Original article

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A phase I, randomized, double-blind study to assess the safety, tolerability and efficacy of the topical RORC2 inverse agonist PF-06763809 in participants with mild-to-moderate plaque psoriasis

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Summary

Background. Transcription factor retinoic acid-related orphan receptor 2 (RORC2/RORγT) mediates interleukin (IL)-17A and IL-17F expression. IL-17A plays a central role in the pathogenesis of several inflammatory disorders, including psoriasis. The RORC2 inhibitor PF-06763809 has been hypothesized to inhibit IL-17A production in T-helper 17 (Th17) cells, thereby reducing psoriasis symptoms.

Aim. To assess the safety, tolerability and effect on skin infiltrate thickness of PF-06763809 in participants with mild/moderate chronic plaque psoriasis.

Methods. This was a randomized, double-blind, first-in-human study (trial registration: ClinicalTrials.gov NCT03469336). Participants received each of the following six treatments once daily for 18 days: three topical doses (2.3%, 0.8%, 0.23%) of PF-06763809, a vehicle and two active comparators (betamethasone and calcipotriol). Primary endpoints included change from baseline in psoriatic skin infiltrate thickness [echo-poor band (EPB) on ultrasonography] at Day 19, and safety. Change in psoriasis-associated gene expression (Day 19), evaluated by real-time reverse transcription PCR of skin biopsies, was an exploratory endpoint.

Results. In total, 17 participants completed the study. Change from baseline in the EPB on Day 19 for all three doses of PF-06763809 was not significantly different from that of vehicle ($P > 0.05$). A significant reduction in EPB from baseline was observed with betamethasone on Day 19 relative to all other treatments ($P < 0.0001$). Treatment-related adverse events were mild/moderate. There were no significant differences in gene expression on Day 19 between vehicle and PF-06763809-treated skin lesions.

Conclusion. Using a psoriasis plaque test design, PF-06763809 was found to be well tolerated with an acceptable safety profile in participants with psoriasis, but without reduction in skin infiltrate thickness or disease biomarkers.

Introduction

Several therapeutic options are available for plaque psoriasis, but there is a clinical need for topical psoriasis medications with fewer adverse effects and with the ability to ameliorate symptoms without a requirement for systemic therapies.[1,2] Transcription factor retinoic acid-related orphan receptor 2 (RORC2, also referred

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to as RORγT) mediates the production of the proinflammatory cytokine interleukin (IL)-17A by T-helper (Th)17 cells.[3,4] IL-17A plays a central role in the pathogenesis of several inflammatory disorders, including psoriasis.[5,6] Compared with healthy individuals, IL-17A-positive cells are upregulated in the blood and skin lesions of individuals with psoriasis.[7,8] Accordingly, antibodies that neutralize homo/heterodimeric IL-17A/A and IL-17A/F (e.g. secukinumab, ixekizumab or bimekizumab) and IL-17 receptor A (e.g. brodalumab) are efficacious in the treatment of psoriasis.[9–12] Moreover, the oral RORC2 inverse agonist VTP-43742 was shown to reduce disease severity in a small cohort of individuals with moderate-to-severe psoriasis.[13]

PF-06763809 is a topical RORC2 inverse agonist that potently inhibits IL-17A production in preclinical assays. This first-in-human study aimed to assess the safety and tolerability of PF-06763809 and evaluate changes in psoriatic skin infiltrate thickness in response to PF-06763809 in a psoriasis plaque test.

Methods

The study was approved by Ethik-Kommission der Ärztekammer Hamburg, Germany, and all participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and was in compliance with the International Council for Harmonization (ICH) and Good Clinical Practice (GCP) Guidelines, and all local regulatory requirements were followed.

Study design

This study (trial registration: ClinicalTrials.gov NCT03469336) was conducted between 24 April 2018 and 20 March 2019 at two sites in Germany. This was a randomized, double-blind, vehicle- and active comparator-controlled, multiple-dose study in participants with psoriasis. Each participant received the following six treatments on up to three comparable plaques (six treatment areas) once daily for 18 days: three topical doses (2.3%, 0.8% and 0.23%) of PF-06763809, the PF-06763809 vehicle and two active comparators [0.1% betamethasone 1 mg/g and calcipotriol 0.005% (50 μg/mL)]. All of the treatments were in solution formulations, and further details of the dose selection are included in the supplementary information (Data S1).

Participants were screened within 28 days prior to the application of the investigational product. Participation in the study was for approximately 7–11 weeks, including the interval from screening to the follow-up call visit on Day 49 (Fig. 1). Participants, investigator site staff and the sponsor study team were blinded to the study treatment. Blinded investigators performed all efficacy and safety assessments; however, a small number of unblinded nurses were designated at each site to ensure that the biopsies were obtained from the correct treatment areas.

Participants

Male or female (of nonchildbearing potential) adults (≥ 18 years old), with a body mass index of 17.5–30.5 kg/m^2, were eligible for enrolment. Participants were required to be in a chronic stable phase of mild-to-moderate psoriasis with a plaque area sufficient for six treatment areas located on one to three plaque lesions, with a skin infiltrate thickness (i.e. EPB) of at least 200 μm. Target lesions were required to be on the trunk and extremities. Exclusion criteria included treatment with locally acting medications, biologics, ultraviolet therapy, or a dose change of systemic medications, which might influence the trial. Full exclusion criteria are described in supplementary information (Data S1).

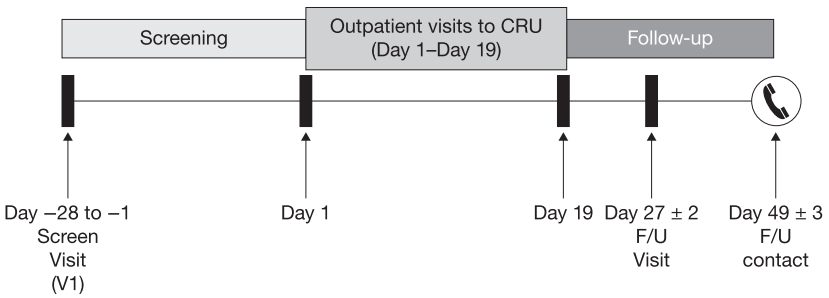

Figure 1 Study design. CRU, Clinical Research Unit; F/U, follow-up; V1, first visit.

Treatment

Each participant received 180 μL of each treatment once daily, which was applied topically to 1.1 cm^2 of skin surface areas under aluminium Duhring® chambers (12 mm inside diameter, 14 mm outside diameter). Further details are included in the supplementary information (Data S1).

Endpoints

Primary endpoint. The primary endpoint was a change from baseline in psoriatic skin infiltrate thickness on Day 19. Measurements were also obtained on Days 1, 7 and 13. Inflammatory infiltrate thickness was assessed by performing 22 MHz high-frequency sonography and by quantifying the width of the EPB (μm). The change in EPB width correlates with the degree of scaling, erythema and thickness components of the Psoriasis Area and Severity Index (PASI).[14] The psoriasis plaque test method used in this study has been successfully performed previously for other investigational topical agents.[15]

Exploratory endpoints. Exploratory endpoints were global clinical assessment scores assessed on Days 1, 7, 13 and 19, and a change in psoriasis-associated gene expression. Gene expression was evaluated by quantitative real-time reverse transcription-PCR. Punch biopsies (3 mm) of the skin treated with PF-06963809 2.3%, PF-06963809 0.23% and vehicle were collected from a subset of consenting participants at Day 19 and were stored frozen in stabilization solution (RNA*later*™; ThermoFisher Scientific, Waltham, MA, USA) until required for analysis. Further details of the gene expression methods are included in the supplementary information (Data S1). Gene expression was first tested in samples that were derived from a phase I study, the methods of which have been previously published.[16]

Safety endpoints. These include adverse event (AE) and serious AE (SAE) monitoring (according to the Medical Dictionary for Regulatory Activities version 21.1), performed during the trial and for a minimum of 28 days after the final administration of the investigational product; clinical laboratory assessments (haematology, chemistry, urinalysis and liver function tests assessed at screening and Days 1–8, 10 and 19), a physical examination (screening and Days 1 and 19) and a vital signs assessment (screening and Days 1, 10 and 19).

Statistical analysis

Statistical methods are described in supplementary information (Data S1).

Results

Participants

In total, 18 eligible participants were assigned to the study treatment, and 17 (94.4%) completed the double-blind treatment and follow-up period (Fig. S1 in Data S1). All participants were male and white with a mean age of 52 years (Table S2 in Data S1).

Psoriatic skin infiltrate thickness (echo-poor band)

No statistically significant differences were observed at any timepoint for the change from baseline between the three PF-06763809 doses (2.3%, 0.8% and 0.23%) and the PF-06763809 vehicle. The active comparator, betamethasone, reduced baseline EPB to a greater extent than did the vehicle but no significant effect was observed with calcipotriol (Fig. 2).

Consistent with the changes in EPB width generally, the global clinical assessment scores were substantially improved at the end of treatment only for the psoriatic lesions treated with betamethasone (Fig. S2 in Data S1).

Psoriasis-associated gene expression

Using samples from a previous phase I study (NCT02310750),[16,17] we found that *IL-17A* and *RORC* gene expression were upregulated and downregulated, respectively, in lesional psoriatic vs. nonlesional skin (Fig. 3). To better understand the pathophysiology of psoriasis, as well as the mechanistic effect of PF-06763809 in the skin in this study, we sought to design and validate a new assay for the *RORC2* isoform using psoriasis biopsies and nonlesional skin from 25 patients enrolled in the previous phase I study.[16] Figure 3 shows the expression in these samples of *IL-17A, RORC* and the two alternatively spliced forms of *RORC*, *RORC1* and *RORC2*, examined using isoform-specific Taqman assays. Expression of both *IL-17A* and *RORC* was increased and decreased, respectively, in lesional compared with nonlesional psoriatic skin. Using specific *RORC1* and *RORC2* primers, we found that whereas *RORC1* had a similar expression pattern to total *RORC*, *RORC2* was expressed at higher levels in lesional compared with nonlesional skin. This is consistent with the role of

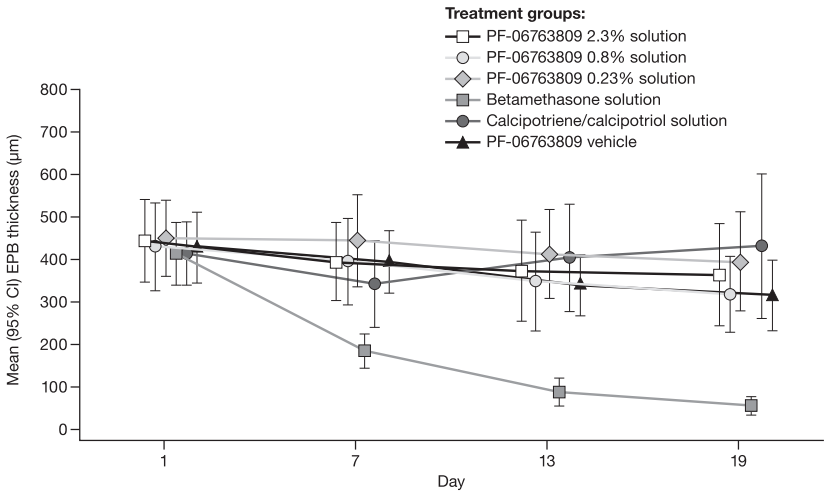

Figure 2 Mean (95% CI) psoriatic skin infiltrate thickness shown by echo-poor band (EPB) in the full analysis set.

RORC2 in stimulating IL-17 production in psoriatic skin lesions.

We then analysed biopsy samples taken from test areas treated with PF-06763809 2.3% or 0.23%, or the vehicle in the current study. No significant difference was observed between psoriatic lesions treated with PF-06763809 or the vehicle for any of the genes that were analysed. Additionally, expression of *RORC1*

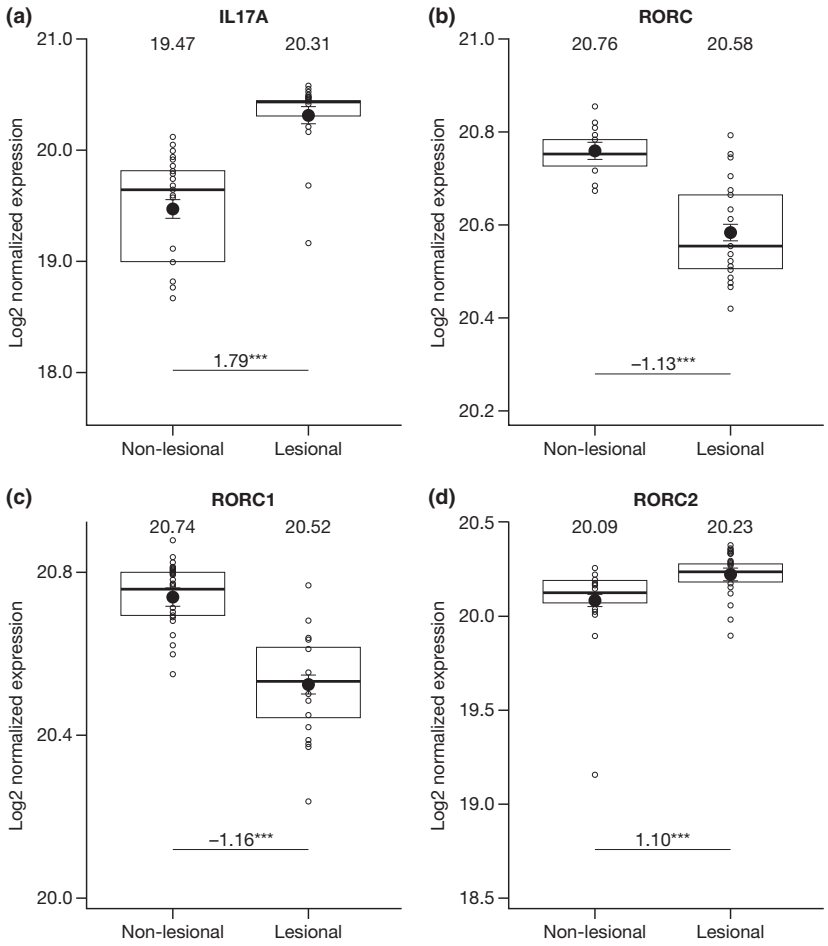

Figure 3 Quantitative real-time reverse transcription PCR analysis of the (a) interleukin (IL)-17A and (b–d) retinoic acid-related orphan receptor (RORC) isoform expression levels in psoriatic skin biopsies at baseline from an independent repository (study NCT02310750). ***$P < 0.0001$. Patient numbers: (a,b) $n = 25$; (c) $n = 24$; (d) $n = 21$. The data are normalized to harmonin-interacting, ankyrin repeat-containing protein (hARP) and represent least squares mean ± SE. The box represents the 25th–75th percentiles.

and *RORC2* was examined using isoform-specific primers; these also did not differ between the PF-06763809-treated and the vehicle-treated areas (Fig. 4). Similar results were observed for the other genes tested (Fig. S3 in Data S1).

Safety

One participant withdrew from the study due to a severe acute exacerbation of psoriasis on Day 10, which was reported to be independent of a treatment area and was not considered treatment-related. The remaining 17 participants completed the double-blind treatment and follow-up period. Four participants (22.2%) had the following five treatment-related AE: one participant reported mild pruritus (Days 5–6) on the PF-06763809 vehicle-treated area, and four participants reported contact dermatitis (two mild at Days 19–28 and 19–22 and two moderate at Days 13–16 and 5–13) on the calcipotriol-treated areas. Two participants with moderate AEs of contact dermatitis discontinued calcipotriol on Days 5 and 13, respectively, but continued all other treatments. No treatment-emergent skin-related serious or severe AEs were reported. The remaining AEs [mild blepharitis (Days 5–7) and nasopharyngitis (Days 15–18)] were not considered treatment-related. No clinically significant laboratory abnormalities, and no changes in vital

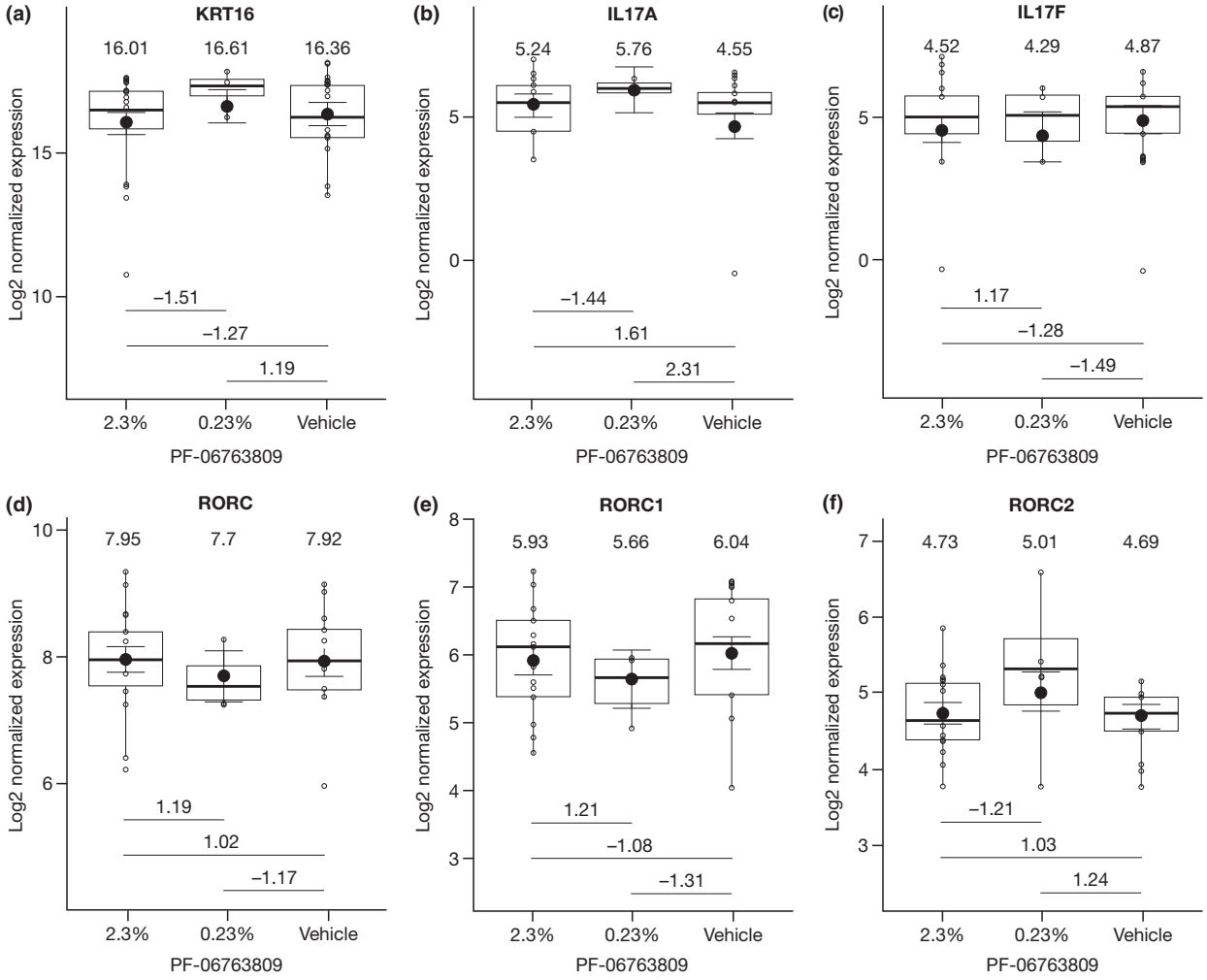

Figure 4 Expression of psoriasis-related genes in psoriatic lesions treated with PF-06763809 or the vehicle at Day 19. The data are normalized to harmonin-interacting, ankyrin repeat-containing protein (hARP) and represent least squares mean ± SE from 34 biopsy samples [2.3% PF-06763809 (n = 13), 0.23% PF-06763809 (n = 4) and PF-06763809 vehicle (n = 17)] with fold-change between groups. The box represents the 25th−75th percentiles. IL, interleukin; KRT16, keratin 16; RORC, retinoic acid-related orphan receptor.

signs or electrocardiography parameters were observed or reported as AEs by the investigator.

Discussion

PF-06763809 is a potent and selective RORC2 inverse agonist that inhibits IL-17 production in human Th17 cells and is active in preclinical skin inflammation models when applied topically (the detailed preclinical characterization of PF-06763809 will be published elsewhere). Thus, we hypothesized that blockade of RORC2 by topical PF-06763809 would ameliorate psoriasis skin infiltrate. However, no significant changes in skin infiltrate thickness or gene expression were observed in this study. Several possible explanations may account for this outcome, including insufficient interaction between the compound and RORC2 in the skin, possibly due to low exposure to the compound or short duration of the study.

The presence of RORC2 in the treated areas was demonstrated by its expression in the biopsies obtained at the end of the treatment period (Fig. 4). However, the concentration of PF-06763809 in the skin biopsies was not examined, as such measurements are unreliable due to contamination of the lower skin layers by the remaining drug on the skin surface[18,19] and uneven drug distribution due to accumulation in the hair follicles.[20–22] Topical application of PF-06763809 may not have achieved the necessary unbound concentrations in the skin required for sufficient RORC2 target engagement. Furthermore, the treatment duration was 18 days, which may have been insufficient to observe changes in psoriasis skin infiltrate thickness. In another relatively small psoriasis study, the oral RORC2 inverse agonist VTP-43742 was reported to cause only a 15% reduction in Psoriasis Area and Severity Score after 21 days of treatment, whereas up to a 30% improvement was observed after 28 days.[13] To date, the inhibition of IL-17 production in T cells located in the lymph nodes or the skin by RORC2 inhibitors has not been tested. Considering that systemic, but not topical, administration of RORC2 inverse agonists showed efficacy in psoriasis, inhibition of RORC2 in secondary lymph organs might be required to suppress Th17 cells in this disease. Our findings are in accordance with a previous report of another topical RORC2 inhibitor.[23]

The active comparator calcipotriol also did not cause a significant decrease in psoriatic skin infiltrate thickness, which was unexpected. Contact dermatitis was observed in four participants on the calcipotriol-treated areas. A sensitivity analysis excluding these four participants increased the numerical difference between calcipotriol and the vehicle, but such a difference did not reach statistical significance (data not shown). However, a notable initial decrease in mean EPB was seen on Day 7 with calcipotriol, which diminished at subsequent timepoints, indicating the potential irritant effect of the calcipotriol's liquid formulation. It is plausible that the calcipotriol solution did not only lead to clinically apparent irritant dermatitis but also led to initial subclinical dermatitis that presented as the return of the EPB to baseline values. Irritation may also have been enhanced by the occlusive application used in this study and potentially explains the lack of effect on EPB. Depending on the vehicle, approximately 6% of conventional calcipotriol ointment and 0.05–0.3% of betamethasone ointment is expected to be absorbed systemically when applied to psoriasis plaques.[24,25]

Conclusion

PF-06763809 was well tolerated in this study; however, its topical application did not show an effect in patients with mild-to-moderate psoriasis, as assessed by sonography measurements of skin infiltrate thickness.

What's already known about this topic?

- RORC2 drives the production of IL-17A by Th17 cells.
- Upregulation of IL-17A is a pathological hallmark of psoriasis; accordingly, IL-17A inhibitors are efficacious in psoriasis.

What does this study add?

- To our knowledge, this study demonstrates for the first time that RORC2 is overexpressed in psoriatic lesions.
- The topical RORC2 inverse agonist PF-06763809 did not reduce skin infiltrate in participants with psoriasis.
- This finding is in accordance with a previous report of another RORC2 topical inhibitor.

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Conflict of interest

GB, YS, EK, GL, AS, TY, HD, KB, CB and BO are employees of Pfizer Inc. and hold stock in the company. ZB was an employee of Pfizer Inc. and held Pfizer stock at the time the study was conducted and continues to hold stock in the company; ZB is currently an employee of Biogen and holds Biogen stock. WW-A, YvM and UK are employees of Bioskin GmbH. RH is Medical Director of Rothhaar Studien GmbH. SG has no conflicts of interest to disclose. JGK declares grants/personal fees from AbbVie, Akros, Allergan, Almirall, Amgen, Arena Pharmaceuticals, Aristea Therapeutics, Asana BioSciences, Aurigene, Avillion, Biogen, Boehringer Ingelheim, Botanix Pharmaceuticals, Bristol-Myers Squibb, Celgene, Eli Lilly, Escalier Biosciences, Exicure, Incyte Corporation, Innovaderm, Janssen Pharmaceutica, Leo Pharma, Menlo Therapeutics, Nimbus Therapeutics, Novan, Novartis, Parexel, Pfizer Inc., Regeneron Pharmaceuticals, Sanofi, Sienna Biopharmaceuticals, Sun Pharmaceutical Industries, UCB, Valeant Pharmaceuticals and Vitae Pharmaceuticals.

Data Availability Statement

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (i) for indications that have been approved in the US and/or EU or (ii) in programmes that have been terminated (i.e. development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for whom an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:
Data S1. Supplementary information.