Safety and pharmacodynamics of intranasal GSK2245035, a TLR7 agonist for allergic rhinitis: A randomized trial

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Summary

Background: Toll-like receptor 7 (TLR7) stimulation in the airways may reduce responses to aeroallergens by induction of type 1 interferons (IFNs). GSK2245035 is a novel selective TLR7 agonist in pharmaceutical development.

Objective: Assessment of safety, pharmacodynamics and nasal allergic reactivity following repeated weekly intranasal (i.n.) GSK2245035.

Methods: This randomized, double-blind, placebo-controlled study (TL7116958) was conducted over two pollen seasons (2013-2014) and follow-up study (204509) conducted 1 year later. Participants with allergic rhinitis (n=42) were randomized to receive eight weekly doses of i.n. GSK2245035 (20 ng [2014 Cohort: n=14] or 80 ng [2013 Cohort; n=14]) or placebo (n=14). Adverse events (AEs) including cytokine release syndrome AEs (CytoRS-AEs) and nasal symptoms were assessed. Nasal and serum IFN-inducible protein 10 (IP-10) were measured after doses 1 and 8, then 1 (follow-up visit [FUV] 1) and 3 (FUV2) weeks after final dose. Nasal allergen challenges (NACs) and allergic biomarker assessment (nasal, serum) were conducted at baseline, FUV1, FUV2 and at a FUV 1 year after final dose (FUV3; 2014 Cohort only). A Bayesian framework enabled probability statements for mean effect sizes.

Results: GSK2245035 induced CytoRS-AEs (most commonly headache, median duration <1 day) in 93% of participants at 80 ng, while AE incidence at 20 ng was similar to placebo. There was no evidence of nasal inflammation. Dose-related increases in nasal and serum IP-10 were observed 24 hours after doses 1 and 8 (>95% certainty). Both doses showed a trend in reducing total nasal symptom score 15 minutes post-NAC at FUV1 and FUV2, but there was no reduction evident at FUV3. Nasal levels of selected allergic biomarkers demonstrated trends for reductions at FUV1, FUV2 and FUV3.

Conclusions and clinical relevance: Weekly i.n. GSK2245035 20 ng was well tolerated and reduced allergic reactivity to nasal challenge for 3 weeks post-treatment.

Keywords
allergic rhinitis, biomarkers, immunomodulation, nasal allergen challenge, safety, toll-like receptor 7
1 | INTRODUCTION

The immunoenvironment of the airways plays a critical role in host responses to aeroallergens. Induction of aberrant Th2 responsiveness drives respiratory allergy and asthma in susceptible individuals, whereas protection from allergy is associated with Th1/T regulatory responses. Therapeutic modulation to rebalance Th2-dominated responses may offer clinical benefit for respiratory allergy and potential for disease remission.

Toll-like receptors (TLRs) are considered the gatekeepers of the immune system. They recognize potential "danger signals" for the host and trigger immune cascades that elicit the most appropriate type of response to sustain homeostasis and health. Because of this critical role, TLRs have become attractive targets for therapeutic intervention in diseases characterized by dysregulated immunity.7,8 In the context of allergy, there is experimental evidence that stimulation of several of the receptors from the TLR family with synthetic ligands produces Th1-type cytokines that attenuate allergen-specific immunoglobulin (Ig) E production and inflammation in target organs, including the airways. Clinical evidence exists for TLR4 or TLR9 agonists as adjuvants of allergen-specific immunotherapy.11,12 and for TLR7, TLR8 and TLR9 agonists as standalone allergy drug candidates.13-15

Toll-like receptor 7 (natural viral ssRNA) is of particular relevance for respiratory allergies. TLR7 polymorphism has been strongly linked with susceptibility to asthma and other atopic disorders. TLR7 agonists effectively prevent Th2-mediated airway disease in animal models, while they also exhibit a lower pro-inflammatory profile in comparison with other classes of TLR ligands. This is in part due to the relative restriction of TLR7 expression to plasmacytoid dendritic cells (pDCs) resulting in predominantly type 1 interferon (IFN) responses, rather than pro-inflammatory cytokines such as tumour necrosis factor (TNF)-α and interleukin (IL)-12, which are produced by monocytes and myeloid dendritic cells (MDCs) in response to TLR8 agonists. Furthermore, TLR7-triggered type 1 IFN elicits a protective antiviral immune response.

GlaxoSmithKline (GSK) has developed GSK2245035, a highly potent and selective TLR7 agonist. The immunomodulatory potential of GSK2245035 was demonstrated in vitro where it reduced IL-5 and IL-13 and enhanced secretion of IL-10 and IFN-γ, in cultures of peripheral blood mononuclear cells from donors with allergic rhinitis (AR). Pharmacological assessment in healthy volunteers and participants with AR indicated that intranasal (i.n.) administration of GSK2245035 results in a dose-dependent activation of TLR7-mediated signalling in the upper airways. Repeat weekly i.n. administration of 40 and 80 ng for 4 weeks was well tolerated and did not result in amplification or tolerization of the pharmacological response. A key challenge with this compound is finding a therapeutic window that allows the induction of the desired local immunomodulatory effects without associated adverse cytokine-mediated events. In this study, we explore the safety and tolerability and pharmacodynamics (PD) of repeat i.n. weekly dosing with GSK2245035 for 8 weeks, specifically the duration of pharmacological changes. Moreover, we examined the effect of treatment on allergic reactivity triggered by nasal allergen challenge (NAC) to generate hypotheses on the immunomodulatory potential of GSK2245035.

2 | METHODS

2.1 | Study design

Study TL7116958 (NCT01788813) was a randomized, double-blind, placebo-controlled, parallel-group Phase IIa study in participants with AR, with or without mild asthma, carried out at Kingston General Hospital, Kingston, Ontario, Canada. The study was initially designed to evaluate the safety and PD of treatment with GSK2245035 80 ng vs placebo during the 2013 ragweed pollen season (Cohort 1; GSK2245035 [n=14]; placebo [n=7]). However, blind review of the safety data from all participants revealed a high incidence of influenza-like symptoms, possibly related to TLR7-mediated cytokine induction (cytokine release syndrome adverse events [CytoRS-AEs]), prompting the evaluation of a lower GSK2245035 dose. Therefore, the protocol was amended in January 2014 and a second cohort of new participants was included to evaluate the effect of GSK2245035 20 ng vs placebo during the 2014 tree/grass pollen season (Cohort 2; GSK2245035 [n=14]; placebo [n=7]). In both cohorts, the participants had seasonal AR driven by pollen sensitization; for each participant, a screening NAC was performed to confirm key pollen sensitivity (based on participant allergic history); subsequent NACs were performed with the same pollen allergen, at the threshold concentration that resulted in a positive response at the screening challenge (ie a total nasal symptom score [TNSS] ≥ 5, peak nasal inspiratory flow [PNIF] reduction of >30% from baseline). As it was hypothesized that the immunomodulatory effect of GSK2245035 on allergic responsiveness would be magnified with natural allergen exposure in parallel to treatment, the study was conducted during the relevant key pollen season.

Both cohorts underwent a screening period (scheduled during a 90-day window prior to and/or during the season), a treatment period during which participants were randomized 2:1 to receive eight weekly doses of either GSK2245035 or placebo i.n. (dosing visits [DV] 1-8) and an extended follow-up period comprising follow-up visit (FUV) 1 (1 week after final dose) and FUV2 (3 weeks after final dose) where NAC was performed. Participants in Cohort 2 were also eligible to participate in a further FUV (FUV3) approximately 1 year after final dose, which constituted the follow-up study, 204509 (NCT02446613; Figure 1). This follow-up study was performed at the original study site with the same investigator, who remained blinded to the findings and treatment assignment from study TL7116958 (although the sponsor was unblinded to those data).

The randomization schedule was generated by the GSK Clinical Statistics Department (Stevenage, Herts, UK) using validated internal software, RandAll NG. Institutional review board clearance was granted by the Queen’s Health Sciences and Affiliated Hospitals Research Ethics Board (ROMEO/TRAQ numbers: 6007721 [study TL7116958]; 6015437 [study 204509]) in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good
Clinical Practice (GCP). The study was conducted in accordance with ICH GCP and ethical principles as outlined in the Declaration of Helsinki, 2008. Written informed consent was provided by each participant prior to study commencement.

2.2 | Participants

Males or females, aged 18-65 years, in good general health with the following key inclusion criteria were eligible: history of symptomatic seasonal AR, with or without mild asthma (asthma diagnosis was confirmed, per protocol, via positive methacholine challenge), for >2 years; positive skin prick test (weal ≥ 3 mm over negative control) for pollen allergens, within a year from the study start; positive screening NAC with the key symptom driving pollen allergen, defined by TNSS response of ≥ 5 (on a 12-point scale); and decrease in PNIF of >30%. Owing to low participant recruitment, and given that the primary end-point related to safety, a protocol amendment in January 2014 removed the requirement for mild asthma; a methacholine provocation test (described in Appendix S1) was then conducted only if the participant had a history of asthma. Exclusion criteria are listed in the Appendix S1.

2.3 | Treatments

GSK2245035 was formulated as a nasal spray solution in normal saline; placebo comprised normal saline spray. Further details are provided in Appendix S1. In the 2013 Cohort, participants received 80 ng GSK2245035 formulated at either 10 ng/actuation or 20 ng/actuation. In the 2014 Cohort, participants received GSK2245035 at a concentration of 10 ng/actuation (total dose of 20 ng).

2.4 | End-points and assessments

2.4.1 | Primary end-points

Primary end-points comprised general safety end-points, nasal tolerability end-points and TLR7-induced serum and nasal PD biomarkers.

Safety end-points

The primary safety end-points included AEs and CytoRS-AEs. CytoRS-AEs (headache, fever, chills/rigour, nausea, arthralgia, myalgia, vomiting, diarrhoea, hypotension) occurring within 24 hours post-dose were graded 0-4 according to severity, based on the National Cancer Institute Common Toxicity Criteria guidelines. Also assessed were vital signs, clinical laboratory parameters and peak expiratory flow.

Nasal tolerability end-points

Nasal tolerability was assessed via nasal examination and participants’ scoring on a 10-cm visual analogue scale (VAS) at 10 hours and 24 hours post-dose to assess itching, discomfort, post-nasal drip, rhinorrhoea and obstruction (ranging from “no symptoms” to “worst symptoms ever experienced”).

TLR7-induced serum and nasal PD biomarkers

The primary PD end-points included levels of the TLR7-induced biomarkers used in the previously reported study to confirm target engagement in all participants (IFN-inducible protein 10 [IP-10; serum and nasal] and also to assess selectivity of GSK2245035 (TNF-α [serum and nasal], IFN-γ [serum] and IL-6 [nasal]), determined as described in Appendix S1. Serum and nasal PD biomarker sample collection took place pre-dose and 24 hours after 1st and 8th doses and prior to NAC at FUV 1 and 2 to determine the reproducibility of the response after eight doses and the duration of the response after last dose.

2.4.2 | Exploratory end-points

Exploratory end-points included efficacy as determined by reduction in nasal symptoms following allergen challenge and allergic reactivity biomarkers.

Nasal allergen challenge (NAC) was performed at screening, to confirm eligibility, prior to randomization to provide baseline data, and at FUV1, FUV2 (all participants) and FUV3 (Cohort 2 only). In the initial screening NAC, a series of nasal provocations took place approximately every 12 minutes. Fourfold increasing allergen concentrations (ragweed [starting concentration 0.1 ragweed antigen E
units/mL], birch [starting concentration 19 protein nitrogen unit/mL] or grass pollen [starting concentration 49 bioequivalent allergy units/mL]; according to participants’ key pollen sensitivity) were used to determine the concentration eliciting a TNSS ≥5 and decrease in PNIF of >30%. The cumulative allergen concentration determined here was employed in subsequent NACs.

Nasal symptoms
Nasal symptoms (congestion, rhinorrhoea, sneezing, itch) elicited by NAC at screening, FUV1, FUV2 and FUV3 were assessed individually and as a TNSS. TNSS and PNIF were assessed prior to the allergen challenge and at 15 (primary NAC comparison time-point) and 30 minutes and 1, 2, 3, 4, 5 and 6 hours after the end of the challenge. TNSS was derived from symptom scores graded as: 0—none; no symptom whatsoever, absent; 1—mild: symptom is present, noticeable but not bothersome; 2—moderate: symptom is bothersome, but tolerable; and 3—severe: symptom is bothersome, hard to tolerate, requiring relief/treatment with a maximum score of 12. PNIF was determined using the In-Check™ PNIF meter (Alliance Tech Medical Inc. TX, USA).

Allergic reactivity biomarkers
Allergic biomarker samples were collected as nasal lavage samples or nasal lining fluid adsorbed onto synthetic absorptive matrix filters (Leukosorb®, Mall Corporation, Port Washington, NY, USA), pre- and 6 hours post-NAC, at screening, FUV1, FUV2 and FUV3, and serum samples 6 hours post-NAC at screening, FUV1 and FUV2. A wide range of allergic biomarkers were measured reflecting potential TLR7-mediated effects on relevant target and effector cells. Further details are given in Appendix S1.

2.5 | Statistical analysis
No formal statistical hypotheses were planned to be tested and no formal sample size estimated. Following the protocol amendment, the anticipated sample size of 14 participants receiving active treatment was considered sufficient for the safety and PD profile of GSK2245035 supporting larger clinical trials. NAC and biomarker analyses were performed on the per-protocol population, which was defined post hoc and excluded three participants receiving incorrect levels of allergen at a FUV. Year-matched placebo data were used for comparisons of TNSS, body temperature, serum and nasal lavage biomarker levels (excluding analyses exploring TLR-7 target engagement during the dosing period; post hoc); placebo cohorts were pooled as planned for all other end-points. Point estimates and corresponding 95% credible intervals (CrI) were obtained for selected assessments to determine the induction of TLR7-associated serum and nasal PD biomarkers. A Bayesian approach was employed to investigate mean effect sizes of exploratory end-point findings. For reference, a significant P-value from a two-sided test at the 5% level is equivalent to the posterior probability (PP) exceeding 0.975. PP>0.9 is generally defined as high certainty of the observed value representing a true treatment effect. Further details on the statistical analyses are presented in Appendix S1.

3 | RESULTS
3.1 | Participant disposition and clinical characteristics
There were 42 participants (March 2013–August 2014), all receiving at least one dose of GSK2245035 or placebo and included in the safety analyses (Figure 2). Demographics and baseline characteristics are summarized in Table 1.

3.2 | Safety and tolerability
3.2.1 | AEs
Overall, 93% (13/14) of participants reported any on-treatment AE in the placebo group, 64% (9/14) in the 20 ng group and 100% (14/14) in the 80 ng group; headache was the most common, reported by 57% (8/14), 50% (7/14) and 86% (12/14) of participants in the placebo, 20 ng and 80 ng groups, respectively. Treatment-related AEs were reported by 71% (10/14) of participants in the placebo group, 43% (6/14) in the 20 ng group and 100% (14/14) in the 80 ng group (Table S1). No serious AEs or deaths were reported.

Only two AEs were reported during the follow-up study; both occurred in the same participant in the placebo group and were not considered related to study treatment.

3.2.2 | CytoRS-AEs
CytoRS-AEs within 24 hours of dosing were observed in 93% (13/14) of participants in the 80 ng group and less frequently in the 20 ng (36%; 5/14) and placebo (29%; 4/14) groups (Table 2). Headache was the most frequent CytoRS-AE in all treatments followed by fever, observed only in the 80 ng group. Apart from one participant in the placebo group who experienced severe headache, severe-grade CytoRS-AEs were only observed in the 80 ng group (36%), where one participant was withdrawn owing to severe myalgia.

In the 80 ng group, headache and fever were reproducible CytoRS-AEs; two participants reported a CytoRS-related headache with each dose, one of whom also had CytoRS-related fever with seven doses (Figure 3). In contrast, of the five participants in the 20 ng group who reported a CytoRS-AE, three reported it at only one visit. The median duration of CytoRS-AEs induced by both doses was <24 hours, with the exception of chills/ rigours in the 20 ng group (n=2; mean 26 hours).

3.2.3 | Vital signs, clinical chemistry and haematology
In the majority of participants in all groups, vital signs were normal for the duration of the study. Further details are provided in the Appendix S1. Decreases in peripheral blood lymphocyte numbers were observed at 24 hours after DV1 and DV8 in the 20 ng group and at 8 hours and 24 hours after DV1 and DV8 in the 80 ng group, with greater than 95% certainty (Figure S1).
FIGURE 2  Participant disposition. AE, adverse event; NAC, nasal allergen challenge. *n=7 in Cohort 1; n=7 in Cohort 2. **n=7 in Cohort 1; †Cohort 2 (2014); ‡Cohort 1 (2013); ††data from the placebo and 20 ng arms of TL7116958 study were reused, even if the participants did not participate in Study 204509. Therefore, there are more participants in the per-protocol population than there are participants who had a NAC in the follow-on study. See note in statistical analysis section within Appendix S1.
3.2.4 | Body temperature

Increases in mean body temperature within the normal range (36-37.5°C) were noted in the 20 ng and 80 ng groups compared with placebo, with the 80 ng group exhibiting a consistently greater increase than 20 ng (Figure 4). The mean body temperature increase after each dosing in both dose groups was less than 1°C, except in the 80 ng group after DV2.

3.2.5 | Nasal tolerability

Nasal AEs were reported by one participant in the placebo group (moderate rhinorrhoea), two participants in the 20 ng group (mild epistaxis and mild nasal congestion; moderate nasal dryness and moderate rhinorrhoea) and two participants in the 80 ng group (mild rhinorrhoea; mild epistaxis, mild nasal congestion, moderate nasal dryness and moderate nasal discomfort). One report of rhinorrhoea in the placebo group, one report of nasal congestion in the 20 ng group and nasal discomfort reported by one participant at DV 2-6 inclusive in the 80 ng group were considered related to the study drug. Mean nasal VAS scores were generally higher for the 80 ng group, including baseline, compared with the 20 ng and placebo groups, at both DV1 and DV8. Mean changes in nasal VAS scores were small for all treatment groups at both DV1 and DV8 (Figure S2; Table 2).

**Table 1** Participant demographics and baseline characteristics

|                      | Placebo (N=14) | GSK2245035 20 ng (N=14) [Cohort 2, 2014] | GSK2245035 80 ng (N=14) [Cohort 1, 2013] |
|----------------------|----------------|------------------------------------------|------------------------------------------|
| Age (years), mean (SD) | 39.4 (11.91)   | 35.9 (12.54)                             | 38.9 (12.67)                             |
| Female, n (%)         | 10 (71)        | 11 (79)                                  | 9 (64)                                   |
| BMI (kg/m²), mean (SD)| 30.8 (7.03)    | 30.8 (7.95)                              | 29.1 (5.67)                              |
| Race, n (%)           |                |                                          |                                          |
| American Indian or Alaskan Native | 2 (14)      | 0                                        | 1 (7)                                    |
| Asian Japanese/East or South-East Asian Heritage | 1 (7)      | 0                                        | 0                                        |
| White                | 11 (79)        | 14 (100)                                 | 12 (86)                                  |
| American Indian or Alaskan Native and White | 0      | 0                                        | 1 (7)                                    |
| Allergen used in NAC, n (%) |            |                                          |                                          |
| Birch                | 3 (21)         | 5 (36)                                   | 0                                        |
| Ragweed              | 7 (50)         | 0                                        | 13 (93)                                  |
| Timothy grass        | 4 (29)         | 9 (64)                                   | 1 (7)                                    |
| Allergens with positive responses, n (%) |          |                                          |                                          |
| Ragweed              | 12 (86)        | 13 (93)                                  | 14 (100)                                 |
| Pigweed              | 2 (14)         | 5 (36)                                   | 3 (21)                                   |
| Plantain             | 3 (21)         | 5 (36)                                   | 4 (29)                                   |
| Cocklebur            | 5 (36)         | 8 (57)                                   | 8 (57)                                   |
| Mugwort              | 4 (29)         | 8 (57)                                   | 6 (43)                                   |
| Birch                | 9 (64)         | 9 (64)                                   | 12 (86)                                  |
| Oak                  | 3 (21)         | 7 (50)                                   | 7 (50)                                   |
| Tree Mix (9)         | 4 (29)         | 3 (21)                                   | 9 (64)                                   |
| Rye grass            | 13 (93)        | 12 (86)                                  | 12 (86)                                  |
| Timothy grass        | 10 (71)        | 11 (79)                                  | 12 (86)                                  |
| Lamb’s quarters      | 3 (21)         | 5 (36)                                   | 5 (36)                                   |
| Cat dander/hair      | 10 (71)        | 8 (57)                                   | 6 (43)                                   |
| Dog dander/hair      | 2 (14)         | 4 (29)                                   | 3 (21)                                   |
| Dermatophagoides pteronyssinus | 8 (57)    | 9 (64)                                   | 9 (64)                                   |
| Dermatophagoides farinae | 8 (57)  | 9 (64)                                   | 10 (71)                                  |
| Alternaria           | 2 (14)         | 0                                        | 2 (14)                                   |

BMI, body mass index; NAC, nasal allergen challenge; SD, standard deviation; GSK, GlaxoSmithKline.

**Table 2** Summary of CytoRS-AEs (occurring within 24 h post-dose)

| CytoRS event | Severity | Placebo (N=14) | GSK2245035 20 ng (N=14) [Cohort 2, 2014] | GSK2245035 80 ng (N=14) [Cohort 1, 2013] |
|--------------|----------|----------------|------------------------------------------|------------------------------------------|
| Any event    | All      | 4 (29)         | 5 (36)                                   | 13 (93)                                  |
| Headache     | Mild     | 1 (7)          | 2 (14)                                   | 2 (14)                                   |
|              | Moderate | 1 (7)          | 2 (14)                                   | 4 (29)                                   |
|              | Severe   | 1 (7)          | 5 (36)                                   |                                          |
| Fever        | Mild     | 4 (29)         |                                          |                                          |
|              | Moderate | 4 (29)         |                                          |                                          |
|              | Severe   | 4 (29)         |                                          |                                          |
| Chills/rigours | Mild | 1 (7)      | 1 (7)                                   | 3 (21)                                   |
|              | Moderate | 3 (21)       |                                          |                                          |
|              | Severe   | 3 (21)         |                                          |                                          |
| Nausea       | Mild     | 3 (21)         |                                          |                                          |
|              | Moderate | 1 (7)          |                                          | 1 (7)                                    |
|              | Severe   | 1 (7)          |                                          |                                          |
| Arthralgia (joint pain) | Mild | 1 (7)      |                                          | 1 (7)                                    |
|              | Moderate | 1 (7)         |                                          | 3 (21)                                   |
|              | Severe   | 1 (7)          |                                          |                                          |
| Myalgia (muscle pain) | Mild | 1 (7)   |                                          | 1 (7)                                    |
|              | Moderate | 4 (29)       |                                          |                                          |
|              | Severe   | 1 (7)          |                                          |                                          |

CytoRS-AEs were analyzed per protocol, whether considered drug related or not. Note that a participant can experience >1 event. Values represent distinct participant(s) experiencing at least one event, and displayed at highest level of severity for those experiencing >1 grade of an event. AE, adverse event; CytoRS, cytokine release syndrome.

*Participant met protocol defined stopping criteria and was withdrawn after two doses.

after each dosing in both dose groups was less than 1°C, except in the 80 ng group after DV2.

3.2.5 | Nasal tolerability

Nasal AEs were reported by one participant in the placebo group (moderate rhinorrhoea), two participants in the 20 ng group (mild epistaxis and mild nasal congestion; moderate nasal dryness and moderate rhinorrhoea) and two participants in the 80 ng group (mild rhinorrhoea; mild epistaxis, mild nasal congestion, moderate nasal dryness and moderate nasal discomfort). One report of rhinorrhoea in the placebo group, one report of nasal congestion in the 20 ng group and nasal discomfort reported by one participant at DV 2-6 inclusive in the 80 ng group were considered related to the study drug. Mean nasal VAS scores were generally higher for the 80 ng group, including baseline, compared with the 20 ng and placebo groups, at both DV1 and DV8. Mean changes in nasal VAS scores were small for all treatment groups at both DV1 and DV8 (Figure S2; Table 2).
nasal VAS scores were obtained at each dosing visit, data for DV1
and DV8 only shown in Figure S2).

Additional safety assessments including peak expiratory flow
measurements, nasal examinations (Table S2) and nasal symptoms as
recorded on daily diary cards did not reveal adverse effects with
repeat dosing.

3.3 | TLR7-induced serum and nasal PD biomarkers

3.3.1 | Serum IP-10

Median fold changes in serum IP-10 levels increased with certainty
(PP > 0.98) at 24 hours after DV1 and DV8 for both doses versus pla-

ccebo (Table 3). The fold changes compared with placebo (95% CrI)
were greatest in the 80 ng group at both DV1 and DV8. In the
80 ng group, an increase in serum IP-10 level was observed at FUV1
(PP > 0.99; Table 3).

3.3.2 | Nasal IP-10

Median fold changes in nasal lavage IP-10 levels increased with cer-
tainty (PP > 1.0) at 24 hours after DV1 and DV8 for both doses, versus
placebo (Table 3). For the 20 ng group, the magnitude of fold change
versus placebo (95% CrI) at 24 hours post-DV8 was higher than post-
DV1. Median fold changes in the 80 ng group remained similar at
24 hours after DV1 and DV8. In the 80 ng group, an increase in nasal
IP-10 levels was observed at FUV1 and at FUV2 (PP > 0.96; Table 3).

3.3.3 | TNF-α, IL-6 and IFN-α

Serum levels of TNF-α were not detectable in any group (lower limit of
quantification [LLQ] 9.38 pg/mL). Serum levels of IFN-α were detect-
able (LLQ 12.5 pg/mL) at one or more study visits in two participants
in the placebo group, eight in the 20 ng group and two in the 80 ng
group.

Median fold changes of TNF-α and IL-6 in nasal lavage samples
increased for both doses (TNF-α approximately 2.5- and eightfold at
20 ng and 80 ng, respectively; IL-6 approximately 2.6- and 4.6-fold
at 20 ng and 80 ng, respectively; and both post-DV8). The absolute
values were very low before and after DV1 and DV8 (TNF-α < 1
pg/mL; IL-6 < 4 pg/mL) (data not shown).

3.4 | Allergen challenge

3.4.1 | TNSS

Median change from baseline in TNSS at 15 minutes post-NAC was
reduced in both GSK2245035 groups, compared with placebo, at
TABLE 3  Median fold changesa in serum and nasal lavage IP-10 (95% credible intervalb)

| Treatment comparison | DV1 | DV8 | FUV1 | FUV2 |
|----------------------|-----|-----|------|------|
| Serum                |     |     |      |      |
| GSK2245035 20 ng     | 1.66| 2.19| 1.00 | 0.85 |
|                      | (1.05, 2.61) | (1.15, 4.20) | (0.70, 1.41) | (0.65,1.11) |
| PP=0.98              |     | PP=0.99 | PP=0.50 | PP=0.12 |
| GSK2245035 80 ng     | 6.06| 6.43| 1.66 | 1.00 |
|                      | (3.80, 9.63) | (3.26, 12.68) | (1.15, 2.38) | (0.76,1.33) |
| PP=1.0               |     | PP=1.0 | PP=1.0 | PP=0.51 |
| Nasal lavage         |     |     |      |      |
| GSK2245035 20 ng     | 4.34| 10.30| 0.92 | 0.92 |
|                      | (2.65, 7.13) | (5.12, 20.93) | (0.49, 1.73) | (0.47, 1.76) |
| PP=1.0               |     | PP=1.0 | PP=0.39 | PP=0.39 |
| GSK2245035 80 ng     | 21.03| 19.05| 2.47 | 1.86 |
|                      | (12.52, 35.11) | (9.28, 38.93) | (1.29, 4.74) | (0.93, 3.72) |
| PP=1.0               |     | PP=1.0 | PP=1.0 | PP=0.96 |

Median absolute nasal IP-10 levels (pg/mL) 24 h post-dose: placebo 256 (DV1), 204 (DV8); 20 ng 1111 (DV1), 2104 (DV8); and 80 ng 5380 (DV1), 3891 (DV8).

DV, dosing visit; FUV, follow-up visit; IP-10, interferon-inducible protein-10; PP, posterior probability. ≥1.0.

Range within which the true value lies with 95% probability (certainty).

FUV1 (PP=0.92 and 0.89 for 20 ng and 80 ng, respectively) and FUV2 (PP=0.84 for both doses; Figure 5). The median treatment effect was similar for 20 ng and 80 ng at both FUV1 (–1.9 and –1.8, respectively) and FUV2 (–1.3 and –1.4, respectively). In the 20 ng group, TNSS reduction was sustained up to 6 hours post-NAC at FUV1 and up to 1 hour post-NAC at FUV2; in the 80 ng group, the effects were sustained up to 6 hours post-NAC at both FUV1 and FUV2 (Table S3). The median change from baseline in TNSS showed no reduction with GSK2245035 20 ng compared with placebo at FUV3 (Figure 5 and Table S3).

3.4.2 | PNIF

No consistent changes were noted in PNIF post-NAC at FUV1, FUV2 or FUV3 for any treatment group (data not shown).

3.5 | Allergic reactivity biomarkers

Nasal lining fluid levels of Th2-associated cytokines/chemokines (IL-5, IL-16, IL-33, eotaxin, thymus and activation-regulated chemokine [TARC], macrophage-derived chemokine [MDC]) and the immunoregulatory cytokine IL-10, and nasal lavage fluid levels of allergen-specific IgA and effector mediator eosinophil cationic protein (ECP), were detectable in a majority of the samples and were analyzed. For the 20 ng group, a decrease in ECP was measured at FUV1 (PP=0.85), FUV2 (PP=0.97) and FUV3 (PP=0.7). Decreases were also noted for IL-5 at FUV 2 (PP=0.66) and FUV3 (PP=0.80) and for IL-16 at FUV1 (PP=0.78) and FUV2 (PP=0.50; Table S4). Increases in allergen-specific IgA were measured at FUV3 (PP=0.71). For the 80 ng group, decreases were measured at both FUV1 and FUV2 in IL-5 (FUV1 PP=0.71; FUV2 PP=0.75), eotaxin (FUV1 PP=0.79; FUV2 PP=0.88), MDC (FUV1 PP=0.89; FUV2 PP=0.92), TARC (FUV1 PP=0.88; FUV2 PP=0.79), and an increase in allergen-specific IgA (FUV1 PP=0.94; FUV2 PP=0.88). No change in IL-10 was detected with either dose (Table S4).

Biomarkers assayed but with levels at or below LLQ included IFN-γ, IL-12p70, IL-4, IL-13, granulocyte-macrophage colony-stimulating factor, IL-25, thymic stromal lymphopoietin (TSLP), allergen-specific IgE and allergen-specific IgG4. Comparisons made with post-NAC allergic biomarker levels in serum at FUV1 and FUV2 (adjusting for the screening value) showed no evidence for consistent treatment effects (data not shown).

FIGURE 5  Change from baseline in TNSS at 15 minutes post-NAC at FUV1, FUV2 and FUV3. Crl, credible interval; FUV, follow-up visit; NAC, nasal allergen challenge; TNSS, total nasal symptom score (0–12). Difference represents placebo minus GSK2245035.
4 | DISCUSSION

Novel treatments to reduce aberrant immune responsiveness to allergen are needed for patients with respiratory allergies requiring daily medication. This i.n. TLR7 agonist, GSK2245035, was developed as a potential immunomodulatory treatment to maximize colocalization with both its target, pDCs, and aeroallergen while minimizing systemic activation. Here we report findings from a Phase IIa clinical trial of i.n. GSK2245035, which demonstrated trends for sustained reductions in responsiveness to NAC in participants with AR treated during pollen seasons. Our findings confirm target engagement with dose-related changes in PD markers and also reveal dose-related increases in the frequency and severity of CytoRS-AEs with repeated i.n. TLR7 agonism.

Previous clinical trials of i.n. GSK2245035 20–80 ng report a varying frequency of mild CytoRS-AEs. Here, 80 ng was poorly tolerated, whereas the tolerability of 20 ng was similar to placebo with infrequent CytoRS-AEs and no fever. Regardless of severity, the duration of CytoRS-AEs was generally ≤1 day. The poor tolerability of 80 ng compared with the previous study may reflect variability in individual responses, apparent with more individuals treated (n=14 vs n=4). As GSK2245035 80 ng retained selective potency for type I IFNs over pro-inflammatory cytokines in this 8-week study. Systemic activation of TLR7 by GSK2245035 seems unlikely as plasma concentrations of GSK2245035 after i.n. administration have not previously been detected. Regardless nasal tolerability, the low frequency of nasal AEs, nasal examination findings and small increases in VAS scores indicate that repeat administration of both doses were well tolerated locally.

Target engagement was demonstrated by dose-related increases in IP-10 levels and body temperature, and by decreases in peripheral blood lymphocytes, each consistent with production of type 1 IFNs. For GSK2245035 20 ng, previously only studied as a single dose, nasal lavage IP-10 levels increased with repeat dosing but not with the 80 ng dose. There was a fivefold difference between 20 ng and 80 ng after one dose, decreasing to a twofold difference after eight doses. The difference in nasal lavage IP-10 may reflect increased recruitment of TLR7-responsive pDCs to the nasal mucosa following repeated exposure to GSK2245035 20 ng, as observed with a topical TLR7/8 agonist. In contrast, the apparent peak in nasal IP-10 after one 80 ng dose may indicate that a maximal response had already been reached. Notably, there were no systemic differences after 8 weeks’ dosing at 20 ng and the nasal lavage IP-10 levels at 80 ng did not increase with repeated dosing. After repeat dosing of 80 ng, IP-10 levels remained elevated (approximately twofold) compared with baseline at 1 (serum and nasal) and 3 (nasal) weeks after final dose suggesting ongoing activation of the IFN-α pathway. The clinical consequences of this finding are uncertain as no AEs consistent with cytokine induction were noted during this period. Indeed, the prolonged activation of the IFN-α pathway could be explored for a respiratory antiviral effect as with inhaled IFN-β for allergic asthma.

Both doses of GSK2245035 reduced clinical symptoms, although not reaching statistical significance, following a direct NAC. The effect sizes were clinically relevant (TNSS difference from placebo >1.0) and sustained (up to 3 weeks after treatment). The similar TNSS reductions observed with the 20 ng and 80 ng doses indicate that efficacy is not likely related to ongoing pharmacologic effects that were only observed at the higher dose. No significant differences were noted between treatment and placebo groups with respect to PNIF measurements following allergen challenge. This was likely due to the variability noted in baseline PNIF readings and the use of a 30% reduction in PNIF to qualify for inclusion, which in hindsight appears less reliable than in protocols where a 50% reduction is required.

While no standardized minimum clinically important difference has been established for TNSS, these results are of a similar or greater magnitude to i.n. corticosteroid studies where the effects are present over a 24-hour dosing period. Here, the probability of a sustained treatment effect on TNSS for both doses was modest to high, about 90%, at 1 week and 84% at 3 weeks after treatment. Data on the long-term effects of GSK2245035 are limited to a subset of participants receiving GSK2245035 20 ng where a clinical effect was not present 1 year after treatment. Therefore, the reductions in nasal symptoms measured up to 3 weeks post-treatment may have been due to an effect of locally induced IFN-α on mast cell numbers or mediator release rather than on adaptive immune responses.

Analyses of nasal allergic biomarkers revealed trends for a response to treatment. The observed reductions in selected Th2-associated cytokines, chemokines and ECP post-NAC are consistent with the known in vitro effect of IFN-α to suppress Th2 responses and eosinophilia. In contrast to the effect on nasal symptoms, nasal biomarker data were not consistent for the two doses, likely reflecting the small sample size.

Exposure to allergen is thought to be important for TLR7-induced immunomodulatory changes. However, the conduct of these studies over multiple different pollen seasons, including grass, ragweed and tree, variable pollen exposure and differences in sensitization patterns among patients represent important limitations, as indicated by differences in biomarker baseline values between the 2013 and 2014 cohorts. GSK2245035 treatment was therefore compared with placebo from the same year rather than pooling as planned. A limitation regarding the detection of changes in nasal biomarkers is that, despite following standardized procedures, the TNSS induced by NAC was modest and may reflect baseline symptomatology from ongoing environmental exposure in poly-sensitized participants. As changes in TNSS were not measured over the 8-week treatment period, clinical efficacy is limited to the NAC model. Further limitations are the single time-point for collecting allergic biomarker data meaning that the true effect on each biomarker may not have been established, a small sample size and short initial follow-up period (3 weeks).

The 3-week duration of treatment effect has not previously been shown with similar treatments under investigation for AR and asthma, the TLR7 agonist AZD8848 and the TLR8 agonist VTX-1463. The magnitude of treatment difference for TNSS (~1.0) provides strong evidence for the therapeutic potential of
GSK2245035 despite the small sample size used in this study. The Bayesian statistical methods allow judgement on the strength of the data by providing a probability that the observed treatment effect is not chance. In this study, the probabilities of mean changes in IP-10 levels exceeded 0.975 and were equivalent to a $P$-value $\leq 0.05$. When applied to exploratory efficacy end-points, Bayesian methods show the probability of each GSK2245035 dose inducing a reduction in nasal symptoms to be high at FUV1 and FUV2, not at the level generally associated with "proof" for definitive efficacy studies, rather as an informative way of assessing data in translational medicine studies such as this. Similarly, the probabilities of reducing individual Th2 cytokines or chemokines were moderate to high. These findings were demonstrated in a relatively small number of participants and would need to be confirmed in larger studies.

In summary, GSK2245035 is a potent, selective TLR7 agonist with clinical effects evident at 20 and 80 ng doses up to 3 weeks after treatment. Despite local administration, systemic influenza-like symptoms, in particular fever and myalgia, consistent with stimulation of the IFN-α pathway were reported. Key questions arising from this study form objectives for future studies. The optimal dosing regimen for maximum clinical effect remains unknown. It is unclear whether the difference in TNSS at each FUV represents a waning effect, and if so, the rate of decline has not been defined. Further, this study, and others with GSK2245035 have all been conducted during pollen seasons. It is important to understand whether there is a threshold level of allergen exposure needed to coincide with GSK2245035 treatment as well as the relationship between allergen exposure and the magnitude and duration of clinical effect. Although the exact mechanism of action for GSK2245035 is yet to be determined, and Th1/Th2 responses were not detected, the i.n. reductions in IL-5, Th2 chemokines and ECP provide evidence for a treatment effect on Th2-associated inflammation. Perhaps the greater challenge will be to link these changes in immune responses to the clinical benefits perceived by the patient.

By altering established immune responses to aeroallergens, TLR7 agonism has broad therapeutic utility. In n. GSK2245035 is conveniently administered once weekly and the relevant therapeutic comparison will be to a daily i.n. corticosteroid. As an immunomodulatory treatment that works with natural allergen exposure, a key advantage might be the low risk of anaphylaxis, and its safe use also in season. Lastly, although the serum allergic biomarkers did not reveal systemic treatment-related effects, the PD data (ie raised serum IP-10 and body temperature, and decreased blood lymphocyte counts) suggest that an effect of i.n. GSK2245035, via the induced type 1 IFN response, may not be restricted to the local nasal environment. Therefore, TLR7 remains a valid target with the prolonged local clinical effects and self-resolving AEs providing evidence for a therapeutic window.

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CONFLICT OF INTEREST

AKE has received honoraria for participation in an advisory board for Circassia Ltd, GSK, Merck and Novartis; has been a speaker for Novartis, Merck, Pfizer, Takeda, Meda and AstraZeneca; and has received research grants from GSK, Circassia Ltd, SunPharma, Merck, Pfizer and Novartis. LAL, DQ and WP are employees of and shareholders in, GSK; DCT was an employee of and shareholder in GSK at the time this research was conducted.

AUTHOR CONTRIBUTIONS

AKE and DQ were involved in the conception and design of the study, acquisition of data, analysis and interpretation of data and drafting of the manuscript. LAL and DCT were involved in the conception and design of the study, analysis and interpretation of data and drafting of the manuscript. WP was involved in the conception and design of the study and analysis and interpretation of data. All authors reviewed and critically revised the manuscript prior to approval.

REFERENCES

1. Broide DH. Molecular and cellular mechanisms of allergic disease. J Allergy Clin Immunol. 2001;108:565-571.
2. Kay AB. The role of T lymphocytes in asthma. Chem Immunol Allergy. 2006;91:59-75.
3. Akdis M. Immune tolerance in allergy. Curr Opin Immunol. 2009;21:700-707.
4. Umetsu DT, DeKruyff RH. The regulation of allergy and asthma. Immunol Rev. 2006;212:238-255.
5. Akdis M, Akdis CA. Therapeutic manipulation of immune tolerance in allergic disease. Nat Rev Drug Discov. 2009;8:645-660.
6. Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nat Immunol. 2010;11:373-384.
7. Ayan Z, Holgate ST, Radzioch D, Rezaei N. A new era of targeting the ancient gatekeepers of the immune system: toll-like agonists in the treatment of allergic rhinitis and asthma. Int Arch Allergy Immunol. 2014;164:46-63.
8. Hennessy EJ, Parker AE, O’Neill LA. Targeting Toll-like receptors: emerging therapeutics? Nat Rev Drug Discov. 2010;9:293-307.
9. Camateros P, Tamaoka M, Hassan M, et al. Chronic asthma-induced airway remodeling is prevented by toll-like receptor-7/8 ligand S28463. Am J Respir Crit Care Med. 2007;175:1241-1249.
10. Xirakia C, Koltsida O, Stavropoulos A, et al. Toll-like receptor 7-triggered immune response in the lung mediates acute and long-lasting suppression of experimental asthma. Am J Respir Crit Care Med. 2010;181:1207-1216.
11. Creticos PS, Schroeder JT, Hamilton RG, et al. Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. N Engl J Med. 2006;354:1445-1455.
12. Rosewich M, Lee D, Zielen S, Pollinx Quattro: an innovative four injections immunotherapy in allergic rhinitis. Hum Vaccin Immunother. 2013;9:1523-1531.
13. Greifl F, Ahlstrom-Emanuelsson C, Alenas M, et al. Biological effects and clinical efficacy of a topical Toll-like receptor 7 agonist in seasonal allergic rhinitis: a parallel group controlled phase IIa study. Inflamm Res. 2015;64:903-915.
14. Horak F. VTX-1463, a novel TLR8 agonist for the treatment of allergic rhinitis. Expert Opin Investig Drugs. 2011;20:981-986.
15. Klimek L, Willers J, Hammann-Haenni A, et al. Assessment of clinical efficacy of CYT003-QbG10 in patients with allergic rhinoconjunctivitis: a phase IIb study. Clin Exp Allergy. 2011;41:1305-1312.
16. Diebold SS, Kaisto T, Hemmi H, Akira S, Reis e Sousa C. Innate antiviral responses by means of TLR7-mediated recognition of single-stranded RNA. Science. 2004;303:1529-1531.
17. Drake MG, Kaufman EH, Fryer AD. Jacoby DB. The therapeutic potential of Toll-like receptor 7 stimulation in asthma. Inflamm Allergy Drug Targets. 2012;11:484-491.
18. Möller-Larsen S, Nyegard M, Haagensen A, Vestbo J, Kruse TA, Borgholm AD. Association analysis identifies TLR7 and TLR8 as novel risk genes in asthma and related disorders. Thorax. 2008;63:1064-1069.
19. Moisan J, Camateros P, Thuraisingam T, et al. TLR7 ligand prevents allergen-induced airway hyperresponsiveness and eosinophilia in allergic asthma by a MYD88-dependent and MK2-independent pathway. Am J Physiol Lung Cell Mol Physiol. 2006;290:L987-L995.
20. Duechs MJ, Hahn C, Benediktus E, et al. TLR agonist mediated suppression of allergic responses is associated with increased innate inflammation in the airways. Pulm Pharmacol Ther. 2011;24:203-214.
21. Gorden KB, Gorski KS, Gibson SJ, et al. Synthetic TLR agonists reveal functional differences between human TLR7 and TLR8. J Immunol. 2005;174:1259-1268.
22. Miller RL, Meng TC, Tomai MA. The antiviral activity of Toll-like receptor 7 and 7/8 agonists. Drug News Perspect. 2008;21:69-87.
23. Biggadik E, Ahmed M, Ball D, et al. V W. Discovery of 6-amino-2-[(1S)-1-methylbutyl]oxy]-9-[5-(1-piperidinyl)pentyl]-7,9-dihydro-8H-purin-8-one (GSK2245035), a highly potent and selective intranasal TLR7 agonist for the treatment of asthma. J Med Chem. 2016;59:1711-1726.
24. Tisoura D, Ambery C, Price M, et al. Early clinical evaluation of the intranasal TLR7 agonist GSK2245035: use of translational biomarkers to guide dosing and confirm target engagement. Clin Pharmacol Ther. 2015;98:369-380.
25. Eccles R. Understanding the symptoms of the common cold and influenza. Lancet Infect Dis. 2005;5:718-725.
26. World Medical Association. WMA Declaration of Helsinki - ethical principles for medical research involving human subjects. 2008. http://www.wma.net/en/30publications/10policies/b3/ Accessed October, 2015.
27. (CTEP) NCICCTEP. Common Terminology Criteria for Adverse Events (CTCAE). 2009. http://evs.nci.nih.gov/ftp1/CTCAE/About.html. Accessed 25 February 2015.
28. Fidock MD, Souberbielle BE, Laxton C, et al. The innate immune response, clinical outcomes, and ex vivo HCV antiviral efficacy of a TLR7 agonist (PF-4878691). Clin Pharmacol Ther. 2011;89:821-829.
29. Rieckmann POCP, Francis GS, Wetherell G, Alteri E. Haematological effects of interferon-beta-1a (Rebit) therapy in multiple sclerosis. Drug Saf. 2004;27:745-756.
30. Kamphuis E, Junt T, Waibler Z, Forster R, Kalinke U. Type I interferons directly regulate lymphocyte recirculation and cause transient lymphopenia. Blood. 2006;108:3253-3261.
31. Ogawa Y, Kawamura T, Matsuizawa T, Aoki R, Shimada S. Recruitment of plasmacytoid dendritic cells to skin regulates treatment responsiveness of actinic keratosis to imiquimod. J Dermatol Sci. 2014;76:67-69.
32. Djukanovic R, Harrison T, Johnston SL, et al. The effect of inhaled IFN-beta on worsening of asthma symptoms caused by viral infections. A randomized trial. Am J Respir Crit Care Med. 2014;190:145-154.
33. Soliman M, Thiele J, Adams D, Steacy LM, Ellis AK. Demonstrating the repeatability of the nasal allergen challenge protocol utilized by the Allergic Rhinitis - Clinical Investigator Collaborative (AR-CIC). Allergy Clin Immunol. 2016;137:AB263.
34. Meltzer EO, Jacobs RL, LaForce CF, Kelley CL, Dunbar SA, Tantry SK. Safety and efficacy of once-daily treatment with beclomethasone dipropionate nasal aerosol in subjects with perennial allergic rhinitis. Allergy Asthma Proc. 2012;33:249-257.
35. Raphael GD, Berger WE, Brenner BM, Finb AF Jr, Kelley L, Tantry SK. Efficacy, safety, and optimal dose selection of beclomethasone dipropionate nasal aerosol for seasonal allergic rhinitis in adolescents and adults. Curr Med Res Opin. 2012;29:1329-1340.
36. van Bavel JH, Ratner PH, Amar NJ, et al. Efficacy and safety of once-daily treatment with beclomethasone dipropionate nasal aerosol in subjects with seasonal allergic rhinitis. Allergy Asthma Proc. 2012;33:386-396.
37. Kim K, Weisswasser M, Nave R, et al. Safety of once-daily ciclesonide nasal spray in children 2 to 5 years of age with perennial allergic rhinitis. Pediatr Asthma Allergy Immunol. 2007;20:229-242.
38. Berger W, Nayak A, Lanier B, et al. Efficacy and safety of once-daily ciclesonide nasal spray in children with allergic rhinitis. Pediatr Asthma Allergy Immunol 2008;21:73-82.
39. Cardet JC, Akin C, Lee MJ. Mastocytosis: update on pharmacotherapy and future directions. Expert Opin Pharmacother. 2013;14:2033-2045.
40. Canonica GW, Passalacqua G, Pronzato C, Corbetta L, Bagnasco M. Effective long-term alpha-interferon treatment for hypereosinophilic syndrome. J Allergy Clin Immunol. 1995;96:131-133.
41. Huber JP, Ramos HJ, Gill MA, Farrar JD. Cutting edge: type I IFN reverses human Th2 commitment and stability by suppressing GATA3. J Immunol. 2010;185:813-817.
42. Matsui H, Tomizawa H, Eho K, et al. Mechanism of action of inhibition of allergic immune responses by a novel antedrug TLR7 agonist. J Immunol. 2012;189;5194-5205.
43. Leaker B, Singh D, Lindgren S, et al. The effects of the novel toll-like receptor 7 (TLR7) agonist AZD8848 on allergen-induced responses in patients with mild asthma. San Francisco, California, USA: American Thoracic Society International Conference; 2012.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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