A Population Pharmacokinetic-Pharmacodynamic Model Evaluating Efficacy of Nalbuphine Extended-Release in Patients with Prurigo Nodularis

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August 29, 2022

Abstract

Population pharmacokinetic (PK) and pharmacokinetic- pharmacodynamic (PK-PD) models were used to quantify the exposure-response (E-R) relationship between nalbuphine exposure and 2 widely used rating scales for itch: the Numerical Rating Scale for the subject's 'average' itch experience (NRS-AV) and the Worst Itch (WI-NRS), with 24-hour recall. Simulations based on the model E-R relationship were used to support dose selection for future clinical investigations and were evaluated with a target of reducing the 7-day average of the 24-hour WI-NRS by at least 30% from baseline in the majority of the analysis population. Data from two clinical trials (NCT02373215: 9 healthy subjects; NCT02174419: 62 subjects with PN), in patients with Prurigo Nodularis (PN) with moderate to severe itch who received treatment with either of 2 doses of Nalbuphine ER versus placebo, were used for the analysis. A two-compartment PK model with serial zero and first-order oral absorption was used to describe drug exposure. A sigmoidal maximum effect (Emax) model with a placebo effect was used to model the itch response endpoints (NRS-AV, WI-NRS). The PK/PD model adequately predicted the exposure-related reduction in both NRS-AV and WI-NRS over time with approximately 63% and 27% of Emax, respectively. Exposures associated with 80% of Emax were achieved in about 78% of the patients at 162 mg BID compared to 35% at 81 mg BID. Simulated dose-response indicated that 108 and 162 mg BID doses result in the highest proportion of patients achieving at least a 30% reduction in NRS-AV and WI-NRS, respectively.

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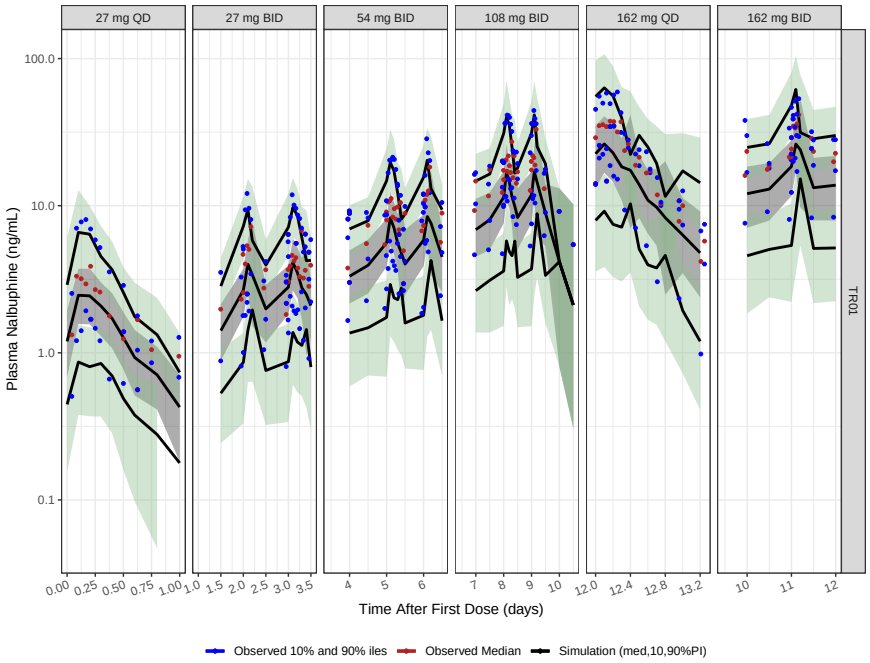
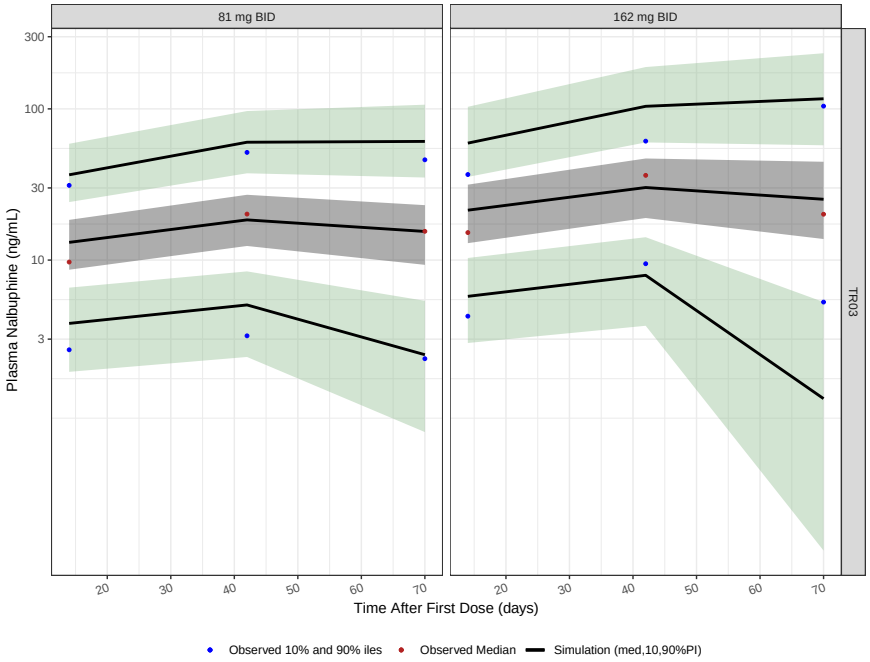
			Estimate	% RSE	95% CI	Shrinkage (%)
Structural model parameters						
CL/F (L/h)	θ_1	Apparent clearance	573	14.3	413, 734	-
V2/F (L)	θ_2	Apparent central volume	4.82e+03	14.1	3.49e+03, 6.15e+03	-
V3/F (L)	θ_3	Apparent peripheral volume	3.76e+04	66.9	-1.17e+04, 8.69e+04	-
Q/F (L/h)	θ_4	Apparent intercompartmental clearance	106	41.1	20.5, 191	-
KA (1/h)	θ_5	First order absorption rate constant	0.826	17.2	0.547, 1.10	-
D1 (h)	θ_6	Duration of zero order absorption	0.947	15.6	0.657, 1.24	-
Covariate effect parameters						
V2/F $\sim$ WT	θ_7	Body weight effect on V2/F	2.46	18.3	1.58, 3.35	-
CL/F $\sim$ Age	θ_8	Age effect on CL/F	-1.70	25.1	-2.54, -0.866	-
Q/F $\sim$ Age	θ_9	Age effect on Q/F	5.31	39.5	1.19, 9.43	-
V3/F $\sim$ Age	θ_{10}	Age effect on V3/F	0.00398	5.84e+04	-4.55, 4.56	-
Interindividual variance parameters						
IIV-CL/F	$\Omega_{(1,1)}$	Variance of clearance	0.694 [CV%=100]	26.4	0.335, 1.05	9.21
IIV - scale	θ_{11}	Scale parameter for V2 RE	0.793	13.7	0.580, 1.01	-
Residual variance						
Proportional	$\Sigma_{(1,1)}$	Variance	0.0851 [CV%=29.2]	5.85	0.0753, 0.0948	1.55
Additive	$\Sigma_{(2,2)}$	Variance	0.0220 [SD=0.148]	110	-0.0253, 0.0693	1.55

Abbreviations: CI = confidence intervals; RSE = relative standard error; RE = random effect, Corr = Correlation coefficient; CV = coefficient of variation; SD = standard deviation; SE = standard error
Confidence intervals = estimate $\pm$ 1.96 $\cdot$ SE
Body weight effects on CL/F and Q/F were fixed at 0.75 and at 1.00 for V3/F
CV% of log-normal omegas = sqrt(exp(estimate) - 1) $\cdot$ 100
CV% of sigma = sqrt(estimate) $\cdot$ 100

Treatment Group	N	$AUC_{0-24,ss}$ (hr mg/L) Mean $\pm$ 90%CI
Nalbuphine 81 mg BID	18	401 (83;841)
Nalbuphine 162 mg BID	13	818 (258;1820)





			Estimate	% RSE	95% CI	Shrinkage (%)
Structural model parameters						
KOUT (1/day)	$\exp(\theta_2)/(1+\exp(\theta_2))$	Offset rate	0.557	-	0.548, 0.565	-
τ	θ_5	Dispersion parameter	14.7	1.26	14.3, 15.1	-
PBOeffect	$\exp(\theta_6)/(1+\exp(\theta_6))$	Onset rate of placebo effect	0.912	-	0.905, 0.918	-
γ_0	θ_7	Boundary condition parameter	1.42	1.21	1.39, 1.46	-
γ_1	θ_8	Boundary condition parameter	0.404	7.00	0.348, 0.459	-
PBOoff	θ_9	Offset rate of placebo effect	0.162	2.78	0.153, 0.171	-
Interindividual variance parameters						
IIV-PBOeffect	$\Omega_{(2,2)}$	Variance of PBOeffect	3.35 [SD=0.210]	32.1	1.24, 5.46	1.00e-10
IIV-KOUT	$\Omega_{(3,3)}$	Variance of KOUT	0.0191 [SD=0.0339]	8.00	0.0161, 0.0221	35.8

Abbreviations: CI = confidence intervals; RSE = relative standard error; RE = random effect, CV = coefficient of variation; MM = Michaelis-menten; SE = standard error
Confidence intervals = estimate $\pm$ 1.96 $\cdot$ SE
CV% of log-normal omegas = sqrt(exp(estimate) - 1) $\cdot$ 100

			Estimate	% RSE	95% CI	Shrinkage (%)
Structural model parameters						
KOUT (1/day)	$\exp(\theta_2)/(1+\exp(\theta_2))$	Offset rate	0.557	-	FIXED	-
τ	θ_5	Dispersion parameter	10.4	1.18	10.2, 10.7	-
PBOeffect	$\exp(\theta_6)/(1+\exp(\theta_6))$	Onset rate of placebo effect	0.814	-	0.788, 0.838	-
γ_0	θ_7	Boundary condition parameter	1.40	0.910	1.38, 1.43	-
γ_1	θ_8	Boundary condition parameter	0.690	2.74	0.653, 0.728	-
PBOoff	θ_9	Offset rate of placebo effect	0.223	4.52	0.204, 0.243	-
Interindividual variance parameters						
IIV-PBOeffect	$\Omega_{(2,2)}$	Variance of PBOeffect	2.10 [SD=0.218]	19.2	1.31, 2.89	1.00e-10
IIV-KOUT	$\Omega_{(3,3)}$	Variance of KOUT	0.0191 [SD=0.0340]	-	FIXED	62.2

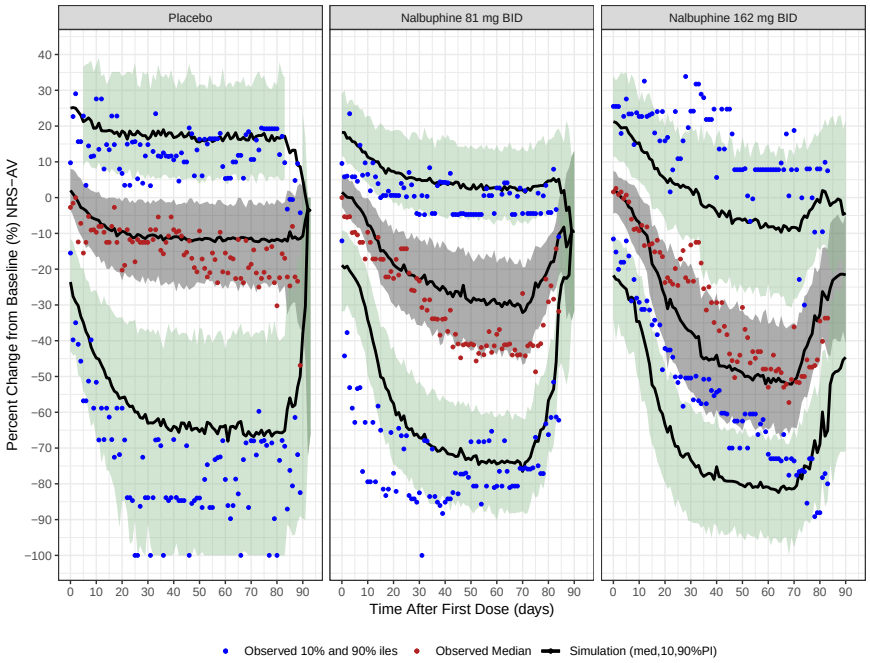
Abbreviations: CI = confidence intervals; RSE = relative standard error; RE = random effect, CV = coefficient of variation; MM = Michaelis-menten; SE = standard error
Confidence intervals = estimate $\pm$ 1.96 $\cdot$ SE
CV% of log-normal omegas = sqrt(exp(estimate) - 1) $\cdot$ 100

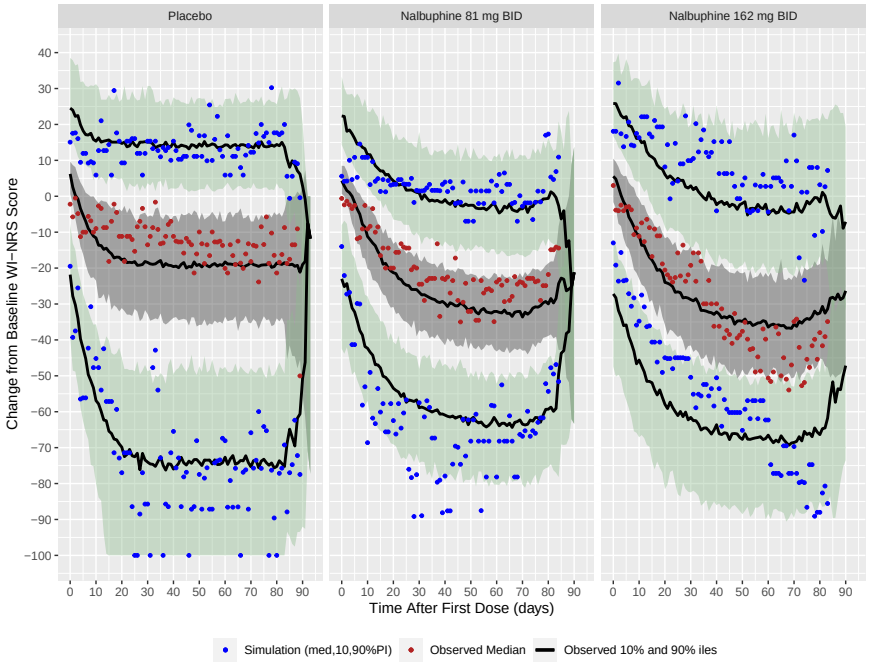
			Estimate	% RSE	95% CI	Shrinkage (%)
Structural model parameters						
KOUT (1/day)	$\exp(\theta_2)/(1+\exp(\theta_2))$	Offset rate	0.608	-	0.604, 0.612	-
EC50 (ng*hr/mL)	θ_3	MM parameter for concentration eliciting half of max effect	317	1.67	306, 327	-
EMAX (score/day)	θ_4	MM parameter for max effect	0.550	6.78	0.477, 0.623	-
τ	θ_5	Dispersion parameter	20.2	0.838	19.9, 20.5	-
γ_0	θ_7	Boundary condition parameter	1.88	0.425	1.86, 1.89	-
γ_1	θ_8	Boundary condition parameter	0.936	1.14	0.915, 0.957	-
Interindividual variance parameters						
IIV-KOUT	$\Omega_{(1,1)}$	Variance of KOUT	5.83 [SD=0.337]	10.6	4.61, 7.04	0.271
IIV-EC50	$\Omega_{(3,3)}$	Variance of EC50	0.115 [CV%=34.9]	0.789	0.113, 0.117	1.00e-10
IIV-EMAX	$\Omega_{(4,4)}$	Variance of EMAX	0.153 [CV%=40.7]	1.59	0.148, 0.158	1.00e-10

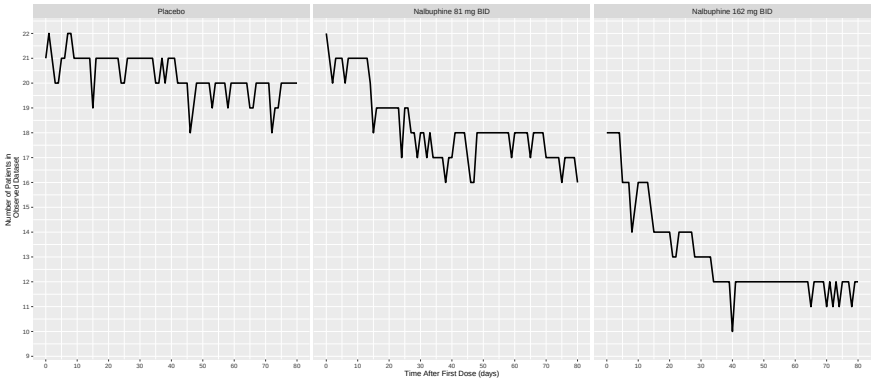
Abbreviations: CI = confidence intervals; RSE = relative standard error; CV = coefficient of variation; MM = Michaelis-menten; SE = standard error
Confidence intervals = estimate $\pm$ 1.96 $\cdot$ SE
CV% of log-normal omegas = sqrt(exp(estimate) - 1) $\cdot$ 100

			Estimate	% RSE	95% CI	Shrinkage (%)
Structural model parameters						
KOUT (1/day)	$\exp(\theta_2)/(1+\exp(\theta_2))$	Offset rate	0.302	0.291	0.301, 0.303	-
EC50 (ng*hr/mL)	θ_3	MM parameter for concentration eliciting half of max effect	93.4	3.57	86.9, 100	-
EMAX (score/day)	θ_4	MM parameter for max effect	-1.01	2.97	-1.06, -0.948	-
τ	θ_5	Dispersion parameter	7.97	0.969	7.82, 8.12	-
PBOeffect	$\exp(\theta_6)/(1+\exp(\theta_6))$	Onset rate of placebo effect	0.815	-	FIXED	-
γ_0	θ_7	Boundary condition parameter	1.46	1.02	1.43, 1.48	-
γ_1	θ_8	Boundary condition parameter	0.550	5.66	0.489, 0.611	-
PBOoff	θ_9	Offset rate of placebo effect	0.223	-	FIXED	-
Interindividual variance parameters						
IIV-EMAX	$\Omega_{(1,1)}$	Variance of EMAX	0.0103 [SD=0.0199]	2.77	0.00976, 0.0109	1.00e-10
IIV-KOUT	$\Omega_{(3,3)}$	Variance of KOUT	0.0110 [SD=0.0220]	3.26	0.0103, 0.0117	1.00e-10
IIV-EC50	$\Omega_{(4,4)}$	Variance of EC50	0.0100 [CV%=10.0]	1.96	0.00965, 0.0104	37.6

Abbreviations: CI = confidence intervals; RSE = relative standard error; CV = coefficient of variation; MM = Michaelis-menten; SE = standard error
Confidence intervals = estimate $\pm$ 1.96 $\cdot$ SE
CV% of log-normal omegas = sqrt(exp(estimate) - 1) $\cdot$ 100







	NRS	WI-NRS
	EMAX = 63.4 (61.7;65.1)% Reduction	EMAX = 26.7 (25.7;27.9)% Reduction
AUClevel	$AUC_{0-24,ss}$ (ng*hr/mL) Mean $\pm 90\% CI$	$AUC_{0-24,ss}$ (ng*hr/mL) Mean $\pm 90\% CI$
AUC_{50}	317 (306,327)	93.4 (86.9,100)
AUC_{80}	445 (430,460)	523 (486,559)
AUC_{90}	543 (525,561)	1430 (1330,1530)