Supplementary Information

An Evaluation of the Pharmacokinetics, Safety, and Tolerability of Aclidinium/Formoterol Fixed-Dose Combination Administered in Chinese Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

Drugs in R&D

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TABLE S1 Permitted medications

Allowed medication	Restrictions	Stabilization period
ICS[a]	Patients who were following a stable regimen of a LABA/ICS combination for at least 4 weeks could be switched to the same ICS as monotherapy without requiring a stabilization period. If treatment was switched to a different ICS monotherapy, a stabilization period of ≥14 days, until the patient was considered stabilized, was required before screening	4 weeks
Continuous oral or parenteral corticosteroids[a]	Dose equivalent of ≤10 mg of prednisone per day or 20 mg every other day	4 weeks
Selective β-blocking agents	-	2 weeks
Oxygen therapy[a]	<15 hours a day	4 weeks
Oral sustained-release theophyllines[a]	Theophylline was to be avoided the morning of study visits and begin after visit completion.	4 weeks

[a]Change in daily dose, dosing schedule, formulation or treatment was unlikely during the course of the trial (the exception being the treatment of a COPD exacerbation)

COPD chronic obstructive pulmonary disease, ICS inhaled corticosteroid, LABA long-acting β_2-agonist

TABLE S2 Prohibited medications

Prohibited medication/	**Washout**
SABAs	6 h
SAMAs or a combination of SABAs+SAMA	12 h
Oral, intra-nasal or parenteral anticholinergic agents	14 days
Once- or twice-daily LAMAs; once- or twice-daily LABAs; oral LABAs	14 days
Combination of LABA+ICS or LABA+LAMA	14 days
Methylxanthines, leukotriene modifiers and PDE IV inhibitors	14 days
Continuous oral or parenteral corticosteroids equivalent to >10 mg of prednisone per day or >20 mg every other day	14 days
Non-selective β-blocking agents[a]	14 days
Herbal/traditional Chinese medicine	30 days

[a]Could be switched to selective β_1-blocking agents, as long as they were at stable dose for ≥2 weeks prior to Visit 1

LABA long-acting β_2-agonist, LAMA long-acting muscarinic antagonist, PDE IV phosphodiesterase type 4 inhibitor, SABA short-acting β_2-agonist, SAMA short-acting muscarinic antagonist

TABLE S3 PK parameters of inactive metabolites of aclidinium (PK analysis set)

	LAS34850		**LAS34823**	
Parameter	**Day 1 (n = 20)**	**Day 5 (n = 19)**	**Day 1 (n = 20)**	**Day 5 (n = 19)**
C_{max}, mean pg/mL (CV%)	3,149 (55.6)	3,691 (56.0)	38.82 (86.6)	81.02 (69.5)
T_{max}, median h (range)	3.00 (1.50–6.00)	3.00 (0.08–4.00)	1.75 (0.08–4.00)	0.50 (0.08–3.00)
AUC_{τ}, mean h·pg/mL (CV%)	20,330 (54.2)	27,300 (52.3)	252.9 (60.6)	540.9 (55.0)
AUC_{last} mean h·pg/mL (CV%)	20,280 (54.3)		201.1 (106.3)	
$t_{½}$, mean h (range)		20.95 (8.77–93.3)		17.34 (6.97–39.6)
MR C_{max}, mean (CV%)	68.72 (77.2)	60.65 (82.9)	0.85 (39.1)	1.33 (63.1)
MR AUC_{τ}, mean (CV%)	237.90 (71.9)	161.70 (45.0)	2.75 (36.7)	3.20 (35.7)
$R_{ac}(C_{max})$, mean (CV%)		1.19 (80.3)		2.07 (113.5)
$R_{ac}(AUC_{\tau})$, mean (CV%)		1.36 (76.5)		2.16 (82.0)

AUC_{last} area under the plasma concentration–time curve from time zero to the time of last quantifiable concentration, AUC_{τ} area under the concentration–time curve during a dosage interval (τ), C_{max} maximum concentration, CV% coefficient of variation, MR metabolite ratio, *PK* pharmacokinetics, Rac(AUC_{τ}) accumulation ratio calculated from AUC_{τ}, R_{ac}(C_{max}) accumulation ratio calculated from C_{max}, $t_{½}$ elimination half-life, T_{max} time to reach maximum concentration

TABLE S4 TEAEs (safety analysis set)

	n (%)	**Events**
Any TEAE	5 (25%)	9
Proteinuria[a]	3 (15%)	3
Blood pressure increased[b]	1 (5%)	1
Bronchitis[c]	1 (5%)	1
Dermatitis	1 (5%)	1
Hematuria[a]	1 (5%)	1
Headache[b]	1 (5%)	1
Rhinorrhea	1 (5%)	1

Total *N = 20*

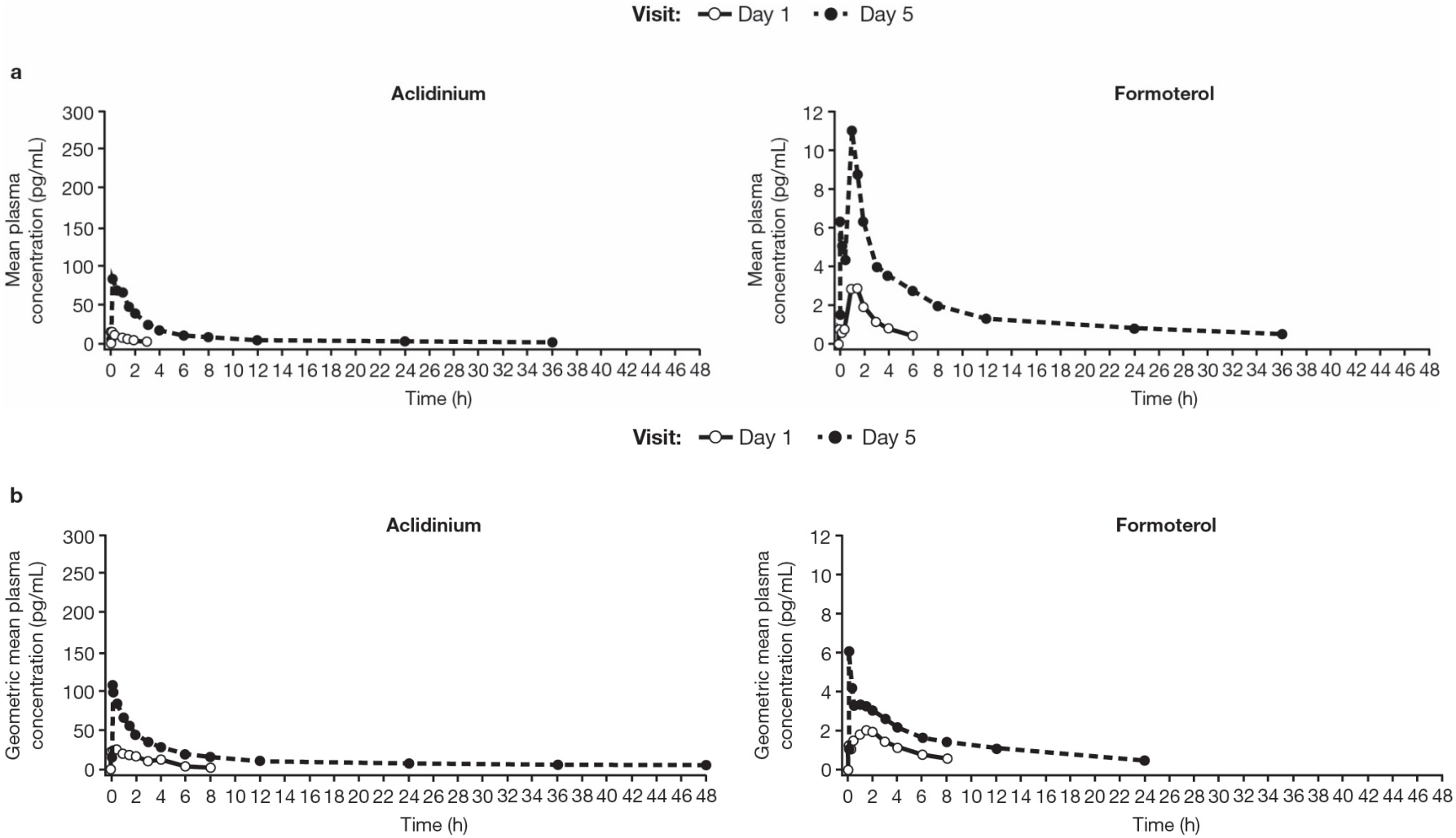
[a]All possibly treatment-related according to investigator's assessment; in two patients, this was already present at baseline

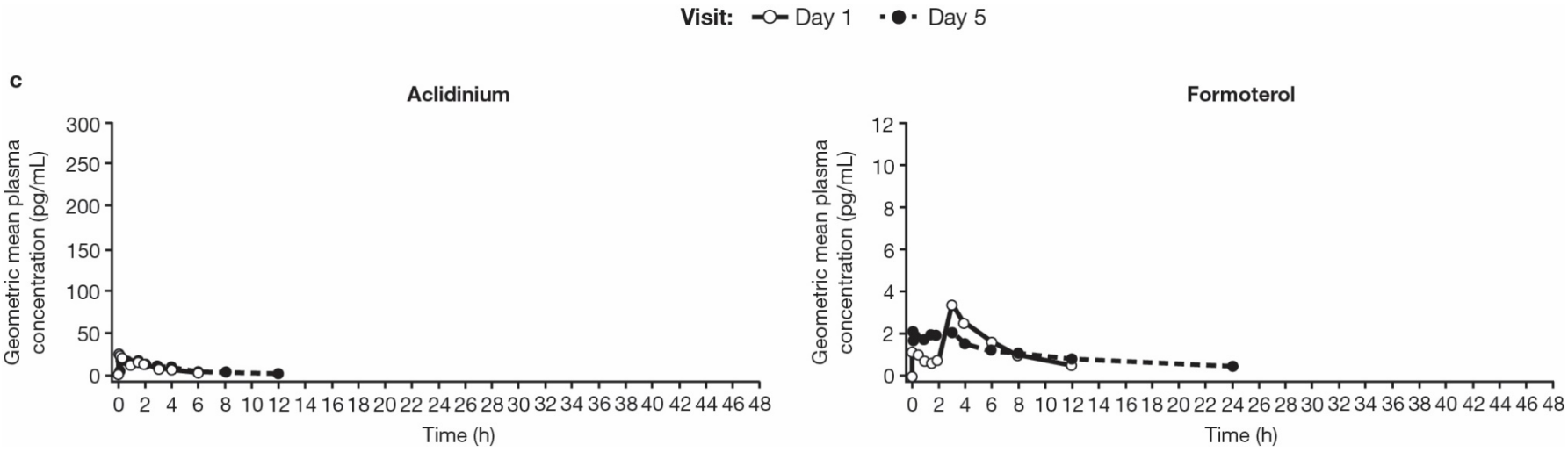
[b]β_2-adrenergic event

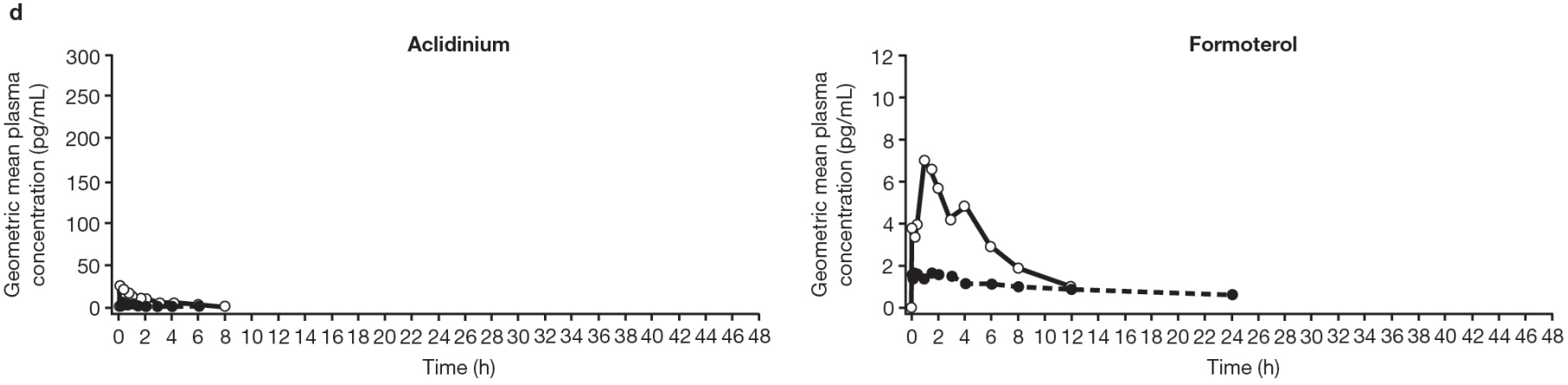
[c]SAE leading to discontinuation; possibly not treatment-related according to investigator's assessment

SAE serious adverse event, TEAE treatment-emergent adverse event

Fig. S1 Patients with poor inhalation technique: **a** Patient 1, **b** Patient 2, **c** Patient 3, **d** Patient 4, and **e** Patient 5




Visit: Day 1 Day 5
c
Aclidinium
Formoterol
Geometric mean plasma concentration (pg/mL)
Time (h)


Visit: Day 1 Day 5
d
Aclidinium
Formoterol
Geometric mean plasma concentration (pg/mL)
Time (h)

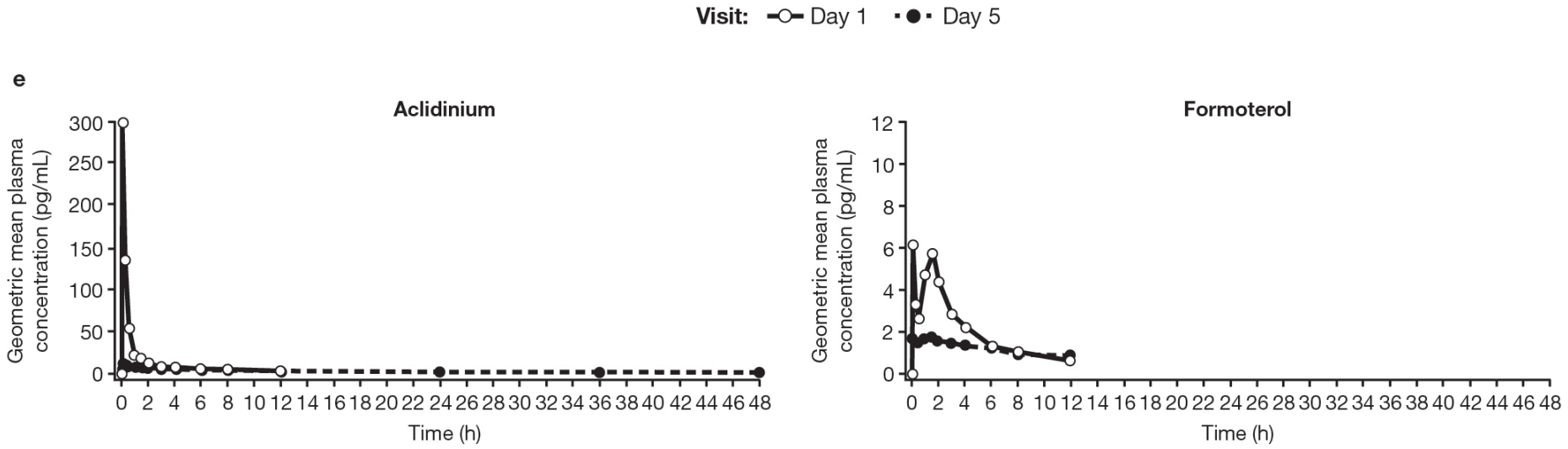
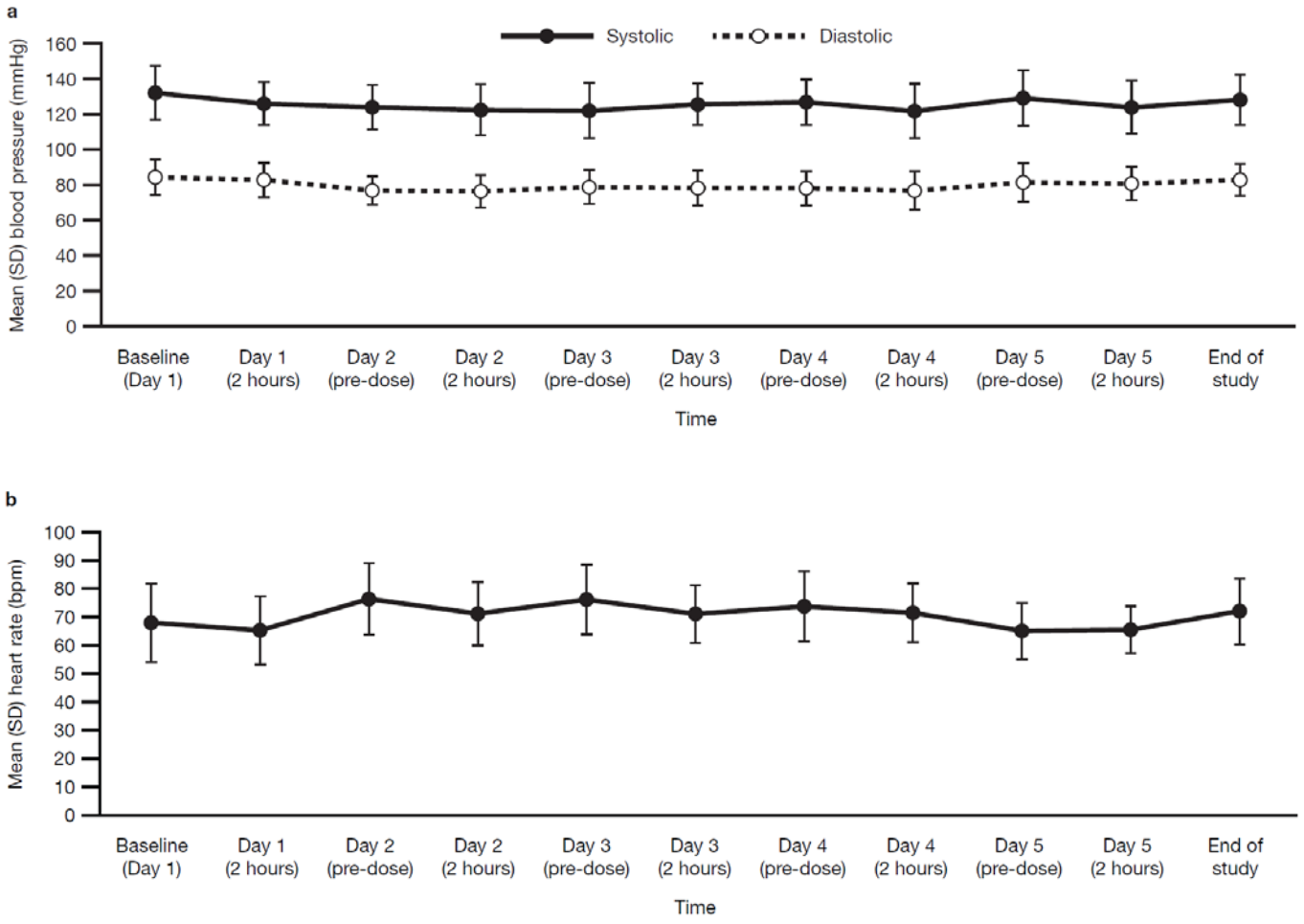

Visit: Day 1 Day 5
e
Aclidinium
Formoterol
Geometric mean plasma concentration (pg/mL)
Time (h)
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48
0 50 100 150 200 250 300
0 2 4 6 8 10 12

Fig. S2 Mean patient **a** blood pressure and **b** heart rate (safety population)



SD, standard deviation