OFFICE OF CLINICAL PHARMACOLOGY REVIEW

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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	(b) (4)
Applicant	Astellas Pharma US, Inc.
Associated IND	IND 058135
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Reference ID: 4135817

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*). (b) (4)

(b) (4) 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.

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1.1 Recommendations

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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.

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1.2 Post-Marketing Requirement and Commitment

(b) (4)

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

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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. (b) (4)

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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. (b) (4)

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

(b) (4)

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).

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, 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 (b) (4) 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?

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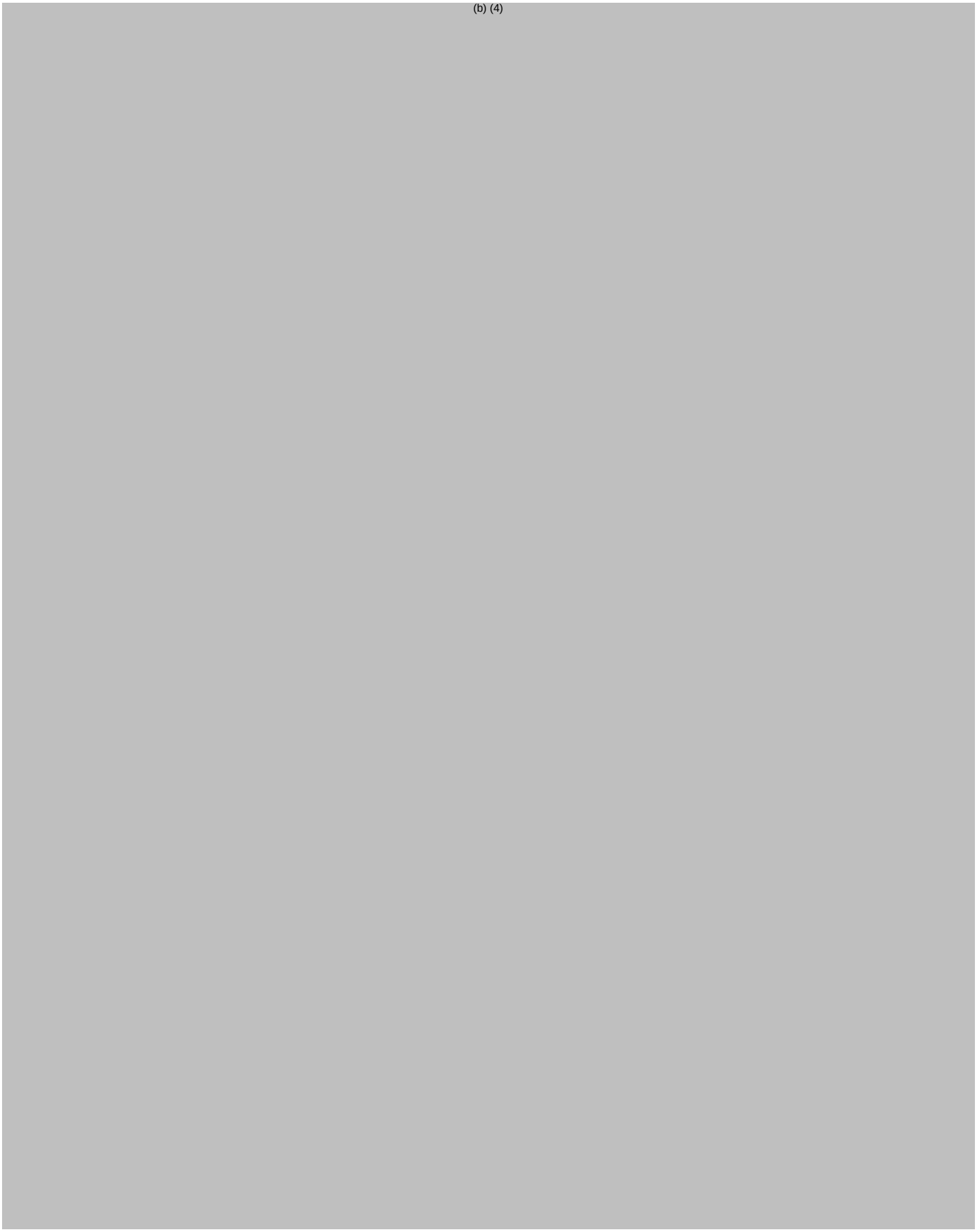
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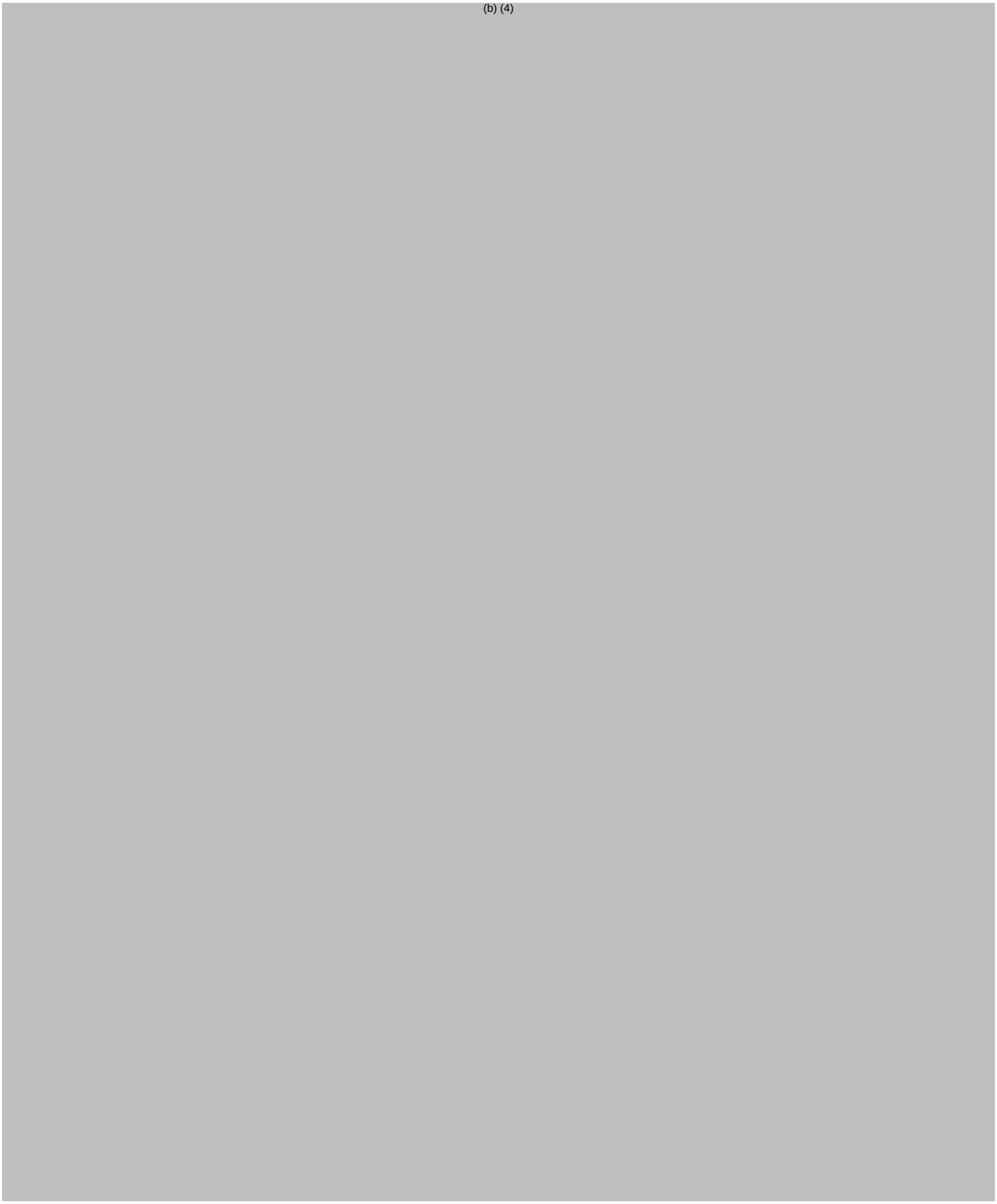
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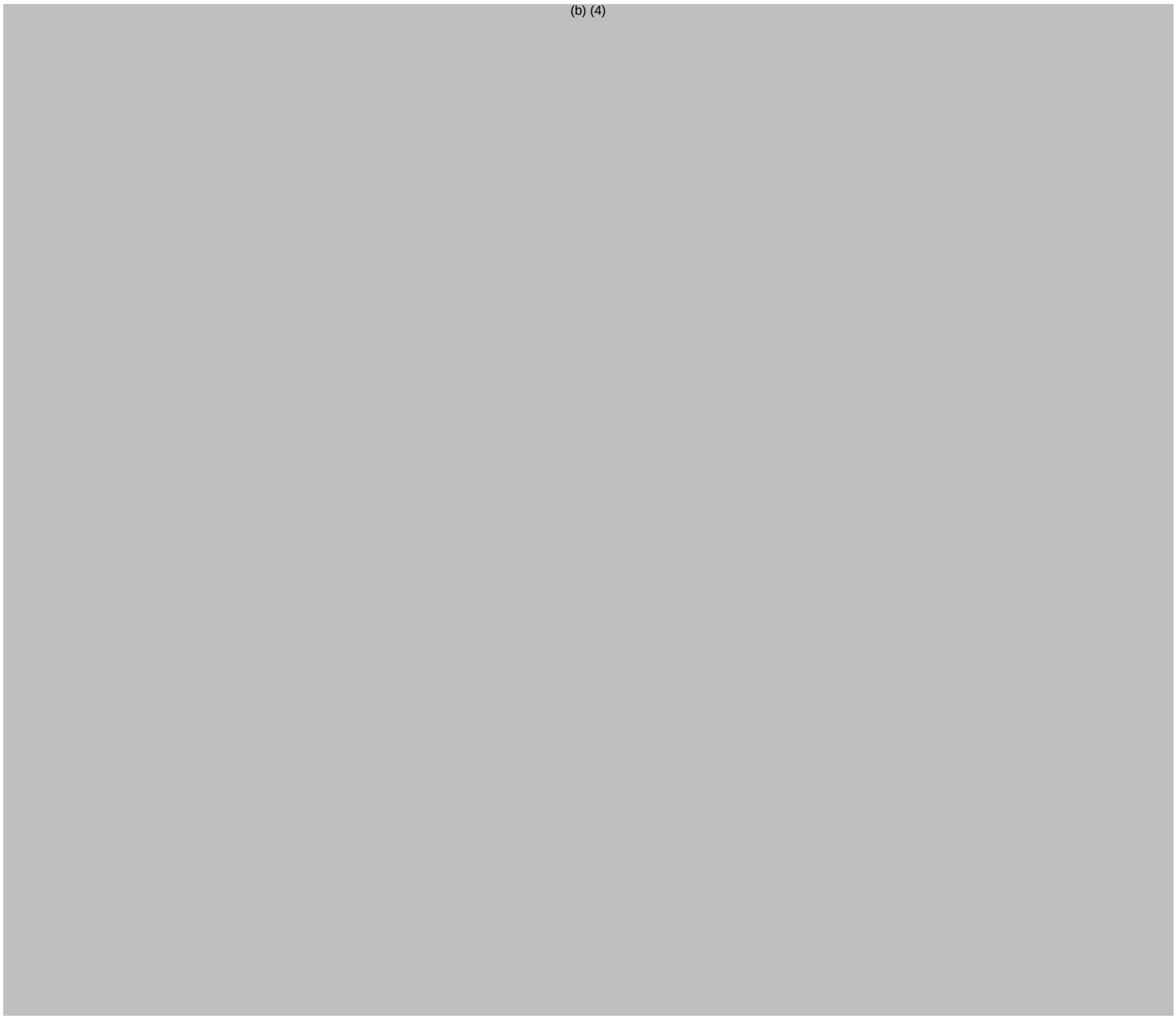

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

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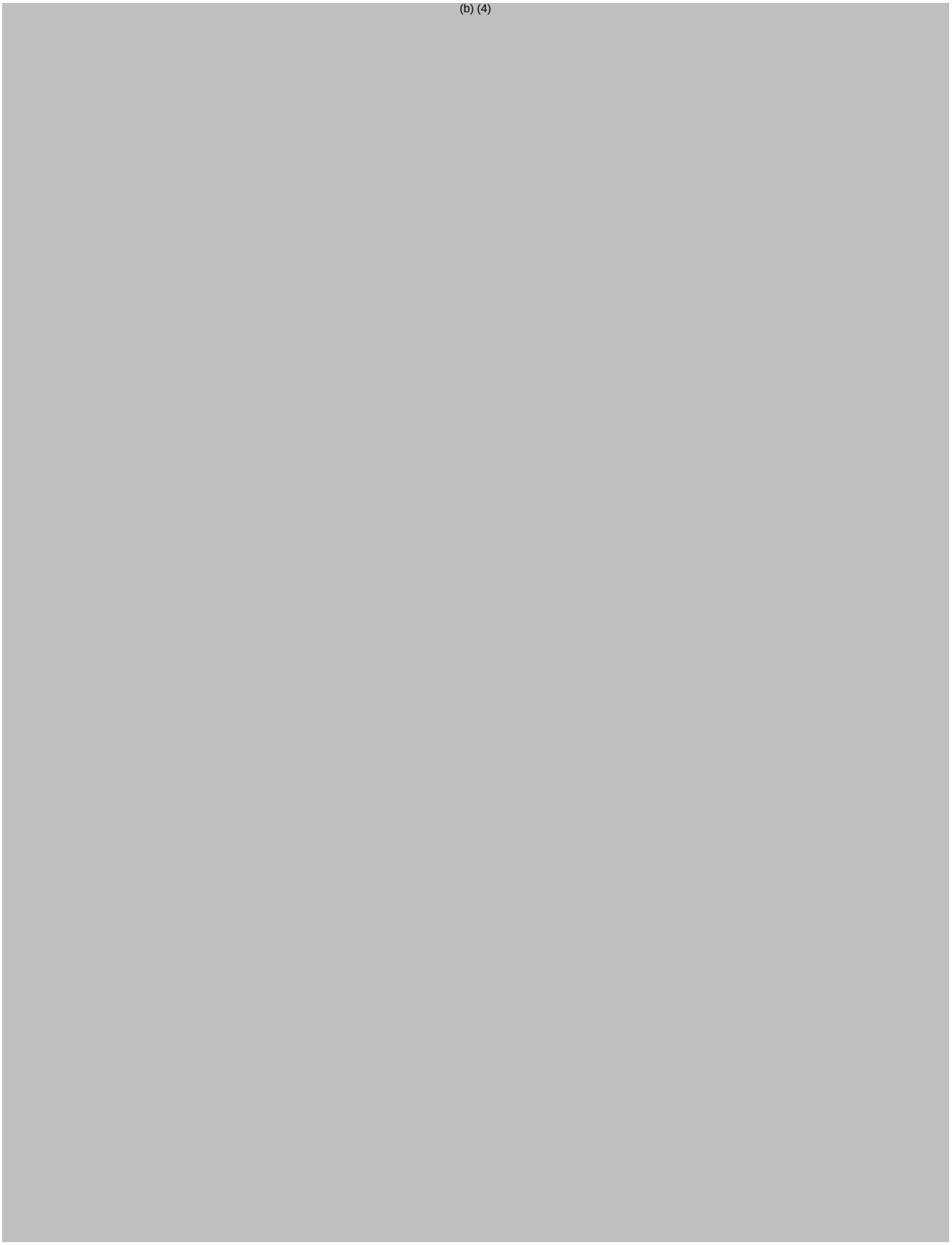
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3.3.4 Are there any clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

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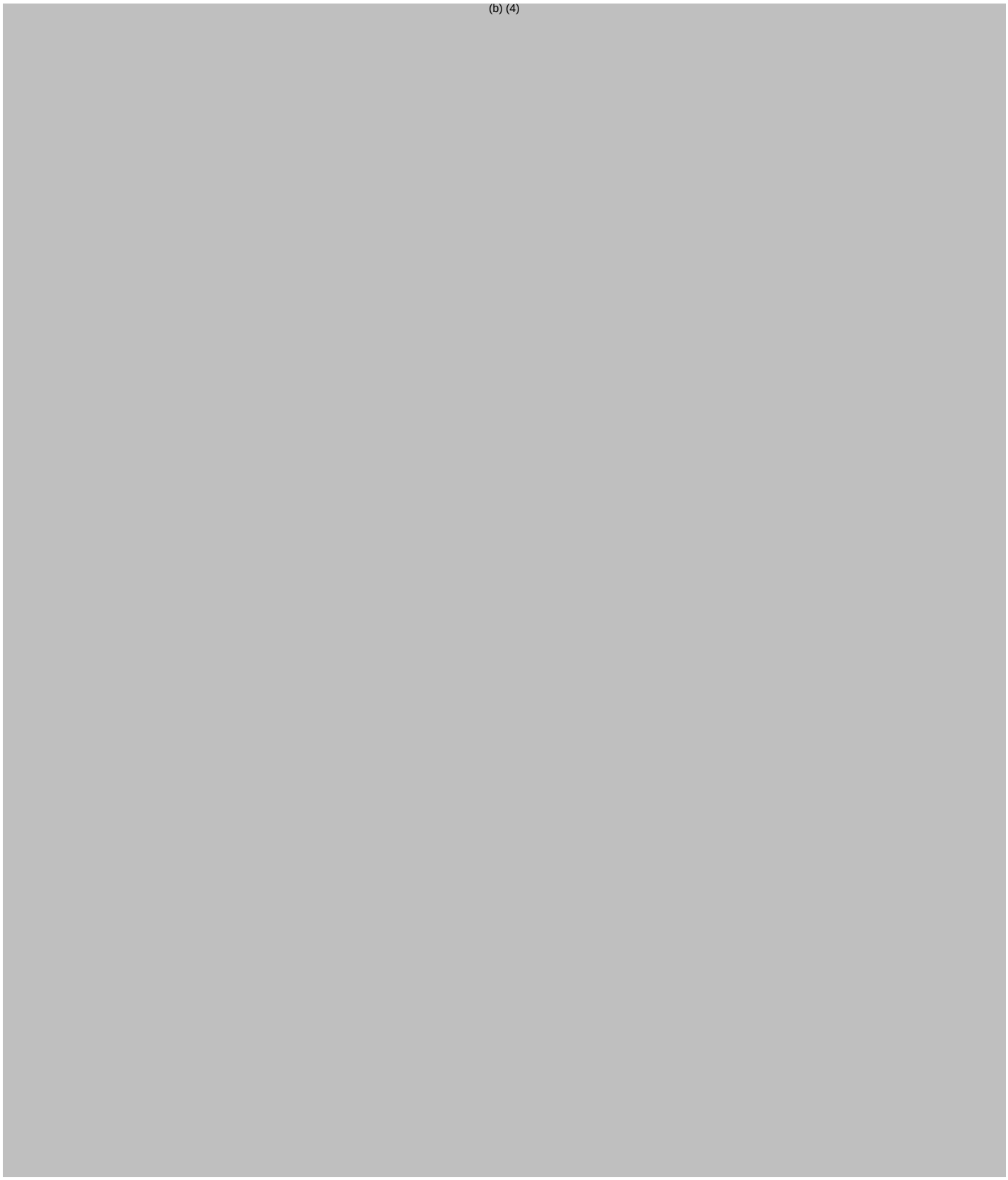

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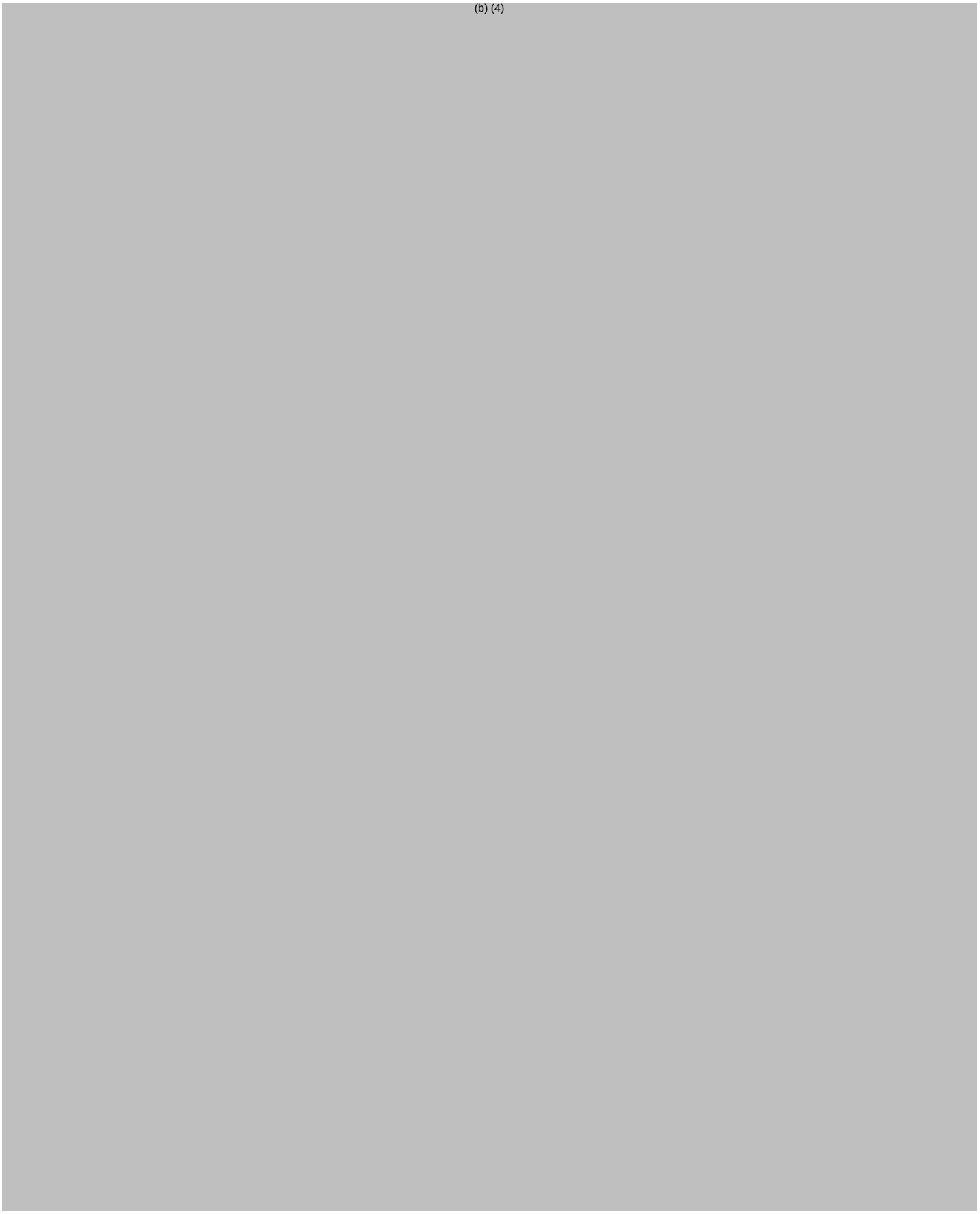

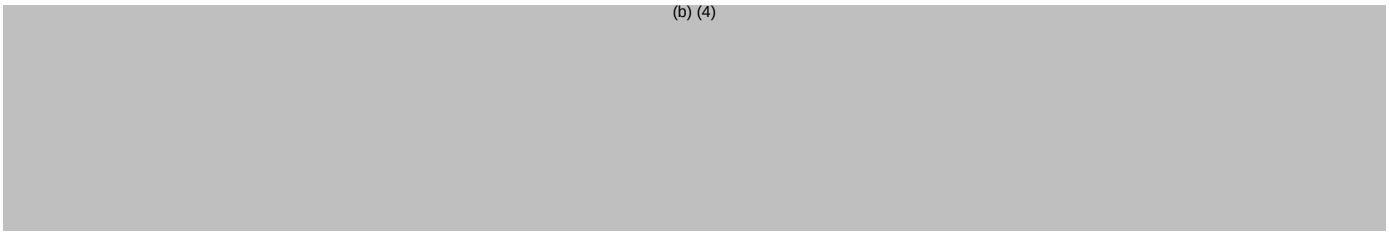
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4 APPENDICES

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

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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

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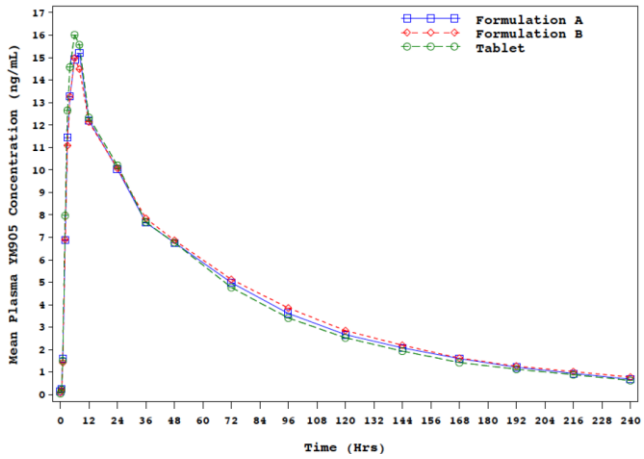

Figure 1. Mean time-solifenacin concentration profile after single dose of solifenacin succinate tablet, Formulation A, or Formulation B in 24 healthy male or female subjects

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 U00025280007 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 U00025280007 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.

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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-U002528007 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

Reference ID: 4135817

· 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

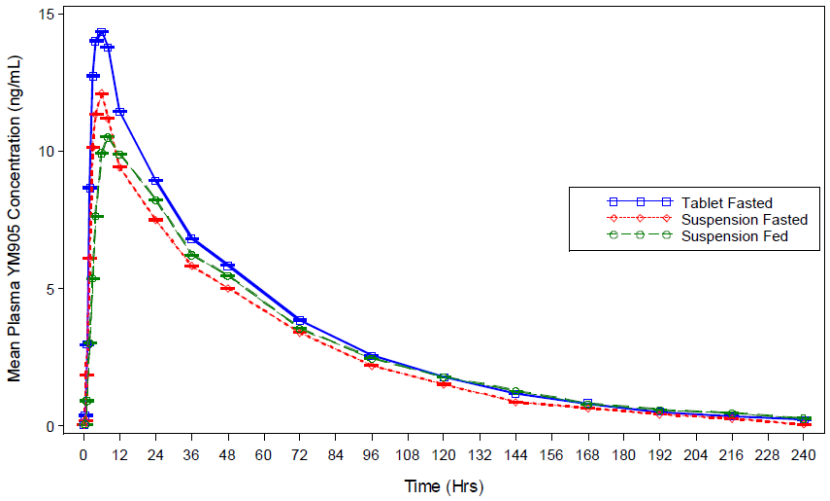

Figure 1. Mean time-solifenacin concentration profile given in tablet or suspension formulations under fasting or fed condition in 24 healthy male or female subjects

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)

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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	

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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.

Study identifier: 905-CL-079

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:

Reference ID: 4135817

· 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.

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- 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.

Reference ID: 4135817

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.

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- 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

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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

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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

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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

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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

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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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