Achieving clinical remission in moderate-to-severe asthma using inhaled triple therapy

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In patients with asthma that was uncontrolled despite inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA), clinical remission was achieved in 22.7% by continuing ICS/LABA, increasing to 29.5% by adding a long-acting muscarinic antagonist. https://bit.ly/4cbp4Q0

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Abstract

Background There is growing interest in evaluating the ability of treatments to deliver clinical remission in patients with asthma. We conducted *post hoc* analyses of TRIMARAN and TRIGGER, two clinical studies comparing the efficacy and safety of fixed-dose combination beclometasone dipropionate (BDP), formoterol fumarate (FF) and glycopyrronium (G) (TRIMARAN, 100/6/10 µg and TRIGGER 200/6/10 µg) with BDP/FF (100/6 µg and 200/6 µg, respectively).

Methods Clinical remission was defined as: no use of oral corticosteroids over 52 weeks, no occurrence of severe exacerbations over 52 weeks, Asthma Control Questionnaire-5 score <1.5 at weeks 26, 40 and 52, and pre-dose forced expiratory volume in 1 s at week 52 equal to, or higher than, the baseline value.

Results Of 2291 patients included in these analyses, 598 (26.1%) met the clinical remission definition (*i.e.* met all criteria) at week 52: 315 (27.4%) in TRIMARAN and 283 (24.8%) in TRIGGER. The proportion of patients who achieved clinical remission was higher in the BDP/FF/G group than in the BDP/FF group in both studies (29.4% and 29.6% in TRIMARAN and TRIGGER, respectively, *versus* 25.4% and 20.0%), with the difference reaching statistical significance in TRIGGER (odds ratio 1.70, 95% confidence interval 1.29–2.23; p<0.001) and when data were pooled (29.5% *versus* 22.7%; 1.44, 1.19–1.73; p<0.001).

Conclusions Among patients with asthma that was uncontrolled by an inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) combination prior to study entry, a higher proportion achieved clinical remission by switching to inhaled triple therapy than by continuing ICS/LABA.

Introduction

The importance of achieving disease control is a key treatment goal in asthma, expressed in two domains – control of current symptoms, and of the future risk of adverse outcomes (no exacerbations, improved or stable lung function, and no medication side effects) [1, 2]. Recently, a more encompassing concept, the induction and maintenance of clinical remission, has been proposed as a new treatment target for asthma [3], with remission defined as sustained (*i.e.*⩾12 months) absence of asthma symptoms and asthma exacerbations, stable lung function and no need for systemic corticosteroids for the treatment of asthma [4, 5]. This concept has subsequently been adopted in a number of national asthma guidelines such as in Germany Italy Japan and Spain.

To date, no interventional clinical studies have prospectively tested this concept (with the exception of a phase IV study that evaluated the ability of patients receiving benralizumab to reduce their inhaled

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corticosteroid (ICS) dose, which included clinical remission at weeks 32 and 48 as a secondary end-point [6]). However, it is possible to apply a definition *post hoc* to clinical trial data or to "real-life", observational or retrospective studies. This has been done extensively for biologic therapies in patients with severe asthma [7–27]. Clinical remission is equally of interest when applied to inhaled therapies in patients with moderate or severe asthma, especially the triple therapy combination of an ICS, a long-acting β_2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA), which is a guideline-recognised option for patients with asthma that is not controlled by an ICS/LABA combination [1]. Indeed, one analysis of severe asthma registry data suggested clinical remission is possible with inhaled triple therapy [21]. A number of single-inhaler triple therapies have been developed for the maintenance therapy of asthma, one containing beclometasone dipropionate (BDP), formoterol fumarate (FF) and glycopyrronium (G) delivered *via* a pressurised metered-dose inhaler (pMDI), and another containing fluticasone furoate/umeclidinium/vilanterol (FluF/UMEC/VI) delivered via dry-powder inhaler. A *post hoc* analysis has been published of the CAPTAIN study that applied a number of different definitions of clinical remission: this was achieved at week 52 by between 30% and 47% of patients receiving FluF/UMEC/VI [28].

TRIMARAN and TRIGGER were two double-blind, phase III, 52-week studies comparing the efficacy and safety of medium-strength BDP/FF/G (100, 6 and 10 µg; TRIMARAN) and high-strength BDP/FF/G (200, 6 and 10 µg; TRIGGER) with that of the respective strengths of BDP/FF in adults with asthma that was poorly controlled on medium-dose (TRIMARAN) or high-dose (TRIGGER) ICS/LABA therapy, with TRIGGER including a third arm in which patients received open-label BDP/FF plus tiotropium [29]. Both studies recruited patients with Asthma Control Questionnaire-7 (ACQ-7) score $\geqslant$1.5, and a history of $\geqslant$1 severe exacerbation, which means they are ideally suited for *post hoc* analyses to evaluate the concept of clinical remission.

Materials and methods

Trial design and participants

The full design and inclusion/exclusion criteria of TRIMARAN and TRIGGER have been previously published (ClinicalTrials.gov: TRIMARAN, NCT02676076; TRIGGER, NCT02676089 [29]). Patients who met the inclusion and exclusion criteria at screening had their asthma maintenance therapy switched to BDP/FF (100 and 6 µg in TRIMARAN and 200 and 6 µg in TRIGGER), two inhalations twice daily *via* pMDI for a 2-week open-label run-in period. At the end of this run-in period, patients were randomised to either continue BDP/FF (100 and 6 µg in TRIMARAN or 200 and 6 µg in TRIGGER) or to receive BDP/FF/G (100, 6 and 10 µg in TRIMARAN or 200, 6 and 10 µg in TRIGGER), all two inhalations twice daily *via* pMDI. A third treatment group was included in TRIGGER: open-label BDP/FF (200 and 6 µg) plus tiotropium in separate inhalers; these patients are not included in the current analyses. Over the 52-week treatment period, patients attended visits at weeks 4, 12, 26, 40 and 52, at which data collected included spirometry evaluations and patient-related outcome measurements such as ACQ. The occurrence of asthma exacerbations was captured throughout the study. Both studies were approved by ethics committee at each site, and all patients provided written informed consent prior to any study-related procedure.

Outcomes and statistical methods

For these *post hoc* analyses, clinical remission was defined as [4, 5]:

- no use of oral corticosteroids over the 52-week period,
- no occurrence of severe exacerbations over the 52-week period (defined as asthma worsening requiring treatment with systemic corticosteroids for at least 3 days),
- ACQ-5 score <1.5 at weeks 26, 40 and 52 (indicating persistent, partly or well-controlled asthma [30], rather than a complete absence of symptoms), and
- pre-dose forced expiratory volume in 1 s (FEV_1) at week 52 equal to, or higher than, the baseline value.

The proportion of patients meeting this definition was calculated overall, and separately for BDP/FF/G and BDP/FF in the two studies and pooled. All patients in the intention-to-treat population were included in these analyses (*i.e.* all randomised patients who received at least one dose of study treatment and had at least one available post-baseline efficacy evaluation), with patients who had missing data for one or more component considered as not achieving clinical remission. For each of the two studies and for the pooled data, the odds ratio (OR) and 95% confidence interval (CI) for the comparison of the proportion of patients achieving clinical remission with BDP/FF/G *versus* BDP/FF was calculated using a logistic regression model including treatment, asthma exacerbations in the previous year (1 or >1) and geographical region as covariates. The baseline characteristics are presented descriptively, separated into those who met the definition of clinical remission, and those who did not. We also conducted an additional series of analyses to evaluate the association between clinical remission (using an alternative 26-week definition; see the results) and subsequent outcomes (over the remaining 26 weeks of the two studies).

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A supportive set of analyses were performed using an alternative definition of clinical remission, in which the lung function criterion was an increase from baseline in pre-dose FEV_1 ⩾100 mL at week 52 OR a 2 h post-dose FEV_1 to forced vital capacity (FVC) ratio >0.7 at week 52. These data are presented in the supplementary material. We then conducted an additional series of analyses to evaluate the association between a revised definition of clinical remission at week 26 and outcomes over the subsequent 26 weeks. The revised definition of clinical remission at week 26 was: no use of oral corticosteroids over the first 26-week period; no occurrence of severe exacerbations over the first 26-week period; ACQ-5 score <1.5 at week 26; and pre-dose FEV_1 at week 26 equal to, or higher than, the baseline value.

Results

Proportion of patients achieving clinical remission

Of the 2291 patients included in these analyses, 598 (26.1%) met the definition of clinical remission (*i.e.* met all the criteria) at week 52: 315 (27.4%) in TRIMARAN and 283 (24.8%) in TRIGGER. The proportion of patients who achieved clinical remission was higher in the BDP/FF/G group than in the BDP/FF group in both studies (29.4% and 29.6% in TRIMARAN and TRIGGER, respectively, *versus* 25.4% and 20.0%), with the difference reaching statistical significance in TRIGGER (*i.e.* with high-dose ICS) and when data were pooled across the two studies (29.5% *versus* 22.7%; figure 1). Results were similar when the "alternative" definition was applied (supplementary figure S1).

The proportion of patients achieving clinical remission according to each of the four criteria was also higher in the BDP/FF/G than the BDP/FF group in both studies and when data were pooled (figure 2). The main limiting factor to the achievement of clinical remission was ACQ-5 score <1.5, a criterion that was only achieved by 35.2–43.1% of patients across groups in the two studies. In contrast with the year before enrolment (when a history of ⩾1 exacerbation was an inclusion criterion), most patients did not use oral corticosteroids and did not have severe asthma exacerbations over the 52-week follow-up period after randomisation. When pulmonary function was considered, a slightly higher proportion of patients met the main definition of FEV_1 equal to, or higher than, the baseline value (56.4–70.6%) than the alternative definition, *i.e.* increase from baseline in pre-dose FEV_1 ⩾100 mL at week 52 or a 2-h post-dose FEV_1/FVC ratio >0.7 (54.1–67.4%; supplementary table S1). A smaller proportion of patients had a change from baseline in pre-dose FEV_1 ⩾100 mL at week 52 (42.0–56.9%), suggesting this might be a more discriminative criterion, although still achievable.

Patient characteristics

At baseline, patients who subsequently achieved clinical remission tended to be slightly younger and were more likely to be nonsmokers than those who did not achieve remission (table 1 and supplementary table

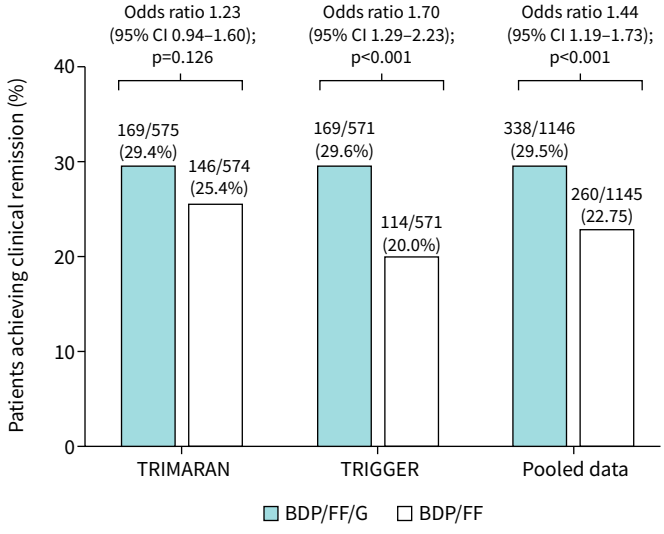


FIGURE 1 Proportion of patients achieving clinical remission at week 52. The four components of clinical remission are: 1) no use of oral corticosteroids over the 52-week period; 2) no occurrence of severe exacerbations over the 52-week period; 3) Asthma Control Questionnaire 5 score <1.5 at weeks 26, 40 and 52; and 4) pre-dose forced expiratory volume in 1 s at week 52 equal to, or higher than, the baseline value. BDP: beclometasone dipropionate; FF: formoterol fumarate; G: glycopyrronium; CI: confidence interval.

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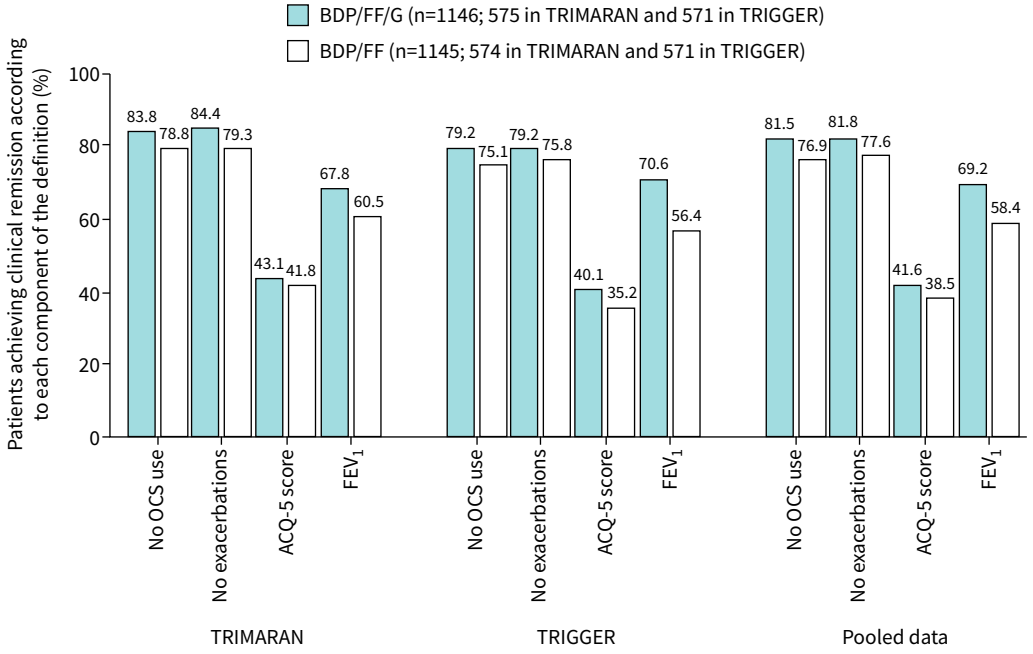


FIGURE 2 Proportion of patients achieving clinical remission at week 52 according to each component of the definition. The four components of clinical remission are: 1) no use of oral corticosteroids (OCSs) over the 52-week period; 2) no occurrence of severe exacerbations over the 52-week period; 3) Asthma Control Questionnaire (ACQ)-5 score <1.5 at weeks 26, 40 and 52; and 4) pre-dose forced expiratory volume in 1 s (FEV_1) at week 52 equal to, or higher than, the baseline value. BDP: beclometasone dipropionate; FF: formoterol fumarate; G: glycopyrronium.

S2). In terms of disease characteristics, patients who subsequently achieved clinical remission had a shorter duration of asthma, were less likely to have experienced multiple asthma exacerbations over the prior year, had a lower (*i.e.* less severe) ACQ-5 score and had a greater degree of FEV_1 reversibility than those who did not achieve remission. There was no clear relationship between body-mass index at baseline and the achievement of clinical remission at week 52.

Association between clinical remission and future outcomes

A total of 214 (37.2%) of patients receiving BDP/FF/G in TRIMARAN met the revised 26-week definition of clinical remission, compared with 181 (31.5%) receiving BDP/FF, with 215 (37.7%) and 170 (29.8%), respectively, meeting the definition in TRIGGER (table 2). Patients who achieved clinical remission at week 26 were less likely to use oral corticosteroids or to have a severe asthma exacerbation over the subsequent 26 weeks, and had a lower (*i.e.* better) ACQ-5 score at week 52 than those who did not achieve clinical remission at week 26. Lung function at week 52 was also slightly better in patients who achieved clinical remission at week 26 than those who did not achieve clinical remission. Of the 780 patients who achieved the week 26 clinical remission criteria, 507 (35.0%, or 22.1% of the overall population) subsequently met the week 52 clinical remission criteria (figure 3, with the data for individual groups in supplementary figures S2 and S3). The most common reason for failing to maintain clinical remission at week 52 was ACQ-5 score (supplementary table S3). Note that given the main clinical remission criteria required patients to meet the criteria throughout the 52 weeks of follow-up, in these analyses we considered it impossible for a patient who did not achieve clinical remission at week 26 to subsequently achieve clinical remission.

Discussion

Asthma is a heterogeneous disease, with no universally accepted definition of “clinical remission”. A number of retrospective or *post hoc* analyses have demonstrated that clinical remission can be achieved by patients with severe asthma, predominantly through the use of biologic therapies [7, 8, 19, 21–23]. The current analyses show that similar results can be achieved in patients with uncontrolled moderate-to-severe asthma by optimising use of inhaled medication, given 25.4% and 20.0% of patients with asthma that was previously uncontrolled by ICS/LABA achieved clinical remission when receiving BDP/FF in TRIMARAN and TRIGGER, respectively. Importantly, these patients were more likely to achieve clinical

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TABLE 1 Patient baseline characteristics grouped according to subsequent week 52 clinical remission status

	TRIMARAN				TRIGGER				Overall	
	BDP/FF/G 100/6/10 µg		BDP/FF 100/6 µg		BDP/FF/G 200/6/10 µg		BDP/FF 200/6 µg			
	NCR (n=406)	CR (n=169)	NCR (n=428)	CR (n=146)	NCR (n=402)	CR (n=169)	NCR (n=457)	CR (n=114)	NCR (n=1693)	CR (n=598)
Age, years	52.9±11.8	51.9±13.6	53.4±11.7	49.5±13.3	53.4±11.8	52.5±13.1	54.7±11.4	51.4±13.1	53.6±11.7	51.4±13.3
Sex, female	246 (60.6)	108 (63.9)	256 (59.8)	97 (66.4)	252 (62.7)	107 (63.3)	264 (57.8)	63 (55.3)	1018 (60.1)	375 (62.7)
BMI, kg·m^{-2}	28.0±4.9	27.8±4.7	27.9±5.0	28.0±5.4	28.7±5.3	27.6±4.6	28.9±5.8	27.8±6.0	28.4±5.3	27.8±5.1
Asthma duration, years	25.2±12.9	23.8±12.8	26.0±12.7	23.1±12.9	24.6±11.8	25.3±13.1	27.0±12.5	23.0±12.5	25.8±12.5	23.9±12.8
Asthma exacerbations in previous year										
1	322 (79.3)	151 (89.3)	349 (81.5)	124 (84.9)	301 (74.9)	138 (81.7)	358 (78.3)	93 (81.6)	1330 (78.6)	506 (84.6)
>1	84 (20.7)	18 (10.7)	79 (18.5)	22 (15.1)	101 (25.1)	31 (18.3)	99 (21.7)	21 (18.4)	363 (21.4)	92 (15.4)
ACQ-5 score	2.21±0.60	1.83±0.57	2.14±0.65	1.95±0.57	2.36±0.59	2.13±0.56	2.28±0.64	1.99±0.58	2.25±0.63	1.97±0.58
Pre-dose FEV_1, % predicted	59.5±12.1	61.7±11.2	59.3±12.2	60.6±11.2	56.8±13.0[#]	58.4±11.4	56.5±13.2[¶]	58.0±12.5	58.0±12.7[+]	59.8±11.6
FEV_1 reversibility, %	31.3±19.0	35.4±34.8	29.6±18.8	34.3±24.6	32.9±19.5	34.1±21.8	33.4±20.9	36.2±25.5	31.8±19.6	34.9±27.3

Data are presented as mean±SD or n (%). Data are missing for [#]one patient, [¶]three patients and [+]four patients. BDP: beclometasone dipropionate; FF: formoterol fumarate; G: glycopyrronium; NCR: did not meet the definition of clinical remission at week 52; CR: met the definition of clinical remission at week 52; ACQ: Asthma Control Questionnaire; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

remission from the addition of a LAMA (*i.e.* single-inhaler triple therapy) than by continuing ICS/LABA. Furthermore, although a similar proportion of patients achieved clinical remission in the two BDP/FF/G arms, the lower proportion of patients achieving clinical remission in the BDP/FF arm in TRIGGER than in TRIMARAN (and the resulting greater difference between the BDP/FF/G and BDP/FF arms in TRIGGER) suggest that the benefit of the addition of a LAMA is greatest in patients receiving high-dose ICS/LABA (*i.e.* who had more severe asthma). In these two studies, patients were repeatedly trained on correct inhaler technique, and their adherence to therapy was much more closely monitored than in clinical practice

TABLE 2 Outcomes at 12 months, with patients grouped according to clinical remission status after 26 weeks of treatment

	TRIMARAN				TRIGGER				Overall	
	BDP/FF/G 100/6/10 µg		BDP/FF 100/6 µg		BDP/FF/G 200/6/10 µg		BDP/FF 200/6 µg			
	Clinical remission status at week 26									
	NCR (n=361)	CR (n=214)	NCR (n=393)	CR (n=181)	NCR (n=356)	CR (n=215)	NCR (n=401)	CR (n=170)	NCR (n=1511)	CR (n=780)
Oral corticosteroid use between weeks 26 and 52										
No	324 (89.8)	204 (95.3)	342 (87.0)	170 (93.9)	313 (87.9)	204 (94.9)	338 (84.3)	162 (95.3)	1317 (87.2)	740 (94.9)
Yes	37 (10.2)	10 (4.7)	51 (13.0)	11 (6.1)	43 (12.1)	11 (5.1)	63 (15.7)	8 (4.7)	194 (12.8)	40 (5.1)
Asthma exacerbations between weeks 26 and 52										
0	324 (89.8)	205 (95.8)	343 (87.3)	170 (93.9)	313 (87.9)	205 (95.3)	338 (84.3)	162 (95.3)	1318 (87.2)	742 (95.1)
⩾1	37 (10.2)	9 (4.2)	50 (12.7)	11 (6.1)	43 (12.1)	10 (4.7)	63 (15.7)	8 (4.7)	193 (12.8)	38 (4.9)
ACQ-5 score at week 52	1.53±0.87 (n=336)	0.82±0.62 (n=209)	1.48±0.89 (n=361)	0.82±0.62 (n=179)	1.69±0.88 (n=328)	0.76±0.58 (n=207)	1.64±0.83 (n=371)	0.93±0.70 (n=167)	1.58±0.87 (n=1396)	0.83±0.63 (n=762)
Pre-dose FEV_1 at week 52, L	2.00±0.70 (n=336)	2.20±0.65 (n=209)	1.91±0.64 (n=360)	2.22±0.72 (n=179)	1.87±0.63 (n=328)	2.15±0.69 (n=207)	1.78±0.62 (n=369)	2.18±0.74 (n=167)	1.89±0.65 (n=1393)	2.19±0.70 (n=762)
Change from baseline	0.10±0.35 (n=336)	0.35±0.38 (n=209)	0.07±0.35 (n=360)	0.33±0.36 (n=179)	0.14±0.37 (n=327)	0.39±0.40 (n=207)	0.06±0.32 (n=367)	0.37±0.45 (n=167)	0.09±0.35 (n=1390)	0.36±0.40 (n=762)
2-h post-dose FEV_1 at week 52, L	2.23±0.74 (n=332)	2.38±0.69 (n=208)	2.10±0.68 (n=356)	2.40±0.74 (n=178)	2.09±0.66 (n=327)	2.34±0.70 (n=207)	1.99±0.67 (n=368)	2.37±0.76 (n=166)	2.10±0.69 (n=1383)	2.37±0.72 (n=759)
Change from baseline	0.33±0.37 (n=332)	0.55±0.42 (n=208)	0.27±0.37 (n=356)	0.52±0.38 (n=178)	0.35±0.38 (n=326)	0.58±0.40 (n=207)	0.26±0.34 (n=366)	0.56±0.48 (n=166)	0.30±0.37 (n=1380)	0.55±0.42 (n=759)

Data are presented as n (%) or mean±SD. BDP: beclometasone dipropionate; FF: formoterol fumarate; G: glycopyrronium; NCR: did not meet the definition of clinical remission at week 26; CR: met the definition of clinical remission at week 26; ACQ: Asthma Control Questionnaire; FEV_1: forced expiratory volume in 1 s.

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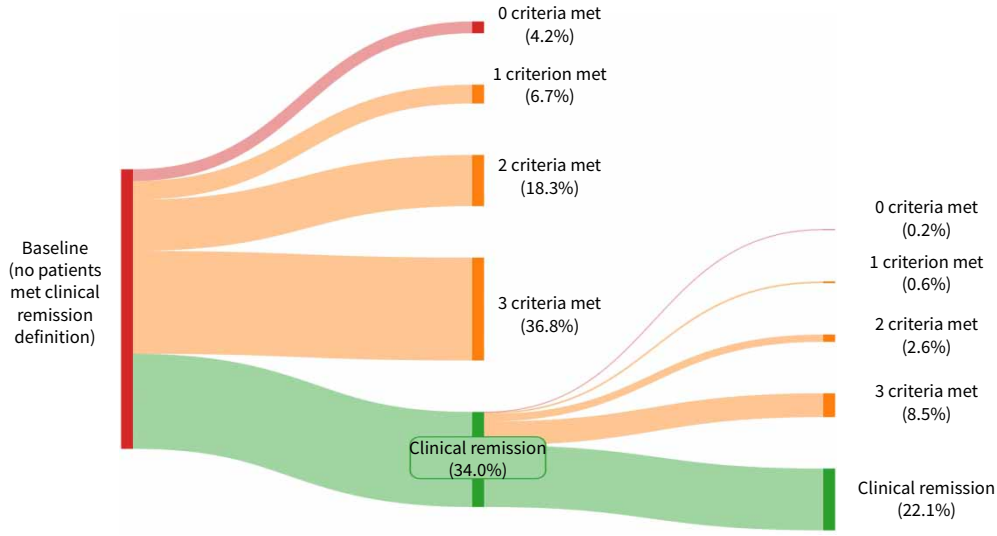


FIGURE 3 Progression of clinical remission at week 26 and week 52 (overall population). Data are the percentage of patients in the overall population (n=2291). Clinical remission at week 26 was defined as: 1) no use of oral corticosteroids (OCS) over the first 26-week period; 2) no occurrence of severe exacerbations over the first 26-week period; 3) Asthma Control Questionnaire (ACQ-5) score <1.5 at week 26, and 4) pre-dose forced expiratory volume in 1 s (FEV_1) at week 26 equal to, or higher than, the baseline value. Clinical remission at week 52 was then defined as: 1) no use of OCS over the 52-week period; 2) no occurrence of severe exacerbations over the 52-week period; 3) ACQ-5 score <1.5 at weeks 26, 40 and 52; and 4) pre-dose FEV_1 at week 52 equal to, or higher than, the baseline value. BDP: beclometasone dipropionate; FF: formoterol fumarate; G: glycopyrronium.

(although without objective measures, such as an electronic inhaler). In contrast, in a previous benralizumab study the focus was presumably on correct use of, and adherence to, the biologic rather than any background inhaled asthma therapy [7]. In that study, only 7.7% of patients receiving placebo (*i.e.* ICS/LABA alone) achieved remission, although those patients had more severe asthma than in either of the two studies included in the current analyses, with most having a history of ⩾2 exacerbations in the prior year [7].

Few patients in TRIMARAN or TRIGGER used oral corticosteroids or had a severe exacerbation over the 52-week follow-up period. The key end-points defining whether a patient achieved clinical remission were therefore asthma control (ACQ-5) and lung function, with the ACQ-5 end-point being especially challenging to achieve (this was also the main criterion that caused patients who achieved remission at week 26 to fail to maintain remission at week 52). One possible reason is that symptoms may be non-asthma related (such as cough resulting from respiratory infections or reflux disease, allergies, cardiovascular disease or anxiety and depression [31]), and may therefore not respond to asthma therapy. If a different population had been studied, such as those with a higher dependence on maintenance oral corticosteroids, it is possible that other components may have been more important in achieving remission. However, the results for all components of the clinical remission definition were consistent with the overall definition: a higher proportion of patients receiving BDP/FF/G met each of the individual components than those receiving BDP/FF in both studies.

When investigating differences in baseline characteristics between patients who subsequently achieved clinical remission at week 52 and those who did not, clinical remission tended to be associated with less severe asthma – in particular a shorter duration of asthma, fewer exacerbations in the previous year, a lower (*i.e.* better) ACQ-5 score, and a greater degree of reversibility. These data suggest that patients are more likely to achieve clinical remission earlier in the disease course, which supports escalating therapy earlier rather than later, with the reversibility data suggesting these patients may have less airway remodelling. Importantly, however, of the 455 patients included in these analyses who had experienced more than one exacerbation in the previous year, 92 (20.2%) still achieved clinical remission.

One challenge in comparing clinical remission data across studies is that the definitions applied across analyses vary (as do the inclusion/exclusion criteria of the studies). Indeed, a systematic review identified

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68 definitions of clinical remission for severe asthma, 48 of which were unique, with little consensus between studies [32]. A number of these definitions require patients to have an improvement from baseline in lung function. We believe that the main definition that we applied (and specifically the maintenance of baseline lung function at week 52) is more appropriate when considering the concept of clinical remission [33], especially since this is consistent with the approach of a number of national asthma treatment guidelines [4]. When a definition consistent with the one that we employed, requiring stable or improved lung function, was applied to observational ("real-world") studies of 146 patients, 27.4% achieved clinical remission after 12 months treatment with mepolizumab [19], and of 225 patients in the Severe Asthma Network in Italy, 45.8% of patients achieved clinical remission after 12 months of treatment with a biologic [21]. When various definitions were applied that did not specifically include lung function, 22.3% adults with severe asthma had clinical remission after a year of treatment with a biologic [22], and 37.6% of patients from the German Asthma Net Severe Asthma Registry using a biologic achieved clinical remission after 12 months, compared with 17.2% in patients not using a biologic [23]. In contrast, when a definition that included an increase from baseline in FEV_1 $\geqslant$100 mL was applied in a *post hoc* analysis of a clinical study in patients with severe, uncontrolled asthma, only 14.5% (85 of 586) achieved clinical remission after 12 months treatment with benralizumab compared with 7.7% (48 of 620) receiving placebo [7]. The *post hoc* analyses of CAPTAIN applied two main definitions of clinical remission – one that was described as "optimisation" of lung function, which required at least a 100-mL improvement from baseline in FEV_1 (achieved at week 52 by 30–38% of patients receiving FluF/UMEC/VI, *versus* 21–24% receiving FluF/VI), and one that involved stabilisation of lung function, so consistent with the definition that we applied (achieved at week 52 by 43–47% of patients receiving FluF/UMEC/VI *versus* 33–34% receiving FluF/VI) [28]. However, a key difference between the CAPTAIN definitions and those that we applied was the timepoints at which asthma control was analysed. In our analyses, we applied arguably a more stringent requirement – to achieve clinical remission at week 52, patients had to have an ACQ-5 score <1.5 at weeks 26, 40 and 52. In contrast, patients in the CAPTAIN analyses were considered to achieve clinical remission at week 52 if they had an ACQ-5 score <1.5 at week 52. Given the ACQ-5 score was the main limiting factor for the achievement of clinical remission in our analyses, this is likely to explain the lower proportion of patients achieving clinical remission with both BDP/FF/G and BDP/FF than in the triple therapy and ICS/LABA groups in CAPTAIN. Overall, however, despite the challenges of comparing data across studies, the broadly consistent results of the current analyses, the CAPTAIN data, and the biologic data suggest that it may be worth using triple therapy prior to considering a biologic in a patient with asthma that is uncontrolled by ICS/LABA.

Although analyses of clinical remission are scientifically interesting, their clinical relevance has still to be fully determined. We therefore decided to evaluate the clinical efficacy of BDP/FF/G and BDP/FF in patients subgrouped according to prior clinical remission status. Ideally, we would have preferred evaluating efficacy in year 2, with patients subgrouped according to clinical remission at the end of year 1. However, both studies were 52 weeks in duration and we therefore applied revised clinical remission criteria at the week 26 time point, with efficacy assessed over the subsequent 26 weeks. The majority of patients who achieved clinical remission at week 26 maintained clinical remission at week 52, with patterns consistent with those of the main analyses, in that higher proportions of patients in the two BDP/FF/G groups met the clinical remission definition than in the BDP/FF groups – and also higher proportions of patients met the clinical remission definitions in TRIMARAN than in TRIGGER. This suggests that although not ideal, applying a 26-week definition is appropriate for the purposes of these analyses. Furthermore, patients who achieved this "early" clinical remission at week 26 had better outcomes over the subsequent 26 weeks, with a lower proportion requiring oral corticosteroids or experiencing a severe exacerbation, accompanied by a lower (*i.e.* better) ACQ-5 score, and slightly better lung function. These results help to validate the use of clinical remission as a possible clinical trial end-point, and potentially as an asthma management target in clinical practice. Furthermore, although the week 52 timepoint definition is consistent with published definitions of clinical remission [3–5, 33], these week 26 analyses suggest that achievement of clinical remission at an earlier timepoint can predict good asthma outcomes.

The limitations of these analyses include the timeframe for assessment, given an evaluation of the implications of clinical remission would ideally include data from multiple years of follow-up. Such prolonged follow-up is not typically implemented in interventional clinical studies (especially involving inhaled triple therapies), although could potentially be analysed using a real-world database or disease registry. In addition, biomarkers such as eosinophil counts and fractional exhaled nitric oxide were not systematically collected in either study. Finally, these are *post hoc* analyses of carefully controlled randomised trials, which therefore need confirmation in appropriately designed prospective studies, potentially conducted in the "real-world" setting, and with durations of multiple years.

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Conclusions

These data demonstrate that clinical remission can be achieved in patients with asthma that is uncontrolled by ICS/LABA through the optimisation (*i.e.* adherence and improved inhaler technique) of the inhaled therapy, and that the proportion achieving clinical remission can be increased by the addition of a LAMA in the form of BDP/FF/G. This supports the recommendation to optimise inhaled asthma treatment prior to escalating to biologic therapies. Patients earlier in their disease course were more likely to achieve clinical remission, supporting the concept of earlier initiation of triple therapy. Furthermore, these data suggest that earlier clinical remission (in our case, at week 26) may predict subsequent asthma outcomes or treatment efficacy.

Prospective, long-term (multiple year) studies are needed to validate these results. If confirmed, this research has important clinical and pharmacoeconomic implications, as it suggests that one in three patients with asthma can achieve clinical remission without receiving treatment with costly biologics.

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Data availability: Chiesi commits to sharing with qualified scientific and medical researchers, conducting legitimate research, the anonymised patient-level and study-level data, the clinical protocol and the full clinical study report of Chiesi Farmaceutici-sponsored interventional clinical trials in patients for medicines and indications approved by the European Medicines Agency and/or the US Food and Drug Administration after 1 January 2015, following the approval of any received research proposal and the signature of a Data-Sharing Agreement. Chiesi provides access to clinical trial information consistently with the principle of safeguarding commercially confidential information and patient privacy. Other information on Chiesi's data-sharing commitment, access and research request's approval process is available here: https://www.chiesi.com/en/science-and-innovation/clinical-trial-transparency-and-data-sharing.

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