

Pooled solifenacin overactive bladder trial data: Creation, validation and analysis of an integrated database



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ABSTRACT

Background: Patient-level data are available for 11 randomized, controlled, Phase III/Phase IV solifenacin clinical trials.

Methods: Meta-analyses were conducted to interrogate the data, to broaden knowledge about solifenacin and overactive bladder (OAB) in general. Before integrating data, datasets from individual studies were mapped to a single format using methodology developed by the Clinical Data Interchange Standards Consortium (CDISC). Initially, the data structure was harmonized, to ensure identical categorization, using the CDISC Study Data Tabulation Model (SDTM). To allow for patient level meta-analysis, data were integrated and mapped to analysis datasets. Mapping included adding derived and categorical variables and followed standards described as the Analysis Data Model (ADaM). Mapping to both SDTM and ADaM was performed twice by two independent programming teams, results compared, and inconsistencies corrected in the final output. ADaM analysis sets included assignments of patients to the Safety Analysis Set and the Full Analysis Set.

Results: There were three analysis groupings: Analysis group 1 (placebo-controlled, monotherapy, fixed-dose studies, $n = 3011$); Analysis group 2 (placebo-controlled, monotherapy, pooled, fixed- and flexible-dose, $n = 5379$); Analysis group 3 (all solifenacin monotherapy-treated patients, $n = 6539$). Treatment groups were: solifenacin 5 mg fixed dose, solifenacin 5/10 mg flexible dose, solifenacin 10 mg fixed dose and overall solifenacin. Patient were similar enough for data pooling to be acceptable.

Conclusions: Creating ADaM datasets provided significant information about individual studies and the derivation decisions made in each study; validated ADaM datasets now exist for medical history, efficacy and AEs. Results from these meta-analyses were similar over time.

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Abbreviation: ADaM, Analysis Data Model; AE, adverse event; BMI, body mass index; CDISC, Clinical Data Interchange Standards Consortium; CMH, Cochran-Mantel-Haenszel; IDB, integrated database; LOCF, last observation carried forward; MedDRA, Medical Dictionary for Regulatory Activities; OAB, overactive bladder; PPIUS, Patient Perception of Urgency Scale; SDTM, Study Data Tabulation Model; TEAE, treatment emergent adverse event.

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1. Introduction

Solifenacin, a competitive muscarinic receptor antagonist that attenuates bladder contraction, was approved in the United States and the European Union as a treatment for overactive bladder (OAB) in 2004 [1]. Due to its long elimination half-life of 40–68 h, it can be given as a single daily dose. Administration is via a flexible-dose regimen, starting at 5 mg once daily, but, if sufficient benefit is not attained, dosage may be increased to 10 mg once daily if well tolerated. This allows better individualized therapy, with the goal of optimizing efficacy and minimizing side effects.

From the 53 known solifenacin Phase I to IV studies identified in

2008, 12 clinical trials met criteria for integration into a single database. Inclusion criteria were studies of Phase II or above, monotherapy only (no combination therapy) and not investigator driven. One study was selected in error (no monotherapy and no placebo) but was removed prior to analysis, so a total of 11 studies were included. These 11 clinical trials took place between 2001 and 2008 and were all Phase III and Phase IV studies with a placebo or active control arm, conducted in Europe (4 studies), US (6 studies) or Canada (1 study). The data were consolidated into an integrated database (IDB) to provide the opportunity to interrogate the data, with the aim of broadening knowledge about solifenacin and also overactive bladder (OAB) in a broader sense. Other global databases have been utilized to probe data in a similar fashion [2–4].

Meta-analyses were conducted on the solifenacin IDB to evaluate the prognostic/predictive value of baseline patient and disease characteristics and to identify subpopulations of patients who might potentially derive benefit from solifenacin. Clinically important questions were formulated *a priori*, by an expert panel of advisors. Questions included: What can an analysis of body mass index (BMI) tell us – does being overweight or obese make a difference to efficacy and/or tolerability? What is the impact of older age? Do men and women react differently to solifenacin? Does baseline symptomatology/syndrome severity correlate with magnitude of treatment response? Do any baseline characteristics predict who will or will not respond to solifenacin? Are patients who requested an increase from 5 mg to 10 mg after 4 weeks of treatment different to those who did not when given the opportunity? Additional objectives of the meta-analyses were to evaluate solifenacin safety in the overall population and in the various subpopulations.

This manuscript describes the methodology for the creation and analysis of the solifenacin IDB including validation of the methodology.

2. Methods

2.1. Studies

The 11 studies included in the meta-analysis are listed in Table 1, along with their main features including study codes, citations and clinical trial registry information (if available). All studies were conducted in compliance with the International Conference of Harmonization—Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki. Institutional Review Board/Independent Ethics Committee approval was obtained at all sites. All patients provided written, informed consent prior to enrolment. Of the 11 studies, 7 were randomized, double-blind, placebo-controlled studies (Fig. 1). Of these 7 studies, 4 were fixed-dose studies and 3 studies allowed for the daily dose of solifenacin to be adjusted between 5 mg and 10 mg for each subject; 4 studies had an antimuscarinic active control arm. All studies were based on a 12-week treatment period, except for study 905-EC-002 (SUNRISE; 16 weeks), study 905-UC-007 (VOLT; 12 weeks plus up to 24 weeks extension period), VES-001 (VECTOR; 8 weeks). Data from all studies were cut off at 12 weeks of treatment to make them comparable. Therefore, VES-001 (VECTOR) was not included in efficacy meta-analyses. One study (905-UC-007; VOLT) had minimal efficacy data and was therefore only used for safety analysis.

2.2. Inclusion criteria

Patient inclusion criteria varied a little across studies, but patients were similar enough for data to be pooled. The following demographic characteristics were collected for all studies: age as a continuous variable; age as a categorical variable (18–<40 yrs,

40–<65 yrs, 65–<75 yrs, ≥75 yrs); gender; race; body mass index (BMI: <25 kg/m² [normal], 25–<30 kg/m² [overweight], 30–<35 kg/m² [obese] and ≥35 kg/m² [severely obese]); region (US/Canada or Europe). BMI data were not available for all studies because height and weight were not collected for all studies.

Entry criteria were micturitions ≥8/24 h (plus ≥3 incontinence episodes, or ≥3 urgency episodes in 3 days); however, for some studies, entry criteria were based on urgency, therefore, for some patients, micturition frequency was <8/24 h.

In study 905-EC-002, assessment of urgency was graded using the Patient Perception of Intensity of Urgency Scale (PPIUS), whereas in all other studies urgency was recorded as such. For PPIUS, a score of 3 or more was considered an urgency episode.

2.3. Efficacy assessments

Efficacy of solifenacin was assessed via micturition frequency/24 h, number of urgency episodes/24 h, number of incontinence episodes/24 h, number of urgency incontinence episodes/24 h, number of nocturia episodes/24 h and volume voided/micturition. Endpoint values were based on last observation carried forward (LOCF). The percent change did not include patients with zero baseline and zero at endpoint for any of the variables. When variables were collected in different ways in the different studies, a remapping process was applied so that a common set of values was used across studies.

Response to treatment was defined as: mild (≥25% reduction from baseline in average number of episodes/24 h); moderate (≥50% reduction from baseline in average number of episodes/24 h); or strong (≥75% reduction from baseline in average number of episodes/24 h). Normalization was defined as: reduction to ≤8 micturitions/24 h on average (in subjects with ≥8 micturitions/24 h); reduction to 0 episodes of incontinence, urgency and urgency incontinence (in subjects with baseline >0); and reduction to 1 episode of nocturia.

2.4. Safety assessments

Safety was assessed by evaluation of Treatment-Emergent Adverse Events (TEAEs), summarized by MedDRA system organ class and preferred term (MedDRA version 11.1). Incidence and severity of TEAEs including those of special interest (dry mouth, constipation, blurred vision, urinary retention, acute urinary retention), seriousness of TEAEs and relationship to study drug, as well as evaluation of withdrawal from study drug and withdrawal from study drug due to AEs were recorded. For study 905-EC-002 (16-week study), AEs collected beyond week 12 were not included in the meta-analysis. The Cochrane-Mantel-Haenszel (CMH) test was used for odds ratios of AEs of interest.

2.5. Statistical methods

A random-effects approach was used for inferential analysis on efficacy data; this was because data were pooled from multiple studies with various sample sizes and different randomization and/or dosing schemes, and the methodology needed to account for heterogeneity across studies to minimize the risk of bias. The effect sizes in the studies were assumed to be a random sample of a distribution of true effect sizes.

The choice of the model was driven by the result of a test of heterogeneity using the classical measure of heterogeneity Cochran's Q. However, heterogeneity that would lead to the use of a different model was not found. Heterogeneity across studies was evaluated by presenting baseline characteristics and efficacy results by study.

Table 1
Main features of individual solifenacin studies included in the meta-analysis.

Study (Region)	ClinicalTrials.gov identifier	Phase	Planned sample size	Placebo-controlled	Double-blind	Fixed-dose monotherapy	Citation
905-CL-013 (US)	N/A	IIIa	Placebo (n = 315) Solifenacin 10 mg (n = 315)	Yes	Yes	Yes	Chu et al., 2009 [6]
905-CL-014 (US)	N/A	IIIa	Placebo (n = 315) Solifenacin 10 mg (n = 315)	Yes	Yes	Yes	Govier et al., 2010 [8]
905-CL-015 (EU)	N/A	IIIa	Placebo (n = 190) Tolterodine 2 × 2 mg (n = 190) Solifenacin 5 mg (n = 190) Solifenacin 10 mg (n = 190)	Yes	Yes	Yes	Chapple et al., 2004 [9]
905-CL-018 (EU)	N/A	IIIa	Placebo (n = 190) Solifenacin 5 mg (n = 190) Solifenacin 10 mg (n = 190)	Yes	Yes	Yes	Cardozo et al., 2004 [10]
905-EC-001 STAR (EU)	NCT00802373	IIIb	Tolterodine 4 mg (n = 474) Solifenacin 5 mg (n = 474)	No	Yes	No Flexible 5 mg–10 mg	Chapple et al., 2005 [11]
905-EC-002 SUNRISE (EU)	NCT00801944	IIIb	Placebo (n = 154) Solifenacin 5 mg (n = 462)	Yes	Yes	No Flexible 5 mg–10 mg	Cardozo et al., 2008 [12]
905-UC-005 VENUS (US)	NCT00454896	IIIb	Placebo (n = 360) Solifenacin 5 mg (n = 360)	Yes	Yes	No Flexible 5 mg–10 mg ^a	Karram et al., 2009 [13]
905-UC-006 VERSUS (US)	NCT00454740	IIIb	Single arm Solifenacin 5 mg (n = 441)	No	No	No Flexible 5 mg to 10 mg ^a	Chancellor et al., 2008 [14]
905-UC-007 VOLT (US)	NCT00463541	IIIb	Single arm Solifenacin 5 mg (n = 2000)	No	No	No Flexible 5 mg to 10 mg ^a	Garely et al., 2006 [15]
905-UC-10 VIBRANT (US)	NCT00573508	IV	Placebo (n = 381) Solifenacin 5 mg (n = 381)	Yes	Yes	No Flexible 5 mg to 10 mg ^a	Vardy et al., 2009 [16]
VES-001 VECTOR (CAN)	NCT00431041	IV	Oxybutynin IR 5 mg (n = 65) Solifenacin 5 mg (n = 65)	No	Yes	Yes	Herschorn et al., 2010 [17]

^a A reduction from 10 mg to 5 mg was also permitted.

N/A = not available.

There was no requirement for registering these studies on ClinicalTrials.gov at this time.

Prognostic factors (gender and age) for change in efficacy variables at endpoint were examined using Odds Ratios and 95% CIs and ANCOVA of pooled placebo arms of all placebo-controlled studies. Predictive factors for change in efficacy variables at endpoint (gender and age) were examined using ANCOVA for placebo-controlled monotherapy studies. For each response/normalization rate comparison between groups, a CMH test, controlling for study, was performed.

In order to report cumulative proportions of AEs, withdrawals from study drug, and withdrawals from study drug due to AEs, the Study Size-based (SS-based) approach described by Chuang-Stein and Beltangady [5] was used so that the risk difference was

collapsible across studies without suffering from Simpson's paradox [6]. In this meta-analysis, special attention was given to the estimation of cumulative proportions of AEs, withdrawals from study drug, and withdrawals from study drug due to AEs. For the purpose of visual comparison between cumulative proportions, a meta-analytic approach was used to adjust the cumulative proportions and account for differences between studies.

2.6. Data integration

The 11 studies included in the IDB took place prior to 2008. In 2009 Astellas implemented a global data standard, fully based on

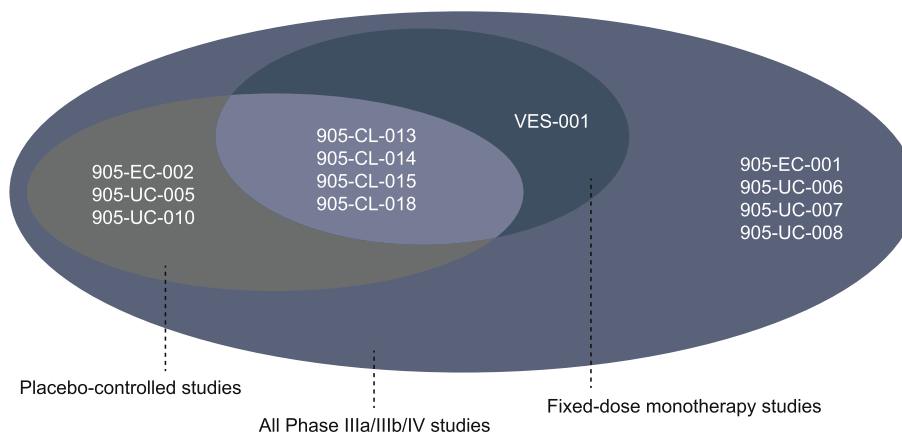


Fig. 1. Studies in the meta-analysis.

the Clinical Data Interchange Standards Consortium (CDISC) – an open, multidisciplinary, neutral, non-profit standards developing organization [7]. Practically, that meant that not all study databases followed the CDISC standard data structure, but instead followed locally agreed data standards applicable at the time of the individual study. Standards changed during the period in which the study databases were set-up. Also, some study databases were built in the US, others in Europe, resulting in different database structures. These time and location differences resulted in 11 study databases that were completely different in structure, format, and code lists.

Another source of variation between studies was the differing study designs. For example, studies had slightly different inclusion criteria; ie, some studies did have an inclusion criteria related to micturition frequency, whereas other studies selected patients on the basis of urgency. In addition, the study duration between studies differed, as did the timing for the visits.

Before integrating the 11 studies into one database, all study datasets of the individual study datasets were mapped towards a harmonized data model, following the Global standard within Astellas – the CDISC Study Data Tabulation Model (SDTM). To do so, a 6-step approach was taken (Fig. 2):

Step 1 – annotation of the case report form (CRF) pages and external data not collected on the CRF, for each study in the IDB. There were roughly 800 annotations to be made. The CRFs were all paper CRFs, which resulted in fully manual annotation. In this step, the current variable name and code list was written to the SDTM variable name and code list.

Step 2 – creation of project-specific SDTM specifications, for example handling of OAB-specific diary data.

Step 3 – the actual mapping of the CRF to the project-specific SDTM specifications. This mapping was carried out in Excel, as much as possible, in a format that could be read and understood by SAS® programs.

Step 4 – the preparation phase for the programming activities. Recoding in MedDRA of AEs was done to a single MedDRA version. Laboratory data, where applicable, were converted to standard units and standardized normal ranges were applied. The coding of concomitant medication was re-done using the same WHO drug dictionary for all studies. For demographics, code lists for race, gender and age groups were harmonized.

Step 5 – the actual programming. This included extraction of actual study data from different data management systems that were used for these studies, transporting the SAS® dataset files containing the study. Extracted data were then mapped following the instructions as created during Step 1 to 3. Some new variables were derived, such as baseline flags, reference dates and unique dataset keys.

Step 6 – verification:

1. Were all original data mapped to the new SDTM structured database?
2. Did the newly created database meet the SDTM structure as specified by the CDISC organization?
 - A tool called OpenCDISC was used to control the structure of the database
 - Study-specific elements were checked manually
3. Were all data derivations done correctly?
4. Were all data properly imported and were all code lists properly applied including MedDRA and the WHO drug dictionary?

As SDTM is uniform in its structure, formats and code lists, the databases of the different studies could be combined into a single database.

Data values were harmonized to ensure identical categorization, for example for race. Although the SDTM structured data is useful for harmonizing data values and data structures, it is not suitable for actual data analysis. The actual integration of the database was performed in a slightly different model – the Analysis Data Model (ADaM). The purpose of ADaM was to provide a framework

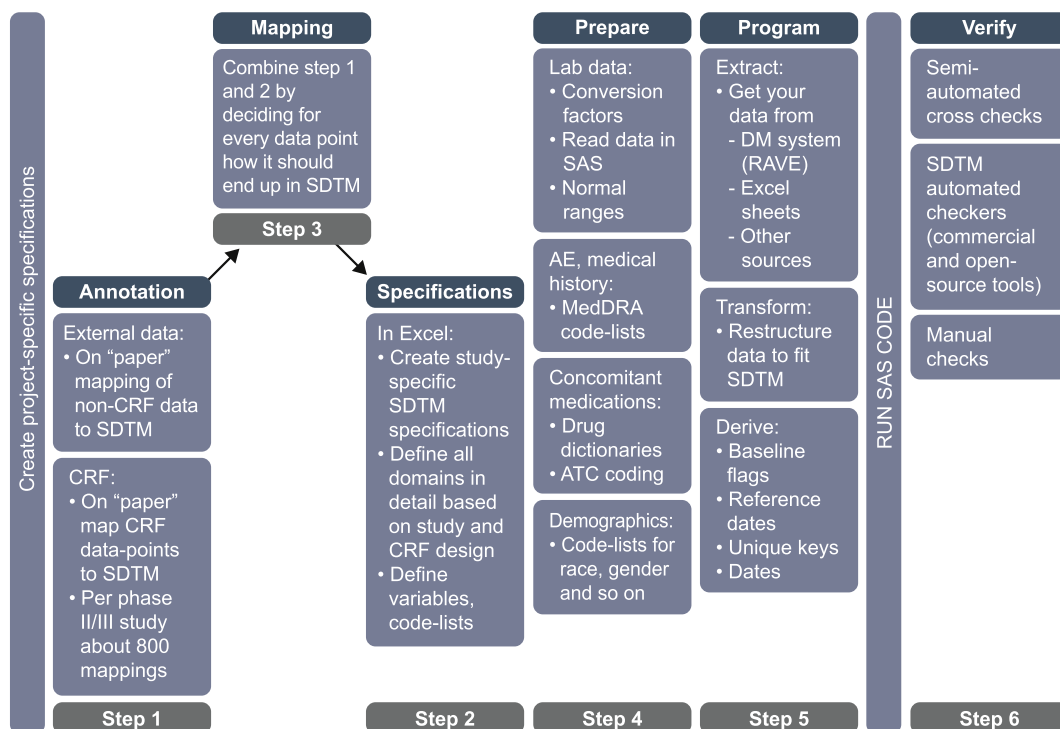


Fig. 2. Flow for creating SDTM datasets.

enabling reproducible and transparent datasets that allowed for efficient analysis of the study results. For the build of the ADaM datasets, specification sheets were created detailing every dataset and variable. First was identification of which domains should be built to fit the analysis plan. Two domains were created – namely a domain specifically for adverse events analysis (ADAE) and a domain for diary data (ADMD). Each domain contained subject IDs, treatment arm, demographic information, study results related to the domain, derived variables and categorical variables. Demographic information included age, region, race, height, weight and gender.

The categorical variables allowed for subgroup analysis, and could be used as covariates in ANCOVA analysis. Categorical variables included categories for age groups, BMI categories, baseline disease severity, and also categories for treatment and pooling. Mean number of micturitions, incontinence episodes and urgency episodes are all examples of derivations of the ADMD domain. Some patients had fewer diary dates than others. It was decided that a patient needed at least two diary visits for a mean number to be derived. This optimized the number of patients that could be used for analysis.

Visits were redefined based on the actual time on treatment. Redefining of visits was carried out using visit windows. For each patient, the last, on-treatment result was noted. For the ADAE, completely or partly missing dates were imputed to understand if an AE was treatment emergent. Imputation was done using a worst-case scenario; ie, if it could not be excluded that an AE was treatment emergent, then it was considered treatment emergent. No other imputation of missing values was done.

As different pooling strategies were used, categorical variables were created to quickly select those patients that belonged to a certain pool, including a variable that indicated the treatment arm for the pooling strategy. For example, for pool 1 it was useful to split between the two solifenacin doses (5 and 10 mg); however for pool 2 it was only useful to understand if patients received solifenacin or placebo.

Fig. 3 shows the process of integrating the database. Firstly, data were mapped towards one single data standard (SDTM). The SDTM formatted study datasets were integrated into one IDB, to which derivations were added. The integrated SDTM including the derivations was mapped towards ADaM.

2.7. Database validation

Mapping to SDTM and subsequently to ADaM was performed twice by two completely independent programming teams. Results of the two programming groups were compared. Any inconsistencies were investigated and, where necessary, corrected in the final output (Fig. 4). Micturition frequency at endpoint and the number of patients included in the SAF were examined. ADaM analysis sets included the Safety Analysis Set: randomized patients who took ≥1 dose of double-blind study medication and the Full Analysis Set: randomized patients who took ≥1 dose of double-blind study medication and had a baseline and ≥1 post-baseline efficacy assessment. Additional validation was via double programming: two programmers programmed the same dataset independent of each other and then compared the results of the two outputs created.

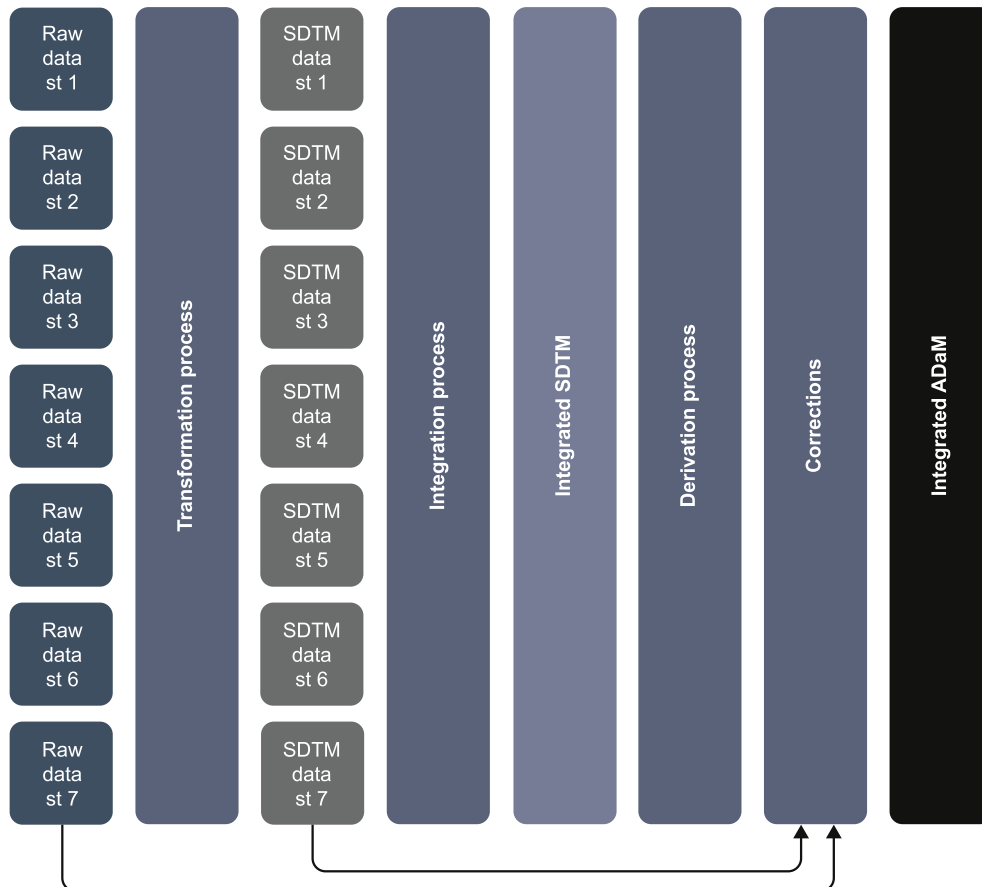


Fig. 3. Integration and derivation process.

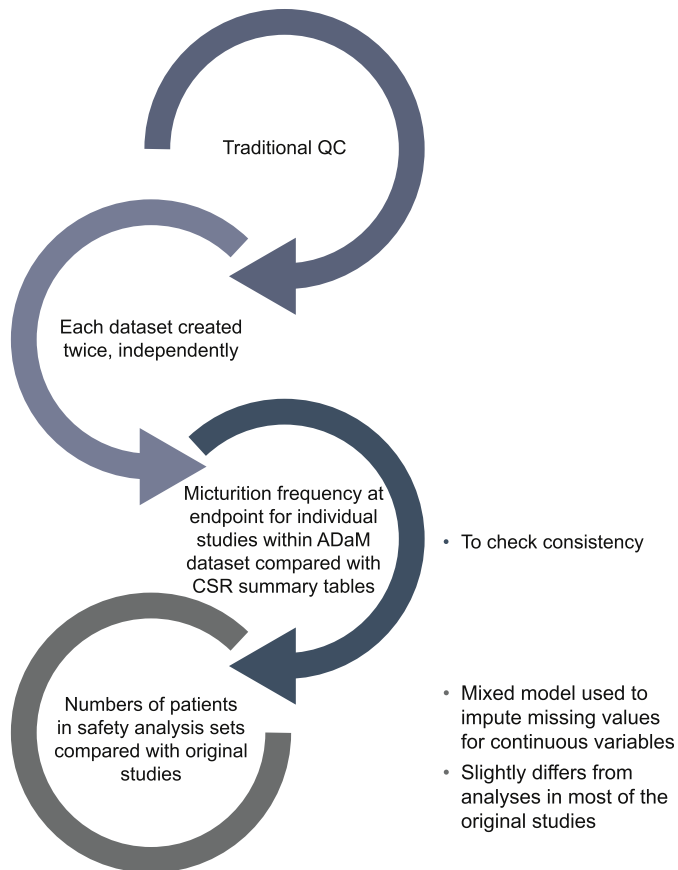


Fig. 4. Database integration validation.

groups were: solifenacin 5 mg fixed dose, solifenacin 5/10 mg flexible dose, solifenacin 10 mg fixed dose and overall solifenacin. Patient inclusion criteria varied a little across studies, but patients were similar enough for pooling of data to be acceptable. Table 3 shows ADaM datasets yielded from integration. When judging reliability of results from a meta-analysis, attention should focus on factors that might systematically influence the overall estimate of treatment difference. An important factor is the selection of studies for inclusion, as bias may be introduced by selective exclusion of some eligible studies. Justification for not including all studies in the pooling groups is as follows: comparisons with placebo excluded those studies that were not placebo-controlled, to minimize the risk of biased comparison; for example, aggregating results from a placebo-controlled study with those from a single-arm study in which subjects responded better on average than in the active group of the former study would result in a biased treatment difference towards inflation of the treatment effect. Flexible-dose regimen studies were excluded from dose-specific comparisons, since if adjusted doses and fixed doses are pooled, results cannot be interpreted as being those of a specific dose. In order to estimate incidence of rare AEs, all monotherapy studies were included so that all solifenacin monotherapy-treated subjects were evaluated. As three different active controls were used in a total of four studies, active control groups were disregarded.

Since the most specific comparisons were between fixed doses of solifenacin and placebo, analysis 1 (placebo-controlled, monotherapy, fixed-dose studies) was evaluated as the most adequate pooling strategy, followed by analysis group 2 (placebo-controlled studies) as a way to account for all placebo-controlled trials in a comparison of solifenacin and placebo that disregards dose and regimen. The third pooling strategy (all solifenacin monotherapy-treated patients) was utilized to detect rare TEAEs.

Table 2
Analysis groups.

Study	Analysis group 1 Placebo-controlled, monotherapy, fixed-dose (n = 3011)	Analysis group 2 Placebo-controlled, monotherapy, fixed- and flexible-dose (n = 5379)	Analysis group 3 All solifenacin monotherapy-treated patients only (n = 6539)
905-CL-013 (12 weeks)	10 mg	10 mg	10 mg
905-CL-014 (12 weeks)	10 mg	10 mg	10 mg
905-CL-015 (12 weeks)	5 mg, 10 mg	5 mg, 10 mg	5 mg, 10 mg
905-CL-018 (12 weeks)	5 mg, 10 mg	5 mg, 10 mg	5 mg, 10 mg
905-EC-002 SUNRISE (16 weeks)		5–10 mg	5–10 mg
905-UC-005 VENUS (12 weeks)		5–10 mg	5–10 mg
905-UC-10 VIBRANT (12 weeks)		5–10 mg	5–10 mg
VES-001 VECTOR (8 weeks) ^a			
905-EC-001 STAR (12 weeks) ^b			5 mg
905-UC-006 VERSUS (12 weeks, open-label)			5–10 mg
905-UC-007 VOLT 12 weeks, open-label)			5–10 mg

^a Control was oxybutynin.

^b Control was tolterodine.

3. Results and discussion

There were three analysis groupings (Table 2). Analysis group 1 comprised placebo-controlled, monotherapy, fixed-dose studies (n = 3011) and contained placebo, solifenacin 5 mg, solifenacin 10 mg and overall solifenacin treatment groups. Analysis group 2 comprised placebo-controlled, monotherapy, pooled, fixed- and flexible-dose (n = 5379), with placebo, solifenacin 10 mg and overall solifenacin groups. Analysis group 3 comprised all solifenacin monotherapy-treated patients (n = 6539). Treatment

Although all endpoints were pre-specified, we recognize the substantial risk of false positive findings due to the large number of endpoints, as no formal adjustment for multiplicity has been applied; therefore P-values need to be interpreted with caution.

Fig. 5 provides an example of an ADaM dataset. There were minor differences between ADaM datasets and the original study reports (Table 4); deviations were expected, due to harmonization of the studies. For example, there were more patients in ADaM than in some study reports because they had sufficient data (≥ 2 days), whereas inclusion in the original analysis demanded ≥ 3 diary

Table 3
ADaM datasets yielded from integration.

	Analysis group 1 Placebo-controlled, monotherapy, fixed-dose (n = 3026)		Analysis group 2 Placebo-controlled monotherapy, fixed and flexible dose (n = 5396)			Analysis group 3 All solifenacin monotherapy-treated patients only (n = 6534)		
	Placebo	Solifenacin 5 mg	Solifenacin 10 mg	Placebo	Solifenacin all	Solifenacin 5 mg	Solifenacin 10 mg	Solifenacin 5–10 mg
Safety Analysis Set	1216 40.2%	577 19.1%	1233 40.7%	2189 40.6%	3207 59.4%	645 9.9%	1233 18.9%	4656 71.3%
Full Analysis Set	1137 37.8%	552 18.3%	1158 38.5%	2077 38.6%	3081 57.3%	620 14.4%	1158 26.9%	2389 55.6%

Study number	Patient number	Test	Result	Visit	Arm	Baseline micturition category	Age	Age group	Gender	BMI	BMI group
905-CL-013	001	Micturitions/24 h	12.00	Baseline	Solifenacin 10 mg	High	67	65–<75 years	Female	29.18	Overweight
905-CL-013	001	Micturitions/24 h	10.33	Week 4	Solifenacin 10 mg	High	67	65–<75 years	Female	29.18	Overweight
905-CL-013	001	Micturitions/24 h	8.67	Week 8	Solifenacin 10 mg	High	67	65–<75 years	Female	29.18	Overweight
905-CL-013	001	Micturitions/24 h	10.67	Week 12	Solifenacin 10 mg	High	67	65–<75 years	Female	29.18	Overweight
905-CL-013	001	Micturitions/24 h	10.67	Endpoint	Solifenacin 10 mg	High	67	65–<75 years	Female	29.18	Overweight
905-CL-013	001	Urgency episodes/24 h	2.00	Baseline	Solifenacin 10 mg	High	67	65–<75 years	Female	29.18	Overweight
905-CL-013	001	Urgency episodes/24 h	0.33	Week 4	Solifenacin 10 mg	High	67	65–<75 years	Female	29.18	Overweight
905-CL-013	001	Urgency episodes/24 h	0.00	Week 8	Solifenacin 10 mg	High	67	65–<75 years	Female	29.18	Overweight
905-CL-013	001	Urgency episodes/24 h	0.67	Week 12	Solifenacin 10 mg	High	67	65–<75 years	Female	29.18	Overweight
905-CL-013	001	Urgency episodes/24 h	0.67	Endpoint	Solifenacin 10 mg	High	67	65–<75 years	Female	29.18	Overweight

**Fig. 5.** Example of ADaM data.

entries. These differences were harmonized into one methodology and therefore ADaM is a valid dataset for analysis.

4. Conclusions

Patient-level data from 11 randomized placebo- and/or active-controlled clinical trials of solifenacin that took place between 2001 and 2008 were consolidated into a large IDB. Analysis group 1 comprised placebo-controlled, monotherapy, fixed-dose studies (n = 3011), analysis group 2 comprised placebo-controlled, monotherapy, pooled, fixed- and flexible-dose (n = 5379), and analysis group 3 comprised all solifenacin monotherapy-treated patients (n = 6539). Creating the ADaM datasets provided a significant amount of information about the individual studies and the derivation decisions made in each study; validated ADaM datasets now exist for medical history, efficacy, and AEs. Although one might think that a study performed in 2001 could produce slightly different results to a study performed in 2008, due to changes in the population or changes in treatment methods or beliefs in each time

period, results from these meta-analyses showed that results were similar over time.

Availability of data and materials

905-CL-013: <https://www.astellasclinicalstudyresults.com/hcp/study.aspx?ID=905-CL-013>
 905-CL-014: <https://www.astellasclinicalstudyresults.com/hcp/study.aspx?ID=905-CL-014>
 905-CL-015: <https://www.astellasclinicalstudyresults.com/hcp/study.aspx?ID=905-CL-015>
 905-CL-018: <https://www.astellasclinicalstudyresults.com/hcp/study.aspx?ID=905-CL-018>
 905-EC-001 STAR: <https://clinicaltrials.gov/ct2/show/NCT00802373?term=NCT00802373&rank=1>
 905-EC-002 SUNRISE: <https://clinicaltrials.gov/ct2/show/NCT00801944?term=NCT00801944&rank=1>
 905-UC-005 VENUS: <https://clinicaltrials.gov/ct2/show/NCT00454896?term=NCT00454896&rank=1>

Table 4
Endpoint mean change for ADaM dataset vs CSR for average micturitions/24 h (differences in bold).

Study	Treatment	ADaM	CSR	ADaM	ADaM	CSR	ADaM	CSR	ADaM	CSR	ADaM	CSR
		n	n	LS mean (SE)	Mean change	Mean	LS mean difference (SE)	LS Mean difference	P-value	P-value	95% CI	95% CI
905-CL-013	Placebo	309	309	-1.55 (0.132)	-1.52	-1.5						
	Solifenacin 10 mg	305	306	-2.96 (0.133)	-2.99	-3.0	-1.41 (0.187)	-1.5	<0.001	<0.001	(-1.77, -1.04)	
905-CL-014	Placebo	295	295	-1.26 (0.143)	-1.31	-1.3						
	Solifenacin 10 mg	298	298	-2.46 (0.142)	-2.41	-2.4	-1.20 (0.202)	-1.1	<0.001	<0.001	(-1.59, -0.80)	
905-CL-015	Placebo	253	253	-1.18 (0.177)	-1.18	-1.20						
	Solifenacin 5 mg	266	266	-2.25 (0.172)	-2.21	-2.19	-1.07 (0.247)	-1.02	<0.001	<0.001	(-1.55, -0.58)	(-1.50, -0.54)
	Solifenacin 10 mg	264	264	-2.58 (0.173)	-2.62	-2.61	-1.40 (0.247)	-1.37	<0.001	<0.001	(-1.88, -0.91)	(-1.85, -0.89)
905-CL-018	Placebo	280	281	-1.64 (0.171)	-1.68	-1.66						
	Solifenacin 5 mg	286	286	-2.50 (0.169)	-2.48	-2.45	-0.86 (0.240)	-0.78	<0.001	<0.01	(-1.33, -0.39)	(-1.27, -0.29)
	Solifenacin 10 mg	290	290	-2.91 (0.168)	-2.90	-2.88	-1.27 (0.239)	-1.22	<0.001	<0.001	(-1.74, -0.80)	(-1.71, -0.72)
905-EC-002 SUNRISE	Placebo	216	216	-1.24 (0.355)	-1.22	-1.3						
	Solifenacin flexible 5/10 mg	636	637	-2.07 (0.324)	-2.08	-2.0	-0.83 (0.480)	-0.7	0.084	0.001	(-1.77, -0.11)	(-1.2, -0.3)
905-UC-005 VENUS	Placebo	347	337	-1.84 (0.153)	-1.86	-1.94						
	Solifenacin flexible 5/10 mg	352	348	-2.65 (0.152)	-2.64	-2.67	-0.81 (0.215)		<0.001	<0.01	(-1.23, -0.39)	
905-UC-10 VIBRANT	Placebo	363	363	-1.27 (0.151)	-1.29	-1.36						
	Solifenacin flexible 5/10 mg	369	369	-2.21 (0.150)	-2.19	-2.23	-0.94 (0.213)	-0.90	<0.001	<0.001	(-1.36, -0.52)	(-1.3, -0.5)

905-UC-006 VERSUS: <https://clinicaltrials.gov/ct2/show/NCT00454740?term=NCT00454740&rank=1>

905-UC-007 VOLT: <https://clinicaltrials.gov/ct2/show/NCT00463541?term=NCT00463541&rank=1>

905-UC-10 VIBRANT: <https://clinicaltrials.gov/ct2/show/NCT00573508?term=NCT00573508&rank=1>

VES-001 VECTOR: <https://clinicaltrials.gov/ct2/show/NCT00431041?term=NCT00431041&rank=1>

Consent to publish

Not applicable.

Competing interests

CRC is a Consultant, Researcher and Speaker for Astellas, Allergan, Medtronic and Recordati; a Consultant and Speaker for Lilly; a Researcher and Speaker for Ono and Pfizer; and a Speaker for Ranbaxy. LC is a Consultant and Speaker for Astellas and Allergan; a Consultant for BMR; and a Consultant and Researcher for Pfizer. RS and ES are employees of Astellas. SH receives grants and personal fees from Astellas and Allergan; and personal fees from Pfizer and Merus.

Authors' contributions

All of the authors participated in the interpretation of the data and writing of the manuscript, reviewed the manuscript drafts and contributed to revision of the manuscript. The decision to submit the article for publication was made by all of the authors.

Category

Study Design, Statistical Design, Study Protocols.

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