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A MULTICENTER, OPEN-LABEL, SINGLE-DOSE STUDY TO EVALUATE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF SOLIFENACIN SUCCINATE SUSPENSION IN PEDIATRIC SUBJECTS FROM 5 TO LESS THAN 18 YEARS OF AGE WITH NEUROGENIC DETRUSOR OVERACTIVITY (NDO). (EUDRACT NUMBER: 2011-000250-28)

Hypothesis / aims of study
To determine the pharmacokinetics, safety and tolerability of solifenacin succinate suspension after single dose administration in children and adolescents with neurogenic detrusor overactivity.To evaluate if the pharmacokinetics of solifenacin in pediatric patients with NDO is similar to that observed in pediatric patients with OAB.

Study design, materials and methods
This was an open-label, multicenter, single dose study in pediatric patients from 5 to less than 18 years of age with NDO. The study was to include a minimum of 12 male and female patients, 6 children (5 to less than 12 years of age) and 6 adolescents (12 to less than 18 years of age). The doses administered were targeted to achieve maximum plasma concentrations equivalent to those observed with solifenacin 5 mg once daily in adults at steady state defined as a pediatric equivalent dose (PED) 5 mg. The PED was estimated mainly using allometric scaling with fixed exponent 0.75. Due to its long $t_{1/2}$, solifenacin accumulates approximately 3-fold at steady-state. Therefore, in this single-dose study a 3-fold higher dose was administered to target similar plasma concentrations as would be achieved at steady-state. Weight range-adjusted doses were used.
Pharmakokinetic endpoints were Cmax, tmax, AUCinf, t1/2, CL/F, and Vz/F; safety endpoints were adverse events, clinical laboratory evaluations (hematology, biochemistry, urinalysis), vital signs, ECG, and physical examination. Pharmacokinetic data analysis was performed using NONMEM version 7. Individual solifenacin plasma concentrations and pharmacokinetic parameters were summarized with descriptive statistics. All safety and tolerability data were summarized and listed by age group and overall. No formal statistical testing was performed on these data.
Five visits were planned:
Visit 1 (D-28 to D-1): Obtain informed consent, screening, confirmation of in- and exclusion criteria
Visit 2 (D1): Check remaining exclusion criteria, receive treatment (single dose)
Visit 3,4,5 (D3, D5, D7): Follow-up period
Number of PK samples and sampling times were dependent on age: 4 samples were taken in children from 5 to ≤ 9 years of age; 6 samples in children from 9 to ≤ 12 years of age and 7 samples in adolescents (12 to ≤ 18 years of age).

Results
Seven adolescents (3 males, 4 females, mean age 14.4 years, weight 33 to 65 kg) and 7 children (4 males, 3 females, mean age 8.6 years, weight 16 to 42 kg) were included.
Descriptive statistics for solifenacin pharmacokinetic parameters following a single dose of solifenacin succinate oral suspension are presented in table 3.

Table 3 – Summary of Pharmakokinetic Parameters (PKAS)

Treatment	Pharmacokinetic Parameters					
	AUC_{inf} (ng•h/mL)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
Adolescents-PED 5.0 mg						
n	7	7	7	7	7	7
Mean	1615	21.91	3.87	52.9	7.71	499
SD-%CV	955-59	7.93-36.2	1.12-28.9	21.1-39.8	4.8-62.3	195-39.1
Median	1382	23.47	3.70	41.0	7.3	432
Min	655	11.67	2.2	36.2	3.3	259
Max	3063	35.71	5.6	83.3	15.4	806
Children-PED 5.0 mg						
n	7	7	7	7	7	7
Mean	832	17.67	4.16	30.7	7.2	299
(SD)	330-40	5.89-33.3	1.06-25.4	8.28-27.0	4.0-55.8	108-36.3
Median	644	17.51	4.40	30.7	5.55	331
Min	425	10.16	2.9	18.6	4.33	146
Max	1239	26.76	5.6	41.3	15.97	427

Interpretation of results
t_{max} was similar across the age groups. CL/F was slightly higher and V_z/F was higher for adolescent patients compared to children. Half-life values show a tendency to be shorter in children. C_{max} and AUC_{inf} were higher in the adolescents compared to the children. However, graphical analysis of the data indicates a substantial overlap between the exposure in the adolescents and children (Figure 1).
No drug-related TEAEs were reported during this study. There were no clinically significant ECG abnormalities. The mean QTcB interval was not increased versus pre-dose values.

No trends were observed in laboratory data. Mean supine pulse rate was increased by up to 7.7 beats per minute (bpm) in adolescents and 12.9 bpm in children following solifenacin administration. Review of the individual patient data did not identify any consistent pattern versus pre-dose values and none of the changes are considered to be clinically relevant.
Comparison of individual pharmacokinetic parameters between this study and the previously conducted study 905-CL-075 (in pediatric OAB patients) indicates similarity between the individual parameters of the 2 populations.

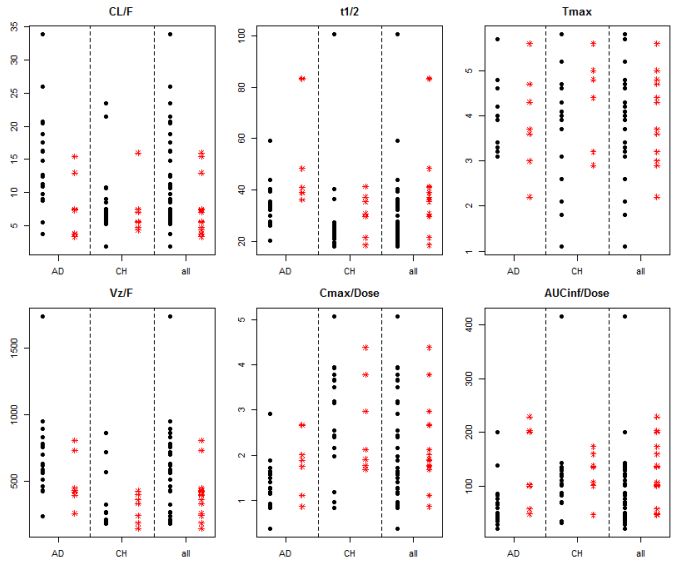

Figure 1 - Filled black circles (●)= 905-CL-075; Red stars (*) = 905-CL-079
AD: Adolescents (12 to <18 years); CH: Children (5 to <12 years)**;** all = all subjects

Concluding message

Oral administration of a single dose of solifenacin succinate suspension in children and adolescents with NDO administered PED 5 mg resulted in plasma exposures which were similar to those observed in children and adolescents with OAB administered the same PED. The doses administered were well-tolerated.

References

1. Abstract presented at ICCS/ERIC/BAPU Joint Congress, London, 12 Oct - 14 Oct 2012, Astellas data on file

Disclosures

Funding: Astellas Pharma Europe B.V. **Clinical Trial:** Yes **Registration Number:** EudraCT,2011-000250-28 **RCT:** No **Subjects:** HUMAN **Ethics Committee:** Belgium: UZ Gent - Ethisch comité Danmark: Den Videnskabsetiske Komité for Region Midtjylland UK: NRES Committee Yorkshire and the Humber – Sheffield NL: CMO Regio Arnhem-Nijmegen Poland: Komisja Bioetyczna przy Instytucie „Pomnik-Centrum Zdrowia Dziecka" w Warszawie Dr.Abdurrahman Yurtaslan Ankara Onchology Education and Research Hospital Clinical Researches Ethics **Helsinki:** Yes **Informed Consent:** Yes