TABLE S1 AUC FEV_1 at day 14 for UMEC/VI *versus* placebo

Time period	UMEC/VI *versus* placebo	
	FEV_1 AUC LS mean difference, L (95% CI)	**p-value**
0–4 h	0.314 (0.258 to 0.371)	<0.0001
0–8 h	0.309 (0.251 to 0.366)	<0.0001
0–12 h	0.295 (0.242 to 0.348)	<0.0001
0–24 h	0.274 (0.224 to 0.324)	<0.0001

AUC: area under the curve; CI: confidence interval; FEV_1: forced expiratory volume in 1 s;

LS: least-squares; UMEC/VI: umeclidinium/vilanterol.

TABLE S2 CAT responder analysis for day 1 to day 14

Navafenterol *versus* placebo		**UMEC/VI *versus* placebo**		**Navafenterol *versus* UMEC/VI**	
Proportion of responders by treatment	**p-value**	**Proportion of responders by treatment**	**p-value**	**Proportion of responders by treatment**	**p-value**
Navafenterol 0.62	0.022	UMEC/VI 0.67	0.008	Navafenterol 0.61	0.63
Placebo 0.45		Placebo 0.44		UMEC/VI 0.66	

CAT: COPD assessment tool; UMEC/VI: umeclidinium/vilanterol.

TABLE S3 Mean frequency of baseline cough (coughs/h) stratified by smoking status

Time period	**Current smoker**			**Ex-smoker**		
	N	**Mean**	**SD**	**N**	**Mean**	**SD**
0–24 h	26	13.8	9.9	41	6.7	7.4
0–12 h	26	12.7	10.6	41	7.0	7.9
0–4 h	27	14.0	12.0	41	8.6	10.9

SD: standard deviation.

TABLE S4 Cough severity using the visual analogue scale at baseline and day 14

Treatment	Day[#]	Cough severity			Mean ratios day 14/baseline			Comparison with placebo[¶]		
		n	Geometric mean	Geometric CV%	n	Geometric mean	Geometric CV%	Estimated ratio	95% CI	p-value
Navafenterol (N=70)	Baseline	67	2.10	1.40						
	Day 14	67	1.42	2.04	67	0.71	1.10	0.83	0.67 to 1.03	0.087
UMEC/VI (N=69)	Baseline	69	1.90	1.31						
	Day 14	68	1.25	1.58	68	0.66	1.14	0.76	0.61 to 0.94	0.013
Placebo (N=68)	Baseline	65	1.86	1.17						
	Day 14	64	1.55	1.77	64	0.89	0.75	–	–	–

CI: confidence interval; CV: coefficient of variation; UMEC/VI: umeclidinium/vilanterol. [#]: Baseline was measured at day −1; [¶]: estimated ratio and 95% CI are transformed back to original scale.

TABLE S5 Pharmacokinetic parameters for navafenterol and LAS191861

Parameter		**Navafenterol**		**LAS191861**	
		Day 1	**Day 14**	**Day 1**	**Day 14**
C_{max}	n	40	41	41	41
	Geometric mean, pg/mL	310.4	532.9	26.64	63.29
	Geometric CV%	61.30	46.58	53.33	52.12
t_{max}	n	40	41	41	41
	Median, h	0.99	0.98	2.00	2.00
	Range, h	0.38–2.02	0.45–2.05	0.98–4.00	0.98–4.03
$AUC_{0–24}$	n	41	41	39	41
	Geometric mean, h × pg/mL	1661	3996	289.5	941.7
	Geometric CV%	83.60	55.66	57.83	63.11
$R_{ac(Cmax)}$	n	NA	40	NA	41
	Geometric mean	NA	1.725	NA	2.377
	Geometric CV%	NA	44.77	NA	40.02
$R_{ac(AUC0–24)}$	n	NA	41	NA	39
	Geometric mean	NA	2.406	NA	3.443
	Geometric CV%	NA	50.37	NA	47.15
$MR_{AUC0–24}$	n	NA	NA	41	41
	Geometric mean	NA	NA	0.1522	0.2356
	Geometric CV%	NA	NA	41.66	30.33

$AUC_{(0–24)}$: area under the plasma concentration–time curve from time 0 h to 24 h post-dose; C_{max}: maximum plasma concentration; CV: coefficient of variation; $MR_{AUC0–24}$: metabolic ratio of area under the plasma concentration–time curve from time 0 h to 24 h post-dose; NA: not applicable; $R_{ac(AUC0–24)}$: accumulation ratio calculated from $AUC_{0–24}$; $R_{ac(Cmax)}$: accumulation ratio calculated from C_{max}; t_{max}: time to C_{max}.

FIGURE S1 Chemical structure of LAS191861, the primary metabolite of navafenterol (AZD8871).

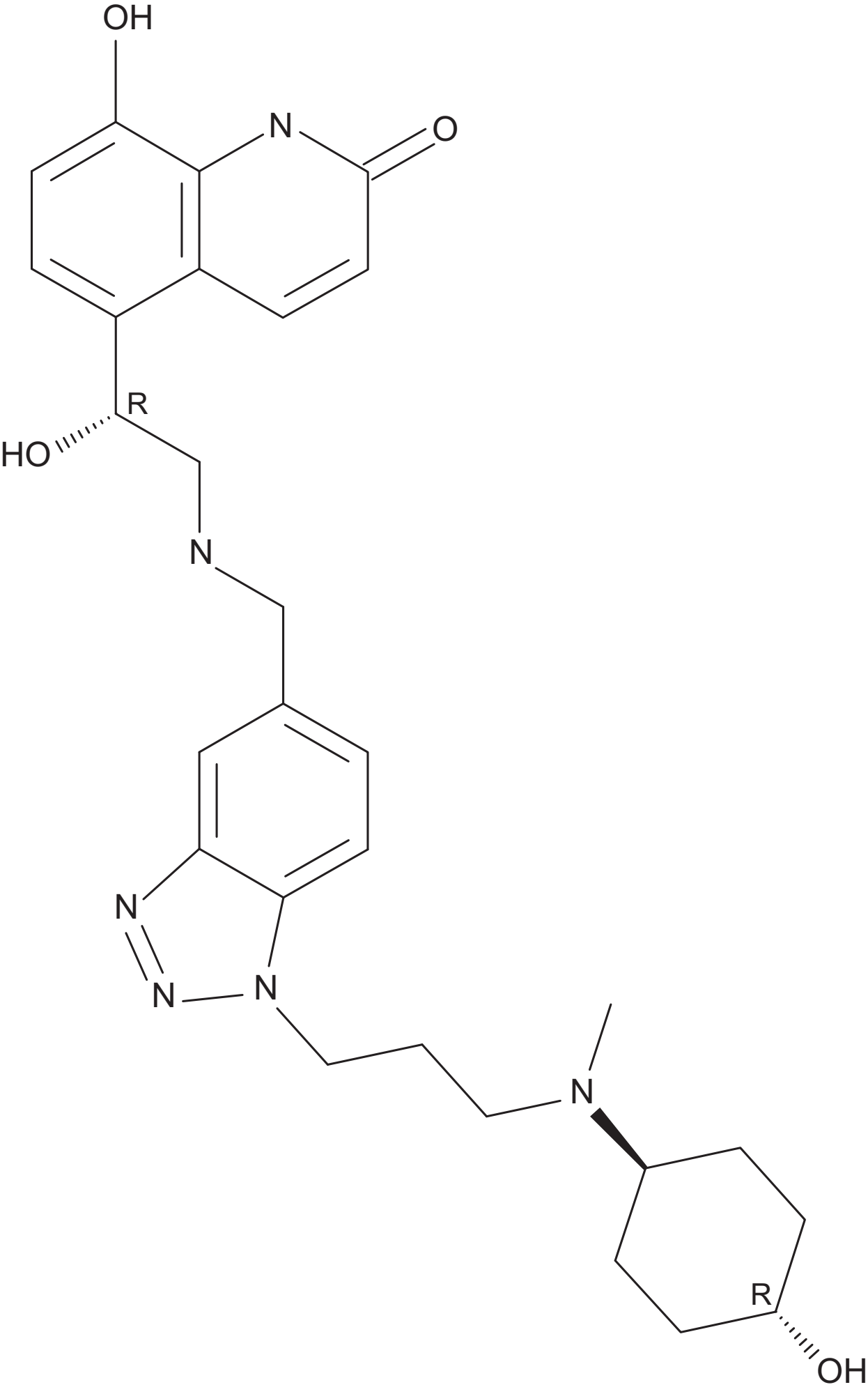

OH
N
O
R
HO
N
N
N
N
N
R
OH

FIGURE S2 FEV_1 in patients with reversible and non-reversible status at screening. a) LS mean change from baseline in peak FEV_1 at day 14. b) LS mean change from baseline in trough FEV_1 at day 15. FEV_1: forced expiratory volume in 1 s; LS: least-squares; UMEC/VI: umeclidinium/vilanterol.

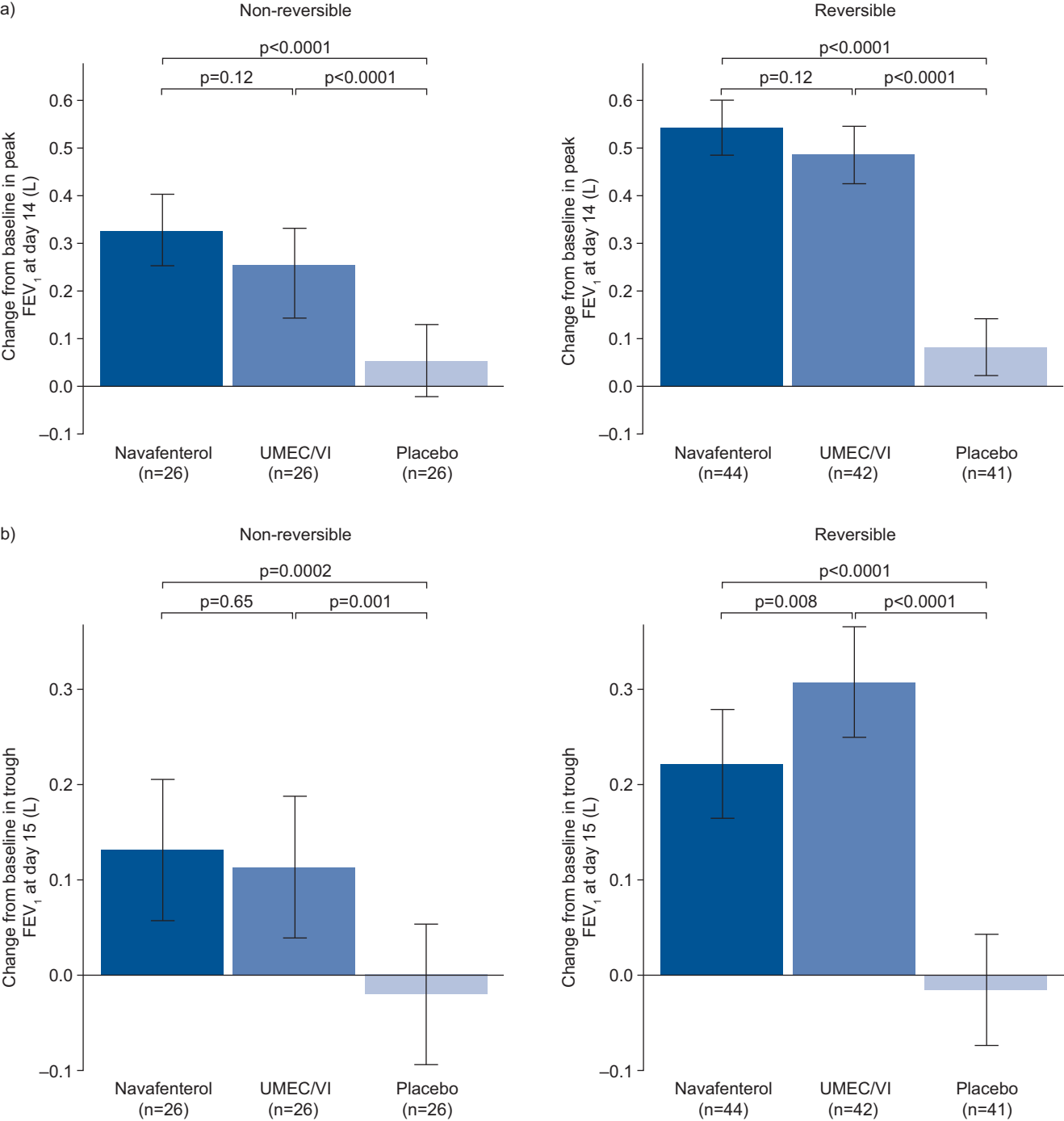
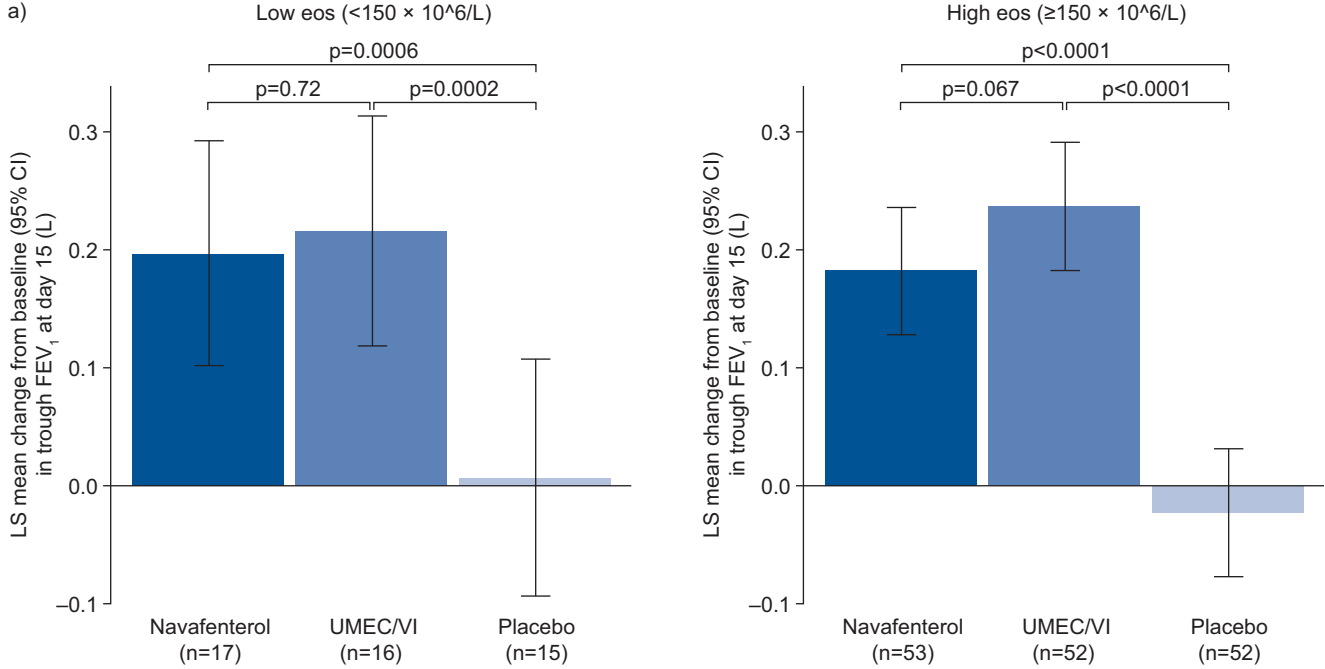

a)
Non-reversible
p<0.0001
p=0.12
p<0.0001
Change from baseline in peak FEV1 at day 14 (L)
0.6
0.5
0.4
0.3
0.2
0.1
0.0
–0.1
Navafenterol (n=26)
UMEC/VI (n=26)
Placebo (n=26)
Reversible
p<0.0001
p=0.12
p<0.0001
Change from baseline in peak FEV1 at day 14 (L)
0.6
0.5
0.4
0.3
0.2
0.1
0.0
–0.1
Navafenterol (n=44)
UMEC/VI (n=42)
Placebo (n=41)
b)
Non-reversible
p=0.0002
p=0.65
p=0.001
Change from baseline in trough FEV1 at day 15 (L)
0.3
0.2
0.1
0.0
–0.1
Navafenterol (n=26)
UMEC/VI (n=26)
Placebo (n=26)
Reversible
p<0.0001
p=0.008
p<0.0001
Change from baseline in trough FEV1 at day 15 (L)
0.3
0.2
0.1
0.0
–0.1
Navafenterol (n=44)
UMEC/VI (n=42)
Placebo (n=41)

FIGURE S3 Subgroup analysis of low (<150 × 10^6/L) and high (≥150 × 10^6/L) eosinophil count. a) LS mean change from baseline in trough FEV_1 at day 15. b) LS mean change from baseline in peak FEV_1 at day 14. CI: confidence interval; eos: eosinophil count; FEV_1: forced expiratory volume in 1 s; LS: least-squares; UMEC/VI: umeclidinium/vilanterol.


a)
Low eos (<150 × 10^6/L)
p=0.0006
p=0.72
p=0.0002
LS mean change from baseline (95% CI) in trough FEV1 at day 15 (L)
0.3
0.2
0.1
0.0
–0.1
Navafenterol (n=17)
UMEC/VI (n=16)
Placebo (n=15)
High eos (≥150 × 10^6/L)
p<0.0001
p=0.067
p<0.0001
Navafenterol (n=53)
UMEC/VI (n=52)
Placebo (n=52)

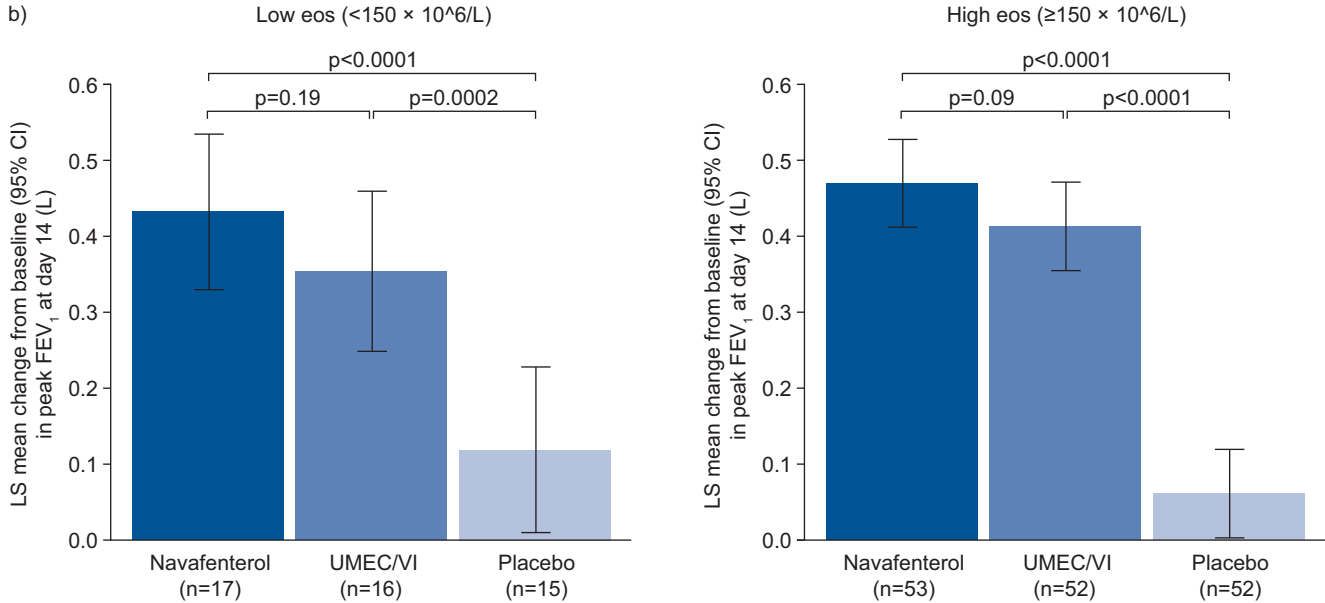

b)
Low eos (<150 × 10^6/L)
p<0.0001
p=0.19
p=0.0002
LS mean change from baseline (95% CI) in peak FEV1 at day 14 (L)
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Navafenterol (n=17)
UMEC/VI (n=16)
Placebo (n=15)
High eos (≥150 × 10^6/L)
p<0.0001
p=0.09
p<0.0001
Navafenterol (n=53)
UMEC/VI (n=52)
Placebo (n=52)

FIGURE S4 Subgroup analysis of patients receiving and not receiving ICS. a) LS mean change from baseline in trough FEV_1 at day 15. b) LS mean change from baseline in peak FEV_1 at day 14. CI: confidence interval; FEV_1: forced expiratory volume in 1 s; ICS: inhaled corticosteroid; LS: least-squares; UMEC/VI: umeclidinium/vilanterol.

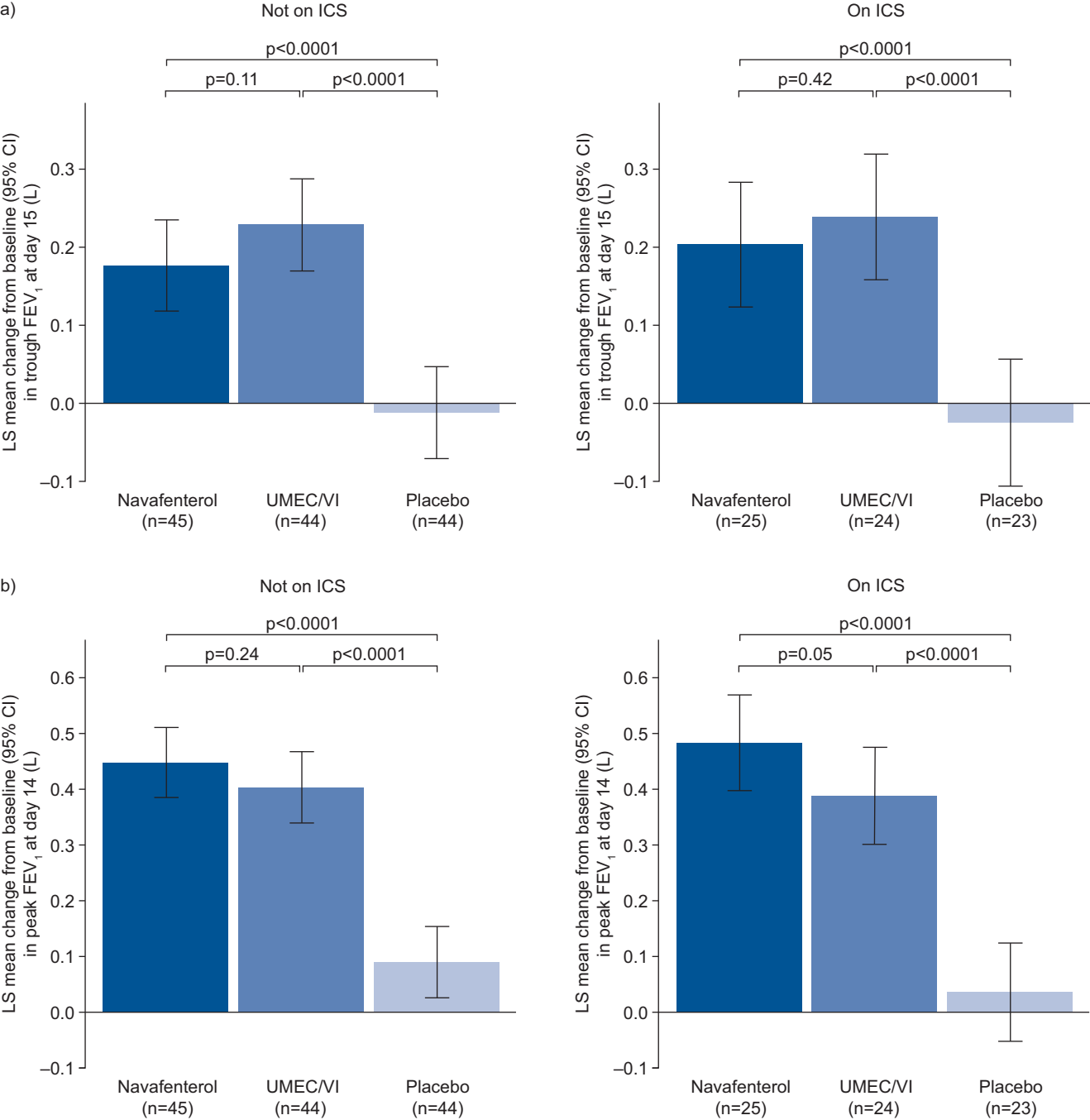

a)
Not on ICS
p<0.0001
p=0.11
p<0.0001
LS mean change from baseline (95% CI) in trough FEV1 at day 15 (L)
0.3
0.2
0.1
0.0
−0.1
Navafenterol (n=45)
UMEC/VI (n=44)
Placebo (n=44)
On ICS
p<0.0001
p=0.42
p<0.0001
LS mean change from baseline (95% CI) in trough FEV1 at day 15 (L)
0.3
0.2
0.1
0.0
−0.1
Navafenterol (n=25)
UMEC/VI (n=24)
Placebo (n=23)
b)
Not on ICS
p<0.0001
p=0.24
p<0.0001
LS mean change from baseline (95% CI) in peak FEV1 at day 14 (L)
0.6
0.5
0.4
0.3
0.2
0.1
0.0
−0.1
Navafenterol (n=45)
UMEC/VI (n=44)
Placebo (n=44)
On ICS
p<0.0001
p=0.05
p<0.0001
LS mean change from baseline (95% CI) in peak FEV1 at day 14 (L)
0.6
0.5
0.4
0.3
0.2
0.1
0.0
−0.1
Navafenterol (n=25)
UMEC/VI (n=24)
Placebo (n=23)

FIGURE S5 Subgroup analysis of current and former smokers. a) LS mean change from baseline in trough FEV_1 at day 15. b) LS mean change from baseline in peak FEV_1 at day 14. CI: confidence interval; FEV_1: forced expiratory volume in 1 s; LS: least-squares; UMEC/VI: umeclidinium/vilanterol.

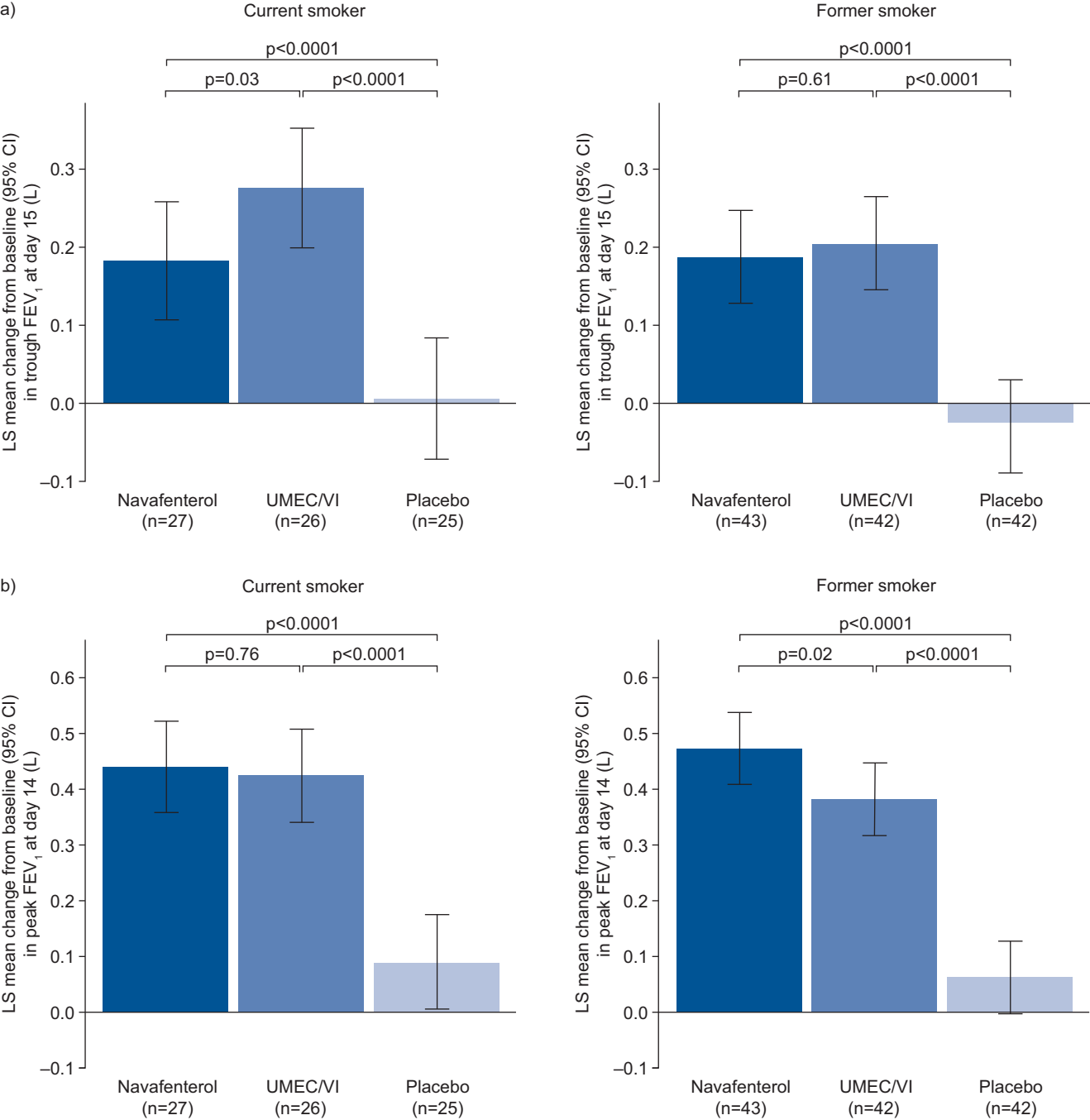

a)
Current smoker
p<0.0001
p=0.03
p<0.0001
LS mean change from baseline (95% CI) in trough FEV1 at day 15 (L)
0.3
0.2
0.1
0.0
−0.1
Navafenterol (n=27)
UMEC/VI (n=26)
Placebo (n=25)
Former smoker
p<0.0001
p=0.61
p<0.0001
LS mean change from baseline (95% CI) in trough FEV1 at day 15 (L)
0.3
0.2
0.1
0.0
−0.1
Navafenterol (n=43)
UMEC/VI (n=42)
Placebo (n=42)
b)
Current smoker
p<0.0001
p=0.76
p<0.0001
LS mean change from baseline (95% CI) in peak FEV1 at day 14 (L)
0.6
0.5
0.4
0.3
0.2
0.1
0.0
−0.1
Navafenterol (n=27)
UMEC/VI (n=26)
Placebo (n=25)
Former smoker
p<0.0001
p=0.02
p<0.0001
LS mean change from baseline (95% CI) in peak FEV1 at day 14 (L)
0.6
0.5
0.4
0.3
0.2
0.1
0.0
−0.1
Navafenterol (n=43)
UMEC/VI (n=42)
Placebo (n=42)

FIGURE S6 LS mean change from baseline in number of puffs of rescue medication per day from days 1–8 and 9–14. CI: confidence interval; LS: least-squares; UMEC/VI: umeclidinium/vilanterol.

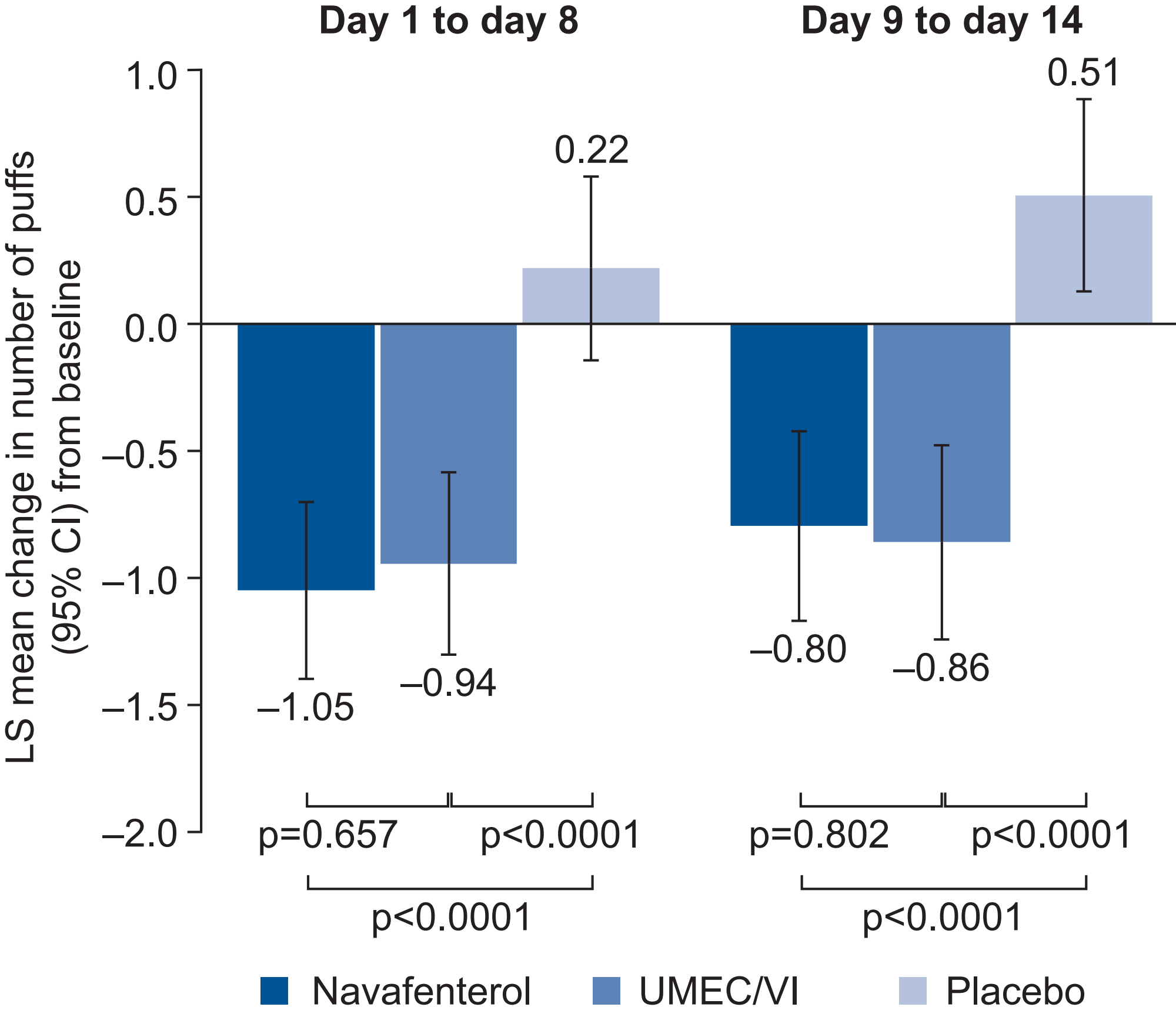
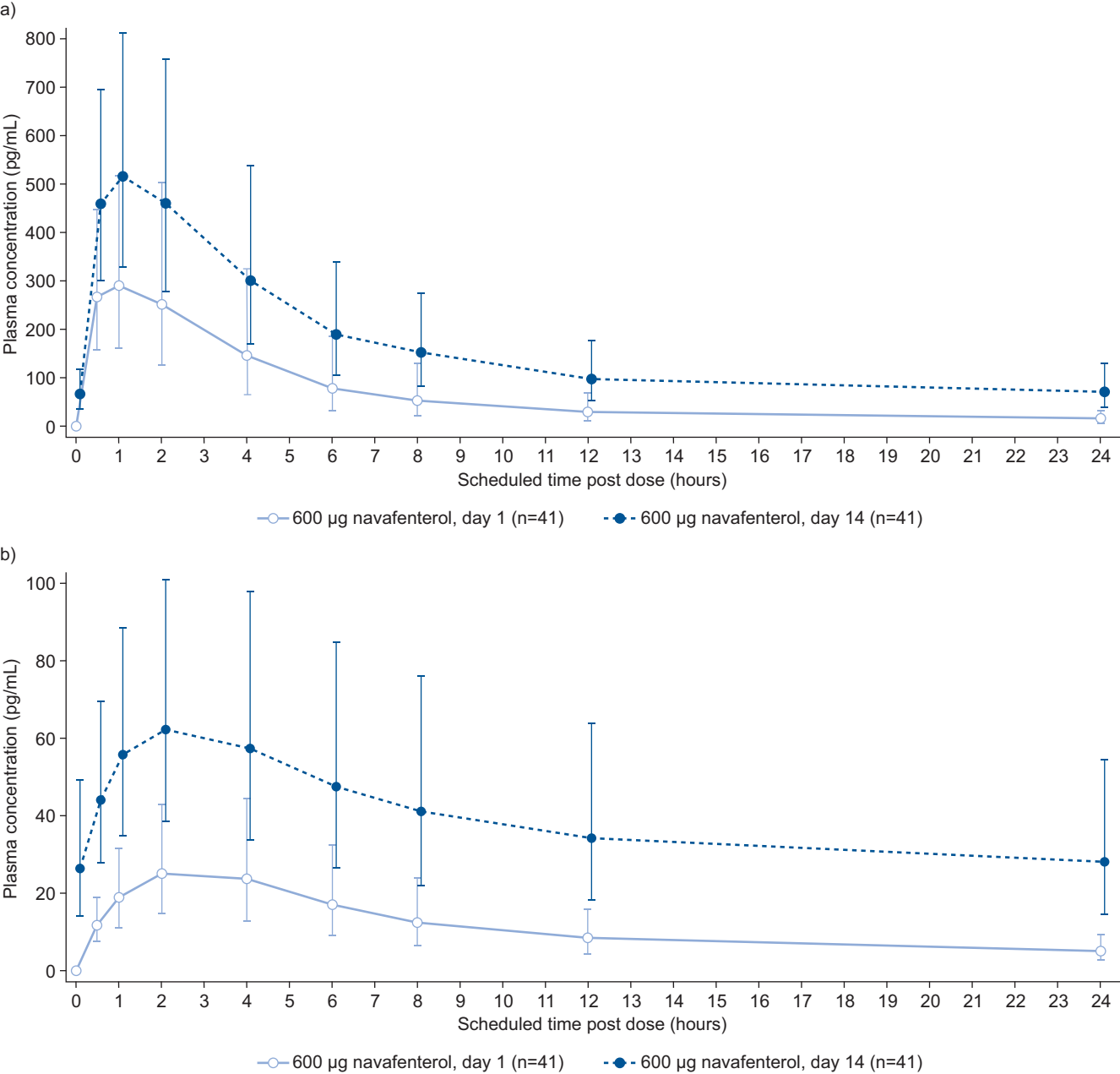

Day 1 to day 8
Day 9 to day 14
LS mean change in number of puffs (95% CI) from baseline
1.0
0.5
0.0
–0.5
–1.0
–1.5
–2.0
0.22
0.51
–1.05
–0.94
–0.80
–0.86
p=0.657
p<0.0001
p=0.802
p<0.0001
p<0.0001
p<0.0001
Navafenterol
UMEC/VI
Placebo

FIGURE S7 Geometric mean plasma concentration–time profiles for a) navafenterol and b) LAS191861. Error bars represent geometric standard deviation.


a)
Plasma concentration (pg/mL)
800
700
600
500
400
300
200
100
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Scheduled time post dose (hours)
600 µg navafenterol, day 1 (n=41)
600 µg navafenterol, day 14 (n=41)
b)
Plasma concentration (pg/mL)
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Scheduled time post dose (hours)
600 µg navafenterol, day 1 (n=41)
600 µg navafenterol, day 14 (n=41)