

Population Pharmacokinetic Analysis of Indacaterol/Glycopyrronium/Mometasone Furoate after Administration of Combination Therapies using the Breezhaler® Device in Patients with Asthma

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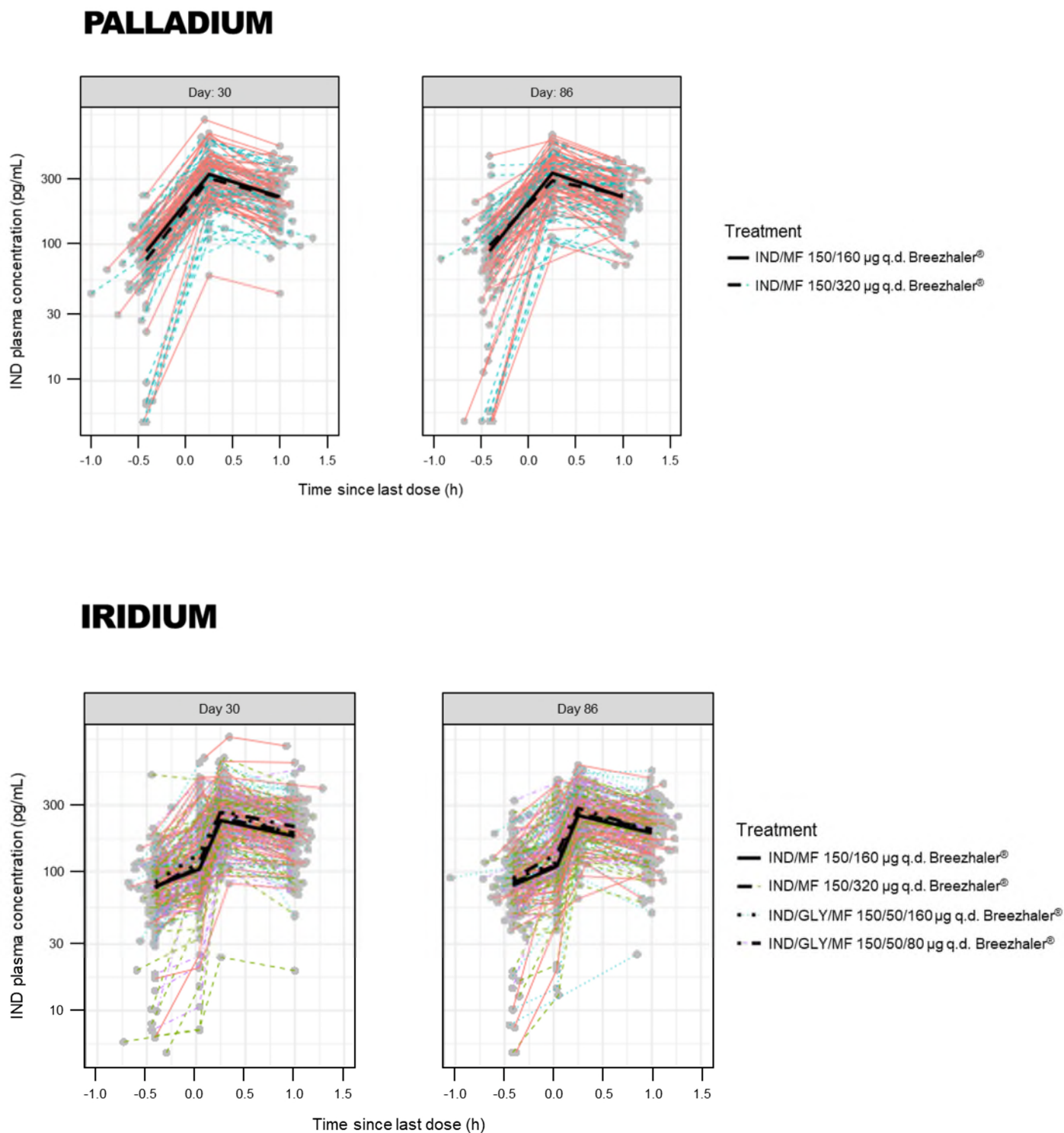
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†At the time of study conduct, Soniya Vaidya was a part of Novartis Institutes for Biomedical Research, Cambridge, USA. Since then, she has moved to a different role outside Novartis and her current affiliation is: Axcella Health Inc., Cambridge, MA, USA

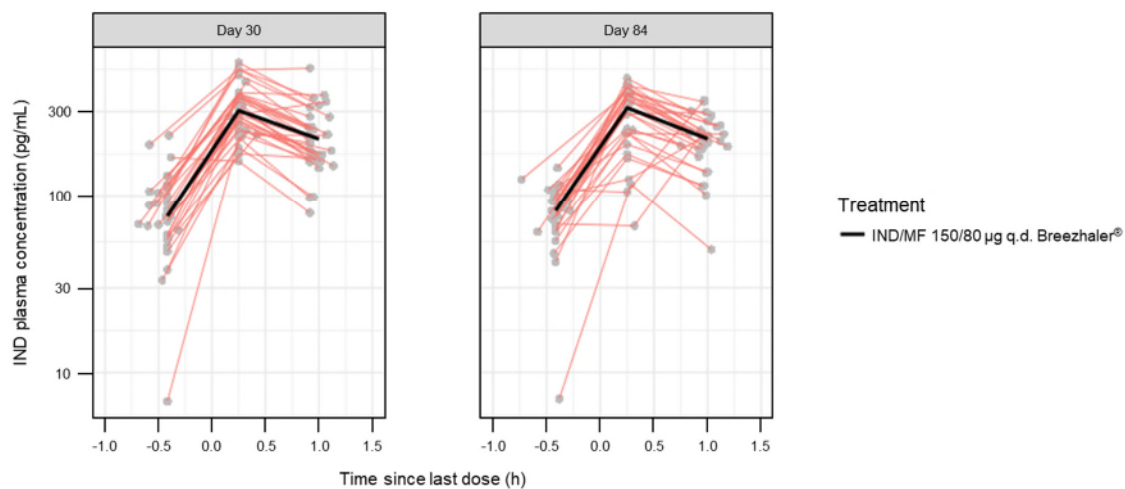
Online Resource 1. Plasma concentration data for a) indacaterol b) glycopyrronium and c)

mometasone furoate

a)

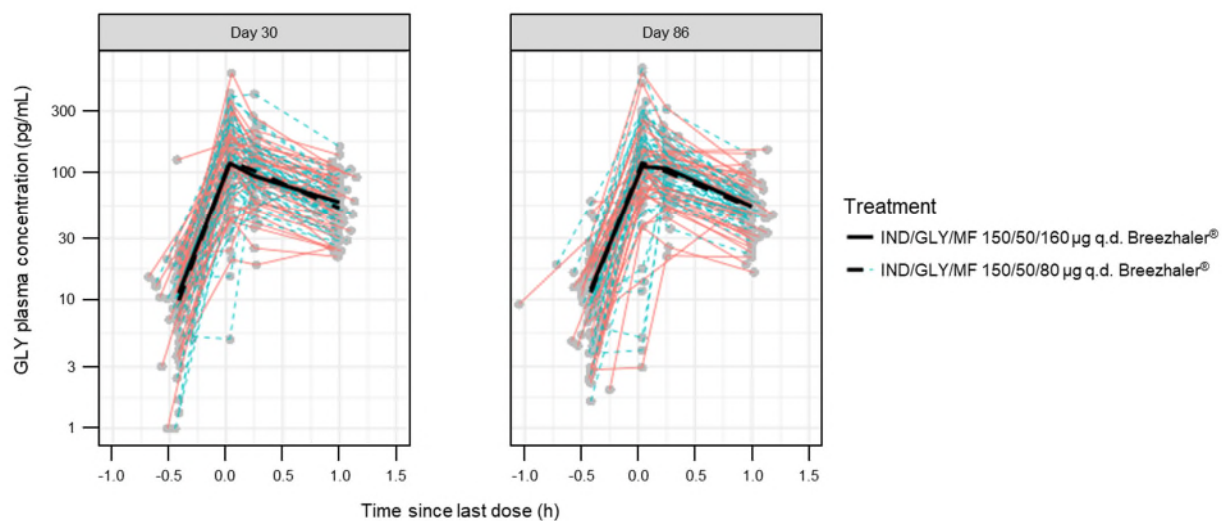


QUARTZ



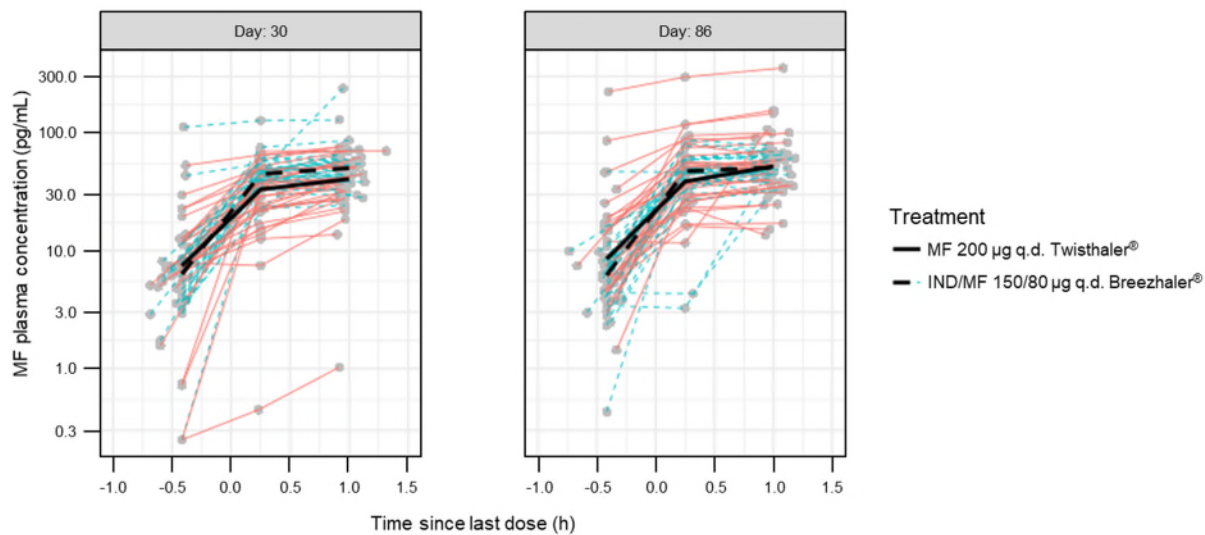
b)

IRIDIUM

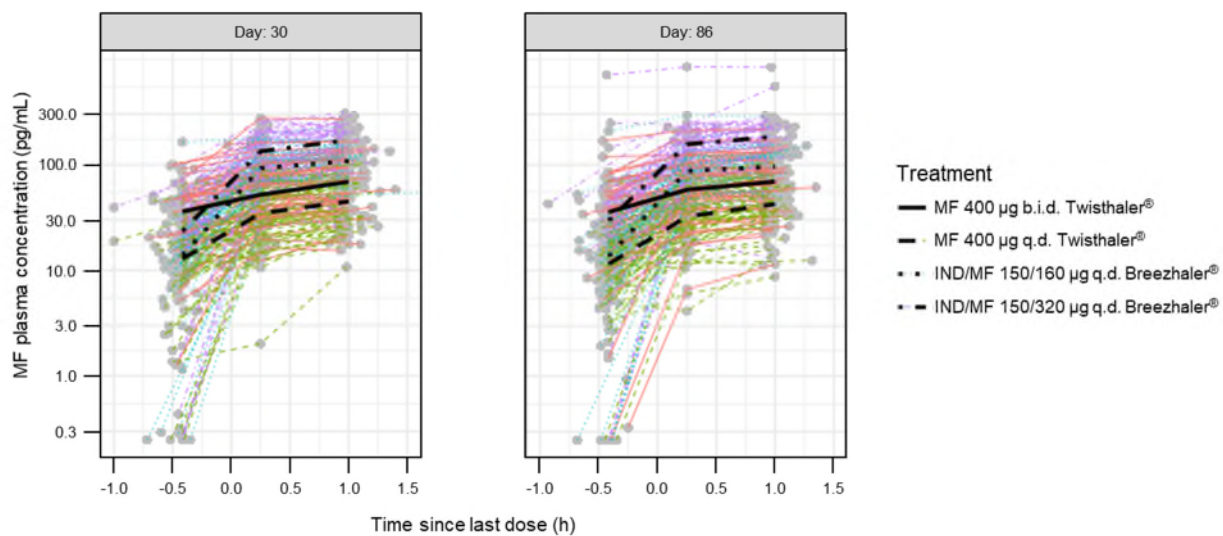


c)

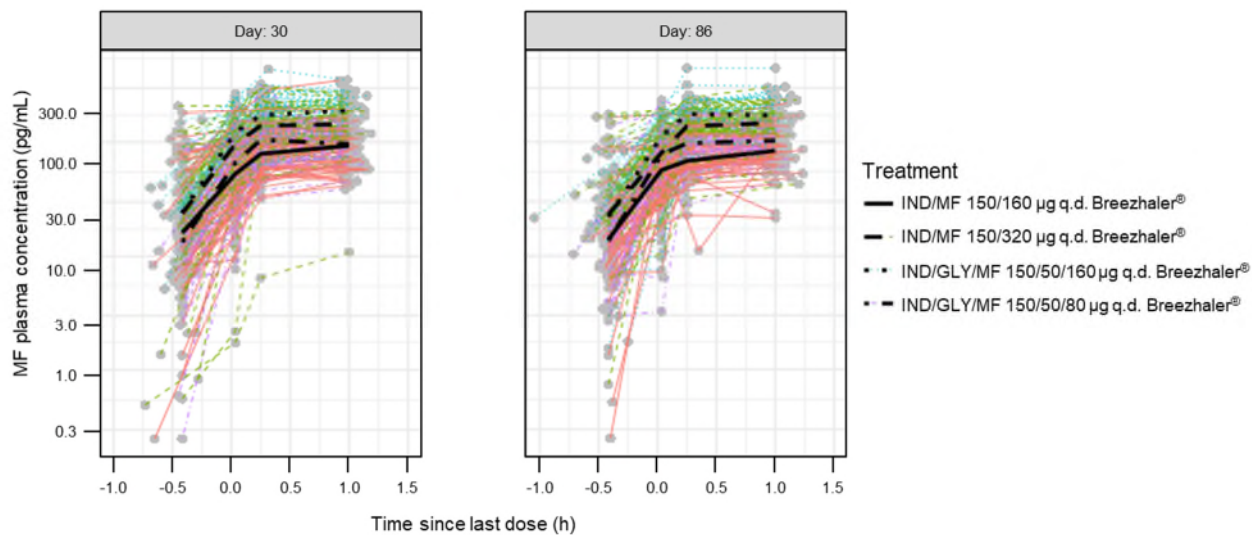
QUARTZ



PALLADIUM



IRIDIUM



Black thick lines show median profiles, thin lines are profiles from individual patients, colors and line type differentiate treatments.

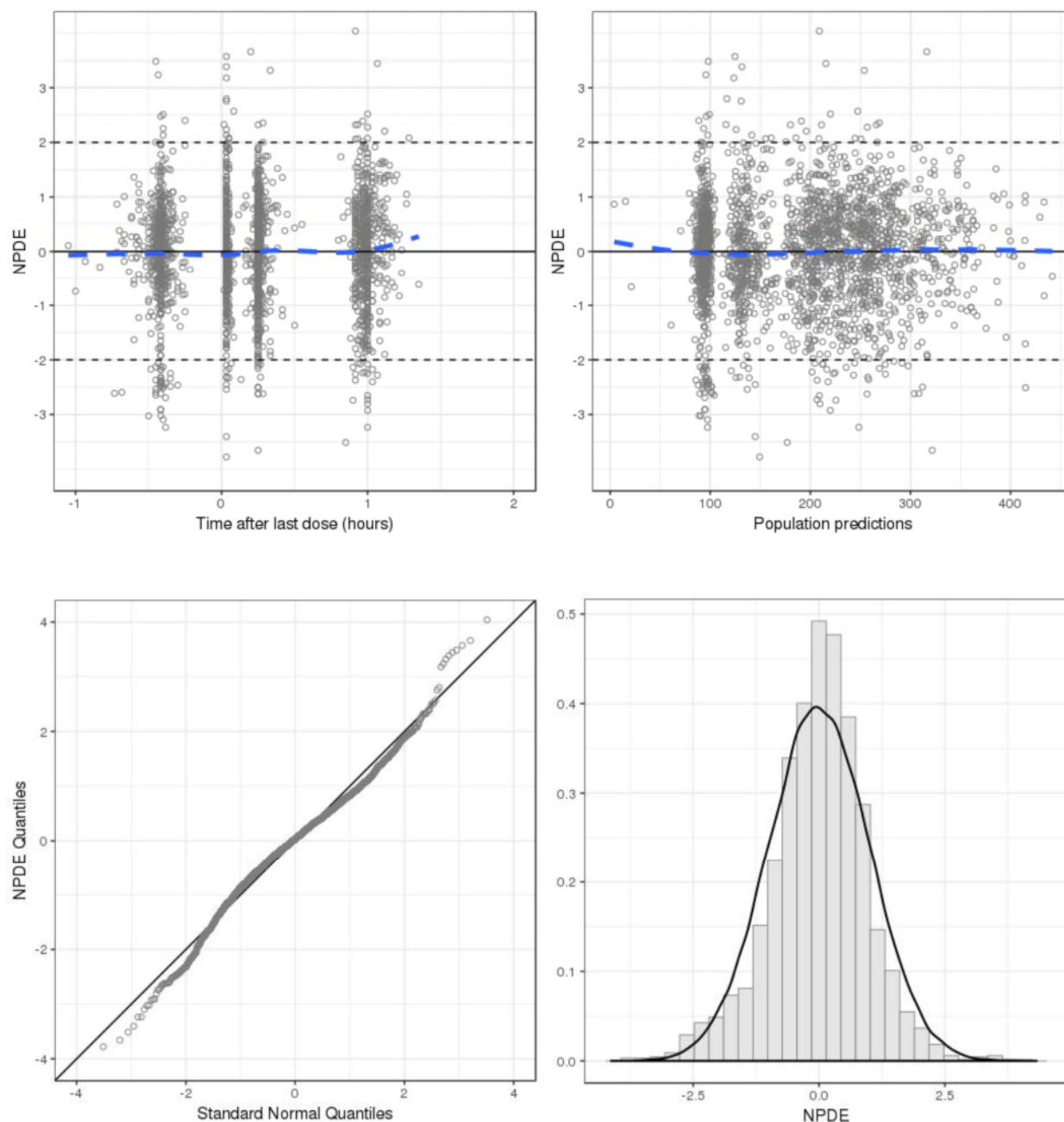
b.i.d., twice-daily; GLY, glycopyrronium; IND, indacaterol; MF, mometasone furoate; q.d., once-daily

Online Resource 2. Summary statistics of C_{trough} and C_{max} for indacaterol and glycopyrronium in patients with asthma and COPD

Study	Treatment	C_{trough} , pg/mL	C_{max} , pg/mL
IND			
QUARTZ	IND/MF 150/80 µg	82.8 (27.1)	307.5 (89.5)
PALLADIUM	IND/MF 150/320 µg	106.8 (71.6)	302.2 (112)
	IND/MF 150/160 µg	94.0 (62.6)	340.3 (120.9)
IRIDIUM	IND/GLY/MF 150/50/160 µg	96.6 (50.9)	275.3 (126.1)
	IND/GLY/MF 150/50/80 µg	101.0 (56.6)	285.9 (97.8)
	IND/MF 150/320 µg	84.7 (41.9)	261.6 (91.2)
	IND/MF 150/160 µg	87.0 (44.8)	265.4 (111.9)
SHINE	IND 150 µg	102.5 (45.4)	257.7 (97.3)
	IND/GLY 110/50 µg	87.4 (34.2)	234.9 (100.8)
GLY			
IRIDIUM	IND/GLY/MF 150/50/160 µg	13.1 (11.4)	140.6 (112.6)
	IND/GLY/MF 150/50/80 µg	12.3 (7.5)	157.7 (106.2)
SHINE	GLY 50 µg	11.7 (11.9)	144.2 (99.6)
	IND/GLY 110/50 µg	13.2 (15.6)	139.3 (104.1)
Data presented as mean (SD) QUARTZ [21], PALLADIUM [18] and IRIDIUM [19] studies were conducted in patients with asthma, data presented from Day 86 for these studies SHINE [22] study was conducted in patients with COPD, data presented for Day 85 <i>COPD</i>, chronic obstructive pulmonary disease, <i>IND</i> indacaterol, <i>GLY</i> glycopyrronium, <i>MF</i> mometasone furoate			

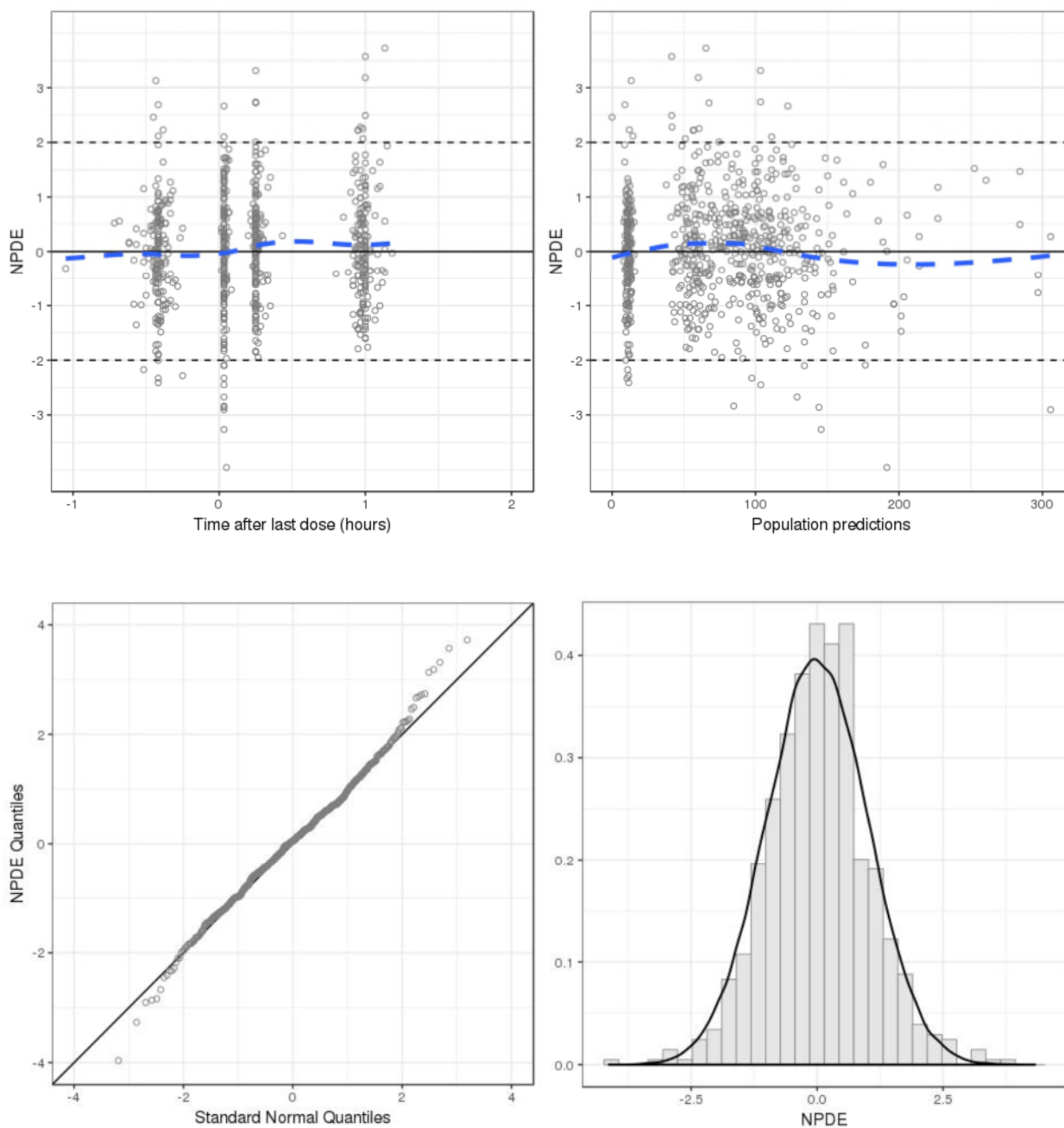
Online Resource 3. Normalised prediction distribution errors diagnostics for popPK model for a) indacaterol, b) glycopyrronium and c) mometasone furoate

a)



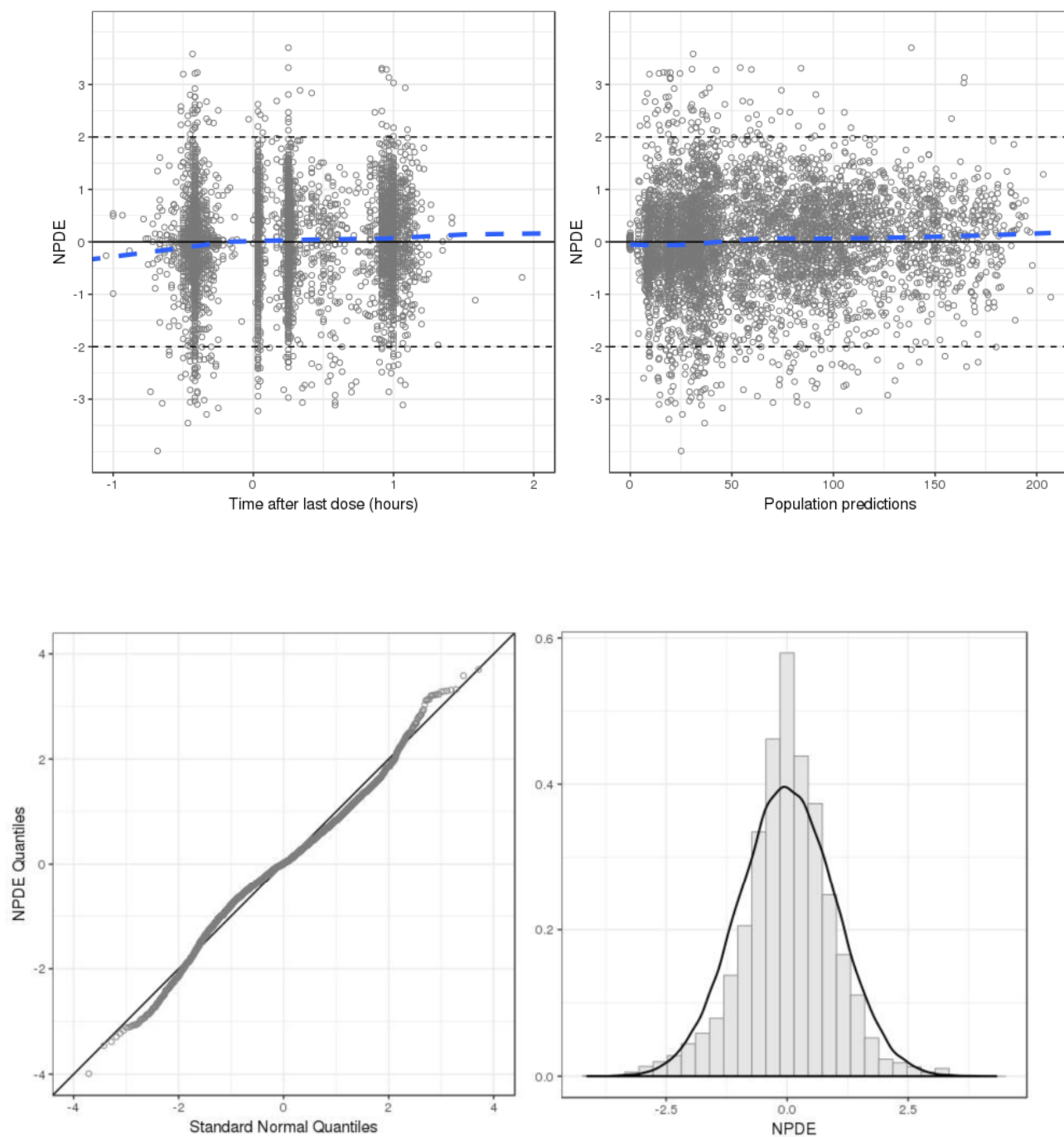
Upper two plots show NPDE versus time after last dose or versus population prediction, respectively; lower two plots illustrate the distribution of the NPDE as quantile-quantile plot or density plot, respectively. Individual values are indicated by circles. LOESS regression shown as thick dashed lines; *LOESS* locally estimated scatterplot smoothing; NPDE, normalised prediction distribution errors

b)



Upper two plots show NPDE versus time after last dose or versus population prediction, respectively; lower two plots illustrate the distribution of the NPDE as quantile-quantile plot or density plot, respectively. Individual values are indicated by circles. LOESS regression shown as thick dashed lines, *LOESS* locally estimated scatterplot smoothing. NPDE, normalised prediction distribution errors

c)



Upper two plots show NPDE versus time after last dose or versus population prediction, respectively; lower two plots illustrate the distribution of the NPDE as quantile-quantile plot or density plot, respectively. Individual values are indicated by circles. LOESS regression shown as thick dashed lines, *LOESS* locally estimated scatterplot smoothing. NPDE, normalised prediction distribution errors

Online resource 4. Parameter estimates for indacaterol, glycopyrronium and mometasone furoate base PK model

Parameter	IND		GLY		MF	
	Estimate (% RSE)	Shrinkage (%)	Estimate (% RSE)	Shrinkage (%)	Estimate (% RSE)	Shrinkage (%)
Structural parameters						
CL/F (L/h)	49 (2.8 %)	-	89 (4.2 %)	-	190 (4.2 %)	-
Vc/F (L)	560 (4.2 %)	-	420 (6.1 %)	-	1700 (5.4 %)	-
Q/F (L/h)	440 (2.5 %)	-	330 (5.9 %)	-	240 (9.3 %)	-
Vp/F (L)	4800 (15 %)	-	1300 (fixed)	-	3200 (24 %)	-
Ka (1/h)	50 (fixed)	-	-	-	2.3 (10 %)	-
Duration of zero order absorption (h)	0.059 (7.1 %)	-	-	-	0.01 (fixed)	-
Fraction absorbed via zero order absorption, Fr	0.35 (15 %)	-	-	-	0.37 (4.2 %)	-
Between-subject variability, SD						
BSV on CL/F	0.43 (5.4 %)	9 %	0.39 (8.1 %)	6 %	0.49 (3.4 %)	8 %
BSV on Vc/F	0.4 (6.7 %)	15 %	0.56 (8.3 %)	7 %	0.42 (4.3 %)	17 %
BSV on Q/F	0.11 (15 %)	81 %	-	-	0.4 (15 %)	78 %
BSV on Vp/F	1.8 (6.4 %)	38 %	-	-	2.1 (7.7 %)	56 %
BSF on Fr	1.3 (13 %)	43 %	-	-	0.29 (13 %)	71 %
Covariate effects						
Body weight on CL/F	0.75 (fixed)	-	0.75 (fixed)	-	0.75 (fixed)	-
Body weight on Vc/F	1 (fixed)	-	1 (fixed)	-	1 (fixed)	-
Body weight on Q/F	0.75 (fixed)	-	0.75 (fixed)	-	0.75 (fixed)	-
Body weight on Vp/F	1 (fixed)	-	1 (fixed)	-	1 (fixed)	-
Residual variability						
Additive error, a (pg/mL)	6.3 (22 %)	-	-	-	-	-
Proportional error, b (Fraction)	0.25 (2.4 %)	-	0.34 (3.3 %)	-	0.36 (1.3 %)	-

BSV between subject variability, CL/F apparent clearance, Fr fraction of dose absorbed rapidly, GLY glycopyrronium, IND indacaterol, Ka absorption constant, MF mometasone furoate, Q/F apparent inter-compartmental clearance, RSE relative standard error, SD standard deviation, Vc/F apparent central volume of distribution, Vp/F apparent peripheral volume of distribution

