CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW MEMORANDUM

NDA Number	209529
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Submission Type	Resubmission
Submission Date	11/27/2019
PDUFA Date	05/27/2020
Review type	Clinical Pharmacology Review Memorandum
Brand Name	VESIcare LS
Generic Name	Solifenacin succinate
Dosage Form and Strength	Solifenacin succinate oral suspension 1 mg/mL
Route of Administration	Oral
Proposed Indication	Treatment of neurogenic detrusor overactivity in pediatric patients aged 2 years and older
Applicant	Astellas Pharma US, Inc.
Associated IND	IND 058135
Office of Clinical Pharmacology Review Team	Division of Cardiometabolic and Endocrine Pharmacology Jihong Shon, M.D., Ph.D. Lu Yanhui, Ph.D.

1. EXECUTIVE SUMMARY

Solifenacin is a competitive muscarinic antagonist that modulates smooth muscle contractility in the urinary bladder. The Applicant owns an oral tablet formulation of solifenacin succinate (VESIcare®, NDA021518) that is approved for the treatment of overactive bladder (OAB) in adults. The Applicant proposed a pediatric study plan for the use of solifenacin succinate in treatment of neurogenic detrusor overactivity (NDO) in pediatric patients (March 23, 2012) and a written response was provided by the Agency (July 27, 2012) to submit pharmacokinetic (PK), safety, and efficacy information of solifenacin succinate in pediatric patients with NDO.

Neurogenic detrusor overactivity (NDO) is a urodynamic dysfunction characterized by involuntary contraction of the bladder detrusor muscle during the filling phase, which results in elevated detrusor pressure and reduced bladder capacity and consequently cause several complications such as urinary tract infections, bladder stones, fibrosis, trabeculation, and autonomic dysreflexia. The Applicant has developed an oral suspension of solifenacin succinate for the treatment of NDO in pediatric patients and originally submitted a New Drug Application (NDA) for the pediatric patients aged 2 years and older on February 28, 2017. The Applicant proposed a weight-range adjusted dosing table for pediatric patients with NDO to achieve plasma exposures equivalent to those in adults with OAB at the approved doses (5 mg and 10 mg) of VESIcare® (Table 1).

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 Division of Pharmacometrics completed reviewing the submitted clinical pharmacology information and concluded that the application was acceptable and recommended

approval from the clinical pharmacology standpoint (OFFICE OF CLINICAL PHARMACOLOGY REVIEW for NDA 209529 dated August 8, 2017 in DARRTS). In the previous review, the OCP recommended that the dosing table should be modified by adding a starting dose of 5 mg and a maximal dose of 10 mg for patients with body weight > 60 kg (Table 2.; Refer to Section 3. SUMMARY OF THE PRIOR OCP'S REVIEW). The Applicant accepted the recommendation and updated the prescribing information.

In the review process for the original submission, the Chemistry, Manufacturing, and Controls (CMC) review team identified three major deficiencies in the drug product specification and the manufacturing facility for the final product. Consequently, the Agency determined that the original NDA could not be approved (Complete Response Letter dated August 28, 2017).

The Applicant had resolved the CMC issues for the complete response and received feedback from the Agency on those issues via a Pre-NDA meeting and resubmitted the NDA on November 27, 2019. This resubmission includes a revised product label and updated safety information. The current resubmission includes no new clinical pharmacology data and thus the clinical pharmacology review team focused on the labeling recommendation in this review cycle.

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.

2. SUMMARY OF LABELING RECOMMENDATON

The Office of Clinical Pharmacology provides the following recommendations on the labeling information:

- Dosing administration information in HIGHLIGHTS and Section 2 DOSAGE AND ADMINISTRATION and 17 PATIENT COUNSELING INFORMATION should include instruction regarding water or milk intake after taking the suspension.
- Each subsection under Section 7 DRUG INTERACTIONS should be revised to include clinically relevant mechanisms, findings and management/mitigation strategies in relation to drug interaction. A subsection can be deleted or relocated unless it provides concrete supporting data and actionable mitigation strategies. Accordingly, DRUG INTERACTIONS in HIGHLIGHTS should be modified to be consistent with the revised contents in Section 7.
- Information described for patients with renal impairment (8.6) or hepatic impairment (8.7) in Section 8 USE IN SPECIFIC POPULATIONS should be revised to include key findings associated with organ impairments and dosage recommendation. (b) (4) (b) (4).

3. SUMMARY OF THE PRIOR OCP'S REVIEW

The Applicant proposed daily doses (i.e. starting and maximum doses) of solifenacin succinate oral suspension based on body weight for pediatric patients aged 2 years and older with NDO. In support of this NDA, the Applicant conducted 3 clinical studies (one phase 1 study and two phase 3 studies) in pediatric patients with NDO for evaluation of PK, efficacy, and safety of the proposed drug. In addition, the

Applicant performed two PK studies in healthy adults to compare the relative bioavailability between suspension and tablet formulations.

The Applicant developed population PK and physiologically based pharmacokinetics (PBPK) models by leveraging clinical information collected in the studies conducted in pediatric patients with NDO or OAB. The developed final model was verified by comparing the PBPK-predicted and observed or estimated exposure in pediatric patients with NDO. The Applicant proposed weight-range adjusted doses for pediatric patients with NDO to achieve plasma exposure equivalent to those following administration of the currently approved doses, 5 mg (staring dose) and 10 mg (maximum dose), of the oral tablet formulation of solifenacin succinate (VESIcare®) in adults with OAB. The Applicant proposed the following dosing table was established based on solifenacin exposure values (area under the plasma concentration-time curve, AUC) estimated by the PBPK model for pediatric patients with NDO (Table 1).

Table 1. Recommended doses by weight range for pediatric patients with NDO aged 2 years to less than 18 years

	Recommended doses by weight range	
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

Solifenacin succinate oral suspension is provided as a 1 mg/mL oral suspension

The OCP review team concluded that the established PBPK model adequately described the exposure of solifenacin in pediatric population aged 2 year and older. However, considering that the pediatric dosing is intended to achieve plasma exposures equivalent to those in adults at the approved doses of 5 mg and 10 mg and some pediatric patients have body weight similar to adults, the OCP review team recommended that the dosing table include an additional dosage of 5 mg starting dose and 10 mg maximal dose for patients with body weight > 60 kg (Table 2). This recommendation was accepted by the Applicant during the previous review cycle and was reflected in the prescribing information submitted in this review cycle.

Table 2. Recommended doses by weight range for pediatric patients with NDO aged 2 years to less than 18 years

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

Solifenacin succinate oral suspension is provided as a 1 mg/mL oral suspension

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/s/

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05/01/2020 03:59:57 PM

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OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA Number	209529
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Submission Dates	02/28/17, 04/20/17, 04/27/17, 05/02/17, 05/11/17, 05/12/17 and 05/18/17
Submission Type	Original
PDUFA Date	08/28/17
Brand Name	Vesicare LS
Generic Name	Solifenacin succinate oral suspension
Dosage Form and Strength	Oral suspension 1 mg/mL solifenacin succinate
Route of Administration	Oral
Proposed Indication	Treatment of neurogenic detrusor overactivity in pediatric patients aged 2 years and older
Applicant	Astellas Pharma US, Inc.
Associated IND	IND 058135
OCP Review Team	Jihong Shon, M.D., Ph.D.; Simbarashe Zvada, Ph.D.; Yuching Yang, Ph.D.; Doanh Tran, Ph.D.; Jeffry Florian, Ph.D.; Yaning Wang, Ph.D.
OCP Final Signatory	Capt. E. Dennis Bashaw, Pharm D Division Director Division of Clinical Pharmacology III

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1 EXECUTIVE SUMMARY

Solifenacin is a competitive muscarinic antagonist that modulates smooth muscle contractility in the urinary bladder. An oral tablet formulation of solifenacin succinate (VESIcare®) is approved for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency in adults (NDA 021518). However, the safety and effectiveness of solifenacin in pediatric patients have not been established.

Neurogenic detrusor overactivity (NDO) is a urodynamic dysfunction characterized by involuntary contraction of the bladder detrusor muscle during the filling phase, which results in elevated detrusor pressure and reduced bladder capacity. It may cause several complications such as urinary tract infections, bladder stones, fibrosis, trabeculation and autonomic dysreflexia (*Consortium for Spinal Cord Medicine 2006*). The Applicant has developed an oral suspension of solifenacin succinate for the treatment of NDO in pediatric patients. The Applicant proposed daily doses (starting and maximum doses) of solifenacin succinate oral suspension based on body weight for pediatric patients aged 2 years and older with NDO. In support of this NDA, the Applicant conducted 3 clinical studies (one phase 1 study and two phase 3 studies) in pediatric patients with NDO for pharmacokinetics (PK), efficacy and safety evaluation. Data from another PK study in pediatric patients with OAB was used to build up a basic population PK model of solifenacin in pediatric patients. In addition, the Applicant performed two PK studies to compare bioavailability among suspension and tablet formulations. The Applicant developed population PK and physiologically based pharmacokinetics (PBPK) models by leveraging the clinical information collected in studies conducted in pediatric patients with NDO or OAB.

This clinical pharmacology review focuses on the use of PK modeling approaches to support a body weight-adjusted dosing table for administration of solifenacin succinate oral suspension in pediatric patients with NDO.

1.1 Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology III and Division of Pharmacometrics have reviewed the information submitted 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 the review team.

The key review issues with specific comments/recommendations are summarized below:

Review issues	Comments and recommendations
Supportive evidence of effectiveness in the pediatric NDO population	Solifenacin as an antimuscarinic agent can relieve NDO-associated symptoms such as urinary urgency and incontinence and may prevent complications including urinary tract infection and renal damage in pediatric patients with NDO. 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.

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, 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.
Dosing or alternative management plan in patient subgroups (intrinsic and extrinsic factors)	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. 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.

1.2 Post-Marketing Requirement and Commitment

None

2 SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Solifenacin is a competitive muscarinic receptor antagonist which is selective for the M3 receptor of muscarinic receptor subtypes and its binding to those receptors modulates cholinergically mediated functions including the contraction of smooth muscle and, in particular, relaxes smooth muscle tone in the urinary bladder. It may cause significant reduction in urgency incontinence episodes and improved urodynamic parameters in patients with NDO whose detrusor pressure is elevated and bladder capacity is reduced.

Clinical PK information of solifenacin following administration of solifenacin succinate oral suspension in pediatric patients with NDO from 2 years to <18 years old was provided based on parameters estimated by population PK approaches using plasma concentrations of solifenacin measured in phase 3 trials

(Studies 905-CL-047 and 905-CL-074). Additional PK information for solifenacin is also provided from the development program for VESIcare® (NDA 021518). The clinical PK of solifenacin is summarized below:

Absorption: In pediatric patients with NDO from 2 years to <18 years old, following oral administration of solifenacin succinate, peak plasma concentrations (C_{max}) of solifenacin are reached within 2 to 6 hours (median: 3 hours) after administration (T_{max}) at steady state. The dose-normalized C_{max} ranged from 2.49 – 29.26 ng/mL/mg (median: 7.79 ng/mL/mg). Food intake does not significantly affect the exposure of solifenacin. The absolute bioavailability of solifenacin in adults is approximately 90%, with plasma concentrations of solifenacin proportional to the dose administered.

Distribution: Solifenacin is approximately 98% (*in vivo*) bound to human plasma proteins, principally to α1-acid glycoprotein (AGP). Solifenacin has a median steady-state volume of distribution of 211.1 L (range: 33 to 750.9 L) in pediatric patients with NDO.

Metabolism: Solifenacin is extensively metabolized in the liver. The primary pathway for elimination is mediated by cytochrome P450 (CYP) 3A4, but alternate metabolic pathways (CYP1A1 and CYP2D6) exist. One pharmacologically active metabolite (4R-hydroxy solifenacin), occurring at low concentrations and unlikely to contribute significantly to clinical activity, and three pharmacologically inactive metabolites (N-glucuronide and the N-oxide and 4R-hydroxy-N-oxide of solifenacin) have been found in human plasma after oral dosing.

Excretion: Following the administration of 10 mg of 14^{C}-solifenacin succinate to healthy adult volunteers, 69.2% of the radioactivity was recovered in the urine and 22.5% in the feces over 26 days. A mean of less than 15% of the dose was recovered in the urine as intact solifenacin. The major metabolites identified in urine were N-oxide of solifenacin, 4R-hydroxy solifenacin and 4R-hydroxy-N-oxide of solifenacin and the major metabolite in feces was 4R-hydroxy solifenacin. The median elimination half-life of solifenacin is approximately 26.4 hours (range: 3.86 to 104.0 hours) in pediatric patients with NDO.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The Applicant proposed a weight-range adjusted dosing table for the oral suspension formulation to achieve plasma concentrations equivalent to exposures in adults at the approved doses of VESIcare® tablets (starting and maximum doses: 5 and 10 mg once daily).

Table 2.2-1 Recommended doses by weight range for pediatric patients with NDO aged 2 years to less than 18 years

	Recommended doses by weight range	
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

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

Efficacy and safety were investigated in the two phase 3 trials (Studies 905-CL-047 and 905-CL-074) in pediatric patients with NDO aged 6 months to < 18 years. Both studies used the pediatric equivalent doses (PEDs) by weight range, which were the doses of solifenacin oral suspension estimated to attain similar exposure as observed in adults at established once-daily doses of 5 and 10 mg. Efficacy results based on urodynamic and patient diary endpoints demonstrated the effectiveness of solifenacin in pediatric patients with NDO. There were no new safety signals specific in pediatric patients during the 52-week treatment period. The clinical effectiveness and safety profile observed in both studies which used the PEDs in pediatric patients with NDO may support an exposure matching approach between children and adults for dose selection of solifenacin oral suspension in pediatric patients with NDO.

The final dosing table was established based on exposure values (area under the concentration curve, AUC) estimated using the PBPK model of solifenacin created in pediatric patients with NDO (Table 2.2-1). The weight-based dosing regimen for patients aged < 5 years used in Study 905-CL-074 was based on this PBPK approach. The model was verified by comparing the PBPK-predicted and observed or estimated exposure in pediatric patients with NDO. The established PBPK model appears to adequately describe the exposure to solifenacin in pediatric population aged 2 year. Because the pediatric dosing is intended to achieve plasma concentrations equivalent to exposures in adults at the approved doses of 5 and 10 mg and some pediatrics have high body weight similar to adults, the review team recommends that the dosing table be modified to add an additional dose of 5 mg starting dose (and 10 mg maximal dose) for patients with body weight > 60 kg. The revised recommended dosing table is shown in Table 2.2-2.

Table 2.2-2 Recommended doses by weight range for pediatric patients with NDO aged 2 years to less than 18 years

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

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

2.2.2 Therapeutic individualization

The Applicant has performed no dedicated clinical trial to assess impacts of intrinsic and extrinsic factors on the PK and pharmacodynamics (PD) of solifenacin in pediatric patients. The dosing recommendations in relation to drug interactions and specific populations are solely reliant on those in the approved oral tablet formulation of solifenacin succinate (VESIcare®). Given that there were no specific physiologic or metabolic factors identified in pediatric patients (2 years and older) significantly affecting the PK of solifenacin differently from adults, the currently proposed individual recommended dosage related to drug interactions and for special populations are acceptable. In addition, contraindication and warnings and precautions that the Applicant proposed are similar to those in the prescribing information for VESIcare®. There are no additional recommendations for these sections from a clinical pharmacology perspective.

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling revisions:

- Given that there are adolescents who have body mass comparable to adults and the metabolic capacity of solifenacin in children (2 years and older) is unlikely to be different from that in adults, the recommended doses for adult patients with OAB can be considered for pediatric population with NDO and high body weight. Simulated AUC data at 8 mg and 10 mg using the developed PBPK model in virtual population > 45 kg demonstrated that pediatric patients weighing > 60 kg are more likely to reach the target exposure range following administration of 10 mg, the maximum dose for adults, than 8 mg, the Applicant's proposed maximum dose. Therefore, 5 mg and 10 mg should be considered as the recommended starting and maximum doses for pediatric patients weighing > 60 kg. Refer to section 3.3.2 and 4.2.4.

- Food intake does not affect the C_{max} and AUC of solifenacin. While the reviewer concludes that there is no significant effect of food intake on the exposure to solifenacin following administration of solifenacin suspension formulation, it should be considered that this conclusion is based on the indirect supporting evidence rather than a result from a dedicated food-effect study. In addition, the food-effect study of Formulation A (Study 905-CL-066) performed in adults demonstrated that food intake may slightly decrease the C_{max} (by about 12%) and increase the AUC (by about 7%) of solifenacin, even though these changes are not expected to have a clinical relevance. Therefore, the currently proposed description of food-effect should be modified to better reflect the available data.

Applicant's proposal	FDA's recommendation
Effect of Food (b) (4)	Food intake does not <u>significantly</u> affect the C_{max} and AUC of solifenacin <u>following oral administration of solifenacin succinate suspension</u>.

3 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Solifenacin is a competitive muscarinic antagonist that relaxes urinary bladder smooth muscle. An oral tablet formulation of solifenacin succinate (VESIcare®) is currently approved for the treatment of OAB. However, the safety and effectiveness of solifenacin in pediatric patients have not been established.

NDO is an urodynamic observation characterized by involuntary contraction of the bladder detrusor muscle during the filling phase, where there is evidence of a neurological disorder (*Abrams P. 2003*). In

children, the most prevalent cause of NDO is a congenital neural tube defect and this bladder dysfunction can cause irreversible renal damage and urinary incontinence (*Lazarus J. 2009*).

The approval letter of NDA 021518 (VESIcare®) required the pediatric studies (pediatric patients with OAB for ages 5 to 11 years old and adolescents for ages 12 to 17 years old) under the Pediatric Research Equity Act (PREA) (November 19, 2004). The Applicant submitted a written request to qualify for pediatric exclusivity including proposal of two clinical trials in pediatric patients with NDO (Study 1: single-dose PK study and Study 2: efficacy and safety study in pediatric patients aged 5 to less than 18 years old) (March 10, 2011) and agreed upon on the amended written requests (June 5, 2015).

The Applicant submitted a New Drug Application (NDA) of solifenacin succinate oral suspension for the treatment of NDO in pediatric patients on February 28, 2017. The Applicant proposed the daily dose (starting and maximum doses) of solifenacin succinate oral suspension based on body weight for pediatric patients with NDO aged 2 to < 18 years old. In support of this NDA, the Applicant conducted 3 clinical studies (one phase 1 study and two phase 3 studies) in pediatric patients with NDO for PK, efficacy and safety evaluation. The Applicant also performed two PK studies to compare the bioavailability between suspension and tablet formulations.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Solifenacin is a competitive muscarinic receptor antagonist which is selective for the M3 receptor of muscarinic receptor subtypes. Its binding to the muscarinic receptor modulates cholinergically mediated functions including the contraction of smooth muscle and, in particular, relaxes smooth muscle tone in the urinary bladder. It causes significant reduction in urgency incontinence episodes and improves urodynamic parameters in patients with NDO.
QT Prolongation	Four patients in Study 905-CL-047 experienced an adverse event (AE) of ECG QT prolongation that resulted in treatment discontinuation. However, this may be due to variability in the baseline measurement because there were no further discontinuation cases when the baseline QTcB calculation was changed from a single measurement to the average of measurements over 2 visits to increase the accuracy of the baseline QTc measurement. The mean changes of QT intervals from baseline to week 52 were negligible in the phase 3 trial. In addition, there was no evidence of any increased QT prolongation-associated risk in the pediatric population compared to that in adults.
General Information	
Bioanalysis	The plasma concentrations of solifenacin in clinical studies were analyzed using validated Liquid Chromatography–Mass Spectrometry / Mass Spectrometry (LC-MS/MS) assays (refer to section 4.1).
The PK profile of solifenacin following	The PK of solifenacin at steady-state following administration of solifenacin succinate oral suspension in pediatric patient with NDO was characterized using

administration of solifenacin succinate oral suspension in pediatric patients with NDO aged 2 to < 18 years old	population PK approach based on data from the two phase 3 studies (Studies 905-CL-047 and 905-CL-074). The estimated dose-normalized PK parameters of solifenacin for each age group are summarized in Table 4.2-18 and 4.2-19. After oral administration of the solifenacin succinate suspension in pediatric patients with NDO from 2 to <18 years old, the C_{max} of solifenacin reached within 2 to 6 hours (median T_{max} = 3 hours) at steady state. The dose-normalized C_{max} and area under the concentration-curve from the time of dosing to the start of the next dosing interval (AUC_{tau}) ranged from 2.49 to 29.26 ng/mL/mg (median: 7.79 ng/mL/mg) and from 48.05 to 559.69 ng·h/mL/mg (median: 146.42 ng·h/mL/mg), respectively. The estimated apparent oral clearance ranged from 1.35 to 15.7 L/h (median = 5.1 L/h). The median elimination half-life ($t_{1/2}$) of solifenacin is approximately 26.4 hours (range = 3.9 - 104 hours) [refer to section 4.2.5].
Absorption	
Bioavailability	The absolute bioavailability of the solifenacin tablet is approximately 90% in adults. Bioavailability of the suspension formulation is bioequivalent to the tablet formulation.
Food effect	Food intake does not significantly affect the exposure of solifenacin following administration of solifenacin succinate oral suspension.
Distribution	
Volume of distribution	Solifenacin has a median steady-state volume of distribution of 211.1 L (range: 33 to 750.9 L) in pediatric NDO patients from 2 to < 18 years old.
Plasma protein binding	Solifenacin is approximately 98% bound to human plasma proteins, principally to AGP. Solifenacin is highly distributed to non-CNS tissues.
Elimination	
Metabolism	Solifenacin is extensively metabolized in the liver. The primary pathway for elimination is by way of CYP3A4. However, alternate metabolic pathways exist. Given that maturation of CYP3A4 activity is fully completed in the population older than 2 years, metabolism of solifenacin via CYP3A4 is the major route of elimination and the metabolic capacity of the liver is similar to adults in children (2 years and older) and adolescents, the metabolism of solifenacin in pediatrics 2 years and older is expected to be similar to adults.
Excretion	Following administration of 10 mg of 14^C-solifenacin succinate to healthy adult volunteers, 69.2% of the radioactivity was recovered in the urine and 22.5% in the feces over 26 days. A mean of less than 15% of the dose was recovered in the urine as intact solifenacin. The major metabolites identified in urine were N-oxide of solifenacin, 4R-hydroxy solifenacin and 4R-hydroxy-N-oxide of solifenacin and the major metabolite in feces was 4R-hydroxy solifenacin. The median elimination half-life of solifenacin is approximately 26.4 hours in pediatric patients with NDO from 2 to < 18 years.

3.3 Clinical Pharmacology Questions

3.3.1 Does the available clinical pharmacology information provide supportive evidence of effectiveness?

Yes. Solifenacin as an antimuscarinic agent suppresses involuntary detrusor contractions and lowers the pressure within the bladder wall. This pharmacological action can relieve NDO-associated symptoms such as urinary urgency and incontinence and may prevent complications including urinary tract infection and renal damage in pediatric patients with NDO. The efficacy data using urodynamic and patient diary endpoints from the two phase 3 trials provide supportive evidence of effectiveness for solifenacin succinate oral suspension in pediatric patients with NDO aged 2 years and < 18 years. In addition, the final dosing table based on PBPK modeling is consistent with dose regimens used in the two phase 3 trials (refer to 3.3.2). It suggests that pediatric patients with NDO would achieve a desired effectiveness with the currently proposed recommended dose regimen. Additional details are discussed below.

- Pharmacological mechanism of action in relation to efficacy

Early treatment of pediatric patients with NDO prevents or minimizes damage to the upper urinary tract and bladder wall and preserves renal function (*Tom et al. 2008*). Antimuscarinic agents inhibit the binding of acetylcholine to muscarinic receptors in the bladder detrusor muscle, suppressing involuntary detrusor contractions and facilitating the drainage from the upper tracts by lowering the pressure within the bladder wall. Through this mechanism, antimuscarinic therapy increases bladder capacity. While antimuscarinic drugs are considered the first-line treatment of NDO (*Gaziev et al. 2015*), oxybutynin is the only drug currently approved in the United State for the treatment of pediatric patients with symptoms of NDO, but this treatment can be limited by its tolerability and poor patient compliance and was approved only for patients aged 5 years and older (*Yarker et al. 1995*). An in vivo study demonstrated that solifenacin selectively binds to the muscarinic M3 subtype in the bladder (*Ito et al. 2009*). A survey of adherence to anticholinergic agents in patients with OAB also showed that solifenacin had the highest rates of patient compliance (*Lua et al. 2017*).

- Efficacy results of solifenacin succinate oral suspension from pivotal phase 3 trials in pediatric patients with NDO

Two phase 3 trials (Study 905-CL-047 and 905-Cl-074) evaluated efficacy of solifenacin succinate oral suspension in children and adolescents (aged 6 months to < 18 years old) with NDO using urodynamic and patient diary outcome measures. The primary endpoint was change from baseline to week 24 in mean maximum cystometric capacity (MCC) as an urodynamic variable. The results are summarized in Table 3.3-1.

Table 3.3-1. Change from baseline to Week 24 in MCC (mL) in two Phase 3 trials

	905-CL-074 2 years to < 5 years		905-CL-047 5 years to 18 years		Phase 3 NDO Population 2 years and older	
	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24
MCC (mL)						

n	17	17	55	49	72	66
Mean (SD)	97.8 (39.5)	137 (36.8)	224 (133)	279 (127)	194.0 (129.1)	242.4 (127.1)
Change from baseline						
n		17		49		66
Mean (SD)		38.9 (35.5)		57.2 (108)		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

The following secondary urodynamic and patient diary endpoints were evaluated to characterize the overall treatment effect: bladder compliance, bladder volume until first detrusor contraction > 15 cm H_2O as a percentage of expected bladder capacity, number of overactive detrusor contractions > 15 cm H_2O until end of bladder filling, maximum catheterized volume and mean number of incontinence episodes per 24 hours. The efficacy variables were also analyzed up to week 52.
The efficacy results demonstrated that treatment with solifenacin succinate oral suspension produced overall beneficial effects in pediatric patients with NDO aged 2 years to < 18 years old.

3.3.2 Is the proposed dosing regimen appropriate for the general pediatric patient population for which the indication is being sought?

Yes. The Applicant proposed a dosing table for pediatric patients with NDO aged 2 years older and < 18 years. This 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 in pediatric patients with OAB or NDO. In addition, the proposed dosing regimen is consistent with those administered in the two phase 3 studies.

Based on the proposed dosing table, the highest starting and maximum doses are 4 mg and 8 mg for pediatric patients with NDO weighing > 45 kg. Given that there are adolescents who have body mass comparable to adults and their metabolic capacity is also similar to them, the recommended doses for adult patients were considered for treatment of pediatric patients who have greater body weight. Simulation AUC data at 8 mg and 10 mg using the developed PBPK model in virtual population > 45 kg indicated that the use of the adult doses should be considered for pediatric patients who have a relatively high body weight. In particular, pediatric patients weighing > 60 kg are more likely to reach the target exposure range following administration of 10 mg, the maximum dose for adults, than 8 mg, the Applicant's proposed maximum dose. These results suggest that the recommended doses for adults, 5 mg and 10 mg, should be considered for pediatric patients with body weight greater than 60 kg. Provided that safety and efficacy reported in the phase 3 trials are acceptable, the reviewers conclude that the Applicant's general dosing recommendation is appropriate for pediatric patients with NDO weighing ≤ 60 kg. The recommended doses for adults, 5 mg and 10 mg, should be considered for pediatric patients with body weight greater than 60 kg. Additional details are discussed below.

- Development strategy for the dosing table

The Applicant developed the weight-range adjusted doses in pediatric patients with NDO to achieve plasma concentrations equivalent to exposures in adults following administration of 5 or 10 mg once

daily doses. A PBPK model was created to derive dosing regimens in pediatric patients to match exposures observed in adults at the two doses for the treatment of pediatric patients with NDO. This model takes into account the maturation of PK processes like clearance and distribution according to physiological changes with age. The target exposure for the maximum dose in the dosing table was (b) (4) (b) (4)). These values were based on the steady-state AUC of the final suspension formulation after daily dosing of 10 mg estimated using the data from the relative bioavailability study in adults (Study 905-CL-080). (b) (4) (b) (4) The lowest weight for the dosing table was 9 kg which was the lowest weight observed in patients in the phase 3 study (Study 905-CL-074) aged approximately 2 years old. The Applicant's goal was to develop a straightforward and conservative dosing table and allow simplified dosing instructions during the dose-optimization process and they included the following objectives: 1) Minimization in the number of weight groups, including only starting and maximum doses and rounding exact doses to 1 mL increments and 2) Selection of the maximum dose to be no more than twice the recommended starting dose in each weight group. The final weight ranges of 9 to 15 kg, > 15 to 30 kg, > 30 to 45 kg and > 45 kg were selected to reduce the risks of dosing errors thus simplifying the dosing regimen. Using simulated AUC in virtual patients aged 2 years to < 18 years, the exact dose that would be required to obtain the target exposure was calculated. The median of the exact doses for all patients within each weight range was calculated, which was designated the optimal dose for the weight range (Table 3.3-2).

Table 3.3-2 Optimal doses by weight range for pediatric patients with NDO aged 2 years to less than 18 years

	Recommended doses by weight range	
Weight range (kg)	**Starting Dose (mL)**	**Maximum Dose (mL)**
9 to 15	(b) (4)	
> 15 to 30		
> 30 to 45		
> 45		

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

The optimal doses were adjusted to the Applicant's final recommended dosing table (Table 2.2-1) based on the defined objectives.

- PBPK modeling approach supporting the development of the dosing table:

Solifenacin PBPK models were developed to describe the plasma PK profiles of solifenacin in adult and pediatric populations. A step-wise modeling approach was used to develop a solifenacin PBPK model for pediatric population (Figure 4.2-1 in section 4.2.2).

The Applicant first built and validated a base solifenacin PK model in healthy adult subjects using in vitro data and clinical human PK datasets. Using the literature-based dataset and scaling functions, PBPK parameters in the adult model were scaled to pediatrics by accounting for age related changes in clearance and distribution processes for children aged 5 to 18 years old. Pediatric solifenacin PBPK model was verified by comparing the simulated solifenacin PK and those observed in pediatric patients with OAB aged 5 to 17 years (Study 905-CL-075; Figure 4.2-2 in section 4.2.2) and pediatric patients with NDO aged 6 to 17 years (Study 905-CL-079; Figure 4.2-3 in section 4.2.2).

Once solifenacin PBPK model had been verified with PK profiles observed in patients with NDO aged 6 to 17 years, the applicant used it to simulate the dose-AUC relationship in children aged 6-month to 5 years old. The Applicant prospectively predicted dose (PED10) in pediatrics that can match the AUC of solifenacin observed in adults at 10 mg daily dosing in Study 905-CL-080. PED10 was adjusted linearly to determine the lower doses, PED2.5, PED5, and PED7.5. This PBPK-based dosing approach (Table 3.3.3) was used for the phase 3 trial in children aged 6-month to 5 years old (Study 905-CL-074). The PK results from this study demonstrated that PBPK-based dosing regimens achieved the target pediatric equivalent exposure in patient age 1.6 to 5 year-old. The submitted solifenacin PBPK models appear to adequately describe solifenacin exposure observed in pediatric population ages 2 years and older. Additional details of PBPK modeling are discussed in section 4.2.2.

- Comparison between dose regimens used in phase 3 trials and final recommended doses

The Applicant's final recommended doses constructed using the PBPK modelling approach is generally consistent with those administered in the two clinical studies (Studies 905-CL-047 and 905-CL-074).

Table 3.3-3 Comparison of the recommended doses and the dose regimens applied in the two phase 3 trials

<table>
<tr><th></th><th>905-CL-074</th><th>905-CL-047</th><th>Applicant's dosing recommendation</th></tr>
<tr><td>Method for developing a dosing table</td><td>The PBPK model, which accounts for age-related physiological changes, was used for determining the allometric-scaling based doses in patients aged 6 months to < 5 years old.</td><td>The population pediatric PK model developed using the data from Study 905-CL-075 and the two relative bioavailability studies (Study 905-CL-066 and 905-CL-080) were used for determining the allometric-scaling based doses in patients aged 5 years to < 18 years.</td><td>The PBPK model was used to derive dosing to match exposures observed in adults at once daily doses (5 mg and 10 mg) for the treatment of pediatric patients with NDO aged 2 years older and < 18 years. Two objectives were applied for a simple dosing table: minimization in the number of weight groups and selection of the maximum recommended dose no more than twice the recommended starting dose.</td></tr>
<tr><td>Doses</td><td>
<table>
<tr><th>Weight range (kg)</th><th>PED5 (mg)</th><th>PED10 (mg)</th></tr>
<tr><td>6.0 - 7.9</td><td>1.6</td><td>3.2</td></tr>
<tr><td>8.0 - 9.9</td><td>1.8</td><td>3.6</td></tr>
<tr><td>10 - 12.4</td><td>2</td><td>4.2</td></tr>
<tr><td>12.5 - 17.4</td><td>2.4</td><td>4.8</td></tr>
<tr><td>17.5 - 23.4</td><td>2.6</td><td>5.2</td></tr>
<tr><td>23.5 - 30.0</td><td>2.8</td><td>5.8</td></tr>
</table>
</td><td>
<table>
<tr><th>Weight range (kg)</th><th>PED5 (mg)</th><th>PED10 (mg)</th></tr>
<tr><td>< 14</td><td>1.4</td><td>2.8</td></tr>
<tr><td>14 - 20</td><td>1.8</td><td>3.6</td></tr>
<tr><td>21 - 31</td><td>2.6</td><td>5.2</td></tr>
<tr><td>32 - 50</td><td>3.4</td><td>7</td></tr>
<tr><td>51 - 69</td><td>4.6</td><td>9</td></tr>
<tr><td>> 69</td><td>5</td><td>10</td></tr>
</table>
</td><td>
<table>
<tr><th>Weight range (kg)</th><th>Starting (mg)</th><th>Maximum (mg)</th></tr>
<tr><td>9 to 15</td><td>2</td><td>4</td></tr>
<tr><td>> 15 to 30</td><td>3</td><td>5</td></tr>
<tr><td>> 30 to 45</td><td>3</td><td>6</td></tr>
<tr><td>> 45</td><td>4</td><td>8</td></tr>
</table>
</td></tr>
</table>

- Consideration of the adult doses for pediatric patients with higher body weight

The Applicant's proposed highest starting and maximum doses are 4 mg and 8 mg for pediatric patients with NDO weighing > 45 kg, while 5 mg and 10 mg are approved for adult patients with OAB. Given that there are adolescents who have body mass comparable to adults and the metabolic capacity of solifenacin in these children is unlikely to be different from that in adults, the recommended doses for adult patients with OAB should be considered for pediatric population with NDO and high body weight. In addition, pediatric patients with NDO weighing > 69 kg were allowed to be administered up to 10 mg in the phase 3 study (Study 905-CL-047).

In consideration of the use of the adult doses in pediatric patients who have a relatively high body weight, the reviewer analyzed simulated AUC data at 8 mg and 10 mg using the PBPK model in virtual population > 45 kg. The percentage of patients whose AUC falls within the target exposure range at 8 mg tended to be lower in the virtual subjects weighing > 60 kg and ≤75 kg or > 75 kg compared to that in the group weighing > 45 kg and ≤ 60 kg. Whereas simulated AUC data at 10 mg in those weight groups showed some improvement in the percentage of patients being within the target exposure range compared to those at the Applicant's proposed dose of 8 mg (Table 3.3-4, refer to section 4.2.4).

Table 3.3-4 The percentages of virtual population falling within the target exposure range in simulated AUC values at 8 mg and 10 mg

		> 45 and ≤ 60 kg	>60 and ≤75 kg	>75 kg	> 60 kg	> 70 kg
Tested dose	8 mg	88.3%	85.2%	80.8%	84.2%	80.6%
	10 mg	86.2%	86.0%	85.9%	86.0%	85.6%

Comparison of simulated AUC values between 8 and 10 mg in the virtual subjects weighing > 60 kg and > 70 kg suggests that a 10 mg dose is likely to be more beneficial for pediatric patients with body weight greater than 60 kg than an 8 mg dose (refer to section 4.2.4).

This reviewer concludes that the use of the adult doses for pediatric patients with a relatively higher body weight should be considered. Given that pediatric patients weighing > 60 kg are more likely to reach the target exposure range following administration of 10 mg, the maximum dose for adults, than 8 mg, the Applicant's proposed maximum dose, the adult doses, 5 mg and 10 mg, are recommended for pediatric patients with body weight greater than 60 kg.

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

Yes. The Applicant proposed dosing recommendation and warning and precautions in pediatric patients with renal or hepatic impairment, which are the same as those in adult patients, as follows: (b) (4) (b) (4) for patients with severe renal impairment or moderate hepatic impairment and solifenacin is not recommended for use in patients with severe hepatic impairment. While no studies have been performed in pediatric patients with renal or hepatic impairment, given that the clearance of solifenacin in pediatric population aged 2 years and older including hepatic metabolism and renal excretion is unlikely to be different from that in adults, the currently proposed warning and dosing guidance for solifenacin succinate oral suspension in pediatric patients with renal or hepatic impairment are acceptable. Additional details are discussed below.

- The use of solifenacin succinate oral suspension in patients with renal impairment

No studies have been performed in pediatric patients with renal impairment. A PK study in adult patients with renal impairment demonstrated that patients with renal impairment have a higher solifenacin exposure and a prolonged elimination $t_{1/2}$ compared to healthy subjects (*Smulders et al. 2007*; *Clinical Pharmacology and Biopharmaceutics Review of NDA 21518*). There was a 2.1-fold increase in AUC and 1.6-fold increase in $t_{1/2}$ of solifenacin in patients with severe renal impairment (measured creatinine clearance < 30 mL/min).

The Applicant proposed that solifenacin succinate oral suspension (b) (4) in patients with renal impairment. They also proposed that (b) (4) (b) (4) for patients with severe renal impairment (CLcr < 30 mL/min/1.73 m^2). Given that the clearance of solifenacin including renal excretion in pediatric population is unlikely to be different from that in adults, it is anticipated that changes in the exposure to solifenacin in pediatric population with renal impairment are similar as observed in adult patients. Therefore, this reviewer concludes that the currently proposed warning and dosing guidance for solifenacin succinate oral suspension in pediatric patients with renal impairment are acceptable. The proposed dose restriction for patients with severe renal impairment is similar to that in adult.

Although the categories of renal impairment in the PK study for VESIcare® supporting this recommendation were defined using 24-hour measured creatinine clearance without body surface normalization, the proposed labeling defines severe renal impairment using a creatinine clearance estimate normalized to body surface area (CLcr < 30 mL/min/1.73 m^2). Given that glomerular filtration rate (GFR)-based renal function in children increases with age and normalizing GFR to body surface area allows reasonable comparison to standard adult values (*Schwartz et al. 2007*), the use of a creatinine clearance estimate normalized to body surface area for the dosing recommendation of pediatric patients with severe renal impairment in the label is acceptable instead of using GFR without body surface area normalization.

- The use of solifenacin succinate oral suspension in patients with hepatic impairment

No studies have been performed in pediatric patients with hepatic impairment. A PK study in adult patients with hepatic impairment demonstrated that patients with moderate hepatic impairment, defined by Child-Pugh score, increased solifenacin AUC by 60% with prolong elimination $t_{1/2}$ for solifenacin and its metabolites compared to healthy subjects (*Kuipers et al. 2006*; *Clinical Pharmacology and Biopharmaceutics Review of NDA 21518*).

The Applicant proposed that solifenacin succinate oral suspension (b) (4) in patients with hepatic impairment. It was also proposed that (b) (4) (b) (4) for patients with moderate hepatic impairment. Solifenacin is not recommended for patients with severe hepatic impairment (Child-Pugh C). Given that the hepatic metabolic capacity of solifenacin in pediatric population is unlikely to be different form that in adults, it is anticipated that changes in the exposure to solifenacin in pediatric population with hepatic impairment are as similar as observed in adult patient. Therefore, the reviewer concludes that the currently proposed warning and dosing guidance for solifenacin succinate oral suspension in pediatric patients with hepatic impairment are acceptable.

3.3.4 Are there any clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Yes. While food intake does not significantly affect the bioavailability of solifenacin following administration of solifenacin succinate oral suspension, the Applicant proposed a caution in the label that patients should avoid simultaneous intake of food and/or drinks due to a potential for a bitter taste. The Applicant noted a chemical interaction risk that oral administration together with food and/or drinks impacts on the complex formation of solifenacin with polacrilin as an adsorbent and increase unbound solifenacin in the mouth, hence causing unmasking of the bitter taste of solifenacin drug substance. When considering pediatric patients' compliance issue in relation to the bitter taste, the proposed recommendation is acceptable.

Solifenacin is extensively metabolized mainly by CYP3A4 in the liver and metabolic capacity including CYP3A4 activity in children and adolescent (2 years and older) is not different from that in adults. Therefore, the dose recommendation and information in relation to DDI interaction based on in vivo studies performed in adults are applicable to pediatric population. Additional details are discussed below.

- The impact of food on the PK of solifenacin following administration of solifenacin succinate oral suspension

While there was no dedicated food-effect study to assess the impact of food on the bioavailability of the to-be-marketed formulation (Formulation B) of solifenacin succinate oral suspension in pediatric patients, the Applicant concluded that food intake does not affect the bioavailability of the final formulation based on the following rationales:

Supporting study	Key findings	Conclusion
· Study 1 (Study 905-CL-079): The PK following administration of single dose in the fasted state · Study 2 (Study 905-CL-047): The PK following administration of multiple doses without regard to food	· Both studies were conducted using Formulation B in pediatric patients with NDO aged 5 years and older. Apparent oral clearance appeared to be comparable between the two studies.	The exposure to solifenacin at a given dose of Formulation B appears to be independent of food intake.
· Prescribing information for VESIcare® tablets. · Food-effect study for suspension Formulation A (Study 905-CL-066) in adults	· A single dose administration of the tablet with food increased C_{max} and AUC by 4% and 3%, respectively. · Mean C_{max} and AUC values were decreased by 13% and increased by 7 %, respectively, under fed condition compared to fasting.	A meal had no significant effect on the exposure to solifenacin with either of the tablet and suspension formulation A in adults.
· Comparative bioavailability study of suspension Formulation A vs B vs Vesicare® (Study 905-CL-080) in adults	· In the comparison between two out of the three formulations, respectively, the geometric mean ratios and 90% confidence intervals of C_{max} and AUC fell within the 80% to 125% boundary.	Suspension Formulation B is bioequivalent to suspension Formulation A and the tablet formulation under fasted condition.
· Comparison of dissolution Profiles of Formulation A and Formulation B	· Dissolution tests of the two suspensions were performed in 0.1 mol/L hydrochloric acid, pH 4.5 acetate buffer and pH 6.8 phosphate	No differences in the dissolution profiles between the two suspension formulations

	buffer · Similar dissolution profiles independent of the test media used	

Comparison of the PK data between the two studies (Studies 905-CL-079 – under fasting and 905-CL-047 - without regard to food) used the PK parameters of solifenacin derived using population PK analysis. The pharmacometric reviewer found the population PK analysis to be acceptable (refer to section 4.2.2). In addition, the relative bioavailability study (Study 905-CL-080) demonstrated that the final formulation (Formulation B) is bioequivalent to Formulation A as well as the marketed tablet, both of which have no significant food-effect in adults. When putting all these supporting evidence together, this reviewer concludes that food intake does not significantly affect the exposure to solifenacin following administration of solifenacin suspension formulation (Formulation B). Solifenacin succinate oral suspension can be taken without a restriction of food intake in terms of the effect of food on its PK.

Notwithstanding the lack of food effect, the Applicant proposed a caution in the label that patients should avoid simultaneous intake of food and/or drinks with solifenacin succinate oral suspension due to a potential for a bitter taste. The Applicant stated that polacrilin potassium is used as an adsorbent for solifenacin in the drug product to mask the bitter taste. The extent of adsorption and release of solifenacin from the polacrilin-solifenacin complex is dependent on environmental conditions. Decreases in pH and increases in ionic strength, as may occur in oral administration together with food and/or drinks, may lead to greater unbound solifenacin in the mouth, hence causing unmasking of the bitter taste of solifenacin drug substance. The rationale for the caution to avoid simultaneous use with food is based on a theoretical chemical interaction risk. However, given that unmasking of the bitter taste of the suspension formulation may result in noncompliance and leading to insufficient exposure to solifenacin, the currently proposed administration method is acceptable.

- Drug-drug interaction (DDI) potential of solifenacin

Solifenacin is extensively metabolized mainly by CYP3A4 in the liver. The literature indicates that despite of large interindividual differences in CYP3A4 expression and activity, maturational change in CYP3A4 activity is fully completed by the age of 2 years (*de Wildt et al. 1999*). Children and adolescent (aged 2 years and older) appeared to have slightly higher CYP3A4-mediated metabolic activity than adults (*de Wildt et al. 1999*). This information suggests that in pediatrics CYP3A4-mediated DDI may occur to similar extent as in adults. The Applicant did not conduct any drug-drug interaction study of solifenacin succinate oral suspension in pediatric population. The DDI information in relation to CYP3A4 inhibitors and inducers for pediatric patients is based on the results of drug interaction studies performed in adults. The Applicant proposed that (b) (4) for patients taking CYP3A4 inhibitors. The Applicant also proposed that inducers of CYP3A4 may decrease the concentration of solifenacin. Given that metabolism of solifenacin via CYP3A4 is the major route of elimination in children and adolescents (2 years and older) and their metabolic capacity of the liver is similar to adults, the clearance of solifenacin in pediatric population is unlikely to be different from that in adults. Thus, this reviewer concludes that the findings from the prior in vivo interaction studies are applicable to pediatric population.

In vitro studies using human liver microsomes demonstrated that solifenacin does not inhibit CYP1A1/2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 at therapeutic concentrations (Clinical Pharmacology and

Biopharmaceutics Review of NDA 21518). DDI studies of solifenacin as a perpetrator performed in adults showed that there were no significant effects on the PK of warfarin, oral contraceptives and digoxin (Clinical Pharmacology and Biopharmaceutics Review of NDA 21518).

4 APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

The plasma concentrations of solifenacin in clinical studies were analyzed using validated LC-MS/MS. The results of bioanalytical methods are summarized in table 4.1-1.

Table 4.1-1. Bioanalytical methods and their performance characteristics for the measurement of solifenacin in clinical study samples

Validation report	Affected studies	Performance characteristics of quality control samples					Long term stability
			Intra-run accuracy	Intra-run precision	Inter-run accuracy	Inter-run precision	
950-ME-110	905-CL-047 905-CL-074 905-CL-079 905-CL-080	0.2 ng/mL (LLoQ) 0.6 - 150 ng/mL (Assay range:0.2 – 200 ng/mL)	6.2% -6.5 – 11.5%	19.6% 2.9 – 5.6%	9.4% -5.2 – 10.1%	11.2% 3.1 – 7.9 %	904 days at -20°C and -80°C
905-MD-107	905-CL-075	0.5 ng/mL (LLoQ) 1.0 – 75.0 ng/mL (Assay range: 0.5 – 100 ng/mL)	-9.2 – -3.0% -6.4 – -1.3%	1.2 – 5.0% 0.8 – 2.9%	-6.4 -5.7 – 2.1%	4.3% 1.6 – 2.2%	53 weeks at -20°C or -70°C
905-ME-103	905-CL-066	0.5 ng/mL (LLoQ) 1.0 – 75.0 ng/mL (Assay range: 0.5 – 100 ng/mL)	-4.2 – -1.9% -4.3 – 3.0%	1.6 – 2.7% 1.3 – 6.3%	-3.0% -1.7 – 0.8%	2.3% 2.0 – 3.6%	At least 87 weeks at -20 °C and -70 °C

LLoQ: Lower limit of quantification

The performance of the quality control determinations for the applied LC-MS/MS methods met the Agency's acceptance criteria (≤ 20% for precision [CV%] and within ±20% for accuracy at the LLoQ and ≤15% or within ±15% at all other concentrations). Assay performance for each individual PK study was assessed using quality control samples and incurred sample repeats (ISR). Reported assay performances were within the acceptance criteria (the ISR criteria: two-thirds of the repeated sample results should be within 20% of reported analyte concentrations).

4.2 Clinical Pharmacology Assessment

4.2.1 PBPK modeling review of NDA 209529 (solifenacin succinate oral suspension) [Division of Pharmacometrics, Office of Clinical Pharmacology]

Application Number	209529
Drug Name	Solifenacin
Proposed Indication	Neurogenic detrusor overactivity (NDO) treatment for pediatric patients aged 2-years and older
Clinical Division	DCP3
PBPK Consult request	Jihong Shon, M.D., Ph.D.
Primary PBPK Reviewer	Yuching Yang, Ph.D.
Secondary PBPK Reviewer	Ping Zhao, Ph.D. and Yaning Wang Ph.D.
Applicant	Astellas
Review Question	Dosing recommendation for pediatric patients

1) Objective

This review evaluates the adequacy of the Applicant's conclusions regarding the ability of its PBPK models to support dosing recommendation for children with NDO. To support its conclusions, the Applicant provided the following PBPK modeling and simulation report and updates:

- Summary of Clinical Pharmacology Studies Draft US Prescription Information
- Prediction of Solifenacin Succinate Pediatric Equivalent Dose using PBPK Modeling
- Response to FDA request #1 for information (April 20, 2017)
- Response to FDA request #2 for information (May 2, 2017)
- Response to FDA request #3 for information (May 18, 2017)

2) Background

Solifenacin is a competitive muscarinic antagonist developed by Astellas for treating OAB. Solifenacin succinate tablet (VESIcare®) was approved for the treatment of OAB in adults in 2004 under NDA 021518. The recommended doses of solifenacin oral tablet in adults are 5 mg once daily and the maximum recommended dose is 10mg once daily.

The Applicant submitted a written request for the use of solifenacin succinate in treatment of NDO in pediatric patients on 27 Jul 2012. Additional trials in OAB and NDO pediatric patients were conducted by the Applicant to support the proposed indication. The Applicant used PBPK model to quantify solifenacin's clearance and distribution processes. The model considered maturation functions of pediatric patients. Table 4.2-1 summarizes the clinical studies used in the development and validation of the adult and pediatric PBPK models. In its proposed prescription information, the Applicant used PBPK predictions to establish the dosing recommendations for pediatric patients with NDO (Table 2.2-1).

Table 4.2-1 Summary of clinical studies to support the development of solifenacin PBPK models

Study number	Description	Subject	Model development and verification
905-CL-009[1]	Bioavailability and PK of solifenacin following single IV and oral dosing	Healthy adult	development
905-CL-080[1,2]	Single dose PK and bioavailability study	Healthy adult	development
905-CL-029[1]	Solifenacin PK at steady state after repeat dosing	Healthy adult	verification
Boehringer-Ingelheim pooled data	Demographic parameters obtained in children with NDO	NDO pediatric patients	Development of virtual NDO pediatric patients
905-CL-075[1,2]	Single dose PK in OAB pediatric patients	OAB pediatric patients age 5-17 yrs	verification
905-CL-079 [1,2]	Single dose PK in NDO pediatric patients	NDO pediatric patients age 6-17 yrs	verification
905-CL-047[2,*]	Long-term efficacy, safety and PK study	NDO pediatric patients age 5-17 yrs	verification
905-CL-074[2]	Long-term efficacy, safety and PK study	NDO pediatric patients age 6mo – 5yrs	verification

[1]. The Applicant's PBPK report , [2]. The Applicant's Clinical Pharmacology Summary

*Pivotal study for efficacy in Pediatric NDO

This review evaluates the adequacy of the Applicant's conclusions regarding the ability of its solifenacin PBPK models to 1) describe the PK profiles for solifenacin in pediatric patients; and 2) establish the dosing recommendations for pediatric patients with NDO in the label.

3) PBPK modeling

3-1) Solifenacin PBPK models in adult

Solifenacin PBPK models were developed using the PK-Sim® v5.1 (b) (4) (b) (4) to describe the clinical plasma PK profiles of solifenacin in adult and pediatric populations (*Edginton 2011; Edginton et al 2006; Willmann et al. 2007*). Figure 4.2-1 shows a workflow of the development, verification and application of PBPK model for solifenacin.

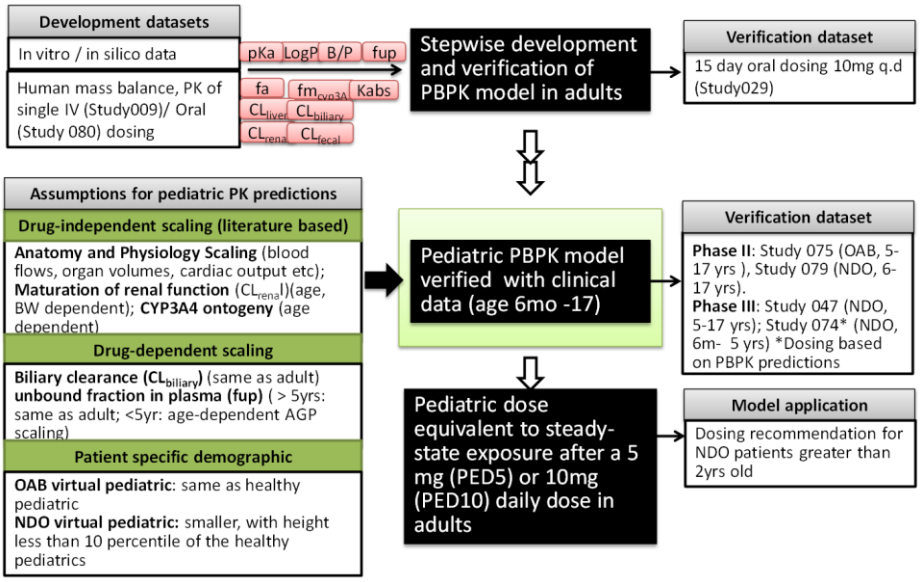


Figure 4.2- 1 Workflow of development, verification and application of solifenacin PBPK models

In vitro data, human PK data and mass balance study were used to construct a base solifenacin model in healthy adult subjects. The disposition of solifenacin based on the mass balance study is summarized in Table 4.2-2.

Table 4.2-2 Proposed disposition of solifenacin

Pathway contribution		Reference
% Renal clearance	9%	Doroshyenko and Fuhr, 2009
% metabolized by liver	59%	Estimated based on adult mass balance data
% metabolized by intestinal CYP3A	<1%	Calculated
% excreted in feces	31%	Calculated

Resource: the Applicant's PBPK report (905-PK-006)

A total clearance was optimized by simultaneously fitting the observed plasma PK data following single intravenous (IV) or oral dose solifenacin (PBPK supplemental Table S1). The final optimized value of total clearance was estimated to be 10.3 L/h, comparable to 9.39 L/h estimated using non-compartmental method in study 905-CL-009. To partition clearance in the final PBPK model, total renal clearance was optimized so that approximately 10% of unchanged solifenacin would excrete in urine, as observed in clinical trials (Report 905-PK-006). While renal clearance due to glomerular filtration can be calculated

(GFR* fup, fraction unbound), tubular secretion was adjusted so the total renal clearance was 8-10% of total clearance.

The Applicant assumed that 59% of the administered drug was metabolized by subtracting the percent excreted unchanged in urine (10%) from the total radioactivity excreted in urine (69%) (*Doroshyenko et al. 2009*). The Applicant also assumed that 100% of solifenacin in the liver was metabolized by CYP3A based on 1) human liver microsomes studies (*Doroshyenko et al. 2009*) and 2) 50% reduction in total clearance when solifenacin was co-administered with ketoconazole (*Swart et al. 2006*). Based on this data, the Applicant assumed that the total CYP3A clearance was approximately 59% of total clearance. Contributions of hepatic and intestinal clearance relative to the total CYP3A clearance were calculated using the relative CYP3A content in the liver (98.73%), duodenum (0.17%), jejunum (0.7%) and ileum (0.4%), as a build-in database in PK-Sim® (*Paine et al. 1997*).

The Applicant reported a temporary increase in plasma concentrations between 1-8 hours following intravenous dosing (Study 905-CL-009). Although not investigated in the clinic, enterohepatic recycling (EHC) was observed in preclinical species (Report 905-PK-006). Therefore, EHC pathway was included in the final solifenacin PBPK model. Drug that is not absorbed or reabsorbed enters the feces. This process resulted in 31% being excreted in feces since 69% of the administered drug excreted in urine. Model parameters and their sources for solifenacin PBPK model are summarized in PBPK supplemental Table S1. Final clearance rates used in the adult PBPK were then used for scaling to children.

Adult virtual population

A virtual population of 500 consisting of 50% males and 50% females, between the ages of 18 and 55, and BMI less than 30 kg/m^2 were generated in PK-Sim® for white American based on the National Health and Nutrition Examination Survey (NHANES) database (PK-Sim®, build-in database; US National center for Health Statistics). In addition to the anatomical and physiological variabilities already incorporated into PK-Sim®, the Applicant also incorporated additional variabilities for selected model parameters based on published literature as listed in PBPK supplemental Table S2.

Adult model verification

The final solifenacin model in adult was independently verified by comparing the simulated plasma PK results for solifenacin with those observed in the clinical study (Study 905-CL-029) following multiple oral administrations.

3-2) Solifenacin PBPK models in pediatric patients

Solifenacin PBPK model for children was scaled from adult model by assigned age-dependent anatomical and physiological parameters using the PK-Sim® build-in database (Report 905-PK-006). Excepting the clearance of the EHC pathway, default algorithms in PK-Sim® were used to scale adult's clearance values to children by accounting for age-dependent difference in glomerular filtration rate, tubular secretion and CYP3A4. Clearance of EHC pathway (intrinsic clearance normalized to the liver volume) in the pediatric group is assumed to be same as those in the adult group due to the lack of information to support the clearance scaling for transporter-mediated pathway. No parameters were optimized to fit the solifenacin PK observed in the pediatric patients. PBPK supplemental Table S3 lists the scaled model parameters in children.

Pediatric virtual population

Pediatric patients with OAB aged 5 to 17 year-old

For each age between 5 and 17 years with 1 year increments, 200 virtual children per age group were created based on the NHANES white American database (Report 905-PK-006). Similar to virtual population in adult, the Applicant also incorporated additional variabilities for the selected model parameters based on published literature as listed in PBPK supplemental Table S4.

Pediatric patients with NDO aged 6 to 17 year-old

A virtual population consisting of 200 individuals per age group (1 year increment) from 6 to 17 years was created based on the NHANES white American database (Report 905-PK-006). Within the populations for each year, there were two separate groups of the virtual individuals. Group 1 (N=100) was individuals sampled from those with lowest 10% of height in the age group in the NHANES white American database. Group 2 (N=100) was generated by matching weight and height of a virtual population to the demographics of pediatric patients with NDO reported in the pooled data of children with NDO (Boehringer-Ingelheim pooled data) and Study 905-CL-079. Additional variabilities for selected model parameters were presented in PBPK supplemental Table S4.

Pediatric patients NDO aged 6 months to 5 year-old

The procedure for building the virtual pediatric populations for children aged 2 to 5 years was the same as those described for pediatric patients with NDO 6 to17 years (Report 905-PK-006. For children aged 6 months to 2 year-old, children with the lowest 10% of heights within the age group were selected. Additional variabilities for selected model parameters were presented in PBPK supplemental Table S4.

Pediatric model verification

The final solifenacin model in children was verified by comparing the simulated plasma PK results for solifenacin with those observed in Studies 905-CL-075 and 905-CL-079 for children with OAB and NDO, respectively. Weight-based PED doses were used in Studies 905-CL-075 and 905-CL-079 for children between 5 and 17 years.

3-3) PBPK model application

The Applicant used the PBPK models to prospectively predict the PED for pediatric patients with NDO aged 6 months to 5 years old and compared simulations with observations. The Applicant also used PBPK model to derive PED doses for different weight groups. The PBPK-based PED dosing table was in Study 905-CL-074 for young children aged 6 months and up after the weight-based PED doses failed to reach the target plasma concentration of solifenacin in Study 905-CL-074. PBPK supplemental Figure S1 compared the PED doses derived using PBPK modeling and weight-based approach.

4) Results

4-1) Does solifenacin PBPK models adequately describe PK profiles of solifenacin in pediatric population age 5-17 years old?

Yes. The final solifenacin PBPK model for children aged 5 to17 years old was verified with the observed solifenacin PK following single oral administrations of solifenacin succinate oral suspension in pediatric

populations with OAB or NDO. Results from these studies were not used to develop and modify solifenacin model.

The solifenacin PBPK model was first developed in adults based on in-vitro data and in-vivo PK datasets. The simulated plasma concentration-time profiles were verified with observed data following repeat oral doses of 10 mg solifenacin once per day for 15 days (Study 905-CL-029). Multiple-dose PK profiles in adults were also described by the model as shown in Table 4.2-3.

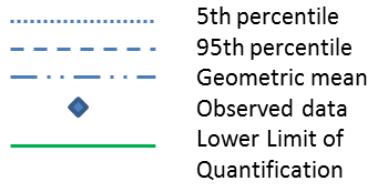
Table 4.2-3. Observed and simulated solifenacin PK in adults after repeat solifenacin dosing

	AUC_{24} at day 14 (ng·h/mL)		C_{max} at day 14 (ng/mL)	
	Observed (N = 22)	Simulated (N=500)	Observed (N = 22)	Simulated (N=500)
Geometric mean (%CV)	1071(34)	1039(70)	54 (30)	57 (66)

Resource: the Applicant's response to the information request

Using the literature-based dataset and PK-sim® default algorithms, PBPK parameters in the adult model were scaled to pediatrics by accounting for age related changes in clearance and distribution processes for children aged 5 to18 years old. Pediatric solifenacin PBPK model was verified by comparing the simulated solifenacin PK and those observed for pediatric patients with OAB aged 5 to 17 years (Study 905-CL-075, Figure 4.2-2) and pediatric NDO patients aged 6 to 17 years (Study 905-CL-079, Figure 4.2-3). Simulated plasma concentration-time profiles were in reasonable agreement with the observed data.

Compare the simulated dose-normalized concentrations (µg/L/mg_{active}, black lines) of solifenacin following a single oral dose of solifenacin in pediatric population with OAB with data observed in Study 905-CL-075 (diamonds)



12 to 17 years old

5 to 11 years old

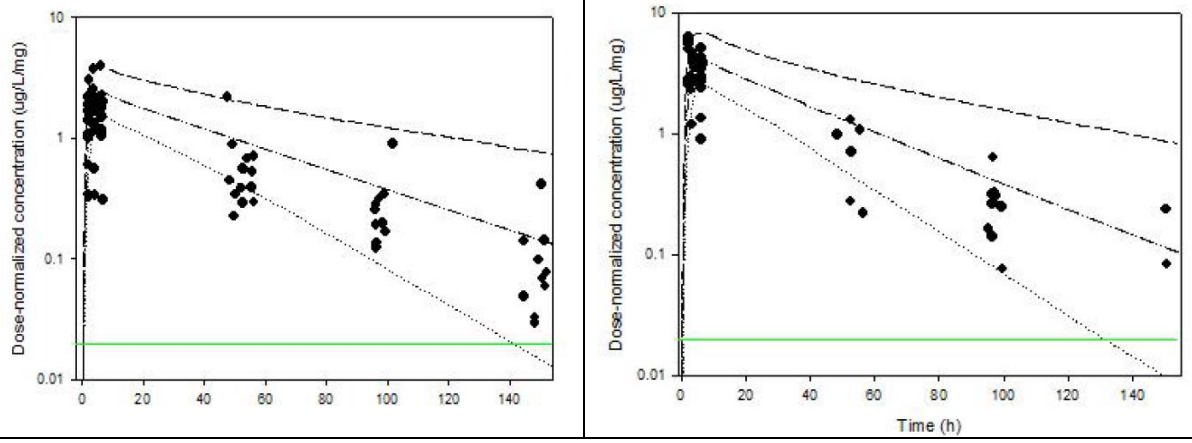


Figure 4.2-2. Observed and simulated plasma concentration-time profiles of solifenacin for pediatric patients with OAB (Resources: Figure 11 and 12 in the Applicant's PBPK report [905-PK-006])

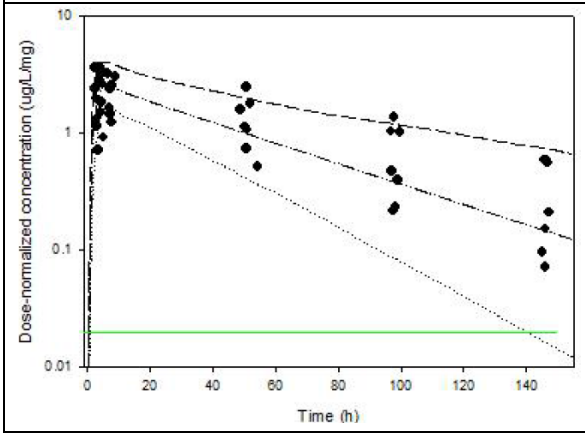
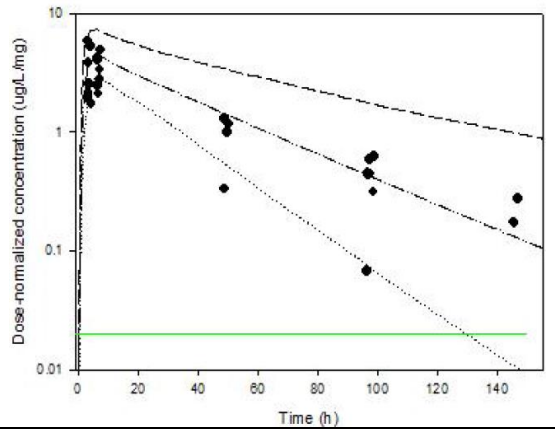
Compare the simulated dose-normalized concentrations (µg/L/mg_{active}, black lines) of solifenacin following a single oral dose of solifenacin in pediatric population with NDO with data observed in Study 905-CL-079(diamonds)	5th percentile 95th percentile Geometric mean Observed data Lower Limit of Quantification
12 to 17 years old	5 to 11 years old
	

Figure 4.2-3. Observed and simulated plasma concentration-time profiles of solifenacin for pediatric patients with NDO (Resources: Figures 16 and 17 of Applicant's PBPK report [905-PK-006])

4-2) Can solifenacin PBPK models prospectively predict PK profiles of solifenacin in pediatric population age 2 years and older?

Yes. The predictability of solifenacin PBPK model for children was verified with clinical observations of solifenacin PK profiles collected in pediatric population aged 1.6 to 5 years old.

Once verified with PK profiles observed in patients with NDO aged 6 to17 years, the Applicant used solifenacin PBPK models to simulate the dose-AUC relationship in children aged 6-month to 5 years old. The Applicant prospectively predicted dose in pediatrics that can match solifenacin AUC observed in adults following 10 mg daily dosing in Study 905-CL-080 (PED10). PED10 then was adjusted linearly to determine PED2.5, PED5, and PED7.5. PBPK supplemental Figure S2 compared the target AUC and simulated AUC of solifenacin based on predicted PED10 for each weight group.

A PBPK-based dosing (Table 4.2-5) was used in Study 905-CL-074 to evaluate the solifenacin PK at steady state, as well as the efficacy and safety of solifenacin treatment in NDO pediatric population under 5 years. The reviewer noted that the youngest children enrolled in the beginning of the Study 905-CL-074 are 1.6 year-old. PBPK supplemental Table S4 summarizes the demographics and dosages administered to patients in Study 905-CL-074.

Table 4.2-5. PBPK-derived dosing table by weight class for PED2.5-PED10

Body weight (kg)	PED2.5 (mg)	PED5 (mg)	PED7.5 (mg)	PED10 (mg)
6 to <8	0.8	1.6	2.4	3.2
8 to <10	0.9	1.8	2.6	3.6
10 to <12.5	1	2	3	4.2
12.5 to <17.5	1.2	2.4	3.6	4.8
17.5 to <23.5	1.3	2.6	3.8	5.2
23.5 to <30	1.4	2.8	4.4	5.8

Data source: Tables 9-12, Report 905-PK-006
Target AUC for PED5 is 889 ng*h/mL based on Study 905-CL-080

In the response to the reviewer's information request (#2), the Applicant compared the observed solifenacin plasma concentration-time profiles in Study 905-CL-074 with PBPK simulations. Figure 4.2-4 and PBPK supplemental Figure S3 present the overlay of the observed and simulated results stratified by age (median age 3.5 years), and body weight (median weight 13.5 kg) respectively. Eighty three percent (83%) of all the observed data (from all patients in Study 905-CL-074) were within the 90% prediction interval. The model appears to over-predict plasma concentrations in comparison with observed data (Figure 4.2-4). The Applicant suggested that the over-prediction could have been a result of outlying variables, such as subjects not taking full doses at the recorded time or following the required 24-hour dosing frequency (the response to the reviewer's information request #2).

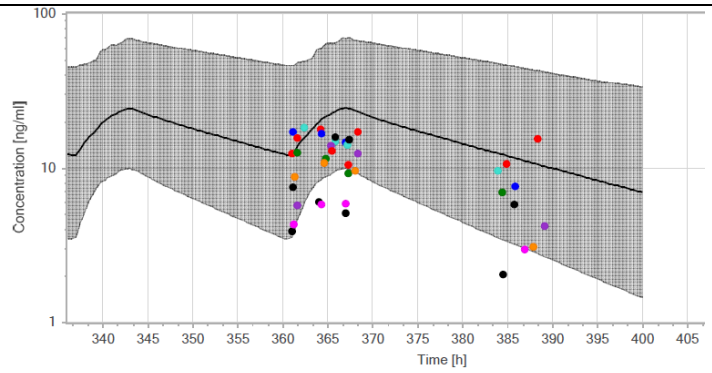
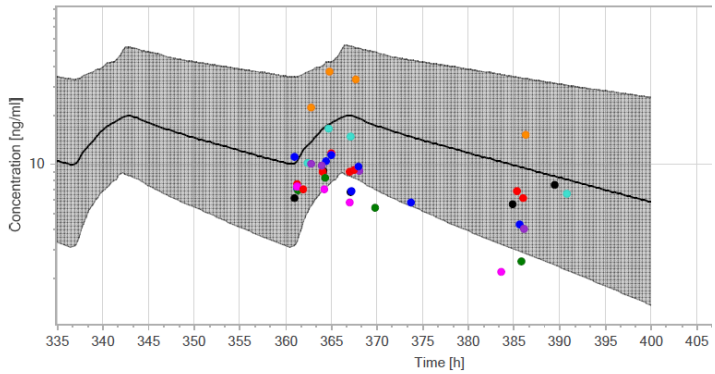
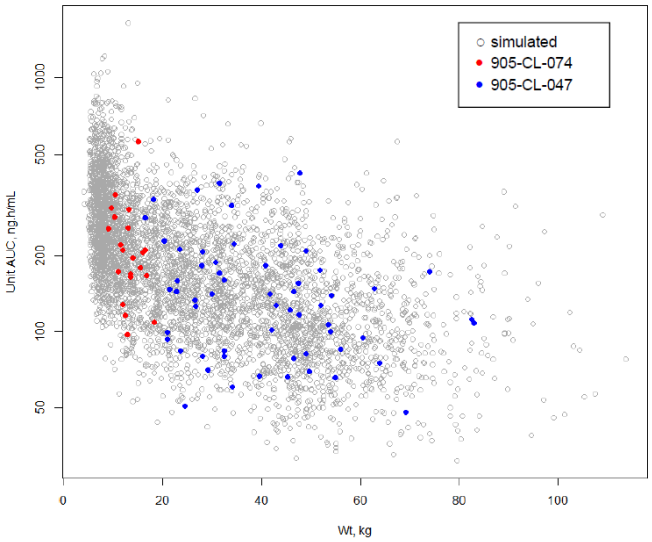
Comparison of the simulated and observed plasma concentration data of solifenacin collected in patients with NDO (n=11) with age ranges 3.5 to 5.22 years-old in Study 905-CL-074 Plasma concentration was normalized to 1 mg active solifenacin (Resource: Figure 5 in the Applicant's response to the Information request [#2])	
Comparison of the simulated and observed plasma concentration data of solifenacin collected in patients with NDO (n=10) with age ranges 1.6 to 3.5 years-old in Study 905-CL-074 Plasma concentration was normalized to 1 mg active solifenacin (Resource: Figure 6 in the Applicant's response to the information request [#2])	

Figure 4.2.4 Overlay of simulated plasma concentration-time profiles of solifenacin with observed plasma concentraions of solifenacin for NDO pediatric patients straified by median age of 3.5 years

The Applicant also compared PBPK model predictions with AUC calculated from post-hoc prediction using population PK analysis (Figure 4.2-5). The Applicant noted that the agreement between PBPK predictions and post-hoc population PK analysis confirmed the predictability of solifenacin PBPK model to predict solifenacin exposure in pediatric patients with NDO.



● Calculated solifenacin AUC using population PK analysis for Studies 905-CL-074 in pediatric patients with NDO aged 6-month to 5 years old

● Calculated solifenacin AUC using population PK analysis for Studies 905-CL-047 in pediatric patients with NDO aged 5 to 18 years old

○ PBPK-simulated solifenacin AUC in NDO pediatric patients

Figure 4.2-5. Comparison of PBPK-simulated solifenacin AUC and calculated solifenacin AUC using population PK analysis in Studies 905-CL-074 and 905-CL-47 for NDO pediatric patients (Resource: Figure 1, Summary of Clinical Pharmacology that the Applicant submitted)

4-3) Is the dose recommendation in proposed prescription information for age 2 years and older acceptable?

Yes. The Applicant's approach to derive the final recommendation dosing table in the proposed prescription information (Table 2.2-1) is acceptable.

The Applicant used PBPK model to simulate solifenacin AUC (normalized to 1 mg solifenacin base) for virtual pediatric patient aged 0.5-17.99 year-old. By stratifying the results along small weight increments, results with similar normalized AUC per weight were grouped together to simplify the dosing regimen. Four weight groups were selected. The lowest weight identified for virtual patients of 2 years-old was approximately 9 kg. Therefore, 9 kg was selected as the lowest weight for the dosing table. The predicted starting dose (PED5) and maximum dose (PED10) was then rounded to the nearest 1 mg as shown in Table 2.2-1. Figure 4.2-6 presented the normalized simulated AUC at the maximum dose (PED10) by weight group.

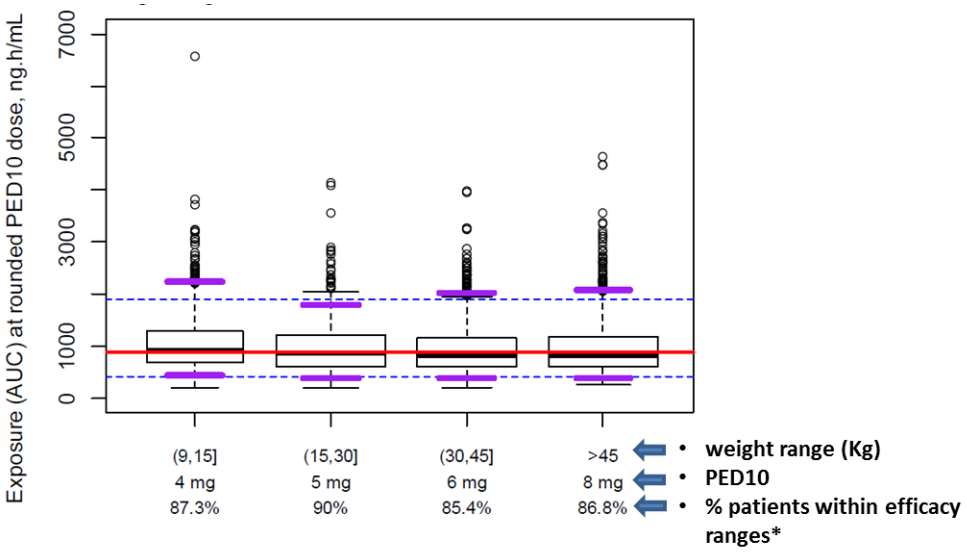


Figure 4.2-6. Distribution of predicted solifenacin AUC with the proposed PED10 for NDO pediatric patients by weight group (Red line represents the median efficacy target [889 ng*h/mL for an adult taking 10 mg dose] Blue dash lines represent the 5th and 95th percentiles of the efficacy target *% patient falling within 90% prediction interval of the efficacy target for each weight range Extracted from Figure 2, Summary of Clinical Pharmacology that the Applicant submitted.)

5) Conclusion

The submitted solifenacin PBPK models appear to adequately describe solifenacin exposure observed in pediatric population aged 2 years to 18 years old. PBPK-based dosing regimens were confirmed in the phase s study (Study 905-CL-074) to reach the target pediatric equivalent exposure in patients aged 1.6 to 5 years old.

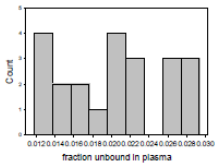
6) Supplemental material for PBPK modeling review

Table S1. Physiochemical and clearance parameters used in PBPK model

Molecular Weight (MW)	362.5 g/mol	Astellas in house
Fraction unbound in plasma (fup)	0.02	Study 905-CL-029
Octanol: water partition coefficient (LogP)	3.96	DrugBank
pKa – acid dissociation constant	8.5 (base)	Doroshyenko and Fuhr, 2009
Water solubility (solifenacin succinate)	610 mg/mL	Astellas in house
Total Clearance	10.3 L/h	Optimized
Biliary clearance (pathway to EHC)	4.4 L/h	Optimized
CYP3A metabolism	4.9 L/h	Optimized
Glomerular filtration (GFR,115 ml/min*fup)	0.13 L/h	Calculated
Tubular secretion	0.9 L/h	Optimized

Ref: extracted from of Report 905-PK-006 Table 1

Table S2. Additional parameter variability for adult populations

Parameter	Mean	Distribution and variation	Notes
Dissolution half-time	180 min	CV=25% under normal distribution	
Small intestinal surface area (per section)	Varied dependent on section	9-fold variation in a uniform distribution (mean*3 - mean/3). Each individual had the same surface enhancement factor applied to all sections (i.e. a multiplication factor of 1.2 was applied to the surface area in every section for one individual).	As taken from Willmann et al [2009]
Time of meal	[a] 3 hours	2-6 hours using a uniform distribution	EHC lag time was set to 0.5h post-meal
Biliary clearance	[b] 1.98 min^{-1}	Geometric SD = 1.25 under a lognormal distribution	
CYP3A clearance	[b] 2.16 min^{-1}	CV=95% under normal distribution	As taken from Barter et al [2010]
GFR	26.6 $ml/min/100g_{tissue}$	CV% = 25% under a normal distribution	As determined from Van Biesen et al [2007]
Tubular secretion	1.37 min^{-1} [a]	Geometric SD = 1.25 under a lognormal distribution	
Unbound fraction in plasma	0.02	Uniform distribution with a range of 0.012 to 0.029	In a study (905-CL-029) of adults age 18-55, fraction unbound had a mean of 0.02 and followed a uniform distribution with a range of 0.012 to 0.029 

Note: extracted from PBPK report (Report 905-PK-006) Table 4

[a] 3 hours represent the time at which gallbladder emptying occurs. A 0.5 h lag time post-meal was implemented to allow gallbladder emptying to occur at 3.5 h post-administration. This corresponded to the secondary peak in the i.v. curve.

[b] Specific clearance is the intrinsic clearance (as derived from plasma clearance based on the well-stirred model) divided by the organ volume.

Table S3. Physiochemical and clearance parameters scaled in children

Anatomy and Physiology	Clearance	
	Liver	Other
Height	CYP1A2	
Weight	CYP2C18	CYP3A4 (intestine)
Blood flows	CYP2C19	
Organ volumes	CYP2C8	GFR (kidney)
Hematocrit	CYP2C9	
Cardiac output	CYP2D6	
	CYP2E1	
	CYP3A4	
Binding protein conc. (albumin, AGP)	CYP3A5	
	UGT1A1	
	UGT1A4	
	UGT1A6	
	UGT1A9	
	UGT2B7	

Summarized from Appendix of Report 905-PK-006

Table S4. Additional parameter and variability for OAB and NDO pediatric populations

Parameter	Mean	Distribution and variation	Notes
Dissolution half-time	180 min	CV=25% under normal distribution	
Small intestinal surface area (per section)	Varied dependent on section	9-fold variation in a uniform distribution (mean*3 - mean/3). Each individual had the same surface enhancement factor applied to all sections (i.e. a multiplication factor of 1.2 was applied to the surface area in every section for one individual).	As taken from Willmann et al [2009]
Time of meal	3 hours	2-6 hours using a uniform distribution	EHC lag time was set to 0.5h post-meal
Biliary clearance	[a] 1.98 min^{-1}	SD = 1.25 under a lognormal distribution	
CYP3A clearance	[a] CYP3A4 ontogeny factor * 2.16 min^{-1}	CV=95% under normal distribution	CYP3A4 ontogeny factor as default in PK-Sim®. Variability taken from Barter et al [2010]
GFR	GFR ontogeny factor * 26.6 $ml/min/100g_{tissue}$	CV% = 25% under a normal distribution	Ontogeny factor from Rhodin et al. Variability as determined from Van Biesen et al [2007]
Tubular secretion	Tubular secretion ontogeny factor * 1.37 min^{-1} [a]	SD = 1.25 under a lognormal distribution	Tubular secretion ontogeny factor from Hayton [2000]
Unbound fraction in plasma	Fraction unbound ontogeny factor * 0.02	CV% = 20% under a normal distribution (see 'Scaling of unbound fraction')	Fraction unbound ontogeny factor for AGP from McNamara and Alcorn [2002]

lmann S et al., J Pharm Pharmacol 2009;61:891-99; Barter ZE et al., Rostami-Hodjegan A. Biopharm Drug Dispos 2010;31:516-32; Rhodin MM et al., . Pediatr Nephrol 2009;24:67-76; Van BW et al., Eur Heart J 2007;28:478-83; Hayton WL et al., AAPS PharmSci 2000;2:E3; McNamara et al., AAPS PharmSci 2002;4:E4

Note: extracted from Report 905-PK-006 Table 6

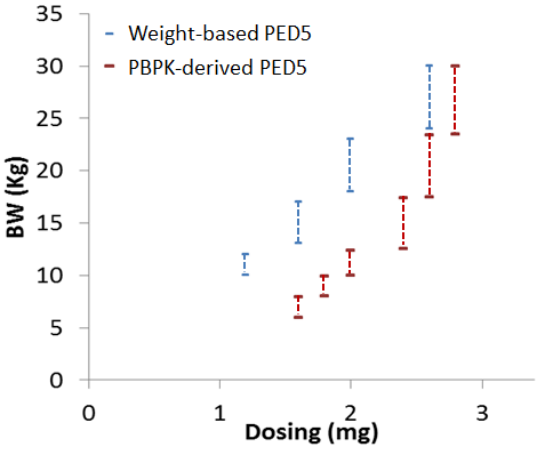
Table S5. Demographics and dosages administered in the patient in Study 905-CL-074

	6 months to <2 years	2 to < 5 years	All
Number of subjects	3	18	21
PED at last PK sample (n on PED5-7.5-10) *	0-1-2	1-5-12	1-6-14
Dose (mg)	4.2 (3.6 - 4.2)	2.6 (1.6 - 4.2)	3.2 (1.6 - 4.2)
Age (years)	1.65 (1.60 - 1.71)	3.65 (2.61 - 5.22)	3.53 (1.60 - 5.22)
Weight (kg)	10.9 (10.3 - 13.0)	13.4 (10.1 - 20.7)	13.3 (10.1 - 20.7)
Height (cm)	83.7 (73.0 - 91)	96.1 (77.5 - 106)	94.8 (73.0 - 106)
BMI (kg/m^2)	15.7 (14.7 - 20.5)	15.2 (13.0 - 21.0)	15.3 (13.0 - 21.0)
FFM (kg)	7.02 (6.51 - 13.5)	12.10 (7.37 - 15.1)	11.80 (6.51 - 15.1)
LBM (kg)	8.78 (8.36 - 11.7)	12.30 (8.29 - 17.2)	12.20 (8.29 - 17.2)
AGP (mg/dL)	66.0 (51 - 69)	73.5 (47 - 128)	70.0 (47 - 128)
Sex (M-F)	1-2	8-10	9-12

AGP: alpha-1 acid glycoprotein; BMI: body mass index; FFM: fat free mass; LBM: lean body mass

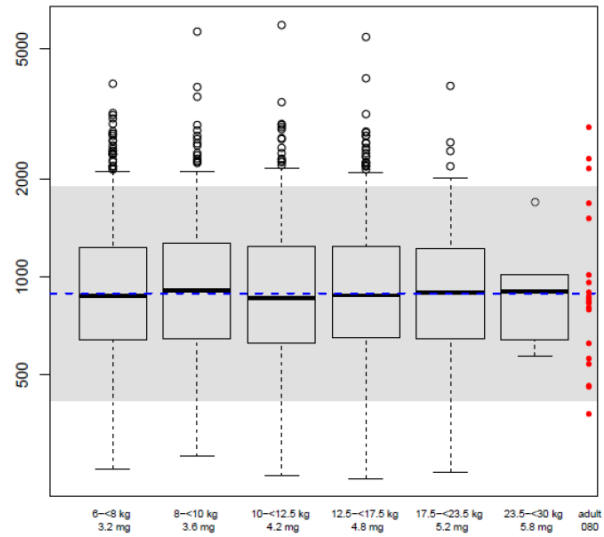
* No patients were at PED2.5 at the time of PK sampling

Note: extracted from Study 905-CL-074 Table 2



Data source: the values of weight-based PED5 were based on Table 3 of applicant's Summary of Clinical Pharmacology [1]. PBPK-derived PED5 is based on Table 11 of applicant's PBPK report [3]

Figure S1. Comparison of the weight-based and PBPK-based PED dosing for children aged 6month to 5years old



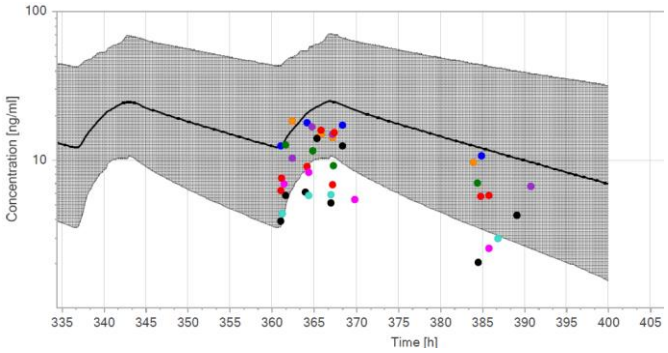
Extracted from of Report 905-PK-006 Figure 18. Target AUC for PED5 is 889 ng*h/mL based on Study 905-CL-080

Figure S2. Comparison of the target AUCinf and simulated AUCinf values by weight class for PED10

Comparison of the simulated and observed plasmas concentration data of solifenacin collected in NDO patients (n=10) below the median body weight of 13.5 kg in Study 905-CL-074

Plasma concentration was normalized to 1 mg active solifenacin

Figure extracted from Applicant's IR



Comparison of the simulated and observed plasmas concentration data of solifenacin collected in NDO patients (n=11) above the median body weight of 13.5 kg in Study 905-CL-074

Plasma concentration was normalized to 1 mg active solifenacin

Figure extracted from Applicant's IR

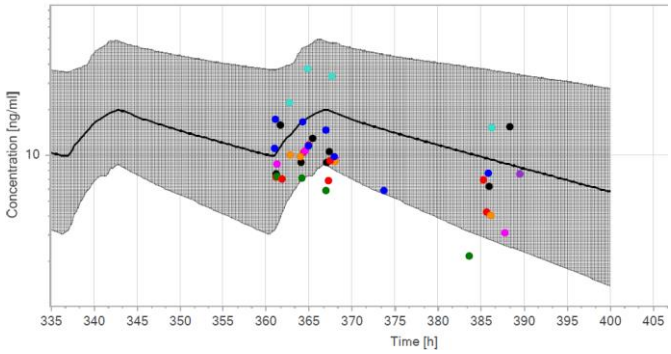


Figure S3. Overlay of simulated plasma concentration-time profiles of solifenacin with observed plasma concentrations of solifenacin for NDO pediatric patients stratified by median body weight of 13.5 kg

Note: Since the administered doses and timing of dosing were different among the subjects in Study 074, applicant normalized the plasma-time profiles to overlay the data for all patients on a single simulation plot. 1) Simulated and observed solifenacin concentrations were normalized to 1 mg active solifenacin. 2) Within each subject, the concentration were ordered by the time post-dose and assumed to be sampled from 1 visit (day 15). Applicant's approach for data normalization appears reasonable since the all plasma data was collected at steady-state.

4.2.2 Population pharmacokinetic assessment of solifenacin following administration of solifenacin succinate oral suspension in pediatrics

The Applicant performed a population PK analysis of solifenacin plasma concentrations from the clinical studies to describe the PK of solifenacin following administration of single and multiple doses in pediatric patients with NDO aged 6 months to < 18 years. The dosing tables for clinical studies performed in pediatric patients with NDO were constructed using a population PK model initially developed using data from pediatric patients with OAB in Study 905-CL-075. The subsequent studies in NDO patients were the two phase 3 studies (Studies 905-CL-047 and 905-CL-074). Since the dosing tables were constructed using PK model developed in pediatric patients with OAB, demonstration of similarity in PK between patient populations with OAB and NDO was crucial. The phase 3 studies in pediatric patients with NDO were conducted after PK similarity between the two patient groups was demonstrated through fitting the model developed in OAB patients (Study 905-CL-075) to data from NDO patients (Study 905-CL-079) following single dose administration in both studies. The AUCs observed from Study 905-CL-080 conducted in adult healthy volunteers was used as target exposure range.

1) Pediatric equivalent dose derivation

The Applicant first performed a population PK analysis for solifenacin using the data collected from Study 905-CL-075 to determine the doses of solifenacin to be administered in the subsequent efficacy and safety study conducted in pediatric patients with NDO aged 5 years and older.

· Population PK modeling

The population PK analysis conducted by the Applicant was based on data collected in pediatric patients with OAB from 5 to less than 18 years of age (Study 905-CL-075) and in healthy adults (Study 905-CL-066 and 905-CL-080) following administration of age-appropriate (weight-based) oral suspensions (formulation A and B), and the commercially available tablet formulation. The population PK analysis was performed in NONMEM using an Intel Fortran compiler, version 10.0.026 (b) (4) (b) (4). All models were estimated using first-order conditional estimation with interaction. Covariates

were included at a significance level of 5% ($p < 0.05$). To demonstrate PK similarity between OAB and NDO patients, PK model developed in Study 905-CL-075 was fitted to the data in Study 905-CL-079 without estimation as shown in Figure 4.2-7.

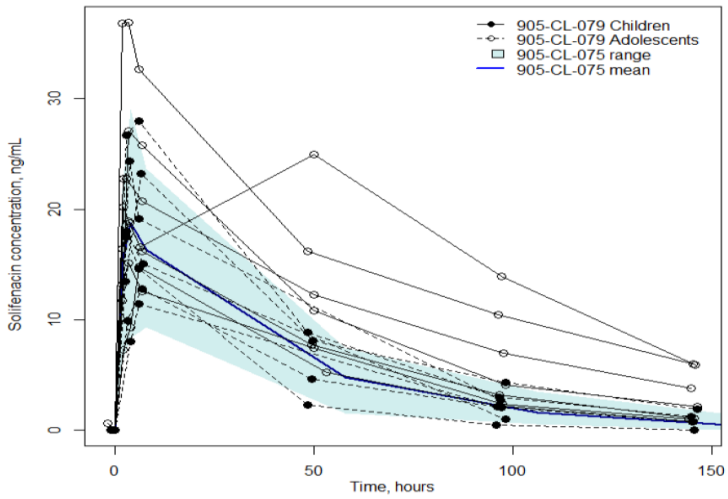


Figure 4.2-7. Concentration-time profiles for pediatric patients with NDO in Study 905-CL-079, overlaying data from Study 905-CL-075.

· Estimated PED in children

The Applicant developed a population PK model for selecting PED in the subsequent safety and efficacy studies (905-CL-047, 905-CL-074). The age-dependent changes on CL/F were calculated using allometric scaling with fat free mass (FFM) as the size parameter, centered on 70 kg. The exponent was 0.807, estimated from modeling the concentration data from pediatric patients in Study 905-CL-075. The intercept was the adult clearance value (8.48 L/h), estimated from Study 905-CL-080 performed in adult healthy volunteers. Weight ranges were selected such that the ratio between the highest and lowest AUC within each range was approximately the same. The resultant doing tables are shown in Table 4.2-6 for Study 905-CL-047 and Table 4.2-7 for Study 905-CL-74.

Table 4.2-6. Solifenacin pediatric equivalent doses per weight range administered once daily for Study 905-CL-047.

Weight (kg) ‡	PED2.5 (mg)	PED5† (mg)	PED7.5 (mg)	PED10 (mg)
< 14	0.6	1.4	2.2	2.8
14 - 20	1.0	1.8	2.8	3.6
21 - 31	1.2	2.6	3.8	5.2
32 - 50	1.8	3.4	5.2	7.0
51 - 69	2.2	4.6	6.8	9.0
> 69	2.4	5.0	7.4	10.0

Table 4.2-7. Predicted pediatric equivalent doses (PED2.5, PED5, PED7.5, and PED10) using allometric scaling and corresponding dose to be administered per weight range for Study 905-CL-074.

Weight range (kg)	PED2.5† (mg)	PED5†‡ (mg)	PED7.5† (mg)	PED10† (mg)
10 - 12	0.6	1.2	1.8	2.6
13 - 17	0.8	1.6	2.4	3.2
18 - 23	1.0	2.0	3.0	4.2
24 - 30	1.2	2.6	3.8	5.0

❖ ***Reviewer's comments***

The reviewer concludes that the PK modelling approach undertaken by the applicant in building the population PK model and derivation of doses for pediatric patients with NDO are acceptable. There was reasonable overlap in AUCs between OAB and NDO pediatric patients to conclude that the use of the structural model employed in OAB Study 905-CL-075 is appropriate for use in evaluating the NDO subjects' data in Study 905-CL-079, and derive dosing tables for children with NDO.

2) Study 905-CL-047

The objective of the modeling exercise was to develop a population PK model to establish the multiple-dose (steady-state) PK for solifenacin oral suspension in pediatric patients aged 5 years and older with NDO using doses shown in Table 4.2-6.

· Methods

Plasma concentrations were collected from 59 (30 children and 29 adolescents) of the 76 enrolled patients and used for population PK modeling. Four samples at steady-state were collected within 3 hours prior to dosing, and 1 to 3 hours, 4 to 6 hours, and 7 to 10 hours post dose. Samples could be taken at 1 visit or across 2 visits (visits 7, 8, and 9/weeks 12, 24, and 36). Table 4.2-8 summarizes the data used from this study. The Applicant began the modeling with a modification of the final model from Study 905-CL-079. The algorithm for modeling was first-order conditional estimation (FOCE) with interaction. A 1-compartment with a lag time was also applied to NDO pediatric patients. The Applicant included covariates such as FFM and AGP which were shown in previous models to be significant and physiologically relevant to the PK of solifenacin. Furthermore, a formal stepwise covariate search was undertaken. Each covariate was tested on CL/F and V/F at each step, and appropriate graphical and statistical tests were carried out to ensure that the addition of the covariates were appropriate. No backward deletion was performed. Each covariate was centered on the median value (30 kg for FFM or 72 mg/dL for AGP), and entered onto CL/F or V/F as a power model.

Table 4.2-8. Summary of data used from Study 905-CL-047

Study Title	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)
Study Objectives	To evaluate the long-term efficacy and safety, and the pharmacokinetics (PK) of solifenacin succinate suspension after multiple dose administration.
Population	Pediatric patients with NDO
Age groups	Children: 5 to < 12 years Adolescents: 12 to < 18 years
Duration of evaluation	52 weeks
Treatment	Starting dose: PED5§ One to four titration steps (Visits 4, 5, 6 and 7/Weeks 3, 6, 9, and 12) were allowed to reach each patient's optimal individual dose (PED2.5, PED5, PED7.5, or PED10). The patients then remained on their optimal dose until Week 52/Visit 10
Formulation	Solifenacin succinate aqueous oral suspension 1 mg/ml (formulation B)
Number of patients in the PK analysis set (PKAS):	Children: 30 (29 with 4 samples, 1 with 1 sample) Adolescents: 29 (24 with 4 samples, 3 with 3 samples, 2 with 1 sample) †
Total PK records:	Children: 117 PK samples Adolescents: 107 PK samples (1 excluded †)
PK Sampling	Four samples at steady-state were collected within 3 h prior to dosing, and 1-3 h, 4-6 h, and 7-10 h post dose. Samples could be taken at one visit or across two visits (Visits 7†, 8, and 9/Weeks 12†, 24, and 36). † If final dose-titration occurs prior to Visit 7

§PED5: pediatric equivalent dose targeting steady-state plasma concentrations equivalent to those observed following once daily administration of 5 mg to adults.

· Results

The final model was a 1-compartment model with first-order oral absorption and a lag time, IIV on CL/F, V/F, and KA with a full OMEGA block, and additive and proportional residual error. FFM was added to the clearance and volume terms as the size parameter for allometric scaling with estimated exponents. AGP was added to CL/F and Vz/F, also with a power model with an estimated exponent. The parameter estimates of the final model are shown in Table 4.2-9.

Table 4.2-9. Parameter estimates of the final model for Study 905-CL-047

THETA	Estimate	SE	RSE	95%CI
θ1: CL/F (L/h)	6.22 §	0.296	4.8%	5.64 - 6.80
θ5: AGP on CL/F*	-1.18	0.164	13.9%	-1.501 – -0.859
θ7: FFM on CL/F*	0.431	0.109	25.3%	0.217 - 0.645
θ2: V/F (L)	283 §	22.6	8.0%	238.7 - 327.3
θ8: AGP on V/F*	-0.184	0.265	144%	-0.703 – -0.335
θ6: FFM on V/F*	1.14	0.222	19.5%	0.705 - 1.575
θ3: KA (h^{-1})	1.38	0.33	23.9%	0.733 - 2.027
θ4: ALAG (h)	0.934	0.0465	5.0%	0.843 - 1.025
OMEGA	Estimate	Shrinkage		
η1: CL/F	0.128	3.70%		
η2: V/F	0.308	23.70%		
η3: KA	0.961	40.20%		
η CL/F-V/F	0.0721			
η CL/F-KA	0.0155			
η V/F-KA	0.299			
SIGMA	**Estimate**	**Shrinkage**		
Proportional	0.0237	24.8%		
Additive	0.0674	24.8%		

CI: confidence interval, SE: standard error; RSE: relative standard error

§ Typical value for a patient with FFM=30 kg and AGP=72 ng/mL

* Value of exponent on centered covariate (30 kg for FFM and 72 ng/mL on AGP)

The diagnostic plots for the final model are shown in Figure 4.2-8. A comparison of exposures by age is shown in Table 4.2-10. A comparison was also made between children and adults (Figure 4.2-9).

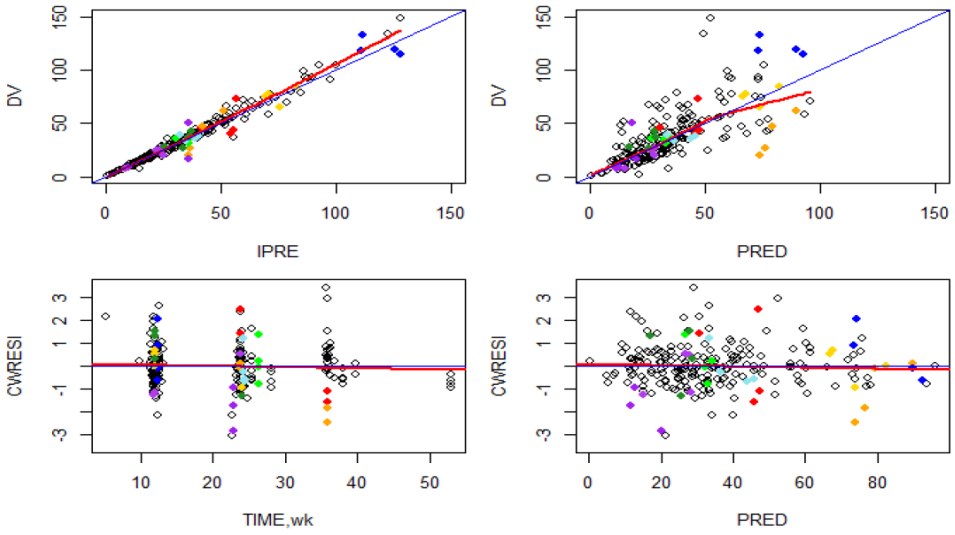


Figure 4.2-8. Goodness of fit plots the final model. The blue line through each plot is the line of identity for the top two plots and CWRESI=0 for the bottom two plots; the red line is the lowess (top row) or least squares fit (bottom row) through the data. Colored symbols are for patients that had initially been excluded from the modeling. CWRESI: individual conditional weighted residual; DV: observed dependent variable (solifenacin concentration); IPRE: individual predicted concentration; PRED: population predicted concentration; TIME: time since first dose (h)

Table 4.2-10. Summary PK parameters and dose-normalized exposure metrics of Study 905-CL-047

Parameter	Median (Range)		
	Children (5 Years to < 12 Years) (n = 30)	Adolescents (12 Years to < 18 Years) (n = 29)	All patients (5 Years to < 18 Years) (n = 59)
C_{max}/D (ng/mL/mg)	7.67 (3.19 - 18.38)	6.04 (2.49 - 18.37)	6.75 (2.493 - 18.38)
AUC_{tau}/D (ng.h/mL/mg)	140.5 (50.68 - 385.8)	121.8 (48.07 - 421.7)	133.4 (48.07 - 421.7)
$t_{1/2}$ (h)	24.42 (3.86 - 68.63)	35.77 (16.57 - 104.0)	30.68 (3.86 – 104.0)
t_{max} (h)	3.00 (2.00 - 6.00)	3.50 (2.00 - 5.00)	3.00 (2.00 - 6.00)
C_{trough}/D (ng/mL/mg)	3.867 (0.4431 - 12.81)	4.173 (1.502 - 16.03)	4.034 (0.4431 - 16.03)
CL/F (L/h)	5.37 (1.95 - 14.88)	6.19 (1.788 - 15.69)	5.65 (1.79 - 15.69)
V_z/F (L)	186.5 (33.01 - 498.7)	325.5 (99.12 - 750.9)	269.3 (33.01 - 750.9)

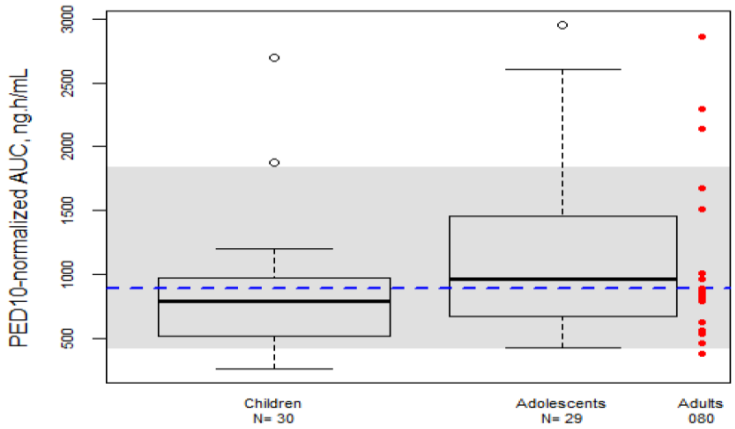


Figure 4.2-9. PED10-normalized AUCtau Values for Children in Study 905-CL-047 Compared to the Adult Target Exposure Range. Each box is the interquartile range (IQR) representing the 25th to 75th percentile of the observed AUCtau values in the age group. The whiskers represent the last point within 1.5 times the IQR of the 25th and 75th percentile. Circles represent all points above or below the whiskers. The blue dotted line is the target AUC (889 ng*h/mL) and the shaded area is the 90th percentile of healthy adult values. Red dots are adult individuals from 905-CL-080.

❖ *Reviewer's comment*

The Applicant well-described the population PK of solifenacin in NDO patients aged 5 to <18 years old. The reviewer agrees with the observation that the median clearance and volume were higher in the adolescents versus children presumably due to a higher FFM. The time to reach peak concentrations was consistent across ages with a range of approximately 2 to 5 hours and a median of 3 hours. The medians of the dose-normalized exposures (AUCtau/D and Cmax/D) were comparable between children and adolescents. There is a clear overlap in exposures which suggests acceptability of weight-based dosing derived based on steady-state adults exposures.

3) Study 905-CL-074

The objective of the modeling exercise was to develop a population PK model to establish the multiple-dose (steady-state) PK for solifenacin oral suspension in pediatric patients from 6 months to < 5 years of age with NDO.

· Methods

The data used in this pediatric patients with NDO of age groups 6 months to < 5 years and 2 to <5 years is summarized in Table 4.2-11. The model development was similar to Study 905-CL-047. The only difference was that the CYP3A4 ontogeny was evaluated on CL/F. The ontogeny factor for CYP3A4 was inserted on clearance. Inclusion of ontogeny was just a reparameterization of the model without estimation; hence the parameter values did not change.

Table 4.2-11. Summary (median and range or count) of dose and covariates in Study 905-CL-074

	6 months to <2 years	2 to < 5 years	All
Number of subjects	3	18	21
PED at last PK sample (n on PED5-7.5-10) *	0-1-2	1-5-12	1-6-14
Dose (mg)	4.2 (3.6 - 4.2)	2.6 (1.6 - 4.2)	3.2 (1.6 - 4.2)
Age (years)	1.65 (1.60 - 1.71)	3.65 (2.61 - 5.22)	3.53 (1.60 - 5.22)
Weight (kg)	10.9 (10.3 - 13.0)	13.4 (10.1 - 20.7)	13.3 (10.1 - 20.7)
Height (cm)	83.7 (73.0 - 91)	96.1 (77.5 - 106)	94.8 (73.0 - 106)
BMI (kg/m^2)	15.7 (14.7 - 20.5)	15.2 (13.0 - 21.0)	15.3 (13.0 - 21.0)
FFM (kg)	7.02 (6.51 - 13.5)	12.10 (7.37 - 15.1)	11.80 (6.51 - 15.1)
LBM (kg)	8.78 (8.36 - 11.7)	12.30 (8.29 - 17.2)	12.20 (8.29 - 17.2)
AGP (mg/dL)	66.0 (51 - 69)	73.5 (47 - 128)	70.0 (47 - 128)
Sex (M-F)	1-2	8-10	9-12

· Results

The final parameter estimates are shown Table 4.2-12 while the diagnostic plots are shown in Figure 4.2-10. A comparison between age groups was performed; the results are summarized in Table 4.2-13, with a comparison with adults shown in Figure 4.2-11. The median clearance and volume between the two age groups was slightly higher in the older age group due to a higher FFM. Even though the medians of the dose-normalized AUCs were slightly higher in the youngest age group, there was high overlap with target AUC. A low sample size in the younger age groups should be noted.

Table 4.2-12. Final parameter estimates for the population PK solifenacin model for Study 905-CL-074.

THETA	Estimate	SE	RSE	95%CI
θ1: CL/F (L/h)	4.03 §	0.312	7.7%	3.418 – 4.642
θ2: V/F (L)	106 §	10.3	9.7%	85.81 – 126.2
θ3: KA (h^{-1})	1.22	0.421	34.5%	0.395 – 2.045
θ4: ALAG (h)	0.688	0.172	25.0%	0.351 – 1.025
θ6: FFM on CL/F*	0.933	0.246	26.4%	0.451 – 1.415
θ5: FFM on V/F*	0.957	0.239	25.0%	0.489 – 1.425
θ7: AGP on CL/F*	-0.382	0.183	47.9%	-0.741 – -0.023
θ8: AGP on V/F*	-0.337	0.357	105.9%	-1.037 – 0.363
OMEGA	**Estimate**	**SE**	**RSE**	**Shrinkage**
η1: CL/F	0.118	0.0471	39.9%	0%
η2: V/F	0.122	0.0771	63.2%	13.30%
η3: KA	0.878	0.412	46.9%	24.70%
SIGMA	**Estimate**	**SE**	**RSE**	**Shrinkage**
Proportional	0.0122	0.0044	40.50%	34.40%

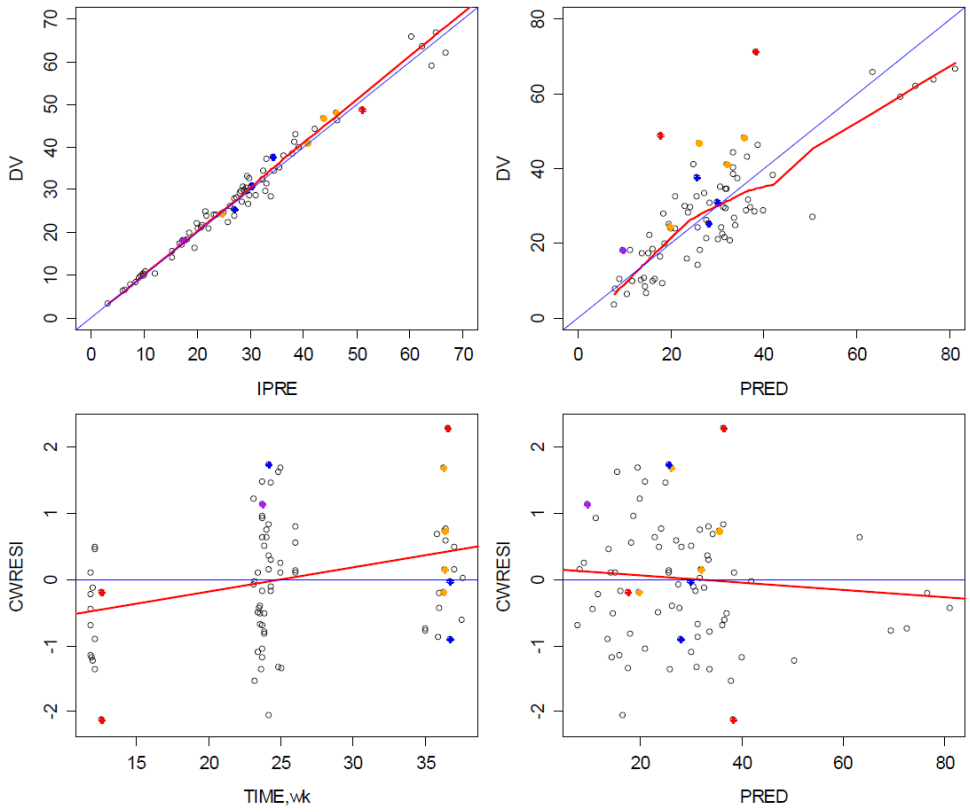


Figure 4.2-10. Goodness of fit plots for the final solifenacin model for Study 905-CL-074. The blue line through each plot is the line of identity for the top two plots and CWRESI=0 for the bottom two plots; the red line is the lowess (top row) or least squares fit (bottom row) through the data. Colored symbols are for patients that had initially been excluded from the modeling: 8207912 (orange), 8201906 (blue), 6301921(red), and 8201905 (purple). CWRESI: individual conditional weighted residual; DV: observed dependent variable (solifenacin concentration); IPRE: individual predicted concentration; PRED: population predicted concentration; TIME: time since first dose (h)

Table 4.2-13. Summary PK parameters and dose-normalized exposure metrics of Study 905-CL-074

Parameter	Median (Range)		
	6 Months to < 2 Years (n = 3)	2 Years to < 5 Years (n = 18)	6 Months to < 5 Years (n = 21)
C_{max}/D (ng/mL/mg)	14.84 (6.45 - 17.00)	11.17 (6.51 - 29.26)	11.19 (6.45 - 29.26)
AUC_{tau}/D (ng.h/mL/mg)	255.0 (115.9 - 308.3)	199.8 (97.00 - 559.7)	204.6 (97.00 - 559.7)
$t_{1/2}$ (h)	18.57 (13.10 - 23.32)	18.20 (11.40 - 29.61)	18.31 (11.40 - 29.61)
t_{max} (h)	4.00 (2.50 - 5.00)	3.00 (2.00 - 6.00)	3.00 (2.00 - 6.00)
C_{trough}/D (ng/mL/mg)	6.190 (3.228 - 9.157)	5.350 (2.091 - 16.84)	5.388 (2.091 - 16.84)
CL/F (L/h)	2.96 (2.45 - 6.50)	3.78 (1.35 - 7.77)	3.69 (1.35 - 7.77)
V_z/F (L)	82.27 (55.87 - 174.2)	105.0 (42.28 - 166.2)	103.0 (42.28 - 174.2)

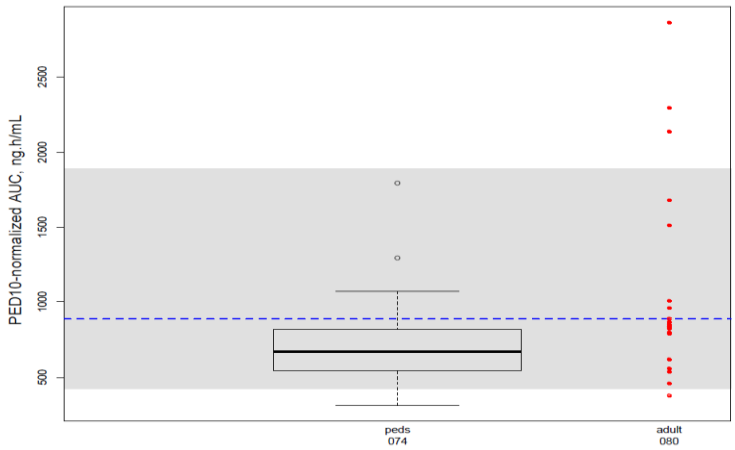


Figure 4.2-11. PED10-Normalized AUCss Values for Children in Study 905-CL-074 Compared to the Adult Target Exposure Range. Each box is the interquartile range (IQR) representing the 25th to 75th percentile of the observed AUCss values in the age group. The whiskers represent the last point within 1.5 times the IQR of the 25th and 75th percentile. Circles represent all points above or below the whiskers. The blue dotted line is the target AUC (889 ng*h/mL) and the shaded area is the 90th percentile of adult values. Red dots are adult individuals from 905-CL-080.

❖ *Reviewer's comments*

The reviewer accepts the methodology used in popPk analysis, the results obtained, and the conclusions reached. However, the low sample size in youngest age group (6 months to <2 years) resulted in inconclusive information for comparing exposure with adults. However, as the sponsor is not pursing dosing in pediatrics 6 months to <2 years, the limited information in this age group is not an issue. These patients should not be included when summarizing exposures from this study for labeling.

4) Reviewer's analysis

· Introduction

Population PK analysis for solifenacin was included in this application to identify covariates which influence solifenacin exposure. The primary objective was to evaluate whether the results from population PK analysis conducted by the applicant support the proposed pediatric dosing which aims to achieve exposures in pediatrics similar to those in adults. The current reviewer's analysis mainly focuses on the effect of weight on the PK of solifenacin in children.

· Methods

The datasets and characteristics of patients used in the analyses are summarized in Table 4.2-8 and Table 4.2-11 for Study 905-CL-047 and Study 905-CL-047, respectively. Table 4.2-14 shows the link to the files and datasets used.

Table 4.2-14. Source for dataset and files used in the analysis

Description	File name	EDR Location
Final model file Final model list file popPK dataset	074-run44-final-mod.txt 074-run44-final-out.txt nm074.xpt	\\CDSESUB1\evsprod\NDA209529\0000\m5\datasets\074-poppk\analysis\programs \\CDSESUB1\evsprod\NDA209529\0000\m5\datasets\074-poppk\analysis\adam\datasets
Final model file	047-run41-final-mod.txt;	\\CDSESUB1\evsprod\NDA209529\0000\m5\dataset

Final model list file	047-run41-final-out.txt	s\047-poppk\analysis\programs
PopPK dataset	nm047.xpt	\\CDSESUB1\evsprod\NDA209529\0000\m5\datasets\047-poppk\analysis\adam\datasets

The reviewer conducted the population PK analysis where estimation of typical population PK parameters, along with their random inter-individual variability (IIV) and inter-occasional variability (IOV), was performed in NONMEM 7.3 using a first-order conditional estimation method with ε–η interaction (FOCE INTER).

Population PK performance based on recommended maximum doses:

In order to compare the performance of population PK to PBPK derived dosing recommendations, final models from Study 905-CL-074 and Study 905-CL-047 were utilized. The datasets used for simulation were replicates of original datasets used in population PK modeling in each study, to make a virtual population with at least a sample of 4000 individuals per study. The maximum doses used to simulate the AUCs were the recommended doses based on PBPK modelling (Table 2.2-1).

The PBPK comparison of AUCs in age groups of 2 - 18 years against those achieved in adults is shown in Figure 4.2-6.

The final models were used to simulate the exposures in virtual populations that will be expected from the proposed maximum doses. The distributions of the simulated AUC values in pediatrics and adults are shown in Figure 4.2-12 for Study 905-CL-074 and Figure 4.2-13 for Study 905-CL-047

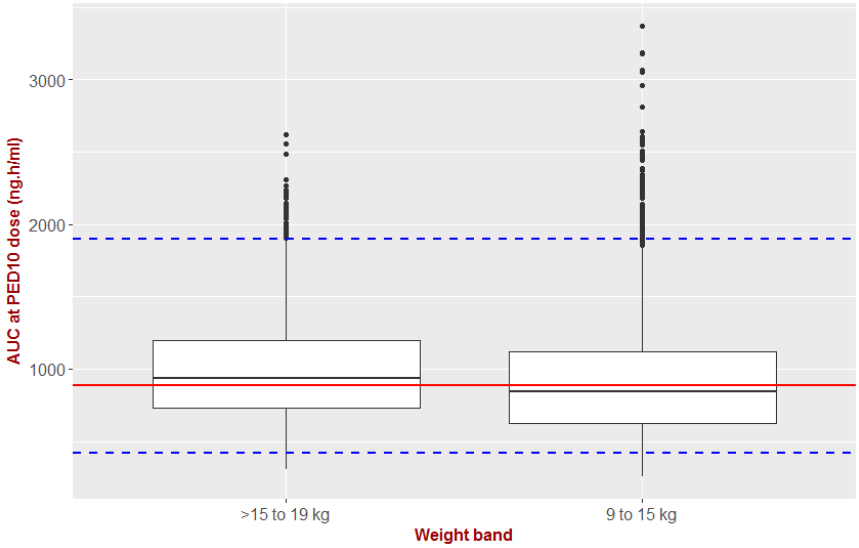


Figure 4.2-12. Study 905-CL-074: AUC (ng.h/mL) at the Recommended Maximum Dose (mg) for Each Weight Range. Each box is the IQR representing the 25th to 75th percentile of the values in the weight band. The thick purple segments represent the 5th and 95th percentile of the values in each box. The recommended maximum dose and percentage of patients falling within the target range are shown for each weight range. The red line represents the median efficacy target (889 ng.h/mL for an adult 10 mg dose); the blue dotted lines are the 5th to 95th percentile and represent the target exposure range (421 to 896 ng.h/mL).

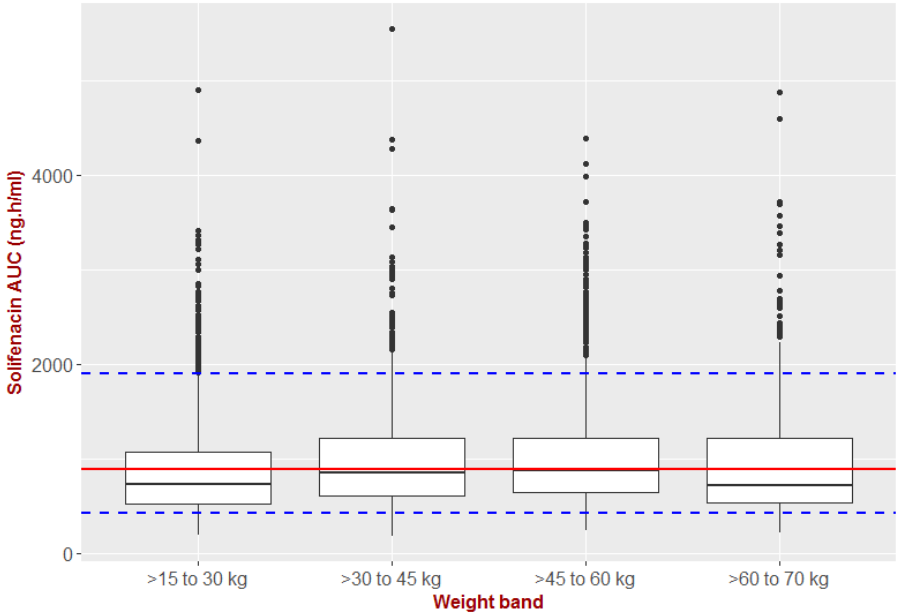


Figure 4.2-13. Study AUC 905-CL-047 (ng.h/mL) at the Recommended Maximum Dose (mg) for Each Weight Range. Each box is the IQR representing the 25th to 75th percentile of the values in the weight band. The thick purple segments represent the 5th and 95th percentile of the values in each box. The recommended maximum dose and percentage of patients falling within the target range are shown for each weight range. The red line represents the median efficacy target (889 ng.h/mL for an adult 10 mg dose); the blue dotted lines are the 5th to 95th percentile and represent the target exposure range (421 to 896 ng.h/mL).

Study 905-CL-074 had most of the patients weighing 9-15 kg while Study 905-CL-047 had patients weighing 15 to 80 kg. Only 3 patients were weighing above 70 kg. These 3 patients had a relatively high AGP and low FFM which resulted in low estimates of AUC since CL was positively correlated with FFM and negatively correlated with AGP. Based on the comparisons shown in Figure 4.2-12 and Figure 4.2-13, it can be concluded that the maximum dose recommended in each weight band would achieve AUC comparable to adults. However, there was a decreasing tendency of the exposure in adolescents weighing >60 kg. As such, it may be considered reasonable to use adult doses in children weighing > 60 kg.

Reviewer's comment

In general, the reviewer accepts the analysis conducted by the applicant as reasonable and confirmed that the weight based dosing using population PK would perform well in deriving recommended doses similar to PBPK. Hence, it is reasonable to conclude that population PK approach would perform equally well as PBPK approach in deriving doses in children.

4.2.3 Assessment on food-effect of solifenacin succinate oral suspension

While the Applicant conducted no dedicated food-effect study to assess the impact of food on the bioavailability of the to-be-marketed formulation (Formulation B) in pediatric patients, they concluded that food intake does not affect the exposure of solifenacin following administration of the final suspension formulation. The Applicant provided evidence supporting the assumption that the exposure to solifenacin following administration of the to-be-marketed formulation is independent of food

conditions. When putting all the supporting evidence together, this reviewer concludes that food intake does not significantly affect the bioavailability of solifenacin following administration of solifenacin succinate oral suspension. Additional details are discussed below.

- Comparison of the PK parameters between administration without regard to food and at fasted state.

The two phase 3 trials had no restriction of food and drink intake (presumably combined fed/fasted state) for medication of study drug. The PK values estimated using population PK analysis from the phase 3 trial (Study 905-CL-074) was compared to those from the PK study (Study 905-CL-079) of single dose in a fasted state. The apparent oral clearance in pediatric patients with NDO appeared to be comparable between the two studies (combined fed/fasted vs fasted) (Figure 4.2-14)

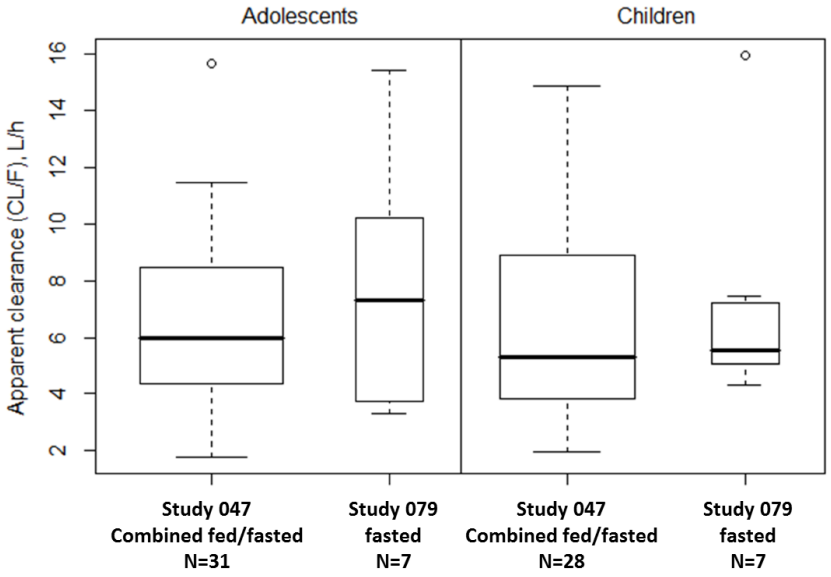


Figure 4.2-14 Comparison of apparent oral clearance (CL/F) in pediatric patients with NDO aged 5 years and older in Study 905-CL-079 (fasted) and Study 905-CL-047 (combined fed/fasted)

The PK parameters from the two studies were estimated based on population PK analysis using 4 to 7 PK samples for each subject. The pharmacometric reviewer found that both population PK analyses that the Applicant performed are generally acceptable (refer to section 4.2.2). Based on an assessment of these population PK analyses, this reviewer concludes that oral clearance of and exposure to solifenacin following administration of solifenacin succinate oral suspension may be independent of food intake.

- Impact of food intake on the PK of the tablet formulation and old oral suspension formulation.

Food-effect studies of the tablet formulation (VESIcare®) (Study 905-CL-003) and old oral suspension formulation (Formulation A) (Study 905-CL-066) demonstrated that food intake does not significantly affect the exposure to solifenacin following administration of both formulations.

Table 4.2-15 Summary of Studies 905-CL-003 and 905-CL-066

<table>
<tr><th>Study [resource]</th><th>Study design</th><th>Results</th></tr>
<tr><td>An open two-period crossover study to assess the effect of food on the PK of a single dose of YM905 in healthy male adult volunteers [NDA 021518; Study 905-CL-003]</td><td>· Two-period cross over with a washout period of 14 days
· With/without a standardized breakfast
· 24 subjects
· Single doses of 10 mg (2 × 5 mg tablets)
· Blood sampling up to post-dose 144 hours</td><td>
<table>
<tr><th></th><th>T_{max} (h)</th><th>C_{max} (ng/mL)</th><th>AUC_t (n·gh/mL)</th><th>AUC_{inf} (n·gh/mL)</th></tr>
<tr><td>Fasting</td><td>6 (1.7)</td><td>14.1 (4.3)</td><td>691 (313)</td><td>820 (423)</td></tr>
<tr><td>Fed</td><td>5.8 (2.1)</td><td>14.7 (4.9)</td><td>736 (290)</td><td>842 (373)</td></tr>
</table>
Mean (S.D.)
<table>
<tr><th></th><th>Geometric mean ratios (90% confidence interval)</th></tr>
<tr><td>AUC_t</td><td>106.8 (99.0, 115.3)</td></tr>
<tr><td>AUC_{inf}</td><td>104.0 (97.6, 110.9)</td></tr>
<tr><td>C_{max}</td><td>103.3 (95.3, 112.0)</td></tr>
</table>
</td></tr>
<tr><td>Phase 1, open-label, randomized, single dose, 3-way crossover study to assess the relative bioavailability of solifenacin liquid suspension 10 mg (fed and fasting) versus the VESIcare® 10 mg tablet (fasting) in healthy adult volunteers [Study 905-CL-066]</td><td>· Single dose, 3-treatment, 3-period crossover study
· 24 healthy male and female subjects
· Treatments: A - 10 mg tablet, B - suspension (fasting) and C - suspension (fed)
· A minimum of 13 days between dosing/ 6 sequences
· Blood sampling up to post-dose 240 hours</td><td>
<table>
<tr><th></th><th>T_{max} (h)</th><th>C_{max} (ng/mL)</th><th>AUC_t (n·gh/mL)</th><th>AUC_{inf} (n·gh/mL)</th></tr>
<tr><td>Fasting</td><td>6 (3-12)</td><td>12.8 (3.70)</td><td>625.7 (233.7)</td><td>672.9 (250.6)</td></tr>
<tr><td>Fed</td><td>8 (4-24)</td><td>11.1 (2.66)</td><td>673.2 (256.2)</td><td>730.6 (301.3)</td></tr>
</table>
Mean (S.D.) except for T_{max} (median and range)
<table>
<tr><th></th><th>Geometric mean ratios (90% confidence interval)</th></tr>
<tr><td>AUC_t</td><td>107.10 (98.98, 115.90)</td></tr>
<tr><td>AUC_{inf}</td><td>107.26 (99.36, 115.79)</td></tr>
<tr><td>C_{max}</td><td>87.52 (80.98, 94.59)</td></tr>
</table>
</td></tr>
</table>

- Bioequivalence of the final suspension formulation to the tablet formulation and old oral suspension formulation

In the relative bioavailability study (Study 905-CL-080), the PK of the final suspension formulation (Formulation B) was compared to that of the tablet formulation (VESIcare®) and old oral suspension formulation (Formulation A). Formulation B was shown to be bioequivalent to Formulation A as well as VESIcare®. The reviewer reanalyzed PK data and conducted independent statistical analysis and came to same conclusion. Additional details are summarized in the individual study report for Study 905-CL-080.

4.2.4 Analysis of simulated AUC data in virtual population weighing > 45 kg

There are adolescents who have body mass comparable to adults. In addition, the metabolic capacity of solifenacin in children is unlikely to be different from that in adults. In these circumstances, the

recommended doses, 5 mg and 10 mg, for adult patients with OAB may be considered for pediatric population with NDO and a certain high body weight. Distribution of simulated AUCs at 8 mg and 10 mg in virtual population > 45 kg may provide an insight into this consideration.

The reviewer analyzed simulated solifenacin AUC data at 8 mg and 10 mg using the PBPK model by weight groups in virtual population > 45 kg. As results, a weight-dependent lower exposure distribution of AUC was observed as body weight increases. The percentage of patients whose AUC falls within the target exposure range at 8 mg tended to be lower in the relatively higher body weight groups, > 60 kg and ≤ 75 kg and > 75 kg, compared to that in the lower weight group, > 45 kg and ≤ 60 kg (Figure 4.2-15). Simulated AUC at 10 mg in those same weight groups showed some improvement on the percentage compared to those at the proposed dose of 8 mg (Figure 4.2-16). These results may imply that 10 mg, the maximum dose for adult patients, may be more beneficial for pediatric patients who have relatively greater body weight than 8 mg, the Applicant's proposed maximum dose.

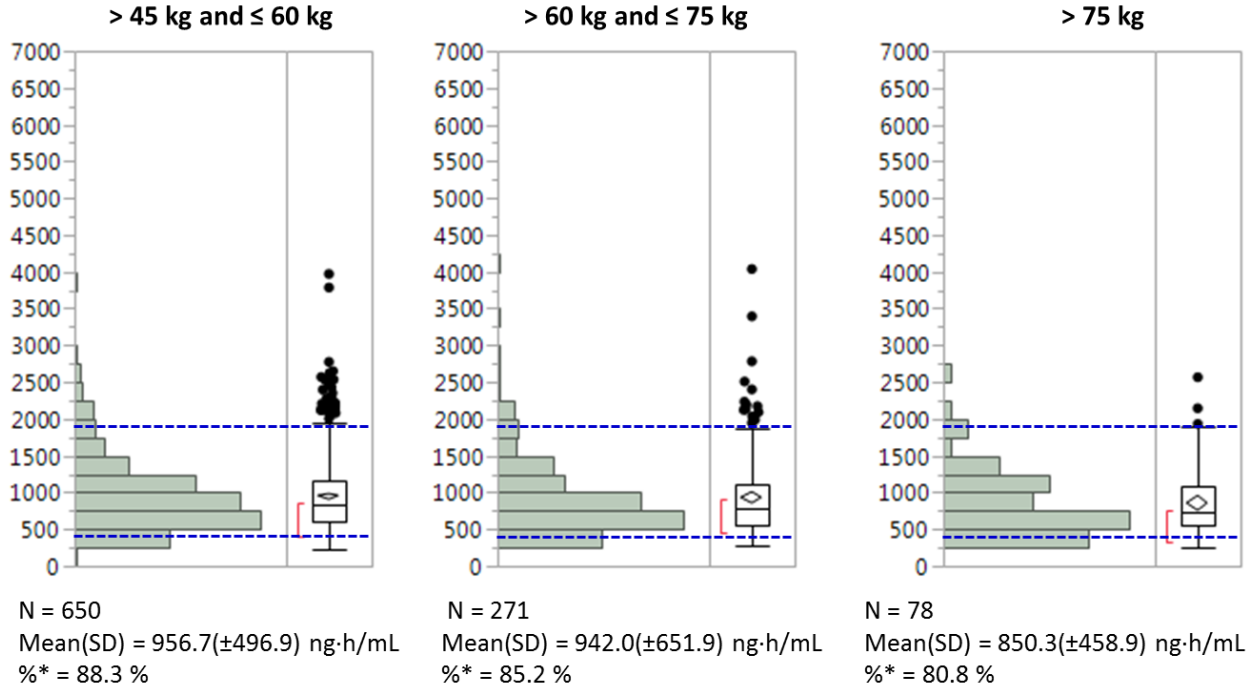


Figure 4.2-15. Distribution of simulated AUC values at 8 mg in virtual population weighing > 45 kg (*the percentage of patients falling within the target exposure range – blue line)

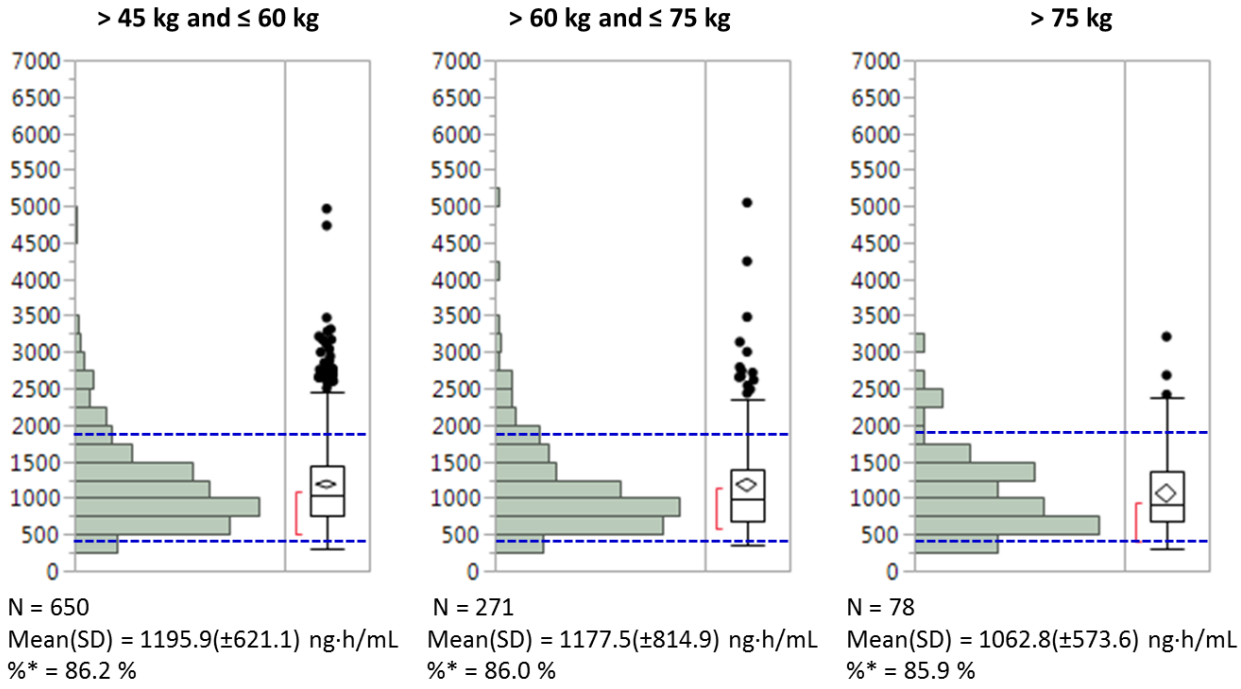


Figure 4.2-16 Distribution of simulated AUC values at 10 mg in virtual population weighing > 45 kg (*the percentage of patients falling within the target exposure range- blue line)

Analysis of simulated AUC data using two cut-off body weights, 60 and 70 kg, demonstrated that the percentage of patients being within the target exposure range at 10 mg improved compared to that at 8 mg (Figure 4.2-17 and 4.2-18).

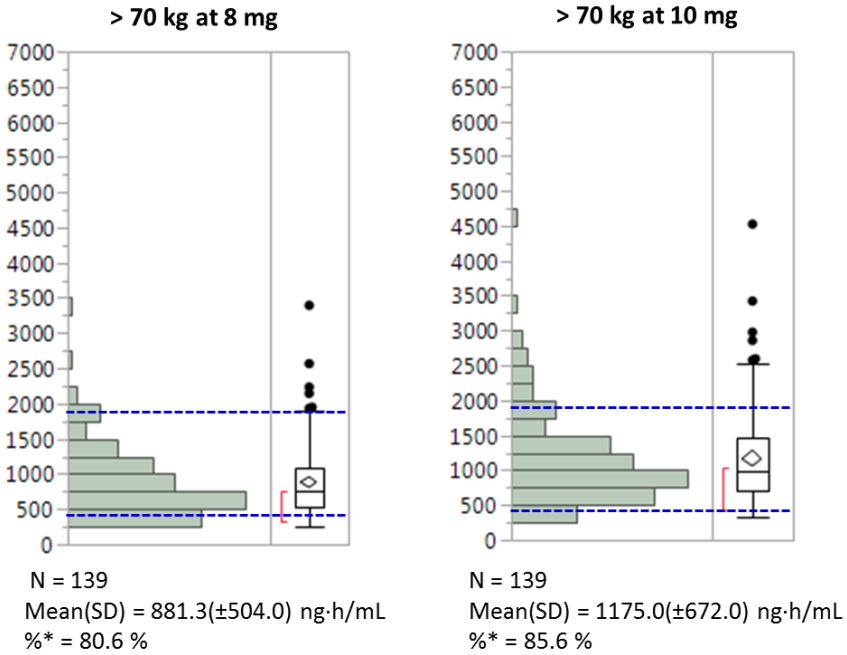


Figure 4.2-17 Distribution of simulated AUC values at 8 and 10 mg in virtual population weighing > 70 kg (*the percentage of patients falling within the target exposure range- blue line)

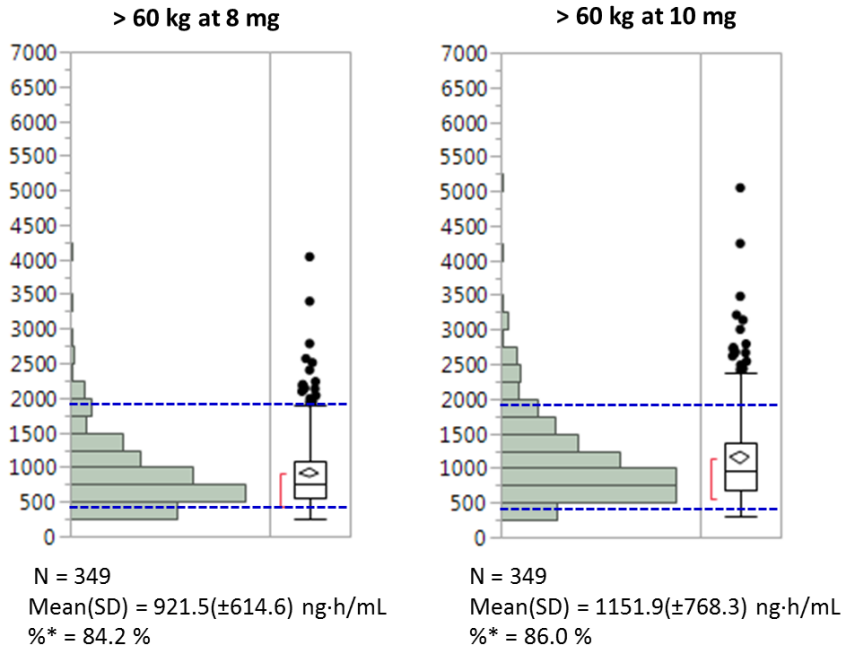


Figure 4.2-17 Distribution of simulated AUC values at 8 and 10 mg in virtual population weighing > 60 kg (*the percentage of patients falling within the target exposure range- blue line)

These findings suggest that the use of the adult doses for pediatric patients with a relatively higher body mass should be considered.

4.2.5 Assessment of QT prolongation

Four patients in Study 905-CL-047 experienced a treatment emergent adverse event (TEAE) of ECG QT prolongation that resulted in treatment discontinuation. QT data of 4 patients are summarized in table 4.2-16.

Table 4.2-16 Summary of the subjects who experience a TEAE of ECG QT prolongation in Study 905-CL-047

Subject ID	Sex, age	Dose	Baseline	Maximum change
(b) (6)	F, 14	3.4 mg (PED 5)	QTcB : 423.0 msec	QTcB : 456.0 msec at Day 59
	F, 8	3.8 mg (PED 7.5)	QTcB : 427.3 msec	QTcB: 461.7 msec at Day 21
	F, 9	3.4 mg (PED 5)	QTcB : 407.0 msec	QTcB: 440.7 msec at Day 22
	M, 13	5.2 mg (PED 7.5)	QTcB : 397.7 msec	QTcB: 429.0 msec at Day 22

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

These subjects discontinued the study based on the criteria (an increase from baseline in QTcB of > 30 ms or a QTcB of > 460 ms). There were no AEs of QT prolongation or associated discontinuations in pediatric patients aged 2 years to < 5 years (Study 905-CL-074). Based on a random effect analysis on data of OAB pediatric patients, the Applicant found that there was absence of changes of concern in the population means of QT intervals and the intrapatient variance in repeat QTcB measurements. In order to increase the accuracy of the baseline QTc measure, its calculating method was amended from one-time to two-time measure over 2 visits. Subsequent to implementing this change, there were no further discontinuation cases in the two phase 3 trials.

QT data observed before and after 52 weeks treatments in all subjects enrolled in phase 3 trial 905-CL-047 are summarized in Table 4.2.-17. The mean changes of QT intervals from baseline to week 52 were negligible.

Table 4.2-17 Summary of QTcB and QTcF at and week 52 (Study 905-CL-047)

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

QTcB and QTcF: QT interval corrected using Bazett's and Fridericia's formula, respectively

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

Based on the observed overall finding of QT prolongation in pediatric patients with NDO, this reviewer concludes that there are no new findings of clinical concern in terms of QT prolongation following solifenacin treatments in pediatric patients. Interdisciplinary Review Team for QT also concluded that solifenacin is unlikely to have a clinically relevant effect on the QTc interval at the proposed doses in pediatric patients. A final conclusion of QT issue is deferred to the medical reviewer.

4.2.6 Clinical pharmacokinetics of solifenacin succinate oral suspension

- Clinical pharmacokinetics of the to-be-marketed solifenacin succinate oral suspension

The PK of solifenacin at steady-state following administration of solifenacin succinate oral suspension in pediatric patient with NDO was characterized based on population PK approach using plasma concentrations sparsely collected in the two phase 3 studies (Studies 905-CL-047 and 905-CL-074). The individual PK parameters were derived from posthocs or Empirical Bayes Estimates, which were used to calculate the exposure parameters (C_{trough}, C_{max} and t_{max} values). The pharmacometric reviewer concluded that the Applicant's population PK approaches are acceptable (refer to section 4.2.2). The estimated PK parameters of solifenacin with dose-normalized exposures for each age group are summarized in Table 4.2-18 and 4.2-19.

Table 4.2-18 Summary of PK of solifenacin in pediatric patients with NDO (Study 905-CL-047)

Age group	5 to < 12 Years (n = 30)	12 to < 18 Years (n = 29)	5 to < 18 Years (n = 59)
	Median (Range)		
C_{max}/D (ng/mL/mg)	7.67 (3.19 - 18.38)	6.04 (2.49 - 18.37)	6.75 (2.493 - 18.38)

AUC_{tau}/D (ng.h/mL/mg)	140.5 (50.68 - 385.8)	121.8 (48.07 - 421.7)	133.4 (48.07 - 421.7)
$t_{1/2}$ (h)	24.42 (3.86 - 68.63)	35.77 (16.57 - 104.0)	30.68 (3.86 – 104.0)
T_{max} (h)	3.00 (2.00 - 6.00)	3.50 (2.00 - 5.00)	3.00 (2.00 - 6.00)
C_{trough}/D (ng/mL/mg)	3.867 (0.4431 - 12.81)	4.173 (1.502 - 16.03)	4.034 (0.4431 - 16.03)
CL/F (L/h)	5.37 (1.95 - 14.88)	6.19 (1.788 - 15.69)	5.65 (1.79 - 15.69)
Vz/F (L)	186.5 (33.01 - 498.7)	325.5 (99.12 - 750.9)	269.3 (33.01 - 750.9)

C_{max}/D: dose-adjusted maximum concentration, AUC_{tau}/D : dose-adjusted area under the curve to the time of the last measureable, $t_{1/2}$: elimination half-life, T_{max}: time to maximum concentration, C_{trough}/D : dose-adjusted trough concentration, CL/F: apparent clearance and Vz/F: apparent volume of distribution

Table 4.2-19 Summary of PK of solifenacin in pediatric patients with NDO (Study 905-CL-074)

Age group	2 to < 5 Years (n = 18)
	Median (Range)
C_{max}/D (ng/mL/mg)	11.17 (6.51 - 29.26)
AUC_{tau}/D (ng.h/mL/mg)	199.8 (97.00 - 559.7)
$t_{1/2}$ (h)	18.2 (11.40 - 29.61)
T_{max} (h)	3 (2.00 - 6.00)
C_{trough}/D (ng/mL/mg)	5.35 (2.091 - 16.84)
CL/F (L/h)	3.78 (1.35 - 7.77)
Vz/F (L)	105 (42.28 - 166.2)

C_{max}/D: dose-adjusted maximum concentration, AUC_{tau}/D : dose-adjusted area under the curve to the time of the last measureable, $t_{1/2}$: elimination half-life, T_{max}: time to maximum concentration, C_{trough}/D : dose-adjusted trough concentration, CL/F: apparent clearance and Vz/F: apparent volume of distribution

- Elimination (metabolism and excretion) of solifenacin

Solifenacin is extensively metabolized in the liver and eliminated through non-renal routes. The primary pathway for elimination is mediated by CYP3A4. However, CYP1A1 and CYP2D6 enzymes are also involved in the metabolism of solifenacin as very minor pathways (*Doroshyenko and Fuhr 2009*). The primary metabolic routes of solifenacin are through N-oxidation of the quinuclidin ring and 4R-hydroxylation of tetrahydroisoquinoline ring. One pharmacologically active metabolite (4R-hydroxy solifenacin), occurring at low concentrations and unlikely to contribute significantly to clinical activity, and three pharmacologically inactive metabolites (N-glucuronide and the N-oxide and 4R-hydroxy-N-oxide of solifenacin) have been found in human plasma after oral dosing (Labeling information of Vesicare®).

While urinary excretion of the parent drug plays a minor role in in the elimination (approximately 10% of the total clearance), the kidneys modestly contribute to excretion of its metabolites: the urinary excreted metabolites, N-oxide, 4R-hydroxy, 4R-hyroxy N-oxide, and N-glucuronide, accounted for 18.8–29.0%, 5.6–7.7%, 4.8–8.3%, and 0.6–0.9% of the dose, respectively (*Krauwinkel et al. 2005*).

Although renal excretion is a relatively minor elimination pathway for solifenacin, patients with renal impairment were found to have significant changes in the PK (refer to section 3.3.3). The reduced excretory functions of the parents and its metabolites in the kidneys and a decrease metabolism in subjects with renal impairment may contribute to this PK change. In addition, total clearance could be reduced because increased concentrations of AGP in patients with renal failure consequently lower unbound fraction of solifenacin (*Doroshyenko and Fuhr 2009*).

- Intrinsic factors affecting variability in the PK of solifenacin in pediatric patients with NDO

The population PK analyses suggest that age, weight, FFM, lean body mass (LBM), sex and AGP contribute to variability in the PK of solifenacin in pediatric patients with NDO.

Age was identified as a major intrinsic variable to significantly affect the systemic exposure of solifenacin in pediatric patients with NDO. In the phase 3 trials (Studies 905-CL-047 and 905-CL-074), the dose-normalized exposures (AUC_{tau}/dose and C_{max}/dose) tended to decrease with increasing age (Table 4.2-18 and 4.2-19). However, the ranges of these exposure parameters in these age groups appeared to be overlapped. This finding is likely to result from the weight based dosing administration method used for the studies to achieve equivalent exposure of solifenacin in adults.

Given that body composition alters with age, different proportions of body mass are likely to affect a child's PK disposition. Size metrics, weight, LBM, and FFM, were investigated in the population PK analyses. FFM was selected as the most robust in the pediatric PK model. The median clearance and volume appeared to be higher in the adolescents than the children. This finding is likely to be attributed to a higher FFM in the adolescents. While FFM is a robust body size measure to be included in the PK model for pediatric patients with NDO, weight-based dosing based on routine body weigh measurement should be used for practical reasons in the clinical setting and was also exercised in the phase 3 trials.

While sex was identified as an intrinsic variable to significantly affect the PK of solifenacin in pediatric patients with NDO, this factor has not been addressed in the population PK analyses as well as the development of the recommended dosing table. However, the studies of solifenacin in adults demonstrated that the PK as well as efficacy of solifenacin is not significantly influenced by gender. Thus, sex is unlikely to play a significant role in dosing recommendation in pediatric patients.

Solifenacin is a highly protein bound drug, which is principally bound to AGP. The population PK and PBPK analyses in pediatric patients with NDO showed that AGP is a significant covariate in the clearance and distribution of solifenacin. Changes in the concentration of AGP may be crucial for the disposition and efficacy due to a modulation in its clearance and free fraction. While the serum concentrations of AGP are lower in neonates and infants (up to 12 months), those in children and adolescents (older than 1 year) are similar in that of adults (*Lerman et al. 1989*). Given that there no significant difference in serum AGP concentrations between children and adolescents and adults, the effect of age on the free fraction of solifenacin may not predispose to an additional risk following administration of solifenacin succinate oral suspension in the proposed pediatric population (aged 2 years and older) unless its concentrations are significantly changed due to a disease condition.

4.2.7 Development of the final suspension formulation of solifenacin succinate

The Applicant originally developed an aqueous suspension formulation (Formulation A) of solifenacin succinate for the pediatric development program. This formulation was used for the first PK study in pediatric patients with OAB (Study 905-CL-075) after performing the relative bioavailability study (Study 905-CL-066). The Applicant found that Formulation A was unsuitable (b) (4) (b) (4). Formulation B as an optimized suspension was developed to improve the usability and was used in the two phase 3 trials (Studies 905-CL-047 and 905-CL-074) as the final suspension formulation. The comparative bioavailability study (Study 905-Cl-080) demonstrated that Formulation B is bioequivalent to Formulation A and the tablet formulation (VESIcare®). In vitro analysis also showed no differences in the dissolution profiles between the two suspension formulations (refer to the Biopharmaceutics review).

4.3 Individual Study Reports

Tables and figures under this section are numbered independently.

Study identifier: 905-CL-080

Title: A phase 1, open-label, randomized, single dose, 3-way crossover study to assess the relative bioavailability of solifenacin liquid suspension 10 mg (Formulation B) versus solifenacin liquid Suspension 10 mg (Formulation A) and to assess the relative bioavailability of solifenacin liquid suspension 10 mg (Formulation A and B) versus the VESIcare® (solifenacin succinate) 10 mg tablet in healthy volunteers

Objectives:

- The primary objective: 1) To determine the relative bioavailability and pharmacokinetics (PK) profile of Formulation B versus Formulation A. and 2) To determine the relative bioavailability and PK profile of Formulation A and B versus the VESIcare® 10 mg tablet.
- The secondary objective: To evaluate the safety and tolerability of single doses of the two different formulations of Formulation A and B and the VESIcare® 10 mg tablet.

Study Design:

- Open-label, single dose, 3-treatment, 3-period crossover study
- 24 healthy male and female subjects
- Single dose treatments with a minimum 13-day washout interval
  - Treatment A: solifenacin succinate 10 mg as a suspension (1 mg/mL), Formulation A.
  - Treatment B: solifenacin succinate 10 mg as a suspension (1 mg/mL), Formulation B.
  - Treatment T: solifenacin succinate 10 mg as a single 10 mg tablet.
  - Administered orally after an overnight fast and food was restricted for 4 hours after dosing.
  - 6 sequences (4 healthy volunteers per sequence)
- PK study
  - Pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours after dosing
  - Assay: Liquid Chromatography Tandem Mass Spectrometry (LC-MS) method (the lower limit of quantification: 0.2 ng/mL)
- Safety evaluation
  - Physical examination, vital signs, 12-lead safety ECG, clinical laboratory evaluations and adverse event recording

Results:

- Of the 24 healthy subjects (14 male and 10 female), 1 subject received Formulation A only and 1 subject received Formulation A and Tablet.
- Assay: Assay performance was assessed using quality control samples ranged from 0.6 to 150 ng/mL. Inter-run accuracy (-5.1% - 2.7%) and precision (4.8% - 7.8%) were within the Agency's acceptance criteria. A total of 137 samples (10% of total number of plasma samples) were analyzed as incurred sample repeats (ISR). 93.6% of the ISR samples (128 out of 137) passed the ISR criteria (within 20% of reported concentration).
- PK results

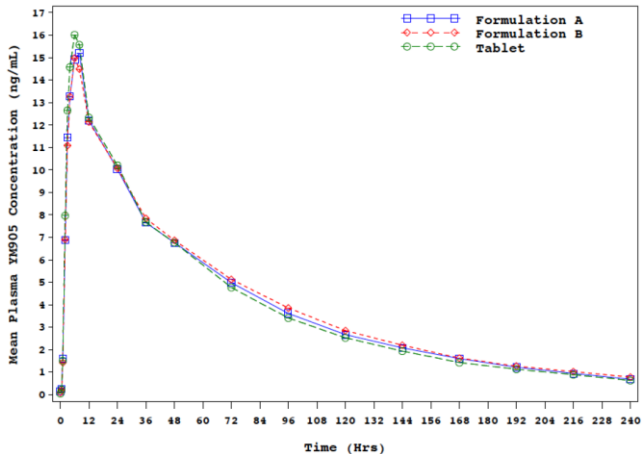


Figure 1. Mean time-solifenacin concentration profile after single dose of solifenacin succinate tablet, Formulation A, or Formulation B in 24 healthy male or female subjects

Table 1. Mean solifenacin PK parameters after single dose of solifenacin succinate tablet, Formulation A, or Formulation B in 24 healthy male or female subjects.

Parameter	C_{max} (ng/mL)	T_{max} (h)	AUC_{last} (ng·h/mL)	AUC_{inf} (ng·h/mL)	CL/F (L/h)	$t_{1/2}$ (h)
	Mean ± SD (CV%, N)*					
Tablet	16.6 ± 4.4 (26%, 23)	6 (3 – 8, 23)	943 ± 475 (50%, 23)	1023 ± 603 (59%, 23)	9.48 ± 4.51 (48%, 23)	51.3 ± 19.3 (38%, 23)
Formulation A	15.9 ± 4.2 (27%, 24)	7 (3 – 8, 24)	956 ± 534 (56%, 22)	1057 ± 703 (67%, 22)	9.63 ± 4.72 (49%, 22)	53.7 ± 24.4 (45%, 22)
Formulation B	15.6 ± 4.4 (28%, 21)	6 (4 – 12, 21)	982 ± 532 (54%, 21)	1075 ± 677 (63%, 21)	9.26 ± 4.44 (48%, 21)	54.1 ± 20.6 (38%, 21)

* T_{max}: median (range, N); Formulation B of subject (b) (6) was excluded from the analysis.

Table 2. Comparative PK between formulations of solifenacin succinate

Parameter	Geometric mean ratios (90% confidence interval)		
	Formulation A/Tablet	**Formulation B/Tablet**	**Formulation B/A**
AUC_{last}	101.40 (96.08, 107.02)	98.99 (93.75, 104.51)	97.62 (92.24, 103.31)
AUC_{inf}	102.09 (96.69, 107.79)	99.11 (93.83, 104.68)	97.08 (91.69, 102.78)
C_{max}	96.52 (91.45, 101.87)	91.23 (86.24, 96.51)	94.52 (89.36, 99.98)

Formulation B of subject (b) (6) was excluded from the analysis.

· Safety
- All treatment emergent adverse events (TEAEs) were of mild severity with the exception of a single-case of iron-deficiency anemia (onset at day 23, Formulation A), which was considered moderate in severity and possibly related to treatment.
- No clinically relevant differences were noted in the frequency and type of TEAEs and drug-related TEAEs between the 3 formulations studied.
- No serious AEs or AEs of special interest were observed during this study. A single healthy volunteer on Formulation A discontinued the study after day 1 due to diarrhea, which was followed by rash on day 5. Both adverse events were considered to be possibly related to treatment. In addition, no deaths were reported.

Sponsor's conclusions:

- Three different formulations of solifenacin succinate (i.e., 10 mg as a liquid suspension 1 mg/mL Formulation A, solifenacin succinate 10 mg as a liquid suspension 1 mg/mL Formulation B, and solifenacin succinate 10 mg Tablet) were shown to be bioequivalent.
- Single doses of solifenacin succinate 10 mg as Formulation A, Formulation B and as a Tablet were considered to be safe and well-tolerated.

Reviewer's comments:

- The study design appears to be reasonable to assess the relative bioavailability of the final suspension formulation (Formulation B) compared to the old suspension formulation (Formulation A) and the tablet formulation (VESIcare®). As results, Formulation B is bioequivalent to Formulation A as well as VESIcare®. The C_{max} of solifenacin tended to be slightly lower in the period of Formulation B compared to the period of the tablet, but the confidence interval of geometric mean ratio (Formulation B/Tablet) met the standard BE acceptance criteria.
- The period 2 (Formulation B) of Subject-(b) (6) was excluded from PK and bioequivalence analyses. This subject presented nausea and vomiting (at 8:30 am) after drug intake (8:12 am). The Applicant concluded that the plasma concentrations might be unreliable due to the vomiting shortly after the medication and decided to exclude the data of the period for the analyses. The plasma concentrations of solifenacin in this subject in period 2 (Formulation B) appeared to be significantly lower than that in the other periods (Formulation A and Tablet). Based on the information that the Applicant provided and the PK profile of solifenacin in that period, exclusion of this data from the analyses is acceptable.
- PK and statistical analyses were independently performed by the reviewer. The results were consistent with those that the Applicant provided.
- While the BA of Formulation A appeared to be relatively lower than that of VESIcare® in Study 905-CL-066, the current study demonstrated that Formulation A is also bioequivalent to VESIcare®.
- The PK profile of Formulation B characterized from this study was used to establish the pediatric equivalent doses used in the phase 3 studies of pediatric patients with neurogenic detrusor overactivity.

Study identifier: 905-CL-066

Title: Phase 1, open-label, randomized, single dose, 3-way crossover study to assess the relative bioavailability of solifenacin liquid suspension 10 mg (fed and fasting) versus the VESIcare® (solifenacin succinate) 10 mg tablet (fasting) in healthy volunteers

Objectives:

- The primary objective: To determine the relative bioavailability and pharmacokinetic (PK) profile of solifenacin suspension (1 mg/mL) dosed at 10 mg in comparison to the 10 mg tablet in the fasting state.
- The secondary objective: To evaluate the effect of food on the PK of a single 10 mg dose of solifenacin suspension.

Study Design:

- Open-label, single dose, 3-treatment, 3-period crossover study
- 24 healthy male and female subjects

· Treatments: a minimum 13-day washout interval, 6 sequences (4 healthy volunteers per sequence)
  - Treatment A: solifenacin succinate 10 mg as a single 10 mg tablet (fasting)
  - Treatment B: solifenacin succinate 10 mg as a suspension (1 mg/mL) (fasting)
  - Treatment C: solifenacin succinate 10 mg as a suspension (1 mg/mL) (fed)
  - Administered orally following a minimum 10-hour fast from food.
  - Fed condition: within 30 minute of the start of a FDA guidance-compliant high-fat breakfast
· PK study
  - Pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours after dosing
  - Assay: Liquid chromatography tandem - mass spectrometry (LC-MS) method (the lower limit of quantification: 0.2 ng/mL)
· Safety evaluation
  - Physical examination, vital signs, 12-lead safety ECG, clinical laboratory evaluations and adverse event recording

Results:

· Study population: Of the 24 healthy subjects (12 male and 12 female), 22 subjects received the solifenacin tablet (Treatment A) and 23 subjects solifenacin suspension both fasting (Treatment B) and fed (Treatment C).

· PK results

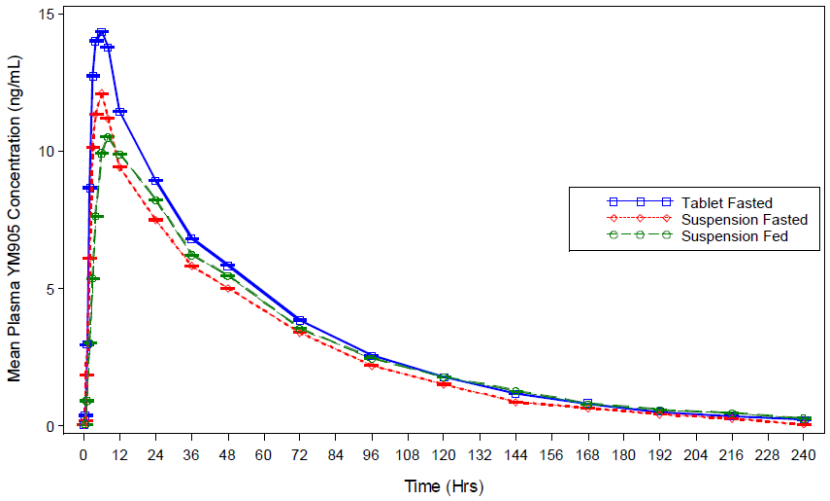


Figure 1. Mean time-solifenacin concentration profile given in tablet or suspension formulations under fasting or fed condition in 24 healthy male or female subjects

Table 1. Mean solifenacin PK parameters after single dose of solifenacin succinate (10 mg) given in tablet or suspension formulations under fasting or fed condition in 24 healthy male or female subjects.

Parameter	C_{max} (ng/mL)	T_{max} (h)	AUC_{last} (ng·h/mL)	AUC_{inf} (ng·h/mL)	CL/F (L/h)	$t_{1/2}$ (h)
	Mean ± SD (CV%, N)*					
Tablet Fasting	15.9 ± 4.80 (29.8%, 22)	6 (2 - 12, 22)	753.2 ± 267.95 (35.6%, 22)	800.8 ± 289.33 (36.1%, 22)	14.0 ± 4.82 (34.4%, 22)	46.4 ± 15.32 (33.0%, 22)
Suspension Fasting	12.8 ± 3.70 (28.9%, 23)	6 (3 - 12, 23)	625.7 ± 233.69 (37.3%, 23)	672.9 ± 250.61 (37.2%, 23)	16.9 ± 6.00 (35.6%, 23)	45.7 ± 14.27 (31.2%, 23)
Suspension Fed	11.1 ± 2.66 (24.0%, 23)	8 (4 – 24, 23)	673.2 ± 265.20 (39.4%, 23)	730.6 ± 301.29 (41.2%, 23)	15.6 ± 5.31 (34.0%, 23)	50.5 ± 20.05 (39.7%, 23)

* Tmax: median (range, N)

Table 2. Comparative PK between formulations of Solifenacin succinate and food-effect on solifenacin oral suspension

Parameter	Geometric mean ratios (90% confidence interval)	
	Suspension/Tablet	Fed/Fasting on suspension
AUClast	80.35 (74.25, 86.95)	107.10 (98.98, 115.90)
AUC_{inf}	81.45 (75.45, 87.94)	107.26 (99.36, 115.79)
C_{max}	79.70 (73.73, 86.16)	87.52 (80.98, 94.59)

· Safety:
  - Solifenacin was well tolerated. Treatment-related AEs were experienced by 1 (4.5%) healthy volunteers following treatment with solifenacin tablet, 4 (17.4%) healthy volunteers following treatment with solifenacin suspension (fasting) and 2 (8.7%) healthy volunteers following treatment with solifenacin suspension (fed). Atrioventricular block, reported in 1 healthy volunteer, was considered possibly treatment-related but not serious, and resolved without treatment.

Sponsor's conclusions:

· The relative bioavailability of solifenacin suspension (1 mg/mL) dosed at 10 mg in the fasting state was approximately 80% of a 10 mg tablet dosed in the fasting state. The observed percent difference between tablet and suspension is not anticipated to have an adverse impact on future use of the formulation in the pediatric population.

· PK values were similar following a single 10 mg dose of solifenacin suspension administered under fasting and fed conditions, indicating no food effect on the PK profile of solifenacin suspension formulation.

Reviewer's comments:

· In this study, the bioavailability of Formulation A appeared to be relatively lower than that of VESIcare®. There is a discrepancy in the result of bioequivalence analysis between the current study and Study 905-CL-080. The AUC values of solifenacin following administration of Formulation A appeared to be relatively lower compared to those observed in Study 905-CL-080, although both studies used the same dose, 10 mg. It is noted that bioanalytical methods applied for each study were different in terms of calibration curve range and performance characteristics.

· High-fat meal tended to slightly decrease the C_{max} and increase the AUC of solifenacin with a delay of T_{max} by around 2 hours following administration of Formulation A, but their comparative statistical results (Fed/Fasting) met a BE acceptance criteria.

· The PK profile of Formulation A characterized from this study was used to establish the pediatric equivalent doses used in the phase 3 studies of pediatric patients with neurogenic detrusor overactivity.

Study identifier: 905-CL-075

Title: A multicenter, open-label, single ascending dose study to evaluate pharmacokinetics, safety and tolerability of solifenacin succinate suspension in pediatric patients aged 5 to 17 years (Inclusive) with overactive bladder

Objectives:

· Primary objective: To evaluate the pharmacokinetics (PK) of solifenacin succinate suspension after single-dose administration at different dose levels in children and adolescents with overactive bladder (OAB).

· Secondary objective: To evaluate the safety and tolerability of solifenacin succinate suspension after single-dose administration at different dose levels in children and adolescents with OAB.

Study Design:

· Multicenter, open-label, single ascending dose study in pediatric patients with OAB

· Study population: children (5 to 11 years) and adolescents (12 to 17 years) diagnosed as OAB according to the International Children's Continence Society (ICCS) criteria.

· Treatments: single dose administration at fasting state

- Weight-range adjusted doses to achieve plasma concentrations equivalent to exposures in adults (2.5, 5 or 10 mg once daily: 2.5, 5 and 10 pediatric equivalent dose, PED)

· The doses selected were based on the PK characteristics in adults and its extrapolation to the pediatric population using allometric scaling

· Multiplied by an accumulation factor of 3 to compensate for the difference between single-dose and multiple dose plasma concentrations

	PED2.5		PED5		PED10	
Pediatric weight range† (kg)	Pediatric equivalent dose (mg)	Actual single dose administered (mg)‡	Pediatric equivalent dose (mg)	Actual single dose administered (mg)‡	Pediatric equivalent dose (mg)	Actual single dose administered (mg)‡
14 – 20	0.67	2.0	1.32	4.0	2.67	8.0
21 – 31	1.00	3.0	2.00	6.0	4.00	12.0
32 – 50	1.47	4.4	3.00	9.0	6.00	18.0
51 – 70	2.25	6.8	4.47	13.4	9.00	27.0
> 70	2.47	7.4	5.00	15.0	10.00	30.0

- Treatment was administered using the following approach:
  Cohort 1: 2.5 PED to adolescents
  Cohort 2: 5 PED to adolescents and 2.5 PED to children
  Cohort 3: 10 PED to adolescents and 5 PED to children
  Cohort 4: 10 PED to children

· Formulation A was used.

· Blood sampling for PK study
  - Age 5-8 years: pre-dose, 2 to 4 hours (h), 6 to 8h, 96 to 106h (4 samples)
  - Age 9-11 years: pre-dose, 2 to 4h, 6 to 8h, 48 to 58h, 96 to 106h, 144 to 154h (6 samples)
  - Age 12-17 years: pre-dose, 2h, 3 to 4h, 6 to 8h, 48 to 58h, 96 to 106h, 144 to 154h (7 samples)
  - In addition to solifenacin, serum levels of α1–glycoprotein were also measured.

· Assay: a validated liquid chromatography-tandem mass spectrometry method

· Population PK analysis using nonlinear mixed effects modeling technique using the program NONMEM (version 7.2.0)

· Safety evaluation
  - Physical examination, vital signs, adverse events, clinical laboratories, ECG and post void residual volume

Results:

· Disposition of subjects:

	Children (5 to 12 years)			Adolescent (13 to 18 years)			Total (n=42)
Dose	2.5 mg	5.0 mg	10.0 mg	2.5 mg	5.0 mg	10.0 mg	

N (Male:Female)	8 (4:4)	8 (6:2)	6 (4:2)	6 (0:6)	6 (2:4))	8 (3:5)	42 (19:23)
Age median (range)	8 (6-11)	6.5 (5-10)	7 (7-9)	13 (12-15)	14.5 (12-16)	12 (12-17)	10.5 (5-17)
Weight at day 1 (kg) median (range)	22.7 (21.5 -63.3)	25.3 (16.8-44.5)	23.0 (21.0-41.2)	52.05 (33.5-73.4)	60.7 (36.0-73.9)	54.5 (40.5-66.3)	40.85 (16.8-73.9)

· PK results: refer to section 4.2.2.

· Safety
  - Of the 42 patients, 9 (21.4%) experienced treatment emergent adverse events (TEAEs): In the adolescent subjects, 2/6 (33.3%) at the 5.0 mg dose and 2/8 (25.0%) at the 10.0 mg dose; in the children subjects, 3/8 (37.5%) at the 2.5 mg dose, 1/8 (12.5%) at the 5.0 mg dose, and 1/6 (16.7%) at the 10.0 mg dose.
  - All TEAEs were mild in severity. None of the TEAEs were considered to be serious adverse events and most of the events resolved without sequelae. No TEAE by individual preferred term occurred in more than 1 patient each of the two groups.
  - Overall, at least 1 AE judged to be related to study drug occurred in 5/42 (11.9%) of patients following treatment with solifenacin succinate suspension. Two patients (25.0%) in the adolescent 10.0 mg group, and 1 patient each in the adolescent 5.0 mg (1/6, 16.7%), children 5.0 mg (1/8, 12.5%) and children 10.0 mg (1/6, 16.7%) groups experienced at least 1 drug-related AE. Two patients (2/42, 4.8%) experienced gastrointestinal disorders; individual AEs by preferred term were each experienced by 1 patient.

Sponsor's conclusions:

· Solifenacin succinate exposure increased proportionally to dose in the dose range of PED 2.5 mg to PED 10 mg. No clear differences were observed in exposure between adolescents and children.

· Solifenacin succinate suspension appeared safe and well tolerated at all doses. There were no dose dependent increases in the number and severity of TEAEs in either age group. The results suggest that the safety profile of solifenacin succinate suspension in children and adolescents is consistent with the established safety profile of the tablet formulation in adults and is suitable for multi-dose clinical studies in pediatric patients.

Reviewer's comments:

· This trial is a single dose PK study using Formulation A (i.e., the old oral suspension formulation) performed in pediatric patients with OAB prior to that in pediatric patients with NDO. Weight-range adjusted doses applied in this study were selected based on extrapolation of the PK characteristics in adults to the pediatric population using allometric scaling.

· PK simulation based on a population PK modeling analysis using concentration data from this study were used as the basis to establish the pediatric equivalent doses used in the phase 3 studies of pediatric patients with neurogenic detrusor overactivity.

<u>Study identifier: 905-CL-079</u>

Title: A multicenter, open-label, single ascending dose study to evaluate pharmacokinetics, safety and tolerability of solifenacin succinate suspension in pediatric patients aged 5 to less than 18 years with neurogenic detrusor overactivity (NDO)

Objectives:

· Primary objective: To evaluate the pharmacokinetics (PK) of solifenacin succinate suspension after single-dose administration in children and adolescents with NDO.
· Secondary objective: To evaluate the safety and tolerability of solifenacin succinate suspension after single-dose administration in children and adolescents with NDO.

Study Design:
· Multicenter, open-label, single ascending dose study in pediatric patients with NDO
· Study population: children (5 to less than 12 years) and adolescents (12 to less than 18 years) diagnosed as NDO by urodynamics
· Treatments: single dose administration at fasting state
- Weight-range based doses predicted to target exposure of solifenacin equivalent to 5 mg once daily in adults at steady state (PED5).
· The doses selected were based on the PK characteristics in adults and its extrapolation to the pediatric population using allometric scaling
· Multiplied by an accumulation factor of 3 to compensate for the difference between single-dose and multiple dose plasma concentrations

Weight Range (kg)	PED 5 (mg)	Actual Dose Administered, (mg†)
14-20	1.32	4.0
21-31	2.00	6.0
32-50	3.00	9.0
51-70	4.47	13.4
>70	5.00	15.0

· Formulation B was used.
· Blood sampling for PK study
  - 5 to less than 9 years of age: pre-dose, 2h to 4h, 6h to 8h, 96h to 106h after dosing or pre-dose, 3h, 7h, 98h after dosing (4 samples)
  - 9 to less than 12 years of age: pre-dose, 2h to 4h, 6h to 8h, 48h to 58h, 96h to 106h, 144h to 154h after dosing or pre-dose, 3h, 7h, 50h, 98h, 146h after dosing (6 samples)
  - 12 to less than 18 years of age: pre-dose, 2h, 3h to 4h, 6h to 8h, 48h to 58h, 96h to 106h, 144h to 154h after dosing or pre-dose, 2h, 3.5h, 7h, 50h, 98h, 146h after dosing (7 samples)
  - In addition to solifenacin, serum levels of α1−glycoprotein were also measured.
· Assay: a validated liquid chromatography-tandem mass spectrometry method
· Population PK analysis using nonlinear mixed effects modeling technique using the program NONMEM (version 7.2.0)
· Safety evaluation: Physical examination, vital signs, adverse events (AE), clinical laboratories, ECG and post void residual volume

Results:
· Disposition of subjects:

	Children (5 to less than 12 years)	Adolescent (12 to less than 18 years)	Total (n=42)
N (Male:Female)	7 (4:3)	7 (3:4)	14 (7:7)
Age: median (range)	9 (6-11)	14 (12-17)	11.5 (6-17)
Weight at day 1 (kg) median (range)	31.0 (16.0 -42.0)	60.0 (33.0-65.0)	39.0 (16.0-65.0)

· PK results: refer to section 4.2.2.
· Safety
  - Five AEs were reported in 2 patients (28.6%) in the adolescent group. No SAEs were reported and none of the patients discontinued the study due to an AE.

- None of the treatment emergent adverse events (TEAEs) were judged by the investigator to be related to the study drug. The investigator assessed the cause of the anxiety AEs as fear/concerns associated with venipuncture and blood draws. There were no drug-related TEAEs reported during this study.

Sponsor's conclusions:

· Based on an assessment of results from this study in NDO patients as compared to previous data in a pediatric OAB population (study 905-CL-075), the pharmacokinetics of solifenacin for pediatric OAB and NDO patients are comparable.
· There were no consistent changes in laboratory evaluations, although low serum creatinine values were observed in the majority of patients, which was attributed to the lower muscle mass in NDO patients.

Reviewer's comments:

· This single dose PK study used Formulation B (the final oral suspension formulation) and was performed in pediatric patients with NDO aged 5 years and older. Weight-range adjusted doses applied in this study were selected based on extrapolation of the PK characteristics in adults to the pediatric population using allometric scaling, which is same as the dosing table used in Study 905-CL-075.
· When PK results from the current study are compared to the PK data in an OAB population (Study 905-CL-075), the PK of solifenacin between the two pediatric patient populations appears to be comparable. The dosing table used in two phase 3 trials of pediatric patients with NDO was developed based on the PK model built up for pediatric patients with OAB from Study 905-CL-075. The PK comparability between two patient populations from Studies 905-CL-075 and 905-CL-079 is supportive of the dosing table applied in the phase 3 trials of pediatric patients with NDO developed using the PK model for pediatric patients with OAB.
· PK results were compared between Study 905-CL-079 (fasting state) and Study 905-CL-047 (administered without regard to food). As the CL/F values in children and in adolescents between the two studies were comparable, food intake is not expected to significantly affect the exposure of solifenacin following administration of Formulation B.

Study identifier: 905-CL-047

Title: 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)

Objectives:

· To evaluate the long-term efficacy, safety and pharmacokinetics (PK) of solifenacin oral suspension after multiple dose administration.

Study Design:

· Open-label, baseline-controlled, multicenter, sequential study
· Pediatric patients with NDO aged 5 years to < 18 years old
· Treatments:
  - Dose regimen: The population pediatric PK model of the data from Study 905-CL-075 and the two relative bioavailability studies (Study 905-CL-066 and 905-CL-080) in adults were used for determining the allometric-scaling based doses in patients aged 5 years to < 18 years. Doses were calculated according to weight, in ranges, targeting equivalent exposure to the 2.5, 5, 7.5 and 10 mg doses in adults at steady state.

Weight (kg)	PED2.5 (mg)	PED5† (mg)	PED7.5 (mg)	PED10 (mg)
< 14	0.6	1.4	2.2	2.8
14 - 20‡	1.0	1.8	2.8	3.6
21 - 31‡	1.2	2.6	3.8	5.2
32 - 50‡	1.8	3.4	5.2	7.0
51 - 69	2.2	4.6	6.8	9.0
> 69	2.4	5.0	7.4	10.0

  - Sequential doses for 12 weeks (titration period) were administered to determine each patient's optimal dose. The initial dose was PED5. During the titration period, doses could be up- or down-titrated every 3 weeks. Decision for titration: urodynamic assessment, the 7-day micturition diary and adverse events
  - A fixed dose of solifenacin oral suspension after titration period was given for at least 40 weeks.
  - Subjects took study drug without regards to food and drink intake except for those that could interact with circulatory, gastrointestinal, liver or renal function.
· Procedure schedule
  - Visit 1 (week -5): screening up to 21 days before visit 2.
  - Visit 2 (day -14): start of the washout of previous NDO medications and completion of a 7-day micturition diary in the week before visit 2 and before all the next visits
  - Visit 3 (day -1): baseline and start of the dose titration period
  - Visit 4 (week 3): opportunity to up- or down-titrate the treatment
  - Visit 5 (week 6): opportunity to up- or down-titrate the treatment
  - Visit 6 (week 9): opportunity to up- or down-titrate the treatment
  - Visit 7 (week 12): opportunity to up- or down-titrate the treatment, potential PK visit, start of the fixed-dose assessment period
  - Visit 8 (week 24): urodynamic assessment for efficacy endpoints, potential PK visit, adjustment of dose volume due to weight change
  - Visit 9 (week 36): fixed-dose assessment period continued, potential PK visit
  - Visit 10 (week 52): End of study visit
· Efficacy
  - Primary efficacy variable: the change from baseline in maximum cystometric capacity (MCC) using urodynamic testing after 24 weeks of treatment.

- Secondary efficacy variables: the change from baseline to the assessment for the last possible titration step of the other urodynamic outcomes (MCC, bladder compliance, expected bladder capacity, bladder volume and so on) at week 24 and week 52 (optional) and changes from baseline of variables based on diary (week 3 up to week 52)

· PK study
- Blood samples were collected at 4 different times when the patient had reached steady-state at their optimal dose: within 3 hours prior to dosing (trough level) and 1 to 3 hours, 4 to 6 hours and 7 to 10 hours post dose.
- The four blood samples were collected either at 1 visit, or spread over 2 visits. Samples could be taken at visit 7 (week 12), visit 8 (week 24) and/or visit 9 (week 36). For a patient whose final dose-titration occurred at visit 7 (week 12), pharmacokinetic sampling was not undertaken until visit 8 (week 24) or later.
- Assay: a validated liquid chromatography - tandem mass spectrometry method
- Population PK analysis using nonlinear mixed effects modeling technique using the program NONMEM (version 7.3)

· Safety evaluation
- Adverse events, laboratory assessments, vital signs, physical examination, ECG, pregnancies, cognitive testing, ocular accommodation assessment and ultrasound of the upper urinary tract

Results:

· Subject disposition:

	Children (5 years to < 12 years)	Adolescent (12 years to < 18 years)	Total (5 years to < 18 years)
Screen	47	45	92
12-week titration period	42	34	76
40-week fixed-dose assessment period	33	29	62
Completion of study	31	27	58

· The number of subjects included in each data analysis set:

	Children	Adolescent	Total
Safety analysis set	42	34	76
Full analysis set	27	28	55
Per protocol set	18	21	39
PK analysis set	40	33	73

· Summary of demographics (safety analysis set)

	Children	Adolescent	Total
N (male:female)	42 (20:22)	34 (17:17)	76 (37:39)
Median age (range)	8 (8-11)	14 (12-17)	11 (5-17)
Median weight (range)	26.2 (15.0-53.7)	48.5 (32.0-83.2)	34.6 (15.0-83.2)
Race W:BA:A:AI:other* (percentage)	22:1:17:0:2 (52.4:2.4:40.5:0:4.8)	23:1:6:1:3 (67.6:2.9:17.6:2.9:8.8)	45:2:23:1:5 (59.2:2.6:30.3:1.3:6.6)

*W:BA:A:AI:other = White: Black/African American: Asian: American Indian: other

· Dose titration: Most of the patients were up-titrated to PED7.5 (14.5%) or PED10 (53.9%) during the treatment period. The majority of doses was up-titrated until week 12 and then remained on the same

dose until week 52. The optimal dose for most patients was PED10 (57.9% at week 12). There was no apparent difference in optimal dose between the age groups.

· Efficacy results:

Table 1. Change from baseline to Week 24 in MCC (mL) (Full analysis set)

	Children		Adolescent		Total	
	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24
MCC (mL)						
n	27	24	28	25	55	49
Mean (SD)	157 (92.0)	212 (104)	288 (136)	344 (114)	224 (133)	279 (127)
Change from baseline						
n	NA	24	NA	25	NA	49
Mean (SD)		59.9 (93.0)		54.6 (122)		57.2 (108)
95% CI		20.7, 99.2		4.2, 105		26.3, 88.1
P-value		0.004		0.035		< 0.001

Table 2. Summary of MCC (mL) up to week 52 in full analysis set

	Visit			
	Baseline	Week 12	Week 24	Week 52
N	55	34	49	42
Mean (SD)	224 (133)	258 (110)	279 (127)	268 (104)
Change from baseline				
Mean (SD)	NA	56.4 (87.6)	57.2 (108)	51.0 (103)

- After 24 weeks of treatment, there was a statistically significant improvement from baseline in most secondary endpoints.
- Results of the analyses of the urodynamic and the diary endpoints were consistent.
- Efficacy was sustained during the 52 weeks of treatment.

· Safety

- Treatment emergent adverse events (TEAEs) were reported by 51 (67.1%) patients (28 children and 23 adolescents). Drug-related TEAEs were reported in 15 (19.7%) patients (9 children and 6 adolescents). Serious TEAEs were reported in 7 (9.2%) patients (2 children and 5 adolescents).
- The most reported TEAEs were urinary tract infection (UTI) (31.6% patients) and constipation (7.9% patients). TEAEs reported were similar between the age groups. TEAEs were mostly mild (31 [40.8%] patients) or moderate in intensity (17 [22.4%] patients). There were 3 severe TEAEs (toxic megacolon, dengue fever and UTI bacterial).
- The most common system organ class (SOC_ for drug-related TEAEs was gastrointestinal disorder (11.8% of all patients). The most commonly reported drug-related TEAEs were constipation (7.9% of all patients) and ECG QT prolonged (3.9%). All drug-related TEAEs were either mild (10 [13.2%] patients) or moderate (5 [6.6%] patients). The proportion of patients who experienced drug-related TEAEs was similar between the age groups.
- Overall, 2 children and 2 adolescents reported a TEAE that resulted in treatment discontinuation. The only reported TEAE that resulted in treatment discontinuation was ECG QT prolonged. The TEAEs leading to permanent discontinuation reported in 3 patients (2 children and 1 adolescent) were considered by the investigator to be related to the study drug.

· Assay: Assay performance was assessed using quality control samples ranged from 0.6 to 150 ng/mL. Inter-run accuracy (-4.2% - 1.8%) and precision (3.7% - 6.1%) were within the Agency's acceptance criteria. A total of 25 samples (10.3% of total number of plasma samples) were analyzed as incurred

sample repeats (ISR). Twenty four of 25 ISR samples (96%) passed the ISR criteria (within 20% of reported concentration).

- PK results: refer to section 4.2.2.

Sponsor's conclusions:

- In pediatric patients with NDO, aged 5 year to < 18 years, during the 12-week titration period, optimal patient doses were achieved; equivalent to the doses of 2.5, 5, 7.5 or 10 mg (PED2.5, PED5, PED7.5, PED10, respectively) in adults.
- After 24 weeks of treatment, a statistically significant increase in MCC (primary endpoint) compared with baseline was observed, demonstrating that solifenacin oral suspension increases functional bladder capacity. This finding is supported by statistically significant improvements in key secondary urodynamic endpoints, including increases in bladder compliance and bladder volume until the first overactive detrusor contraction, and a decrease in the number overactive detrusor contractions. Diary endpoints also showed a statistically significant improvement after 24 weeks of solifenacin oral suspension treatment.
- The majority of TEAEs were mild or moderate in severity. The most reported TEAE was UTI. The observed incidence of UTIs is consistent with the known incidence of UTIs in pediatric patients practicing clean intermittent catheterization. The cardiovascular profile of solifenacin in pediatric patients with NDO aged 5 years to < 18 years of age appears to be safe. There were no clinically relevant changes in QTcB or other ECG parameters. Solifenacin oral suspension did not have any effect on cognitive function or ocular accommodation.
- Solifenacin oral suspension is effective, safe and well-tolerated in pediatric patients with NDO aged 5 years to < 18 years. The efficacy and safety profiles support a positive benefit versus risk profile of solifenacin oral suspension in the pediatric NDO population.

Reviewer's comments:

- This study was to evaluate efficacy and safety of solifenacin succinate oral suspension in pediatric patients with NDO aged 5 years and older. Weight-range adjusted doses applied in this study was determined based on the population pediatric PK model established from Study 905-CL-075 in pediatric patients with OAB and the two relative BA studies (Studies 905-CL-066 and 905-CL-080) in adults.
- In general, urodynamic endpoints and secondary endpoints based on diary showed significant improvement from baseline. The effectiveness sustained during the 52 weeks of treatment. The optimal dose for most patients appeared to be PED 7.5 or PED10 up-titrated from PED 5.
- Four subjects were discontinued due to a TEAE of ECG QT prolongation. The baseline QTc in those patients was calculated from one-time measure. However, there was no further discontinuation case since baseline QTc was captured from two-time measure.
- The PK of solifenacin at steady-state following administration of solifenacin succinate oral suspension in these pediatric patients was characterized based on population PK approaches using concentration data from the current study. The dose-normalized exposures based on estimated PK parameters of solifenacin appeared to be not significantly different between the two age groups, children (5 to < 12 Years) and adolescents (5 to < 12 Years).

Study identifier: 905-CL-074

Title: 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 less than 5 years of age with neurogenic detrusor overactivity (NDO)

Objectives:

· To evaluate the long-term efficacy, safety and pharmacokinetics (PK) of solifenacin suspension after multiple dose administration.

Study Design:

· Open-label, baseline-controlled, multicenter study for 12 months

· Pediatric patients with NDO aged 6 months to < 5 years old (The lower age limit for patients enrolled under initial protocol was 2 years due to a toxicological issue. Children aged < 2 years were enrolled under Protocol version 4.0 and 4.1 after it was concluded that children of that age could be safely included in the study).

· Treatments:

- Initial dose regimen: The population pediatric PK model of the data from Study 905-CL-075 and the two relative bioavailability studies (Study 905-CL-066 and 905-CL-080) in adults were used for determining the allometric-scaling based doses in patients aged 2 years to < 5 years. Doses were calculated according to weight, in ranges, targeting equivalent exposure to the 2.5, 5, 7.5 and 10 mg doses in adults at steady state.

Weight range (kg)	PED2.5† (mg)	PED5†‡ (mg)	PED7.5† (mg)	PED10† (mg)
10 - 12	0.6	1.2	1.8	2.6
13 - 17	0.8	1.6	2.4	3.2
18 - 23	1.0	2.0	3.0	4.2
24 - 30	1.2	2.6	3.8	5.0

- Changed dose regimen (Protocol version 4, dated 24 Jun 2014): the model used to select the drug dose was updated to a PBPK model to account for age-related physiological changes (maturation in clearance and distribution processes) in clearance and distribution processes. This model was calibrated to extensive adult PK data and to data from children (aged > 5 years old) with OAB and children with NDO. This new PBPK model was used to estimate the daily PEDs of NDO patients aged 6 months to < 5 years old.
- Patients enrolled under the initial regimen were allowed to transition to the higher volumes permitted by the changed regimen in their same weight range at visit 5 (week 9) or visit 8 (week 36) if they had not achieved sufficient efficacy with the maximum allowable PED volume in the allometric dosing table.
- In addition, lower weight limit was decreased from 10 kg to 6 kg due to a direct consequence of change in the lower age limit (from 2 years to 6 months).

Weight range (kg)	PED2.5†‡ (mg)	PED5† (mg)	PED7.5† (mg)	PED10† (mg)
6.0 to 7.9	0.8	1.6	2.4	3.2
8.0 to 9.9	0.9	1.8	2.6	3.6
10 to 12.4	1.0	2.0	3.0	4.2
12.5 to 17.4	1.2	2.4	3.6	4.8
17.5 to 23.4	1.3	2.6	3.8	5.2
23.5 to 30.0	1.4	2.8	4.4	5.8

- Titration period for 12 weeks were administered to determine each patient's optimal dose. Under protocol version 1.1 (dated February 12, 2013), the initial dose was PED5. For patients enrolled under Protocol version 4.0, the initial dose administered was PED2.5 given once daily. During the titration

period, doses could be up- or down-titrated every 3 weeks. Decision for titration: diary endpoints, urodynamic assessment and adverse events
  - A fixed dose of solifenacin oral suspension after titration period was given for at least 40 weeks.
  - Patients enrolled under Protocol version 1.1 (dated 12 Feb 2013) were allowed to transition to the higher volumes permitted by the PBPK table in their same weight range at visit 5 (week 9) or visit 8 (week 36) if they had not achieved sufficient efficacy with the maximum allowable PED volume in the allometric dosing table.
  - Subjects took study drug without regards to food and drink intake except for consuming grapefruit or Seville orange products during the study. Xanthine or caffeine-containing food such as chocolate milk and chocolate were not to be taken on the visit days.
- Procedure schedule
  - Visit 1 (week -4): screening up to 28 days before visit 2.
  - Visit 2 (day -1): baseline and start of the dose titration period
  - Visit 3 (week 3): opportunity to up- or down-titrate the treatment
  - Visit 3 (week 6): opportunity to up- or down-titrate the treatment
  - Visit 5 (week 9): opportunity to up- or down-titrate the treatment
  - Visit 6 (week 12): opportunity to up- or down-titrate the treatment and PK visit
  - Visit 7 (week 24): start of the fixed-dose assessment period, PK visit
  - Visit 8 (week 36): fixed-dose assessment period continued, PK visit
  - Visit 9 (week 52): End of study visit
- Efficacy
  - Primary efficacy variable: the change from baseline in maximum cystometric capacity (MCC) using urodynamic testing after 24 weeks of treatment.
  - Secondary efficacy variables

    1) Urodynamic assessment: the change from baseline to optimal dose at steady state, to week 24, and week 52 (option) of the other urodynamic outcomes (MCC, bladder compliance, detrusor pressure, catheterized volume, bladder volume and so on)

    2) Diary: change from baseline to each visit up to week 52 (catheterized volume, maximum catheterization volume [MCV], incidence of catheterization and incontinence and so on)

    3) The Infant and Toddler Quality of Life Short Form-47 questionnaire
- PK study
  - Blood samples: Four samples for pharmacokinetic analysis were required. In order to allow for flexibility in the duration of the study visits in which blood samples for pharmacokinetic analysis were collected, blood draws were done in a single visit or on multiple visits. For patients with a weight < 10 kg, collection of 1 to 4 of the total number of PK samples required could only be made at visit 6 (week 12) and/or visit 8 (week 36). For patients with a weight ≥ 10 kg, collection of 1 to 4 PK samples could be taken on visit 6 (week 12), visit 7 (week 24) and/or visit 8 (week 36). These were taken under steady state conditions within 3 hours before dosing, 1 to 3 hours, 4 to 6 hours and 7 to 10 hours after study dose intake.
  - Assay: a validated liquid chromatography - tandem mass spectrometry method
  - Population PK analysis using nonlinear mixed effects modeling technique using the program NONMEM (version 7.3)
- Safety evaluation
  - Adverse events, laboratory assessments, vital signs, physical examination, ECG, pregnancies, cognitive testing, ocular accommodation assessment and ultrasound of the upper urinary tract

Results:

- Subject disposition: A total of 24 children were screened and 23 were enrolled (4 children aged 6 months to < 2 years old and 19 children aged 2 years to < 5 years old. The number of subjects included

in each data analysis set was 23 for safety analysis set, 22 for full analysis set, 19 for per protocol set, 21 for PK analysis set.

· Summary of demographics (safety analysis set)

N (male:female)	23 (9:14)
Median age (range)	36 months (13.0-58.9 months)
Median weight (range)	13.0 kg (8.8-20.3 kg)
Race (W:BA:A:AI:other percentage)*	12:0:11 (52.2:0:47.8%)

*W:BA:A = White: Black/African American: Asian

· Dose titration: Most of the patients were up-titrated to PED7.5 (26.1%) or PED10 (60.9%) during the treatment period. The PED for all but 1 patient remained the same from week 12 until week 52. The dose for 1 child was up-titrated at week 24. The optimal dose for most patients (14 [60.9%] patients) was PED10.

· Efficacy results:

Table 1. Change from baseline to Week 24 in MCC (mL) (Full analysis set)

	Children	
	Baseline	Week 24
n	21	21
Mean (SD)	92.3 (38.2)	129 (40.2)
Change from baseline		
n	NA	21
Mean (SD)		37.0 (35.9)
95% CI		20.7, 53.4
P-value		< 0.001

Table 2. Summary of MCC (mL) up to week 52 in full analysis set

	Visit			
	Baseline	Week 12	Week 24	Week 52
n	21	16	21	14
Mean (SD)	92.3 (38.2)	124 (46.2)	129 (40.2)	148 (45.8)
Change from baseline				
Mean (SD)	NA	40.2 (37.9)	37.0 (35.9)	58.6 (34.1)

- After 24 weeks of treatment, solifenacin-treated children had a statistically significant improvement in most secondary endpoints.
- The observed increases in catheterized volume parameters and decrease in incontinence were consistent with the observed improvements in the urodynamic parameters and reflect a positive treatment response.
- Results of the analyses of the urodynamic and the diary endpoints were consistent.
- After 52 weeks of treatment, the changes from baseline in primary and secondary endpoints were greater or similar to the changes from baseline observed at week 24.

· Safety

- Treatment emergent adverse events (TEAEs) were reported by 14 (60.9%) children (4 children aged 6 months to < 2 years and 10 children aged 2 years to < 5 years). Drug-related TEAEs were reported in 4 (17.4%) children (2 aged 6 months to < 2 years old and 2 aged 2 years to < 5 years old). Serious

TEAEs were reported in 3 (13.0%) children (2 children aged 6 months to < 2 years and 1 child aged 2 years to < 5 years old).

- The system organ classes (SOCs) for which most patients reported TEAEs were infections and infestations (47.8% of all patients) and gastrointestinal disorders (21.7% of all patients). The most reported TEAEs were UTIs (26.1% of all patients), nasopharyngitis (17.4% of all patients), and upper respiratory tract infection (13%). These TEAEs were expected as urinary tract infections (UTIs) are commonly reported in patients performing clean intermittent catheterizations and nasopharyngitis and upper respiratory tract infections are common community acquired infections. TEAEs were mostly mild (8 [34.8%] children) or moderate in intensity (5 [21.7%] children). The only severe TEAE reported was severe dental caries in a female child aged 2 years to < 5 years old which was not related to the study drug.
- The most common SOC for drug-related TEAEs was gastrointestinal disorders (13.0% of all patients). The most commonly reported drug-related TEAEs were constipation (8.7% of all patients) and dry mouth (8.7%). All drug-related TEAEs were mild in intensity.

· Assay: Assay performance was assessed using quality control samples ranged from 0.6 to 150 ng/mL. Inter-run accuracy (-2.3% - 4.5%) and precision (3.4% - 7.4%) were within the Agency's acceptance criteria. A total of 9 samples (11.1% of total number of plasma samples) were analyzed as incurred sample repeats (ISR). Eight out of 9 ISR samples (88.9%) passed the ISR criteria (within 20% of reported concentration).

· PK results: refer to section 4.2.2.

Sponsor's conclusions:

· Solifenacin demonstrated efficacy on the primary endpoint in children with NDO which was supported by positive findings in sensitivity analyses and the majority of secondary endpoints. The improvements in urodynamic and diary efficacy parameters demonstrate that the treatment aims of reducing bladder pressure during filling and reducing the incidence of incontinence by increasing bladder capacity were achieved. Solifenacin appears to be safe and well-tolerated in the pediatric NDO patient population aged 6 months to < 5 years old. This observation together with the relatively low incidence of typical antimuscarinic AEs supports a positive benefit versus risk profile of solifenacin in the pediatric NDO population.

Reviewer's comments:

· This study was to evaluate efficacy and safety of solifenacin succinate oral suspension in pediatric patients with NDO aged 6 months to < 5 years old. Initial weight-range adjusted doses applied in this study were determined based on the population pediatric PK model established from Study 905-CL-075 in pediatric patients with OAB and the two relative BA studies (Studies 905-CL-066 and 905-CL-080) in adults (i.e., same as used in Study-CL-047). However, dose regimen during the trial was updated based on a PBPK model to account for age-related physiological changes. The dose increased slightly compared to the prior dosing table. In addition, lower weight limit was also decreased from 10 kg to 6 kg because the age limit was lowered from 2 years to 6 months.

· In general, urodynamic endpoints and secondary endpoints based on diary showed significant improvement from baseline. The effectiveness sustained during the 52 weeks of treatment. The optimal dose for most patients appeared to be PED 7.5 or PED10 up-titrated from PED 5.

· Baseline QTc was measured from two-time measure. There was no discontinuation case due to a QT prolongation event.

· The PK of solifenacin at steady-state following administration of solifenacin succinate oral suspension in these pediatric patients was characterized based on population PK approaches using concentration

data from the current study. The dose-normalized exposure based on estimated PK parameters of solifenacin in this age group (< 5 years old, AUC_{tau}/Dose: median = 204.6 and range = 97.0 – 559.7 ng·h/mL/mg) appeared to be relatively higher than that in the older groups, children (5 to < 12 years, AUC_{tau}/Dose: median = 140.5 and range = 50.7 – 385.8 ng·h/mL/mg) and adolescents (12 to < 18 years, AUC_{tau}/Dose: median = 121.8 and range = 48.1 – 421.7 ng·h/mL/mg), from Study 905-CL-047. However, elimination half-life tended to be shorter in the younger children group (median = 18.31 hours and range = 11.40-29.61 hours) than the older children group (median = 30.68 hours and range = 3.86-104 hours).

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