

Mexiletine Paediatric Investigation Plan, PIP4 study: safety and pharmacokinetic findings in children with myotonia

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Introduction

- Mexiletine is approved within the European Union and the United Kingdom for the treatment of myotonia in adults with non-dystrophic myotonia (NDM).^{1,2}
- Many people with NDM or myotonic dystrophy (DM) experience myotonia during childhood.^{3,4}
 - Myotonia in childhood can adversely impact physical, educational, and social development;
 - Therefore there is particular interest in examining the safety of mexiletine treatment in children and adolescents.
- Consequently, the Paediatric Investigation Plan (PIP) has been undertaken, to explore mexiletine treatment in children and adolescents with myotonic disorders.
- This poster examines the safety and pharmacokinetic (PK) findings from PIP4, a study within the PIP involving children aged 6 to <18 years of age.

Methods

- PIP4 (EudraCT2019-003757-28) was a 12-week open-label exploration of mexiletine in sequential cohorts of children with NDM or DM:
 - Cohort 1:** participants aged from 12 to <18 years;
 - Cohort 2:** participants aged from 6 to <12 years.
- Cohort 2 would only be enrolled after the Data Safety Monitoring Board assessed data and concluded that there were no safety concerns regarding mexiletine use:
 - Mexiletine dosing for the younger age group was determined by PK modelling.
- PIP4 included 4 weeks' screening; 4 weeks' mexiletine titration (62, 83 or 167mg once-daily titrated to maximum 3-times-daily*), and 4 weeks' maintenance treatment (best-tolerated dose):
 - During titration, the mexiletine dose was increased every 14 days based on tolerability.
- Primary endpoints of PIP4 included safety, PK, tolerability, adverse-event (AE) profiling (including electrocardiogram [ECG]) at baseline and end of study (EOS).
- Before commencing, this study received appropriate Institutional Review Board/Independent Ethics Committee approval.
- The clinical study was conducted in compliance with International Council on Harmonization Guidelines and Good Clinical Practice.
- Informed consent was obtained from study participants (or their legal representatives).

Results

Patient cohorts and mexiletine dosing/exposure

Table 1 provides an overview of participant characteristics and mexiletine use during the study:

- Cohort 1 (N=7):** mean age, 13 years, n=4 female, n=3 NDM;
- Cohort 2 (N=5):** mean age, 8 years, n=3 female, n=2 NDM;
- Total mexiletine exposure, ≥53 days;
- All participants completed PIP4 and continued into the PIP7 ≥24-month extension (EudraCT: 2019-003758-97).**

Table 1. Overview of participant characteristics and daily mexiletine use during the PIP4 study

	Age, completed years	Sex	NDM subtype	Body weight, baseline, kg	Total maximum mexiletine dose, mg	Treatment duration, days
COHORT 1	12	F	DM type 1	27.3	186	60
	12	F	Becker MC	44.8	372	57
	12	M	Thomsen MC	58.1	248	60
	13	M	Becker MC	60.2	334	59
	14	F	Becker MC	68.0	500	54
	15	F	Thomsen MC	50.0	248	53
	16	M	DM type 1	68.5	500	55
COHORT 2	6	F	Becker MC	21.0	186	56
	7	F	Thomsen MC	21.0	186	56
	8	F	Thomsen MC	26.0	186	56
	10	M	Thomsen MC & PMC	32.6	249	59
	10	M	Thomsen MC & PMC	31.4	249	59

MC, myotonia congenita; PMC, paramyotonia congenita

*Mexiletine hydrochloride 75 mg capsules containing 62 mg mexiletine, 100 mg capsules containing 83 mg mexiletine, or 200 mg capsules containing 167 mg mexiletine.

Safety

- ECGs were normal excluding one abnormal baseline assessment (not clinically significant).
- Mexiletine was well tolerated (**Table 2**):
 - All treatment-emergent AEs (TEAEs) were mild; most resolved without intervention and were unrelated to treatment;
 - No mexiletine dose modifications were reported;
 - TEAEs were reported in 6 patients (86%) in Cohort and in 1 patient (20%) in Cohort 2; overall N=7 (58%);
 - No deaths, serious TEAEs, or TEAEs leading to study discontinuation were reported;
 - The most frequently reported TEAEs were abdominal pain and nausea;
 - Two patients in Cohort 1 reported 9 TEAEs that were considered treatment-related:
 - Patient 1.** Headache, nausea, vertigo, cardiac palpitations, and diarrhoea that resolved and caused dosing delay;
 - Patient 2.** Abdominal pain, nausea, asthenia, and pallor that resolved and resulted in temporary treatment withdrawal.
 - Physical examinations and haematological, biochemical, and muscle-function assessments revealed no clinically significant changes.

Table 2. PIP4 AE summary, indicating that mexiletine was well tolerated in the paediatric cohorts

System Organ Class Preferred Term	Cohort 1 (N=7)	Cohort 2 (N=5)	Combined (N=12)
At least one TEAE	6 (85.7)	1 (20.0)	7 (58.3)
Serious TEAE	0	0	0
Study drug-related TEAE	2 (28.6)	0	2 (16.7)
TEAEs leading to study drug discontinuation	0	0	0
Deaths	0	0	0
Participants experiencing AEs, n			
Gastrointestinal disorders			
Abdominal pain	3 (42.9)	0 (0.0)	3 (25.0)
Nausea	3 (42.9)	0 (0.0)	3 (25.0)
Vomiting	1 (14.3)	0 (0.0)	1 (8.3)
Diarrhea	1 (14.3)	0 (0.0)	1 (8.3)

Infections and infestations

Nasopharyngitis	2 (28.6)	0 (0.0)	2 (16.7)
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Respiratory, thoracic and mediastinal disorders

Asthma	0 (0.0)	1 (20.0)	1 (8.3)
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Musculoskeletal and connective tissue disorders

Musculoskeletal chest pain	1 (14.3)	0 (0.0)	1 (8.3)
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Nervous system disorders

Headache	2 (28.6)	0	2 (16.7)
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Cardiac disorders

Palpitation	1 (14.3)	0 (0.0)	1 (8.3)
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Vascular disorders

Pallor	1 (14.3)	0 (0.0)	1 (8.3)
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Renal and urinary disorders

Proteinuria	1 (14.3)	0 (0.0)	1 (8.3)
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Ear and labyrinth disorders

Vertigo	1 (14.3)	0	1 (8.3)
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General disorders and administration site conditions

Asthenia	1 (14.3)	0 (0.0)	1 (8.3)
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Reproductive system and breast disorders

Amenorrhoea	1 (14.3)	0 (0.0)	1 (8.3)
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Pharmacokinetics

- PK data confirm dose-dependent paediatric mexiletine exposure, consistent with well-established adult posology
- Mean maximum concentration (C_{max}) and area under the curve (AUC) values at maximum dose (501 mg, as 1×167 mg capsule, three-times daily) were 1392.21 ng/mL and 8551.64 ng/mL respectively (Day 42; steady state).
- PK modelling adequately described mexiletine concentration data, showing good agreement between observed and predicted concentrations:
 - Paediatric doses required to achieve mexiletine concentrations are similar to adult doses (**Figures 1 and 2; Table 1**);
 - Bootstrap analysis indicates the model is robust (**Table 3**).

Figure 1. Individual predicted mexiletine concentrations (lines) were consistent with individual observed concentrations (open circles) after oral administration of mexiletine in paediatric patients (N=12; PIP4) from the final PK model

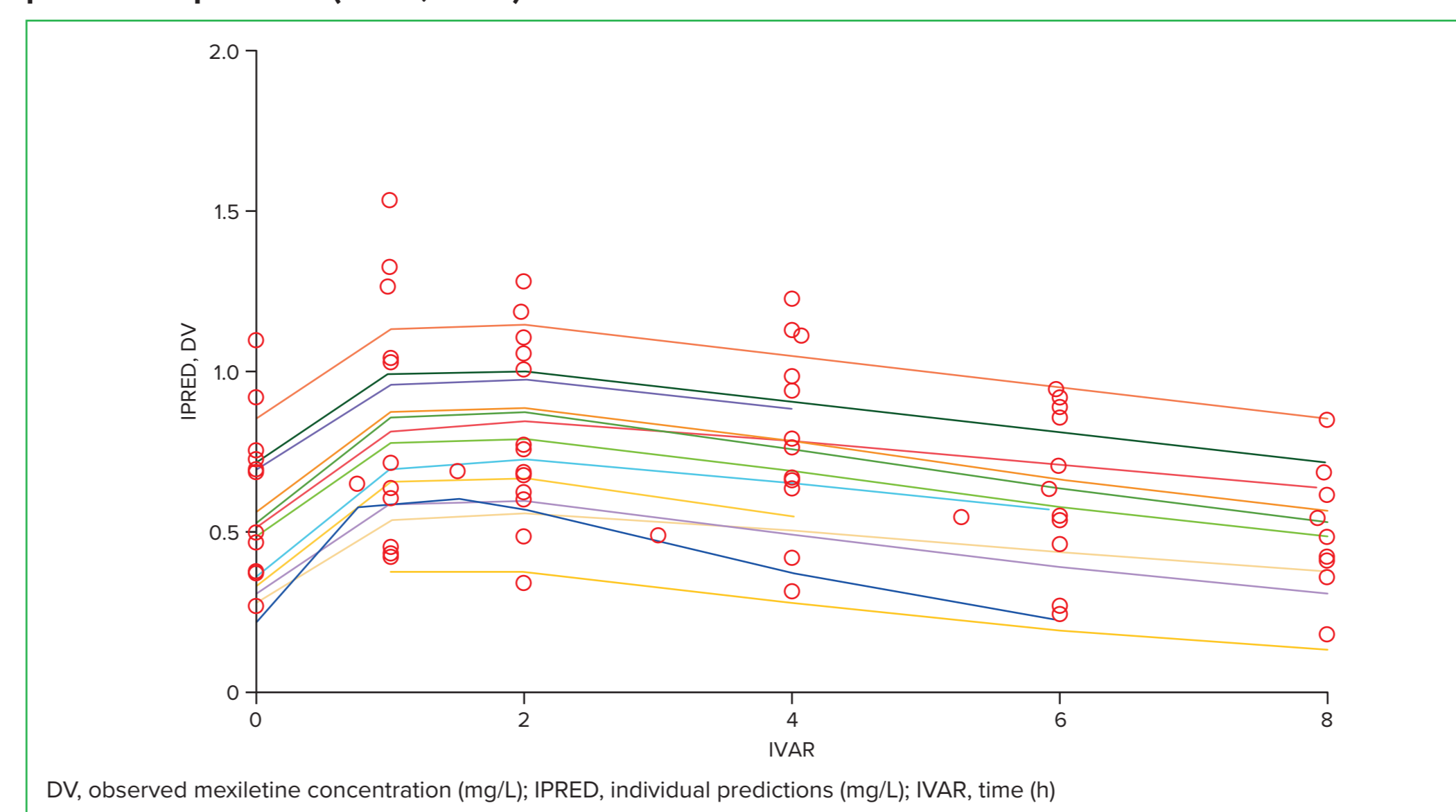
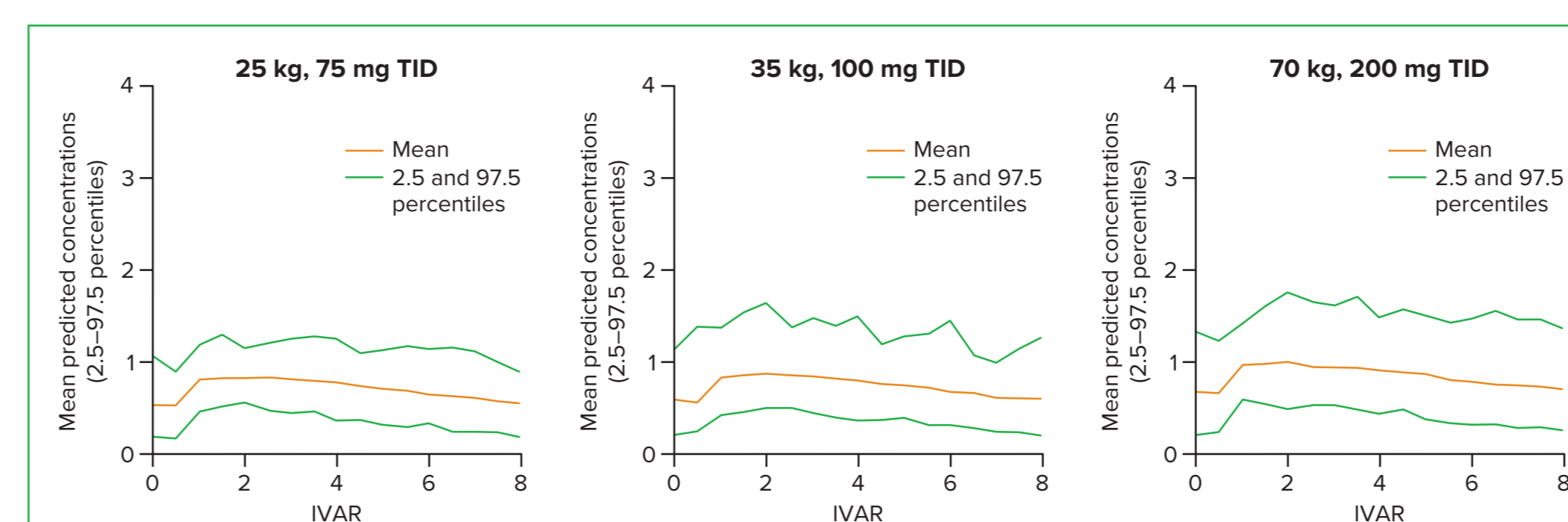


Figure 2. Model-based simulated concentration–time profiles of mexiletine use for paediatric patients with body weights of 25 kg and 35 kg, respectively, vs. simulation for 70 kg body weight (8-h dosing interval). Orange line, mean; green lines indicate 2.5 and 97.5 percentiles; IVAR, time (h)



Predicted steady-state PK parameters			
Body weight, kg	Mexiletine dose, mg*	Variable	Median (95% prediction interval)
25	75	C_{max} (mg/L)	0.93 (0.57,1.31)
		C_{min} (mg/L)	0.44 (0.17,0.86)
		AUC_{0-8h} (mg ² /h/L)	5.45 (2.90,8.62)
35	100	C_{max} (mg/L)	0.95 (0.54,1.63)
		C_{min} (mg/L)	0.49 (0.20,0.99)
		AUC_{0-8h} (mg ² /h/L)	5.78 (2.96,10.53)
70	200	C_{max} (mg/L)	1.05 (0.63,1.76)
		C_{min} (mg/L)	0.58 (0.22,1.16)
		AUC_{0-8h} (mg ² /h/L)	6.37 (3.50,11.39)

*Mexiletine hydrochloride 75 mg capsules containing 62 mg mexiletine, 100 mg capsules containing 83 mg mexiletine, or 200 mg capsules containing 167 mg mexiletine.

AUC_{0-8h} , area under the concentration-time curve in one dosing interval; C_{max} , maximum concentration; C_{min} , minimum concentration

Table 3. Comparison of bootstrapped population PK parameters with final PK model, showing that the model adequately describes mexiletine concentrations from paediatric and adult data

Parameter	Final model		Bootstrap (N=1000)	
	Estimate	95% CI	Estimate	95% CI
K_a 1/h	0.74	0.44, 1.03	0.80	0.49, 1.29
V (L)	38.76	24.00, 53.52	41.10	27.58, 61.98
V2 (L)	336.64	284.12, 389.17	333.54	286.33, 377.71
CL (L/h/70kg)	28.21	18.94, 37.47	26.88	18.34, 38.72
Q (L/h/70kg)	506.91	431.59, 582.21	501.08	417.80, 612.31
Residual variability	0.32	0.22, 0.42	0.30	0.22, 0.38

K_a , absorption rate (constant); V, volume of distribution; CL, clearance; Q, intercompartmental clearance

Conclusions

- There were no unexpected safety or PK findings in PIP4, a study within the mexiletine Paediatric Investigation Plan, undertaken in children with NDM or DM aged between 6 and <18 years.
- In paediatric patients with myotonia, the safety profile of mexiletine was consistent with the NaMuscla[®] SMPC.^{1,2}
- No AEs resulted in mexiletine discontinuation.
- PK analyses confirm that weight-based paediatric dosing of mexiletine results in drug exposure that is comparable to adult treatment.
- Dosing recommendations for mexiletine treatment, developed following the PIP4 study for children with myotonia aged 6 to <18 years, are presented in **Table 4**.

Table 4. Dosing recommendations for mexiletine treatment in children aged 6 to <18 years are based on body weight

Body weight, kg	Approximate age group, years	Mexiletine dosing*			
		Once daily (morning)	Twice daily (morning and evening)	Three-times daily (morning, afternoon, evening)	Maintenance/maximum total daily dose
20–30	6–9	62 mg (1 × 62 mg capsule)	125 mg (2 × 62 mg capsules)	187 mg (3 × 62 mg capsules)	187 mg
30–40	10–11	83 mg (1 × 83 mg capsule)	167 mg (2 × 83 mg capsules)	250 mg (3 × 83 mg or 4 × 62 mg capsules)	250 mg
40–60	12–15	125 mg (2 × 62 mg capsules)	250 mg (3 × 83 mg or 4 × 62 mg capsules)	375 mg (6 × 62 mg capsules)	375 mg
≥ 60	16–17	167 mg (1 × 167 mg or 2 × 83 mg capsules)	333 mg (2 × 167 mg or 4 × 83 mg capsules)	500 mg (3 × 167 mg or 6 × 83 mg capsules)	500 mg

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