Efficacy and safety of AZD7594, an inhaled non-steroidal selective glucocorticoid receptor modulator, in patients with asthma: a phase 2a randomized, double blind, placebo-controlled crossover trial

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Abstract

Background: Inhaled corticosteroids reduce inflammation in asthma but chronic use may cause adverse effects. AZD7594, an inhaled non-steroidal selective glucocorticoid receptor modulator, has the potential of an improved risk-benefit profile. We investigated the safety and efficacy of AZD7594 in asthma.

Methods: This phase 2a multi-center, randomized, double-blind, placebo-controlled crossover study enrolled adults with asthma aged 18 to 75 years. Patients were treated with budesonide 200 μg twice daily for 2–3 3 weeks (run in part one). If controlled, as demonstrated by an asthma control questionnaire-5 score of < 1.5, patients entered a three-week run-in (part two) where they received a short acting bronchodilator alone. Thereafter, patients with a fractional exhaled nitric oxide (F_ENO) ≥25 ppb and pre-dose FEV_1 40 to 90% predicted were randomized to one of nine treatment sequences. Each patient received placebo and two of three dose levels of AZD7594 (58, 250, 800 μg) once daily via inhalation, in 14-day treatment periods, separated by three-week washout periods. The primary endpoint was the change from baseline in morning trough FEV_1 versus placebo on day 15. Secondary endpoints included measures of airway inflammation and asthma control.

Results: Fifty-four patients were randomized and received at least 1 dose of treatment, 48 patients completed the study. Overall 52 patients received placebo, 34 received AZD7594 58 μg, 34 received AZD7594 250 μg, and 34 received AZD7594 800 μg. AZD7594 800 μg demonstrated a significant improvement in Day 15 morning trough FEV_1 versus placebo (LS means difference 0.148 L 95% CI 0.035–0.261, $p = 0.011$), with a dose-dependent response seen in the 250 μg (0.076 L -0·036–0·188, $p = 0.183$) and 58 μg (0·027 L -0·086–0·140, $p = 0.683$). All secondary endpoints showed statistically significant improvement at the 800 μg dose. All doses demonstrated a significant reduction in F_ENO at day 15 $p < 0.01$. No statistically significant difference in plasma cortisol level was observed between AZD7594 and placebo at any dose. AZD7594 was considered safe and well tolerated.

Conclusions: Two-week treatment with AZD7594 demonstrated a favorable risk-benefit profile in patients with mild to moderate asthma. Further clinical studies are needed to fully characterize AZD7594.

Trial registration: ClinicalTrials.gov number NCT02479412.

Keywords: Asthma, Inhaled corticosteroids, Selective glucocorticoid receptor modulator, Pharmacokinetics, Cortisol

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Background

Asthma is characterized by chronic inflammation and glucocorticoid receptor (GR) agonists as inhaled corticosteroids (ICS) are the preferred anti-inflammatory treatment at all asthma severity levels [1]. ICS alone and in combination with long acting beta adrenergic agonists (LABAs) have demonstrated improvement in symptoms and lung function, reduction in exacerbations, improved asthma control and quality of life [2–4]. As ICS are administered topically and have low systemic absorption, the major limitation for ICS therapy is the risk of local adverse effects including candidiasis and dysphonia which are inconvenient for the patient, but typically not serious in nature. ICS therapy has the potential to cause systemic adverse effects mediated by the hypothalamic-pituitary-adrenal (HPA) axis, such as a reduction of growth velocity in children [5, 6] and effects on bone mineral density [7] although this effect is less clear [8]. Systemic effects are less common and usually associated with chronic use of high doses [9, 10].

Several development programs have aimed to improve selectivity for the glucocorticoid receptor to preserve efficacy while reducing adverse effects. Four compounds prior to AZD7594 have advanced to clinical trials in asthma [11], but none have advanced beyond phase 2 trials.

AZD7594 is a novel nonsteroidal, potent and selective glucocorticoid receptor modulator (SGRM) being developed as a once daily inhaled treatment for asthma. Pre-clinical data using the Rat Sephadex®-induced lung edema model of pulmonary inflammation supports an improved therapeutic ratio when delivered by inhalation [12]. In this phase 2a randomized study, the first to evaluate clinical efficacy, we aimed to assess the efficacy, safety, and pharmacokinetics (PK) of AZD7594 given once daily by inhalation in adults with asthma uncontrolled on short acting beta agonists (SABAs) alone. We investigated the effect of AZD7594 on morning trough FEV_1, airway inflammation, and measures of asthma control. Some results of this study were presented at the European

Respiratory Society meeting in 2017, [13, 14] this paper provides the complete results from the study.

Methods

Study design

This phase 2 randomized, double-blind, multi-dose, placebo controlled, three-period, incomplete block crossover study was conducted in nine centers in Germany and one center in Bulgaria between June 25, 2015 and February 8, 2016 (Fig. 1).

Patients

Eligible patients were men and women of non-child bearing potential 18 to 75 years of age with mild to moderate asthma. Patients must have had a documented clinical diagnosis of asthma at least 6 months prior to enrollment and were either steroid naïve or treated with monteleukast, ICS or low dose ICS / LABA. Current or recent smokers (who quit within the last 6 months) and patients with ≥10 years total smoking history were excluded. Patients were required to have a fraction of exhaled nitric oxide (F_ENO) level ≥ 25 parts per billion (ppb) before randomization, demonstrating evidence of airway inflammation. Full inclusion and exclusion criteria are provided in the Additional file 1: appendix.

Randomization and masking

Eligible patients were randomized via an interactive voice response system prior to the first dose in treatment period one, to one of nine treatment sequences according to the randomization schedule produced by independent PAREXEL Informatics. Each treatment sequence included two out of three possible treatments: AZD7594 58 μg, AZD7594 250 μg, AZD7594 800 μg, and each patient received placebo during one of the three periods in a balanced crossover design. The study was performed in a double-blind manner. Placebo was supplied as identical dry powder vehicle to AZD7594 in identical packaging,
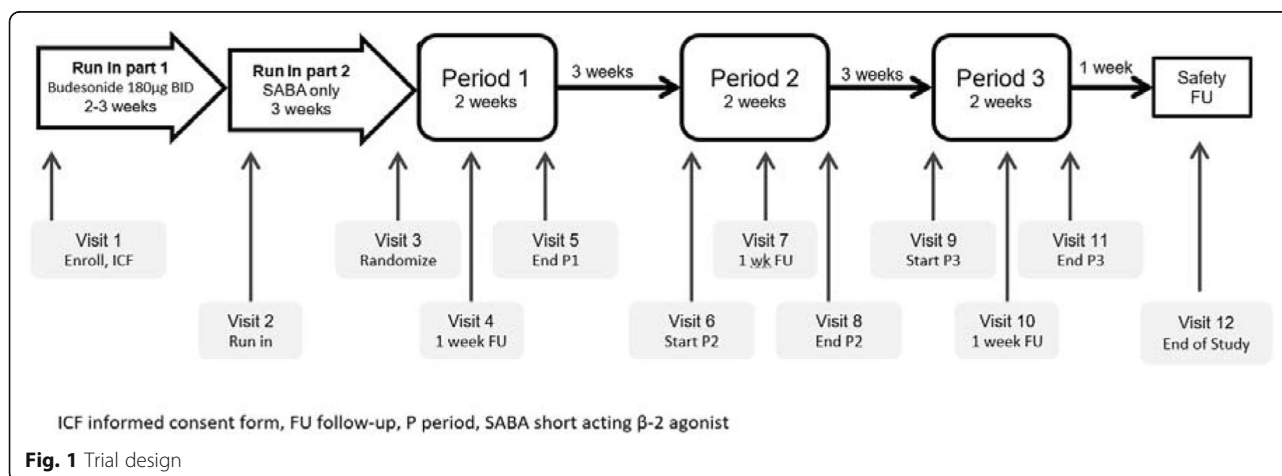

Fig. 1 Trial design

and budesonide (used during run-in) and salbutamol (rescue medication) were open label.

Treatment

During a two to 3 week run-in (part one) patients received low dose budesonide (200 μg twice daily). Patients whose asthma was controlled (as demonstrated by an Asthma Control Questionnaire-5 [ACQ-5] score ≤ 1.5), were eligible for a second run-in (part two) during which budesonide was stopped and washed out over 3 weeks while patients received only the SABA, salbutamol, as needed. At the end of the second run-in, patients with pre-bronchodilator forced expiratory volume in 1 second (FEV_1) between 40 to 90% and with a F_ENO of ≥25 ppb were randomized and entered the double-blind treatment period. Patients who were poorly controlled as evidenced by rescue medication use of ≥12 puffs on three or more days or an ACQ-5 ≥ 3 during the enrollment period were excluded. Randomized patients received study medication once daily by inhalation via a monodose dry powder inhaler (DPI) for a 2 week treatment period. Each treatment period was separated by a three-week washout, where the only asthma treatment that patients received was as needed salbutamol. A stability criterion was applied at baseline of treatment periods 2 and 3 to ensure that there was no detectable carry-over effect or any acute worsening compared to baseline at the start of those periods. Patients were evaluated to confirm that the pre-dose FEV_1 was ±20% of the pre-dose baseline value for treatment period 1.

Endpoints

The primary efficacy endpoint was change from baseline in morning trough FEV_1 on Day 15 versus placebo for each of the three AZD7594 dose levels. Baseline was defined as the average of the measurements obtained at 60 and 30 min before dosing on day 1 in each treatment period, and trough as the average of the 2 spirometric measurements at 23:00 and 23:30 h after the last dose of study medication on Day 14. Spirometry was assessed centrally.

Secondary efficacy endpoints included change from baseline in: F_ENO on Day 8 and Day 15, morning trough FEV_1 on Day 8, and in morning and evening peak expiratory flow (mPEF, ePEF) over the treatment period. Patient reported outcomes for asthma control were assessed with the five item asthma control questionnaire (ACQ-5) recorded at each study visit. Asthma symptoms, night-time awakenings, rescue medication use and lung function as measured by morning and evening peak flow were recorded daily in the eDiary. Asthma symptoms were captured twice daily using a four point scale where patients recorded 0 for no symptoms and 3 if their asthma prevented them from doing normal daily activities or sleeping. The eDiary data was used to calculate the number of symptom free days, defined as those days on which no asthma symptoms or night-time awakenings

occurred and the number of asthma control days which included the same criteria as symptom free days and no rescue medication use. The pharmacokinetic (PK) profile was also assessed as a secondary endpoint, with rich sampling in a subset of patients, blood samples were collected on Day 1 and Day 14 of each treatment period. PK parameters, C_{max} and AUC_{0-24} were derived using non-compartmental methods with Phoenix® WinNonlin® (Pharsight Corp., Mountain View, California, USA). In addition, the dose proportionality was assessed by dose normalized C_{max} and AUC_{0-24} across three dose levels. A 24 h plasma cortisol profile was performed on Day – 1 and Day 14, in the PK subset, for each study period to obtain $AUEC_{0-24}$ pre-treatment and post-treatment respectively, to evaluate cortisol suppression.

Statistical analysis

Thirty-six patients were needed to achieve approximately 88% power to detect 200 mL change from baseline in trough FEV_1 compared to placebo using a two-sided test at 5% significance level, assuming an intra-patient standard deviation (SD) of 210 mL. Assuming a dropout rate of 25%, 48 patients randomized to nine sequences were needed to ensure 36 evaluable patients completing the study.

The analysis of the efficacy endpoints was based on the full analysis set (FAS), defined as all randomized patients following the principle of intention to treat (ITT) that includes all randomized patients who received at least one dose of randomized study drug. Patients were included in the analysis according to the treatment to which they were randomized. All safety analyses were based on the safety analysis set (SAF) defined as all randomized patients who received at least one dose of randomized study drug during the Treatment Period. Classified by actual treatment received.

The efficacy endpoints were analyzed using a linear model with treatment, period, and sequence as fixed effects, baseline as continuous covariate, and patient within sequence as random effect. No multiplicity adjustment for the analysis of the secondary variables was performed. In addition, dose-response for trough FEV_1 day 15 was analyzed *posthoc* using nonlinear mixed-effects modeling. In this analysis an empirical Emax model was estimated to the change from baseline trough FEV_1 data, applying different baseline definitions (see Additional file 1). This study is registered with ClinicalTrials.gov , number NCT02479412.

Results

One hundred ten patients were enrolled and screened, 54 of whom were randomized. Thirty-four patients received AZD7594 58 μg, 34 received AZD7594 250 μg, 34 AZD7594 800 μg and 52 patients received placebo. Baseline demographics characteristics of participants were similar across treatment groups. (Table 1). Trough PK was

Table 1 Baseline demographic and clinical characteristics

	Placebo	AZD7594		
	(n = 52)	58 μg (n = 34)	250 μg (n = 34)	800 μg (n = 34)
Demographics				
Age, years Mean (SD)	51 (12)	51 (12)	50 (12)	51 (12)
Male n (%)	44 (84.6%)	26 (76.5%)	30 (88.2%)	28 (82.3%)
White n (%)	51 (98.1%)	33 (97.1%)	33 (97.1%)	34 (100%)
Black n (%)	1 (1.92%)	1 (2.94%)	1 (2.94%)	0 (0.00)
BMII kg/m² Mean (SD)	27 (3)	27 (4)	28 (3)	27 (3)
Asthma Characteristics				
Prebronchodilator FEV_1 (L), Mean (SD)	2.53 (0.74)	2.54 (0.73)	2.59 (0.72)	2.55 (0.69)
% patients meeting FEV_1 reversibility criteria[a]	78.8%	88.2%	73.5%	70.6%
ACQ-5 score mean (SD)	1.2 (0.7)	1.2 (0.6)	1.2 (0.6)	1.2 (0.7)
Asthma symptom score (SD)	0.8 (0.5)	08 (0.5)	0.8 (0.5)	0.8 (0.5)
F_ENO ppb (SD)	57 (45)	60 (47)	53 (34)	57 (39)

[a]Reversibility was defined as ≥12% and ≥ 200 ml increase from pre-bronchodilator FEV1, *ACQ-5* Asthma Control Questionnaire-5, *BMI* body mass index, *F_ENO* Fraction exhaled nitric oxide, *kg* kilogram, *m* meter, *SD* standard deviation

collected in all study participants, 15 were included in an intensive PK sampling subset. Forty-eight patients (89%) completed the study, four withdrew due to development of pre-specified study withdrawal criteria. and One patient was withdrawn due to randomization into the wrong PK group and one for an adverse event (vitamin B12 deficiency and elevated liver enzymes). Three patients had major protocol deviations and were excluded from the per protocol set (failed inclusion criteria, use of prohibited concomitant medication, and withdrawn without primary endpoint). Patients recorded daily in the eDiary if they took their study medication. Drug accountability records were kept by the investigator and remaining supplies, including spent capsules were sent to the sponsor. Across all treatment groups, mean compliance was > 96%.

Efficacy

Lung function improved at all doses (Fig. 2). The greatest improvement in the primary endpoint, the change from baseline in morning trough FEV_1 on Day 15 versus placebo, occurred with the 800 μg dose (LS Means difference 0.148 L 95% CI 0.0349 to 0.261 $p = 0.011$) (Table 2).

The 800 μg dose also showed the greatest improvement in change from baseline in morning trough FEV_1 versus placebo on Day 8 (LSMeans difference 0.156 L 95% CI 0.039 to 0.273 $p < 0.01$). The change from
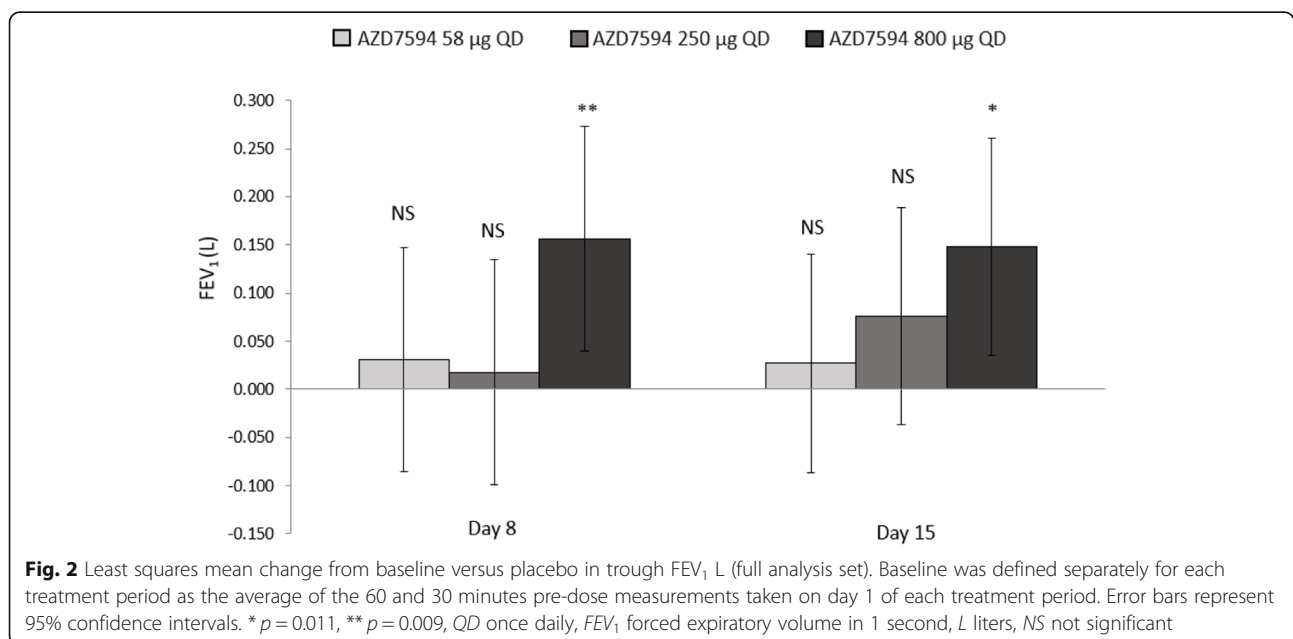

Fig. 2 Least squares mean change from baseline versus placebo in trough FEV_1 L (full analysis set). Baseline was defined separately for each treatment period as the average of the 60 and 30 minutes pre-dose measurements taken on day 1 of each treatment period. Error bars represent 95% confidence intervals. * $p = 0.011$, ** $p = 0.009$, *QD* once daily, *FEV_1* forced expiratory volume in 1 second, *L* liters, *NS* not significant

Table 2 Efficacy endpoints Least Squares Means full analysis set

	Placebo (n = 52)	AZD7594 58µg (n = 34)	AZD7594 250µg (n = 34)	AZD7594 800µg (n = 34)
Primary efficacy endpoint				
Morning pre-bronchodilator FEV_1				
Change from baseline (L) on day 15	0.059	0.086	0.136	0.207
Treatment difference (L) (95% CI)	N.A.	0.027 (-0.086, 0.140)	0.076 (-0.036, 0.188)	0.148 (0.035, 0.261)
P value	N.A.	0.638	0.183	0.011
Key secondary efficacy endpoints				
Morning pre-bronchodilator FEV_1				
Change from baseline (L) on day 8	0.071	0.102	0.089	0.227
Treatment difference (L) (95% CI)	N.A.	0.031 (-0.086, 0.147)	0.017 (-0.010, 0.134)	0.156 (0.039, 0.273)
P value	N.A.	0.604	0.767	0.009
Key secondary efficacy endpoints				
Morning pre-bronchodilator FEV_1				
Change from baseline (L) on day 8	0.071	0.102	0.089	0.227
Treatment difference (L) (95% CI)	N.A.	0.031 (-0.086, 0.147)	0.017 (-0.010, 0.134)	0.156 (0.039, 0.273)
P value	N.A.	0·604	0·767	0·009
Fraction exhaled nitric oxide (F_ENO)				
Change from baseline (ppb) on day 8	-4.296	-9.153	-14.71	-19.04
Treatment difference (ppb) (95% CI)	N.A.	-4.857 (-11.24, 1.528)	-10.41 (-16.75, -4.075)	-14.75 (-21.18, -8.319)
P value	N.A.	0.134	0.002	<0.0001
Change from baseline (ppb) on day 15	-0.549	-14.40	-14.81	-20.44
Treatment difference (ppb) (95% CI)	N.A.	-13.85 (-24.06, -3.642)	-14.26 (-24.37, -4.149)	-19.90 (-30.10, -9.689)
P value	N.A.	0.008	0.006	0.0002
Morning peak expiratory flow (mPEF)				
Change from baseline Day 1-14	0.0814	10.42	5.334	12.60
Treatment difference (L/min) (95% CI)	N.A.	10.34 (-1.335, 22.01)	5.253 (-6.427, 16.93)	12.52 (0.748, 24.29)
P value	N.A.	0.082	0.374	0.037
Evening peak expiratory flow (ePEF)				
Change from baseline Day 1-14	-8.257	7.475	6.04	11.65
Treatment difference (L/min) (95% CI)	N.A.	15.73 (5.039, 26.43)	14.30 (3.534, 25.06)	19.91 (9.068, 30.75)
P value	N.A.	0.004	0.010	0.0004
Forced vital capacity (FVC)				
Change from baseline (L) on day 8	0.0844	0.062	0.084	0.153
Treatment difference (L) (95% CI)	N.A.	-0.023 (-0.137, 0.091)	-0.0003 (-0.115, 0.114)	0.068 (-0.046, 0.183)
P value	N.A.	0.694	0.996	0.240
Change from baseline (L) on day 15	0.0765	0.042	0.104	0.138
Treatment difference (L) (95% CI)	N.A.	-0.035 (-0.141, 0.072)	0.028 (-0.078, 0.134)	0.062 (-0.045, 0.168)
P value	N.A.	0.521	0.598	0.254
Asthma symptom score				
Change from baseline day 1 - 14	-0.012	-0.119	-0.094	0.215
Treatment difference (95% CI)	N.A.	-0.107 (-0.206, -0.008)	-0.082 (-0.182, 0.018)	-0.203 (-0.303, -0.103)
P value	N.A.	0.035	0.105	0.0001
Asthma symptom free days				
Change from baseline day 1 - 14	0.050	0.603	0.318	1.01

Table 2 Efficacy endpoints Least Squares Means full analysis set *(Continued)*

	Placebo (n = 52)	AZD7594 58μg (n = 34)	AZD7594 250μg (n = 34)	AZD7594 800μg (n = 34)
Treatment difference (95% CI)	N.A.	0.553 (0.036, 1.069)	0.268 (-0.252, 0.788)	0.956 (0.433, 1.48)
P value	N.A.	0.036	0.308	0.0005
Asthma control days				
Change from baseline day 1 - 14	0.277	0.950	0.705	1.219
Treatment difference (95% CI)	N.A.	0.673 (0.088, 1.258)	0.428 (-0.161, 1.017)	0.942 (0.348, 1.535)
P value	N.A.	0.025	0.152	0.002
ACQ-5 day 15				
Change from baseline	0.014	-0.293	-0.168	-0.416
Treatment difference (95% CI)	N.A.	-0.307 (-0.516, -0.098)	-0.182 (-0.393, 0.028)	-0.430 (-0.640, -0.221)
P value	N.A.	0.004	0.088	<0.0001
Rescue medication use (day 1 – 14)				
Change from baseline (inhalations) per day	-0.334	-0.678	-0.819	-1.137
Treatment difference (95% CI)	N.A.	-0.344 (-0.719, 0.0318)	-0.485 (-0.863, -0.1073)	-0.803 (-1.183, -0.422)
P value	N.A.	0.072	0.012	<0.0001
Nighttime awakenings				
Change from baseline day 1- 14	0.007	-0.412	-0.173	-0.760
Treatment difference (95% CI)	N.A.	-0.419 (-0.741, -0.956)	-0.179 (-0.503, 0.144)	-0.766 (-1.091, -0.441)
P value	N.A.	0.0116	0.273	<0.0001

ACQ-5 Asthma Control Questionnaire-5, CI confidence interval, FEV_1 forced expiratory volume in 1 second, L liters, ppb parts per billion

baseline in F_ENO values demonstrated a dose ordered improvement (Fig. 3), with the 250 μg and 800 μg doses significant versus placebo at Day 8 $p < 0.05$ and a significant treatment difference across all doses at Day 15 p < 0.01(Table 2). Over the course of the treatment period, evening PEF improved relative to placebo at all dose levels ($p < 0.01$) while morning peak flow was significantly improved only with the AZD7594 800 μg dose level (Fig. 4, Table 2). The greatest reduction in average (Day 1 to Day 14) daily use of rescue medication from baseline occurred at the 800 μg dose (LS Means difference – 0.80 $p < 0.0001$) and the 250 μg dose also demonstrated a significant reduction (– 0.49 $p = 0.012$). Asthma control improved, as evidenced by significant improvement in mean ACQ-5 score versus placebo at Day 15 in both the 58 μg and 800 μg doses, (Fig. 5). Both symptom free days and asthma control days as well as reduction in nighttime awakenings were significant versus placebo with AZD7594 800 μg (Table 2).

In the *posthoc* analysis, the dose-response in change from baseline trough FEV_1 was described by an empirical Emax model (Additional file 1). An adequate fit could only be achieved when the average baseline across all periods was used. The ED_{50} was estimated to 140 [95%CI 26–763] μg, and the Emax to 0.213 [0.078–0.348] L. The model predicted trough FEV_1 Day 15 versus placebo is shown in Additional file 1: Figure S1. The predicted effects are numerically larger, compared to the primary analysis.

Pharmacokinetics

Following inhalation administration, AZD7594 was rapidly absorbed and reached maximum plasma concentration within 15 min; this was followed by a rapid decline in plasma concentration over 2 h, and then a slow elimination phase. The observed AZD7594 concentration-over-time profiles for all three dose levels are shown in Fig. 6. The increases in AZD7594 mean systemic exposures [C_{max} and AUC_{0-24} values] were less than dose proportional as indicated by the dose-normalized values (C_{max}/D, $C_{max,ss}/D$ and $AUC_{(0-24)}/D$). There was moderate to high between-subject variability in AZD7594 PK parameters (Table 3). The geometric coefficient of variation (CV%) ranged from 19.70 to 43.21% in C_{max} (Days 1 and 14), and from 17.91 to 52.48% in AUC_{0-24}.

Safety and tolerability

AZD7594 was well tolerated. Adverse events (AEs) were reported by 17 (32%) of patients in the placebo group, 13 (38%) of patients in the AZD7594 58 μg group, 9 (26%) in the 250 μg group and 12 (35%) in the 800 μg group (Table 4). There were no severe adverse events (SAEs) or deaths during the study. One patient was discontinued due to an AE of pernicious anemia (vitamin B12 deficiency anemia) and increased hepatic enzymes noted on the blood safety samples drawn at the end of the first washout period after receiving placebo in period
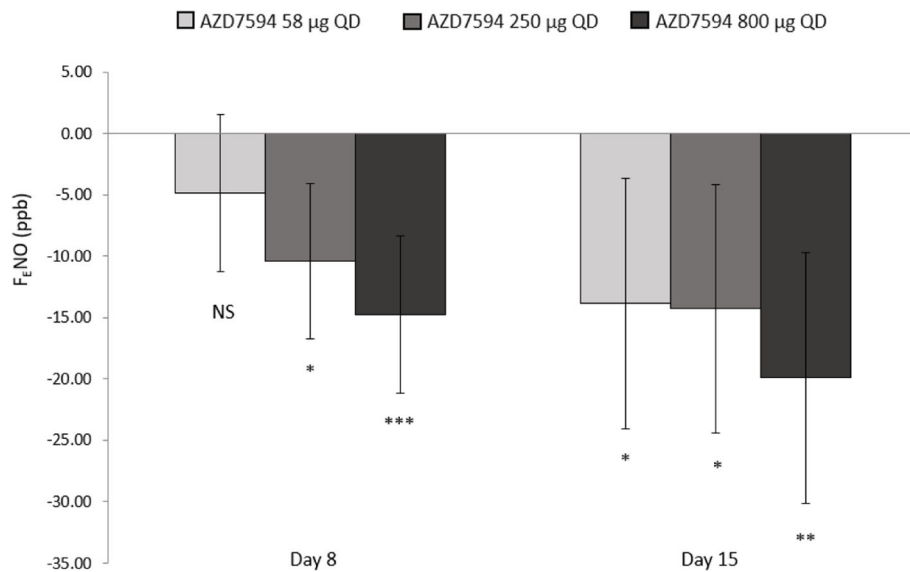
Fig. 3 F_ENO Least square mean change from baseline versus placebo (full analysis set). Baseline was defined separately for each treatment period as the measurement performed on day 1 of each treatment period. Error bars represent 95% confidence intervals. * p <0.01, ** p = <0.001, *** p < 0.0001 QD once daily, F_ENO fraction exhaled nitric oxide, *ppb* parts per billion, *NS* not significant

one. No clinically important differences were seen between treatments with regard to the number and overall pattern of patients reporting adverse events by system organ class. Adverse events are summarized in Table 4. Nasopharyngitis and headache were the most commonly reported AEs. No statistically significant difference in plasma cortisol level versus placebo was observed for any dose level of AZD7594, geometric mean ratio 1·03

(95% CI 0.90–1.19) for 58 μg, 1.02 (0.88–1.18) for 250 μg and 0.91 (0.79–1.05) for 800 μg (Table 5).

Discussion

This phase 2a study was the first to evaluate clinical efficacy of AZD7594 administered once daily via inhalation for 2 weeks in patients with mild to moderate asthma. AZD7594 reduced lung inflammation and improved
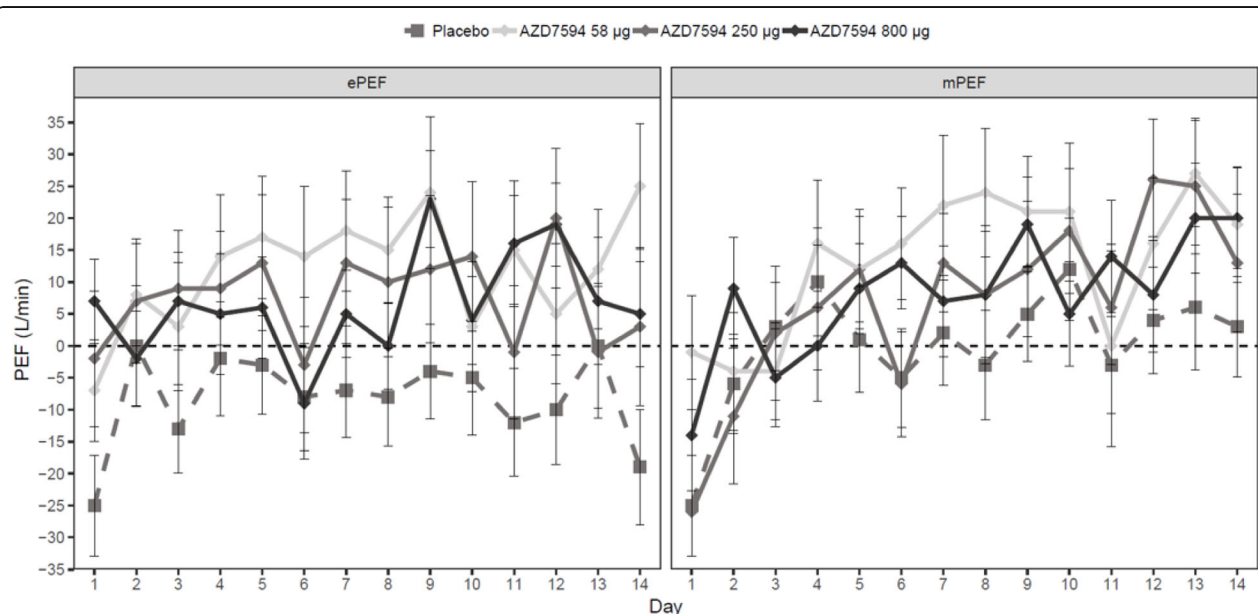
Fig. 4 ePEF (left) and mPEF (right) Arithmetic mean change from baseline versus day (full analysis set). Baseline is defined as the average of the Day -1 and Day -7 during the run-in period. Error bars represent standard errors. ePEF evening peak expiratory flow, mPEF morning peak expiratory flow
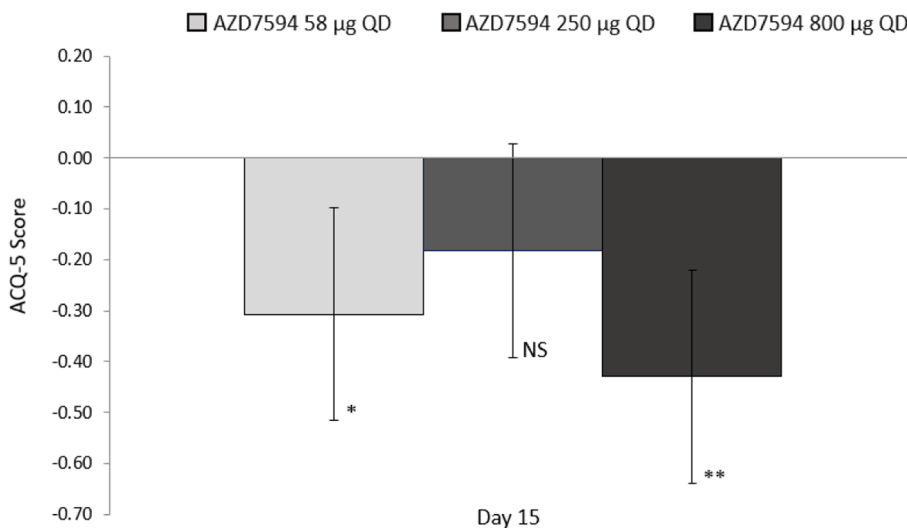
Fig. 5 ACQ-5 Least squares mean change from baseline versus placebo on Day 15 (full analysis set). Baseline was defined separately for each treatment period as the pre-dose score on day 1 of each treatment period. Error bars represent 95% confidence intervals. * $p < 0.05$, ** $p < 0.001$, *NS* not significant, *QD* once daily, *ACQ-5* Asthma Control Questionnaire-5

lung function as evidenced by a clinically and statistically significant improvement in the primary endpoint, Day 15 trough FEV_1 versus placebo at the 800 μg dose, improved daily peak flow and asthma symptoms, reduced nocturnal awakenings and average daily rescue medication use.

Treatment with AZD7594 was associated with a significantly lower inflammatory burden as measured by F_ENO compared to placebo. F_ENO levels dropped in a dose-ordered manner at Day 8 and after 2 weeks of treatment all AZD7594 doses achieved a significant difference versus placebo $p < 0.01$. A clinically meaningful
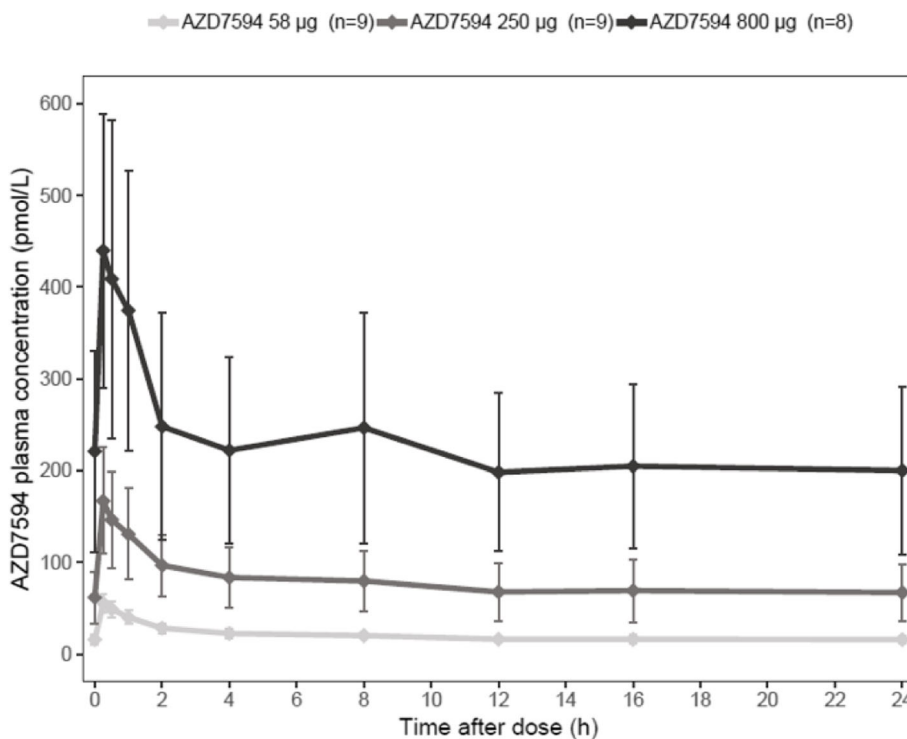

Fig. 6 AZD7594 Plasma concentrations at Steady-state (Day 14) Arithmetic means by dose level vs time after dose (pharmacokinetic analysis set). Error bars represent standard deviation. n: number of subjects

Table 3 Summary of the PK Parameters of AZD7594 at Steady-State (Day 14) by Dose Levels

Geometric mean (CV%)	AZD7594 58 µg (n = 9)	AZD7594 250 µg (n = 9)	AZD7594 800 µg (n = 8)
$C_{max, ss}$ (pmol/L)	54.97 (19.70)	158.7 (35.01)	421.6 (37.26%)
AUC(0-24) (h×pmol/L)	467.1 (17.91)	1725 (44.33)	4894 (52.48%)
$C_{avg, ss}$ (pmol/L)	19.48 (17.93)	71.89 (44.33)	203.9 (52.55%)

AUC(0-24): area under the plasma concentration-time curve from time zero to 24 hours after dose administration; $C_{avg,ss}$: average plasma concentration during a dosing interval at steady-state; $C_{max,ss}$: observed maximum plasma concentration at steady-state; CV%: geometric coefficient of variation; n: number of patients in the PKS for each treatment

mean reduction of > 20% [15] was observed for all dose levels, with the greatest F_ENO reduction (35%) occurring at the 800 µg dose. As an effective biomarker of eosinophilic airway inflammation with a greater predictive value than spirometry and PEF in assessing ICS responsiveness in asthma, the clinical improvement observed, provides confidence in the anti-inflammatory properties of AZD7594 across a dose range [15, 16]. Though this study measured many common asthma endpoints as well as F_ENO as marker of inflammation, other endpoints of interest for future studies include markers of inflammation in sputum, as well as direct measurement of bronchial hyperresponsiveness.

The objective of the study was to assess efficacy and tolerability across a wide dose range. Although the two lower doses did not significantly improve trough FEV_1, there was a numerical improvement at all dose levels. A *posthoc* analysis conducted to gain a better understanding of dose-response showed a dose-dependent increase in trough FEV_1, although the uncertainty in dose-response is large as can be expected for a GR agonist [17, 18]. Lung function improved significantly at all doses as assessed by ePEF and at the 800 µg dose for mPEF. Peak flow has the advantage over spirometry of being assessed daily. In this study, improvements in peak flow measurements were accompanied by a reduction in symptoms and nighttime awakenings and an increase in symptom free days, all important indicators of asthma control. The correlation of peak flow and asthma control has been previously reported [19].

In this study, ACQ-5 scores improved significantly with both the low (58 µg) and high (800 µg) dose of AZD7594. Although improvement was shown, a conclusion regarding the clinically meaningful effect with this relatively small sample over a 2 week treatment cannot be drawn.

The current crossover study in a small number of subjects, was designed to assess the potential of AZD7594 as an anti-inflammatory treatment rather than fully characterize the clinical profile. A two part run in ensured appropriate patient selection for treatment with a GR agonist alone. By including patients who had an ACQ-5 of ≤1.5 on low dose ICS as assessed during run in part one, we aimed to include patients at GINA step 2,3 [1]. Inclusion of patients who had a minimum F_ENO of 25 ppb at the end of run-in part two enabled the enrollment of patients who demonstrated airway inflammation and were more likely to respond to a GR agonist; American Thoracic Society (ATS) guidelines suggest patients with F_ENO levels lower than 25 ppb are unlikely to respond to GR agonist therapy [15]. The selection of a responder patient population provided more confidence in evaluating anti-inflammatory effect in a small number of subjects.

The 14-day treatment period allows adequate time to achieve clinical response. Previous studies demonstrate within 2 weeks near maximal improvement in lung function, as measured by FEV_1 [2, 20, 21] and reduction of F_ENO, a measure of airway inflammation. [15, 22, 23]. Lung function may have continued to improve with a longer treatment period. Personal best peak flow is typically reached within 1 to 3 weeks of initiating GR agonist therapy, but daily average peak flow may continue to improve for 3 months or more [24]. In future studies, a longer treatment period will be preferred to assess asthma control.

Table 4 Treatment emergent adverse events reported by ≥2 patients in any dose level (safety analysis set)

Adverse Event	Placebo N = 52 n (%)	AZD7594 58 µg N = 34 n (%)	AZD7594 250 µg N = 34 n (%)	AZD7594 800 µg N = 34 n (%)
Patients with any AE	17 (32.69)	13 (38.24)	9 (26.47)	12 (35.29)
Nasopharyngitis	8 (15.38)	4 (11.76)	2 (5.88)	4 (11.76)
Headache	0 (0.00)	0 (0.00)	3 (8.82)	2 (5.88)
Gastroenteritis	0 (0.00)	3 (8.82)	0 (0.00)	0 (0.00)
Diarrhoea	0 (0.00)	0 (0.00)	0 (0.00)	3 (8.82)
Cough	1 (1.92)	2 (5.88)	0 (0.00)	0 (0.00)
Dyspnoea	2 (3.85)	0 (0.00)	0 (0.00)	0 (0.00)

MedRA version 18.1, AE adverse event

Table 5 AUEC0-24 for plasma cortisol on Day 14

Dose	n	Geometric mean ratio to baseline compared to placebo (95% CI)	*p*-value
placebo	14		
58 µg	9	1.03 (0.90-1.19)	0.6342
250 µg	9	1.02 (0.88-1.18)	0.7620
800 µg	9	0.91 (0.79-1.05)	0.2008

AUEC 0-24 Area under plasma concentration time curve from time zero to 24 hours after dose administration, CI confidence Interval

The three-week washout was supported by the pharmacokinetic profile of AZD7594 [25], and glucocorticoid receptor agonist studies which demonstrate both FEV_1 and F_ENO return to baseline levels within 14 to 21 days [20–22]. To limit the potential of any detectable carry-over effect, a baseline stability criterion was included for each period. The results should be interpreted with care since no correction for multiple testing was done for the secondary variables. For many of the secondary endpoints, the 250 µg dose resulted in a lower response than the lowest dose. This is likely a result of variability and a small sample size, and dose-response modeling provides further support to select doses to investigate in the future studies.

Overall, in this study, AZD7594 was safe and well tolerated. The incidence of AEs was similar across treatment groups, the most common AE was nasopharyngitis. While cortisol suppression has been seen at higher doses of AZD7594 [26], only limited cortisol suppression was observed at the highest dose in this study, no significant difference versus placebo was observed. The absence of candidiasis and dysphonia in all patients is encouraging but a longer treatment period is needed to more fully assess the adverse effect profile.

Although the current study met its objective of assessing short term efficacy and safety of AZD7594, a parallel design study over a longer treatment period in broader patient population is needed to adequately assess the minimally efficacious and optimal doses. A novel once daily inhaled non-steroidal glucocorticoid modulator with an improved therapeutic risk-benefit profile would be a welcome addition to current asthma therapies, further clinical studies, including comparison to an active ICS comparator, are needed to fully characterize AZD7594.

Conclusions

In this phase 2a study, the first to evaluate clinical efficacy in patients with mild to moderate asthma, once daily inhaled administration of AZD7594, a novel non-steroidal selective GR modulator demonstrates improved lung function as measured by FEV_1 and PEF, a reduction of airway inflammation as evidenced by a reduction in F_ENO and a positive impact on symptoms

and asthma control. AZD7594 was well tolerated with an adverse effect profile similar to placebo. This study supports that a once daily inhaled non-steroidal SGRM is effective and well tolerated and may provide an alternative to ICS for patients in the future. Further clinical work is required to fully characterize the clinical profile and compare to currently available ICS.

Additional file

Additional file 1: Supplementary appendix. (PDF 175 kb)

Abbreviations
ACQ-5: Asthma Control Questionnaire-5; AE: Adverse Effect; AMP: Adenosine monophosphate; ATS: American Thoracic Society; AUC(0-24): Area under the plasma concentration-time curve from time zero to 24 hours after dose administration; AUEC(0-24): Area under the effect curve from time zero to 24 hours after dose administration; BID: Twice daily; CI: Confidence interval; Cmax: Observed maximum plasma concentration; Cmax, ss: Observed maximum plasma concentration at steady-state; Cmax, ss/D: Dose-normalized observed maximum plasma concentration at steadystate; Cmax/D: Dose-normalized observed maximum plasma concentration; CV%: Geometric coefficient of variation; DPI: Dry powder inhaler; [ED]50: Dose that produces the desired therapeutic effect in 50% of the patients; Emax: Maximum effect; ePEF: Evening peak expiratory flow; FAS: Full Analysis Set; F_ENO: Fractional exhaled nitric oxide; FEV_1: Forced expiratory volume in 1 second; GINA: Global Initiative for Asthma; GR: Glucocorticoid receptor; HPA: Hypothalamic-pituitary-adrenal; ICS: Inhaled corticosteroids; IEC: Independent Ethics Committee; IRB: Institutional Review Board; ITT: Intention to treat; L: Liter; LABA: Long-acting β-2 agonist; mPEF: Morning peak expiratory flow; PEF: Peak expiratory flow; PK: Pharmacokinetic; ppb: Parts per billion; SABA: Short-acting β-2 agonist; SAE: Serious Adverse Effect; SAF: Safety Analysis Set; SD: Standard deviation; SGRM: Selective glucocorticoid receptor modulator

Availability of data and materials
Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Authors' contributions
AA, HS, YC, HF, MB, RF, JB, HJ provided input into the study design, AA, HS, YC, HF, MB, RF, JB, UWH, HJ contributed to the analysis and interpretation. Study conduct and data collection was performed by AA, RF, JB, HF. HS contributed to statistical analysis. UWH conducted the dose-response post hoc analysis. MB, AA, HS and YC wrote the first draft of the manuscript. All authors contributed to the revision and approved the final version before submission.

Ethics approval and consent to participate
The study protocol was approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) at each center. The study

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(NCT02479412) was done in accordance with the Declaration of Helsinki, the International Council of Harmonisation guidelines for good clinical practice, and applicable regulatory requirements. All patients provided written informed consent before being enrolled in the study.

Consent for publication
Not applicable.

Competing interests
MB, YC, HF, UWH are current employees of AstraZeneca, AA and HS are former employees of AstraZeneca and own stock, and HJ is a former employee of AstraZeneca and does not own stock. JB has received consultancy and speaking fees from AstraZeneca RF is an employee of PAREXEL. AstraZeneca provided funding to PAREXEL for the conduct of this study.

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References
1. GINA 2018 Global strategy for asthma management and prevention. Updated 2018. Available from http://www.ginasthma.org/ accessed 29 Mar 2018.
2. Noonan M, Rosenwasser LJ, Martin P, O'Brien CD, O'Dowd L. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in adults and adolescents with moderate to severe asthma. A randomized clinical trial. Drugs. 2006;66(17):2235–54.
3. Lotvall J, Bleeker ER, Busse WW, O'Byrne PM, Woodcock A, Kerwin EM, et al. Efficacy and safety of fluticasone Furoate 100μg once-daily in patients with persistent asthma: a 24-week placebo and active controlled randomized trial. Respir Med. 2014;108:41–9.
4. Nathan RA, Nolte H, Pearlman DS. Twenty-six-week efficacy and safety study of mometasone Furoate / formoterol 200/10μg combination treatment in patients with persistent asthma previously receiving medium-dose inhaled corticosteroids. Allergy and Asthma Proc. 2010;31(4):269–79.
5. Kelly W, Sternberg A, Lescher R, Fuhlbrigge A, Willaims P, Zeiger R, et al. And the CAMP research group. Effect of inhaled glucocorticoids in childhood on adult height. N Engl J Med. 2012;367(10):904–12.
6. Pruteanu AI, Chauhan BF, Zhang L, Prietsch S, Ducharme FM. ICS in children with persistent asthma: dose response effects on growth. Cochrane Database Sys Rev, 2014 issue 7.
7. Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med. 2000;343(26):1902–9.
8. Ferguson G, Calverley P, Anderson J, Jenkins C, Jones P, Willits L, et al. Prevalence and progression of osteoporosis in patients with COPD. Results from the TORCH study. CHEST. 2009;136:1456–65.
9. Christensson C, Thoren A, Lindberg B. Safety of inhaled budesonide. Drug Saf. 2008;31(11):965–88.
10. Pandya D, Puttanna A, Balagopal V. Systemic effects of inhaled corticosteroids: an overview. Open Respir Med J. 2014;8:59–65.
11. Westergaard CG, Porsbjerg C, Baker V. Emerging corticosteroid agonists for the treatment of asthma. Expert Opinion Emerging Drugs. 2015;20(4):653–62.
12. Karrman Mardh C, Russel W, Gustavsson M, Kurian N, Jansson A, Smailagic A, Edman K. A novel inhaled non-steroidal modulator of inflammation for the control of asthma; AZD7594. Am J Respir Crit Care Med. 2016;193:A1329.
13. Brown M, Fuhr R, Su H, Chen Y, Forsman H, Jackson H, Aggarwal A. A randomized trial of AZD7594 a novel non-steroidal anti-inflammatory drug in asthma patients. Presentation September 10, 2017 European Respiratory Society 2017, Milan Italy.
14. Akkermans R; Annual Congress of the European Respiratory Society; Lancet Respir Med 2017, 2017, S2213–S2600(17)30374.
15. Dweik R, Boggs P, Erzurum S, Irvin C, Leigh M, Lundberg J, et al. An official ATS clinical practice guideline: interpretation of FeNO for clinical applications. Am J Respir Crit Care Med. 2011;184:602–15.
16. Donohue J, Jain N. Exhaled nitric oxide to predict corticosteroid responsiveness and reduce asthma exacerbation rates. Respir Med. 2013;107:943–52.
17. Masoli M, Holt S, Weatherall M, Beasley R. Dose-response relationship of inhaled budesonide in adult asthma: a meta-analysis. Eur Respir J. 2004;23:552–8.
18. Holt S, Suder A, Weatherall M, Cheng S, Shirtcliffe P, Beasley R. Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis. Br Med J. 2001;323:1–8.
19. Peters SP, Kunselman SJ, Icitovic N, Moore W, Pascual R, Ameredes B, et al. For the NHLBI asthma clinical research network. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med. 2010;363:1715–26.
20. Gershman N, Wong H, Liu J, Fahy J. Low and high-dose fluticasone propionate in asthma; effects during and after treatment. Eur Respir J. 2000;15:11–8.
21. Phillips K, Oborne J, Lewis S, Harrison TW, Tattersfield AE. Time course of action of two inhaled corticosteroids, fluticasone propionate and budesonide. Thorax. 2004;59:26–30.
22. van Rensen E, Straathof K, Veselic-Charvat M, Zwinderman A, Bel E, Sterk P. Effect of inhaled steroids on airway hyperresponsiveness, sputum eosinophils, and exhaled nitric oxide levels in patients with asthma. Thorax. 1999;54:403–8.
23. Reid D, Johns D, Feltis B, Ward C, Walters E. Exhaled nitric oxide continues to reflect airway hyperresponsiveness and disease activity in inhaled corticosteroid-treated adult asthmatic patients. Respirology. 2003;8:479–86.
24. Reddel HK, Marks GB, Jenkins CR. When can personal best peak flow be determined for asthma action plans? Thorax. 2004;59:922–4.
25. Chen Y, Prothon S, Su H, Brown MN, Forsman H, Jackson H, et al. Pharmacokinetics (PK) of a single dose of AZD7594 administered intravenously (IV), orally and inhaled via two dry powder inhalers (DPI) and a pressurized metered-dose inhaler (pMDI) European Respiratory Society, Milan poster presentation September 10, 2017 A531.
26. Chen Y, Prothon S, Aurivillius M, Eriksson U, Aggarwal A. Safety, tolerability, pharmacokinetics, and pharmacodynamics of AZD7594 after single and multiple ascending inhaled doses in healthy male volunteers. Am Soc Clinical Pharmacol and Ther. 2016;99(S1):S5–S107 Abstract PI-033.