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Single-Inhaler Combination Therapy for Maintenance and Relief of Asthma

A New Strategy in Disease Management

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Abstract

When an adequate standard of asthma control is not achieved with maintenance treatment of inhaled corticosteroids, the addition of a long-acting β_2-adrenergic receptor agonist (LABA) bronchodilator is recommended. Using a combination product, salmeterol/fluticasone propionate (Seretide® or Advair®) or budesonide/formoterol (Symbicort®) is preferred for convenience and avoids any risk that LABA might be used as monotherapy. As formoterol has a rapid onset of bronchodilator effect, the budesonide/formoterol combination can be used for both the maintenance and reliever components of asthma treatment (Symbicort SMART®) and this is endorsed as an effective treatment by the Global Initiative for Asthma.

The efficacy of this approach has been evaluated in a series of well conducted, controlled studies. Current control of asthma symptoms is improved or achieved with reduced total dose administration with Symbicort SMART® compared with any reasonable alternate option. In every study, the risk of severe exacerbations was lower with Symbicort SMART® than comparator treatment. Patients who benefit to the greatest extent are those with evidence of more severe asthma and greater exacerbation risk. When initiated in suitable patients in conjunction with appropriate education, Symbicort SMART® is dominant in pharmacoeconomic terms. Symbicort SMART® delivers improved asthma outcomes with lower treatment and social costs than any alternative.

There have been many changes in the treatment of asthma since the 1960s. One constant has been the organization of asthma treatment into a group of maintenance agents, also referred to as preventer or controller agents, supplemented with one of the reliever or bronchodilator treatments that address short-term breakthrough symptoms.[1] This began with oral prednisone and epinephrine (adrenaline) or isoprenaline, moving though to beclomethasone with salbutamol.[2] Currently, combinations of a long-acting β_2-adrenergic receptor agonist (LABA) bronchodilator and an inhaled corticosteroid (ICS) are supplemented with a short-acting β_2-adrenergic receptor agonist (SABA) bronchodilator in patients with moderate and severe asthma.[3] The maintenance dose is adjusted by clinicians based on intuitive judgements or, in some cases, highly structured criteria as in the GOAL (Gaining Optimal Asthma ControL) study.[4] It is also clear that patients adjust maintenance treatment independent of their medical carers – reducing or omitting doses when well and being more adherent during times of increased symptoms.

Considering this history, the use of budesonide/formoterol (Symbicort®) as both maintenance

and reliever treatment for asthma (Symbicort SMART®) is not a revolution in asthma treatment but simply the latest in a long line of maintenance-reliever combinations. Correctly implemented, it can satisfy the desire of both patient and clinician to increase and decrease asthma treatment in line with the clinical course. A particular claim is that Symbicort SMART® should deliver treatment increases during the period before a severe exacerbation, as both symptoms and reliever use increase,[5] and that this may prevent the exacerbation or reduce its severity.

The conceptual basis of Symbicort SMART® is illustrated in figure 1.

1. What is Asthma Control in 2008?

The introduction of the use of Symbicort® as both maintenance and reliever treatment for asthma comes at a time when there is debate about exactly what control of asthma is and, more broadly, what we are trying to achieve in asthma. Not so long ago, the idea of total control of asthma was developed. This is a clinical state in which a patient has essentially no features of asthma other than the need for treatment and close monitoring.[4] This structured approach required maintenance dose increases for sometimes minimal residual symptoms, but still only achieved the specified level of control in a minority of patients despite prescription of the highest doses of ICS in the majority.[4]

A more pragmatic approach is to separate asthma control into two elements. The first is the achievement of good current control, i.e. few or no symptoms, minimal need for reliever use and maintenance of good lung function. The second element is future risk, i.e. avoidance of exacerbations that require emergency care, hospitalization or the need for oral corticosteroids together with, preservation of good lung function and reduction of treatment-related adverse effects. Considering both elements in the assessment of asthma control is critical and they are not always coincident. For example, when asthma is poorly controlled on a SABA alone, the addition of a LABA will improve symptoms and lung function, but unless ICS are used as well, there will be a persistent, perhaps increased, risk of severe exacerbations and death from asthma.[8,9]

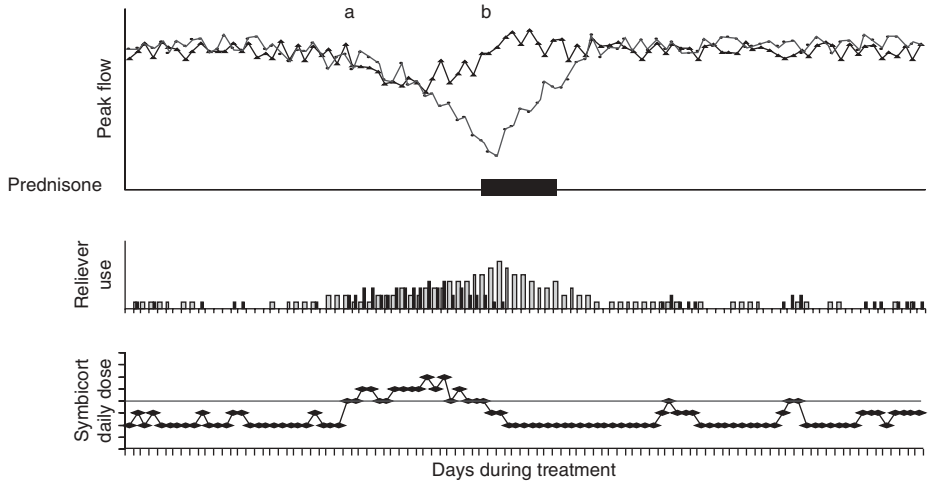

Fig. 1. The conceptual basis of Symbicort SMART®, showing the course of a potential severe exacerbation with standard fixed-dose treatment (thinner line) or Symbicort SMART® using the reduced-dose comparison made in the COMPASS study.[6] From timepoint **a**, there is an increase in reliever use associated with decline in lung function. In the standard treatment group, at point **b** a course of oral corticosteroids is required. With Symbicort SMART®, reliever use increases the daily Symbicort® dose above baseline and, perhaps importantly, spreads extra doses through the day. As symptoms settle, treatment reverts to baseline levels. The concept of benefit derived from the use of extra reliever doses during the so-called 'window of opportunity' between points **a** and **b** is proven from the analysis of high reliever use events in the AHEAD study.[7]

2. Where Symbicort SMART® may Fit into Current Asthma Treatment

The initial treatment for asthma should be ICS alone supplemented by a SABA as needed.[3] Even in the GOAL study, the majority of patients who achieved total control would have done so with ICS monotherapy.[4] Two treatment choices are available when treatment with low-dose ICS alone has not achieved agreed clinical goals: (i) increment the ICS dose; or (ii) add a LABA. Within the series of Symbicort SMART® clinical studies (see table I), there are comparisons with each of these choices in a population enriched for the risk of a severe asthma exacerbation. Most of the data are from large, randomized double-blind, double-dummy studies with this information supplemented by several open-label studies.

There is a previously published excellent review based on the key preplanned outcomes of these studies.[10] Simplicity in any novel asthma treatment approach is intrinsically valuable; however, to have real merit, Symbicort SMART® needed to address well the basic elements of asthma control, i.e. achievement of good current control and reduction in future risk without a large increase in total asthma treatment. Symbicort SMART® should also be cost effective compared with other treatment approaches and be deliverable with suitable educational material. This analysis of the Symbicort SMART® studies focuses on outcomes based on emerging concepts of asthma control, optimization of current control and reduction in future risk. This is supplemented by a sequence of interpretive analyses that have been conducted within and subsequent to key publications.

3. Comparisons between Symbicort SMART® and a Higher Dose Inhaled Corticosteroid (ICS) as Maintenance with Short-Acting β-Adrenergic Receptor Agonist (SABA)

Three studies have compared Symbicort SMART® and higher dose ICS as maintenance with a SABA. In each study, the population evaluated had evidence of active asthma symptoms despite regular continued ICS use for at least 3 months prior to inclusion. The study of Rabe et al.,[11] the STEAM study, evaluated a group with somewhat milder asthma. Current reversibility in forced expiratory volume in 1 second (FEV_1) was not required if there was significant diurnal variability in peak expiratory flow rate (PEFR). The STEP study of Scicchitano et al.[12] included the most severe patient group as it required the highest dose of ICS at entry and had the additional requirement of a clinically important asthma exacerbation within 12 months of recruitment. The STAY study[13] was somewhat between the two. Table I highlights key subject characteristics, pooled for the participants in each study.

In relation to current asthma symptoms, in each study there was a greater increase in clinic FEV_1 and morning PEFR and reliever use fell to a greater extent with Symbicort SMART®. Future risk, as assessed by the number of exacerbations requiring intervention or the number of days when oral corticosteroids were prescribed was consistently reduced with Symbicort SMART®. The number needed to treat (NNT) with Symbicort SMART® rather than higher dose ICS maintenance for 1 year to avoid one severe exacerbation requiring intervention was 3.7 in STEAM,[11] 3.1 in STAY[13] and 5.0 in the STEP study.[12] In each study, there was a substantial reduction in inhaled and oral corticosteroid use with Symbicort SMART®. For all the advantages seen, these results need to be interpreted cautiously as only the Symbicort SMART® recipients had the known benefits of a LABA added to ICS.

4. Comparisons between Symbicort SMART® and the Same Maintenance Dose Long-Acting β-Adrenergic Receptor Agonist/ICS with a SABA

The logical comparison arising from the previous observations was to compare Symbicort SMART® with the same maintenance dose LABA/ICS plus a SABA, and this was addressed in two studies: a further comparison within the STAY study[13] and the SMILE study.[14] The essential question posed was whether Symbicort® is a more effective reliever than terbutaline in

Table I. Comparison of clinical features of the patients recruited into the pivotal Symbicort SMART® studies

Feature	Comparator maintenance treatment							
	higher-dose ICS monotherapy			fixed-dose budesonide/formoterol			fixed-dose salmeterol/fluticasone propionate	
	STEAM[11]	STAY[13]a	STEP[12]	STAY[13]a	SMILE[14]	COMPASS[6]	COMPASS[6]	AHEAD[7]
Patient demographics								
Total subjects	697	1851	1890	1834	3394	2212	2230	2309
Mean age (y)	38	36	43	36	42	38	38	39
Male subjects (%)	39	45	42	45	40	42	42	40
Prestudy clinical parameters								
FEV_1 (% predicted)	75	73	70	73	72	73	73	71
Reversibility (% baseline)	17	21	24	21	24	24	23	24
Reliever use (doses/day)	1.7	1.7	2.0	1.7	1.9	2.3	2.3	2.3
Prestudy treatment								
Mean ICS dose (μg delivered)	348	610	746	610	755	742	742	712
LABA use at entry (%)	11	28	35	28	59	25	23	24

a Required doses for children in the STAY study were 200–500 μg/day. The STEP, COMPASS, SMILE and AHEAD studies had the additional requirement of a severe asthma exacerbation in the 12 months before recruitment.

FEV_1 = forced expiratory volume in 1 second; **ICS** = inhaled corticosteroid; **LABA** = long-acting β-adrenergic receptor agonist.

patients using LABA/ICS for maintenance. The SMILE study included a group that used formoterol rather than terbutaline as a reliever allowing a determination of whether the benefits of Symbicort SMART® are related to budesonide, formoterol or both components. Patient characteristics are shown in table I.

In these studies, although all patients received a LABA, current asthma symptoms were improved as reflected in clinic FEV_1, morning PEFR and reliever use (table II). Future risk, as assessed by the number of exacerbations requiring medical intervention or the number of days when oral corticosteroids were prescribed was reduced with Symbicort SMART® in both studies. The NNT with Symbicort SMART® rather than fixed-dose Symbicort® for 1 year to avoid a severe exacerbation requiring medical intervention was 3.1 in STAY[13] and 5.5 in SMILE with terbutaline as reliever.[14] Key outcomes for the group receiving formoterol as a reliever were superior to those for terbutaline but inferior to Symbicort® reliever, both in relation to current symptoms and future risk.

Both study designs dictated that the patients allocated to Symbicort SMART® could only have used the same or more Symbicort®, never less, than the controls. Some clinical benefit should surely have been expected. However, the average reliever use at one dose per day yielded only a 50% average increase in Symbicort® dose. This was arguably modest for the benefits seen. Without question, both the formoterol and budesonide components of Symbicort® are required for the benefits seen.

5. Comparison between Symbicort SMART® and Treatment with Regular Symbicort® at Twice the Maintenance Dose

Arguably, the pivotal proof of concept study is a comparison between Symbicort SMART® and regular Symbicort® at twice the maintenance dose, and scientifically the most interesting. In the COMPASS study,[6] patients allocated to Symbicort SMART® used half the maintenance dose of the comparison group. This study had the potential to address the question of whether the benefits of Symbicort SMART® related only to higher Symbicort® dose administration during worsened symptoms or, alternatively, prescribed undertreatment in the comparator subjects. Here,

Table II. Comparison of treatments and outcomes in the major randomized and blinded studies that evaluated the efficacy of Symbicort SMART®[a]

Study name	Symbicort SMART®		Comparator		Daily ICS dose (budesonide μ/day)		Current control			Future risk (Symbicort SMART® vs comparator)	
	maintenance Symbicort® (μg)	reliever Symbicort® (μg)	maintenance Symbicort® (μg)	reliever (μg)	Symbicort SMART®	comparator	FEV_1 difference vs comparator (L)	daily reliever use: Symbicort SMART®	daily reliever use: comparator	severe exacerbations (%)	oral corticosteroid days (%)
Comparisons of Symbicort SMART® with regular treatment containing higher dose ICS											
STEAM[11]	160/9 od	80/4.5	Budesonide 320 od	Terbutaline 400	243	320	+0.15 ($p<0.001$)	1.04[b]	1.48	−76[b]	−77[b]
STEP[12]	320/9 od	160/4.5	Budesonide 320 bid	Terbutaline 400	466	640	+0.10 ($p<0.001$)	0.9[b]	1.42	−45[b]	−44[b]
STAY[13]	80/4.5 bid[c]	80/4.5	Budesonide 320 bid	Terbutaline 400	241	640	+0.10 ($p<0.001$)	1.01[b]	1.47	−50[b]	−51[b]
Comparisons of Symbicort SMART® with regular maintenance Symbicort® and other relievers											
STAY[13]	80/4.5 bid[c]	80/4.5	80/4.5 bid	Terbutaline 400	241	160	+0.08 ($p<0.001$)	1.01[b]	1.21	−55[b]	−57[b]
SMILE[14]	160/4.5 bid	160/4.5	160/4.5 bid	Terbutaline 400	473	320	+0.08 ($p<0.001$)	0.96[b]	1.26	−49[b]	−55[b]
SMILE[14]	160/4.5 bid	160/4.5	160/4.5 bid	Formoterol 4.5	473	320	+0.05 ($p<0.001$)	0.96[a]	1.23	−34[b]	−39[b]
Comparisons of Symbicort SMART® with regular Symbicort® at twice the maintenance dose											
COMPASS[6]	160/4.5 bid	160/4.5	320/9 bid	Terbutaline 400	483	640	+0.01 (NS)	1.02	1.05	−28[b]	−39[b]
Comparisons of Symbicort SMART® with regular Seretide® at higher than equivalent maintenance dose											
COMPASS[6]	160/4.5 bid	160/4.5	Seretide® 250/50 bid	Terbutaline 400	483	640	+0.01 (NS)	1.02	0.96	−39[b]	−41[b]
AHEAD[7]	320/9 bid	160/4.5	Seretide® 500/50 bid	Terbutaline 400	792	1280	+0.01 (NS)	0.95	1.01	−21[b]	−23[b]

a In the STEAM, STEP and STAY studies, where severe exacerbations could be defined by peak flow fall alone, the difference in severe exacerbations shown relates only to events requiring medical intervention. Reductions in severe exacerbations and oral corticosteroid days were significant in all studies.

b Significant reduction vs fixed-maintenance comparator treatment.

c Children aged 4–11 years in the STAY study used maintenance dose od.

bid = twice daily; **FEV_1** = forced expiratory volume in 1 second; **ICS** = inhaled corticosteroid; **NS** = not significant; **od** = once daily.

the Symbicort SMART® regimen was the same as in the SMILE study, but the regular maintenance treatment in the comparator arm was doubled.[6] Subjects' baseline features are shown in table I.

In the whole study, average reliever use was one dose per day so that the total Symbicort® dose in the Symbicort SMART® patients was 25% lower than the control subjects. Further analysis of reliever use and its effect on total Symbicort® doses used showed that 65% of Symbicort SMART® subjects averaged more than 25% dose reduction (one dose), whereas 7% of subjects had a greater than 25% dose increase above what they would have received as control subjects.[6]

Outcomes for a range of parameters, reflecting current asthma symptoms, including clinic FEV_1, morning PEFR, diary-recorded day and night symptoms and reliever use were similar in both patient groups (table II). Future risk, even in the face of the lower Symbicort® doses, was reduced with Symbicort SMART®. The number of exacerbations requiring medical intervention was 28% lower and there was a 39% reduction in days where oral corticosteroids were used versus comparator. The NNT, with Symbicort SMART® rather than higher dose combination treatment for 1 year to prevent one severe exacerbation, was 11.[6]

6. Comparisons between Symbicort SMART® and Fixed Maintenance Treatment with Salmeterol/Fluticasone Propionate, at a Higher Equivalent Dose, and a SABA

The comparison of the Symbicort® arms in the COMPASS study is the purest test of the scientific merit of Symbicort SMART®. However, salmeterol/fluticasone propionate (Seretide® or Advair®) is a widely used and effective combination ICS/LABA treatment for asthma. Comparisons were made in two separate studies. The first was a part of the COMPASS study,[6] indeed the prespecified primary comparison. The second study by Bousquet et al.,[7] the AHEAD study, featured a comparison at higher maintenance doses. Symbicort® maintenance was 320/9 μg twice daily compared with Seretide® 500/50 μg twice daily. Based on generally accepted dose equivalence, Symbicort SMART® patients had 50% reduction in the maintenance component of treatment as in COMPASS. Although, it was planned that the AHEAD study would recruit patients with more severe asthma, in the end, clinical characteristics were similar (table I).

7. Once Daily versus Twice Daily Maintenance in Symbicort SMART®

In addition to the major randomized, double-blind, double-dummy studies, three significant, randomized but unblinded, studies have been reported that each yielded favourable outcomes compared with fixed-dose LABA/ICS.[15-17] Of these, that reported by Lundborg et al.[17] is perhaps the most interesting; in part because it is the only study that compares once versus twice daily maintenance treatment as part of Symbicort SMART® but also because of the outcomes. It also tests a population in which nearly 70% were well controlled at entry and mean FEV_1 was within the normal range at 95% predicted.

The key findings are highlighted in table III. As reflected in higher reliever use and fewer asthma control days, there is deterioration in current control when once daily maintenance is used. However, there is no increase in exacerbations that were numerically lowest in the once daily group. Self-rated asthma status was similar with all treatments. This study highlights that the achievement of good current symptom control and reduction in future risk are not always coincident. Below a threshold for maintenance treatment, current symptoms increase but the benefit of Symbicort SMART® in reducing exacerbation risk is not lost.

8. Patterns of Reliever Use in Patients Using Symbicort SMART® or Comparator, and Outcomes Following Episodes of High Reliever Use

In all arms of the studies already discussed, reliever use declined with time as asthma control improved. In subjects randomized to Symbicort SMART®, reliever use averaged close to one dose per day (table II) and days of high reliever use

Table III. Comparison of treatment arms and major outcomes in the study by Lundborg et al.[17][a]

Maintenance (μg)	Reliever (μg)	Change in asthma control days (%)	Daily reliever use (doses/day)	Daily treatment dose (μg)		Severe exacerbations	Healthcare costs in trial period (SEK)
				budesonide	formoterol		
Symbicort® 160/4.5 bid	Symbicort® 160/4.5	+3	0.5	392	11	19	2 577
Symbicort® 160/4.5 od	Symbicort® 160/4.5	–6	1.1	336	9	11	1 683
Symbicort® 320/9 bid	Formoterol 4.5	+7	0.5	640	20	17	3 183

a Children aged 4–11 used half the maintenance dose with Symbicort® 80/4.5 μg as needed in the Symbicort SMART® groups. Asthma control days are lower and reliever use higher in the od SMART® group. Healthcare costs are significantly lower with od Symbicort SMART® than either comparator. Differences in the number of severe exacerbations were not significant.[17]

bid = twice daily; **od** = once daily; **SEK** = Swedish kroner.

were infrequent. In the COMPASS and SMILE studies, more than four reliever doses were used on only 3.1% and 2.7% of days, respectively, and more than eight doses on 0.3% and 0.1%, respectively.[6] When Symbicort SMART® was compared with higher fixed-dose maintenance treatment regimens, reliever use was similar as was the frequency of high reliever use days.

High reliever use days are not necessarily a problem. In the AHEAD study,[7] the risk of a severe exacerbation developing within 28 days of the first study day when a subject used 2, 4, 6 or 8 reliever doses was calculated as illustrated in table IV. Subjects randomized to Symbicort SMART® were less likely to ever use a high number of reliever doses in a single day. If they did, the risk of developing a severe exacerbation in the following 28 days was greatly reduced.[7] This observation supports the concept that there is a window of opportunity during which Symbicort SMART® is effective as represented conceptually in figure 1. Of considerable interest, the majority of high-use episodes, even with the inferior fixed-dose regimen, will settle without oral corticosteroids, highlighting the need for asthma action plans that do not hasten the use of oral corticosteroids.

9. Apportionment of Clinical Benefit to Intervention with Symbicort SMART® versus Attention to General Principles of Asthma Care

Whenever a long-term study is conducted in asthma, there is the potential for an immediate treatment effect, a benefit of improved treatment over time and general benefits from improved asthma knowledge, adherence to treatment and better inhaler technique. While these general benefits may be unimportant to the comparison between treatments in the study itself, they are important in placing treatment outcome differences in context with other important asthma care measures.

In the COMPASS and AHEAD studies, there was a period of 2 weeks between the baseline visit 1 and the randomization visit. At the initial visit, general asthma education was provided and inhaler technique reviewed. In those 2 weeks, the COMPASS patients were receiving ICS alone as they had been for 3 days before visit 1. Examining only those subjects eventually randomized to Symbicort SMART®, mean baseline FEV_1 was 2.23 L, improving to 2.44 L in the 2 weeks before randomization. It increased to 2.69 L at the end of 6 months of treatment.[6] Patients recruited into the AHEAD study had no treatment changes and continued on a LABA if prescribed prior to enrolment. In this study, baseline FEV_1 was 2.08 L, improving to 2.30 L in the 2 weeks before randomization and increasing to 2.55 L at the end of treatment.[7]

Therefore, in each study, about half of the benefit in terms of increased FEV_1 was seen before study treatment commenced. This confirms that simple principles of asthma care remain of great value even when there are real benefits from choosing the optimal asthma management strategy.

Table IV. The risk of a severe exacerbation developing within 28 days of the first study day vs reliever use from the AHEAD study[7]

Daily reliever use (doses)	Symbicort SMART®		Seretide® fixed-dose maintenance	
	events (no.)	exacerbations (%)	events (no.)	exacerbations (%)
>2	722	5	726	7
>4	305	9	333	13
>6	106	15	151	20
>8	32	16	49	29

10. Is there a Benefit with a Higher Maintenance Dose as Part of Symbicort SMART® Treatment for Moderate or Severe Asthma?

None of the large, randomized studies discussed so far included Symbicort SMART® regimens with more than one maintenance dose level. Therefore, this question can only be answered by inherently imperfect comparisons in outcomes between studies. The SMILE, COMPASS and AHEAD studies recruited patients with similar baseline characteristics. It is possible to construct such comparisons for both current control and future risk. Firstly, increasing the maintenance treatment component above 160/4.5 μg twice daily did not reduce the as needed treatment component or improve the number of asthma control days. As reflected in diary variables, the number of symptom-free days in the final month of study was very similar with maintenance of 160/4.5 μg twice daily or 320/9 μg twice daily.[6,7,14]

It is not possible to compare the reported increase in FEV_1 during the studies because patients during the run-in period in the COMPASS study were not permitted to use a LABA, patients in AHEAD who were using a LABA continued to do so and in SMILE all patients used Symbicort® during the run-in period. However, some comparisons can be made of the effect of study treatment on the change in FEV_1 between the first study visit and end of study treatment. The increase in FEV_1 from the initial study visit was 0.49 L in COMPASS, 0.47 L in SMILE and 0.47 L in AHEAD.[6,7,14]

In relation to future risk, the best numerical comparator is the number of days during which oral corticosteroids were required. This represents a composite of exacerbation frequency, severity and length. In the SMILE study, oral corticosteroids were required on 1.25 days/patient-year and the corresponding figures for COMPASS were 1.4 days/patient-year. In AHEAD, the figure was 1.5 days/patient-year.[6,7,14] While in each case this number of days represented an advantage compared to fixed-dose comparators, there seems again to be no advantage for future risk in increasing the maintenance dose above 160/4.5 μg twice daily.

11. Identified Subgroups with Greater Than Average Benefit from Symbicort SMART®

Two patient subgroups have been evaluated in the context of who may obtain the greatest benefit from Symbicort SMART®. The first is the subset of patients who entered the COMPASS study with unstable asthma despite using a higher dosage range of ICS. In the COMPASS study, 16% of the study cohort used more than 1000 μg/day beclomethasone dipropionate equivalents. This group tended to be older, have lower FEV_1 (% predicted) and to use more reliever doses during the run-in period.

Higher dose ICS subjects allocated to Symbicort® fixed-dose maintenance had a higher annualized exacerbation rate; increased from 27 in the remainder of the cohort to 55 per 100 patient-years.[18] With Symbicort SMART®, this increased risk was still significantly reduced to 32 events/100 patient-years. The relative reduction in exacerbations was similar in the high-dose group and the remainder. The NNT with Symbicort SMART® rather than Symbicort® fixed-dose to prevent one severe exacerbation was 4.3 in the high-dose ICS cohort and lower if compared with fixed-dose Seretide®.[18] The higher-dose ICS group, when allocated to Symbicort SMART®, did use more reliever Symbicort® doses than the remainder, but there was still a 16% reduction in total Symbicort® used compared

with the Symbicort® fixed-dose maintenance group.[18]

There have been two further *post hoc* analyses examining patterns of reliever use and effect of Symbicort SMART® on asthma outcomes. From the COMPASS study, the subgroup that used more than one reliever dose on average has been examined.[19] Subjects allocated to higher Symbicort® fixed-dose maintenance who still used more than one reliever dose per day, had a higher exacerbation rate at 34 per 100 patient-years. The same reliever use was associated with fewer exacerbations, 16 per 100 patient-years, for patients allocated to Symbicort SMART® in spite of lower maintenance and overall treatment burden.[19] Of interest, in the majority of subjects who averaged less than one reliever use per day, there is no difference in the annual exacerbation rates between Symbicort SMART® and Symbicort® fixed-dose – both 7 per 100 patient-years.

In this analysis, the total benefit of exacerbation reduction within the COMPASS study was related to subjects who used more than average reliever. On the other hand, the remainder of patients receiving Symbicort SMART® had a similar exacerbation rate in the face of a substantial reduction in total Symbicort® dose and this has clinical merit. A similar disproportionate benefit for high reliever users was found in an analysis of subjects within the AHEAD study who ever used more than four reliever doses on a single study day.[20] One has to be cautious in interpreting these findings. However, it is likely that Symbicort SMART® has greater intrinsic merit in more severe asthma, especially in those patients who are prepared to use reliever in response to relevant symptoms.

12. Which Patients or Groups are or may be Unsuitable for Symbicort SMART®?

A critical question is which patients or groups are or may be unsuitable for Symbicort SMART®. It is untested in the major studies and can be answered only with opinion. One fundamental requirement for use of Symbicort SMART® is that the patient has asthma and that asthma is responsible for the symptoms for which they would use reliever. In all studies, it could be confidently concluded that subjects had current asthma based on physiology and a reasonable conclusion was that symptoms for which they used reliever were asthma related. This is clearly not always so. Patients with a diagnosis of asthma who use a reliever for effort dyspnoea related to unfitness or being overweight, or because of intercurrent cardiac or other disease may use an expensive reliever without a reasonable basis for likely benefit. The same, to a large degree, would apply to patients who have anxiety or vocal cord dysfunction as key contributors to symptoms.

At the other extreme, potential subjects for the major studies who, in spite of abnormal lung function and current reversibility, did not perceive asthma symptoms or react by using a reliever, could not meet the studies' inclusion criteria. The correlate, in the clinical setting, is that patients must be relied upon to both perceive symptoms and use reliever in response. Concerns such as the higher reliever cost per dose or fear of the effects of incremental corticosteroid doses should not be allowed to deter patients from simply using their new reliever in response to the same symptoms for which a SABA would have been previously used.

There were relatively small numbers of current smokers in all studies. Smoking impairs the response to asthma treatment[21] and, as a treatment strategy that may result in lower treatment doses, the benefit of Symbicort SMART® in smokers must presently be regarded as uncertain. In the clinic setting, current smokers with unstable asthma might be better brought to focus on the proven benefit of smoking cessation rather than uncertain benefits of switching to Symbicort SMART®.

13. Health Economic Analysis

Prior to the development of Symbicort SMART®, the use of formoterol as reliever had been proven to be cost effective compared with terbutaline when either was combined with Symbicort® as fixed-dose maintenance. The

actual cost increment between formoterol and Symbicort® is substantially less than that from terbutaline. Drug treatment costs vary from country to country. Unit pricing set for the SMILE study based on German costs was €0.11 for terbutaline, €0.48 for formoterol 4.5 μg and €0.57 for Symbicort® 160/4.5 μg. At the present time in Australia, costs per inhalation in are $A0.09 for terbutaline, $A0.43 for formoterol 4.5 μg and $A0.48 for Symbicort® 160/4.5 μg.

Analysis of the cost effectiveness of going the step further to Symbicort SMART® is critically dependent on the alternate treatment strategy. The simplest analysis is that comparing Symbicort SMART® with twice the maintenance dose Symbicort® in the COMPASS study.[22] Healthcare costs were 12% lower with improved clinical outcomes. Once economic comparisons are made between Symbicort SMART® and fixed-dose Seretide®, a dependence on national price differences emerges. In the COMPASS study, Symbicort SMART® was more cost effective than Seretide® on all analyses,[6] as it also was in the AHEAD study based on preplanned analysis of Spanish costs. The reduction in drug treatment costs would also be evident in Germany and Australia, but not in France.[7] In the Lundborg et al.[17] study, the lowest treatment costs were associated with the use of Symbicort SMART® with once daily maintenance, but this strategy allowed an increase in symptoms and reduced asthma-free days.

These data have been reanalysed using standard methodology based on Canadian standard costs. The combination of improved outcomes with lower treatment costs means that Symbicort SMART® can be judged dominant from a pharmacoeconomic perspective compared with fixed-dose maintenance treatment and a SABA.[23] The situation is less straightforward when the alternate treatment option is Symbicort® at the same maintenance dose supplemented by terbutaline as needed. In the SMILE study, direct and calculated indirect costs were 12% higher numerically with either formoterol or Symbicort® as reliever, rather than terbutaline. This increase was not statistically significant; however, an increase of this magnitude would be important in a community setting were it not offset by clinical benefits.

14. Safety

The use of combination LABA/ICS as the sole asthma treatment completely eliminates the risk that bronchodilator alone, long or short acting, can be used without ICS. This is recognized by Global Initiative for Asthma (GINA) as one of the principal advantages afforded by combination asthma treatments.[3] Beyond this, there are three aspects to clinical safety. The first is the potential for lack of efficacy and this is well addressed in the previous sections. In the trials reported, there are consistently lower numbers of discontinuations related to lack of effectiveness. The second is that extra doses of β-adrenergic receptor agonist and ICS used as needed could lead to adverse effects of cumulative higher doses given over time. The third is the potential for adverse events associated with occasions of use of very high reliever doses.

In the suite of studies that compared Symbicort SMART® with ICS maintenance treatment,[11-13] there was no excess of adverse events that might be attributable to adrenergic effects and markers of adrenal function were also similar when measured.[12,13] There was similarly no difference in the frequency or nature of adverse events in the two studies in which total budesonide and formoterol doses were inevitably higher with Symbicort SMART® that for control subjects using fixed-dose Symbicort®.[13,14] In the COMPASS study, when Symbicort SMART® is compared with higher fixed-dose maintenance Symbicort®, the cumulative dose of Symbicort® is actually 25% lower and there is no potential for cumulative adverse drug effect in this comparison.

Occasions of very high use were infrequent in all studies as discussed in previous sections and the absence of excess of palpitations, arrhythmias or tremor can be regarded as generally reassuring. One has to be cautious as the supportive context of a clinical trial could be protective. Going beyond these studies, data do support the safety of Symbicort® in acute asthma. Symbicort® in a total dose of budesonide 1280 μg

and formoterol 36 μg (eight standard inhalations) delivered over 5 minutes yielded no differences in heart rate, serum potassium or blood pressure compared with salbutamol 1600 μg, delivered in the same period.[24] The therapeutic response was also similar. Again, this safety is seen in an even more regulated environment in an Emergency Department and, in clinical practice, asthma action plans should be used as a routine.

Finally, mouth washing after use of Symbicort® as reliever has not been recommended as necessary and was not required in these studies. Reports of dysphonia were low and not different from the comparator in any study, but this is an adverse effect that many recognize as underreported in clinical studies. Whether dysphonia will be prevented by lower total treatment doses or increased because dose administration intervals are reduced will only be known if a study specifically examining this effect is conducted.

15. How do the Symbicort SMART® Data Reflect on Current Concepts of Asthma Control?

Symbicort SMART® is clearly dominant over alternate treatment regimens, for moderate and severe asthma, in clinical and economic terms. However, most subjects used reliever above the GINA threshold for loss of control – more than two per week. From this, it has been argued that Symbicort SMART® is a treatment strategy that is inappropriately permissive of symptoms in many patients only to avoid severe exacerbations in some.[25] The implication is that Symbicort SMART® has failed these patients and that treatment should be changed, presumably to a high fixed-dose regimen. This argument requires exploration.

Firstly, based on data, reliever use would not be lower with the alternate fixed-dose regimen; switching would not address the problem. Secondly, exacerbations that are another critical factor in assessment of control would be increased. Thirdly, total treatment would increase and with it the potential for adverse effects. Furthermore, it is clear from the *post hoc* analysis of the COMPASS study, that those whose treatment would not be successful using this measure are those who stand to benefit the most from continuing with Symbicort SMART® rather than being switched to a higher-dose fixed-combination treatment. Nonetheless, it is critical for our understanding of this issue that studies be conducted to determine if there is a benefit from increasing the maintenance component of Symbicort SMART® when reliever use is frequent.

Another clinical setting where defining control will also be important is during down titration of a well controlled patient, previously prescribed high-dose combination treatment, to lower-dose maintenance supplemented by Symbicort® as needed. In theory, this may prove to be one of the more useful purposes for Symbicort SMART®. Emerging symptoms should be well addressed by Symbicort® as needed. If a stable patient is, by down titration, changed to one at increased risk of exacerbation, this risk will be reduced by 50% or more if the reliever used is Symbicort® rather than a SABA.[13] Consider this scenario: a patient who was using 28 Symbicort® doses and one dose of reliever SABA per week is down-titrated to 14 maintenance doses with an increase in reliever to three per week. Is he or she worse off or better for the change? Should the opinion of a doctor seeking control with infrequent reliever use hold sway over that of a patient less concerned by this level of symptoms and happy with fewer overall treatment doses? These are important, unresolved issues.

16. Symbicort SMART® in the US

All Symbicort SMART® studies have used the Turbuhaler® device and this device is not approved for use in the US. There is a Symbicort® metered dose inhaler (MDI) that is proven effective in asthma but this has been developed as a two-dose device.[26] If not used correctly, there is variation in the doses delivered by the first and second actuation.[27] The overall effect is that the Symbicort® MDI has not been studied as a reliever and is not licensed for the relief of acute bronchoconstriction in the US or elsewhere. This situation is unlikely to change in the foreseeable future.

17. Implementation of Symbicort SMART® into Clinical Practice

Patient selection is important for implementation of Symbicort SMART® into clinical practice. While there are benefits across the spectrum of asthma severity, these are greater in patients with more severe asthma, those who use reliever frequently and/or with greater than average risk of exacerbations. If the expected benefits are to be delivered, there are a number of important preconditions. Asthma should be the correct diagnosis and the cause of symptoms for which a patient might use reliever. This might seem trite but, within the current GINA guidelines is the requirement to consider these issues when asthma control is not achieved with initial maintenance treatment.[3] It serves no useful purpose to initiate this treatment in patients with vocal cord dysfunction or who use reliever in response to predictable exercise-related breathlessness caused by obesity or unfitness.

All the major studies were conducted with investigators assessing and managing exacerbations blinded to treatment allocation and in the absence of a uniform asthma action plan. In the clinical setting, patients should be well educated and provided with an action plan suitable for their treatment regimen.[28] This education need not be complex. Symbicort SMART® simply requires that a maintenance treatment be used with an extra reliever used as needed, exactly as with any other asthma treatment plan. Standard action plans, suitable for fixed-dose maintenance treatment, are not compatible with Symbicort SMART®. These generally monitor for specific patterns of symptoms or lung function change and specify a consequential change in asthma treatment. To follow such a plan would be to deviate from the fundamental strategy inherent in

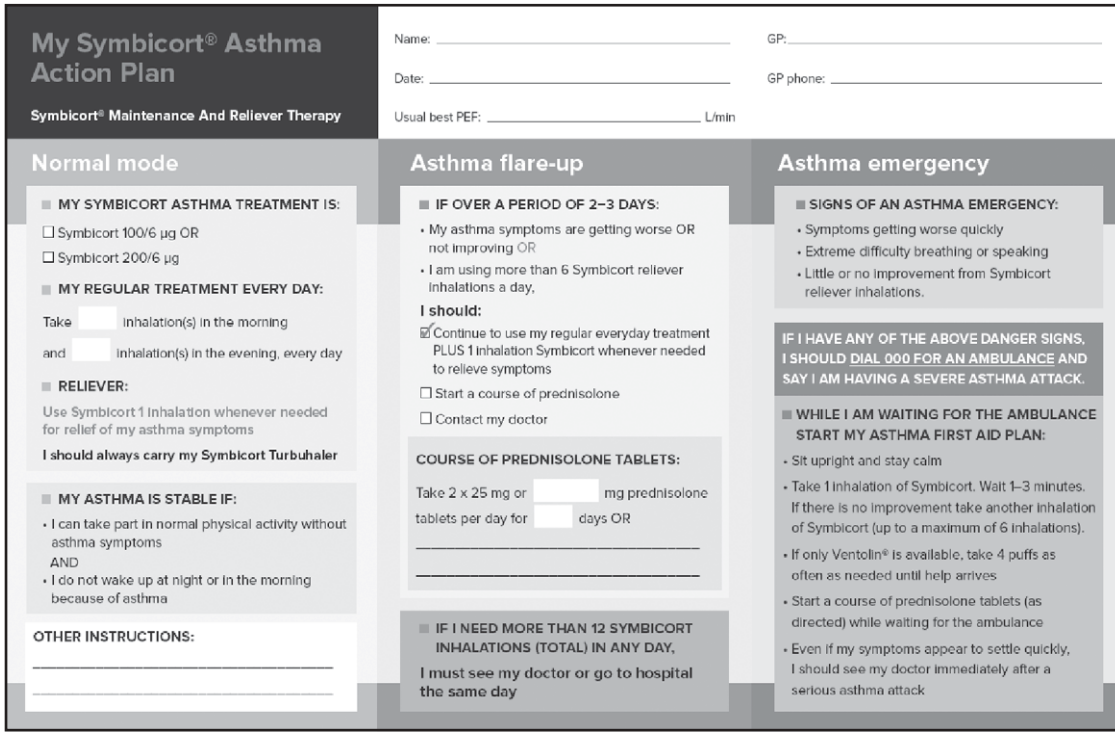

Fig. 2. The Australian Symbicort SMART® Asthma Action Plan.

Symbicort SMART® – use of a suitable maintenance treatment, with any treatment 'action' determined by the use of as-needed doses.

The Asthma Action Plans (AAPs) for Symbicort SMART® developed in Australia and endorsed by the Australian National Asthma Council are presently unique.[29] They describe a state of usual asthma control and treatment, a state of some decline in control where ongoing treatment with vigilance is required and emergency situation with necessary responses. One plan is based totally on symptoms, whereas in the second, actions during a period of increased symptoms are determined in part by measurement of PEFR. This AAP can be administered quickly. Its creation with a patient provides an opportunity to briefly reiterate the principle of the treatment and key actions needed to maximize benefit (figure 2).

18. Conclusions

When all issues are well addressed, the majority of patients with asthma should be managed with ICS as their preventer. When control with this is inadequate, the use of budesonide/formoterol as both maintenance and reliever treatment improves current asthma symptoms and reduces future risk of episodes of poor control compared with any of the range of currently available alternative treatment strategies and is cost effective. An adequate maintenance dose is required to achieve satisfactory current control and the key role of as-needed Symbicort® may be to address future risk. Appropriate education, emphasizing the simplicity of this change in treatment, is critical to delivering the potential benefits and an opportunity is presented to widen the use of asthma action plans that is presently suboptimal.[30]

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