Supplementary Materials: New data for Nebivolol after in silico PK study: focus on young patients and dosage regimen

Table S1. Demographic characteristics (mean ± standard deviation) of patients in each clinical study.

Individual	Age (years)	BMI (kg/m²)	Genotype	Ethnic	Study Number
1	34.4	26	EM	Caucasian	1
2	25.7	24	EM	Caucasian	2
3	25.08	23.29	EM	Caucasian	3
4	29.67	24.17	PM	Caucasian	3
5	24.83	22.30	EM	Caucasian	4
6	24.83	22.30	EM	Caucasian	5
7	24	23.19	IM	Asian	6
8	24	20.10	IM	Asian	6
9	24	21.85	IM	Asian	6
10	20	20.26	IM	Asian	6
11	24	21.89	IM	Asian	6
12	25	22.87	EM	Asian	6
13	24	19.93	IM	Asian	6
14	24	20.71	EM	Asian	6
15	23	19.22	EM	Asian	6
16	25	21.08	IM	Asian	6
17	27	20.01	EM	Asian	6
18	23	19.73	IM	Asian	6
19	24	21.41	EM	Asian	6
20	24	21.16	EM	Asian	6
21	24	22.19	EM	Asian	6
22	22	19.90	EM	Asian	6
23	21	22.19	IM	Asian	6
24	23	22.53	EM	Asian	6
25	25	20.55	EM	Asian	6
26	24	23.63	EM	Asian	6
27	22	22.34	EM	Asian	6
28	24	21.62	IM	Asian	6
29	23	21.83	IM	Asian	6
30	25	21.00	IM	Asian	6

Table S2. Pharmacokinetics (PK) parameters (mean ± standard deviation) of patients in each clinical study.

Study Number 1	
PK parameters	**n = 26**
C*max* (ng.mL^{-1})	8.02 ± 3.47
AUC (ng.mL^{-1})	41.50 ± 29.76

T*max* (h)	1.32 ± 0.67
K*el* (L/h)	ND
$t_{1/2}$ (h)	11.03 ± 2.12
Study Number 2	
PK parameters	**n = 23**
Cmax ($ng.mL^{-1}$)	1.78 ± 1.17
AUC ($ng.mL^{-1}$)	12.09 ± 24.51
Tmax (h)	1.37 ± 0.88
Kel (L/h)	0.25 ± 0.30
$t_{1/2}$ (h)	6.65 ± 8.55
Study Number 3	
PK parameters	**n = 43**
Cmax ($ng.mL^{-1}$)	139.22 ± 20.80 (PM) 9.19 ± 8.91 (EM)
AUC ($ng.mL^{-1}$)	5.24 ± 0.48 (PM) 1.66 ± 0.86 (EM)
Tmax (h)	ND
Kel (L/h)	ND
$t_{1/2}$ (h)	ND
Study Number 4	
PK parameters	**n = 18**
Cmax ($ng.mL^{-1}$)	1.67 ± 0.69
AUC ($ng.mL^{-1}$)	10.38 ± 10.53
Tmax (h)	1.81 ± 1.19
Kel (L/h)	0.13 ± 0.09
$t_{1/2}$ (h)	7.05 ± 3.69
Study Number 5	
PK parameters	**n = 18**

Cmax (ng.mL^{-1})	1.67 ± 0.69
AUC (ng.mL^{-1})	10.40 ± 10.50
Tmax (h)	1.81 ± 1.19
Kel (L/h)	0.13 ± 0.09
$t_{1/2}$ (h)	7.05 ± 3.69
Study Number 6	
PK parameters	**n = 24**
Cmax (ng.mL^{-1})	2.65 ± 1.33
AUC (ng.mL^{-1})	18.21 ± 14.11
Tmax (h)	1.5 ± 0.9
Kel (L/h)	ND
$t_{1/2}$ (h)	12.52 ± 5.72

C*max* – maximum observed concentration; *AUC* – area under the curve from the time of dosing to the last measurable positive concentration; T*max* – time of maximum observed concentration; K*el* – elimination rate constant; $t_{1/2}$ – half-life time.

Table S3. Different basic population pharmacokinetic models of Nebivolol.

Project name	Compartment	Error model	BIC
PK_N_01	Two	Combined 1	-278.87
PK_N_02	One	Combined 1	42.83
PK_N_03	One	Combined 1	128.53
PK_N_04	Two	Combined 1	-170.82
PK_N_05	Two	Combined 1	-275.68
PK_N_06	Two	Proportional	-401.07
PK_N_07	One	Combined 1	51.63

BIC: Bayesian information criteria; ΔOFV: Based on the BIC values, PK_N_06 (yellow) were the selected model for the study, due to their best description of the population pharmacokinetic profile.