I-070

Population Pharmacokinetic Modeling to Support Dose Selection of Zavegepant Nasal Spray in Pediatrics

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INTRODUCTION

- Zavegepant nasal spray is a calcitonin gene-related peptide receptor antagonist indicated in the United States for acute treatment of migraine in adults, with a recommended dose of 10 mg as needed up to once a day.[1]
- Pediatric migraine is common, with an estimated prevalence of 11% in children and adolescents.[2]

OBJECTIVES

- Predict zavegepant exposures in pediatric populations 6 to 17 years old and across different ranges of body weight using a zavegepant population pharmacokinetic (PPK) model, which was developed using adult pharmacokinetic (PK) data and assuming empirical allometric scaling.
- Provide dosing selection of zavegepant nasal spray for pediatric populations 6 to 17 years old and across different ranges of body weight by matching pediatric exposures to adult exposures.

METHODS

PPK MODEL

- The PPK model was previously developed and validated using data from 10 phase 1 studies of zavegepant (intravenous, oral, and intranasal formulations) in adults. It is a 3-compartment model with sequential zero- and first-order absorption and first-order elimination from the central compartment (**Supplementary Figure**).
  - Body weight–based empirical allometric scaling was applied to all disposition parameters using standard exponents (0.75 for clearances and 1 for volumes of distribution).
  - Interindividual variability terms were included on elimination clearance, central and first peripheral volumes of distribution, bioavailability of nasal spray and soft gelatin capsules, and absorption rate constant and duration of absorption for nasal spray and soft gelatin capsules (**Supplementary Table**).

SIMULATIONS

- The PPK model was used to simulate exposure in virtual pediatric populations (6 to 17 years old) following single administrations of zavegepant nasal spray.
  - Simulations were performed across the age groups 6 to 17 years old (1000 subjects per 1-year age groups) following a single dose of 10 mg zavegepant nasal spray.
  - Simulations were also performed across the range of body weights, with 5-kg increment per range (based on a CDC growth chart describing age–body weight distribution across pediatric groups 6 to 17 years old[3]; 1000 subjects per age range) following a single dose of 3 mg, 5 mg, and 10 mg zavegepant nasal spray.

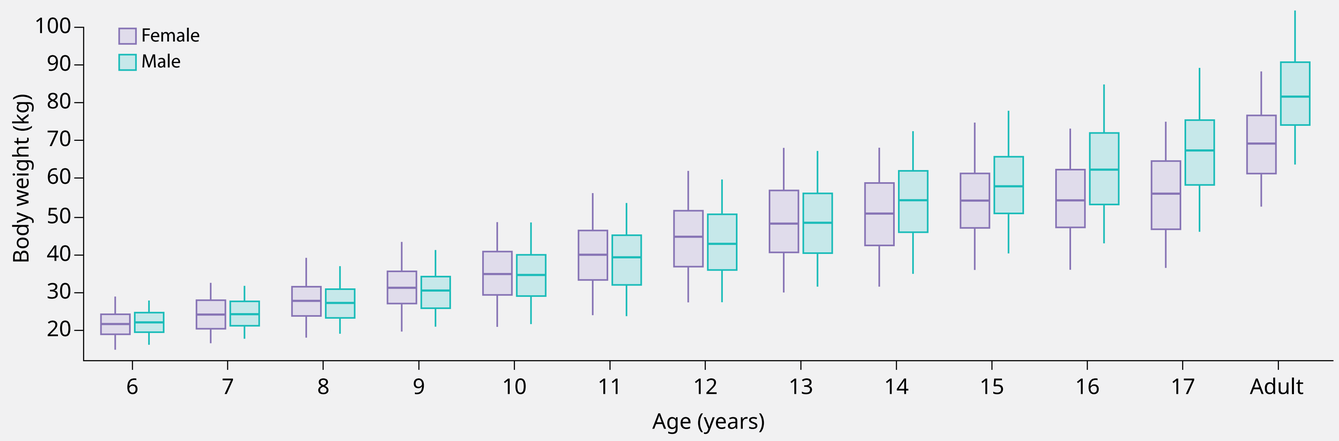
ANALYSIS

- Predicted exposures (maximum concentration in plasma [C_{max}] and area under the curve from 0 to infinity [$AUC_{0\text{-}inf}$]) in pediatric populations following administration of zavegepant nasal spray were compared with predicted exposures in adults receiving a single dose of 10 mg zavegepant nasal spray.
  - Ratios of median pediatric exposure to median adult exposure were calculated and, for pediatric dose selection, ratios between 1 and 2 for both C_{max} and $AUC_{0\text{-}inf}$ were considered adequate.
  - Analyses were carried out according to US and EU regulatory guidance.[4-6] Nonlinear mixed-effects modeling software (NONMEM®; v7.4.3; ICON) and/or R software were used for simulations and analysis.

RESULTS

- Parameter estimates for the final PPK model are shown in the **Supplementary Table**.
- Weight distribution in the virtual pediatric population 6 to 17 years old (based on the CDC growth chart) and in adults (based on trials of zavegepant) is shown in **Figure 1**.
- Simulated median exposure ratios following a single dose of 10 mg zavegepant nasal spray in pediatric 6 to 17 years old and following a single dose of 10 mg zavegepant nasal spray in adults are shown in **Table 1**.
  - Simulations predict that, following a single dose of 10 mg zavegepant nasal spray, median exposure ratios in adolescents 12 to 17 years old vs adults are within 1 to 2.
- Simulated median exposure ratios following administration of a single dose of 3 mg, 5 mg, and 10 mg zavegepant nasal spray in pediatric 6 to 17 years old (across 12 different weight ranges) and a single dose of 10 mg zavegepant nasal spray in adults are shown in **Table 2**.
  - Simulations predict that median exposure ratios are within 1 to 2 in pediatric 6 to 17 years old vs adults receiving a single dose of 10 mg zavegepant nasal spray when:
    - Pediatrics with a body weight >30 kg received a single dose of 10 mg zavegepant nasal spray.
    - Pediatrics with a body weight >15 to ≤30 kg received a single dose of 5 mg zavegepant nasal spray.
    - Pediatrics with a body weight ≤15 kg received a single dose of 3 mg zavegepant nasal spray.

Figure 1: Weight distribution in the virtual pediatric and observed adult populations



Population	Body weight percentile (kg) 5%	25%	50%	75%	95%
Adult (observed)	54.5	63.1	74.2	81.5	91.9
Pediatric 12 to <18 y (simulated)	34.1	45.6	53.8	63.9	77.3
Pediatric 6 to <12 y (simulated)	17.8	23.0	28.3	34.8	47.4

Boxes represent the interquartile range, horizontal line in the box represents the median, and whiskers display the 5th and 95th percentiles.

Table 1: Ratio of median exposure in pediatrics 6 to 17 years old following a single dose of 10 mg zavegepant nasal spray vs adult exposure following a single dose of 10 mg zavegepant nasal spray

	Age, y											
Median ratio	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
10 mg zavegepant												
$AUC_{0\text{-}inf}$	2.53	2.80	2.31	2.18	2.29	1.89	1.83	1.63	1.65	1.28	1.29	1.20
C_{max}	2.89	3.14	2.70	2.17	2.49	2.11	1.93	1.84	1.55	1.37	1.26	1.16

Simulated adult exposures after a single dose of 10 mg zavegepant nasal spray were used as the comparator for ratio calculations.
Ratios in pink indicate dosing levels where the median ratios for $AUC_{0\text{-}inf}$ and C_{max} were both between the target range of 1 to 2.
$AUC_{0\text{-}inf}$=area under the curve from 0 to infinity; C_{max}=maximum concentration in plasma

Table 2: Ratio of median exposure in pediatrics 6 to 17 years old (across body weight ranges, with 5-kg increment per range) following a single dose of 3 mg, 5 mg, or 10 mg zavegepant nasal spray vs adult exposure following a single dose of 10 mg zavegepant nasal spray

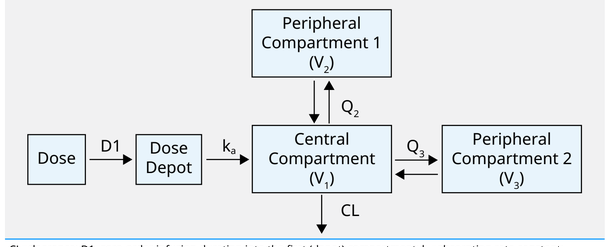
	Body weight category, kg											
Median ratio	**≤15**	**15 to ≤20**	**20 to ≤25**	**25 to ≤30**	**30 to ≤35**	**35 to ≤40**	**40 to ≤45**	**45 to ≤50**	**50 to ≤55**	**55 to ≤60**	**60 to ≤65**	**>65**
10 mg zavegepant												
$AUC_{0\text{-}inf}$	4.22	3.21	2.39	2.16	1.89	1.68	1.53	1.42	1.45	1.20	1.17	1.08
C_{max}	4.82	3.51	2.63	2.32	1.99	1.75	1.56	1.38	1.41	1.19	1.19	1.08
5 mg zavegepant												
$AUC_{0\text{-}inf}$	1.98	1.52	1.23	1.13	0.973	0.918	0.760	0.721	0.641	0.635	0.578	0.536
C_{max}	2.27	1.71	1.35	1.20	1.020	0.965	0.765	0.748	0.674	0.624	0.573	0.527
3 mg zavegepant												
$AUC_{0\text{-}inf}$	1.25	0.923	0.764	0.637	0.589	0.516	0.465	0.424	0.400	0.369	0.352	0.323
C_{max}	1.45	1.02	0.821	0.677	0.613	0.542	0.483	0.426	0.396	0.364	0.351	0.317

Simulated adult exposures after a single dose of 10 mg zavegepant nasal spray were used as the comparator for ratio calculations.
Ratios in pink indicate dosing levels where the median ratios for $AUC_{0\text{-}inf}$ and C_{max} were both between the target range of 1 to 2.
$AUC_{0\text{-}inf}$=area under the curve from 0 to infinity; C_{max}=maximum concentration in plasma

CONCLUSIONS

- Based on PPK simulations, zavegepant nasal spray doses selected for pediatrics were 10 mg for adolescents (12 to 17 years old) and for children 6 to <12 years old with a body weight >30 kg, and 5 mg for children 6 to <12 years old with a body weight >15 to ≤30 kg.
- The pediatric dose selection has been agreed to by the US Food and Drug Administration for a zavegepant PK study in pediatrics for ages 6 to 12 years, and no additional PK data are needed for adolescents.

Supplementary Figure: Zavegepant structural PPK model



CL=clearance; D1=zero-order infusion duration into the first (depot) compartment; k_a=absorption rate constant; PPK=population pharmacokinetics; Q_2=intercompartmental clearance between central and first peripheral compartment; Q_3=intercompartmental clearance between central and second peripheral compartment; V_1=central volume of distribution; V_2=first peripheral volume of distribution; V_3=second peripheral volume of distribution

Supplementary Table: Parameter estimates for the final PPK model

Parameter	Estimate	RSE	%IIV (%RSE) [% shrinkage]
Absorption			
Nasal spray F	5.12%	11%	66.1 (4.8) [6.8]
Soft gelatin capsule F	0.649%	17.5%	–
Nasal spray k_a	5.79 h^{-1}	5.1%	44 (11) [41.1]
Soft gelatin capsule k_a	0.81 h^{-1}	6.1%	–
Nasal spray absorption duration	0.144 h	8.73%	114.5 (7.7) [11.6]
Soft gelatin capsule absorption duration	0.954 h	14.4%	–
Distribution			
Central volume of distribution (V_1)	12.1 L	8.8%	32.2 (10.9) [49.9]
First peripheral volume of distribution (V_2)	65.9 L	10.7%	26.1 (23.1) [49.9]
Second peripheral volume of distribution (V_3)	10.7 L	10.1%	–
Clearance			
Elimination CL	13.3 L/h	9.9%	26.8 (6.1) [17.8]
CL between V_1 and V_2 (Q_2)	2.65 L/h	10.5%	–
CL between V_1 and V_3 (Q_3)	5.19 L/h	16.3%	–
Covariates			
Body weight on CL, Q_2, and Q_3	0.75 fixed	–	–
Body weight on V_1, V_2, and V_3	1 fixed	–	–
Metabolic status on F of soft gelatin capsules (fed state vs fasting)	–50.9%	9.8%	–
Scaling factor on nasal spray volume of distribution	+110%	7.4%	–
Scaling factor on soft gelatin capsules volume of distribution	+17.2%	87%	–
Moderate hepatic impairment on CL	–43.9%	13.5%	–
Co-administration of rifampicin on CL	–41.1%	12.1%	–
Co-administration of itraconazole on CL when administered orally	–27.9%	26.3%	–
Residual errors			
Additive error (FIXED)	0.001 ng/L	–	–
Proportional error	37.8%	2.9%	–

Parameters in gray were part of the model but were not used in pediatric simulations.
CL=clearance; F=bioavailability; IIV=interindividual variability; k_a=absorption rate constant; PPK=population pharmacokinetics; Q_2=intercompartmental clearance between central and first peripheral compartment; Q_3=intercompartmental clearance between central and second peripheral compartment; RSE=relative standard error; V_1=central volume of distribution; V_2=first peripheral volume of distribution; V_3=second peripheral volume of distribution

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DISCLOSURES

CMC, JF, and RB: Employees of Certara. **GM:** Former employee of Pfizer.
JH, BG, MHS, and JL: Employees of Pfizer and may own stock/stock options in Pfizer.

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