The evidence base for ICS/formoterol maintenance and reliever therapy in severe asthma

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Reply to P.J. McDowell and co-workers:

We agree with P.J. McDowell and co-workers that the patients whose data are recorded in the UK Severe Asthma Registry (UKSAR) have, on average, more severe asthma than participants in randomised controlled trials (RCTs) of inhaled corticosteroid (ICS)/formoterol maintenance and reliever therapy (MART) [1, 2]. However, poor generalisability from RCTs to severe asthma registries is also the case for RCTs of high dose ICS/long-acting β-agonist (LABA) plus short-acting β-agonist (SABA) reliever therapy. There are similar differences in average baseline severity between patients in the UKSAR database and participants in RCTs of high dose *versus* medium dose ICS/LABA plus SABA therapy, as with those in the MART studies (table 1) [3–13]. Of particular note, the MART study populations had an overall higher baseline rate of severe exacerbations, a marker of both severity and future exacerbation risk. In our view, it is unreasonable to discount one group of RCTs (MART) while concluding there is robust evidence from other RCTs (high dose ICS/LABA), which suffer similar (or greater) limitations in generalisability.

Further, P.J. McDowell and co-workers state that there is no evidence that MART would have any beneficial impact on disease burden in UKSAR [2]. We consider that this statement is incorrect because it discounts high quality RCT evidence demonstrating the safety and efficacy of medium dose MART *versus* medium and high dose ICS/LABA plus SABA-based regimens. This evidence can be summarised as follows.

1) ICS/formoterol reliever is superior to SABA reliever in moderate and severe asthma. ICS/formoterol reliever is superior to SABA reliever across the spectrum of asthma severity [14]. In moderate and severe asthma, ICS/formoterol reliever reduces severe exacerbation risk by 32% (risk ratio (RR) 0.68, 95% CI 0.58 to 0.80) *versus* SABA reliever, when taken together with the same maintenance ICS/LABA dose [15].

2) ICS/formoterol MART is superior to higher maintenance dose ICS/LABA plus SABA. ICS/formoterol MART reduces severe exacerbation risk by 23% (RR 0.77, 95% CI 0.60 to 0.98) *versus* ICS/LABA maintenance plus SABA, when the ICS dose in the maintenance ICS/LABA plus SABA treatment is double that of the maintenance ICS dose in ICS/formoterol MART [15].

3) Timing of ICS/LABA dose is an important determinant of its efficacy. The greater reduction in severe exacerbation risk achieved with ICS/formoterol MART *versus* higher maintenance dose ICS/LABA plus SABA, despite lower total cumulative ICS doses, indicates that the timing of the ICS dose, when titrated through the vehicle of reliever therapy, is an important determinant of its efficacy, as well as total daily ICS dose. ICS/formoterol reliever therapy has greater potency than fixed-dose maintenance ICS/formoterol in reducing severe exacerbation risk [16], and increased use of as-needed ICS/formoterol reduces the risk of an exacerbation in the next 4 weeks, compared with increased SABA use with higher maintenance dose ICS/LABA [9].

4) Formoterol contributes to efficacy of as-needed ICS/formoterol. The formoterol component in ICS/formoterol reliever therapy contributes to exacerbation risk reduction due to its greater efficacy than as-needed SABA [17]. In patients receiving maintenance ICS/formoterol, the reduction in severe exacerbation risk with as-needed formoterol *versus* as-needed SABA is similar in magnitude to the reduction in severe exacerbation risk with as-needed ICS/formoterol *versus* as-needed formoterol [17].

Shareable abstract (@ERSpublications)
ICS/formoterol MART is an evidence-based alternative to high dose ICS/LABA in asthma patients at high risk of severe exacerbations; limited generalisability of RCTs to severe asthma registries applies similarly to high dose ICS/LABA therapy as to MART https://bit.ly/4aVFrNH

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TABLE 1 Characteristics of patients included in the UK Severe Asthma Registry (UKSAR) and randomised controlled trials (RCTs) of high dose inhaled corticosteroid (ICS)/long-acting β-agonist (LABA) and of medium dose ICS/formoterol maintenance and reliever therapy (MART)

Study	N	Age	FEV_1, %	ACQ	Participants with no severe exacerbation in past year, %	Severe exacerbations in past year	Blood eosinophils, $\times10^9$	F_{ENO}, ppb	Adherence assessment	mOCS, %	LABA, %	Baseline ICS treatment, $\mu g \cdot day^{-1}$	Comparator treatments	
McDowell [2] (UKSAR)	1111	52	70[§]	3.2[f]	6	5	0.40	43	MPR, F_{ENO} suppression, cortisol/ prednisolone levels	58	93	2000		
High *versus* medium dose ICS/LABA RCTs													**Medium dose ICS/LABA plus SABA**	**High dose ICS/LABA plus SABA**
Busse [3]	403	39	74	NR	69	NR	NR	NR	Inhaler dose counters	0	NR	NR	FF/VI 100/25	FF/VI 200/25
Bernstein [4]	692	46	62	NR	71	NR	NR	NR	eDiary	0	64	NR	FF/VI 100/25	FF/VI 200/25
Gessner [5][§§]	1426	53	63	2.6[##]	0	NR	NR	NR	NR	NR	100	NR	MF/IND/GLY 80/150/50	MF/IND/GLY 160/150/50
van Zyl-Smit [6][###]	2216	48	67	2.3[##]	69	NR	NR	NR	eDiary	0	72	NR	MF/IND 160/150 MF 400	MF/IND 320/150 MF 800 FP/Salm 1000/100
Kerstjens [7]	3092	52	55	2.5[##]	0	NR	NR	NR	eDiary	NR	100	NR	MF/IND/GLY 80/150/50 MF/IND 160/150	MF/IND/GLY 160/150/50 MF/IND 320/150 FP/Salm 1000/100
Lee [8]	2436	53	58	2.8[##]	37	NR	0.23[¶¶]	20[¶¶]	eDiary	NR	100	NR	FF/VI 100/25 FF/UMEC/VI 100/31.25/25 100/62.5/25	FF/VI 200/25 FF/UMEC/VI 200/31.25/25 200/62.5/25

Continued

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TABLE 1 Continued

Study	N	Age	FEV_1, %	ACQ	Participants with no severe exacerbation in past year, %	Severe exacerbations in past year	Blood eosinophils, $\times 10^9$	F_{ENO}, ppb	Adherence assessment	mOCS, %	LABA, %	Baseline ICS treatment, $\mu g \cdot day^{-1}$	Comparator treatments		
Medium dose ICS/formoterol MART *versus* comparator RCTs													**Medium dose ICS/LABA MART**	**Medium dose ICS/LABA plus SABA**	**High dose ICS/LABA plus SABA**
Bousquet [9]	2309	40	71	1.9[f]	0	1.9	NR	NR	Participant diary	NR	55	713[#]	BUD/Form 640/18 + 160/4.5 *p.r.n.*		FP/Salm 1000/100 + Terb *p.r.n.*
Vogelmeier [10][§§]	2143	45	73	1.9[f]	0	NR	NR	NR	Self-report at each clinic visit	NR	38	884[¶]	BUD/Form 640/18 + 160/4.5 *p.r.n.*	FP/Salm 500/100 + Salb *p.r.n.*	
Patel [11]	303	42	81[§]	1.9[##]	8	1.6	NR	NR	Electronic inhaler monitoring	NR	65	809[+]	BUD/Form 800/24 + 200/6 *p.r.n.*	BUD/Form 800/24 + Salb *p.r.n.*	
Takeyama [12]	63	40	69[§]	NR (ACT 15)	0	NR	NR	NR	Participant diary	NR	100	592	BUD/Form 640/18 + 160/4.5 *p.r.n.*	BUD/Form 640/18 + Salb *p.r.n.*	
Jackson [13][ƒƒ]	168	58	76	0.5[f]	NR	NR	0[++]	27	Electronic inhaler monitoring	0	100	NR	BUD/Form 800/24 + 200/6 *p.r.n.*		BUD/Form 1600/48 + Salb *p.r.n.*

FEV_1: forced expiratory volume in 1 s; ACQ: Asthma Control Questionnaire; F_{ENO}: fractional exhaled nitric oxide; mOCS: maintenance oral corticosteroids; MPR: medicines possession ratio; SABA: short-acting β-agonist; NR: none recorded; ACT: Asthma Control Test; FF: fluticasone furoate; VI: vilanterol; MF: mometasone furoate; IND: indacaterol; GLY: glycopyrronium; FP: fluticasone propionate; Salm: salmeterol; UMEC: umeclidinium; BUD: budesonide; Form: formoterol; Terb: terbutaline; Salb: salbutamol. McDowell *et al.* [2] present data as median; RCT data are presented as mean, which have been calculated from included study arms when summarised data are not available within study publication. ICS daily dose at baseline is expressed as equivalent to beclomethasone dipropionate (BDP). [#]: ICS dose assumed to be BDP equivalent; [¶]: ICS dose not adjusted for BDP equivalence; [+]: ICS dose budesonide or equivalent. Pre-bronchodilator FEV_1 is presented, unless denoted by §, which is on-treatment FEV_1 or unspecified. ACQ is either the 5-item version (denoted by ƒ) or the 7-item version (denoted by ##). [¶¶]: geometric mean; [++]: median; [§§]: titration of randomised treatment in response to asthma control during study; [ƒƒ]: down titration of treatment in MART randomised arm from medium dose MART, to low dose MART to BUD/Form reliever alone in accordance with maintenance of asthma control; [###]: different inhaler devices were used for the MF and the MF/IND medications.

5) ICS/formoterol MART has better efficacy/safety profile than ICS/LABA plus SABA. In high risk asthma, medium dose ICS/formoterol MART reduced severe exacerbation risk by 46% (relative rate 0.54, 95% CI 0.36 to 0.82) *versus* medium dose maintenance ICS/LABA plus SABA [11]. The MART regimen also led to significant reductions in days with no ICS therapy, days with β-agonist overuse episodes, and β-agonist overuse episodes associated with delay in seeking medical review, all risk factors for asthma mortality [11].

6) ICS/formoterol can be considered "optimal" inhaled treatment in moderate–severe asthma. Low and medium dose ICS/formoterol MART are ranked higher than low, medium and high dose ICS/LABA maintenance plus SABA, when RCTs of inhaled treatments in moderate and severe asthma are included in a systematic review and network meta-analysis [18].

7) Flat dose–response curve for efficacy with ICS beyond medium doses. In a Cochrane review, there was no significant difference in number of severe exacerbations requiring treatment with oral corticosteroids with fluticasone propionate (FP) 400 to 500 *versus* 800 to 1000 $\mu g \cdot day^{-1}$, (Peto OR 1.24, 95% CI 0.88 to 1.83) [19]. The potential benefit with increasing from medium to high dose ICS/LABA may be less than transferring across to medium dose ICS/formoterol MART [14, 15]. Further increasing the ICS dose from 1000/1500 to 2000 $\mu g \cdot day^{-1}$ FP may facilitate a small reduction in daily oral corticosteroid dose in oral corticosteroid-dependent asthma (2.0 $mg \cdot day^{-1}$ prednisolone, 95% CI 0.1 to 4.0) [19]; however, this is likely to be due to systemic absorption of ICS [20].

8) ICS/LABA dose–response relationship. Until recently, exploration of the dose–response relationship of ICS/LABA has not shown significant reductions in severe exacerbation risk with high *versus* medium dose ICS [3–6]. However, in 2021 the CAPTAIN study of triple therapy in moderate/severe asthma reported that the severe exacerbation rate was 32% lower (rate ratio 0.68, 95% CI 0.47 to 0.98) in the fluticasone furoate/vilanterol 200/25 µg *versus* 100/25 µg treatment groups, and in a *post hoc* analysis, that the effect was greater in the subgroup with high *versus* low T2 inflammatory status [8]. This latter finding suggests that high T2 status might identify a subgroup of moderate/severe asthma patients who obtain greater benefit from high dose ICS/LABA therapy. However, MART is also a therapeutic option for patients with high T2 status; although the benefit of ICS/formoterol MART for reducing severe exacerbations is seen across all blood eosinophil levels, it is greatest in those with high blood eosinophils [21].

9) Important adverse systemic effects with high dose ICS. Marked adrenal suppression, a significant reduction in bone density, and a greater risk of cataracts occurs with long term treatment with doses of ICS above 500 to 750 $\mu g \cdot day^{-1}$ of FP, within the range of high dose ICS therapy [22, 23]. The extent of the potential difference in ICS dose with ICS/formoterol reliever therapy regimens *versus* high dose ICS/LABA in severe asthma is shown in the recent study of patients receiving benralizumab [13]. Continued treatment with high dose ICS/LABA resulted in exposure to budesonide in excess of 800 $\mu g \cdot day^{-1}$ greater than that in patients transferred to medium dose ICS/formoterol MART, who then reduced to low dose MART and then ICS/formoterol reliever alone as asthma control allowed, without significant differences in exacerbation rate [13].

In conclusion, the available evidence suggests that medium dose ICS/formoterol MART has a superior efficacy/safety profile than high dose ICS/LABA plus SABA. We propose that "optimising" treatment for high risk patients with asthma on medium dose ICS/LABA plus SABA is more likely achieved by switching to medium dose ICS/formoterol MART, than by further increasing the maintenance ICS/LABA dose, in addition to systematically addressing treatable traits, considering other add on treatments such as long-acting muscarinic antagonists (LAMAs), and for those with persisting high T2 status, trialling additional ICS. This personalised medicine approach is consistent with the Global Initiative for Asthma (GINA) strategy for difficult-to-treat asthma, where MART is recommended as part of optimisation of therapy before considering high dose ICS/LABA [24].

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and Teva, and is Chair of the Asthma and Respiratory Foundation of New Zealand adolescent and adult asthma guidelines. J. Noble and M. Weatherall have no potential conflicts of interest to declare.

References

1 Beasley R, Noble J, Weatherall M. Clinical remission with biologic therapies in severe asthma: a matter of definition. *Eur Respir J* 2023; 62: 2301844.
2 McDowell PJ, McDowell R, Busby J, *et al.* Clinical remission in severe asthma with biologic therapy: an analysis from the UK Severe Asthma Registry. *Eur Respir J* 2023; 62: 2300819.
3 Busse WW, Bleeker ER, Bateman ED, *et al.* Fluticasone furoate demonstrates efficacy in patients with asthma symptomatic on medium doses of inhaled corticosteroid therapy: an 8-week, randomized, placebo-controlled trial. *Thorax* 2012; 67: 35–41.
4 Bernstein DI, Bateman ED, Woodcock A, *et al.* Fluticasone furoate (FF)/vilanterol (100/25 mcg or 200/25 mcg) or FF (100 mcg) in persistent asthma. *J Asthma* 2015; 52: 1073–1083.
5 Gessner C, Kornmann O, Maspero J, *et al.* Fixed-dose combination of indacaterol/ glycopyrronium/mometasone furoate once-daily *versus* salmeterol/fluticasone twice daily plus tiotropium once-daily in patients with uncontrolled asthma: a randomized, phase IIIb, non-inferiority study (ARGON). *Respir Med* 2020; 170: 106021.
6 van Zyl-Smit RN, Krüll M, Gessner C, *et al.* Once-daily mometasone plus indacaterol *versus* mometasone or twice-daily fluticasone plus salmeterol in patients with inadequately controlled asthma (PALLADIUM): a randomised, double-blind, triple-dummy, controlled phase 3 study. *Lancet Respir Med* 2020; 8: 987–999.
7 Kerstjens HAM, Maspero J, Chapman KR, *et al.* Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium *versus* mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study. *Lancet Respir Med* 2020; 10: 1000–1012.
8 Lee LA, Bailes Z, Barnes N, *et al.* Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) *versus* FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomised, phase 3A trial. *Lancet* 2021; 9: 69–84.
9 Bousquet J, Boulet LP, Peters MJ, *et al.* Budesonide/formoterol for maintenance and relief in uncontrolled asthma *vs*. high-dose salmeterol/fluticasone. *Respir Med* 2007; 101: 2437–2446.
10 Vogelmeier C, D'Urzo A, Pauwels R, *et al.* Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? *Eur Respir J* 2005; 26: 819–828.
11 Patel M, Pilcher J, Pritchard A, *et al.* Efficacy and safety of maintenance and reliever combination budesonide–formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. *Lancet Respir Med* 2013; 1: 32–42.
12 Takeyama K, Kondo M, Tagaya E, *et al.* Budesonide/formoterol maintenance and reliever therapy in moderate-to-severe asthma: effects on eosinophilic airway inflammation. *Allergy Asthma Proc* 2014; 35: 141–147.
13 Jackson DJ, Heaney LG, Humbert M, *et al.* Reduction of daily maintenance inhaled corticosteroids in patients with severe eosinophilic asthma treated with benralizumab (SHAMAL): a randomised, multicentre, open-label, phase 4 study. *Lancet* 2024; 403: 271–281.
14 Beasley R, Bruce P, Houghton C, *et al.* The ICS/formoterol reliever therapy regimen in asthma: a review. *J Allergy Clin Immunol Pract* 2023; 11: 762–772.
15 Sobieraj DM, Weeda ER, Nguyen E, *et al.* Association of inhaled corticosteroids and long-acting β-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: a systematic review and meta-analysis. *JAMA* 2018; 319: 1485–1496.
16 Beasley R, Harper J, Bird G, *et al.* Dose–response relationship of ICS/fast-onset LABA as reliever therapy in asthma. *BMC Pulm Med* 2019; 19: 264.
17 Rabe KF, Atienza T, Magyar P, *et al.* Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006; 368: 744–753.
18 Rogliani P, Ritondo BL, Ora J, *et al.* SMART and as-needed therapies in mild-to-severe asthma: a network meta-analysis. *Eur Respir J* 2020; 56: 2000625.
19 Adams NP, Bestall JC, Jones P, *et al.* Fluticasone at different doses for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2008; 4: CD003534.
20 Maijers I, Kearns N, Harper J, *et al.* Oral steroid-sparing effect of high-dose inhaled corticosteroids in asthma. *Eur Respir J* 2020; 55: 1901147.
21 Brusselle G, Nicolini G, Santoro L, *et al.* Beclometasone dipropionate/formoterol maintenance and reliever therapy asthma exacerbation benefit increases with blood eosinophil level. *Eur Respir J* 2021; 58: 2004098.
22 Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy. A systematic review and meta-analysis. *Arch Intern Med* 1999; 139: 941–955.
23 Beasley R, Harper J, Bird G, *et al.* Inhaled corticosteroid therapy in adult asthma: time for a new therapeutic dose terminology. *Am J Respir Crit Care Med* 2019; 199: 1471–1477.
24 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) Update 2023. www.ginasthma.org/