

Dose-response effects of TPI ASM8 in asthmatics after allergen

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allergen challenge; antisense oligonucleotides; asthma; beta subunit of IL-3, IL-5, and GM-CSF receptors; CCR3 receptor.

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Abstract

Background: TPI ASM8 contains two modified antisense oligonucleotides (AON) targeting the beta subunit (β_c) of the IL-3, IL-5, GM-CSF receptors and the chemokine receptor CCR3. A previous study suggested that TPI ASM8 had broader effects than just inhibition of eosinophils in asthmatics.

Objective: We assessed whether TPI ASM8 caused a dose-dependent attenuation in the inflammatory and physiological changes after inhaled allergen challenge (AIC).

Methods: This single-center, open-label, stepwise-ascending dose study was conducted in fourteen stable, mild allergic asthmatics. Following placebo AIC, subjects underwent AIC after 4 days treatment with 1, 2, and 4 mg BID and finally 8 mg once daily (OD) of TPI ASM8, inhaled via the I-Neb™ nebuliser. Treatments were separated by 2–3-week washout periods.

Results: TPI ASM8 was safe and well tolerated at all doses. TPI ASM8 8 mg OD reduced eosinophils in sputum after AIC (by 60.9% at 7 h and 68.4% at 24 h post-AIC, $P = 0.016$ and $P = 0.007$, respectively). Additionally, TPI ASM8 8 mg OD significantly attenuated the early and late airway responses as shown by the reduction in the area under the curve by 45% ($P = 0.016$) and 59%, ($P = 0.0015$), respectively, the increase in eosinophil cationic protein (ECP) by up to 57% ($P = 0.021$), and airway responsiveness to methacholine by more than 1 doubling dose ($P = 0.012$). A dose-response relationship was noted, and efficacy was maintained with once per day administration.

Conclusions: TPI ASM8 attenuated a broad range of inflammatory and physiological changes after AIC, suggesting that CCR3, IL-3, and GM-CSF also are important targets for the management of asthma.

Asthma is characterized by airway inflammation, reversible airway obstruction, and airway hyper-responsiveness (1). Airway inflammation is believed to be a major contributor to the physiological changes and remodeling in asthma (1–3). Eosinophils, basophils, and mast cells are increased in the

sputum and airways of patients with asthma. Whether eosinophils are capable of causing airway obstruction and hyper-responsiveness has been the subject of debate for the last 10 years (4). Indeed, although anti-IL-5 antibody has impressive inhibitory effects on eosinophils and decreases exacerbations in severe asthma, it exhibits small effects on airway obstruction and no effects on airway hyper-responsiveness in patients with asthma (4–7).

TPI ASM8 is a drug product containing two antisense oligonucleotides (ODN): TOP004 directed against the human beta subunit of IL-3, IL-5, and GM-CSF receptors (β_c) and TOP005 directed against the human chemokine receptor CCR3. ODNs directed against CCR3 and β_c have been shown to inhibit mRNA and protein expression and also

Abbreviations:

β_c , beta subunit of IL-3, IL-5, and GM-CSF receptors; AIC, allergen challenge; EAR, early airway response; LAR, late airway response; ODN, antisense oligonucleotide; ECP, eosinophil cationic protein; AUC, area under the curve; FEV₁, forced expiratory volume in one-second; PC₂₀, provocative concentration of methacholine causing a 20% fall in FEV₁; AE, adverse event; BID, twice daily; OD, once daily.

attenuate antigen-induced eosinophil influx into the airways of rats and airway hyper-responsiveness (8–11). In asthmatics, TPI ASM8 has been shown to decrease eosinophil influx into the sputum after allergen challenge (AIC), significantly affect the early airway response (EAR), and have a trend for effects on the late airway response (LAR) (12). While anti-IL-5 antibody similarly decreases sputum eosinophils, it has no effects on the EAR and LAR after AIC (13), suggesting that the physiological effects reported with TPI ASM8 are because of the broader effects. The current study was performed to assess whether TPI ASM8 caused a dose-dependent attenuation in the inflammatory cell influx and physiological changes after AIC.

Methods

Subjects

Subjects were nonsmoking, steroid-naïve, eight men/six women, aged 18–59 years old (Table 1), with mild to moderate, stable, allergic asthma as defined by American

Thoracic Society (ATS/ERS 2005) criteria, and whose baseline forced expiratory volume in one-second (FEV₁) was $\geq 70\%$ of predicted value, methacholine PC₂₀ (the concentration of methacholine causing a 20% fall in FEV₁) ≤ 16 mg/ml and had a positive skin-prick test to at least one common aeroallergen. During a screening allergen challenge, subjects exhibited an EAR ($\geq 20\%$ fall in FEV₁ 0–2 h post-AIC) and LAR ($\geq 15\%$ fall in FEV₁ 3–7 h post-AIC) with a sputum eosinophil level $> 6\%$ at either 7 h or 24 h post-AIC. Subjects used infrequent inhaled beta₂-agonist for the treatment of asthma. A total of 14 subjects were enrolled; 12 subjects completed the study protocol as two subjects were withdrawn because of unstable asthma between dose 1 and 2 of TPI ASM8.

Study design

This trial was a single-center, open-label, stepwise, dose-profiling study to evaluate the efficacy and safety of four dose regimens [1 mg twice daily (BID), 2 mg BID, 4 mg BID, and 8 mg once daily (OD)] of inhaled (*via* an I-neb™ nebuliser, Phillips) TPI ASM8 in subjects with mild allergic asthma (Fig. 1). The study was approved by the ethics research board, and signed informed consent was obtained from subjects. During screening (Fig. 1), saline was administered to subjects as a placebo, and AIC were conducted. Those subjects who fulfilled the inclusion/exclusion criteria then underwent four treatment periods with TPI ASM8 (4 mg/ml, Pyramid Laboratories Inc, Costa Mesa, CA, USA), each consisting of four consecutive days of dosing. The timeline for sputum and methacholine and allergen challenge is described in Fig. 1. Blood samples were collected on day 1, predosing, 0.5 h and 2.5 h postdosing and on day 4 predosing and postdosing at 0.5 h, 2.5 h, and 24 h for pharmacokinetic assessment. Between each dose escalation were 2–3 weeks of washout periods.

Table 1 Demographics and baseline characteristics

Number patients enrolled	14
Age (years $\pm$ SD)	30.8 $\pm$ 12.5
Females/males (#)	6/8
Baseline FEV ₁ (% of predicted value $\pm$ SD)	91.4 $\pm$ 8.9
Methacholine PC ₂₀ geometric mean, mg/ml (range)	3.2, (0.2–19.5)
Screening early asthmatic response (% fall in FEV ₁ $\pm$ SD)	32.6 $\pm$ 6.9
Screening late asthmatic response (% fall in FEV ₁ $\pm$ SD)	22.9 $\pm$ 6.0

FEV₁, forced expiratory volume in one-second.

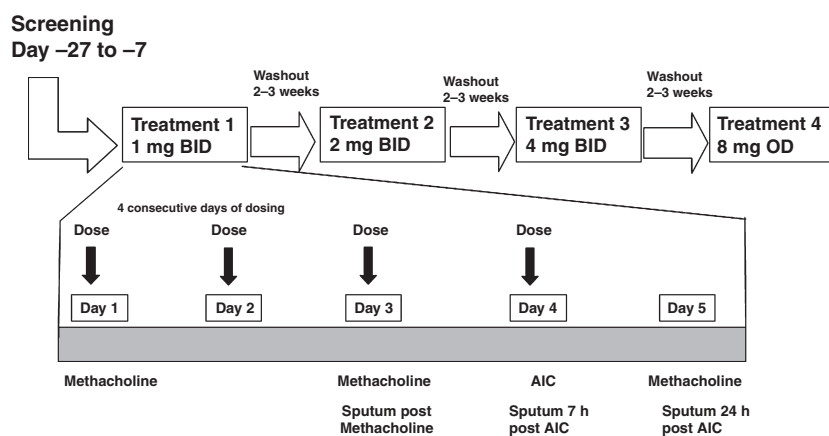


Figure 1 Open-label study, stepwise, dose-profiling study schematic to evaluate the efficacy and safety of four dose regimens of inhaled TPI ASM8 compared with screening (placebo), in subjects

with mild allergic asthma (Clinicaltrials.gov identifier NCT00822861). BID, twice daily dosing; OD, once daily dosing; AIC, allergen inhalation challenge.

TPI ASM8 inhalation

TPI ASM8 is a 1 : 1 (w : w) mixture in saline of modified phosphorothioate ODN; TOP004 directed against the β_c of IL-3, IL-5, and GM-CSF receptors with the following sequence: 5'-GGGTCTGCDGCGGGDTGGT and TOP005 directed against the chemokine receptor CCR3 with the following sequence: 5'-GTTDCTDCTTCCDCCTGCCTG, where D = 2-amino-2'-deoxyadenosine.

Inhalation challenges

Methacholine challenge was performed as described by Cockcroft (14, 15), using tidal breathing, from a Wright nebulizer, with the test terminated when a fall in FEV₁ of 20% of the baseline value occurred. Allergen inhalation challenge (AIC) was performed as described (16, 17), and doubling concentrations of allergen were given until a $\geq 20\%$ fall in FEV₁ at 10 min postallergen was reached. The FEV₁ was then measured at regular intervals until 7 h after allergen inhalation. The same dose of allergen was inhaled for the screening (placebo) and the four TPI ASM8 treatment periods.

Sputum analyses

Sputum was induced and processed (18), and the total cell count (number of cells/gram sputum) was determined using a Neubauer hemocytometer chamber (Hausser Scientific, Blue Bell, PA, USA). Cells were prepared on glass slides, stained with either Diff Quik (American Scientific Products, McGaw Park, IL, USA) for differential counts or toluidine blue for basophil quantification, and then enumerated blindly. Total RNA was extracted from sputum cells, processed (12), and CCR3 and β_c expressions reported normalized to the expres-

sion of house-keeping genes. Eosinophil cationic protein (ECP) was detected in sputum supernatant using the Mescup ECP ELISA kit from MBL (Naka-ku, Nagoya, Japan). Quantitation of TPI ASM8 was performed using a hybridization/ligation ELISA (HL-ELISA) assay (12).

Statistical analyses

Statistical analysis was performed to assess treatment effects on the per-protocol population for all variables between 8 mg OD of TPI ASM8 and screening (placebo). Two-sided paired tests or the nonparametric equivalent [Wilcoxon paired signed-rank test (2 sided)] were employed with statistical significance defined as $P < 0.05$.

Results

Sputum inflammation

TPI ASM8 significantly inhibited sputum eosinophil increase in response to AIC (Fig. 2). The mean sputum eosinophil levels (%) showed median reductions of 60.9% ($P = 0.016$) and 68.4% ($P = 0.007$) at 7 h and 24 h post-AIC, respectively, with 8 mg OD of TPI ASM8. Similar results were also found for absolute numbers of sputum eosinophils ($P < 0.05$, Fig. 2). At 7 h following AIC, there was a trend for the % of sputum basophils to decrease with TPI ASM8 (86% inhibition with 8 mg OD, $P = \text{N.S.}$)

Baseline sputum ECP levels were significantly reduced with TPI ASM8 from 92.1 ± 31.2 ng/ml at screening (placebo), to 19.9 ± 5.1 ng/ml at a dose of 8 mg OD on day 3, prior to AIC (Fig. 2). TPI ASM8 progressively reduced sputum ECP levels after AIC with maximal effects at 8 mg OD (57% inhibition, $P = 0.021$) 24 h post-AIC (Fig. 2).

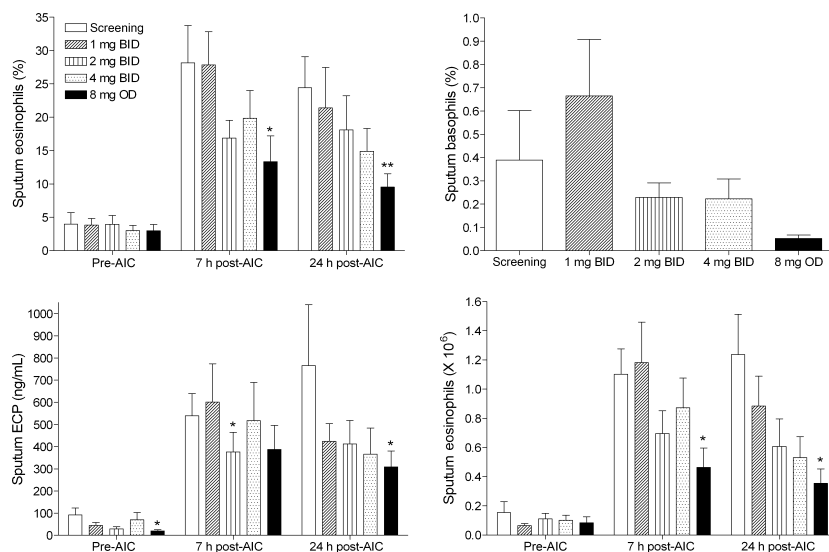


Figure 2 Pre- and postallergen challenge sputum % eosinophils, eosinophil cationic protein (ECP) concentration, % basophils, and absolute numbers of eosinophils in response to increasing doses of

TPI ASM8. Data are shown as mean $\pm$ SEM with statistical difference between levels at screening (placebo) and indicated doses denoted by * $P < 0.05$, ** $P < 0.01$.

Total number of sputum cells pre-AIC were significantly reduced by TPI ASM8 (1 mg BID, 2 mg BID and 8 mg OD, $P < 0.05$, Table 2). Variability among subjects at the 4-mg BID dose led to an observed lack of effect for statistical significance but the overall changes are in line with a dose response. Furthermore, pre-AIC numbers of neutrophils were decreased at 1 mg BID and 2 mg BID ($P < 0.05$, Table 2). Post-AIC, neither percent nor total numbers of macrophages, neutrophils, and lymphocytes were affected by TPI ASM8 at any of the doses studied (macrophages and neutrophils Table 2, lymphocyte data not shown).

Allergen-induced early and late phase airway response

The maximum percent fall in FEV₁ during the EAR (Fig. 3) was significantly attenuated with 8 mg OD of TPI ASM8 from a level at screening of $32.6 \pm 1.9\%$ to $21.7 \pm 3.6\%$, ($P = 0.03$). The maximum percent fall in FEV₁ during the LAR at screening was significantly attenuated from a level at screening of $22.8 \pm 1.6\%$ (Fig. 3) to $12.9 \pm 1.8\%$ ($P = 0.0024$) and $10.7 \pm 2.1\%$ ($P = 0.0024$) at 4 mg BID and 8 mg OD, respectively. TPI ASM8 (8 mg OD) attenuated the area under the FEV₁ curve (Fig. 3) by 45% and 59% for EAR and LAR, respectively ($P < 0.05$).

Airway hyper-responsiveness

During screening, methacholine PC₂₀ fell from 3.2 mg/ml pre-AIC to 1.1 mg/ml at 24 h post-AIC. This level was unchanged when subjects returned for the first dose of TPI

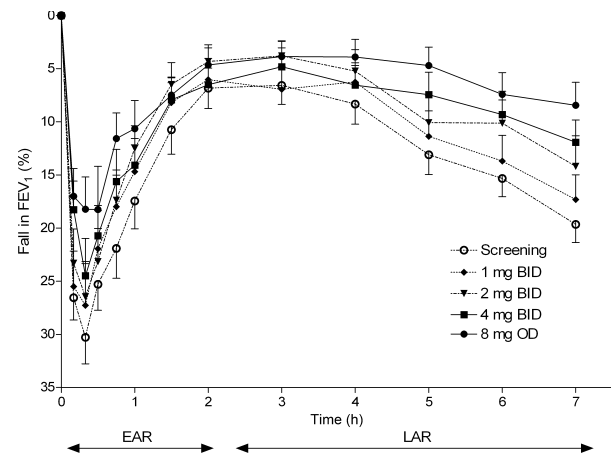


Figure 3 Allergen-induced % fall in mean forced expiratory volume in one-second (FEV₁) measured during the early (0–2 h) and late (3–7 h) airway responses at screening (placebo treatment) and with increasing doses of TPI ASM8. Data are shown as mean $\pm$ SEM.

ASM8 (2.6 mg/ml), but, when subjects returned after each washout period, methacholine PC₂₀ tended to improve (4.9 mg/ml prior to 8 mg OD, Fig. 4). Following 2 days treatment with TPI ASM8 at 2 mg BID and 8 mg OD, the pre-AIC methacholine PC₂₀ significantly increased to 6.6 mg/ml and 7.6 mg/ml, respectively ($P < 0.05$, Fig. 4). The methacholine PC₂₀ measured 24 h post-AIC was significantly increased to 2.3 mg/ml, 2.9 mg/ml, and 3.5 mg/ml at 2 mg

Table 2 Sputum cells pre and postallergen challenge (7 and 24 h)

		Screening	Dose 1 mg BID	Dose 2 mg BID	Dose 4 mg BID	Dose 8 mg OD
Pre-AIC		<i>n</i> = 14	<i>n</i> = 14	<i>n</i> = 12	<i>n</i> = 12	<i>n</i> = 12
Total cells	Cells ($\times 10^6$ /g)	4.0 $\pm$ 0.6	2.0 $\pm$ 0.3*	2.8 $\pm$ 0.4*	4.4 $\pm$ 1.9	2.5 $\pm$ 0.4*
Macrophages	%	51.7 $\pm$ 7.5	68.6 $\pm$ 4.8	64.7 $\pm$ 5.87	52.7 $\pm$ 7.6	63.9 $\pm$ 7.2
	Cells ($\times 10^6$ /g)	1.7 $\pm$ 0.3	1.3 $\pm$ 0.2	1.7 $\pm$ 0.3	1.4 $\pm$ 0.3	1.4 $\pm$ 0.2
Neutrophils	%	43.3 $\pm$ 7.7	27.1 $\pm$ 4.6	28.9 $\pm$ 5.8	43.6 $\pm$ 7.8	32.4 $\pm$ 6.60
	Cells ($\times 10^6$ /g)	2.1 $\pm$ 0.6	0.6 $\pm$ 0.2*	0.9 $\pm$ 0.2*	2.9 $\pm$ 1.8	1.1 $\pm$ 0.4
7 h post-AIC		<i>n</i> = 14	<i>n</i> = 14	<i>n</i> = 12	<i>n</i> = 12	<i>n</i> = 12
Total cells	Cells ($\times 10^6$ /g)	4.5 $\pm$ 0.6	4.8 $\pm$ 0.9	4.1 $\pm$ 1.1	5.6 $\pm$ 1.8	4.1 $\pm$ 0.9
Macrophages	%	26.9 $\pm$ 4.4	30.4 $\pm$ 5.8	32.3 $\pm$ 4.0†	31.9 $\pm$ 7.0	35.4 $\pm$ 7.5
	Cells ($\times 10^6$ /g)	1.0 $\pm$ 0.2	1.3 $\pm$ 0.3	1.1 $\pm$ 0.2†	1.2 $\pm$ 0.2	1.1 $\pm$ 0.2
Neutrophils	%	44.7 $\pm$ 6.2	41.4 $\pm$ 5.0	51.8 $\pm$ 4.6†	48.0 $\pm$ 7.1	50.9 $\pm$ 7.4
	Cells ($\times 10^6$ /g)	2.3 $\pm$ 0.6	2.3 $\pm$ 0.6	2.6 $\pm$ 1.0†	3.5 $\pm$ 1.7	2.4 $\pm$ 0.9
24 h post-AIC		<i>n</i> = 14	<i>n</i> = 13	<i>n</i> = 12	<i>n</i> = 12	<i>n</i> = 12
Total cells	Cells ($\times 10^6$ /g)	5.3 $\pm$ 0.8	5.0 $\pm$ 0.7	4.4 $\pm$ 1.1	3.8 $\pm$ 0.8	3.7 $\pm$ 0.7
Macrophages	%	31.4 $\pm$ 3.9	33.1 $\pm$ 6.5	35.0 $\pm$ 5.8	38.0 $\pm$ 6.0	43.8 $\pm$ 5.3
	Cells ($\times 10^6$ /g)	1.6 $\pm$ 0.4	1.5 $\pm$ 0.3	1.1 $\pm$ 0.1	1.1 $\pm$ 0.2	1.4 $\pm$ 0.3
Neutrophils	%	43.9 $\pm$ 5.8	44.8 $\pm$ 8.6	46.4 $\pm$ 8.2	46.5 $\pm$ 7.2	46.4 $\pm$ 5.6
	Cells ($\times 10^6$ /g)	2.4 $\pm$ 0.5	2.7 $\pm$ 0.8	2.7 $\pm$ 1.1	2.1 $\pm$ 0.6	1.9 $\pm$ 0.5

BID, twice daily; OD, once daily.

Data are shown as mean $\pm$ SE.

*Statistical difference compared to respective value at screening.

†*n* = 11 for these set of values.

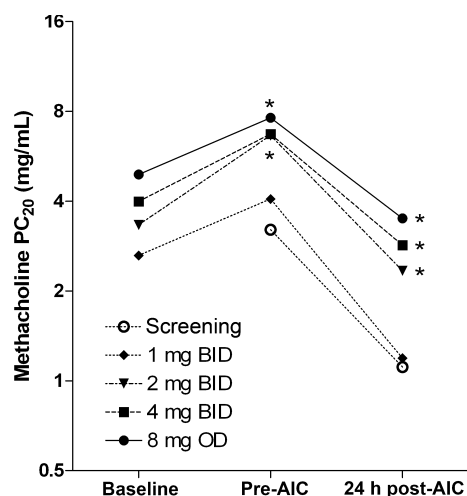


Figure 4 Methacholine PC₂₀ pre- and 24 h. post-AIC during screening (placebo period) and at baseline before drug administration, pre (day 3) and post-AIC with increasing doses of TPI ASM8. Data are shown as geometric means on log 2 axis. Statistical analyses were performed on log 2 transformed data with differences between levels at screening (placebo) denoted by * $P < 0.05$.

BID, 4 mg BID, and 8 mg OD, respectively ($P < 0.05$, Fig. 4).

mRNA expression of β_c and CCR3 in sputum cells

The mRNA levels of both β_c and CCR3 were increased 7 h post-AIC and fell by 24 h post-AIC. This pattern of increase following 7 h post-AIC was reduced with TPI ASM8 (8 mg OD) for a 49% and 42% decrease in normalized values of CCR3/B2M and β_c /B2M, respectively (data not shown). These reductions were not statistically significant because of a high degree of variation between subjects.

TPI ASM8 pharmacokinetics in sputum and plasma

Pharmacokinetic measurements were analyzed for the two highest drug doses only. TOP004 and TOP005 were not measurable in the plasma. In sputum, quantification of after dosing with 4 mg BID was 60.9 ± 15.7 ng/ml at 7 h and 48.2 ± 8.9 ng/ml after 24 h with similar levels of TOP005 levels at 63.9 ± 15.1 ng/ml after 7 h and 55.5 ± 9.7 ng/ml after 24 h. For 8 mg OD, 7 h after dosing TOP004 and TOP005 levels were similar at 142.7 ± 37.6 ng/ml and 149.4 ± 39.1 ng/ml, respectively. At 24 h after dosing, levels of both TOP004 and TOP005 fell as this dose was administered only once daily.

Safety

There were no serious adverse events (AE) in this study. None of the 23 nonserious AEs reported during the study were considered to be definitely drug related, and only two

were deemed to be possibly drug related (shortness of breath during 8 mg OD and chest tightness during 2 mg BID). The incidence of reported AEs were three AEs during screening, six AEs by four subjects at 1 mg BID, seven AEs by four subjects at 2 mg BID, one AE at 4 mg BID, and six AEs by four subjects at 8 mg OD. The most frequently reported AE was headache on six occasions.

Hematology parameters did not fluctuate during the study for most subjects. Mild hematuria was observed in four subjects at screening and remained unchanged throughout the study except for one additional mild and nonclinically significant case at a dose of 8 mg OD. Complement pathway activation (Bb split product measurements) remained within normal ranges during the study. Baseline lung function as measured by FEV₁ or DLCo was not affected by TPI ASM8.

Discussion

Inhibition of airway inflammation is believed to be one of the most important therapeutic goals in asthma (1, 3) as inflammation is present in the airways of most patients with asthma, and corticosteroids are the most effective agents in these patients (19). As corticosteroids possess potent immunosuppressive and toxic effects, specific inhibitors of airway inflammation with the potential for less toxicity have been studied (20), although those targeting only one mediator or one cell type have had limited or no success.

Over the last 15 years, much attention has been paid to allergic airways inflammation and in particular, to the role of eosinophils. The relatively limited efficacy obtained with anti-IL-5 antibodies in human asthma (4–7, 13, 21) has curtailed enthusiasm for eosinophil-specific drugs as therapies for asthma. In the AIC model, anti-IL-5 antibodies effectively inhibit eosinophil influx yet have no significant effects on the EAR, LAR, and airway hyper-responsiveness in primates (22) and in humans (13). In contrast, TPI ASM8 (three daily doses) significantly attenuated the EAR with a trend for an effect on the LAR after AIC (12). The current exploratory dose-profiling study was designed to better characterize the effects of TPI ASM8 on eosinophils, EAR, LAR, and airway hyper-responsiveness in asthmatic subjects after AIC.

TPI ASM8 had significant inhibitory effects on total eosinophil influx in sputum and ECP, a marker of eosinophil activation and degranulation after AIC. Interestingly, the decrease in sputum ECP levels (74%, day 3) after the second dose of TPI ASM8 suggests that the inhibitory effects of TPI ASM8 on baseline eosinophil mediators were rapid and prior to AIC.

TPI ASM8 significantly affected both the EAR and the LAR vs screening (placebo). Similar improvements were noted in airway hyper-responsiveness prior to and after methacholine, the inhibition being more than one log dose. Anti-IL-5 antibody had no effects on these parameters in the same model, suggesting that cells other than eosinophils are also important in asthma. β_c has been shown to be involved in the regulation of the lymphocyte TH2 response (23, 24). IL-3 affects basophil differentiation and mast cell activation and survival (23, 25, 26) and in the presence of IgE, induces mast

cell survival in an autocrine fashion even in the absence of allergen (25). Mast cells release mediators that affect airway smooth muscle contractile responses (27, 28). GM-CSF acts on inflammatory cells including neutrophils, macrophages, and dendritic cells (23). Inhibition of GM-CSF may prevent the production of dendritic cells that are involved in the differentiation and persistence of allergic inflammation (29).

The second ODN in TPI ASM8, TOP005, is directed against CCR3, a receptor present on eosinophils, basophils, mast cells, TH2 cells, and epithelial cells (30). The ligands for CCR3 are increased in lung lavage of asthmatics and are involved in the chemotaxis of eosinophils (31). CCR3 is also involved in the differentiation of eosinophils from progenitors, an event that also occurs within the lungs (32, 33). Pre-treatment with ligands for β_c has been shown to increase the response of eosinophil progenitors and other cells to ligands for CCR3 (33, 34).

TPI ASM8 was designed to be nonimmunostimulatory, and this has been confirmed *in vitro* in mouse and human cell lines where TPI ASM8 did not elicit cytokine release (unpublished observations). We do not believe that the effects of TPI ASM8 were attributed to immunostimulation, especially as ODNs specifically designed to be immunostimulatory in humans did not affect eosinophil influx, the EAR, or the LAR post-AIC when administered at a dose of 36 mg per week by nebulisation in allergic asthmatics (35).

The trend for an improved baseline PC₂₀ to methacholine each time the subjects returned for a higher dose of TPI ASM8 would suggest a carry-over effect of TPI ASM8 on airway responsiveness between the stepwise dose escalations. As washout periods of sufficient duration were included between each dose escalation, this prolonged effect may result from inhibition of the gene targets, suggesting an advantage of TPI ASM8 with long-term administration.

TPI ASM8 appeared to be safe at all the doses tested. Assessment of sputum cells after 3 days of TPI ASM8

found a significant decrease in total cells and a trend for lower neutrophils, indicating that TPI ASM8 did not induce cellular infiltration. The absence of negative effects on FEV₁ and DLCO also shows that TPI ASM8 is well tolerated.

We conclude that TPI ASM8 inhibits eosinophil recruitment/accumulation with effects on ECP, EAR, LAR, and airway hyper-responsiveness post-AIC. The effects are dose dependent and were achieved with once daily dosing. As inhibition of IL-5 affects only eosinophilia in the AIC model whereas TPI ASM8 also had significant effects on the physiological responses, our results suggest that CCR3, IL-3, and GM-CSF are important targets for the management of asthma.

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Author's contributions

Study was designed by GG, RP, MPB, and PMR. Study was performed, and data collated by GG, HC, RW, MM, DC, and KK. Laboratory and data analyses performed by GG, RS, JG, HD, RP, MPB, and PMR. Manuscript written by GG, RS, and PMR.

Conflict of interest statement

The study was performed at McMaster University where GG, HC, RW, MM, and KK are employees. GG has received funding from Pharmaxis Ltd for conference attendance. RP, RS, DC, JG, HD, MPB are employees of Topigen Pharmaceuticals Inc, a member of the Pharmaxis Ltd. Group. PMR is a paid consultant by Pharmaxis Ltd.

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