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Venous thromboembolic events in the tofacitinib ulcerative colitis clinical development programme

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Summary

Background: Tofacitinib is an oral, small molecule JAK inhibitor for the treatment of ulcerative colitis (UC).

Aim: To report incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) in the tofacitinib UC programme.

Methods: DVT and PE were evaluated from one phase 2 and two phase 3 induction studies, one phase 3 maintenance study and an ongoing, open-label, long-term extension (OLE) study (September 2018 datacut). Data were analysed in induction, maintenance and overall (patients receiving ≥ 1 dose of tofacitinib 5 or 10 mg b.d. in any phase 2, 3 or OLE study) cohorts.

Results: 1157 patients (2404 patient-years' exposure; ≤ 6.1 years' tofacitinib treatment) were evaluated in the overall cohort. In induction, one placebo-treated patient had DVT and one had PE; no tofacitinib-treated patients had DVT/PE. In maintenance, one placebo-treated patient had DVT and one had PE; no tofacitinib-treated patients had DVT/PE. In the overall cohort, one patient had DVT (incidence rate [patients with events/100 patient-years; 95% CI]: 0.04 [0.00-0.23]); four had PE (0.16 [0.04-0.41]); all received predominant dose tofacitinib 10 mg b.d.; all had venous thromboembolism risk factors alongside UC.

Conclusions: In this post hoc analysis of patients with UC, during tofacitinib exposure, one patient had DVT and four had PE, all during the OLE study, on predominant dose 10 mg b.d. (83% of overall cohort patients received predominant dose 10 mg b.d.) with venous thromboembolism risk factors. This analysis is limited by small sample size and limited drug exposure; further studies are needed. ClinicalTrials.gov: NCT00787202, NCT01465763, NCT01458951, NCT01458574, NCT01470612.

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1 | INTRODUCTION

Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of ulcerative colitis (UC). Tofacitinib safety in UC was evaluated in phase 2 and phase 3 randomised controlled studies,[1,2] and in an ongoing, open-label, long-term extension (OLE) study.[3]

Recently, the data safety monitoring board for tofacitinib rheumatology studies determined that the frequency of pulmonary embolism (PE) in the tofacitinib 10 mg twice daily (b.d.) arm was higher than the frequency of PE in the tumour necrosis factor inhibitor comparator arm in an FDA post-marketing requirement safety study (A3921133; NCT02092467)[4] designed to evaluate the long-term risk of major adverse cardiovascular events and malignancy.

Study A3921133 is an ongoing, open-label, endpoint-driven study, evaluating the safety of tofacitinib 5 mg b.d. and tofacitinib 10 mg b.d. compared with tumour necrosis factor inhibitors in patients with rheumatoid arthritis. Patients had to be 50 years of age or older, had at least one cardiovascular risk factor and be on a stable dose of methotrexate to be eligible for enrolment. Subsequently, based on the information from study A3921133 and consideration of information pertaining to PE for other Janus kinase inhibitors, Pfizer has determined as part of its pharmacovigilance procedures that PE is an important potential risk for treatment with tofacitinib.

The non-A3921133 rheumatoid arthritis studies included placebo-controlled (≤ 3 months of follow-up), active-controlled (up to 24 months of follow-up) and OLE (up to 9.5 years of tofacitinib treatment follow-up) periods.[5,6] Data from these phase 2, phase 3 and OLE studies of tofacitinib in rheumatoid arthritis (excluding study A3921133) showed that incidence rates (IRs; patients with events per 100 patient-years) for deep vein thrombosis (DVT) and PE in the placebo group during the placebo-controlled period were 0.41 [95% confidence interval (CI): 0.01-2.30] for DVT and 0.41 [0.01-2.30] for PE. The IRs in tofacitinib-treated patients (5 mg b.d. and 10 mg b.d. doses) from all periods were in the range of 0.00-0.21 for DVT and 0.00-0.15 for PE, and were similar with tofacitinib 5 mg b.d. and 10 mg b.d. doses.[5,6]

DVT/PE events have been reported in rheumatoid arthritis clinical studies of other Janus kinase inhibitors including baricitinib (all baricitinib doses: DVT IR: 0.4; PE IR: 0.2)[7] and upadacitinib (all upadacitinib doses: DVT: 0/329 patients through Week 12; 1/498 patients through Week 24; PE: 2/329 patients through Week 12; 6/498 patients through Week 24).[8] All patients with DVT/PE events in the rheumatoid arthritis studies of the Janus kinase inhibitors baricitinib and upadacitinib had additional DVT/PE risk factors.[7,8]

Reported literature values for IRs of thromboembolic events among persons with rheumatoid arthritis treated with a variety of biologic and/or conventional therapies ranged between 0.04-0.79.[9-22] Rheumatoid arthritis is a known risk factor for DVT/PE events, with a risk ratio for DVT of 2.08 and a risk ratio for PE of 2.17 for rheumatoid arthritis vs nonrheumatoid arthritis, based on a meta-analysis of nine observational studies in patients with rheumatoid arthritis.[23]

UC is a known risk factor for DVT/PE events, with reported IRs of 0.07-0.30 for DVT and 0.04-0.20 for PE.[24-26] We report incidence of venous thromboembolic events in the tofacitinib UC clinical development programme as of September 2018.

2 | MATERIALS AND METHODS

We evaluated DVT and PE events in the tofacitinib UC clinical development programme in three cohorts. The induction cohort included patients receiving placebo or tofacitinib 10 mg b.d. in phase 2 (A3921063) or phase 3 induction studies (OCTAVE Induction 1 and 2). The maintenance cohort included patients receiving placebo, tofacitinib 5 mg b.d. or tofacitinib 10 mg b.d. in the phase 3 maintenance study (OCTAVE Sustain). The overall cohort included patients receiving ≥ 1 dose of tofacitinib 5 mg b.d. or tofacitinib 10 mg b.d. in any phase 2, phase 3 or OLE study (data as of September 2018; database not locked). Study designs were described previously.[1-3,27]

DVT and PE events were identified using clinically relevant preferred terms in the Standardised Medical Dictionary for Regulatory Activities query 'Embolic and thrombotic events, venous'. IRs were calculated based on the unique number of patients with events per 100 patient-years of exposure. Exact Poisson CIs (adjusted for patient-years) are provided. For the overall cohort, patients were categorised by average daily dose of tofacitinib: predominant dose 5 mg b.d. (average total daily dose < 15 mg) and predominant dose 10 mg b.d. (average total daily dose ≥ 15 mg). For patients with DVT and PE events, prior medical history was reviewed for information on risk factors for DVT/PE.

All studies received appropriate Institutional Review Board and/or Independent Ethics Committee approval.

3 | RESULTS

Treatment exposure and IRs for DVT and PE in the three cohorts are presented in Table 1. In the induction cohort (N = 1220 [placebo: N = 282; tofacitinib 10 mg b.d.: N = 938; median age = 39 years), there was one patient receiving placebo with DVT and one patient receiving placebo with PE (both events assessed as moderate in severity by the investigators). No tofacitinib-treated patients in the induction cohort had DVT or PE. In the maintenance cohort (N = 592; median age = 41 years), there was one patient in the placebo group with DVT (severity assessed as moderate) and one patient in the placebo group with PE (two separate events in the same patient; the first assessed as moderate and the second assessed as mild); both had received tofacitinib 10 mg b.d. during induction studies. No patients in the tofacitinib dose groups of the maintenance cohort had DVT or PE. In the overall tofacitinib-treated cohort (N = 1157; median age = 39 years), there was one patient with DVT (IR [95% CI]: 0.04 [0.00-0.23]; severity assessed as moderate) and four patients

with PE (0.16 [0.04-0.41]; severities assessed as moderate [2] and severe [2]; one patient died due to one of the events assessed as severe). Each of the events in the overall tofacitinib-treated cohort occurred during the OLE study; all patients were from the predominant dose tofacitinib 10 mg b.d. group. Demographics and clinical characteristics for patients with DVT/PE events are presented in Table 2. Further details for each of the patients with DVT/PE events are provided below.

In the induction studies, DVT/PE events occurred in two placebo-treated patients:

1. A 30-year-old male with ulcerative pancolitis had DVT, 3 days following the first dose of placebo (Day 3 in the phase 2 induction study). The patient had prior history of Factor V mutation, PE and superficial thrombophlebitis. The patient had a body mass index of 22.1 kg/m^2 (normal weight) and had never smoked. The patient had moderate disease activity at baseline of A3921063 (total Mayo score of 8, the latest Mayo score available before the event). C-reactive protein (CRP) level at Day 1 in A3921063 (latest available data prior to onset of DVT) was 24.9 mg/L. The patient was taking concomitant methylprednisolone 4 mg/d at the time of the DVT event.
2. A 32-year-old female with extensive colitis/pancolitis had PE requiring hospitalisation 59 days following the first placebo dose (Day 59 in OCTAVE Induction 1). The patient had no significant prior medical history. The patient had a body mass index of 30.0 kg/m^2 (obese) and had never smoked. The patient had moderate disease activity at baseline of induction (total Mayo score of 9) and had mild disease activity (partial Mayo score of 4) at Day 55 (latest available data prior to PE onset). CRP level at Day 55 in OCTAVE Induction 1 (latest available data prior to onset of PE) was 1.3 mg/L. The patient was taking concomitant methylprednisolone 8 mg/d during OCTAVE Induction 1 including at the time of the PE event.

In the maintenance study (OCTAVE Sustain), DVT/PE events occurred in two patients in the placebo treatment group:

1. A 48-year-old male with left-sided colitis had DVT on Day 61 of OCTAVE Sustain while receiving placebo, having previously received 63 days' treatment with tofacitinib 10 mg b.d. in OCTAVE Induction 2. The patient had no significant prior medical history. The patient had a body mass index of 25.6 kg/m^2 (overweight) and was an ex-smoker. The patient had mild disease at baseline of OCTAVE Sustain (total Mayo score of 4, the latest available Mayo score prior to the event) and severe disease (partial Mayo score of 8) at Day 62 in OCTAVE Sustain (the closest available partial Mayo score data to time of event). CRP level at Day 62 in OCTAVE Sustain was 98.3 mg/L. The patient discontinued OCTAVE Sustain due to treatment failure. The patient was not receiving concomitant corticosteroids during OCTAVE Sustain, including at the time of the event.
2. A 48-year-old male with extensive colitis/pancolitis had PE requiring hospitalisation on Day 22 of OCTAVE Sustain while receiving placebo, having previously received 63 days' treatment with

TABLE 1 IRs of DVT and PE among patients in the induction, maintenance and overall cohorts of the tofacitinib UC clinical development programme

	Induction cohort (8 wk)		Maintenance cohort (52 wk)			Overall cohort (≤ 6.1 y)[b]		
	Placebo (N = 282)	Tofacitinib 10 mg b.d. (N = 938)	Placebo (N = 198)	Tofacitinib 5 mg b.d. (N = 198)	Tofacitinib 10 mg b.d. (N = 196)	Predominant dose tofacitinib 5 mg b.d. (N = 197)	Predominant dose tofacitinib 10 mg b.d. (N = 960)	Tofacitinib All (N = 1157)
Patient-years of exposure	44.8	156.2	100.4	146.2	154.3	595.5	1808.1	2403.6
DVT,[a] n (%)	1 (0.4)[c]	0 (0.0)	1 (0.5)[c]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)[c]	1 (0.1)
IR [95% CI]	1.99 [0.05-11.07]	0.00 [0.00-2.22]	0.97 [0.02-5.39]	0.00 [0.00-2.48]	0.00 [0.00-2.35]	0.00 [0.00-0.61]	0.05 [0.00-0.30]	0.04 [0.00-0.23]
PE,[a] n (%)	1 (0.4)[c]	0 (0.0)	1 (0.5)[d]	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.4)[e]	4 (0.3)
IR [95% CI]	1.98 [0.05-11.04]	0.00 [0.00-2.22]	0.98 [0.02-5.44]	0.00 [0.00-2.48]	0.00 [0.00-2.35]	0.00 [0.00-0.61]	0.21 [0.06-0.55]	0.16 [0.04-0.41]

Abbreviations: b.d., twice daily; CI, confidence interval; DVT, deep vein thrombosis; IR, incidence rate (unique patients with events per 100 patient-years of exposure); N, number of patients; n, unique number of patients with event; OLE, open-label, long-term extension; PE, pulmonary embolism; UC, ulcerative colitis.

[a]Excluding events occurring after 28 days from the last dose of the corresponding cohort (except patients that are ongoing in the OLE study); no events were reported beyond 28 days from the last dose.

[b]Data are as of September 2018 (OLE study database not locked).

[c]Severity was assessed as moderate.

[d]One patient experienced two separate events; the first assessed as moderate (1); the second assessed as mild (1).

[e]Severities were assessed as moderate (2) and severe (2).

tofacitinib 10 mg b.d. in OCTAVE Induction 1. The patient had prior history of venous thrombosis. The patient had a body mass index of 24.3 kg/m^2 (normal weight) and was an ex-smoker. The patient had moderate disease at baseline of OCTAVE Sustain (total Mayo score of 7, the latest available Mayo score prior to the event) and mild disease (partial Mayo score of 4) at Day 29 in OCTAVE Sustain (the closest available partial Mayo score data to time of event). CRP level at baseline of OCTAVE Sustain (latest available data prior to onset of PE) was 9.8 mg/L. The patient was receiving concomitant prednisolone during OCTAVE Sustain, including at the time of the event (dose at time of event: 7.5 mg/d).

In the overall cohort, DVT/PE events occurred in five patients (1 DVT and 4 PE), and all occurred during the OLE study in patients receiving tofacitinib 10 mg b.d. at the time of event (2 patients stopped tofacitinib treatment 4-5 days prior to the event onset, one of whom resumed tofacitinib treatment afterwards). All patients had received a predominant dose of tofacitinib 10 mg b.d. during the entire UC clinical programme:

1. A 58-year-old female with proctosigmoiditis had DVT in the right lower extremity while receiving tofacitinib 10 mg b.d., after 1149 days of treatment with tofacitinib 10 mg b.d. (Day 1149 in the OLE; the patient received placebo for 62 days in OCTAVE Induction 1, prior to entering the OLE). DVT was diagnosed following a long-haul flight and management of an infected leg wound sustained in a recent motorbike accident, for which the patient was hospitalised. The patient had a body mass index of 22.2 kg/m^2 (normal weight) and had never smoked. The patient had severe disease at baseline of OLE (total Mayo score of 11) and was in remission (partial Mayo score of 0) at Day 1082 of the OLE (latest available data prior to DVT onset). CRP level at baseline of the OLE (latest available data prior to DVT onset) was 2.2 mg/L. The patient was receiving ongoing prophylactic oestrogen for post-menopausal changes.
2. A 25-year-old male with left-sided colitis had PE within the right lower lobe requiring hospitalisation while receiving tofacitinib 10 mg b.d., after 216 days of treatment with tofacitinib 10 mg b.d (Day 153 in the OLE; the patient received tofacitinib 10 mg b.d. for 64 days in OCTAVE Induction 2, prior to entering the OLE). The patient had prior history of DVT and PE, but was not receiving anti-coagulation medication at baseline of OCTAVE Induction 2. The patient had a body mass index of 25.2 kg/m^2 (overweight) and had never smoked. The patient had moderate disease activity at baseline of OLE (total Mayo score of 8) and had mild disease activity (partial Mayo score of 2) at Day 124 of the OLE (latest available data prior to PE onset). CRP level at baseline of the OLE (latest available data prior to PE onset) was 0.2 mg/L.
3. A 57-year-old male with left-sided colitis had bilateral PE requiring hospitalisation while receiving tofacitinib 10 mg b.d., after 236 days of treatment with tofacitinib 10 mg b.d. (Day 174 in the OLE; the patient received tofacitinib 10 mg b.d. for 62 days in OCTAVE Induction 1, followed by placebo for 63 days in OCTAVE Sustain, prior to entering the OLE). The patient had prior history of phlebothrombosis, stroke, hypertension and hypercholesterolaemia. The patient had a body mass index of 28.6 kg/m^2 (overweight) and was an ex-smoker. The patient had moderate disease activity at baseline of OLE (total Mayo score of 10) and had mild disease activity (partial Mayo score of 2) at Day 125 of the OLE (latest available data prior to PE onset). CRP level at baseline of the OLE (latest available data prior to PE onset) was 3.4 mg/L.
4. A 70-year-old male with proctosigmoiditis had a right segmental and sub-segmental acute PE while receiving tofacitinib 10 mg b.d., after 447 days of treatment with tofacitinib (Day 383 in the OLE; the patient received tofacitinib 15 mg b.d. for 64 days in OCTAVE Induction 1, followed by placebo for 175 days in OCTAVE Sustain, prior to entering the OLE), with cholangiocarcinoma and metastases to the peritoneum. The patient was hospitalised for jaundice and dilation of the biliary tract and died due to the event of PE. The patient had a body mass index of 32.1 kg/m^2 (obese) and was an ex-smoker. The patient had moderate disease activity at baseline of OLE (total Mayo score of 10) and had mild disease activity (partial Mayo score of 3) at Day 373 of the OLE (latest available data prior to PE onset). CRP level at baseline of the OLE (latest available data prior to PE onset) was 4.9 mg/L.
5. A 21-year-old female with extensive colitis/pancolitis had bilateral PE requiring hospitalisation while receiving tofacitinib 10 mg b.d., after 629 days of treatment with tofacitinib (Day 569 in the OLE; the patient received tofacitinib 15 mg b.d. for 60 days in OCTAVE Induction 2, followed by placebo for 61 days in OCTAVE Sustain, prior to entering the OLE). The patient was receiving oral contraceptives for dysfunctional uterine bleeding. The patient had a body mass index of 32.9 kg/m^2 (obese) and had never smoked. The patient had moderate disease activity at baseline of OLE (total Mayo score of 10) and was in remission (partial Mayo score of 0) at Day 547 of the OLE (latest available data prior to PE onset). CRP level at baseline of the OLE (latest available data prior to PE onset) was 30.3 mg/L.

None of the tofacitinib-treated patients with DVT/PE in the overall cohort were taking corticosteroids at the time of event. Data on deficiency of Protein C, Protein S, or anti-thrombin 3, presence of Leiden factor V, presence of methylenetetrahydrofolate reductase gene mutation and presence of lupus anti-coagulant were not routinely collected in the clinical study database.

4 | DISCUSSION

In this post hoc analysis of patients from the tofacitinib UC clinical development programme as of September 2018, one patient had DVT and four patients had PE during tofacitinib treatment. In the overall tofacitinib-treated cohort, the IR (95% CI) for DVT was 0.04 [0.00-0.23] and the IR for PE was 0.16 (0.04-0.41). In the placebo group of the induction cohort, there was one patient with

TABLE 2 Demographics and clinical characteristics of patients with DVT and PE in the tofacitinib UC clinical development programme

Event	Age at time of event, y	Gender, (M/F)	Treatment at time of event (PD for overall cohort)	Days of treatment with placebo prior to event	Days of treatment with tofacitinib prior to event	Disease extent	Body mass index, kg/m^2
Induction studies							
DVT	30	M	Placebo	3	0	Ulcerative pancolitis	22.1
PE	32	F	Placebo	59	0	Extensive colitis/ pancolitis	30.0
Maintenance study							
DVT	48	M	Placebo	61	63	Left-sided colitis	25.6
PE	48	M	Placebo	22	63	Extensive colitis/ pancolitis	24.3
Overall – all events occurred in OLE study							
DVT	58	F	10 mg b.d.[a] (PD 10 mg b.d.)	62	1149	Proctosigmoiditis	22.2
PE	25	M	10 mg b.d. (PD 10 mg b.d.)	0	216	Left-sided colitis	25.2
PE	57	M	10 mg b.d. (PD 10 mg b.d.)	63	236	Left-sided colitis	28.6
PE	70	M	10 mg b.d.[a,b] (PD 10 mg b.d.)	175	447	Proctosigmoiditis	32.1
PE	21	F	10 mg b.d. (PD 10 mg b.d.)	61	629	Extensive colitis/ pancolitis	32.9

Abbreviations: b.d., twice daily; DVT, deep vein thrombosis; F, female; HDL, high-density lipoprotein; LDL, low-density lipoprotein; M, male; N, no; N/A, not applicable; OLE, open-label, long-term extension; PD, predominant dose; PE, pulmonary embolism; PMS, partial Mayo score; TC, total cholesterol; TG, triglycerides; TMS, total Mayo score; Y, yes.
[a]Tofacitinib treatment was stopped 4-5 days prior to the event onset.
[b]Tofacitinib treatment was resumed 14 days after the event onset.
[c]Per the latest available data prior to event onset.
[d]Partial Mayo score at Day 62 in OCTAVE Sustain, 1 day after the event onset date (the closest available Mayo score data to time of event).
[e]Partial Mayo score at Day 29 in OCTAVE Sustain, 7 days after the event onset date (the closest available Mayo score data to time of event).

DVT and one patient with PE. In the maintenance cohort, one patient in the placebo group had DVT and one patient in the placebo group had PE.

All DVT/PE events in patients receiving tofacitinib at the time of the event occurred during the OLE study, after at least 7 months of treatment, in patients receiving PD 10 mg b.d. (83% of all patients

Smoking status	Disease activity at time of event[c]	Platelet count at time of event,[c] 10^3 cells/mm^3	Hypertension, (Y/N)	Lipid levels at time of event,[c] mg/dL	Oral contraceptive and/or hormonal therapy, (Y/N)	Notes
Never smoked	TMS: 8	186	N	TC: 159 HDL: 38 LDL: 108 TG: 65	N/A	Prior history of Factor V mutation, PE and superficial thrombophlebitis. Receiving methylprednisolone (4 mg/d) at the time of event
Never smoked	TMS: 5	444	N	TC: 216 HDL: 70 LDL: 127 TG: 97	N	No significant prior medical history. Receiving methylprednisolone (8 mg/d) at the time of event
Ex-smoker	PMS: 8[d]	390	N	TC: 233 HDL: 41 LDL: 160 TG: 160	N/A	Received tofacitinib 10 mg b.d. in induction for 63 d
Ex-smoker	PMS: 4[e]	216	Y	TC:164 HDL: 50 LDL: 102 TG: 165	N/A	Prior history of venous thrombosis. Received tofacitinib 10 mg b.d. in induction for 63 d
Never smoked	PMS: 0	233	N	TC: 200 HDL: 75 LDL: 110 TG: 74	Y	DVT diagnosed following long-haul flight and management of an infected leg wound
Never smoked	PMS: 2	446	N	TC: 190 HDL: 49 LDL: 123 TG: 92	N/A	Prior history of DVT and PE
Ex-smoker	PMS: 2	193	Y	TC: 259 HDL: 82 LDL: 157 TG: 101	N/A	Prior history of phlebothrombosis, stroke, arterial hypertension and hypercholesterolaemia
Ex-smoker	PMS: 3	259	Y	TC: 249 HDL: 10 LDL: 183 TG: 279	N/A	Cholangiocarcinoma and metastases to the peritoneum
Never smoked	PMS: 0	330	N	TC: 201 HDL: 57 LDL: 113 TG: 157	Y	Oral contraceptives for dysfunctional uterine bleeding

in the overall cohort received PD 10 mg b.d.), and all had venous thromboembolism risk factors. Patients who were eligible to receive tofacitinib 10 mg b.d. in the OLE study were those who completed OCTAVE Induction 1 and 2 without clinical response, and those who completed OCTAVE Sustain but were not in remission, or were early withdrawals due to treatment failure in OCTAVE Sustain. IRs

for DVT and PE events with tofacitinib were comparable with those reported for patients with UC.[24,26]

The present post hoc analysis provides information for physicians regarding the incidence of DVT and PE in patients with UC who were treated with tofacitinib, but is limited by small sample size and drug exposure. Further studies of venous thromboembolism in patients with UC treated with tofacitinib are needed. Additional analyses are ongoing to further characterise the association between treatment with tofacitinib and PE in other populations, including patients with rheumatoid arthritis. Given that PE has been determined as an important potential risk of treatment with tofacitinib, prescribers should review information pertaining to PE and tofacitinib in their current local product labelling (eg USPI in the US[28] and SmPC in the EU[29]) and individualise treatment by considering risk factors for venous thromboembolism.

5 | DATA SHARING 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 (a) for indications that have been approved in the US and/or EU or (b) in programmes that have been terminated (ie 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 which 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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