A phase 1 study of single and repeat oral doses of GSK3439171A, a highly selective H-PGDS inhibitor, in healthy adult participants

Thomas Haws[1], Nilay Thakkar[2], Summer Goodson[2], Caroline Sychterz[1], Nisha George[1], Rebecca Zhang-Roper[2], Geo Derimanov[1], David Neil[1], and Victoria Ballard[2]

[1]GlaxoSmithKline
[2]GlaxoSmithKline Research and Development

July 5, 2021

Abstract

Aim: Prostaglandin D2 (PGD2) is implicated in the pathophysiology of inflammatory diseases. GSK3439171A is a potent, reversible, and highly selective azetidine urea inhibitor of haematopoietic prostaglandin D synthase (H-PGDS, a key promoter of PGD2 production in several inflammatory cell types). Based on favourable preclinical data, we performed a first-time-in-human study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of GSK3439171A, and the effect of food on these parameters. Methods: This was a phase 1, randomized, double-blind, placebo-controlled, dose-escalation study. Single and repeat oral doses of GSK3439171A were administered to healthy males aged 18–65 years. Levels of inflammatory markers including tetranor-prostaglandin D metabolite (tPGDM) were measured in urine samples. Results: Sixty-six participants were enrolled, with 57 receiving GSK3439171A. Single doses (5–180 mg) and repeat once-daily doses (5 and 11 mg for 14 days; 40 mg for 7 days) were administered. Seven participants (12%) had adverse events (AEs) related to study drug, mainly drug hypersensitivity (n=4 [7%]; non-serious, transient skin rash). There were no serious AEs (SAEs) or clinically significant changes in vital signs, electrocardiogram, or laboratory parameters. Dose-proportional increases in Cmax and AUC(0–inf) were observed, and the geometric mean half-life of GSK3439171A was up to 12 hours. Results were similar when GSK3439171A was taken with or without food. No consistent suppression of tPGDM levels was observed. Conclusion: GSK3439171A was well tolerated in healthy participants and there were no SAEs. Selective inhibition of H-PGDS offers therapeutic potential for muscle-related disorders (e.g. Duchenne Muscular Dystrophy) and muscular recovery following injury.

A phase 1 study of single and repeat oral doses ofGSK3439171A, a highly selective H-PGDS inhibitor, in healthy adult participants

Authors: Thomas Haws[1*], Nilay Thakkar[2], Summer G. Goodson[3*], Caroline Sychterz[4*], Nisha George[4,5], Rebecca Zhang-Roper[6*], Geo Derimanov[1], David Neil[1*], Victoria Ballard[7*]

Affiliations: [1]Clinical Pharmacology & Experimental Medicine, Discovery Medicine, GlaxoSmithKline, Collegeville, PA, USA; [2]Clinical Pharmacology, Modeling and Simulation, GlaxoSmithKline Research and Development, Collegeville, PA, USA; [3]Global Clinical and Study Delivery, GlaxoSmithKline Research and Development, Collegeville, PA, USA; [4]Bioanalysis, Immunogenicity & Biomarkers, GlaxoSmithKline, Collegeville, PA, USA;[5]Biostatistics, GlaxoSmithKline Asia Pvt Ltd, Bengaluru, India; [6]Global Safety Department, GlaxoSmithKline Research and Development, GSK House, Brentford, Middlesex, UK; [7]Early Development Leader Group, GlaxoSmithKline Research and Development, Collegeville, PA, USA *Author departed from GlaxoSmithKline after the study was completed

Corresponding author:

Thomas Haws 1609 West Lynn Dr West Chester PA 19382 USA

Email: Tom_Haws@yahoo.com

Tel: +1 302-521-9971

Principal Investigator: There is no Principal Investigator for this study. Authors had medical responsibility for the study (GD) and for the clinical development programme (RZR, DN).

Running head: Phase 1 study of GSK3439171A

Keywords: GSK3439171A, H-PGDS inhibitor, pharmacokinetics, pharmacodynamics, phase 1, tolerability

Word count (excluding abstract and references) = 3,259 (4,000-word limit)

What is already known about this subject

Haematopoietic prostaglandin D synthase (H-PGDS) is a key promoter of prostaglandin D_2 production, which plays an important role in the pathophysiology of inflammatory diseases.

Studies of the selective H-PGDS inhibitor TAS-205 suggest that this treatment approach could be beneficial.

What this study adds

- GSK3439171A is a potent, reversible, and highly selective H-PGDS inhibitor. Here, we present results from the first-time-in-human, phase 1 study of GSK3439171A, performed to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics in 57 healthy adult male participants.
- GSK3439171A showed a favourable safety profile and was well tolerated in single doses (range 5–180 mg) and repeat once-daily doses (range 5–40 mg).
- These results warrant further studies of GSK3439171A in the target population with inflammatory diseases.

Abstract

Aim: Prostaglandin D_2 (PGD_2) is implicated in the pathophysiology of inflammatory diseases. GSK3439171A is a potent, reversible, and highly selective azetidine urea inhibitor of haematopoietic prostaglandin D synthase (H-PGDS, a key promoter of PGD_2 production in several inflammatory cell types). Based on favourable preclinical data, we performed a first-time-in-human study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of GSK3439171A, and the effect of food on these parameters.

Methods: This was a phase 1, randomized, double-blind, placebo-controlled, dose-escalation study. Single and repeat oral doses of GSK3439171A were administered to healthy males aged 18–65 years. Levels of inflammatory markers including tetranor-prostaglandin D metabolite (tPGDM) were measured in urine samples.

Results: Sixty-six participants were enrolled, with 57 receiving GSK3439171A. Single doses (5–180 mg) and repeat once-daily doses (5 and 11 mg for 14 days; 40 mg for 7 days) were administered. Seven participants (12%) had adverse events (AEs) related to study drug, mainly drug hypersensitivity (n=4 [7%]; non-serious, transient skin rash). There were no serious AEs (SAEs) or clinically significant changes in vital signs, electrocardiogram, or laboratory parameters. Dose-proportional increases in C_{max} and $AUC_{(0–inf)}$ were observed, and the geometric mean half-life of GSK3439171A was up to 12 hours. Results were similar when GSK3439171A was taken with or without food. No consistent suppression of tPGDM levels was observed.

Conclusion: GSK3439171A was well tolerated in healthy participants and there were no SAEs. Selective inhibition of H-PGDS offers therapeutic potential for muscle-related disorders (e.g. Duchenne Muscular Dystrophy) and muscular recovery following injury.

ClinicalTrials.gov Identifier: NCT03627494

1 INTRODUCTION

Prostaglandin D_2 (PGD_2) is synthesised by cells of the immune system (e.g. mast cells, antigen-presenting cells) in response to injury or cellular activation. It plays a key role in the mechanisms of inflammation in allergy and asthma [1–4]. Accordingly, large increases (>150-fold) in bronchoalveolar lavage fluid levels of PGD_2 have been reported in asthma patients upon exposure to an allergen [5]. Strong biological evidence demonstrates haematopoietic prostaglandin D synthase (H-PGDS)-mediated PGD_2 production impairs skeletal muscle repair [3]. Blockade of this signal via gene manipulation, using dystrophin knock-out (KO) mdx mice, and small-molecule inhibition of either H-PGDS or the PGD_2 receptors DP_1 and DP_2 accelerates the kinetics of muscle remodelling and functional recovery. Additionally, tissue levels of H-PGDS and PGD_2 are elevated in acutely injured tissue and chronically inflamed tissue. Notably, H-PGDS inhibitors increase markers of myogenesis (MyoD and myogenin) following muscle injury in animals [2,3,6].

PGD_2 has also been associated with muscle necrosis and PGD_2-mediated inflammation is suggested to be involved in the pathology of Duchenne Muscular Dystrophy (DMD) [3,6,7]. Urinary excretion of tetranor-prostaglandin D metabolite (tPGDM, a major metabolite of PGD_2 and a marker of PGD_2production) has been reported to be higher in children with DMD than in age-matched healthy subjects or children with other diseases [8]. Urinary tPGDM levels are higher in non-ambulant versus ambulant DMD patients, indicating a relationship with disease progression and severity [8].

PGD_2 synthesis is promoted by two types of prostaglandin D synthase: haematopoietic and lipocalin (H-PGDS and L-PGDS, respectively) [9]. H-PGDS, the key mediator in immune cells, is expressed in myonecrotic areas in DMD patients [8]. Animal studies have shown that inhibition of H-PGDS can suppress PGD_2production, ameliorate muscle necrosis, and improve muscle strength [3]. The H-PGDS inhibitor TAS-205 was shown in a phase 1 trial to enable suppression of urinary tPGDM in boys with DMD [10]. A small, 24-week phase 2 trial of this drug has been conducted in patients with DMD [7]. No significant difference was seen in the primary endpoint (change from baseline in a 6-minute walk distance), but high-dose TAS-205 significantly attenuated the reduction in right lower leg muscle volume index. The safety profile of TAS-205 was also favourable (i.e. similar incidence of adverse events [AEs] as placebo and no tolerability issues). A phase 3 study of TAS-205 in sufficient numbers of patients to enable robust efficacy assessment is now underway [11].

GSK3439171A is a potent, reversible, and highly selective azetidine urea inhibitor of H-PGDS. In a mouse model of DMD, involving a challenge of eccentric contraction repetitions to induce muscle injury, treatment with GSK3439171A enabled superior recovery of limb function versus placebo in both wild-type and mdx mice [12]. In preclinical toxicity studies, the drug produced minor hepatic effects in dogs and reversible changes in the ovary, mammary gland, and pituitary gland in juvenile rats, but no genotoxic effects [12]. Pharmacokinetic (PK) studies in animals were used to predict human PK parameters [12]. The dosing strategy for initial clinical assessment was based on these predictions, the target half-maximal inhibitory concentration (IC_{50}) and the preclinical toxicity profile [12]. Here we report data from the first-time-in-human (FTiH) study of GSK3439171A, conducted in healthy volunteers.

2 MATERIALS AND METHODS

2.1 Study design and participants

This was a phase 1, randomized, double-blind (sponsor unblinded), placebo-controlled, FTiH, dose-escalation study. The primary objectives of the study were to assess the safety, tolerability, and PK of GSK3439171A following single and repeat oral doses in healthy participants. The secondary objective was to assess the effect of food on the PK of GSK3439171A; exploratory objectives included the evaluation of pharmacodynamics (PD) and biomarkers and GSK3439171A metabolic pathways (plasma, urinary, and biliary) in healthy participants. Further details of the objectives are available in the study protocol [12].

The study was conducted at a single US centre and comprised three parts: single ascending doses (Part A), single and repeat doses up to 14 days (dose rising, Part B), and the effect of food on PK (Part C) (Figure 1).

This study enrolled healthy male participants aged 18–65 years, with a bodyweight of [?]50.0 kg, and a body mass index (BMI) of 18.5–31.0 kg/m^2. Key exclusion criteria included history or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, haematological, or neurological disorders capable of constituting a risk when taking the study intervention or interfering with the interpretation of data. For each part of the study, screening occurred approximately 30 days before the first dose.

The study was conducted in accordance with Good Clinical Practice and all applicable regulatory requirements, as well as the guiding principles of the Declaration of Helsinki. All participants provided written informed consent before the start of the study.

2.2 Part A (single ascending dose)

Part A was a crossover design with three treatment periods. Two sequential ascending-dose cohorts were enrolled (A1 and A2) of the three planned, each involving nine participants. Cohort A3 was not conducted as the exposure seen at the last dose level (180 mg) in Cohort A2 was close to the single-dose exposure limit (defined according to preclinical toxicity data). Within each cohort, participants were randomly assigned to one of three treatment sequences (1:1:1) so that each participant received two dose levels of active drug (GSK3439171A) and one dose of placebo, with a washout period of approximately 7 days between each dosing session.

The starting dose for Part A was 5 mg GSK3439171A, with subsequent dose escalations determined based on safety and PK data. The doses selected were 5 mg, 10 mg, and 30 mg for Cohort 1 and 60 mg, 120 mg, and 180 mg for Cohort 2. Participants returned for a follow-up visit approximately 14 days after receiving their last dose.

2.3 Part B (multiple ascending dose)

Part B was conducted with parallel study groups. In each of three cohorts, 12 participants were randomly assigned to one dose of GSK3439171A or placebo (3:1 ratio). Plasma and urine samples were collected for up to 72 hours after the first dose, and participants subsequently began a repeat-dosing regimen consisting of one dose per day for up to 14 days. Participants were discharged on Day 13 (3 days after the last dose when the repeat-dosing period was 7 days) or Day 20 (3 days after the last dose when the repeat-dosing period was 14 days), following completion of study assessments.

Doses in this part of the study were administered sequentially and chosen after a review of safety, tolerability, and PK data from the preceding cohort. The regimens selected were as follows: Cohort 1, 5 mg/day for 14 days; Cohort 2, 11 mg/day for 14 days; Cohort 3, 40 mg/day for 7 days. Skeletal muscle biopsies were obtained from the vastus lateralis under local anaesthetic, before and after administration of GSK3439171A or placebo. This was to assess the effect of GSK3439171A on prostanoid levels in muscle tissue. In Cohort 2, bile was sampled using the Entero-Test to provide a qualitative assessment of drug metabolites [13]. Participants in each cohort returned for a follow-up visit approximately 14 days after receiving their last dose.

2.4 Part C (food effect)

In Part C, approximately 12 participants were randomly assigned 1:1 to one of two treatment sequences in a 2-period crossover design (fed/fasted or fasted/fed) comprising two 4-day study sessions separated by a 7-day washout period. In each study session, participants were admitted to the clinic and received a single oral 60 mg dose of GSK3439171A either in a fasted state or after a high-fat meal. Participants were discharged

on Day 4 after completion of safety and PK assessments and returned for a follow-up visit approximately 14 days after receiving their last dose.

2.5 Safety assessments

Safety assessments throughout the study included monitoring of AEs, physical examinations, vital signs (oral temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure), cardiac telemetry monitoring, clinical laboratory tests, pregnancy status of female partners, and recording of electrocardiograms (ECGs) at predefined timepoints. In addition, levels of the following hormones were monitored: adrenocorticotropic hormone (ACTH), cortisol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), tri-iodothyronine (T3), free thyroxine (T4), total testosterone, and dihydrotestosterone (DHT).

2.6 Pharmacodynamic assessments

Urine samples were analysed to measure prostaglandin and inflammatory PD markers, including tPGDM, tetranor-prostaglandin E metabolite (tPGEM), and creatinine. Muscle biopsies were examined to assess the PK-PD relationship of GSK3439171A and the inhibition of H-PGDS in muscle tissue.

2.7 Determination of GSK3439171A and prostaglandins

High-performance liquid chromatography with tandem mass spectrometry was used to measure concentrations of GSK3439171A in plasma, muscle homogenate, and urine samples. Details are provided in the online Supporting Information: Methods. All PK parameters were calculated using Phoenix WinNonlin® software (Certara®).

Concentrations of prostaglandins in muscle and urine samples were determined by validated high-performance liquid chromatography–tandem mass spectrometry methods. A validated colorimetric method was used to assess creatinine concentrations in urine samples, enabling correction of tPGDM and tPGEM values. Please refer to the online Supporting Information: Methods for details.

2.8 Assessment of GSK3439171A metabolism

Metabolites of GSK3439171A were analysed in plasma, urine, and bile samples obtained after administration of the 40 mg dose (plasma and urine samples) or the 11 mg dose (bile samples). Please refer to the online Supporting Information: Methods for details.

3 RESULTS

3.1 Participant characteristics

In total, 18 participants were randomised to treatment in Part A, 36 in Part B, and 12 in Part C. Participant characteristics are summarised in Table 1. All participants were male, with a mean age of approximately 43 years. Mean height, weight, and BMI were similar among participants in Parts A–C. The majority of participants in Part A (67%) and half of the participants in Part C (50%) were Black or African American, and the majority of participants in Part B were of White/Caucasian/European heritage (58%).

3.2 Safety

In total, 8 (44%) of participants in Part A, 16 (59%) in Part B, and 4 (33%) in Part C who received active doses of GSK3439171A experienced an AE (Table 2). All AEs were mild or moderate in intensity. No AEs in

Parts A or C were reported in more than one participant. The most common AE in Part B was procedural pain related to the muscle biopsy, reported by 8 (30%) participants; these events were determined to be unrelated to the study drug.

Two participants in each part withdrew from the study due to non-serious AEs; mild gastroenteritis and moderate streptococcal pharyngitis in Part A, moderate abdominal pain and moderate allergic rash in Part B, and moderate allergic rash and ventricular tachycardia in Part C.

The most common drug-related AE across all parts of the study was drug hypersensitivity. These events presented as a non-serious skin rash in 4 out of the 57 participants (7%) exposed to GSK3439171A (1 participant in Part A, 2 participants in Part B, and 1 participant in Part C). Three of the cases were considered to be related to GSK3439171A treatment and, based on dermatologist assessment, they were most likely allergic in nature. The rashes were moderate in intensity, maculo-papular in appearance, non-pruritic, and without any systemic complications. One participant consented to a skin biopsy which showed a mild perivascular infiltrate of lymphocytes with scattered eosinophils surrounding the superficial vascular plexus, consistent with an allergic reaction. These events all resolved spontaneously without any treatment. The other drug-related AEs were headache, facial flushing, intermittent abdominal pain, and non-sustained ventricular tachycardia (all n = 1).

No deaths, serious AEs (SAEs), or clinically significant changes in vital signs, ECG, or laboratory parameters were reported during the study. Hormone monitoring during the repeat-dose part of the study did not show any consistent or clinically significant changes.

3.3 Pharmacokinetics

The single-dose PK of GSK3439171A from Part A are presented in Table 3. The geometric mean of the highest studied maximum observed concentration (C_{max}) and area under the concentration-time curve from time zero extrapolated to infinite time ($AUC_{(0–inf)}$) were 2938.0 ng/mL and 46844.6 ng/mL, respectively, corresponding to a single 180 mg dose of GSK3439171A. Dose-proportional increases in C_{max} and $AUC_{(0–inf)}$ were observed for GSK3439171A following single doses of 5–180 mg. The observed geometric mean half-life of GSK3439171A in Part A ranged from 9.8 to 12.0 hours.

The multiple-dose PK of GSK3439171A from Part B are presented in Table 4. Trough plasma concentration (C_{trough}) values indicated that steady state was achieved by the sixth day of treatment. The geometric mean of the highest studied C_{max} and $AUC_{(0–T)}$ were 1016.3 ng/mL and 11851.0 ng*h/mL, respectively, corresponding to the 40 mg once-daily (QD) GSK3439171A dose. Dose-proportional increases in C_{max} and $AUC_{(0–\tau)}$ were observed over the dose range of 5–40 mg QD. Multiple-dose administration of GSK3439171A led to accumulation over time in AUC and C_{max} values. Observed steady-state accumulation was comparable to predicted accumulation, and time-invariant PK was observed for doses 5–40 mg QD. GSK3439171A was detected in muscle tissue at the measured time points in healthy participants, with an estimated mean muscle:plasma ratio of 0.4.

In Part C, no notable differences were observed in the PK profile of GSK3439171A following a single 60 mg dose taken with or without food (Table 5).

3.4 Pharmacodynamics

The presence of GSK3439171A was detected in muscle biopsies from participants, but no modulation was observed in any of the biomarkers tested in the muscle samples, i.e. PGD_2, prostaglandin E_2 (PGE_2), 6-keto prostaglandin F1α (6-KETO-PGF), prostaglandin F2a (PGF2A), and thromboxane B2 (TXB2). The urinary biomarker tPGDM was detected in participants, but no consistent suppression with GSK3439171A was observed. In Part A, urinary tPGDM aggregated values were increased two-fold as compared to baseline 12–24 hours after receiving doses of placebo, 5 mg, and 30 mg of GSK3439171A (Supporting Information Table S1). Similar observations were reported for creatinine-corrected tPGDM aggregated values. In Part

B, the urinary tPGDM aggregated value showed a two-fold increase versus baseline 12–24 hours after the 5 mg dose of GSK3439171A on Day 17 (Supporting Information Table S2). Changes versus baseline with the other doses and at other timepoints were smaller. tPGEM values (aggregated and creatinine-corrected aggregated) showed little change from baseline in Part A or Part B. No dose-dependent changes from baseline were observed in any of the biomarkers that were assessed.

3.5 PK/PD interaction

Although there were some trends, overall, there was no relationship between creatinine-corrected urinary tPGDM change from baseline and GSK3439171A concentrations at the different doses studied. A reference plot of GSK3439171A concentration versus creatinine-corrected urinary tPGDM ratio to baseline after a single 60 mg dose in Part A is presented in Figure 2.

3.6 Metabolism

Unchanged GSK3439171A comprised approximately 82% of drug-related material (DRM) in the plasma. Several metabolites were formed by oxidation of the benzothiazole ring to an aniline, and these comprised approximately 14% of total DRM (including a potential major metabolite accounting for approximately 10% of circulating DRM).

Unchanged GSK3439171A represented approximately 8% of the dose in urine. The majority of the dose in urine was eliminated as metabolites, with approximately 23% related to oxidation of the benzothiazole ring. Minor metabolites, each representing 3% or less of the dose in urine, included products of oxidation, glucuronidation, sulfation, hydration plus methylation, dehydrogenation, and combinations thereof. In duodenal bile, the only drug-related material was unchanged GSK3439171A.

4 DISCUSSION

This FTiH study evaluated the safety, tolerability, PK, and PD of GSK3439171A in 57 healthy adult male participants. The results show that GSK3439171A was well tolerated, with no SAEs being reported.

Most AEs observed in our study were unrelated to the study drug. A minority of patients in each cohort ([?]17%) experienced AEs that may have been caused by GSK3439171A, most commonly drug hypersensitivity (n = 4 [7%]), manifested as non-serious skin rash that resolved spontaneously without the need for treatment. No further safety concerns were raised, with a lack of any SAEs or clinically significant changes in vital signs, ECG, or laboratory parameters including hormone levels. These results suggest consistency with the safety profile of TAS-205 and support the viability of H-PGDS inhibition as a method of treating inflammatory diseases [7,10].

Our study showed that GSK3439171A has a dose-proportional and linear PK profile in healthy male participants. PK parameters were consistent regardless of whether the drug was taken with or without food, and the geometric mean half-life was 10–15 hours. Further studies are needed to confirm whether the findings of our study are applicable to the target patient populations.

Although GSK3439171A was detected in muscle biopsies, urinary tPGDM levels were not consistently suppressed by GSK3439171A in healthy participants. This may be a result of ongoing prostaglandin synthesis via L-PGDS under basal, non-inflammatory conditions. The expression patterns of L-PGDS are distinct from those of H-PGDS: L-PGDS is located principally in the central nervous system, heart, and male genital organs, with further (lower-level) expression in muscle cells [2,14,15]. L-PGDS is not suppressed by GSK3439171A, as the drug is selective for H-PGDS. Basal levels of H-PGDS are low in healthy individuals. It is only in certain settings (e.g. increased inflammation, muscle necrosis, DMD) that H-PGDS activity is elevated, with associated increases in tPGDM levels [7,8]. Therefore, it is unsurprising that GSK3439171A

does not reduce tPGDM levels in healthy volunteers; studies in patients with higher pre-treatment levels of tPGDM are needed to show an effect.

Although a potentially reactive metabolite of GSK3439171A (aniline) was identified in plasma and urine, further metabolism of the aniline or glutathione-conjugated metabolites was not detected in either matrix. However, metabolites generated by further oxidation of the sulphur on the resulting methylthioaniline have been identified in human urine (˜21% of the dose), indicating a possible alternative clearance pathway from the aniline.

In contrast to PGD_2, some products of arachidonic acid metabolism produce beneficial signalling in muscle tissue, such as prostaglandin E_2 and prostaglandin $F_{2\alpha}$. Therefore, treatments that decrease global inflammatory signalling (e.g. non-steroidal anti-inflammatory drugs [NSAIDs]) may not be efficacious [16]. For example, in patients recovering from surgical interventions involving tendons and their associated structures, NSAIDS can block tendon healing [17,18]. We showed that GSK3439171A has no measurable effect on levels of the PGE_2 metabolite tPGEM, suggesting that this drug could help control inflammation without reducing the beneficial effects of arachidonic acid metabolites other than PGD_2 [3]. Thus, selective inhibition of H-PGDS offers therapeutic potential for muscle-related disorders (e.g. DMD) and muscular recovery following injury.

This exploratory study was conducted in healthy participants. An important limitation was lack of inflammation in the study participants, meaning that only basal levels of PGD_2 were observed. We hypothesize that this basal PGD_2 was primarily synthesized by L-PGDS, meaning that the pharmacodynamic effects of GSK3439171A (an H-PGDS inhibitor) and its clinical efficacy could not be observed. It is possible that the safety profile will be slightly different in patients with inflammatory diseases, many of whom are likely to require long-term treatment. The number of patients in our study was too small for detection of rare AEs. This FTiH study was conducted as a precursor to investigating the effects of H-PGDS inhibition in DMD. Almost all cases of this disease are in males, hence our selection of male participants. Study strengths included the randomized, double-blind design, and administration of multiple as well as single doses. Measurement of PK and PD in the target tissue (muscle) as well as in systemic circulation represents a further strength.

5 CONCLUSIONS

This FTiH study shows that GSK3439171A was well tolerated in healthy participants and there were no SAEs. A range of single doses and once-daily doses over 7–14 days were administered. Inhibition of H-PGDS is a promising approach to treating inflammatory diseases, although follow-up studies are required to further investigate the potential of GSK3439171A.

Acknowledgements

GSK3439171A was discovered under a research and development collaboration and license agreement with Astex Pharmaceuticals.

Medical writing support was provided by Chris Williams and Tony Reardon of Aura, a division of Spirit Medical Communications Group Ltd, funded by GlaxoSmithKline.

Conflict of interest

At the time of the study, all authors were employees of GlaxoSmithKline and TH, NT, CS, RZR, and VB held stocks/shares in GlaxoSmithKline.

Study funding

This study was supported by GlaxoSmithKline.

Data availability

The datasets used and/or analyzed during the current study are available from www.clinicalstudydatarequest.com on reasonable request.

Author contributions

All authors contributed to the design and conduct of this study, data analyses/ interpretation, and manuscript writing.

References

1. Boie Y, Sawyer N, Slipetz D, Metters K, Abramovitz M. Molecular cloning and characterization of the human prostanoid DP receptor. J Biol Chem 1995; 270:18910-18916.
2. Urade Y, Hayaishi O. Prostaglandin D synthase: structure and function. Vitam Horm 2000; 58:89-120.
3. Mohri I, Aritake, K, Taniguchi H, et al. Inhibition of prostaglandin D synthase suppresses muscular necrosis. Am J Pathol 2009; 174:1735-1744.
4. Hirata T, Narumiya S. Prostanoid receptors. Chem Rev 2011; 111:6209-6230.
5. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. Arterioscler Thromb Vasc Biol 2011; 31:986–1000.
6. Rittchen S, Heinemann A. Therapeutic potential of hematopoietic prostaglandin. Cells 2019; 8:619.
7. Komaki H, Maegaki Y, Matsumura T, et al. Early phase 2 trial of TAS-205 in patients with Duchenne muscular dystrophy. Ann Clin Transl Neurol 2020; 7:181-190.
8. Takeshita E, Komaki H, Tachimori H, et al. Urinary prostaglandin metabolites as Duchenne muscular dystrophy progression markers. Brain Dev 2018; 40:918-925.
9. Lee K, Lee SH, Kim TH. The biology of prostaglandins and their role as a target for allergic airway disease therapy. Int J Mol Sci 2020; 21:1851.
10. Takeshita E, Komaki H, Shimizu-Motohashi Y, Ishiyama A, Sasaki M, Takeda S. A phase I study of TAS-205 in patients with Duchenne muscular dystrophy. Ann Clin Transl Neurol 2018; 5:1338-1349.
11. ClinicalTrials.gov. A phase 3 study of TAS-205 in patients with Duchenne muscular dystrophy (REACH-DMD). Updated February 2021. https://clinicaltrials.gov/ct2/show/NCT04587908. Accessed June 7, 2021.
12. GlaxoSmithKline. A three-part FTiH study to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of single and repeat oral doses of GSK3439171A, in a randomized, double-blind (sponsor unblinded), placebo-controlled, dose escalation study and to evaluate the effect of food on a single oral dose of GSK3439171A in healthy adult participants. 2019. https://clinicaltrials.gov/ProvidedDocs/94/NCT03627494/Prot_000.pdf. Accessed June 7, 2021.
13. Guiney WJ, Beaumont C, Thomas SR, et al. Use of Entero-Test, a simple approach for non-invasive clinical evaluation of the biliary disposition of drugs. Br J Clin Pharmacol 2011; 72:133-142.
14. Eguchi Y, Eguchi N, Oda H, et al. Expression of lipocalin-type prostaglandin D synthase (beta-trace) in human heart and its accumulation in the coronary circulation of angina patients. Proc Natl Acad Sci U S A 1997; 94:14689-14694.

15. Urade Y, Eguchi N, Hayaishi O. Lipocalin-type prostaglandin D synthase as an enzymic lipocalin. In: Madame Curie Bioscience Database [Internet]. Austin (TX): Landes Bioscience; 2000–2013. https://www.ncbi.nlm.nih.gov/books/NBK6621/. Accessed June 7, 2021.
16. Korotkova M, Lundberg IE. The skeletal muscle arachidonic acid cascade in health and inflammatory disease. Nat Rev Rheumatol 2014; 10:295-303.
17. Cohen D, Kawamura S, Ehteshami J, Rodeo S. Indomethacin and celecoxib impair rotator cuff tendon-to-bone healing. Am J Sports Med 2006; 34:362-369.
18. Connizzo BK, Yannascoli SM, Tucker JJ, et al. The detrimental effects of systemic ibuprofen delivery on tendon healing are time dependent. Clin Orthop Relat Res 2014; 472:2433-2439.

Tables

TABLE 1 Participant characteristics

Participant characteristics	**Part A**	**Part B**	**Part C**
N	18	36	12
Age, mean (SD)	42.4 (8.4)	42.7 (9.6)	43.1 (10.9)
Sex, % male	18 (100)	36 (100)	12 (100)
Completed, n (%)	16 (89)	34 (94)	10 (83)
Withdrawn from the study for any reason, n (%)	2 (11)	2 (6)	2 (17)
Withdrew from the study due to AEs, n (%)	2 (11)	2 (6)	2 (17)
BMI (kg/m^2), mean (SD)	26.4 (2.6)	26.1 (2.6)	26.5 (1.9)
Height (cm), mean (SD)	178.4 (9.8)	176.6 (6.8)	177 (5.2)
Weight (kg), mean (SD)	84.4 (13.9)	81.5 (8.2)	82.4 (6.9)
Race, n (%)			
Black or African American	12 (67)	13 (36)	6 (50)
Asian – East Asian heritage	0	2 (6)	0
White/Caucasian/European heritage	6 (33)	21 (58)	5 (42)
Multiple	0	0	1 (8)

Abbreviations: AE, adverse event; BMI, body mass index; SD, standard deviation.

Incidence of AEs

Part A

(N = 18)

Part B

(N = 27)

Part C

(N = 12)

Number of participants with any AE, n (%)

8 (44)[a]

16 (59)[b]

4 (33)[a]

Number of participants with any AE related to study drug, n (%)

3 (17)[a]

2 (7)[b]

2 (17)[a]

TABLE 2 Summary of adverse events

[a]Includes one patient with drug hypersensitivity.[b]Includes two patients with drug hypersensitivity. Abbreviation: AE, adverse event.

TABLE 3 Pharmacokinetic parameters following GSK3439171A single oral dose

Dose (mg)	$AUC_{(0–inf)}$ (ng.h/mL), geometric mean, (%CVb)	C_{max} (ng/mL), geometric mean, (%CVb)	$t_{1/2}$ (h), geometric mean, (%CVb)	T_{max} (h), geometric mean, (%CVb)
5 (n = 6)	1247.2 (51.9)	111.0 (10.9)	9.8 (46.4)	1.3 (103.4)
10 (n = 6)	2305.3 (34.5)	214.0 (28.1)	11.2 (44.6)	1.1 (87.6)
30 (n = 5)	9441.8 (22.2)	635.4 (26.8)	12.0 (7.5)	1.4 (77.5)
60 (n = 6)	17257.9 (28.7)	1272.3 (19.4)	11.2 (17.8)	1.5 (78.6)
120 (n = 6)	36478.0 (26.1)	2132.5 (19.1)	11.8 (19.3)	3.4 (28.6)
180 (n = 6)	46844.6 (15.2)	2938.0 (21.2)	11.1 (22.1)	2.8 (37.4)

Abbreviations: $AUC_{(0–inf)}$, area under concentration-time curve from time zero extrapolated to infinite time; C_{max}, maximum observed concentration; CVb, between-participant coefficient of variation; $t_{1/2}$, terminal phase half-life; t_{max}, time of occurrence of maximum observed concentration.

TABLE 4 Pharmacokinetic parameters following GSK3439171A repeat dosing for 14 days (5 and 11 mg doses) and for 7 days (40 mg dose)

Dose (mg)	Visit	$A\Upsilon^{\urcorner}{}_{(0–\tau)}{}^{\propto}$ ($\nu\gamma.\eta/\mu\Lambda$), geometric mean, (%CVb)	C_{max} (ng/mL), geometric mean, (%CVb)	$t_{1/2}$ (h), geometric mean, (%CVb)	T_{max} (h), geometric mean, (%CVb)
5 (n = 9)	Day 1	1171.4 (20.4)	117.4 (25.1)	15.4 (26.6)	1.3 (103.1)
	Day 17	1627.4 (24.3)	138.1 (19.3)	13.3 (23.8)	2.3 (54.2)
11 (n = 7)	Day 1	1892.9 (25.2)	192.6 (20.8)	14.3 (32.4)	2.2 (36.6)
	Day 17	2903.3 (34.0)	243.9 (28.0)	11.6 (11.3)	2.4 (28.6)
40 (n = 9)	Day 1	7943.9 (21.1)	682.6 (24.8)	11.9 (18.9)	2.9 (57.2)
	Day 17	11851.0 (21.7)	1016.3 (24.3)	10.9 (18.4)	2.8 (22.1)

[a]Refers to steady-state $AUC_{(0-\tau)}$ at Day 17 for 5 mg and 11 mg QD dose, and Day 10 for 40 mg dose.

Abbreviations: $AUC_{(0-\tau)}$, area under concentration-time curve from time zero to the end of the dosing period; C_{max}, maximum observed concentration; CVb, between-participant coefficient of variation; QD, once daily; $t_{1/2}$, terminal phase half-life; t_{max}, time of occurrence of maximum observed concentration.

TABLE 5 Pharmacokinetic parameters following single-dose GSK3439171A in fed versus fasted state

Dose (mg)	$AUC_{(0-\tau)}$[1] (ng.h/mL), geometric mean, (%CVb)	C_{max} (ng/mL), geometric mean, (%CVb)	$t_{1/2}$ (h), geometric mean, (%CVb)	T_{max} (h), geometric mean, (%CVb)
60 mg fasted (n = 11)	16458.9 (27.4)	1156 (16.3)	10.8 (13.7)	2.5 (54.5)
60 mg fed (n = 11)	14995.0 (29.7)	1025 (21.2)	11.7 (19.7)	3.2 (34.2)

Abbreviations: $AUC_{(0-inf)}$, area under concentration-time curve from time zero extrapolated to infinite time; C_{max}, maximum observed concentration; CVb, between-participant coefficient of variation; $t_{1/2}$, terminal phase half-life; t_{max}, time of occurrence of maximum observed concentration.

Figure 1. Study design

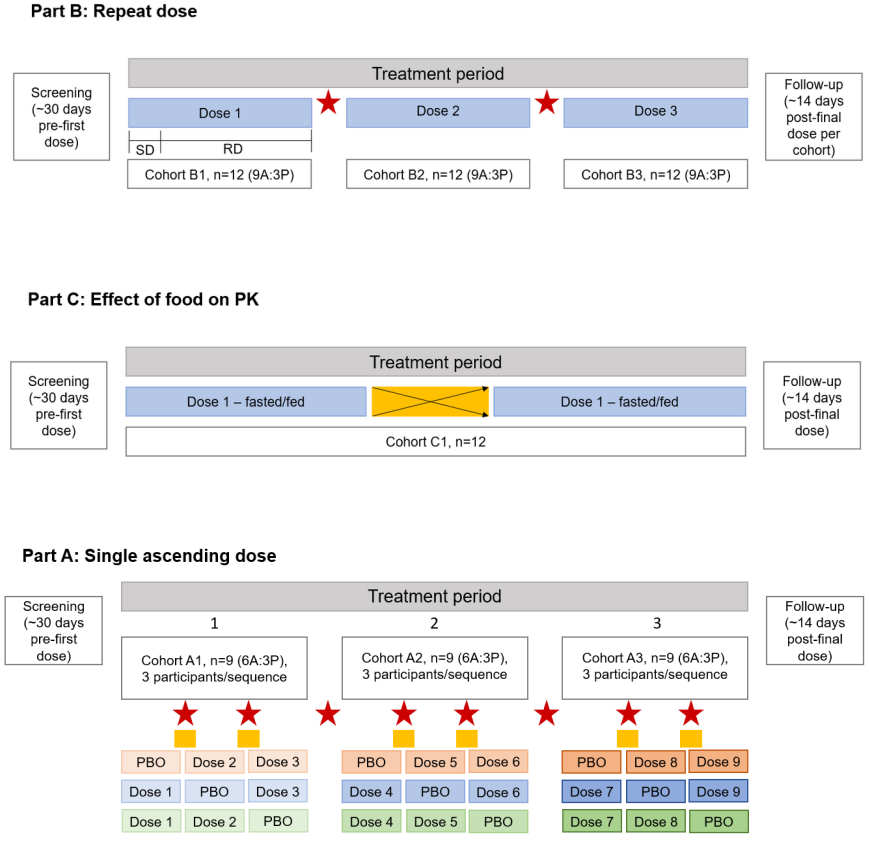
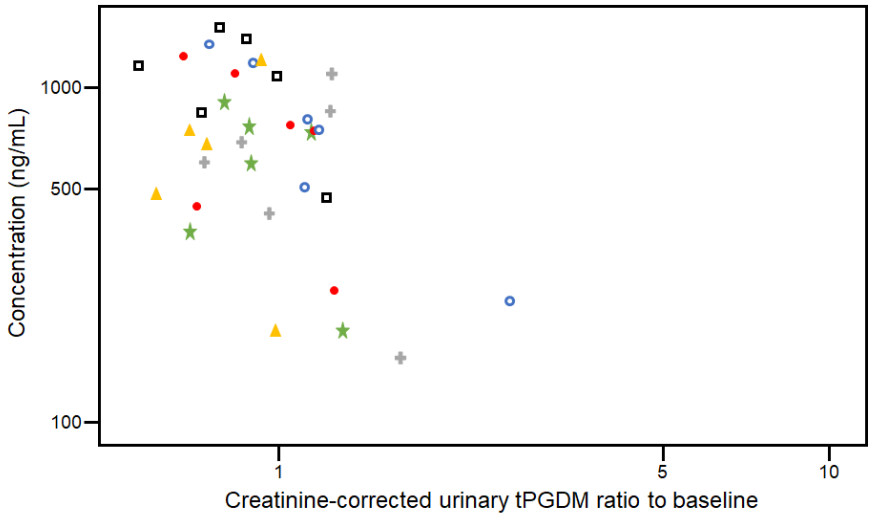


Figure 2. Reference plots of GSK3439171A concentration versus creatinine-corrected urinary tetranor ratio to baseline following a single 60 mg dose (Part A). Each symbol represents an individual subject. For each subject, concentration of GSK3439171A is plotted against creatinine-corrected urinary tPGDM ratio to baseline for 6 time points (2 hr, 4 hr, 6 hr, 8 hr, 12 hr and 24 hr).



Hosted file

Figure 1.pptx available at https://authorea.com/users/423929/articles/529135-a-phase-1-study-of-single-and-repeat-oral-doses-of-gsk3439171a-a-highly-selective-h-pgds-inhibitor-in-healthy-adult-participants

Hosted file

Figure 2.pptx available at https://authorea.com/users/423929/articles/529135-a-phase-1-study-of-single-and-repeat-oral-doses-of-gsk3439171a-a-highly-selective-h-pgds-inhibitor-in-healthy-adult-participants