) as well as the post-approval requirements for VESIcare® tablets under NDA 021518. Together, these requirements included 2 phase 3 studies for the evaluation of solifenacin oral suspension, as follows:

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

These two Phase 3 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. A total of 112 pediatric patients with NDO were screened and 95 enrolled into these two Phase 3 studies that were conducted all over the world.

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

The secondary efficacy endpoints based on urodynamics in both studies were change from baseline to the assessment for the last possible titration step in:

- MCC (for last possible titration step only)
- Bladder compliance (change in volume/change in detrusor pressure)
- Bladder volume until first detrusor contraction (> 15 cmH_{2O}) as a percentage of expected bladder capacity (EBC)
- Number of overactive detrusor contractions (> 15 cmH_2O) until leakage or until end of bladder filling

- Detrusor pressure at leakage or until end of bladder filling

The additional secondary efficacy endpoints, some based on patient voiding diary, in both studies 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) as measured by the PinQ questionnaire score.

7.2 DEMOGRAPHICS

The main diagnostic criteria for the Phase 3 were pediatric patients, ages 2–17 years inclusive, with detrusor overactivity secondary to a known neurologic deficit (e.g., spina bifida), who were performing clean intermittent catheterization (CIC).

In brief, the demographics of the study population were as follows:

Of the 95 total patients aged 2 years and above, 47% were male and 53% were female. The mean patient age was 9.2 years, with 19 patients aged 2 to < 5 years and 76 patients aged 5 to < 18 years. A total of 58% of patients were White, 33% were Asian. 2% were Black/African American and 6% were of Other ethnicity.

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

7.3 DISPOSITION OF SUBJECTS

Of the 95 subjects aged 2 years and above who were enrolled and received study drug in Studies 047 and 74, a total of 20 patients (21%) discontinued prematurely. Tables 2 and 3 provide summaries of the subject disposition in the two Phase 3 studies:

Table 2: 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%)
Withdrawal 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 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.

Table 4 provides a summary of the patient data analysis sets:

Table 4: Analysis Sets; Phase 3 NDO Population

Analysis Set	Number of Patients (%)		
	905-CL-074 2 Years to < 5 Years	905-CL-047 5 Years to < 18 Years	Phase 3 NDO Population 2 Years to < 18 Years
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 ; NDO: neurogenic detrusor overactivity; SAF: safety analysis set; FAS: full analysis set; PPS: per protocol set. Source: ISE Table 8.1.2; ISS Table 13.1.1.1

Of note, in Study 047, a total of 55 of the 76 subjects who received treatment in Study 047 were included in full analysis set (FAS) for evaluation of efficacy. In response to an April 17, 2017, FDA Information Request, on May 26, 2017, the Sponsor submitted detailed information to explain why 21 subjects in Study 047 were excluded from the FAS. The Clinical Reviewer confirmed that the reasons for exclusion were acceptable.

7.4 EFFICACY RESULTS

7.4.1 Assessment of Efficacy

The primary efficacy endpoint was the change from baseline in maximum cystometric capacity (MCC) after 24 weeks of treatment. This is an acceptable endpoint for the proposed indication based upon its prior use as a primary efficacy endpoint in the clinical studies that supported approval of oxybutynin for the same indication, as well as its routine use in clinical practice as a marker of bladder filling capacity.

A total of 72 patients from both Phase 3 studies were included in the primary efficacy analysis (FAS) and showed an overall mean change from baseline to Week 24 of 52.5 mL in MCC (95% CI 29.2 mL, 75.7 mL). This data is shown in more detail, including by study, in Table 5 below.

The primary efficacy endpoint was also analyzed (secondarily) based on mean change from baseline to last possible titration step. This secondary analysis of the primary endpoint supported the results of the primary analysis.

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
- Bladder volume until first detrusor contraction (> 15 cmH_2O) as a percentage of expected bladder capacity (EBC)
- Number of overactive detrusor contractions (> 15 cmH_2O) until leakage or until end of bladder filling
- Detrusor pressure at leakage or at end of bladder filling

There was also 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 patient voiding 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

Another secondary efficacy endpoint was change from baseline to visit 8 (week 24) and visit 10 (week 52) in Quality of life (QoL) as measured by the PinQ questionnaire score.

As an exploratory analysis, efficacy data collected in the two solifenacin pediatric studies were compared to data from historical controls (e.g., published results from other studies).

7.4.1.1 Primary Efficacy Analysis

At Week 24, pediatric patients aged 2 years to < 5 years and pediatric patients aged 5 years and older had statistically significant increases 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. This difference was expected due to the different age-related bladder volumes and baseline MCC between the 2 groups. The primary efficacy data are shown in Table 5.

Table 5: 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

An analysis of MCC using last possible titration step, and an analysis of MCC expressed as a percentage of expected bladder capacity (EBC) or maximum catheterized volume (MCV), supported the results from the primary analysis of the primary endpoint at Week 24.

7.4.1.2 Secondary Efficacy Analysis

In this section, results from secondary efficacy endpoints are provided.

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. See Table 6. 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: 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

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

Bladder volume until first detrusor contraction (>15 cmH_20) was significantly improved from baseline in both Phase 3 studies. See Table 7.

Table 7: Change from Baseline in Bladder Volume (mL) Until First Detrusor Contraction> 15 cmH_2O Expressed 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		
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: FDA 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.
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.

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

At Week 24, there was a decrease in the number of overactive detrusor contractions > 15 cmH_2O until leakage or 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. See Table 8.

Table 8: 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 Single Day

At Week 24, there was an increase in the MCV in a single 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 (the MCC). At Week 24, both pediatric patients aged 2 years to < 5 years and pediatric patients aged ≥ 5 years had an increase in the MCV in a single day compared with baseline. See Table 9.

Table 9: Change from Baseline to Week 24 in Maximum Catheterized Volume in a Single 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

Studies 074 and 047 measured incontinence using different variables but the variables are related. Therefore, the incontinence data can be compared between studies but cannot be pooled.

At Week 24, both pediatric patients aged 2 years to < 5 years and pediatric patients aged ≥ 5 years had a decrease in incontinence per 24 hours compared with baseline. See Table 10.

Table 10: Change from Baseline to Week 24 in Incontinence (FAS) per 24 Hours; 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.

After 24 weeks of treatment with solifenacin oral suspension, there were increases 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).
- Average catheterized volume per catheterization: (mean±SD: 43.82±45.28 mL) in the Phase 3 NDO population (95% CI: 32.8, 54.9).
- Average first morning catheterized volume: (mean±SD: 43.10±66.74 mL) in the Phase 3 NDO population (95% CI: 26.8, 59.4).

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

- Detrusor pressure at end of bladder filling: (mean±SD:-7.5±29.7 cmH2O) in the Phase 3 NDO population (95% CI:-14.9, 0.0).

Statistician's Conclusion

In their final review dated August 18, 2017, the Statistical Review team of Jia Guo and Mahboob Sobhan, had the following conclusion:

> "(From the Statistical perspective) b*oth studies demonstrated that there is clinical benefit of solifenacin succinate in treatment of neurogenic detrusor overactivity (NDO) in pediatric patients."*

Notable summary comments from the Biometrics review included:

- *"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"*. (CDTL Note: The analyses were pre-defined and consistent with prior agreement between the Sponsor and the Division).
- *"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).*"

7.4.2 Overall Assessment of Efficacy

The efficacy of solifenacin suspension in the treatment of pediatric NDP patients aged 2 to < 18 years old has been demonstrated through achievement of both the primary and secondary efficacy endpoints

8. Safety

8.1 SAFETY RESULTS

The Clinical safety review encompassed primarily the safety results from the two Phase 3 studies in pediatric NDO patients (Studies 074 and 047), but also included safety results from one randomized, double-blind, placebo-controlled, Phase 3, efficacy and safety study in idiopathic OAB pediatric patients (Study 905-CL-076 [n=189; 12 weeks]), and one open-label, sequential dose-titration, long-term extension study in idiopathic pediatric OAB patients (Study 905-CL-077 [n=148; 40 weeks]). Studies 076 and 077, in idiopathic OAB pediatric patients, were conducted at the request of European regulators for European regulatory approval purposes.

The safety results shown hereafter focus primarily on the pediatric NDO population.

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

In brief, solifenacin oral suspension was well-tolerated in the pediatric population; the safety findings were consistent with findings previously identified in adults with OAB and tended to reflect the known pharmacologic properties of solifenacin as well as co-morbidities in the NDO population.

8.1.1 Deaths, Serious Adverse Events and Discontinuations Due to Adverse Events

Deaths

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

Serious Adverse Events (SAEs)

Overall, 8 of 95 (8.4%) Phase 3 NDO patients reported SAEs. Seven of these were reported in Study 047 (2 children and 5 adolescents). Only UTI was reported by more than 1 patient, and this was reported in just 2 patients. The list of SAEs is: UTI (n=2), tachycardia, megacolon, dengue fever, orchitis, pharyngitis, tethered cord syndrome, spinal cord operation, and hypertension (n=1 each).

The reader is referred to the primary Clinical review for brief narratives for each of these SAEs. None of the SAEs appears to be drug-related, including the events of tachycardia and hypertension that accompanied a patient's serious E. Coli UTI and resolved with treatment of the UTI and despite continuation of solifenacin.

Nine (9) SAEs were reported in 8 idiopathic OAB patients in the clinical studies of pediatric idiopathic OAB. The list of SAEs in this group included: appendicitis (n=2), and lymphadenitis, hypertension, tachycardia, frontal lobe epilepsy, pyelonephritis, abdominal pain, and gastroenteritis (n=1 each).

None of these SAEs appeared to be drug-related either, including the events of tachycardia and hypertension that occurred in a patient taking placebo. Among these SAEs, there is one report of QT prolongation (change from baseline of 36 milliseconds in corrected QTcB) but this case is confounded by a concomitant serious UTI causing pyelonephritis.

Discontinuations due to Adverse Events

The only reported TEAE that resulted in treatment discontinuation in Study 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. Table 11 below shows summary data for these 4 cases

Table 11: Summary of QTcB from 4 Patients with NDO Discontinued from Phase 3 Study 905-CL-047

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

PED: pediatric equivalent dose; QTcB: QT interval corrected using Bazett's formula

CDTL Note: During the conduct of the phase 3 pediatric program, a random effects analysis was performed on all ECG data to provide insight into the 4 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) 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 (see Section 11.2 of this memo below). 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 artifact of high variability at Baseline without repeat baseline measures as conducted early in the study.

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

8.1.2 Other Adverse Events

Commonly Reported Adverse Events

Table 12 shows the commonly reported adverse events (>5% incidence) in the pediatric OAB and NDO populations.

Table 12: 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.

In the NDO population, the most commonly reported AEs were: urinary tract infection

(30.5%), constipation (7.4%), upper respiratory tract infection (6.3%), nasopharyngitis (6.3%), headache (4.2%), ECG prolonged (4.2%), pyrexia (4.2%), diarrhea (4.2%), and gastroenteritis (6.3%).

CDTL Note: Please refer to the previous CDTL Note and Section 11.2 of this memo in regard to "ECG prolonged". This is not considered a drug-related AE. In regard to UTI, the occurrence of UTI is not unexpected in the NDO population, especially in light of all patients performing continuous clean intermittent bladder catheterization.

Drug-related AEs were reported in 18 pediatric patients with NDO (18.9%) and included: constipation (7.4%), dry mouth (3.2%), ECG prolonged (3.2%), UTI (2.1%), and abdominal pain, urinalysis bacterial test positive, viral rash, and pharyngotonsillitis (1.1% each). Drug-related AEs were similar in the pediatric patients with idiopathic OAB.

CDTL Note: Please refer to the previous CDTL Note and Section 11.2 of this memo in regard to "ECG prolonged". This is not considered a drug-related AE.

In regard to AE severity, in the overall Phase 3 pediatric population, most TEAEs were reported as mild (124 [51.0%] patients) or moderate (53 [21.8%] patients). Seven patients reported 1 severe TEAE each, as follows: 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.

Routine Laboratories, Vital Signs and Electrocardiograms (ECGs)

Laboratories
Overall, there were few changes of clinical relevance in biochemistry, hematology and urinalysis tests throughout the studies. Renal function was maintained. However, shifts from normal urinalysis to abnormal were relatively common (60.9% for urine bacteria quantitiative, and 48% for positive urine leukocytes)

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 likely the result of expected changes based on the annual age-related changes for patients in the age groups in these studies [National Institute of Health Blood Pressure Tables for Children and Adolescents, 2005; Fleming et al, 2011].

For the Phase NDO population (Studies 047 and 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).

ECGs
The mean changes from baseline in all ECG measurements in the Phase 3 NDO or total Phase 3 pediatric population were negligible over 52 weeks of treatment. Most of the 12-lead ECGs that were collected in the pediatric population were assessed by the investigator as normal. No dose-dependent effect on ECGs was identified.

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.

Targeted Adverse Events

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

UTI
Urinary tract infection (UTI) was a commonly reported TEAE with 2 cases reported as SAEs 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."

Constipation
All constipation cases in Study 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.

Changes in Vital Signs:
For the Phase NDO population, after 52 weeks of treatment, there was a small increase from baseline in mean systolic blood pressure (SBP) (0.7 mmHg), a decrease from baseline in mean diastolic blood pressure (DBP) (-1.6 mmHg) and a decrease from baseline in mean pulse rate (-2.9 beats/min). These were not considered as likely drug-related changes, but were more

likely related to normal growth and maturation over the 52 weeks of study treatment. One SAE of hypertension was reported in an actively treated patient, but that patient had a serious UTI requiring hospitalization and his blood pressure returned to normal while remaining on solifenacin.

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

Ocular Accomodation
Ocular accommodation was assessed in Study 047. Based on those assessments, the Sponsor concluded that overall, accommodative accuracy was improved. According to the Sponsor, the small changes from baseline to Week 12 (-0.25 diopters [95% CI: -0.87, 0.36]) and to week 52 were expected based on the annual age-related changes for patients in this study's age group, demonstrating that solifenacin did not have an effect on ocular accommodation. Dr. Chambers of DTOP was of the opinion that the accommodation testing was not conducted properly, thus conclusions are premature (see Section 11.1 of this review). Nonetheless, no significant ocular AEs were reported in the pediatric population.

Attention / Cognition
At the Division's request, cognitive testing was conducted in Study 047, and the results of those tests appear to show improvement, not decline, in cognitive function after treatment with solifenacin oral suspension. However, improvements in cognition are expected in patients of this age due to the rapid developmental maturation that occurs during late childhood and adolescence. There was one report of somnolence in a 15-year old male with NDO in which the role of solifenacin could not be excluded.

8.1.3 Postmarketing Safety Findings

Solifenacin oral suspension has not yet been approved for use in pediatric patients. However, there have been reports of off-label use of solifenacin tablets in pediatric patients for the treatment of voiding dysfunction. The Sponsor conducted a search of their global postmarketing safety databases from the launch of VESIcare tablets in 2004 up until September 2016 and 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. Of the 20 SAEs, 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. These included: 1) A 9 year old male with Down's Syndrome and history of obstipation who was hospitalized for fecal disimpaction, 2) a 14 year old male with history of severe ocular accommodation disorder who experienced vision loss, and 3) one case of "aggression" among 7 such cases that were reported in a published article that lacked sufficient detail to assess drug causality.

8.1.4 Overall Assessment of Safety Findings

Safety results from the Phase 3 studies in NDO and OAB demonstrated the expected adverse reactions to solifenacin, with no new safety signals identified. Solifenacin oral suspension was generally well tolerated in pediatric NDO patients. The safety profile of solifenacin oral suspension in the pediatric NDO population was fully consistent with the safety profile of approved solifenacin tablets in adults with OAB. There were no new or unresolved safety issues.

9. Advisory Committee Meeting

An Advisory Committee was not held for this application. No issues were identified that required advice from the Bone, Reproductive and Urologic Drugs Advisory Committee.

10. Pediatrics

The clinical studies conducted in support of this NDA were conducted in pediatric patients only, and were intended to meet 1) PREA-related postmarketing requirements under NDA 21-518 and 2) the Agency's specific requests in a July 27, 2012, Written Request for Pediatric Studies (WR). For those reasons, the application went before the Pediatric Exclusivity Board (PedEX) and the Pediatric Review Committee (PeRC).

10.1 Pediatric Exclusivity Board (PedEX) ,

In their final memo dated July 20, 2017, Matthew Bacho and Peter Stein, Chairman of PeDEX, agreed to grant Pediatric Exclusivity.

10.2 Pediatric Review Committee (PeRC)

In regard to PeRC, the Division met with the PeRC on July 26, 2017 to briefly discuss the NDA. In the final August 8, 2017, minutes from that July 26, 2017 PeRC meeting (authored by Jacqueline Yancy), the PeRC stated:

- PeRC acknowledged and agreed with the Division's intent to label VESIcare LS for use in pediatric NDO patients aged 2 years and above.
- PeRC acknowledged that a facility inspection-related Chemistry deficiency would preclude approval of the NDA at this time
- PeRC congratulated the Division for its persistent efforts to obtain information that would support approval of a new product for this patient population.

10.3 Division of Pediatric and Maternal Health Consultation (DPMH)

DPMH was consulted to provide input on documents to be prepared for the PedEX and PeRC meeting and to assist in the review of product labeling from a clinical pediatrics perspective.

In their final consultation report dated August 2, 2017, Melanie Bhatnagar, Mona Khurana and John Alexander provided advice, recommendations and comments on the Complete

Response (CR) regulatory action letter, the proposed VESIcare LS labeling, and section 8.4 (Pediatric Use) of the VESIcare tablets labeling.

For those items, DPMH had the following comments of note:

- The CR action letter for VESicare LS should contain a statement reminding the Sponsor of their obligation to market VESicare LS within one year of being granted pediatric exclusivity as stated in the Best Pharmaceuticals for Children Act (BPCA).
- Since all pediatric use information will appear in the eventual VESIcare LS labeling and no new safety signals were identified, the VESIcare tablets label should be revised to state that the "Safety and effectiveness of VESIcare tablets in pediatric patients has not been established for the treatment of OAB, because the OAB indication has not been studied in pediatric patients."
- Several section-specific labeling recommendations for the VESicare LS labeling, for example, for the Indications and Pediatric Use sections.

CDTL Note: The Clinical review team will consider the DPMH recommendations for labeling of both VESIcare LS and VESIcare tablets when labeling discussions re-commence.

11. Other Regulatory Issues, Including Consultations

11.1 Consultation: Division of Transplant and Ophthalmology Products (DTOP)

DTOP was consulted to review safety results related to ocular accommodation testing conducted in the Phase 3 studies. This specific testing was conducted by Sponsor at the request of the Division based on solifenacin's pharmacologic mechanism as an antimuscarinic, with a potential for effects on ciliary muscle function and ocular accommodation.

In his final consultation report dated June 23, 2017, Wiley Chambers, Deputy Director and ophthalmologist in DTOP had the following Ophthalmology recommendation and summary comments:

"*The application does not contain reliable information concerning the drug product's effect on accommodation.*

- *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.*
- *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.*
- *The variability of triplicate measurements used to construct the accommodation response-stimulus curve suggests that the collected values are not reliable measures of accommodation.*

- *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. There was no explanation for the exclusion of data.*
- *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 ability of the methodology used to detect a difference if a true difference was to be present."*

CDTL Note: Dr. Chambers' comments and conclusions are acknowledged. The ocular accommodation data provided by Sponsor in the application will not support labeling claims of safety. However, the Pediatric Exclusivity Board agreed with the Division that the Sponsor had done due diligence in testing ocular accommodation as the Sponsor had agreed to do at the Agency's request, and the deficiencies noted by Dr. Chambers do not preclude granting additional marketing exclusivity based on Sponsor's meeting the terms of the WR. Further, it is notable that no medically significant ocular AEs were reported during the clinical studies in pediatric patients with NDO or OAB. Therefore, this issue, while important for product labeling, does not unto itself preclude NDA approval.

11.2 Consultation: Interdisciplinary Review Team for QT Studies (IRT-QT)

IRT-QT was consulted to review results from QT interval assessments collected from electrocardiograms (EKGs) done in all patients at baseline and during treatment in the Phase 3 studies. In developing the Phase 3 protocols, the Sponsor had pre-defined certain QT interval changes that would lead to premature subject discontinuation. Early in the course of the Phase 3 clinical studies, it became clear that QT prolongation requiring subject discontinuation was being reported at a rate uncharacteristic for solifenacin (4 subjects were prematurely discontinued early in the studies for this reason). Thus, the Sponsor sought to determine the reason for this outcome. The Sponsor postulated that highly variable QT intervals at baseline with no repeat EKG at baseline may have led to unreliable baseline QT assessments in some patients. Thus, the Sponsor amended the study protocols to include multiple baseline EKGs and averaging of the baseline QT interval in all future patients. Subsequent to this protocol amendment, no further QT prolongation was reported and no additional subjects required study discontinuation for QT prolongation. IRT-QT was consulted to review this issue to determine whether the initial QT prolongation events were indeed related to variability at baseline and whether the Sponsor's amendment to require repeat baseline measurements and averaging was successful in correcting the problem.

In their final consultation report dated June 23, 2017, Lars Johannesen and Christine Garnett had the following IRT-QT recommendation and summary comments:

- "*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 pre-treatment 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 intra-subject variability and modified ongoing study protocols to define the baseline QTcB as an average of multiple pre-dose ECGs rather than a single ECG. 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.*"
- "*To better understand the potential for QTc prolongation in pediatrics due to solifenacin exposure with the proposed doses, we reviewed a prior thorough QT study for solifenacin 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 (Table 2) at supratherapeutic exposures in pediatrics.*"
- *"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."*

CDTL Note: The comments and conclusions from IRT-QT are acknowledged. The Clinical review team concurs with the IRT-QT comments and conclusions. We agree that the 4 events of QT prolongation that led to subject discontinuation early in the course of the Phase 3 studies were likely to have been a consequence of baseline variability and not a true drug-related effect. Further, based on pediatric and adult data, especially considering the prior TQT study in adults and the systemic exposures expected for solifenacin in the pediatric population, we agree with IRT-QT that it does not appear that solifenacin will have a clinically relevant effect on the corrected QT interval at the proposed doses in the pediatric NDO population.

11.3 Consultation: Office of Scientific Investigations (OSI)

OSI was consulted to conduct routine clinical site inspections for the purpose of assuring the quality of the clinical trial efficacy and safety data in support this application. Initially, clinical sites were selected in the Philippines and in Poland. However, it was not possible for OSI to visit the Philippines due to unforeseen political and military turmoil in that country. Therefore, clinical sites in Belgium were selected to replace the Philippines sites.

In their final review dated August 1, 2017, Roy Blay, Phillip Kronstein and Kassa Ayalew, had the following OSI recommendation and summary comments:

"*The clinical sites of Drs. Hoebeke, Vande Walle, and Baka-Ostrowska were inspected*

in support of this NDA.

Discrepancies in the secondary efficacy endpoint of bladder compliance were noted at the sites of Drs. Hoebeke and Dr. Baka Ostrowska in addition to some recordkeeping deficiencies at the latter site and are discussed in further detail below. Nevertheless, based on the overall results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication. The pending classification of all three inspections is No Action Indicated (NAI)."

The final OSI consult noted that the study sites had been selected to capture the large enrolling sites. Taken together, the clinical sites of Drs. Hoebeke, Vande Walle, and Baka-Ostrowska enrolled 38 of the 95 total enrolled patients aged 2 years and older.

In regard to "discrepancies" noted in the secondary endpoint, bladder compliance, those were resolved by a re-read of the study protocol and a straightforward explanation by the Sponsor. Specifically, discrepancies were noted between source data and case report forms (CRFs) with regard to bladder compliance, which is based on the interpretation of urodynamic tracing reports. The Sponsor's written response to the field investigators explained that the clinical investigator's assessment of bladder compliance was recorded in the CRF; however, the data line listings provided by the Sponsor contained the assessment of bladder compliance by a centralized reader, as specified in the protocol. The Sponsor's explanation was clear and acceptable to the Clinical review team.

11.4 Consultation: Office of Surveillance and Epidemiology (OSE)/ Division of Medication Errors Prevention and Analysis (DMEPA)

11.4.1 DMEPA Tradename Review

In their final review, dated May 23, 2017, Briana Rider, Lolita White, and Danielle Harris, stated that the proposed proprietary tradename, VESIcare LS, was "*acceptable*".

It is notable that the final DMEPA review fully addresses the initial concerns of the Clinical review team that the suffix "LS" could lead to medication errors, as follows:

- DMEPA first conducted a search of FDA's Adverse Event Reporting System (FAERS) that identified no concerns related to the root name VESIcare.
- DMEPA then conducted a safety assessment of the modifier "LS".
    - DMEPA inquired to Sponsor as to the rationale for the modifier "LS". DMEPA states their concurrence with the Sponsor's rationale that the modifier "LS" stands for "Liquid Suspension" and that it is important as a differentiator between solifenacin oral suspension and solifenacin tablets.
    - DMEPA sought out other information to inform the safety decision, for example, searching for drug products with the same modifier. DMEPA found no evidence that the modifier "LS" adversely affected safety for those two products (Acular LS ophthalmic solution and Mico-K LS liguid suspension).
    - DMEPA acknowledged that no responders in a Sponsor-conducted tradename safety study were able to identify "LS" as meaning "liquid suspension", as most

stated that LS did not convey any particular meaning to them; however, the majority did recognize that the new product was for pediatric/children's use.

- DMEPA provided a number of additional points concerning the general safety of the modifier "LS", concluding that: "*Based on the totality of the information considered above, we find the use of the proposed modifier, "LS", acceptable for this product."*

CDTL Note: Based on the extensive review and consideration of the issue by DMEPA, the Clinical review team does not object to the tradename "VESIcare LS"

11.4.2 DMEPA Container/Carton/Package Insert Labeling

DMEPA completed three consultative reviews for VESicare LS labeling; two initial reviews on May 23, 2017, and a final one June 5, 2017. In their final review dated June 5, 2017, Briana Rider and Lolita White concluded:

> "*The revised expiration date format for the carton labeling and container labels for VESIcare LS is acceptable form a medication error perspective. We have not further recommendations at this time.*"

CDTL Note: The input from DMEPA has allowed us to reach agreement with Sponsor on container and carton labeling. The input from DMEPA on the PI has been conveyed to Sponsor and those PI issues will be re-visited when labeling discussions re-commence.

11.5 Consultation: Office of Surveillance and Epidemiology (OSE)/Division of Medical Policy Programs (DMPP)

In their final memo dated August 11, 2017, Twanda Scales and Marcia Williams had the following DMPP conclusion

> *"Due to outstanding facility deficiencies, DBRUP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the CR letter."*

11.6 Financial Disclosure

In compliance with the FDA regulation concerning financial disclosure (21 CFR Part 54), the Sponsor disclosed the absence of proprietary interest in this product by any clinical investigator in the VESIcare LS clinical studies, as well as the lack of financial arrangements between any clinical investigator in the VESIcare LS clinical studies and the Sponsor.

12. Labeling

Despite the Complete Response (CR) regulatory action that is planned, the NDA review team nonetheless conducted a full review of the Sponsor's proposed Package Insert (PI), including offering FDA edits and comments on all parts of the PI (except for the Highlights section and

the glaucoma-related Contraindication and Warning).

An FDA-edited PI was conveyed by emails to Sponsor in two parts: the first part on August 7, 2017, and the second on August 21, 2017.

When the NDA is resubmitted, labeling discussions will re-ensure. At that time, we will complete edits to the Highlights section of the PI, we will discuss with Dr. Chambers of DTOP possible edits to the glaucoma-related Contraindication and Warning, and we will ask DMPP to review the patient labeling once a substantially complete PI (SCIPI) is available.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend a Complete Response action for this application based on unresolved Chemistry deficiencies.

The specific Chemistry deficiencies and the specific Information Needed to Resolve the Chemistry Deficiencies are shown in Section 3 ("CMC") of this CDTL memo.

13.2 Risk Benefit Assessment

The data included in the submission demonstrated this product has a positive benefit / risk ratio for use in pediatric patients with NDO, aged 2 years and older.

The efficacy of solifenacin suspension in the treatment of pediatric NDO patients aged 2 to < 18 years old has been demonstrated through achievement of both the primary and secondary efficacy endpoints in two Phase 3 studies.

Safety results from the Phase 3 studies in NDO and OAB demonstrated the expected adverse reactions to solifenacin, with no new safety signals identified. Solifenacin oral suspension was generally well tolerated in pediatric NDO patients. The safety profile of solifenacin oral suspension in the pediatric NDO population was fully consistent with the safety profile of approved solifenacin tablets in adults with OAB. There were no new or unresolved safety issues.

When the Chemistry deficiencies are resolved, VESIcare LS (solifenacin oral solution) will represent an important child-friendly option for use in conjunction with CIC for NDO in pediatric patients aged 2 years and older.

13.3 Recommendation for Postmarketing Risk Management Activities

No postmarketing risk management activities are recommended.

13.4 Recommendation for other Postmarketing Study Commitments

No postmarketing studies are recommended.

13.5 Recommended Comments to Applicant

None.

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/s/

MARK S HIRSCH
08/27/2017

CHRISTINE P NGUYEN
08/28/2017
I concur with Dr. Hirsch's summary review and regulatory recommendation that this NDA should receive a Complete Response due to CMC deficiencies.