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APPLICATION NUMBER:

209529Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

PHARMACOLOGY/TOXICOLOGY REVIEW

Date:	24 April 2020
NDA #	209529
Sponsor:	Astellas Pharma US, Inc.
Drug/Indication:	VESIcare LS oral suspension; Neurogenic detrusor overactivity (NDO)
Reviewer:	Laurie McLeod-Flynn

Background:

The sponsor is seeking marketing approval for VESIcare LS oral suspension for treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 2 years and older.

Astellas originally filed NDA 209529 on 28 February 2017, submitting a juvenile mouse study and relying additionally on pharmacology, safety pharmacology, toxicology pharmacokinetics, mutagenicity, carcinogenicity, and reproductive toxicology studies from the existing marketing authorization for 5 mg and 10 mg VESIcare film-coated (solifenacin succinate) tablets (NDA 021518).

A complete response was issued on 28 August 2017, based on a deficiency in the drug product and an unresolved drug product microbiology issue.

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

Outstanding Nonclinical Issue:

There are no outstanding nonclinical issues.

Conclusion(s):

At this time there is no impediment to Approval of this drug from a Pharmacology/ Toxicology perspective.

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/s/

LAURIE L MCLEOD FLYNN
04/27/2020 12:59:38 PM

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04/27/2020 02:24:56 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	209529
Supporting document/s:	0000
Applicant's letter date:	28 February 2017
CDER stamp date:	28 February 2017
Product:	Solifenacin succinate
Indication:	Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 2 years and older
Applicant:	Astellas
Review Division:	DBRUP
Reviewer:	Laurie McLeod-Flynn, Ph.D., DABT
Supervisor/Team Leader:	Mukesh Summan, Ph.D., DABT
Division Director:	Hylton Joffe. M.D., M.S.Sc
Project Manager:	Nenita Crisostomo

Disclaimer

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1 Executive Summary

1.1 Introduction

Solifenacin succinate is a muscarinic M3 receptor antagonist, approved in adults for overactive bladder in 2003. The current application is for treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 2 years and older.

1.2 Brief Discussion of Nonclinical Findings

In adult animals, a complete package of nonclinical pharmacology and toxicology studies was submitted under NDA 21518. As with other antimuscarinics, the most common effects at pharmacological doses were mydriasis and salivation. At higher doses, mortality was observed, often accompanied by CNS toxicity (underactivity, ataxia, tremors, convulsions, prostration, hunched posture, piloerection and abnormal respiration).

In juvenile mice dosed beginning PND10, a no-observed-adverse-effect-level was 10 mg/kg/day (AUC 0.3- to 1.7-fold the 10 mg MRHD). At 30 (0.5- to 5.5-fold), and 60 mg/kg/day (1.3- to 8.3 fold), some increase in lethality and effects on triglyceride levels were reported.

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

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

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

Reproductive toxicology was studied for approval of solifenacin succinate in adults, as described in the labeling below.

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Carcinogenicity was studied for approval of solifenacin succinate in adults, as described in the labeling below.

1.3 Recommendations

1.3.1 Approvability

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

1.3.2 Additional Non Clinical Recommendations

none

1.3.3 Labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4)

Data

Animal Data

Oral administration of ^{14}C-solifenacin succinate to pregnant mice resulted in the recovery of radiolabel in the fetus indicating that solifenacin-related product can cross the placental barrier. In pregnant mice, administration of solifenacin succinate at ~~a dose of~~ 250 mg/kg/day (7.9 times the systemic exposure at the MRHD of 10 mg) resulted in an increased incidence of cleft palate (b) (4) (b) (4) and increased maternal lethality. Administration of solifenacin succinate to pregnant mice during organogenesis at greater than or equal to 3.6 times (b) (4) (100 mg/kg/day (b) (4) ~~and~~ greater) (b) (4) the systemic exposure at the MRHD, (b) (4), resulted in reduced fetal

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body weights and reduced maternal body weight gain. No embryo-fetal toxicity or teratogenicity was observed in fetuses from pregnant mice treated with solifenacin succinate at ~~a dose of~~ 30 mg/kg/day (1.2 times the systemic exposure at the MRHD). Administration of solifenacin succinate to pregnant rats and rabbits at ~~a dose of~~ 50 mg/kg/day (< 1 times and 1.8 times the systemic exposure at the MRHD, respectively) resulted in no findings of embryo-fetal toxicity. O(b) (4) ~~o~~ral pre- and post-natal administration of solifenacin succinate at (b) (4) 100 mg/kg/day (3.6 times the systemic exposure at the MRHD) ~~during the period of organogenesis through weaning~~ resulted in reduced peripartum and postnatal survival, reduced body weight gain (b) (4) ~~by~~ the pups, and delayed physical development (eye opening and vaginal patency). An increase in the percentage of male offspring was also observed in litters from offspring (F2 generation) exposed to maternal doses of 250 mg/kg/day. There were no effects on natural delivery in mice treated with 1.2 times (30 mg/kg/day) the expected systemic exposure at the MRHD.

8.2 Lactation

Risk Summary

(b) (4)

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for [BRAND NAME] and any potential adverse effects on the breastfed child from [BRAND NAME] or from the underlying maternal condition.

Data

Animal Data

Oral administration of ^{14}C-solifenacin succinate to lactating mice, resulted in the recovery of radioactivity in maternal milk. Lactating female mice orally administered solifenacin succinate at a dose of 100 mg/kg/day (3.6 times the systemic exposure at the (b) (4) MRHD) had increased postpartum pup mortality, pups with reduced body weights, or delays in the onset of reflex and physical development. Pups from lactating dams orally administered solifenacin succinate at a dose of 30 mg/kg/day (1.2 times the systemic exposure at the (b) (4) MRHD) had no discernible adverse findings.

8.4 Pediatric Use

(b) (4)

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(b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No increase in tumors was found following the administration of solifenacin succinate to male and female mice for 104 weeks at doses up to 200 mg/kg/day (5 and 9 times, respectively, of the exposure at the maximum recommended human dose [MRHD] of 10 mg), and male and female rats for 104 weeks at doses up to 20 and 15 mg/kg/day, respectively (< 1 times the exposure at the MRHD).

Solifenacin succinate was not mutagenic in the *in vitro Salmonella typhimurium* or *Escherichia coli* microbial mutagenicity test or chromosomal aberration test in human peripheral blood lymphocytes with or without metabolic activation, or in the *in vivo* micronucleus test in rats.

Solifenacin succinate had no effect on reproductive function, fertility or early embryonic development of the fetus in male and female mice treated with 250 mg/kg/day (13 times the exposure at the MRHD) of solifenacin succinate, and in male rats treated with 50 mg/kg/day (< 1 times the exposure at the MRHD) and female rats treated with 100 mg/kg/day (1.7 times the exposure at the MRHD) of solifenacin succinate.

13.2 Animal Toxicology and/or Pharmacology

Dose-related increased mortality without preceding clinical signs occurred in juvenile mice treated before weaning for a duration of 12 weeks, from day 10 after birth, with doses that achieved a pharmacological effect. Animals dosed from postnatal day 10 onwards had higher mortality compared to the mortality in adult mice. No increased frequency in mortality was observed in juvenile mice that were treated after weaning for a duration of 4 weeks, from day 21 after birth onwards. Plasma exposure at postnatal day 10 was higher than in adult mice; the systemic exposure at postnatal day 21 was comparable to the systemic exposure in adult mice.

(b) (4)

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2 Drug Information

2.1 Drug

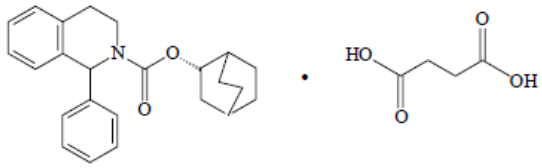
Generic Name: solifenacin succinate

Code Name: YM905

Chemical Name: (+)-(IS,3'R)-3'-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline-2-carboxylate monosuccinate

Molecular Formula/Molecular Weight: $C_{23}H_{26}N_2O_2 \cdot C_4H_6O_4$ / 480.56

Structure or Biochemical Description:



Pharmacologic Class: M3 muscarinic receptor antagonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 21518

2.3 Drug Formulation (sponsor's table)

Composition of Solifenacin Succinate Oral Suspension

Component	Function	Reference to Quality Standard	Quantity (mg/mL)
Solifenacin Succinate[1]	Active ingredient	(b) (4)	(b) (4)
Polacrilin Potassium	(b) (4)	NF	
Methylparaben		NF	
Propylparaben		NF	
Propylene Glycol		USP	
Simethicone Emulsion 30%		USP	
Carbomer Homopolymer Type B		NF	
Xylitol		NF	
Acesulfame Potassium		NF	
Natural Orange Flavor[2]		(b) (4)	
Sodium Hydroxide		NF	
Purified Water		USP	

USP: United States Pharmacopeia, NF: National Formulary
1 The quantity is expressed as the succinate salt. 1 mg solifenacin succinate is equivalent to 0.75 mg solifenacin active moiety.
2 The flavor consists of water and ingredients that are listed as generally recognized as safe in the Flavor and Extract Manufacturing Association (FEMA) GRAS list. Detailed information is found in the Drug Master File (DMF) (b) (4).
(b) (4)

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(b) (4)

2.4 Comments on Novel Excipients

No issues were identified

2.5 Comments on Impurities/Degradants of Concern

No issues were identified

2.6 Proposed Clinical Population and Dosing Regimen

Dosing regimen in children with neurogenic detrusor overactivity

Weight range (kg)	Starting dose (mL)§[1]	Maximum dose (mL)§[2]
9 to 15	2	4
> 15 to 30	3	5
> 30 to 45	3	6
> 45	4	8

§ The oral suspension formulation of [BRAND NAME] has a concentration of 1 mg/mL.
1 Equivalent to steady-state exposure after a 5 mg daily dose in adults
2 Equivalent to steady-state exposure after a 10 mg daily dose in adults

2.7 Regulatory Background

Solifenacin succinate is approved for adults with overactive bladder, at 10 mg/day.

3 Studies Submitted

3.1 Studies Reviewed

Four-Week Oral (Gavage) Repeated-Dose Toxicity Study of YM905 in Juvenile Mice with a Four-Week Recovery Period

A 12-week Repeated-dose Oral Toxicity Study of YM905 in the Juvenile Mouse with a 4-week Recovery Period

In Vitro Metabolic Stability of YM905 using Juvenile Mouse Liver Microsomes

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

NDA 21518 review by Lynnda Reid.

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4 Pharmacology

No new pharmacology studies were conducted.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Study title: *In Vitro* Metabolic Stability of YM905 using Juvenile Mouse Liver Microsomes (ISN: 905-ME-111, AE-6903-G, 16 April 2012)

The *in vitro* metabolic rates of YM905 (1 and 5 μM) were compared in juvenile (days 10 and 20 after birth) mouse and adult mouse liver microsomes. After incubation with microsomes for 120 minutes, metabolism of solifenacin was observed to be decreased in Day 10 juvenile mice compared to Day 20 juvenile mice and adult mice (sponsor's data tables).

Concentration of YM905 after Incubation with Male Mouse Liver Microsomes

YM905 concentration (μmol/L)	Replicate	Incubation time (min)	Back-calculated concentration (nmol/L)					
			Male juvenile mouse (day 10 after birth)		Male juvenile mouse (day 20 after birth)		Male mature mouse	
			Individual	Average	Individual	Average	Individual	Average
1	1	0	(b) (4)	1030.6	(b) (4)	916.6	(b) (4)	955.6
	2							
	1	10		982.4		947.1		927.6
	2							
	1	30		978.2		737.2		715.0
	2							
	1	60		936.0		558.3		534.3
	2							
	1	120		833.2		365.5		393.4
	2							
5	1	0		4936.0		5021.6		5015.0
	2							
	1	10		4919.5		4929.3		4957.2
	2							
	1	30		4895.7		4022.2		3913.4
	2							
	1	60		4573.7		2999.3		3090.9
	2							
	1	120		4313.6		2115.3		2310.8
	2							

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Concentration of YM905 after Incubation with Female Mouse Liver Microsomes

YM905 concentration (µmol/L)	Replicate	Incubation time (min)	Back-calculated concentration (nmol/L)					
			Female juvenile mouse (day 10 after birth)		Female juvenile mouse (day 20 after birth)		Female mature mouse	
			Individual	Average	Individual	Average	Individual	Average
1	1	0	(b) (4)	1079.8	(b) (4)	1053.2	(b) (4)	1083.0
	2							
	1	10		1114.0		1007.9		1019.5
	2							
	1	30		1068.9		796.5		822.0
	2							
	1	60		984.7		587.2		607.8
	2							
	1	120		905.1		388.4		435.9
	2							
5	1	0		5383.7		5575.9		5464.2
	2							
	1	10		5714.8		5182.6		5286.2
	2							
	1	30		5222.4		4253.5		4054.2
	2							
	1	60		5019.6		3255.4		3371.6
	2							
	1	120		4587.1		2323.4		2380.0
	2							

Remaining Ratio of YM905 after incubation with Mouse Liver Microsomes

YM905 concentration (µmol/L)	Incubation time (min)	RR (%)					
		Juvenile mouse (day 10 after birth)		Juvenile mouse (day 20 after birth)		Mature mouse	
		Male	Female	Male	Female	Male	Female
1	0	100.0	100.0	100.0	100.0	100.0	100.0
	10	95.3	103.2	103.3	95.7	97.1	94.1
	30	94.9	99.0	80.4	75.6	74.8	75.9
	60	90.8	91.2	60.9	55.8	55.9	56.1
	120	80.8	83.8	39.9	36.9	41.2	40.2
5	0	100.0	100.0	100.0	100.0	100.0	100.0
	10	99.7	106.2	98.2	92.9	98.8	96.7
	30	99.2	97.0	80.1	76.3	78.0	74.2
	60	92.7	93.2	59.7	58.4	61.6	61.7
	120	87.4	85.2	42.1	41.7	46.1	43.6

RR (%) = YM905 concentration after incubation (nmol/L) / YM905 concentration at 0-min incubation (nmol/L) × 100

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Metabolism of YM905 after Incubation with Mouse liver Microsomes

YM905 concentration (μmol/L)	Incubation time (min)	Metabolic activity (pmol/min/mg protein)					
		Juvenile mouse (day 10 after birth)		Juvenile mouse (day 20 after birth)		Mature mouse	
		Male	Female	Male	Female	Male	Female
1	0	–	–	–	–	–	–
	10	48.2	–*	–*	45.3	28.0	63.5
	30	17.5	3.63	59.8	85.6	80.2	87.0
	60	15.8	15.9	59.7	77.7	70.2	79.2
	120	16.5	14.6	45.9	55.4	46.9	53.9
5	0	–	–	–	–	–	–
	10	16.5	–*	92.3	393	57.8	178
	30	13.4	53.8	333	441	367	470
	60	60.4	60.7	337	387	321	349
	120	51.9	66.4	242	271	225	257

–: Not calculated
*: Not calculable since remaining ratio was over 100%.

Liver Intrinsic Clearances of YM905 in Liver Microsomes

Microsomes	YM905 concentration (μmol/L)	$CL_{int,\ in\ vitro}$ (mL/min/mg protein)	
		Male	Female
Juvenile mouse (day 10 after birth)	1	0.00816	0.00847
	5	0.00602	0.00802
Juvenile mouse (day 20 after birth)	1	0.0412	0.0445
	5	0.0390	0.0390
Mature mouse	1	0.0415	0.0414
	5	0.0357	0.0372

Metabolism in Female Mouse Liver Microsomal Suspension

Specific contents and activities	Content or activity		
	Juvenile mouse (day 10 after birth)	Juvenile mouse (day 20 after birth)	Mature mouse
Protein content (mg protein/mL)	14.4	17.2	15.9
Cytochrome P450 (nmol/mg protein)	0.341	0.637	0.758
Cytochrome b_5 (nmol/mg protein)	0.268	0.304	0.402
7-Ethoxycoumarin *O*-deethylase (pmol/mg protein/min)	1636	2811	3273
NADPH Cytochrome c reductase (nmol/mg protein/min)	53.3	78.8	97.5

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5.2 Toxicokinetics

Exposure Margins Based on Human and Animal C_{max} and AUC of Solifenacin (sponsor's table)

Species, age at sampling/ Study Duration/ Study number	Dose	Sex (M/F)	C_{max} (ng/mL)	AUC_{24h} (ng·h/mL)	Exposure ratio based on the C_{max}	Exposure ratio based on the AUC
Mice, PND21 / 4 weeks [905-TX-049]	10 mg/kg (NOAEL)	M	67.5	285	0.54	0.13
		F	140	348	1.11	0.16
	30 mg/kg (LOAEL)	M	651	2550	5.17	1.16
		F	380	1150	3.02	0.52
Mice, PND48 / 4 weeks [905-TX-049]	10 mg/kg (NOAEL)	M	91.5	214	0.73	0.10
		F	677	814	5.38	0.37
	30 mg/kg (LOAEL)	M	282	895	2.24	0.41
		F	351	1190	2.79	0.54
Mice, PND10 (study day 1) / 12 weeks [905-TX-055]	10 mg/kg (NOAEL)	M	192	2134	1.53	0.97
		F	192	1705	1.53	0.77
	30 mg/kg (LOAEL)	M	452	6614	3.59	3.00
		F	456	5947	3.62	2.70
Mice, PND20 (study day 10)/ 12 weeks [905-TX-055]	10 mg/kg (NOAEL)	M	96	366	0.76	0.17
		F	123	367	0.98	0.17
	30 mg/kg (LOAEL)	M	204	655	1.62	0.30
		F	247	859	1.96	0.39
Mice, PND93 (study day 83) / 12 weeks [905-TX-055]	10 mg/kg (NOAEL)	M	128	314	1.02	0.14
		F	143	305	1.14	0.14
	30 mg/kg (LOAEL)	M	576	1376	4.58	0.62
		F	377	862	2.99	0.39
Human; children 2 to <5 years†	PED10‡	M/F	125.9 (52.99)	2206 (1066)	NA	NA
Human; children 5 to <18 years§	PED10¶	M/F	76.86 (40.87)	1528 (887.3)	NA	NA

Exposure ratio was calculated by dividing the Cmax or AUC in animals by the highest Cmax or AUC in children (PED10), to provide a worst case.

AUC: area under the curve; M: male; F: female; NA: not applicable; LOAEL: lowest observed adverse effect level, based on mortality and reversible decreases in triglyceride concentrations when dosing started from PND10 onwards, and reduced food consumption and/or body weight gains when dosing started from PND21 onwards; NOAEL: no observed adverse effect level. †source 905-CL-074, reported in 905-PK-0008; ‡PED10: pediatric equivalent dose targeting steady-state plasma concentrations equivalent to those observed following once daily administration of 10 mg to adults. Data is presented as (mean [SD]), dose-normalized values multiplied by 10 to describe PED10;§source 905-CL-047, reported in 905-PK-0009.

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6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: A 12-week Repeated-dose Oral Toxicity Study of YM905 in the Juvenile Mouse with a 4-week Recovery Period

Study no.:	902224 (ISN: 905-TX-055) Sponsor Reference No.: K10108
Study report location:	archives (b) (4)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	24 May 2011
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	YM905, Lot No.: GLP-K9050112, 99.7% pure by HPLC

Key Study Findings

A no-observed-adverse-effect-level for juvenile mice was 10 mg/kg/day (AUC 0.3- to 1.7-fold the 10 mg MRHD). At 30 (0.5- to 5.5-fold), and 60 mg/kg/day (1.3- to 8.3 fold), some increase in lethality and effects on triglyceride levels were reported.

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Methods

Doses:	0, 10, 30, and 60 mg/kg/day
Frequency of dosing:	daily
Route of administration:	oral gavage
Dose volume:	10 ml/kg/day
Formulation/Vehicle:	0.5% (w/v) methylcellulose
Species/Strain:	Crl:CD1(ICR) mouse
Age:	10 days
Study design:	Juvenile animals were administered YM905 from Day 10 postpartum through Day 93 postpartum (young adult). Dosing was based on a dose ranging study in which YM905 (solifenacin succinate) was administered orally (by gavage) to juvenile Crl:CD1 (ICR) mice for 11 days from Days 10 to 20 *postpartum*, in which mortality and reduced body weight gains were observed at 100 mg/kg/day and slight changes in clinical chemistry parameters (increased urea nitrogen, decreased glucose and triglycerides) were observed in female pups at 30 and 100 mg/kg/day. No effects were observed at 10 mg/kg/day. (Sponsor's table)

Group No.	Dose Level (mg/kg/day)	No. of Animals Subgroup							
		Main Study (A)		Recovery Study (B)		Functional Testing (C)		Toxicokinetic Study (D)[a]	
		Males	Females	Males	Females	Males	Females	Males	Females
1/ Vehicle Control	0	12	12	6 [2]	6 [2]	20	20	9 [3]	9 [3]
2/ YM905	10	12	12	6 [2]	6 [2]	20	20	45 [3]	45 [3]
3/ YM905	30	12	12	6 [2]	6 [2]	20	20	45 [3]	45 [3]
4/ YM905	60	12 [4]	12 [4]	6 [6]	6 [6]	20 [4]	20 [4]	45 [7]	45 [7]

Observations and Results

Mortality

There were 13 deaths during the pre-weaning period (1 control male, 1 female at 10 mg/kg/day, 2 males at 30 mg/kg/day and 5 males and 4 females at 60 mg/kg/day) and 23 deaths after weaning (2 males and 2 females in the control group, 2 females at 10 mg/kg/day, 3 males and 5 females at 30 mg/kg/day and 6 males and 3 females at 60 mg/kg/day). No signs of reaction to dosing were observed for the pups prior to death. Two deaths (male pup at 60 mg/kg/day on Day 15 post partum and control female on Day 26 postpartum) were attributed to a gavage accident.

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	10	30	60	0	10	30	60
Premature deaths __preweaning __postweaning	 1 2		 2 3	 5 6	 2	 1 2	 5	 4 3

Clinical Signs

No treatment related effects were observed.

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Body Weights

No treatment related effects were observed.

Feed Consumption

No treatment related effects were observed.

Clinical Chemistry

There were minimal to mild decreases in triglyceride concentrations at 30 and 60 mg/kg/day at the end of the dosing period, reversible by the end of the recovery period.

Gross Pathology/ Organ Weights/ Histopathology

No treatment related effects were observed.

Special Evaluation

Physical development:	No treatment related effects were observed on Preputial Separation or Mean Age of Vaginal Patency (days). No treatment related effects on bone measurements were observed.
Neurological assessment:	No treatment related effects were observed in a Functional Observation Battery, on Motor Activity, on Auditory Startle, in a Biel Water Maze, or on Passive Avoidance.
Reproduction:	No treatment related effects were observed.

Toxicokinetics

Doses in children were set to be approximately equivalent at maximum to those achieved in adult humans, an AUC of about 1200 ng·hr/ml.

Exposure in rats on Days 10-93 postpartum

	Males (mg/kg/day)			Females (mg/kg/day)		
	10	30	60	10	30	60
AUC_{0-24} (nghr/ml)						
__Day 10	2133.50	6614.34	9993.59	1704.75	5947.39	9711.26
__Day 20	366.40	655.19	4460.09	366.86	858.57	1596.82
__Day 93	313.57	1376.45	2954.00	304.84	862.12	2396.22
Cmax (ng/ml)						
__Day 10	192.15	451.97	909.84	192.18	456.19	925.71
__Day 20	96.30	204.02	453.07	123.17	247.10	488.86
__Day 93	128.44	576.39	703.97	142.93	377.19	749.26

Reference ID: 4131171
Reference ID: 4616891

Study title: A Preliminary 11-day Repeated-dose Oral Toxicity Study of YM905 in the Juvenile Mouse

Study no.:	ISN: 905-TX-054 (902223)
Study report location:	archives (b) (4)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	9 September 2010
GLP compliance:	No
QA statement:	Yes
Drug, lot #, and % purity:	YM905, Lot No.GLP-K9050112

Key Study Findings

YM905 (solifenacin succinate) was administered orally (by gavage) to juvenile Crl:CD1 (ICR) mice for 11 days from Days 10 to 20 postpartum, at doses of of 0, 10, 30 or 100 mg/kg/day. Mortality (1 male and 1 female at 10 mg/kg/day, 1 male at 30 mg/kg/day, 3 males and 5 females at 100 mg/kg/day) and reduced body weight gains were observed at 100 mg/kg/day and slight changes in clinical chemistry parameters (increased urea nitrogen, decreased glucose and triglycerides) were observed in female pups at 30 and 100 mg/kg/day. There were no treatment related organ weight (absolute and relative to body weight) or macroscopic changes. No effects were observed at 10 mg/kg/day.

There were no clear sex differences in the C_{max} and AUC_{24} values of YM905.
The Cmax values on Day 10 postpartum were 1.8 to 3.4 times higher than those on Day 20 postpartum. The AUC_{24} values on Day 10 postpartum were 5.3 to 10.8 times higher than those on Day 20 postpartum.

Toxicokinetics

Mouse plasma concentration and toxicokinetic parameters of YM905

	Males (mg/kg/day)			Females (mg/kg/day)		
	10	30	100	10	30	100
AUC_{0-24} (nghr/ml)						
__Day 10	2586.39	5451.34	32146.5	1617.0	6125.17	29892.15
__Day 20	422.71	1018.99	4217.08	256.82	874.33	2762.23
Cmax (ng/ml)						
__Day 10	259.01	468.81	1900.48	189.48	559.50	1892.97
__Day 20	87.44	258.58	750.05	62.77	183.11	558.33

Reference ID: 4131171
Reference ID: 4616891

Study title: Four-Week Oral (Gavage) Repeated-Dose Toxicity Study of YM905 in Juvenile Mice with a Four-Week Recovery Period

Study no.:	ISN: 905-TX-049 (FTA00012)
Study report location:	Archives of (b) (4)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	26 October 2006
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	YM905 (FR817164), Lot No. GLP-K9050112, 100% pure

Key Study Findings

Solifenacin succinate was well tolerated at 10 mg/kg/day (AUC 0.2 to 0.7-fold) and 30 mg/kg/day (0.9- to 3-fold.) No unique target organs were identified. No compound-related effect on mortality or body weight gain was reported in juvenile mice dosed from post-natal Day 21. Fertility was reduced to 75% at 100 mg/kg/day (3- to 10-fold.) No effects on learning and memory, passive avoidance behavior, motor activity, performance in an open field, or mating performance were observed.

Methods

Doses:	0, 10, 30, and 100 mg/kg/day
Frequency of dosing:	daily
Route of administration:	Oral gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	0.5% aqueous methylcellulose
Species/Strain:	Crl:CD1(ICR) mice
Number/Sex/Group:	12
Age:	21 days
Satellite groups:	18/sex/group for toxicokinetic
Unique study design:	Dosing on days 1 through 28 of study [days of study (DSs) 1 through 28, corresponding to days postpartum (DPs) 21 through 48]
Deviation from study protocol:	None significant

Observations and Results

Mortality

Apparent drug related mortality at 100 mg/kg/day was considered to be from dosing accidents while administering a relatively viscous formulation.

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	10	30	100	0	10	30	100
Premature deaths	0	0	1	3	1	2	1	5

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Clinical Signs

No drug related effects were observed.

Body Weights

No drug related effects were observed.

Body weight, treatment phase (g)	Males (mg/kg/day)				Females (mg/kg/day)			
	0	10	30	100	0	10	30	100
Number (N)	30	30	30	30	30	30	30	30
Day 1	12.8	13.0	12.3	12.5	12.3	12.0	12.3	11.9
Day 5	17.6	18.2	16.8	17.0	15.7	15.5	15.5	14.7
Day 8	21.4	22.2	20.6	20.7	17.4	17.4	17.4	16.1**
Day 12	24.6	25.7	24.1	24.1	19.4	19.8	19.7	18.7
Day 15	25.8	26.9	25.7	25.8	20.9	21.2	21.0	20.2
Day 19	26.6	27.6	26.6	26.7	22.2	22.6	22.2	21.9
Day 22	27.3	28.4	27.4	27.9	22.8	23.2	22.6	22.2
Day 26	28.3	29.3	28.4	29.0	23.9	23.8	23.4	23.1
Day 29	28.6	29.9	29.1	29.6	24.1	23.8	23.5	23.2

Body weight gain (g)	Males (mg/kg/day)				Females (mg/kg/day)			
	0	10	30	100	0	10	30	100
Day 1- 29	15.8	16.9	16.8	16.8	11.7	11.8	11.2	11.4

Body weight, recovery phase (g)	Males (mg/kg/day)				Females (mg/kg/day)			
	0	10	30	100	0	10	30	100
Number (N)	18	18	17	17	17	17	17	16
Day 36	28.3	30.3	29.3	30.0	24.3	23.8	23.9	23.2
Day 43	29.8	32.0	30.9	31.7	25.9	25.3	25.0	24.4
Day 50	31.1	33.5*	32.1	33.2	26.9	26.4	26.2	25.3
Day 57	32.2	34.5	33.7	34.2	27.6	27.1	27.1	25.9
Day 64	32.2	34.4	33.5	33.7	--	--	--	--
Day 72	32.6	35.2**	34.6*	34.8*	--	--	--	--
Day 78	32.7	34.4	34.3	34.5	--	--	--	--

Feed Consumption

Feed consumption was reduced at 30 and 100 mg/kg/day. Increased feed consumption was observed in these groups during recovery.

Treatment phase	Males (mg/kg/day)				Females (mg/kg/day)			
	0	10	30	100	0	10	30	100
Day 1 – 5	3.8	3.9	3.6**	3.6**	3.7	3.6	3.5	3.5**
Day 5 – 8	4.8	5.0	4.7	4.6	4.5	4.5	4.4	3.6**
Day 8 – 12	6.2	6.0	5.4*	5.1**	5.0	5.1	5.0	4.2**
Day 12 -15	5.3	5.7	5.4	5.0	5.2	5.2	5.2	4.4**
Day 15 -19	5.4	5.3	5.4	4.8##	5.3	5.3	5.4	4.6**
Day 19 -22	5.4	5.6	5.4	5.3	5.8	5.9	5.7	4.9**
Day 22 – 26	5.6	5.9	6.0	5.2	5.4	5.4	5.2	5.1
Day 26 – 29	5.2	5.3	5.2	5.0	5.6	5.9	5.7	5.3

Recovery phase	Males (mg/kg/day)				Females (mg/kg/day)			
	0	10	30	100	0	10	30	100
Day 29 -36	5.0	5.5**	5.3	5.4**	5.7	6.1	5.2	5.0
Day 36 – 43	4.9	5.4**	5.1	5.2	5.5	5.2	5.3	5.0
Day 43 – 50	5.0	5.4*	5.0	5.2	5.8	5.3	5.3	5.5
Day 50 – 57	4.8	5.4**	5.1*	5.2**	5.3	5.4	5.2	5.2

Dunnett's test: * p<0.05, ** p<0.01; Aspin-Welch test with Bonferroni adjustment: # p<0.05, ## p<0.01

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Gross Pathology/ Organ Weights/ Histopathology

No treatment related effects were observed.

Special Evaluation

F_1 behavioral evaluation:
No treatment related effects were observed at any dose on performance in an open field, reaction to removal or handling, rearing, defecation, urination, level of arousal, gait pattern, palpebral closure, eye prominence, lacrimation, salivation, piloerection, abnormal respiration, appearance, visual, tactile, auditory or tail-pinch reaction, visual placing response, air righting response or pupil response to light.

Summary of behavioral evaluation

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	10	30	100	0	10	30	100
Passive avoidance test	No treatment effects				No treatment effects			
Motor activity	No treatment effects				No treatment effects			
Open field observation	No treatment effects				No treatment effects			

F_1 reproduction:
Fertility was reduced to 75% at 100 mg/kg/day (the historical control range for the testing facility is 80% - 100% with an average of 94%). The percentage of live male fetuses per litter was considered to reflect a higher than usual incidence of male fetuses in the vehicle control group (Historical mean percentage: 35.0% to 60.5%). All placentae appeared normal. No treatment related malformations or variations of fetuses were observed.

Summary of reproductive effects

	Males/Females (mg/kg/day)			
	0	10	30	100
Number evaluated (N)	17	17	17	16
Mean days prior to mating	3.6	2.2	3.6	2.2
Mice that mated (%)	100	100	94.1	100
Fertility index (% of mated)	94.1	100	100	75.0**
Sex ratio (% males/litter)	61.5	49.8	48.2*	40.5**
Number pregnant	16	17	16	12
Gestation body weights (g)				
__GD0	27.6	26.7	26.4	25.4**
__GD7	32.0	31.1	30.6	30.0
__GD14	43.4	42.9	41.2	42.1
__GD18	56.5	56.0	53.6	56.0
Gestation food consumption (g)				
__GD0-7	5.9	5.7	5.7	5.8
__GD7-14	6.7	6.8	6.4	6.8
__GD14-18	7.8	7.6	7.2*	7.8
Mean no. of corpora lutea	13.8	13.3	12.6	13.0
Mean no. of implantations	13.2	12.9	12.4	12.7
Mean no. of live fetuses	11.4	11.8	10.6	12.1

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Mean no. of resorptions __mean no. of early resorptions __mean no. of late resorptions	1.9 1.6 0.2	1.0 0.9 0.0	1.8 1.7 0.1	0.6* .5 0.1
Mean no. of dead fetuses	0.0	0.2	0.0	0.0
Mean postimplantation loss (%)	14.2	9.0	14.9	4.5
Mean fetal body weights (g) __males __females	 1.33 1.29	 1.34 1.28	 1.36 1.26	 1.36 1.29
Gross external anomalies	No treatment effects			

Toxicokinetics

	Males (mg/kg/day)			Females (mg/kg/day)		
	10	30	100	10	30	100
AUC_{0-24} (nghr/ml) __Day 1 (postpartum Day 21) __Day 28(postpartum Day 48)	 825.3 250.5	 3705.8 1029.7	 7936.5 3756.0	 440.3 870.4	 1341.5 2008.2	 6413.5 12750.5
Cmax (ng/ml) __Day 1(postpartum Day 21) __Day 28(postpartum Day 48)	 67.5 91.5	 651.0 282.0	 900.0 823.0	 140.0 677.0	 380.0 351.0	 1080.0 948.0

Dosing Solution Analysis

Test article suspensions of YM905 used for dosing were within 15% of the nominal target.

Study title: Preliminary Two-Week Oral (Gavage) Repeated-Dose Toxicity Study Of YM905 in Juvenile Mice (dose ranging)

Study no.: ISN: 905-TX-048 (Study No.: FTA00010)
Study report location: GLP-archives (b) (4)
(b) (4)
Conducting laboratory and location:
Date of study initiation: 21 June 2006
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: YM905 (or FR817164), Lot No.: GLP-K9050112, 100% pure

Key Study Findings

In mice dosed from postpartum 21 through 34, 10 g/kg/day was a no-observable-adverse-effect-level (NOAEL) and lethality was observed at 250 mg/kg/day. Dose related effects on body weight were observed at 100 mg/kg/day.

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Methods

Doses:	0, 10, 30, 100, and 250 mg/kg/day
Frequency of dosing:	Daily
Route of administration:	Oral, gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	0.5% aqueous methylcellulose
Species/Strain:	Crl:CD1(ICR) juvenile mice
Number/Sex/Group:	6
Age:	21 days postpartum
Unique study design:	Administration to juvenile mice on days 1 through 14 of study, corresponding to days postpartum 21 through 34
Deviation from study protocol:	None significant

Observations and Results

Mortality

Two mice (one male and one female) in the 250 mg/kg/day died or were sacrificed early.

Clinical Signs

Dehydration (based on skin turgor) was observed in 5 males (including the one found dead.) One male was cold to touch. The prematurely sacrificed female exhibited decreased motor activity, whole body tremors, dehydration, cold to touch and bradypnea on Day 3.

Body Weights

Body weights on Day 14 in male mice were 100.4%, 92.6%, 84.8% and 60.5% of the control group value and in female mice, 98.5%,97.5%, 86.2% and 79.3% in the 10, 30, 100 and 250 mg/kg/day dose groups, respectively.

Feed Consumption

Feed consumption in the males were 98.1%, 88.7%,77.4% and 54.7% of control and in females, 92.1%, .90.2%, 84.3% and 52.9% in the 10, 30, 100 and 250 mg/kg/day dose groups, respectively.

Gross Pathology/ histopathology

No treatment related effects were observed.

Summary of effects

	Males (mg/kg/day)					Females (mg/kg/day)				
	0	10	30	100	250	0	10	30	100	250
Day 14, C_{1h} (ng/ml)	--	80.2	195	558	627	--	78.8	295	460	1010
Day 14, C_{24h} (ng/ml)	--	0	0	0	0	--	0	0	0	0
Died or sacrificed moribund					1					1

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Clinical observations __dehydration __cold to touch					5 1					3 1
Body weight (g) __Day1 __Day 4 __Day 7 __Day 10 __Day 14	11.5 15.3 19.4 23.3 25.6	12.0 15.7 19.6 23.2 25.7	12.0 14.7 18.0 21.1 23.7	12.2 14.4 16.4 18.3 21.7	11.4 11.4 13.1 13.2 15.5	11.0 13.7 15.9 18.3 20.3	10.6 12.9 15.2 17.6 20.0	10.8 13.0 15.0 17.5 19.8	10.9 12.4 14.0 15.8 17.5	10.6 12.0 12.9 14.3 16.1
Body weight gain (g), Day1-14	14.1	13.6	11.7	9.5	4.2	9.3	9.4	9.0	6.6	5.2
Food consumption (g/day) __Day 1-4 __Day 4-7 __Day 7-10 __Day 10-14	3.6 5.1 5.8 6.3	3.8 5.0 5.8 6.0	3.4 4.6 5.0 5.4	3.1 4.1 4.2 4.8	2.1 2.9 2.8 3.4	3.4 6.0 5.1 5.6	3.2 5.0 4.9 5.5	3.1 5.0 4.9 5.2	3.0 4.9 5.1 4.2	2.6 3.7 3.8 3.8
Gross pathology	--	--	--	--	--	--	--	--	--	--

Dosing Solution Analysis

Test article suspensions of YM905 used for dosing were within 15% of the nominal target.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

No new studies were submitted. Labeling from VESICARE (solifenacin succinate) approved for adults with overactive bladder will be used for the pediatric drug.

7.2 *In Vitro* Assays in Mammalian Cells

No new studies were submitted. Labeling from VESICARE (solifenacin succinate) approved for adults with overactive bladder will be used for the pediatric drug.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

No new studies were submitted. Labeling from VESICARE (solifenacin succinate) approved for adults with overactive bladder will be used for the pediatric drug.

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8 Carcinogenicity

No new studies were submitted. Labeling from VESICARE (solifenacin succinate) approved for adults with overactive bladder will be used for the pediatric drug.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

No new studies were submitted. Labeling from VESICARE (solifenacin succinate) approved for adults with overactive bladder will be used for the pediatric drug.

9.2 Embryonic Fetal Development

No new studies were submitted. Labeling from VESICARE (solifenacin succinate) approved for adults with overactive bladder will be used for the pediatric drug.

9.3 Prenatal and Postnatal Development

No new studies were submitted. Labeling from VESICARE (solifenacin succinate) approved for adults with overactive bladder will be used for the pediatric drug.

10 Special Toxicology Studies

Local tolerance study:

Solifenacin succinate oral suspension (1 mg/ml) did not cause irritation to the eyes of rabbits (Study no. 905-TX-053.)

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11 Integrated Summary and Safety Evaluation

Juvenile mice were dosed orally from postnatal day (PND) 21 for 4 weeks, or from PND10 for 12 weeks. Solifenacin exposure levels based on AUC at PND10 were approximately 5 to 10-fold higher than on PND20/21. Increased exposure levels on PND10 are consistent with reduced in vitro metabolic rates of solifenacin measured in liver microsomes from juvenile mice on PND10 as compared to those measured from microsomes from mice at PND21 and adult mice.

In juvenile mice dosed beginning PND10, a no-observed-adverse-effect-level was 10 mg/kg/day (AUC 0.3- to 1.7-fold the 10 mg MRHD). At 30 (0.5- to 5.5-fold), and 60 mg/kg/day (1.3- to 8.3 fold), some increase in lethality and effects on triglyceride levels were reported.

In juvenile mice dosed beginning PND21, solifenacin succinate was well tolerated at 10 mg/kg/day (AUC 0.2 to 0.7-fold) and 30 mg/kg/day (0.9- to 3-fold). No unique target organs were identified. Fertility was reduced to 75% at 100 mg/kg/day (3- to 10-fold). Slightly decreased food consumption and/or reduced body weight gains were also

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observed at this dose. No effects on learning and memory, passive avoidance behavior, motor activity, performance in an open field, or mating performance were observed.

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

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

Since the maximum proposed average exposure via AUC at the 10 mg dose in pediatric populations is the same as the adult exposure following a 10 mg exposure, labeling from VESICARE will be adopted for Pregnancy and Carcinogenesis, Mutagenesis, Impairment of Fertility.

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/s/

LAURIE L MCLEOD FLYNN
07/27/2017

MUKESH SUMMAN
07/28/2017
Nonclinical Recommends AP