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ORIGINAL RESEARCH ARTICLE

Development of a Weight-Band Dosing Approach for Vosoritide in Children with Achondroplasia Using a Population Pharmacokinetic Model

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Abstract

Background and Objective Vosoritide is a recently approved therapy for achondroplasia, the most common form of disproportionate short stature, that has been shown to be well tolerated and effective in increasing linear growth. This study aimed to develop a population pharmacokinetic (PPK) model to characterize pharmacokinetics (PK) of vosoritide and establish a weight-band dosing regimen.

Methods A PPK model was developed using data from five clinical trials in children with achondroplasia (aged 0.95−15 years) who received daily per-kg doses of vosoritide. The model was used to simulate expected exposures in children with a refined weight-band dosing regimen. Simulated exposure was compared with the observed exposure from the pivotal clinical trial to evaluate appropriateness of the weight-band dosing regimen.

Results A one-compartment model with a change-point first-order absorption and first-order elimination accurately described PK of vosoritide in children with achondroplasia. Body weight was found to be a predictor of vosoritide's clearance and volume of distribution. Additionally, it was observed that dosing solution concentration and duration of treatment influenced bioavailability. The weight-band dosing regimen resulted in simulated exposures that were within the range demonstrated to be well tolerated and effective in the pivotal clinical trial and showed improved consistency in drug exposure across the achondroplasia population.

Conclusions The weight-band dosing regimen reduced the number of recommended dose levels by body weight and is expected to simplify dosing for children with achondroplasia and their caregivers.

Clinical Trial Registration NCT02055157, NCT02724228, NCT03197766, NCT03424018, and NCT03583697.

1 Introduction

Achondroplasia is the most common form of disproportionate short stature and is characterized by severe height deficit accumulated from a very young age [1–4]. People affected by achondroplasia have impaired endochondral bone growth causing shortened limbs and a small cranial base with resulting macrocephaly [2]. Based on pooled data from the literature, the prevalence of achondroplasia is estimated to be 4.6 per 100,000 births worldwide [5].

Achondroplasia is an autosomal dominant genetic disorder caused by a single common nucleotide pathogenic variant in the fibroblast growth factor receptor 3 gene. This gain-of-function mutation leads to a protein that inappropriately activates the mitogen-activated protein kinase/extracellular signal-regulated kinase inhibitory signaling pathway in chondrocytes [6]. The constitutive overactivation of this pathway in people with achondroplasia impairs and inhibits endochondral ossification, leading to short stature [6].

Until recently, there were no approved pharmacological therapies for achondroplasia that specifically target the underlying molecular causes of the condition [7]. C-type natriuretic peptide (CNP), through the natriuretic peptide receptor B, downregulates the intracellular inhibition of endochondral bone formation, thereby allowing more normalized growth. As such, CNP analog therapies are promising treatment options for achondroplasia because they can help restore growth and development [8]. Vosoritide, also

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Key Points

A model describing the population pharmacokinetics of vosoritide in children with achondroplasia was developed using data from five clinical trials.

A one-compartment model with a change-point first-order absorption and first-order elimination adequately described vosoritide pharmacokinetics in children with achondroplasia.

Body weight was found to be predictive for the apparent clearance and the apparent volume of distribution, whereas the dosing solution concentration and the duration of treatment were found to be predictive for the relative bioavailability; no other covariates were identified as being predictive of the population pharmacokinetics of vosoritide in children.

Model simulations were used to generate a weight-band dosing regimen for vosoritide for the treatment of children with achondroplasia.

known as BMN 111, is a modified form of CNP that has been shown to allow more normalized endochondral ossification [9]. Treatment with vosoritide has been approved in the USA for use in children with achondroplasia who have open epiphyses, with further approvals granted in Europe, Brazil, Australia, and Japan [10–13].

Previous studies have demonstrated the efficacy, safety, and dose selection of daily treatment with vosoritide [2, 9, 10]. In a phase III clinical trial (NCT03197766), vosoritide administered at a dose of 15 µg/kg per day in children with achondroplasia over a 1-year period resulted in a statistically significant increase in annualized growth velocity of 1.57 cm/year (least squares mean change from baseline) compared with placebo based on analysis of covariance [14]. This increase in growth velocity was maintained in the extension study (NCT03424018) [7]. This and another open-label extension study (NCT02724228) are ongoing to evaluate the longer-term efficacy, tolerability, and safety of vosoritide in children, as well as to determine the treatment effect on final adult height.

Sampling for pharmacokinetic (PK) analysis of vosoritide was conducted as part of three phase II studies and two phase III studies that included the use of a daily subcutaneous dose of 15 µg/kg. In an analysis of two of these studies [2], the mean maximum observed plasma concentration (C_{max}) ranged from 4750 to 7180 pg/mL, the area under the plasma concentration–time curve (AUC) from time 0 to the time of the last measurable concentration ranged from 175,000 to 290,000 pg·min/mL, the terminal half-life ranged from 21.0 to 27.9 min, and the mean time to maximal plasma concentration ranged from 13.8 to 16.8 min after a single subcutaneous 15-µg/kg dose of vosoritide [2]. The PK data also demonstrated a positive correlation between plasma exposure to vosoritide (AUC) and body weight in patients treated daily with a per-kg dose of vosoritide, which suggests that an alternative to weight-based dosing with vosoritide may yield more consistent exposure across the patient weight range [2].

The purpose of the current study was to develop a population PK (PPK) model for vosoritide in children with achondroplasia, as well as to evaluate the influence of clinically relevant covariates on the PK of vosoritide to better understand the sources of variability following subcutaneous administration. The original weight-based dosing regimen (15 µg/kg) utilized in clinical trials for vosoritide required 17 different dose levels for children weighing between 10 and 83 kg. We aimed to develop a weight-band dosing regimen for vosoritide to account for the characterized effect of body weight on vosoritide clearance and volume of distribution and to ensure more consistent exposure of the drug over the duration of a patient's treatment. This regimen would also allow for fewer required dose levels and fewer dose changes, as a new dose would only be needed when a child progresses from one weight band to the next, and therefore may simplify dosing for children with achondroplasia and their caregivers. The PPK model was used to perform simulations to develop the optimized dosing recommendations.

2 Materials and Methods

2.1 Ethics

The ethical principles outlined in the Declaration of Helsinki, the US Code of Federal Regulations, and the International Conference on Harmonisation Guideline for Good Clinical Practice E6 were followed during the conduct of the study. The study protocols were approved by relevant ethics review boards and informed consent was obtained from all parents or guardians in writing.

2.2 Study Population

PK, laboratory, and demographic data from children with achondroplasia were included in this PPK analysis. The data were collected from five clinical trials (Table S1): study 111-202 (NCT02055157), a phase II non-randomized, open-label, sequential-cohort, dose-finding trial of vosoritide (2.5, 7.5, 15, or 30 µg/kg) administered for 24 months in 35 children (5–14 years of age) with achondroplasia [2, 15]; study 111-205

(NCT02724228), an ongoing phase II open-label extension trial of vosoritide (15 or 30 µg/kg) administered in 30 children with achondroplasia who completed 24 months of treatment in study 111-202 [15]; study 111-301 (NCT03197766), a phase III randomized, double-blind, parallel-assignment, efficacy and safety trial of vosoritide (15 µg/kg) administered for 12 months in 121 children (5–18 years of age) with achondroplasia, in which 60 patients were allocated to receive vosoritide, while the remaining 61 patients received a placebo; those who initially received placebo in study 111-301 were subsequently included in the extension study 111-302 (NCT03424018) [2], an ongoing phase III open-label extension, safety and efficacy trial of vosoritide (15 µg/kg) administered in children (≥ 6 years of age) with achondroplasia who completed 12 months of treatment in study 111-301; and study 111-206 (NCT03583697), a phase II randomized, double-blind, parallel-assignment, safety and efficacy trial of vosoritide (15 or 30 µg/kg) administered for 12 months in 75 children (≤ 5 years of age) with achondroplasia; at the time of construction of the PPK model, the study was ongoing, so only interim data from sentinel patients were available for inclusion in model development.

2.3 PK Sampling and Quantitative Measurement

Table S2 summarizes the PK sampling frequency and collection timepoints for the five clinical trials. Plasma samples from the phase II clinical trials (studies 111-202 and 111-205) were analyzed for vosoritide concentrations using a validated enzyme-linked immunosorbent assay, and samples from studies 111-206, 111-301, and 111-302 were analyzed with an optimized vosoritide PK electrochemiluminesence assay. The lower limit of quantification was 0.391 µg/L for studies 111-202 and 111-205 and 0.137 µg/L for studies 111-206, 111-301, and 111-302. Solution concentrations (SOLNC) of 0.2 or 2 mg/mL were used for study 111-202, SOLNC of 2 mg/mL was used for study 111-205, and SOLNC of 0.8 or 2 mg/mL were used in studies 111-206, 111-301, and 111-302.

2.4 PPK Model Development

Data were pooled into a single nonlinear mixed effects modeling (NONMEM™, version 7.4.4, ICON Development Solutions, Dublin, Ireland) database. A log transform both sides approach and stochastic approximation expectation maximization followed by importance sampling method was used for the PPK modeling of vosoritide.

The PPK model was developed in a series of steps. The base model was created with no consideration of covariate effects and was used to describe the structural and stochastic components of the model and to conduct a graphical evaluation of the covariates (Table S3). The single-covariate model was used to test pre-specified covariate–parameter relationships graphically using covariates that were known to influence the PK of vosoritide or that were physiologically plausible. Once all single covariate evaluations were completed, a full model was constructed using all single-covariate models that were statistically significant ($p < 0.01$) and were well estimated. Backward elimination was then carried out on the full covariate model, with one covariate being removed from the model at a time. Covariates that increased the objective function ($p < 0.001$) were retained in the final model.

The following equations were used to model the covariate effects on each of the parameters:

$$\text{Apparent clearance } (\text{CL}/F) = \exp(\theta 1 + \eta 1 + \eta 6) * \left(\frac{WT(\text{Kg})}{20}\right)^{\theta 14}$$

$$\text{Apparent volume of distribution } (V/F) \text{of the central compartment} = \exp(\theta 2 + \eta 2 + \eta 7) * \left(\frac{WT(\text{Kg})}{20}\right)^{\theta 15}$$

$$\text{Absorption rate1}(Ka1) = \exp(\theta 5 + \eta 5)$$

$$\text{Absorption rate2}(Ka2) = \exp(\theta 6 + \eta 8)$$

$$\text{Change-point} = \theta 7 + \eta 9$$

If the condition "time after dose < change-point" is true, then the value of absorption rate (Ka) is set to $Ka1$. Otherwise, the value is set to $Ka2$. Model event TIME (MTIME) was used to estimate the time at which the change in Ka occurred.

$$\text{SD1} = \theta 8$$

$$\text{SD2} = \theta 9$$

$$\text{Bioavailability } F = \exp(\theta 16 * \text{Time}/10000)$$

The additional hierarchical level of non-linear mixed modeling was represented by $\eta 6$ and $\eta 7$, which allowed for the identification of apparent differences between studies on the inter-individual variability (IIV) for apparent clearance (CL/F) and apparent volume of distribution (V/F), respectively. The reference body weight was established as 20 kg. Model performance was evaluated through a visual predictive check (VPC), in addition to evaluation of standard goodness-of-fit plots and other model diagnostics. To assess the performance of the vosoritide PPK model, diagnostic goodness-of-fit plots, VPCs, and dose-normalized VPCs were created using data from patients who received ≥ 1 dose of vosoritide and using all available data in the PPK model.

2.5 Simulation Process

The final PPK model parameters were used for the simulation without consideration for parameter precision. A total of 500 replicates were run using the PPK model to generate intensive concentration–time profiles over the first 5 h (at 5-min intervals) following subcutaneous administration of varying stratified doses of vosoritide in pediatric patients weighing 10–90 kg. The simulations were conducted using doses from the commercial stock keeping units [0.8 mg/mL (0.5 mL); 0.8 mg/mL (0.70 mL); 2 mg/mL (0.60 mL)]. The highest withdrawal doses (0.32, 0.48, 1, and 1.2 mg) were included in the simulation. PK non-compartmental analysis (PKNCA) to calculate AUC 0–5 h and C_{max} values was performed on simulated data using the PKNCA package in R, version 0.9.3. The simulated exposures were compared with the observed exposure data from study 111-301. The median, 5th percentile, and 95th percentile of PK parameters from the simulation were compared with the PK parameters calculated from the observed data evaluated at 15-µg/kg daily doses.

2.6 Software

PPK modeling and simulation were conducted using NONMEM software, version 7.4.4 (ICON plc, Dublin, Ireland). Dataset preparation, exploration, and data visualization were performed using R data analysis language, version 3.6.2.

3 Results

3.1 Database for the PPK Model

The initial database for the PPK model contained 6181 observations from a total of 159 children with achondroplasia who received a daily dose of vosoritide. A total of 23.3% of observations were excluded (Table S4), with the majority of exclusions being pre-dose observations where concentrations were expected to be non-measurable because of the short half-life of vosoritide relative to the once-daily dosing regimen. Other reasons for exclusion included apparent assay error, duplicate timepoint, hemolyzed sample, no concentration, sample and dose at the same time, and sample time error. One patient was also excluded due to a substantial number of oscillations in weight over time. The final database used contained 4741 observations from 158 patients aged 0.95 to 15 years, with a mean age of 8.43 years (Table 1). The weight of patients ranged from 9 to 74.5 kg, with a mean baseline weight of 23.8 kg. Actual doses administered during the study to patients whose data were included in the PPK model included 2.5 µg/kg/day (6 patients), 7.5 µg/kg/day (12 patients), 15 µg/kg/day (151 patients), and 30 µg/kg/day (11 patients).

3.2 PPK Model for Vosoritide

The final PPK model consisted of a one-compartment system with first-order elimination and a change-point first-order absorption that allowed a time-dependent change in absorption rate coefficient. Body weight was found to be a predictive factor for CL/*F* and *V*/*F* of the drug (Table 2). Additionally, the SOLNC of 0.2 mg/mL, which was only used in study 111-202, and the duration of treatment were found to be predictive for the relative bioavailability (*F*) of vosoritide (Tables 3, 4, respectively). Separate residual errors for the two assay types were estimated. The model also accounted for the IIV in CL/*F*, V/*F*, and change-point. An additional secondary study identity number (SIDN) was used to represent the clinical trial in which each patient was enrolled, but allowed for the fact that patients may have been enrolled in > 1 study. The effects of SIDN on the IIV of CL/*F* and *V*/*F* were modeled by an additional hierarchical level of effect (StudyCL and StudyV). The parameter estimates' typical values and parameter precision (percentage of standard error) of the PPK model are presented in Table 5. The parameter precision was < 30%, with the exception of the terms IIV StudyCL and IIV StudyV, because there were only three SIDN values in the present database. The estimated typical parameter values were consistent with the median bootstrap parameter estimates, and the confidence intervals were reassuringly narrow and did not include the null.

3.3 Evaluation of the Performance of the PPK Model for Vosoritide

The performance of the PPK model for vosoritide was evaluated using diagnostic goodness-of-fit plots (Fig. 1) and VPCs (Fig. 2). These showed that the model was able to accurately describe the data. The model's predictive distributions of median concentrations within various time intervals were compared with the observed medians using VPCs (Fig. 2). The lower and upper bounds of the observed and simulated data were generally similar, with the observed concentrations falling within the 5th and 95th percentiles of the predictive distribution for the final model across time intervals.

3.4 Development of Weight-Band Dosing Recommendations for Children with Achondroplasia Using the PPK Model

The PPK model for vosoritide was used to develop improved dosing recommendations for pediatric patients

Table 1 Summary of baseline demographic characteristics for the PPK database

Characteristic	$N = 158$
Study (*n*)	
111-202[a]	29
111-206	8
111-301	60
111-302	61
Sex (*n*)	
Male	84
Female	74
Race (*n*)	
White	114
Black	6
Asian	28
Other	10
Injection location (*n*)	
Arm	54
Abdomen	15
Thigh	33
Buttock	56
Dose (mg)	
Mean (SD)	0.37 (0.18)
Median	0.36
Min, max	0.04, 1.16
Dose (μg/kg)	
Mean (SD)	15 (4.43)
Median	15
Min, max	2.5, 30
Age (years)	
Mean (SD)	8.43 (2.73)
Median	8
Min, max	0.95, 15
Weight (kg)	
Mean (SD)	23.8 (8.96)
Median	22.2
Min, max	9, 74.5
BMI (kg/m^2)	
Mean (SD)	22.4 (4.43)
Median	21.5
Min, max	16.5, 61
BSA (m^2)	
Mean (SD)	0.81 (0.21)
Median	0.8
Min, max	0.44, 1.51
BSA2 (m^2)	
Mean (SD)	0.70 (0.17)
Median	0.7
Min, max	0.40, 1.22
FFM (kg)	
Mean (SD)	17.2 (5.57)
Median	15.9
Min, max	7, 38.4
LBW (kg)	
Mean (SD)	18 (5.48)
Median	17.3
Min, max	7.0, 39.1
ALB (g/dL)	
Mean (SD)	43.3 (2.68)
Median	43
Min, max	37, 52
ALT (IU/L)	
Mean (SD)	16.8 (5.44)
Median	16
Min, max	6, 44
AST (IU/L)	
Mean (SD)	28.2 (6.9)
Median	27.5
Min, max	10, 54
BILI (μmol/L)	
Mean (SD)	5.89 (4.13)
Median	4.8
Min, max	1.8, 30.6
CrCL (mL/min)	
Mean (SD)	127 (46.2)
Median	117
Min, max	26.4, 373
EGFR ($mL/min/1.73\ m^2$)	
Mean (SD)	177 (45.6)
Median	179
Min, max	0, 310

ALB albumin, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BILI* bilirubin, *BMI* body mass index, *BSA* body surface area, *BSA2* pediatric body surface area, *CrCL* creatinine clearance, *EGFR* estimated glomerular filtration rate, *FFM* fat-free mass, *IU* international unit, *LBW* lean body weight, *max* maximum, *min* minimum, *n* number of patients per characteristic, *N* total number of patients in the PPK database, *PPK* population pharmacokinetics, *SD* standard deviation

[a]Study 111-205 was an extension study of study 111-202. All patients who were initially enrolled in study 111-202, except for those who discontinued participation, were included in the subsequent study 111-205

with achondroplasia. Simulations were conducted for various weight strata. An initial regimen of four weight bands was identified: 0.32 mg for a weight of 10–19 kg, 0.48 mg for a weight of 20–34 kg, 0.7 mg for a weight of 35–64 kg, and 1 mg for a weight of ≥ 65 kg. The simulated AUCs for patients weighing < 65 kg were within or slightly beyond the upper limit of the AUCs observed in studies 111-301, 111-202, and 111-205. However, the simulated AUCs for patients weighing ≥ 65 kg exceeded the upper limit. Given

Table 2 Average clearance (CL/*F*) and volume of distribution (*V*/*F*) across body weight range

WT (kg)	CL/*F* (L/h)	Percentage of reference	*V*/*F* (L)	Percentage of reference
9	35.72	75.26	7.54	41.88
20 (reference)	47.47	100.00	17.99	100.00
40	60.75	127.99	38.30	212.87
60	70.18	147.86	59.59	331.18
74.5	75.80	159.71	75.45	419.30

CL/F apparent clearance, *F* relative bioavailability, *V/F* apparent volume of distribution, *WT* body weight

the results obtained with the initial regimen of four weight bands, a revised dosing regimen was tested (Table 6). The new dosing regimen included more weight bands (eight compared with four) to generate simulated exposure that better aligned with the observed exposure. The best weight-band dosing regimen identified was 0.24 mg for a weight of 10–11 kg, 0.28 mg for a weight of 12–16 kg, 0.32 mg for a weight of 17–21 kg, 0.40 mg for a weight of 22–32 kg, 0.50 mg for a weight of 33–43 kg, 0.60 mg for a weight of 44–59 kg, 0.70 mg for a weight of 60–89 kg, and 0.80 mg for a weight of ≥ 90 kg (Table 6). The proposed regimen includes doses < 15 µg/kg for patients weighing ≥ 44 kg, and doses > 15 µg/kg for patients weighing 10–16 kg. The new weight-band dosing regimen was found to yield more consistent exposure across the body weight range. The 5th to 95th percentiles of the simulated AUCs were within the range of the observed AUCs at 15 µg/kg, and the median simulated AUC values were distributed around the median observed AUC (Fig. 3). Additionally, the median values of simulated C_{max} were generally consistent with the observed C_{max} at 15 µg/kg, but the 5th and 95th percentiles of the simulated C_{max} were lower than the 5th and 95th percentiles of the observed C_{max} (Fig. 4). This discrepancy can be attributed to the model underestimating C_{max} as shown in VPC plots, and it could also be a result of the simulation being conducted with only one SIDN instead of the three SIDNs present in the model.

4 Discussion

In this study, a PPK model was developed to characterize the PK of vosoritide in children with achondroplasia, and a recommended weight-band dosing regimen was derived from this model. A PPK model was successfully developed to identify covariates that influence variability in PK of vosoritide in children with achondroplasia. The PK of vosoritide were accurately represented by a one-compartment model with change-point first-order absorption and first-order

Table 3 Effect of SOLNC on relative bioavailability

Time after starting dose (h)	Time after starting dose (years)	Relative bioavailability for SOLNC of 0.2 mg/mL	Percentage increase over reference (SOLNC of 0.8 or 2.0 mg/mL) (%)
0	0	1.56	56
1000	0.11	1.59	56
5000	0.57	1.73	56
10,000	1.14	1.92	56
15,000	1.71	2.14	56
20,000	2.28	2.37	56
25,000	2.85	2.64	56

SOLNC solution concentration

Table 4 Effect of time on relative bioavailability

Time after starting dose (h)	Time after starting dose (years)	Relative bioavailability	Percentage increase over reference (time, 0 h) (%)
0	0.00	1.00	0.00
1000	0.11	1.02	2.12
5000	0.57	1.11	11.07
10,000	1.14	1.23	23.37
15,000	1.71	1.37	37.03
20,000	2.28	1.52	52.20
25,000	2.85	1.69	69.05

Table 5 Parameter estimates of the PPK model

Parameter (units)	Typical value	Standard error (%)	Bootstrap lower 2.5th percentile	Median	Bootstrap upper 97.5th percentile
CL/*F* (L/h)	47.47	1.8	40.45	47.7	57.97
V/*F* (L)	17.99	3.3	15.18	18.36	23.09
Ka1 (1/h)	2.21	14.7	1.8	2.3	3.19
Ka2 (1/h)	0.06	3.8	0.04	0.06	0.09
Change-point (h)	0.31	7.3	0.27	0.3	0.33
Residual error 1[a] (CV, %)	66.5	1.6	61.71	66.3	72
Residual error 2[b] (CV, %)	61	1.5	56.61	60.85	65.4
Effect of SOLNC (0.2 mg/mL)	1.56	15.3	1.18	1.54	2.03
Effect of weight on CL/*F*	0.356	25.1	0.02	0.35	0.68
Effect of weight on V/*F*	1.09	8.1	0.85	1.1	1.31
Effect of time on *F*	0.21	8.1	0.16	0.21	0.26
IIV CL (CV, %)	33.6	8.3	27.3	33	40.49
IIV *V* (CV, %)	24.2	13.6	17.7	23.9	29.99
IIV study CL (CV, %)	25.7	47.4	18.51	26.15	34.6
IIV study *V* (CV, %)	1.2	51.8	0.4	2.05	5.7
IIV change-point (fixed)	22.4	0	NE	NE	NE

Residual error 1, residual error for concentrations arising from the ELISA assay; residual error 2, residual error for concentrations arising from the ECL assay

CL/F apparent clearance, *CV* coefficient of variation, *ECL* electrochemiluminescence, *ELISA* enzyme-linked immunosorbent assay, *F* relative bioavailability, *IIV* inter-individual variability, *Ka1* absorption rate constant 1, *Ka2* absorption rate constant 2, *NE* not estimated, *PPK* population pharmacokinetics, SOLNC solution concentration, *StudyCL* nested variability based on study identifier number, *StudyV* nested variability based on study identifier number, *V/F* apparent volume of distribution

elimination. Body weight was found to be a predictive factor for CL/*F* and *V*/*F* of vosoritide, which supports dosing of the drug based on weight. This is consistent with the reported dependence of the PK of many peptides on body weight or size [10]. During model development, additional parameterizations—including models with baseline weight and body size metrics and models with time-varying weight—were tested to investigate the effect of body size on CL/*F*. Body metrics tested as covariates included the following: lean body weight (LBW), fat-free mass, body mass index (BMI), BMI computed using LBW instead of weight, and surface area [Mosteller method and Mosteller body surface area (BSA) using LBW instead of weight for pediatric patients]. Compared with these models, the model that included a time effect on *F* had a positive coefficient that was well estimated and consistent with the reported trends for non-compartmental parameter estimates. Thus, this model was selected for further consideration [2].

The *F* of vosoritide was also affected by a lower dose solution (0.2 mg/mL in this case), similar to what has been reported for insulin [16]. However, it should be noted that this specific concentration was used only in study 111-202. Other concentrations (0.8 and 2 mg/mL) used in the phase III studies and in commercial formulations did not have any effect on *F*. As a result, adjustments in dosing for different commercial vosoritide products are not necessary. The duration of vosoritide treatment also had an impact on *F*. Subcutaneous absorption may be affected by vascular congestion or higher skinfold in patients with achondroplasia when compared with individuals without achondroplasia [16, 17], which may result in slower or incomplete absorption. However, it is important to note that the relationship between treatment duration and *F* was only informed by data from one study (study 111-205, which has long-term data to inform this relationship). This may not accurately represent the entire population, and additional analysis is needed to fully evaluate the relationship between treatment duration and *F*.

The PPK model was used to simulate drug concentrations and exposures with the goal of developing a more

refined weight-band dosing regimen. Although a regimen of four weight bands was initially proposed, greater consistency between simulated and observed exposures was achieved with eight weight bands. The weight-band dosing regimen provided more consistent drug exposure across the body weight range. Specifically, for patients weighing > 44 kg, doses < 15 µg/kg were proposed to account for the correlation between observed non-linear relationship exposure and patient body weight. Similarly, for children aged 2–5 years and/or patients weighing 10–16 kg, doses > 15 µg/kg were proposed to avoid suboptimal exposure and to take into consideration an extrapolation approach. The 30-µg/kg

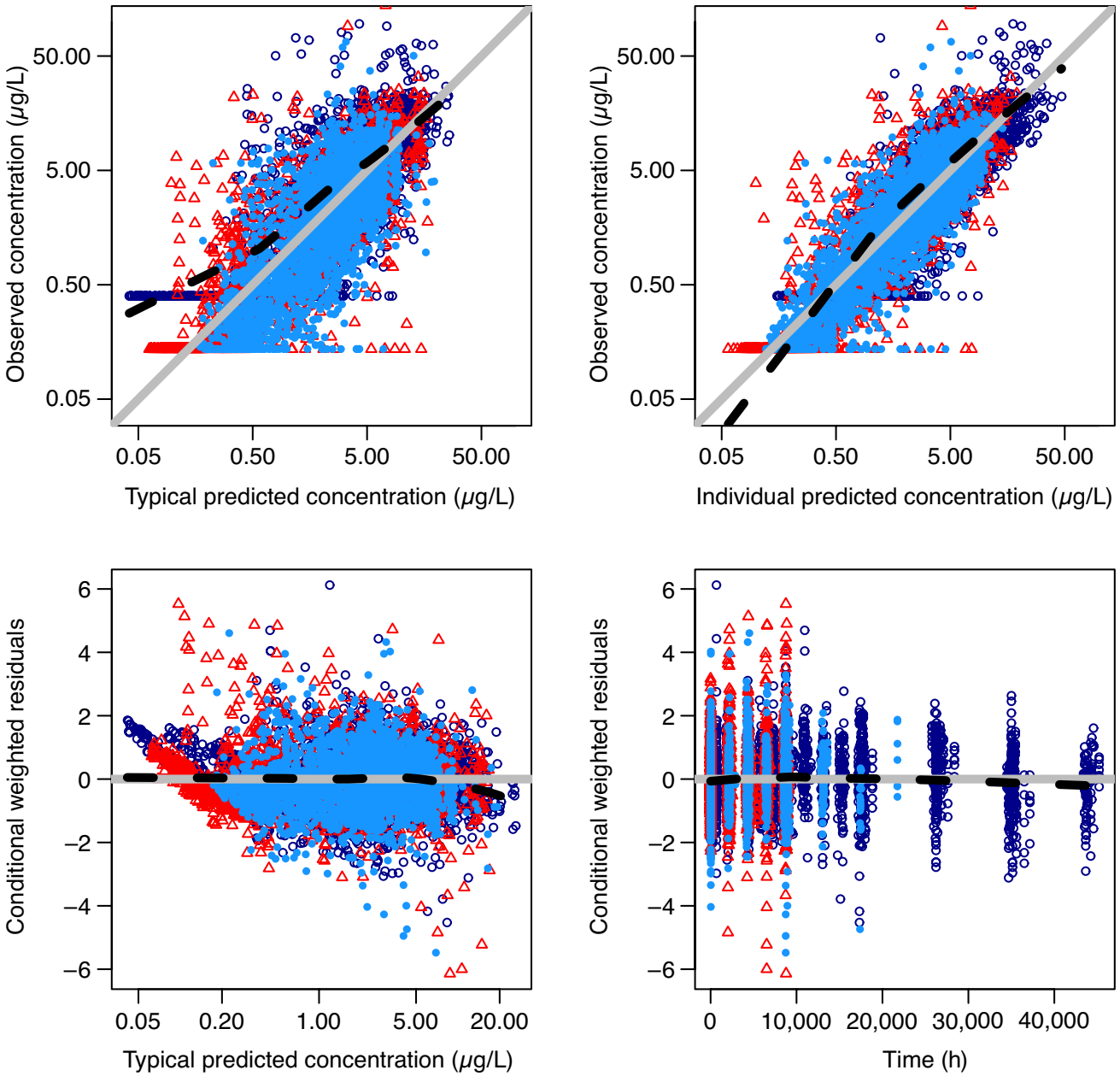

Fig. 1 Goodness of fit of the final PPK model. Basic goodness-of-fit plots are provided. Open blue symbols represent studies 111-202 and 111-205, study 111-206 is represented with open red symbols, and studies 111-301 and 111-302 are represented with filled blue symbols. Concentration is given in µg/L, the solid gray line is the line of unity or identity as appropriate, and the dashed black line is a loess smooth. *PPK* population pharmacokinetics

dose has been tested in the phase II studies (studies 111-202, 111-205 [2, 15], and 111-206 [unpublished data]) and demonstrated a similar safety profile as the 15-µg/kg dose. The simulated exposure from the proposed eight weight-band dosing regimen fell within the range demonstrated to be well tolerated and effective in previous studies [2]. Importantly, the proposed weight-band dosing regimen will ensure more consistent vosoritide exposure, both within the patient population and over the duration of treatment for an individual patient, while simplifying dosing for children with achondroplasia and their caregivers.

This study has several strengths. Firstly, data from five clinical trials investigating various doses of vosoritide were used to develop the PPK model, providing a robust integrated dataset. Additionally, the study investigated the effects of a broad range of patient covariates on the PK of

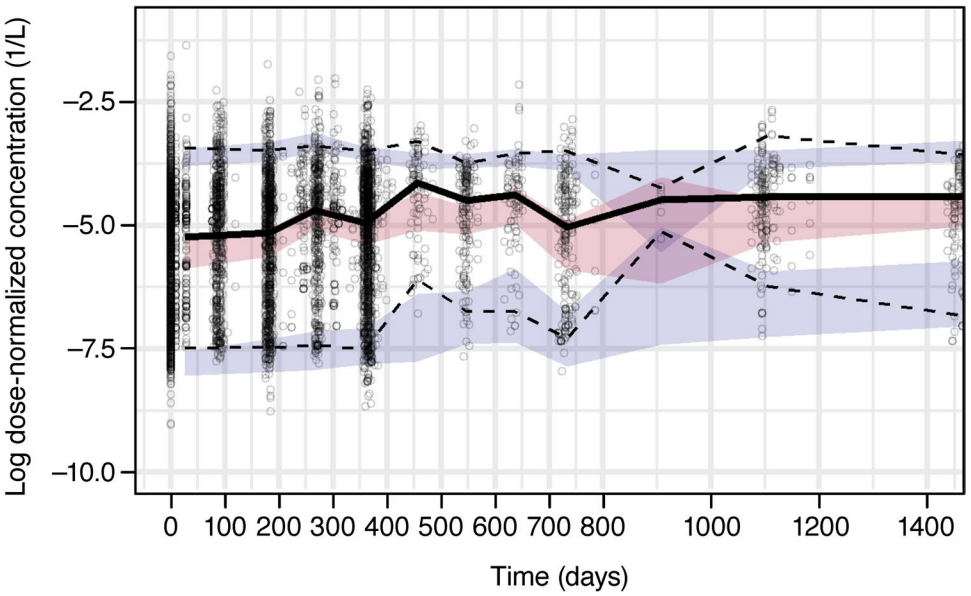

Fig. 2 Dose-normalized VPC results for the PPK model; dose-normalized observed and simulated vosoritide concentrations versus time after first dose. Dose-normalized VPC simulated with the PPK model and dose-normalized observed versus time after first dose are presented. Observed data are represented with black open circles, the median of the observed data is represented by a solid black line, the dashed lines are the upper and lower 90th percentiles of the observed data, the red area is the 90% confidence interval of the median of the simulated data, and the purple shaded areas are the 90% confidence intervals of the upper and lower 90th percentiles of the simulated data. *PPK* population pharmacokinetics, *VPC* visual predictive check

Table 6 Proposed weight-band dosing for vosoritide

Body weight (kg)	SKU 1 concentration: 0.8 mg/mL (0.50 mL)	SKU 2 concentration: 0.8 mg/mL (0.70 mL)	SKU 3 concentration: 2 mg/mL (0.60 mL)
10–11	0.24 mg/0.30 mL (22–24 µg/kg)		
12–16		0.28 mg/0.35 mL (18–23 µg/kg)	
17–21		0.32 mg/0.40 mL (15–19 µg/kg)	
22–32		0.40 mg/0.50 mL (13–18 µg/kg)	
33–43			0.50 mg/0.25 mL (12–15 µg/kg)
44–59			0.60 mg/0.30 mL (10–14 µg/kg)
60–89			0.70 mg/0.35 mL (8–12 µg/kg)
≥ 90			0.80 mg/0.40 mL (≤ 9 µg/kg)

SKU stock keeping unit

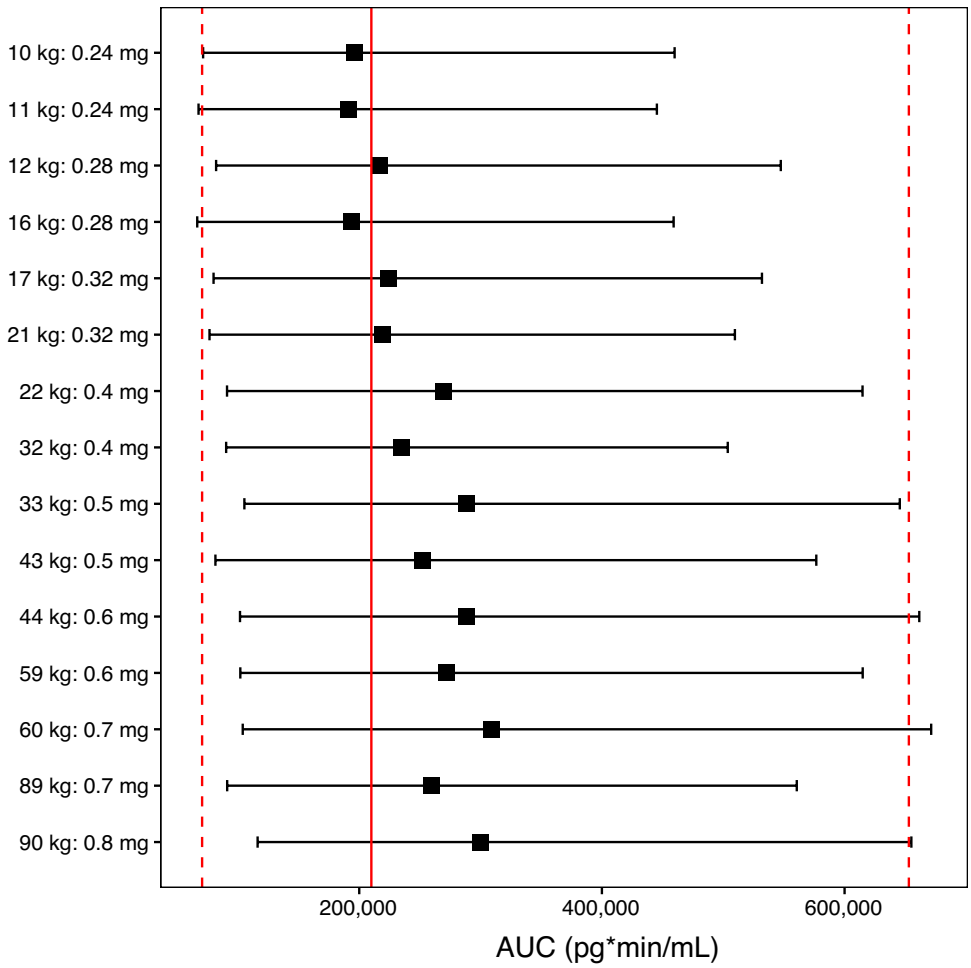

Fig. 3 Simulated vosoritide AUC values compared with observed AUC values at 15 µg/kg from study 111-301. The median simulated exposure metrics for each weight are represented by the black squares, the upper and lower whiskers represent the lower 5th and upper 95th percentiles of exposure, the lower 5th and upper 95th percentiles of observed metrics from the comparison study are represented by red dashed lines, and the red solid line represents the median. *AUC* area under the plasma concentration–time curve

vosoritide in children with achondroplasia, providing a detailed understanding of how different factors may affect drug exposure in children. Lastly, the study applied simulations using the PPK model to optimize a weight-band dosing regimen. However, the study has some limitations that should be acknowledged. Firstly, the PPK model underestimated the C_{max}, as the 5th and 95th percentiles of the simulated C_{max} were lower than the 5th and 95th percentiles of the observed C_{max}. Additionally, data from study 111-206 were limited to sentinel patients, which may not accurately represent the entire achondroplasia population in this age range. This contributes to the data presented in the manuscript being limited by a small sample size for patients with a low body weight. However, an update to the PPK model is planned when the study is completed, which will address these limitations and evaluate their potential impact.

In conclusion, this study successfully developed a performant PPK model that accurately described the data and provided adequate predictive performance. This model can be used to predict drug concentrations and exposures for a range of doses, including those in the development of a weight-band dosing regimen. The proposed weight-band dosing regimen is expected to improve consistency of drug exposure in children with achondroplasia treated with vosoritide and simplify dosing for this population and their health care providers. Overall, this study demonstrates important insights into the PK of vosoritide in children with achondroplasia and provides a valuable tool for dosing recommendations to optimize treatment.

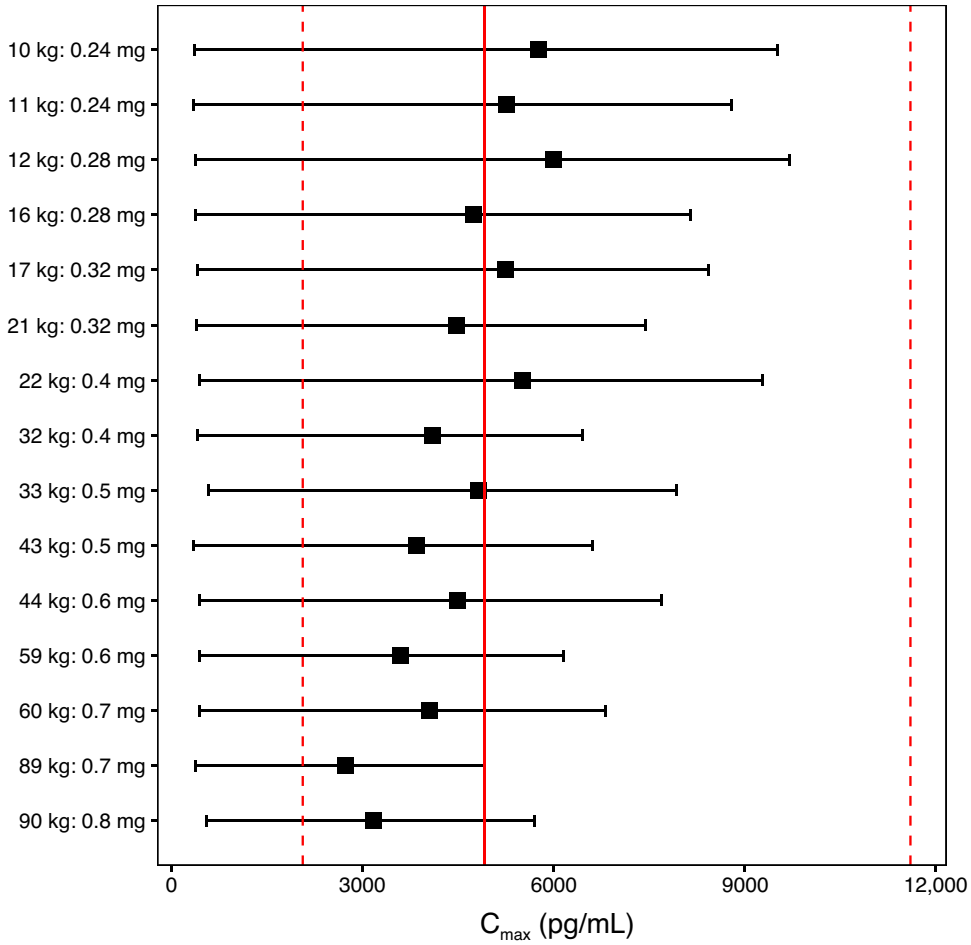

Fig. 4 Simulated vosoritide C_{max} values compared with observed C_{max} values at 15 µg/kg from study 111-301. The median simulated exposure metrics for each weight are represented by the black squares, the upper and lower whiskers represent the lower 5th and upper 95th percentiles of exposure, the lower 5th and upper 95th percentiles of observed metrics from the comparison study are represented by red dashed lines, and the red solid line represents the median. C_{max} maximum observed plasma concentration

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Role of the sponsor BioMarin Pharmaceutical Inc. was involved in the study design, data collection, data analysis, and preparation of the manuscript.

Conflict of interest Y.Q., K.L., E.F., A.C., J.D., and J.H.: employees and shareholders of BioMarin Pharmaceutical Inc. M.L.C.: former employee and stockholder of BioMarin Pharmaceutical Inc. D.R.M.: paid consultant for BioMarin Pharmaceutical Inc. R.S. and K.O.: honoraria from BioMarin Pharmaceutical Inc. M.I.: honoraria for consultancy services relating to the subject of this manuscript. C.A.B. and K.M.: no conflicts of interest. J.H.-F.: institution received funding from BioMarin Pharmaceutical Inc. to execute the study presented in this manuscript. Funds were also received from Pfizer and QED for other achondroplasia-related studies. J.H.-F.: consultant for BioMarin Pharmaceutical Inc., Pfizer, QED, and Sanofi, related to achondroplasia. W.R.W.: local principal investigator for the vosoritide studies at Emory University, funded by a clinical trial contract from BioMarin Pharmaceutical Inc. to Emory University. W.R.W. received honoraria for advisory committee meetings from BioMarin Pharmaceutical Inc. BioMarin Pharmaceutical Inc. paid for writing assistance for the manuscript. M.B.B.: employed by the Nemours Foundation, which has received institutional support for research from Ascendis Pharma, BioMarin Pharmaceutical Inc., QED, and Therachon/Pfizer. His institution has received consulting fees from BioMarin Pharmaceutical Inc. and Tyra Biosciences. M.B.B. has received consulting fees from Ascendis Pharma, BioMarin Pharmaceutical Inc., QED, and Therachon/Pfizer. He has received compensation for speaking on behalf of the Alexion speaker's bureau and from Novo Nordisk and Tyra Biosciences. In the future, he will be employed by Tyra Biosciences.

Data availability statement The de-identified individual participant data that underlie the results reported in this article (including text, tables, figures, and appendixes) will be made available together with the research protocol and data dictionaries, for non-commercial, academic purposes. Additional supporting documents may be available on request. Investigators will be able to request access to these data, along with supporting documents, via a website beginning at 6 months and ending 2 years after publication. Data associated with any ongoing development program will be made available within 6 months after

approval of the relevant product. Requests must include a research proposal clarifying how the data will be used, including proposed analysis methodology. Research proposals will be evaluated relative to publicly available criteria at the BioMarin website to determine whether access will be given, contingent on execution of a data access agreement with BioMarin Pharmaceutical. For data access requests, see http://www.BioMarin.com.

Ethics approval The ethical principles outlined in the Declaration of Helsinki, the US Code of Federal Regulations, and the International Conference on Harmonisation Guideline for Good Clinical Practice E6 were followed during the conduct of the study. The study protocols were approved by relevant ethics review boards and informed consent was obtained from all parents or guardians in writing.

Consent to participate Informed consent was obtained from all parents or guardians in writing.

Consent to publish Not applicable.

Code availability Not applicable.

Author contributions Y.Q., M.L.C., and J.H. contributed to the conceptualization of the study. Y.Q., E.F., A.C., and J.D. curated the data. Y.Q., D.R.M., and A.C. conducted formal analysis. J.D., R.S., M.I., J.H.-F., K.M., W.R.W., and M.B.B. contributed to the investigation. Y.Q., M.L.C., K.L., C.A.B., and J.H. contributed to the methodology. Y.Q. and M.L.C. took on project administration. Y.Q., M.L.C., K.O., W.R.W., and J.H. provided supervision. K.L. oversaw bioanalytical method development, validation, and sample testing. Y.Q., M.L.C., and D.R.M. were responsible for visualizing the data. All authors provided meaningful and substantial edits and critically reviewed/approved the final version of the manuscript.

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