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Investigating the effect of TRPV4 inhibition on pulmonary-vascular barrier permeability following segmental endotoxin challenge

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Research

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Abstract

Background

Acute Respiratory Distress Syndrome (ARDS) is associated with increased pulmonaryvascular permeability. In the lung, transient receptor potential vanilloid 4 (TRPV4), a Ca^{2+}-permeable cation channel, is a regulator of endothelial permeability and pulmonary edema. We performed a Phase I, placebocontrolled, doubleblind, randomized, parallel group, proofofmechanism study to investigate the effects of TRPV4 channel blocker, GSK2798745, on pulmonaryvascular barrier permeability using a model of lipopolysaccharide (LPS)induced lung inflammation.

Methods

Healthy participants were randomized 1:1 to receive 2 single doses of GSK2798745 or placebo, 12 hours apart. Two hours after the first dose, participants underwent bronchoscopy and segmental LPS instillation. Total protein concentration and neutrophil counts were measured in bronchoalveolar lavage (BAL) samples collected before and 24 hours after LPS challenge, as markers of barrier permeability and inflammation, respectively. The primary endpoint was baseline adjusted total protein concentration in BAL at 24 hours after LPS challenge. A Bayesian framework was used to estimate the posterior probability of any percentage reduction (GSK2798745 relative to placebo). Safety endpoints included the incidence of adverse events (AEs), vital signs, 12-lead electrocardiogram, clinical laboratory and haematological evaluations, and spirometry.

Results

Forty-seven participants were dosed and 45 completed the study (22 on GSK2798745 and 23 on placebo). Overall, GSK2798745 was well tolerated. Small reductions in mean baseline adjusted BAL total protein (~ 9%) and neutrophils (~ 7%) in the LPS-challenged segment were observed in the GSK2798745 group compared with the placebo group; however, the reductions did not meet pre-specified success criteria of at least a 95% posterior probability that the percentage reduction in the mean 24hours post LPS BAL total protein level (GSK2798745 relative to placebo) exceeded zero. Median plasma concentrations of GSK2798745 were predicted to inhibit TRPV4 on lung vascular endothelial cells by ~ 7085% during the 24 hours after LPS challenge; median ureacorrected BAL concentrations of GSK2798745 were 3.0 to 8.7fold higher than those in plasma.

Conclusions

GSK2798745 did not affect segmental LPS-induced elevation of BAL total protein or neutrophils, despite blood and lung exposures that were predicted to be efficacious.

Background

Acute respiratory distress syndrome (ARDS) is characterized by inflammation in the lung, increased pulmonaryvascular permeability, and influx of proteinrich fluid into the alveoli, leading to profound inhibition of pulmonary surfactant [Günther, 1996] with loss of aerated lung tissue [Bellani, 2016]. ARDS represents a significant unmet need and substantial healthcare burden, with limited pharmacological treatment options and a mortality rate of up to 40% [Bellani, 2016; Matthay, 2012]. Determining efficacy of new pharmacological interventions in ARDS patients has proved challenging, due to a heterogenous patient population and a lack of intermediate endpoints, requiring large trials to demonstrate efficacy [Spieth, 2014; Rubenfeld, 2015; Matthay, 2017]. Thus, confirming proofofmechanism of a prospective therapy in healthy people, using models relevant to the pharmacological action of the intervention, can be useful before embarking on trials in vulnerable ARDS patients.

A common surrogate model of acute lung injury involves challenge with lipopolysaccharide (LPS), either by inhalation or direct instillation into the lung. Although LPS challenge models traditionally have been used to test antiinflammatory effects [Michel, 2007; Hohlfeld, 2008; Janssen, 2013; Hernandez, 2015; Singh, 2015], endotoxin also causes barrier disruption, as indicated by increases in large molecules in the alveolar space of LPStreated tissue [Holz, 2015].

Transient receptor potential vanilloid 4 (TRPV4) has been implicated as a key regulator of lung endothelial barrier integrity, specifically, the integrity of the alveolar capillary endothelium. Activation of TRPV4 by hydrostatic stretch in lung microvessels leads to increased endothelial Ca^{2+} concentration and an increase in endothelial permeability [Morty, 2014]. The importance of TRPV4 in maintaining pulmonary barrier function has been demonstrated in the settings of elevated pulmonary venous [Thorneloe, 2012] or airway pressure [Hamanaka, 2010] and following treatment with chemical and biological toxins such as HCl and platelet activating factor [Balakrishna, 2014; Morty, 2014; Yin, 2016]. In those studies, TRPV4 blockade limited lung damage by reducing plasma fluid leak into the alveolar space and by modulating neutrophil and macrophage recruitment and activity, thus improving oxygenation and reducing overall mortality [Balakrishna, 2014, Morty, 2014, Yin, 2016; Dalsgaard, 2016]. This collective evidence suggests that blockade of the TRPV4 channel may provide benefit in patients with ARDS where alveolar capillary leak is a primary driver of injury.

GSK2798745 is a potent and selective TRPV4 channel blocker [Brooks, 2019] that has been tested in healthy participants [Goyal, 2019] and patients with heart failure [Glenn, 2020] and chronic cough [Ludbrook, 2019]. The primary aim of this study was to determine the effect of GSK2798745 on BAL total protein following segmental LPS challenge, as a marker for pulmonaryvascular barrier disruption, secondary to acute inflammation.

Methods

Study Design

This placebo-controlled, double-blind, randomized, parallel group study was conducted from June to December 2018 at a single site in Germany. Participants were randomized 1:1 to receive GSK2798745 (4.8 mg, following by 2.4 mg 12 hours later) or placebo. The dosing regimen was selected to achieve maximum exposure during the 24 h experimental period, after LPS challenge, without exceeding margins determined by pre-clinical toxicity studies. The treatment visit is detailed in Fig. 1.

The study was approved by the Ethical Committee of Hannover Medical School (Hannover, Germany) and was conducted in accordance with the revised Declaration of Helsinki (2008), the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and Good Clinical Practice. Full written informed consent was obtained from all participants before the performance of any study-specific procedures. (ClinicalTrials.gov identifier: NCT03511105; EudraCT number: 2017-002388-16.)

Population

A total of 47 healthy, non-smoking participants, defined as > 6 months non-smoking and < 5 pack years, were enrolled in the study (GSK2798745: n = 22; placebo: n = 25). Participants were all males, aged 20–42 years, and had normal lung function, as determined by spirometry. Fortyfive (45) participants (GSK2798745: n = 22; placebo: n = 23) completed the study and were included in the primary analysis. Two participants in the placebo group discontinued: one because of an adverse event (AE) that was not related to study treatment or procedures; one was unable to tolerate the bronchoscopy procedure.

Bronchoscopy and challenge procedure

Bronchoscopy and LPS challenge were performed as previously described [Holz, 2015]. A baseline BAL of a segment in the left lower lobe was performed with 100 mL of prewarmed sterile saline (0.9%). Following baseline lavage, LPS (Endotoxin from *E.coli* Type O113 [Clinical Center Reference Endotoxin], List Biological Laboratories, Campbell, CA, USA) 40 EU per kg body weight in 10 mL of pre-warmed sterile saline (equivalent to 4 ng/kg) was instilled into the right middle lobe and 10 mL of pre-warmed sterile saline was given into one lingula segment of the contralateral side as control challenge. Twentyfour hours later, a second bronchoscopy was performed and both instilled segments were lavaged with 100 mL saline each.

Biomarkers

Biomarkers were chosen to represent pathways that are modulated by LPS, including barrier permeability (albumin, total protein, surfactant protein D [SPD]), vascular injury (von Willebrand factor [vWF]) and inflammation (C-reactive protein [CRP], myeloperoxidase [MPO], Interleukin6 [IL6], IL8 and tumour necrosis factor α [TNFα]). Urea was collected for use as a correction factor. Total protein, albumin and urea were assayed in BAL supernatant and plasma, using a colorimetric detection method (Thermo Scientific). CRP was assayed in serum using an immunoturbidimetric method (Automated analyser (AU640) using Randox Reagents; method defined by manufacturers guidelines). SPD and vWF were assayed in serum and BAL supernatant, and MPO was assayed in BAL supernatant, using an

enzymelinked immunosorbent assay (SPD: Biovendor; vWF: ThermoFisher; MPO: R&D Systems). TNFα, IL-6 and IL-8 were assayed in serum and BAL supernatant using an immunoassay (MSD).

BAL cell counts were determined by hemocytometry after staining with trypan blue. Differentiation of macrophages, monocytes, neutrophils, lymphocytes, eosinophils, and bronchial epithelial and squamous cells was performed by light microscopy after staining of cytospin slides with Diff Quik (Medion Diagnostics). For differentiation and counting of monocytes, cells were stained with cluster of differentiation (CD)14- Allophycocyanin (APC) (Beckmann Coulter) and analysed using a Beckman Coulter Navios Flow cytometer, gating on cells with high expression of CD14 and low granularity [Schaumann, 2004].

Pharmacokinetics

Plasma and BAL samples were analysed for GSK2798745, using a validated analytical method based on solid phase extraction, followed by HPLC-MS/MS analysis [Goyal, 2019]. BAL concentrations of GSK2798745 were corrected for dilution, as follows: corrected concentration = BAL concentration x dilution factor, where, dilution factor = plasma/BAL urea concentration [Rennard, 1986].

Statistics

An analysis of covariance model (fitted in a Bayesian framework with noninformative priors for model parameters) was used to estimate the posterior probability of any percentage reduction in mean BAL total protein level and neutrophil count (GSK2798745 relative to placebo). Study success was predefined as at least a 95% posterior probability that the percentage reduction in the mean 24 hours postLPS BAL total protein level (GSK2798745 relative to placebo) exceeded zero. Baseline BAL total protein levels from both treatment groups were used to determine a single baseline value, which was then used to calculate baseline-adjusted 24hour postLPS BAL total protein in both groups. Data are presented as model-adjusted medians and 95% credible intervals.

The sample size was based on an upper limit of feasibility and ensured that there was at least 80% probability of success. Assuming a true treatment effect of a 30% reduction in mean BAL total protein in participants receiving GSK2798745 relative to placebo at 24 hours after segmental LPS challenge to the lung, the probability of study success in relation to the primary endpoint was 82%.

Two interim analyses were conducted: the first included 10 evaluable participants per arm and the second included 20 evaluable participants per arm. Each was based on the predictive probability of meeting the end of study success criterion in the primary endpoint, BAL total protein at 24 hours after LPS challenge. The predictive probability was calculated using predictive inference methods [Hughes, 2009]. At the interim, based on estimates from the observed data, studies of the planned sample of 60 participants were simulated thousands of times and the proportion achieving success in relation to the primary endpoint was calculated. The study was terminated early after the second interim analysis because the predictive probability of success was low (the proportion of simulated studies achieving success was < 7%).

Results

Effect of GSK2798745 on pulmonary-vascular barrier permeability and inflammation following LPS

Segmental LPS induced increases in surrogate markers of pulmonaryvascular permeability and inflammation in BAL, as expected, whereas saline did not affect permeability and induced only small changes in BAL neutrophils (Table 1) [Holz, 2015]. Baseline values were generally consistent between GSK2798745 and placebo groups.

Baselineadjusted BAL total protein in the LPS-challenged segment was − 30.5 (127.1, 65.5) mg/L in the GSK2798745 group compared with the placebo group (Fig. 2). The percentage reduction was 8.73 (21.41, 31.30). The posterior probability of any reduction in mean BAL total protein for GSK2798745 compared with placebo was 74%, which did not meet the pre-defined success criterion of at least 95%.

Baselineadjusted BAL neutrophil count in the LPS-challenged segment was − 4.3 (31.5, 22.9) x 10^6 cells/mL in the GSK2798745 group compared with the placebo group (Fig. 3). The percentage reduction was 7.3 (48.2, 41.6). The posterior probability of any reduction in mean BAL neutrophil count for GSK2798745 compared with placebo was 63%.

BAL albumin, vWF, IL6, IL8, MPO, TNFα and other inflammatory cells (eosinophils, macrophages and monocytes) were elevated following segmental LPS challenge, while BAL SPD appeared to decrease (Supplementary Figures S1 and S2). Blood CRP, IL6 and IL8 were increased following LPS challenge, while blood total protein, albumin, SPD, urea, vWF and TNFα were unchanged (Supplementary Figures S3 and S4).

Apart from BAL vWF, the posterior probability of any reduction (GSK2798745 relative to placebo) following LPS challenge in all barrier permeability, endothelial cell injury and inflammatory markers in BAL and blood was < 95%. For vWF, the probability of any difference was 98%; however, a large proportion of the results were below the lower limit of quantification.

Pharmacokinetics of GSK2798745

Median plasma concentrations of GSK2798745 from 2 h after first dose (the time of LPS challenge) ranged from ~ 6–13 ng/mL (Fig. 4), which correlates to a predicted TRPV4 inhibitory concentration range of 70–85% (IC_{70}–IC_{85}) [Goyal, 2019]. Median ureacorrected GSK2798745 levels in BAL were up to 8.7fold higher than in plasma (Table 2).

Table 1
Effect of GSK2798745 on Total Protein and Neutrophils following LPS

	Total protein (mg/L)		**Neutrophils (10^6 cells/mL)**	
	GSK2798745 *n = 22*	*Placebo* *n = 23*	*GSK2798745* *n = 22*	*Placebo* *n = 23*
Baseline	71.20 (62.59, 81.01)	73.59 (65.02, 83.29)	0.06 (0.04, 0.08)	0.08 (0.05, 0.11)
LPS	315.88 (254.53, 392.00)	351.01 (285.41, 431.70)	53.18 (38.87, 72.74)	60.49 (42.69, 85.71)
Saline	68.23 (59.89, 77.72)	81.94 (69.62, 96.44)	0.15 (0.10, 0.25)	0.25 (0.19, 0.33)

Mean and 95% confidence intervals in BAL samples taken at baseline (2 hours post first GSK2798745/placebo dose), and at 24 h after LPS and saline challenges (26 hours post first GSK2798745/placebo dose).

Table 2
Comparison of plasma and BAL concentrations of GSK2798745

	Median (SD) GSK2798745 concentration (ng/mL)			**Fold difference (BAL urea-corrected/plasma)**
	Plasma ***n = 22***	***BAL*** ***Urea-corrected*** ***n = 22***	***BAL*** ***Uncorrected*** ***n = 22***	
Baseline	13.05 (3.361)	113.82 (40.560)	0.91 (0.321)	8.7
LPS	6.14* (2.086)	18.60 (10.062)	0.25 (0.162)	3.0
Saline		40.81 (20.559)	0.28 (0.165)	6.6

Median (SD) plasma and BAL (urea-corrected and uncorrected) concentrations. Baseline = 2 h post first dose of GSK2798745; LPS and saline = 26 h post-first dose of GSK2798745 (in the relevant segment for BAL concentrations). *Plasma concentration at 26 h post first dose is used for comparison with both the LPS and saline BAL samples.

Safety and tolerability

GSK2798745 was well-tolerated with no drug-related adverse events. The reporting of AEs was similar between groups. Headache and pyrexia were the most frequently reported AEs; both were reported by similar proportion of participants (≤ 20%) in each group (Supplementary Table S1) and are consistent with the systemic effects of LPS challenge [Zielen, 2015; Holz, 2015]. One participant was withdrawn due to an elevated alanine aminotransferase after receiving a single dose of placebo; the event was not considered related to the study treatment or procedures.

As expected and consistent with the effects of LPS, serum CRP, heart rate and temperature were moderately increased after the challenge [Zielen, 2015; Holz, 2015]. All values returned to baseline by follow-up. There were no trends or changes of clinical concern in clinical laboratory values, ECGs, vital signs, or spirometry.

Discussion

This study was conducted to determine whether a TRPV4 antagonist could reduce pulmonaryvascular barrier dysfunction and inflammation following local application of LPS to the human lung, as a model inflammatory stimulus. The model itself performed as expected, with increases in markers of barrier permeability and inflammation in line with those observed previously [Holz, 2015]. Variability was low, allowing a confident decision to be made following an interim analysis of the primary endpoint, total protein in BAL at 24 h after LPS challenge.

Although small reductions were observed in markers of barrier permeability and inflammation in GSK2798745treated compared with placebotreated participants, the probabilities that the reductions indicated a true improvement were below the pre-defined threshold for study success, leading to early termination.

Most biomarkers of barrier permeability and inflammation in BAL and blood behaved as previously reported in response to segmental LPS challenge [Holz, 2015]. In contrast, BAL SPD has previously been shown to be modestly elevated at 24 hours after challenge, but was found to decrease in this study. However, in both studies, the variability in SPD concentrations was large, which may have contributed to marginal changes from baseline that were observed. Although blood concentrations of TNFα and vWF have not previously been reported after segmental LPS challenge, we anticipated an increase in both, given the inflammation and cell damage caused by LPS. However, neither showed any change postchallenge. It is possible that the limited damage caused by the segmental LPS model was insufficient to cause detectable changes. Alternatively, samples may not have been taken at appropriate time points to show an effect.

TRPV4 has been shown to be relevant in several pre-clinical models of pulmonaryvascular barrier dysfunction [Balakrishna, 2014; Hamanaka, 2007; Morty, 2014; Thorneloe, 2012; Yin, 2016] and there is evidence to support a role for TRPV4 in the inflammatory response [Balakrishna, 2014; Yin, 2016]. Even with this body of evidence, it is possible that TRPV4 might be of less relevance to endothelial injury in humans than in the pre-clinical models tested to date. For example, TRPV4 inhibition might not be necessary to modulate the pathophysiological effects of an LPS challenge model in which damage and

inflammation resolve, without intervention, after 48 – 72 hours. While a TRPV4 blocker has been shown to increase survival by 70% in a murine, LPSinduced sepsis model [Dalsgaard, 2016], that model resulted in death of all control mice. Thus, TRPV4 might play a critical role in a severe systemic LPS injury model but be of lesser importance in a less severe model that can resolve spontaneously. A recent study indicates that TRPV4 expressed on macrophages may protect the lung against bacterial (*Pseudomonas aeruginosa*) infectionassociated lung tissue injury by enhancing bacterial clearance and reducing proinflammatory cytokine release [Scheraga, 2020]. However, those data contrast with the majority of published pre-clinical data, including results from a similar study where $TRPV4^{-/-}$ mice were protected against lung edema and protein leak caused by bacterial (*Streptococcus pneumoniae*) infection [Erfinanda, 2017]. In addition, in our study, we found no evidence to suggest that inhibiting TRPV4 caused increases in barrier permeability or inflammatory markers.

Another consideration is that the dose of GSK2798745 might have been insufficient. The dose in this study was selected to give the highest systemic exposure possible in blood, without exceeding margins determined by pre-clinical toxicity studies. The median plasma concentration was predicted to give ~ 85% inhibition (IC_{85}) at peak and IC_{70} at trough [Goyal, 2019]. Importantly, GSK2798745 was detected in BAL, indicating that drug reached the target site. Median ureacorrected concentrations were ~ 4fold IC_{90} immediately before LPS challenge, at 2 hours postfirstdose of GSK2798745, and were at ~ IC_{85} in the LPS challenged lobe at 24 hours after challenge. What is unknown is whether a higher fold inhibitory concentration (e.g. IC_{90} at trough in plasma) is needed for clinical translation of TRPV4 target engagement. Therefore, systemic exposure cannot be discounted as a possible reason for failure to show an effect, though it is unlikely.

In addition to understanding the effects of GSK2798745 on LPS-induced damage, the study had a unique opportunity to understand how differences in lung inflammation and/or pulmonaryvascular permeability might affect drug concentration in BAL samples. The standard technique for estimating epithelial lining fluid (ELF) concentrations of a drug in the lung is to urea correct [Rennard, 1986]. Briefly, under normal physiological conditions, urea concentration in ELF equilibrates to blood concentration. When fluid is applied to the lung and removed quickly, before significant reequilibration of urea has occurred, as is the aim during BAL sampling, urea can be used to estimate the extent of dilution in the resulting sample. In this study, urea levels were higher in the LPS compared with the saline challenged segment, presumably owing to increased pulmonary-vascular barrier permeability leading to increased ELF with additional entry of urea from plasma. That resulted in lower dilution factors in the LPS segment, which in turn could have resulted in lower ureacorrected concentrations of GSK2798745 in the LPS BAL sample. In support, median uncorrected concentrations of GSK2798745 at 26 hours were similar in the LPS and saline-challenged segments (0.25 and 0.28 ng/mL, respectively). Therefore, the impact of increased urea levels on the BAL dilution factor in inflammatory conditions needs to be considered when interpreting urea-corrected BAL data from inflamed and diseased lungs.

Of additional importance, median urea-corrected BAL concentrations of GSK2798745 were 3.0 to 8.7fold higher than in plasma, suggesting higher partitioning from the plasma to the lung compartment. Although the drug was expected to be present in the lung, consistent with its high lipophilicity and good permeability, the levels were not expected to exceed those in plasma to such a high degree, based on pre-clinical assessment (unpublished data). However, the phenomenon is not unprecedented. An area in which plasma/lung partitioning following oral administration has been well-studied is in anti-microbial drugs [Rodvold, 2011; Rodvold, 2017]. Many have lower concentrations in the lung compared with plasma; however, there are several that accumulate in the lung. For example, following oral administration of solithromycin, a lipophilic drug with good permeability, ureacorrected BAL concentrations are 2–28fold higher than plasma concentrations [Rodvold, 2012; Salerno, 2017]. Furthermore, in our study, plasma and BAL concentrations were compared at 2 discrete time points, rather than over the pharmacokinetic profile of GSK2798745. The latter is thought to be more accurate [Rodvold, 2011], therefore the plasma:lung ratios observed here could be affected by the limitations on the time points at which BAL samples were taken during the study. It is also possible that the result was owing to inherent variability in the ureacorrection procedure, as the dilution factor can be affected hugely by small changes in BAL-urea concentration.

Conclusions

GSK2798745 was welltolerated, but did not affect segmental LPS-induced elevation of BAL total protein or neutrophils, despite blood and lung exposures that were predicted to be efficacious. This study does not support GSK2798745, at the exposures observed, as a treatment for pulmonary-vascular barrier dysfunction in ARDS patients.

Finally, consideration should be given to the inflammatory or disease status of the lung before urea-correction is applied. Although ureacorrection of drug concentration in BAL fluid appears to be applicable in healthy lung tissue, damage to the lung tissue might affect the rate of urea equilibration between blood and ELF, invalidating its use as a correction factor.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethical Committee of Hannover Medical School. All participants provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

Competing interests

SM, AH, AF, SH, JW, SW, MB, DJB and ALL are employees of and own shares in GlaxoSmithKline. JMH's institution received funding from GSK for study conduct. JMH received honoraria for consulting and lectures from Boehringer Ingelheim, HAL Allergy, Merck and Novartis outside the scope of this work. PB, MM and CF have no competing interests to declare.

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GlaxoSmithKline authors, together with JMH, were involved in the design, analysis and interpretation of data and preparation of the manuscript. The US Department of Health and Human Services approved the prepared manuscript.

Author Contributions

SM wrote the initial manuscript draft and edited subsequent drafts responding to author comments (AH; AF; SH; JW; SW; MB; DJB; PB; MM; CF; ALL; JMH). Authors who contributed to study design are SM; AH; AF; SH; JW; SW; MB; PB; JMH, those who contributed to data collection are PB; MM; CF; JMH and those who contributed to data interpretation and writing of the manuscript are SM; AH; SH; JW; MB; DJB; ALL; JMH.

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Additional Files

Additional file 1: supplementary figures.pdf

Markers of barrier permeability, endothelial damage and inflammation in BAL and blood, following LPS challenge (GSK2798745 v placebo).

Additional file 2: supplementary table.pdf

Summary of AEs.

Figures

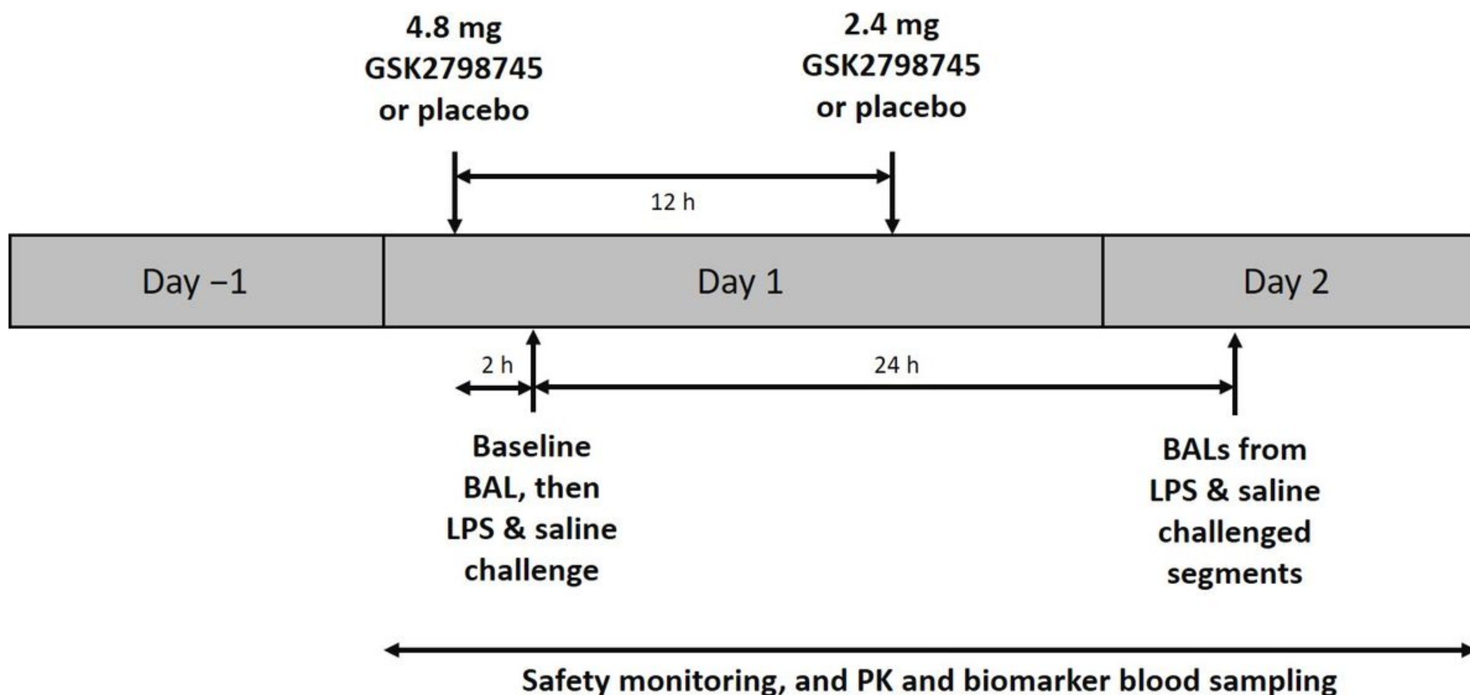

Figure 1

Treatment visit design Healthy participants were randomised 1:1 to receive 2 doses of GSK2798745 or placebo, 12 hours apart. The first and second doses were administered orally, respectively, 2 hours before and 10 hours after LPS instillation; LPS was administered by bronchoscopy. Markers of barrier permeability and inflammation were measured in BAL and blood samples collected before and after LPS challenge.

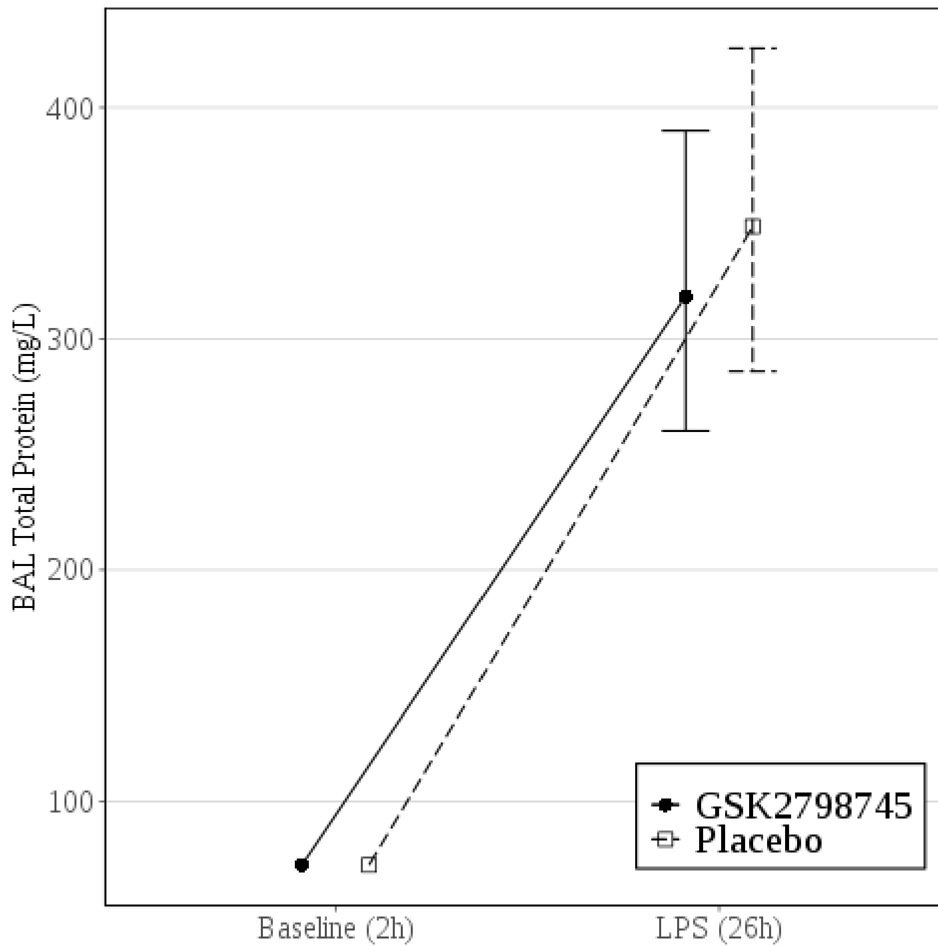

Figure 2

Total Protein in bronchoalveolar lavage, following LPS challenge: GSK2798745 v placebo Model-adjusted median and 95% credible interval of total protein concentration in BAL samples taken at baseline (2 hours post-first GSK2798745/placebo dose), and at 24 h after LPS challenge (26 h post first GSK2798745/placebo dose) (n = 22 for GSK2798745 and 23 for placebo).

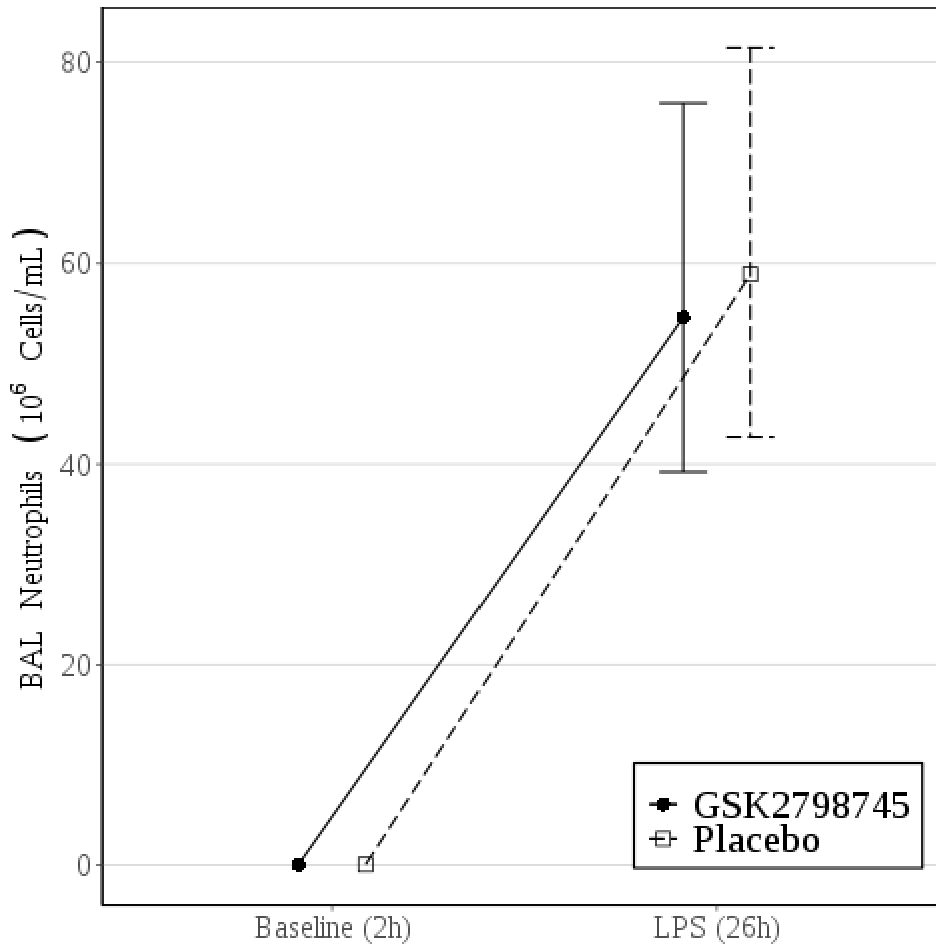

Figure 3

Neutrophils in bronchoalveolar lavage, following LPS challenge: GSK2798745 v placebo Model-adjusted median and 95% credible interval of neutrophils counts in BAL samples taken at baseline (2 hours post-first GSK2798745/placebo dose), and at 24 h after LPS challenge (26 h post first GSK2798745/placebo dose) (n = 22 for GSK2798745 and 23 for placebo).

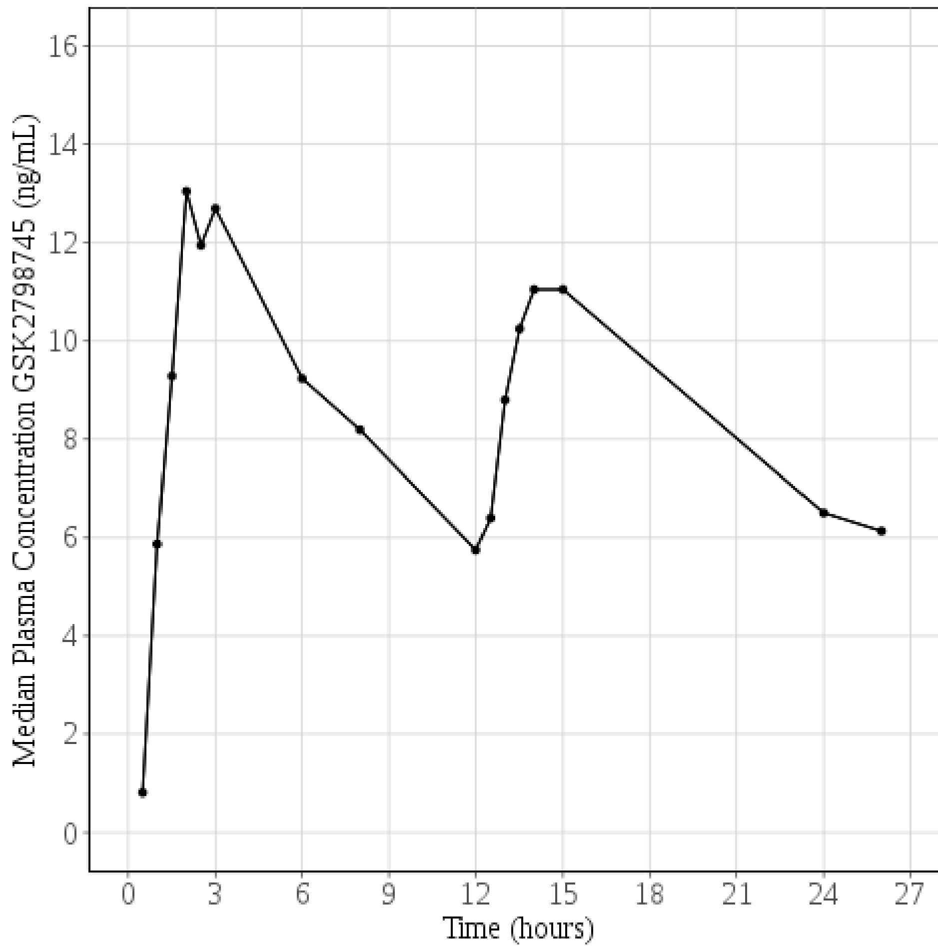

Figure 4

Plasma concentrations of GSK2798745 Median plasma concentrations versus time post-first dose following 4.8mg, followed by 2.4mg 12 h later (n=22).

Supplementary Files

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