U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA Serial Number:	213801
Drug Name:	Myrbetriq Granules (Mirabegron for extended release oral suspension)
Indication(s):	Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 3 years and older
Applicant:	Astellas Pharma Global Development, INC.
Date(s):	Receipt Date: 09/28/2020
	PDUFA Date: 03/28/2021
Review Priority:	Priority
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Jia Guo, Ph.D.
Concurring Reviewers:	Daphne Lin, Ph.D. Acting Team Leader, Deputy Director
Medical Division:	Division of Urology, Obstetrics and Gynecology (DUOG)
Clinical Team:	Elena Boley, M.D., Clinical Reviewer
	Mark Hirsch, M.D., Clinical Team Leader
Project Manager:	Nenita Crisostomo

Keywords: Change from Baseline

Table of Contents

LIST OF TABLES

1 EXECUTIVE SUMMARY

Myrbetriq® 25 mg and 50 mg tablets (Mirabegron) is currently approved under NDA 202611 for treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency in adults. A Written Request (WR) for the use of mirabegron in treatment of neurogenic detrusor overactivity (NDO) in pediatric patients was issued under NDA 202611 on 18 March 2016.

In this submission, the Applicant submitted the safety and efficacy data from one study to fulfill the WR and seek approval of mirabegron for NDO in pediatric patients. This review is to evaluate from a statistical perspective if the submitted information supports this claim.

The study was a multinational, multi-center, open-label, single arm phase 3 study with a 12-week dose titration period followed by 40 weeks of treatment with fixed dose in subjects between 3 to 18 years old.

The primary efficacy endpoint was the change from baseline in maximum cystometric capacity (MCC) during treatment period at week 24 (measured in mL). It was summarized using descriptive statistics and the mean change from baseline estimate, together with 95% CI. The lower bound of the two-sided 95% CI was assessed to see if it excluded 0. Due to lack of a control group, the interpretation of the results is descriptive in nature. Secondary efficacy endpoints based on urodynamics and patient diary were also evaluated in a similar way as the primary efficacy endpoint.

In children (3-12 years old), the MCC was increased by 72.1 mL (SD: 87.1, 95% CI 45.3 to 98.9); in adolescents (12-18 years old), the MCC was increased by 113.2 mL (SD: 83.0, 95% CI 79.0 to 147.5);

The study demonstrated that there is clinical benefit of mirabegron in treatment of NDO in pediatric subjects.

2 INTRODUCTION

2.1 Overview

The Applicant, Astellas Pharma Global Development INC., submitted an original New Drug Application (NDA 213801) for mirabegron granules oral suspension for treatment of neurogenic detrusor overactivity (NDO) in pediatric subjects.

According to the Applicant,

> *"mirabegron acts to relieve the symptoms of overactive bladder via its agonist effects on beta-3 adrenoceptors resulting in bladder smooth-muscle relaxation and increased bladder compliance."*

Mirabegron (25mg and 50 mg tablets) is currently approved in the US under NDA 202611 for treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency in adults. A Written Request (WR) for the use of mirabegron in treatment of neurogenic detrusor overactivity (NDO) in pediatric subjects was issued under NDA 202611 on 18 Mar 2016.

The statistical review for this NDA is based on one open-label, single arm phase 3 studies, 178-cl-206a, which is briefly summarized in Table 1.

Table 1: List of all Studies included in the Statistical Review

Study	Phase and Design	Treatment Period	# of Subjects per Arm	Study Population
178-cl-206a	Phase 3, open label, baseline controlled, multicenter	Titration: 12 weeks Fixed dose: 40 weeks	Enrolled: 91 subjects Completed: 70 subjects	pediatric subjects with NDO aged 3-18 years old

Source: Statistical reviewer's summary.

2.2 Data Sources

The study protocols, reports, data and additional information were submitted electronically, and are located in the Electronic Document Room at \\cdsesub1\evsprod\NDA213801 under submission dates 09/28/2020, 12/22/2020, 12/24/2020, 2/11/2021, 2/19/2021, 3/08/2021, and 3/09/2021.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The Applicant submitted both tabulation data and analysis data for the study. Data sets were complete and documented. Statistical analysis programs were submitted.

The statistical analyses of efficacy endpoints were carried out following the pre-specified statistical analysis plan with some exceptions.

It was noted that the Applicant conducted an ad-hoc analysis for a secondary efficacy endpoint, i.e. mean number of leakage episodes, excluding a subject with data error and imputing subjects who did not report any leakage episodes during the visit with a "0" leakage episode for that visit. In the response to FDA's information request on the justification of the above imputation approach, the Applicant clarified that in the ediary, a subject was asked, whether he/she had any leakage episodes between catheterizations (Y/N). If "Yes", the next ediary screen asked for the number of leakages or to check a box for "I Don't Know". The subject should provide either a number or checkmark to continue. If "No", then no number is recorded and the ediary continues to the next module. However, the Applicant found that the imputation rule did not entirely follow the above logic in the ediary when constructing the analysis dataset. The Applicant submitted the updated dataset for this endpoint considering the logic in the ediary and reanalyzed it following FDA's recommendation on missing data imputation.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 178-cl-206a was a phase 3, open-label, baseline-controlled, multicenter study to assess the efficacy, safety and pharmacokinetics, of mirabegron in 3 to <18 years old children with NDO.

The study consisted 3 periods:

- Pretreatment period: for a maximum of 28 days before baseline, including screening, washout (if applicable) and baseline;
- Efficacy treatment period: beginning the day after baseline and continuing to visit 8/week 24;
- Long-term safety period: beginning after visit 8/week 24 and continuing to visit 10/week 52 (end of study [EOS]), or to the end of treatment (EOT).

At visit 4/week 2, visit 5/week 4 or visit 6/week 8, subjects must be up-titrated to the pediatric equivalent dose of 50 mg in adults (PED50), based on the given dose titration criteria. At visit 8/week 24, efficacy was assessed. For long-term safety evaluation, following visit 8/week 24, subjects stayed on their individual dose level until visit 10/week 52 (EOT/EOS).

The primary efficacy endpoint was the change from baseline to week 24 in maximum cystometric capacity (MCC) measured in mL based on the urodynamic data. The secondary efficacy endpoints of clinical interest were as follows.

Changes from baseline to week 24 in:

- Bladder compliance (mL/cm H_2O);
- Number of overactive detrusor contractions (> 15 cmH_2O) until leakage or end of bladder-filling;
- Bladder volume prior to first detrusor contraction > 15 cmH_2O;
- Maximum catheterized volume per day;
- Mean number of leakage episodes per day;

3.2.2 Statistical Methodologies

The Applicant pre-defined the following analysis sets in the study protocol,

Safety Analysis Set (SAF): all subjects who took at least one dose of study drug. The SAF was used for summaries of demographic and baseline characteristics and all safety and tolerability related variables.

Full Analysis Set (FAS): all subjects who took at least one dose of study drug and provided both valid baseline and at least one post-baseline value for the primary efficacy endpoint (MCC). The FAS was used for analyses of efficacy data.

Per Protocol Set (PPS): all subjects of the FAS who fulfilled the protocol in terms of their eligibility, interventions and outcome assessments, and for whom MCC measurements at baseline/visit 3 and at visit 8 (week 24) were reported.

Analysis of primary efficacy endpoint

MCC and changes from baseline in MCC at visit 8/week 24 were summarized using descriptive statistics for all subjects in the FAS. Missing MCC observations at visit 8/week 24 were imputed using the last observation carried forward (LOCF) method. Mean change from baseline estimates, together with 95% CIs were provided. The lower bound of the two-sided 95% CI was assessed to see if it excluded 0.

The primary analysis was conducted in children (3 to <12 years old) and adolescents (12 to <18 years old) as well.

The Applicant also conducted the following analyses of the primary efficacy endpoint including

- the analysis with LOCF for the PPS;
- the analysis without LOCF for the FAS and PPS;
- the analysis using BOCF for all enrolled subjects;
- the sensitivity analysis using repeated measures ANCOVA in the FAS and PPS;
- the sensitivity analysis using the Wilcoxon signed-rank test, with or without LOCF in the FAS.

Analysis of secondary efficacy endpoints

Each of the secondary efficacy endpoints was summarized with descriptive statistics. The mean change from baseline estimate together with 95% CI was provided. All analyses of secondary endpoints were conducted for subjects in the FAS.

The bladder volume (mL) until the first detrusor contraction (>15 cm H_2O) was imputed using MCC if no contraction occurred. No imputation was done for other secondary efficacy endpoints.

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

Subject Disposition

The disposition of study subjects and the analysis sets are summarized for the study (Table 2). A total of 113 subjects were screened and 91 subjects were enrolled. 86 subjects received treatment and 16 subjects discontinued the study drug.

Table 2: Summary of Subject Disposition and Analysis Sets

	Children 3 to <12 years old n (%)	**Adolescents 12 to <18 years old n (%)**	**Total n (%)**
Screened	69	44	113
Enrolled	56	35	91
Received study drug	55 (100%)	31 (100%)	86 (100%)
Treatment discontinuation[1]	12 (21.8%)	4 (12.9%)	16 (18.6%)
Primary reasons for discontinuation [1]			
Adverse event	3 (5.5%)	0	3 (3.5%)
Other	9 (16.4%)	4 (12.9%)	13 (15.1%)
Safety analysis set	55 (98.2%)	31 (88.6%)	86 (94.5%)
Full analysis set	43 (76.8%)	25 (71.4%)	68 (74.7%)
Per protocol set	38 (67.9%)	22 (62.9%)	60 (65.9%)

Source: Tables 12.1.1.4.4 and Table 3 in study report.

1 The percentage is calculated using number of treated as the denominator.

Demographics and Baseline Characteristics

In the SAF, among all subjects (age 3 to < 18 years old), approximately half were female (54.7%); most were White (72.1%) and 3 (3.5%) subjects were Hispanic or Latino. The mean age (SD) was 10.1 (3.7) years and the mean weight (SD) was 37.45 (16.90) kg. There were more children than adolescents in this study (55 and 31, respectively in the SAF). The mean age (SD) and weight (SD) for children was 7.9 (2.5) years and 29.83 (13.41) kg. The mean age (SD) and weight (SD) for adolescents was 14.0 (1.7) years and 50.96 (13.78) kg. The demographic and baseline characteristics are summarized for each age group as shown in Table 11 (Appendix).

3.2.4 Results and Conclusions

Maximum Cystometric Capacity

The analysis results for the primary efficacy endpoints are shown in Table 3. At week 24, both children and adolescents had increase in MCC compared with baseline with a mean (SD) of 72.1

(87.1) mL and 113.2 (83.0) mL, respectively. The corresponding 95% CIs are (45.3, 98.9) and (79.0, 147.5) with lower bounds are all above 0.

Table 3: Change from Baseline in Maximum Cystometric Capacity (mL) (FAS)

Statistic	Children (3 to < 12 Years) n = 43	Adolescents (12 to < 18 Years) n = 25	All Subjects (3 to < 18 Years) n = 68
Baseline Mean (SD)	158.6 (94.5)	238.9 (99.1)	188.2 (103.2)
Week 24 Mean (SD)	230.7 (129.2)	352.1 (125.2)	275.4 (139.9)
Mean Change from Baseline (SD)	72.1 (87.1)	113.2 (83.0)	87.2 (87.3)
95% CI	(45.3, 98.9)	(79.0, 147.5)	(66.1, 108.3)

Source: Table 9 in study report. FAS: full analysis set; LOCF: last observation carried forward;

Sensitivity analysis results are consistent with the primary analysis results.

Bladder Compliance

At week 24, the mean change in bladder compliance from baseline was 14.6 (95% CI: -0.3, 29.5) mL/cm H_2O in children, and 13.6 mL/cm H2O (95% CI: 6.7, 20.4) in adolescents.

Table 4: Change from Baseline to Week 24 in Bladder Compliance (mL/cm H_2O) (FAS)

Statistic	Children (3 to < 12 Years) n = 43	Adolescents (12 to < 18 Years) n = 25	All Subjects (3 to < 18 Years) n = 68
Baseline			
n	33	21	54
Mean (SD)	16.0 (55.8)	11.1 (10.7)	14.1 (43.9)
Week 24			
Mean (SD)	30.6 (54.2)	24.7 (15.2)	28.3 (42.3)
Mean Change from Baseline (SD)	14.6 (42.1)	13.6 (15.0)	14.2 (34.0)
95% CI	(-0.3, 29.5)	(6.7, 20.4)	(4.9, 23.5)

Source: Table 12.3.3.1, Table 12.3.3.2 in study report and FDA reviewer's analysis.

Number of Overactive Detrusor Contractions (> 15 cm H_2O) Until End of Bladder-filling

At week 24, the mean change in number of overactive detrusor contractions (> 15 cmH_2O) from baseline was -1.9 (95% CI: -3.3, -0.4) in children and -0.8 (95% CI: -2.5, 0.9) in adolescents.

Table 5: Change from Baseline to Week 24 in Number of Overactive Detrusor Contractions (> 15 cm H_2O) Until End of Bladder-filling (FAS)

Statistic	Children (3 to < 12 Years) n = 43	Adolescents (12 to < 18 Years) n = 25	All Subjects (3 to < 18 Years) n = 68
Baseline			
n	36	22	58
Mean (SD)	3.0 (4.0)	2.1 (3.1)	2.7 (3.7)
Week 24			
Mean (SD)	1.1 (2.2)	1.5 (2.4)	1.2 (2.3)
Mean Change from Baseline (SD)	-1.9 (4.2)	-0.8 (3.9)	-1.4 (4.1)
95% CI	(-3.3, -0.4)	(-2.5, 0.9)	(-2.5, -0.4)

Source: Table 12.3.4.2 in study report and FDA reviewer's analysis.

Bladder Volume until First Detrusor Contraction > 15 cm H_2O

At week 24, the mean change in bladder volume until first detrusor contraction > 15 cm H_2O was 93.1 (95% CI: 64.1, 122.1) mL compared with baseline in children, and 121.3 (95% CI: 53.8, 188.8) mL in adolescents.

Table 6: Change from Baseline to Week 24 in Bladder Volume until First Detrusor Contraction > 15 cm H_2O

Statistic	Children (3 to < 12 Years) n = 43	Adolescents (12 to < 18 Years) n = 25	All Subjects (3 to < 18 Years) n = 68
Baseline			
n	38	24	62
Mean (SD)	114.8 (82.9)	177.4 (117.3)	139.0 (101.5)
Week 24			
n	38	24	62
Mean (SD)	207.9 (97.8)	298.7 (144.4)	243.0 (125.1)
Mean Change from Baseline (SD)	93.1 (88.1)	121.3 (159.8)	104.0 (120.6)
95% CI	(64.1, 122.1)	(53.8, 188.8)	(73.4, 134.6)

Source: Table 12.3.6.3 submitted on 3/8/20201.

Maximum Catheterized Volume per day

At week 24, the mean change in maximum catheterized volume per day compared to baseline was 49.9 mL (95% CI: 17.1, 82.6) in children and 84.4 mL (95% CI: 31.6, 137.1) in adolescents.

Table 7: Change from Baseline to Week 24 in Maximum Catheterized Daytime Volume (mL) (FAS)

Statistic	Children (3 to < 12 Years) n = 43	Adolescents (12 to < 18 Years) n = 25	All Subjects (3 to < 18 Years) n = 68
Baseline			
n	41	23	64
Mean (SD)	304.1 (109.4)	360.0 (111.4)	324.2 (112.5)
Week 24			
n	41	23	64
Mean (SD)	354.0 (104.5)	450.0 (146.6)	386.4 (128.2)
Mean Change from Baseline (SD)	49.9 (103.7)	84.4 (122.0)	62.3 (110.9)
95% CI	(17.1, 82.6)	(31.6, 137.1)	(34.6, 90.0)

Source: Table 12.3.8.2 in study report and FDA reviewer's analysis.

Mean Number of Leakage Episodes per 24 Hours

The Applicant identified that subject (b) (6) entered the weight of the leakages in the ediary instead of the number of leakage episodes, which resulted that this subject had values that were 10-fold higher than those of the other subjects.

In the study report, the Applicant conducted an ad-hoc analysis excluding this subject and imputing subjects who did not report any leakage episodes during the visit with a "0" leakage episode for that visit. The reviewer found this imputation approach is NOT appropriate because it is impossible to differentiate scenarios between missing leakage episodes and no leakage episodes using the data itself. Such best-scenario imputation approach might introduce strong bias toward positive treatment effect.

In the response to FDA's information request on the justification of the above imputation approach, the Applicant clarified the logic in the ediary. In the ediary, the subject was asked, whether he/she had any leakage episodes between catheterizations (Y/N). If "Yes", the next ediary screen asked for the number of leakages or to check a box for "I Don't Know". The subject had to provide either the number of leakages or checkmark to continue. If "No", then no number was recorded and the ediary continued to the next module. The Applicant found that imputation approach did not entirely follow this logic when constructing the analysis dataset.

Following FDA's recommendation that if "no leakage episode" was confirmed, then number of leakages should be set as 0; if leakage occurred, but number of leakage episodes was not reported, then number of leakages should be set as missing, the Applicant submitted updated dataset for this endpoint and reanalyzed it.

At week 24, the mean number of leakage episodes per day decreased by -2.0 (95% CI: -3.2, -0.7) and -1.0 (95% CI: -1.5, -0.5) from baseline in children and adolescents respectively (Table 8).

Table 8: Change from Baseline to Week 24 in Mean Number of Leakage Episodes per 24 Hours (FAS)

Statistic	Children (3 to < 12 Years) N = 43	Adolescents (12 to < 18 Years) N = 25	All Subjects (3 to < 18 Years) N = 68
Baseline			
n	26	21	47
Mean (SD)	2.8 (3.7)	1.8 (1.7)	2.3 (3.0)
Week 24			
n	26	21	47
Mean (SD)	0.8 (1.3)	0.8 (1.1)	0.8 (1.2)
Mean Change from Baseline (SD)	-2.0 (3.2)	-1.0 (1.1)	-1.5 (2.5)
95% CI	(-3.2, -0.7)	(-1.5, -0.5)	(-2.3, -0.8)

Source: Table 12.3.11.16 submitted on 12/22/2020; FDA reviewer's analysis. Subject (b) (6) was excluded.

3.3 Evaluation of Safety

Refer to the clinical reviewer's report for evaluation of safety data.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Efficacy of mirabegron was also explored by subgroups defined by gender (female, male), race (White, Asian) descriptively.

MCC and change from baseline in MCC are summarized by gender for all subjects and for children and adolescents respectively in the FAS (see Table 9). In both male and female subjects, there was an increase in the MCC at week 24 comparing to baseline.

Table 9: Subgroup Analysis of Change from Baseline to Week 24 (LOCF) in Maximum Cystometric Capacity (mL) by Gender (FAS)

Statistic	Male	Female
All Subjects		
Baseline		
n	32	36
Mean (SD)	202.9 (110.4)	175.1 (95.9)
Week 24 (LOCF)		
Mean (SD)	309.7 (157.6)	244.8 (115.8)
Mean Change from Baseline (SD)	106.9 (83.9)	69.7 (87.7)
95% CI	(76.6, 137.1)	(40.1, 99.4)
Children (3 to <12 Years)		
Baseline		
n	17	26
Mean (SD)	173.2 (109.8)	149.1 (83.9)
Week 24 (LOCF)		
Mean (SD)	267.1 (169.1)	207.0 (90.9)
Mean Change from Baseline (SD)	93.8 (83.9)	57.9 (87.8)
95% CI	(50.7, 137.0)	(22.4, 93.3)
Adolescents (12 to < 18 Years)		
Baseline		
N	15	10
Mean (SD)	236.5 (104.5)	242.6 (83.9)
Week 24 (LOCF)		
Mean (SD)	358.1 (132.6)	343.1 (119.6)
Mean Change from Baseline (SD)	121.7 (84.2)	100.5 (83.9)
95% CI	(75.0, 168.3)	(40.5, 160.6)

Source: Table 16 in study report and FDA reviewer's analysis.

In both White and Asian subjects, there was an increase in the MCC at week 24 comparing to baseline for the overall population. Within children and adolescents respectively, Asian subjects seems to have less improvement from baseline compared to White subjects. However, the number of Asian subjects was limited, no definitive conclusion can be drawn.

Table 10: Change from Baseline to Week 24 in Maximum Cystometric Capacity (mL) at Week 24 (LOCF) by Race (FAS)

Statistic	White	Asian
All Subjects		
Baseline		
n	49	19
Mean (SD)	189.9 (109.0)	183.7 (88.9)
Week 24		
Mean (SD)	294.7 (149.0)	225.5 (99.8)
Mean Change from Baseline (SD)	104.8 (89.8)	41.8 (62.0)
95% CI	(79.0, 130.6)	(12.0, 71.7)
Children (3 to <12 Years)		
Baseline		
n	31	12
Mean (SD)	162.6 (99.5)	148.3 (83.4)

Week 24 (LOCF) Mean (SD) Mean Change from Baseline (SD) 95% CI	 251.3 (142.4) 88.7 (91.7) (55.0, 122.3)	 177.6 (64.3) 29.3 (56.9) (-6.9, 65.4)
Adolescents (12 to < 18 Years)		
Baseline N Mean (SD)	 18 236.8 (111.3)	 7 244.3 (64.7)
Week 24 (LOCF) Mean (SD) Mean Change from Baseline (SD) 95% CI	 369.4 (132.5) 132.6 (81.5) (92.0, 173.1)	 307.7 (99.1) 63.4 (68.7) (-0.1, 127.0)

Source: Table 17 in study report and FDA reviewer's analysis.

4.2 Other Special/Subgroup Populations

The Applicant also conducted subgroup analysis by drug formulation (oral suspension vs. tablet). However, this subgroup is highly confounded by age. In the FAS set, 70% (30 out of 43) of children took suspension formulation and 88% (22 out of 25) of adolescents took tablet formulation. Therefore, this subgroup analysis can't provide supportive information to evaluate if there is differential effect due to formulation after adjusting for the age groups.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The Applicant submitted an open-label, single-arm, phase 3 study to evaluate the efficacy and safety of mirabegron in pediatric subjects and to fulfill the written request. The study had limitations due to lack of control group for ethical reason. Therefore, the evaluation of the treatment effect on efficacy is descriptive in nature.

The primary and secondary efficacy endpoints based on the urodynamic assessments and patient diaries demonstrated improvement at week 24 compared to baseline in general.

5.2 Conclusions and Recommendations

The purpose of this review is to evaluate the efficacy data in support of mirabegron in the treatment of NDO in pediatric patients. Based on reviewer's analyses, the submitted study demonstrated clinical benefit for this indication in pediatric patients.

6 APPENDICES

Table 11: Summary of Demographics and Baseline Characteristics (SAF)

Parameter Category/ Statistics	Children (3 to < 12 Years) n = 55	Adolescents (12 to < 18 Years) n = 31	All Subjects (3 to < 18 Years) n = 86
Sex, n (%)			
Male	22 (40.0%)	17 (54.8%)	39 (45.3%)
Female	33 (60.0%)	14 (45.2%)	47 (54.7%)
Age, years†			
Mean (SD)	7.9 (2.5)	14.0 (1.7)	10.1 (3.7)
Median	9.0	14.0	10.0
Min - Max	3 - 11	12 - 17	3 – 17
Race, n (%)			
White	40 (72.7%)	22 (71.0%)	62 (72.1%)
Black/African American	0	0	0
Asian	13 (23.6%)	7 (22.6%)	20 (23.3%)
American Indian/Alaska Native	0	1 (3.2%)	1 (1.2%)
Native Hawaiian/Pacific Islander	0	0	0
Other	2 (3.6%)	1 (3.2%)	3 (3.5%)
Ethnicity, n (%)			
Hispanic or Latino	1 (1.8%)	2 (6.5%)	3 (3.5%)
Not Hispanic or Latino	54 (98.2%)	29 (93.5%)	83 (96.5%)
Weight, kg‡			
n	55	31	86
Mean (SD)	29.83 (13.41)	50.96 (13.78)	37.45 (16.90)
Median	28.00	47.50	35.85
Min – Max	12.6 – 69.7	28.2 – 78.5	12.6 – 78.5
Height, cm‡			
n	55	31	86
Mean (SD)	124.77 (18.69)	152.91 (12.06)	134.91 (21.40)
Median	128.00	152.00	138.75
Min – Max	92.1 – 160.0	120.0 – 178.0	92.1 – 178.0
BMI, kg/m^2‡			
n	55	31	86
Mean (SD)	18.18 (3.94)	21.96 (6.02)	19.55 (5.10)
Median	17.10	19.80	18.35
Min – Max	11.9 – 27.2	10.5 – 33.3	10.5 – 33.3

Source: Table 5 in study report.
All subjects who received ≥ 1 dose of study drug (SAF).
BMI: body mass index; eCRF: electronic case report form; Max: maximum; Min: minimum; SAF: safety analysis set.
† Age at screening was calculated as (date of last informed consent given at screening - date of birth +1)/365.25. If the date of birth was not given, the age at screening was equal to the value recorded on the demographics page of the eCRF (an integer number of years) plus 0.5.
‡ BMI = weight (kg)/ [height (m^2)]. Height and weight were assessed at screening.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JIA GUO
03/11/2021 02:02:54 PM

TSAE YUN D LIN
03/11/2021 03:07:11 PM