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Rheumatic & Musculoskeletal Diseases

### EXTENDED REPORT

The incidence of tuberculosis in patients treated with certolizumab pegol across indications: impact of baseline skin test results, more stringent screening criteria and geographic region

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#### ABSTRACT

**Objectives:** We report the incidence of tuberculosis (TB) across certolizumab pegol (CZP) clinical trials in rheumatoid arthritis (RA), psoriasis, psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA), before and after the introduction of stricter TB screening.

**Methods:** TB incidence rates (IRs) were assessed and stratified according to screening guidelines used at the time of CZP trials. Before 2007 (*original* trials), purified protein derivative (PPD) tuberculin skin test positivity varied according to local standards (induration  $\geq$ 5 up to  $\geq$ 20 mm). Since 2007, all CZP trial protocols have been amended, including trials spanning (*intermediate*) and initiated after 2007 (*current*), mandating that any patient with PPD $\geq$ 5 mm receives treatment for latent TB infection (LTBI). All cases of suspected TB or PPD $\geq$ 5 mm, in pooled data from 5402 CZP patients across all CZP trials up to 2012, underwent blinded central review by independent experts.

**Results:** 44 TB cases were confirmed in pooled CZP RA trials (IR 0.47/100PY, patient-years) with no cases in Japanese RA trials (J-RAPID, HIKARI). Single TB cases were confirmed in psoriasis and axSpA trials (RAPID-axSpA), and no cases in the PsA trial (RAPID-PsA). IR of TB was 0.51/100PY across *original* or *intermediate* RA trials and 0.18/100PY in *current* trials. The majority of TB cases in RA occurred in Eastern (IR 1.02/100PY) and Central Europe (IR 0.58/100PY). Of 242/370 PPD $\geq$ 5 mm patients who received 9 months isoniazid (INH) treatment for latent TB infection (LTBI), none developed TB, versus 7.8% of 128 untreated PPD $\geq$ 5 mm patients.

**Conclusions:** Implementation of more stringent LTBI screening, plus treatment for LTBI, reduced the IR of TB, even when INH was administered after starting CZP therapy.

#### **INTRODUCTION**

Antitumour necrosis factors (anti-TNFs) have provided a major breakthrough in the

#### Key messages

#### What is already known on this subject?

 Antitumour necrosis factors (anti-TNFs) are associated with an increased risk of opportunistic infections, including active tuberculosis (TB).

#### What might this study add?

► Using a strict purified protein derivative (PPD) cut-off of ≥5 mm induration, as well as a TB questionnaire, may reduce the incidence of TB in patients receiving anti-TNF therapy.

#### How might this impact on clinical practice?

Antibiotic treatment for latent TB infection (LTBI) at screening, or in patients already on anti-TNF therapy if a history of PPD ≥5 mm is documented, decreases the incidence of TB in patients receiving anti-TNF therapy.

treatment of chronic inflammatory diseases but are associated with an increased risk of opportunistic infections, including active tuberculosis (TB).<sup>1 2</sup> The onset of TB soon after initiation of anti-TNF therapy indicates the probable reactivation of latent TB infection (LTBI), while TB appearing after several months or more of continuous exposure to anti-TNF is likely to arise due to a new infection.<sup>2–4</sup> Reports suggest that the incidence of TB in patients treated with biologics has decreased over the past decade thanks to screening of LTBI, as recommended in several countries.<sup>5</sup> However, the risk of active TB (particularly non-pulmonary TB) associated with anti-TNFs $^{1\ 2\ 4}$  and underlying inflammatory diseases<sup>5–7</sup> remains an important concern. Thus, patients being considered for anti-TNF therapy should undergo initial screening for LTBI, and regular screening for TB infection should be performed during

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anti-TNF treatment if patients are living in, or have travelled to, TB endemic regions. However, the benefits of repeat screening in TB endemic regions are debatable<sup>8</sup> and the perfect approach for screening patients with anti-TNF has not yet been resolved, with different strategies being used to try to identify patients at risk of developing TB.

Prior to 2007, certolizumab pegol (CZP) trials screened for TB by a purified protein derivative (PPD) tuberculin skin test were evaluated according to the respective national guidelines of the recruiting centre. The cut-off value for positivity varied widely (from  $\geq 5$  up to  $\geq 20$  mm induration), particularly in countries with higher bacillus Calmette-Guérin (BCG) vaccination rates.<sup>9 10</sup>

In 2007, the WHO introduced stricter practical guidelines to reduce the risk of TB in patients starting anti-TNF treatment and to help identify those at increased risk of developing TB (PPD test results  $\geq 5 \text{ mm}$  were considered positive).<sup>11 12</sup> Similar screening recommendations have since been introduced by several national rheumatology societies to reduce the risk of TB infection in patients with immune-mediated inflammatory disease (IMID).13-18 In response to an increasing number of TB cases, mainly from high TB incidence countries, and WHO recommendations for more stringent TB screening, CZP trial protocols were amended in 2007;<sup>11</sup><sup>12</sup> mandating that any patient with PPD  $\geq$ 5 mm should begin 9 months isoniazid (INH) treatment for LTBI. This included patients already receiving CZP, even without any signs or symptoms considered to be TB-related. Patient TB questionnaires were also administered, every 6 months, to increase patient/investigator awareness of the symptoms and risk factors for TB (figure 1).

CZP is approved for the treatment of adult patients with moderate-to-severe RA, psoriatic arthritis (PsA), axial spondyloarthritis (axSpA; including ankylosing spondylitis) and Crohn's disease.<sup>19 20</sup> This paper reports the incidence rate (IR) of TB during long-term CZP treatment across indications (RA, psoriasis, PsA and axSpA) and examines whether stricter screening rules for LTBI, with subsequent INH treatment when indicated, can reduce the risk of reactivation of TB in CZP-treated patients. The effects of baseline PPD status or different geographic regions on the IR of TB were also evaluated.

#### **METHODS**

#### Patient population and study designs

For RA, the pooled CZP safety database included 4049 patients with RA from 14 studies (including randomised controlled trials (RCTs) and open label extensions (OLEs); figure 2A), with maximum CZP exposure of 7.6 years as previously described.<sup>21</sup> The first patient was enrolled by the end of 1998 and the safety cut-off date was 30 November 2011. Safety data were also assessed in 528 patients with RA enrolled in two Japanese CZP RCTs and their OLEs (J-RAPID (NCT00791999, NCT00851318), HIKARI (NCT00791921, NCT00850343)) from 19 November 2008 up to 6 June 2013 (figure 2B).

In addition, safety data were assessed for psoriasis phase 2 CZP studies conducted between October 2005 and May 2007 (N=117 patients; C87040 (NCT00245765) and C87044 (NCT00329303)). Safety data were also assessed for the RAPID-PsA<sup>15</sup> (N=393 patients; NCT01087788) and RAPID-axSpA<sup>18</sup> studies (N=315 patients; NCT01087762) initiated in March 2010, using the new TB screening cut-off criteria of  $\geq$ 5 mm induration for PPD positivity, up to the cut-off date of 16 November 2012 (figure 2B).

For the majority of RA studies, and for RAPID-PsA and RAPID-axSpA, a loading dose of CZP 400 mg was administered subcutaneously at weeks 0, 2 and 4, followed by CZP 200 mg every 2 weeks (Q2W) or CZP 400 mg every 4 weeks (registered doses). During RAPID1 and RAPID2 RCTs (NCT00152386, NCT00160602), and for  $\geq$ 6 months during their OLEs (NCT00175877, NCT00160641), CZP was also administered at 400 mg Q2W (twice the registered dose) for all patients. Across trials, patients were exposed to CZP either as a monotherapy or in combination with methotrexate and/or other DMARDs.

#### TB screening and protocol amendment

All patients were screened for TB at study baseline. The safety database was manually reviewed retrospectively by independent experts (JC, RvV, XM, KW, LC for RA; JC, RvV, XM, KW, LC, JV, JG-R, MW, OL for psoriasis, PsA and axSpA). All cases of suspected TB (PPD positive or exhibiting signs/symptoms compatible with TB) were classified as active TB, LTBI or PPD positive, or as non-evaluable. Active TB cases reported in this paper were confirmed according to the WHO or Centers for Disease Control and Prevention (CDC) criteria for TB.<sup>22</sup>

In CZP studies before 2007, TB screening was conducted according to respective national guidelines of the recruiting study centre (cut-off for PPD positivity ranged from  $\geq 5$  up to  $\geq 20$  mm). Since 2007, patients were screened for PPD positivity  $\geq 5$  mm at baseline and subsequently received INH treatment for LTBI if they tested PPD positive. This amendment was also enforced retrospectively for all patients already on CZP treatment at the time of protocol amendment. Thus, patients with a baseline PPD of  $\geq 5$  mm or no precise information on the wheal size, and no evidence of TB infection, were treated with INH for 9 months, regardless of prior exposure to CZP.<sup>11</sup> <sup>12</sup> Patient TB questionnaires were also administered every 6 months (figure 1).

#### Stratification of RA studies

Data from the pooled RA safety database<sup>21</sup> (which excluded the Japanese RA trials) were assessed for trials initiated prior to 2007 (2367 patients) in two subgroups: (1) *original* trials (837 patients), completed prior to TB screening protocol amendment; and (2) *intermediate* trials (1530 patients from the RAPID1 and RAPID2 trials), which were initiated using PPD positivity cut-off from  $\geq 5$  to  $\geq 20$  mm but amended retrospectively. Group (3), *current* trials (1682 patients), were initiated after protocol amendment in 2007 and any patient was

EVALUATION FOR SIGNS AND SYMPTOMS OF TUBERCULOSIS QU	JESTIONNAIRE
Patient identifier: Visit number	Date:
Subjects must be evaluated for signs and symptoms of active TB as part of the physical study. The following questions are to be asked to the patient for evaluation of risk factors for Responses to each question must be documented on this source document.	examinations in the or tuberculosis (TB).
If the answer to the following question is "Yes", then the patient must be starte therapy or be withdrawn from the trial:	ed on prophylactic
• Has the patient been in close contact (i.e., sharing the same household or other enclosed environment) with an individual with active TB or an individual who has recently been treated for TB?	No 🗌 YES 🗌
Additionally, the patient must be assessed for the following. It is recomment response to any of the following questions should trigger further careful assesses determine if prophylactic or curative treatment is required:	nded that a "Yes" ment of the risk to
• Does the patient have a new cough lasting more than 14 days or a change in a chronic cough?	No 🗌 YES 🗌
• Does the patient have night sweats?	No 🗌 YES 🗌
• Does the patient have a persistent fever?	No 🗌 YES 🗌
• Does the patient have unintentional weight loss (more than 10% of body weight)?	No 🗌 YES 🗌
• Did the patient have an abnormal chest X-ray, since the last evaluation?	No 🗌 YES 🗌
• Is the patient a hospital employee or in frequent contact with hospital employees (example: providing catering service to hospital employees or married to one)?	No 🗌 YES 🗌
• Is the patient frequently exposed to other patients (study visits/ hospitalizations) that are on study drug or other immunosuppressive drugs?	No 🗌 YES 🗌
• Does the patient reside in, did the patient ever reside in, or is the patient frequently traveling to a TB endemic region(s)?	No 🗌 YES 🗌
• Does the patient reside in, did the patient ever reside in, or is the patient frequently visiting densely populated areas such as highly urbanized city centers?	No 🗌 YES 🗌
• Does the patient frequently use public transportation?	No 🗌 YES 🗌
• Is the patient in frequent contact with elderly or underprivileged populations (homeless or other people needing social assistance)?	No 🗌 YES 🗌
• Does the patient appear malnourished?	No 🗌 YES 🗌



subsequently treated for LTBI if they tested PPD positive at study baseline.

#### **Statistical analyses**

Safety assessments included all confirmed TB events that occurred after the first dose of CZP or placebo (PBO), and up to 84 days after the last study dose or patient withdrawal. Total exposure to CZP, as used in the IR calculation, was defined as the time from the first dose until the date that the TB event was reported. Exposure-adjusted IRs per 100 patient-years (PY), with 95% CI, are presented in this analysis. In some instances, data are also presented as the percentage of patients with events divided by the total number of patients. All statistics were performed using SAS V.9.1 or a later version.

#### RESULTS

#### Incidence of TB in CZP-treated patients across indications

The incidence of TB was assessed in a total of 5402 CZP patients treated for RA, psoriasis, PsA and axSpA, with



B Study design of Japanese RA, axSpA, PsA and psoriasis trials



**Figure 2** Study design of CZP trials included in the safety analysis for the incidence of tuberculosis (TB). CZP, certolizumab pegol; OLE, open label extensions; RA, rheumatoid arthritis;

an overall IR of 0.42/100 PY (95% CI 0.31 to 0.57). For RA, 4049 patients were included in the pooled safety database (9277 PY; mean CZP exposure 782 days, median exposure 267 days).<sup>21</sup> Up to 30 November 2011, 44 confirmed TB cases were reported in CZP-treated patients with RA (IR 0.47/100 PY (0.34 to 0.64); also, there were 30 cases of pulmonary TB and 14 cases of non-pulmonary (including isolated lymph node TB) or disseminated TB (occurring in two or more non-continuous organs)). No TB cases were reported in PBO patients during RCTs; however, the total exposure time was relatively short (total exposure 373 PY; mean exposure 110 days), mainly due to mandatory early escape to

active CZP treatment for non-responders at weeks 12 and 14 in the RAPID1 and RAPID2 studies, as compared to CZP exposure (total exposure 9277 PY; mean exposure 782 days). Separate analysis of safety data from 528 patients with RA enrolled in Japanese CZP trials (J-RAPID and HIKARI and their OLEs) conducted up to 6 June 2013 confirmed no cases of TB (figure 3).

Incidence of TB was also assessed in 117 study patients with psoriasis (85 PY; mean CZP exposure 206 days) up to 9 May 2007 and confirmed one case of disseminated TB after 61 days of CZP exposure (IR 1.18/100 PY (0.03 to 6.58)). The incidence of TB was also assessed in 393 RAPID-PsA patients (612 PY; mean CZP exposure



Figure 3 Summary of TB cases across indications and trial periods. †A total of 42 TB cases were reported in rheumatoid arthritis (RA) trials initiated or completed prior to protocol amendment; 20 cases in *original* RA trials (completed prior to protocol amendment) and 22 in *intermediate* RA trials (initiated before but completed after the introduction of more stringent PPD screening criteria in 2007). \*Of the 22 TB cases in patients with RA from *intermediate* RA trials (RAPID1 and RAPID2), 9 cases were reported after protocol amendment. AxSpA, axial spondyloarthritis; PsA, psoriatic arthritis; IR, incidence rates; PY, patient-years; TB, tuberculosis.

568 days) and 315 RAPID-axSpA patients (481 PY; mean CZP exposure 558 days). Up to 16 November 2012, a single case of pulmonary TB was confirmed in RAPID-axSpA (IR 0.21/100 PY (0.01 to 1.15)), with no confirmed cases in RAPID-PsA.

## Incidence of TB in patients with RA by protocol period and duration of TB exposure

Overall, the IR of TB in CZP-treated patients with RA in trials initiated prior to protocol amendment was 0.51/100 PY (0.37 to 0.69) (42/2367 patients); 2.63/100 PY (1.61 to 4.06) in *original* trials (20/837 patients) and 0.30/100 PY (0.19 to 0.45) in *intermediate* trials spanning

the period of protocol amendment (22/1530 patients). For *current* trials initiated with the standardised 5 mm PPD cut-off after protocol amendment was enforced, the IR was 0.18/100 PY (0.02 to 0.66) (2/1682 patients). In total, 11/44 TB cases in RA trials were diagnosed after protocol amendment (9 from *intermediate* trials [RAPID1 and RAPID2] and 2 from *current* trials; figures 3 and 4). Of these 11 TB cases, 10 patients were considered PPD negative at baseline (PPD<5 mm) and one patient had an unknown PPD value. All nine patients from the *intermediate* and were from Central or Eastern Europe, with TB onset occurring ≥718 days after the first dose of CZP. Of the confirmed





**Figure 5** PPD status of CZP-treated patients with RA in the pooled RA safety database (N=4049) at baseline and TB incidence by INH treatment. †One patient who developed TB started INH treatment 393 days after the first CZP dose was administered. INH was administered from 517 to 251 days before TB was diagnosed. CZP, certolizumab pegol; PPD, purified protein derivative; INH, isoniazid; RA, rheumatoid arthritis; TB, tuberculosis.

TB cases in patients with RA, 21/44 were reported during the first year of CZP exposure. This included both cases of TB in *current* RA CZP trials, reported in patients with either negative or unknown baseline PPD test values.

#### Incidence of TB in relation to baseline PPD status and INH treatment for LTBI

A total of 370/4049 patients in the pooled RA safety database had baseline PPD  $\geq 5$  mm. Of these, 242 patients received treatment for LTBI (figure 5); 27 began INH treatment prebaseline, 15 at study baseline, and 200 patients started treatment for LTBI postbaseline following the protocol amendment. No PPD positive patients with RA in receipt of INH treatment for 9 months developed TB (figure 5). One hundred twenty eight patients did not receive INH treatment as they were considered PPD negative according to local guidelines at the time of study enrolment, or had no symptoms of active TB. Of these, 10 patients recruited prior to protocol amendment went on to develop TB. According to the stricter guidelines for PPD positivity cut-off, these patients would have been considered PPD positive at the time of screening. Four had a PPD test result of 5-10 mm and the remaining six patients had baseline PPD >10 mm (table 1). The average

time of TB onset after the first dose of CZP was between  $\sim$ 1 and 1.5 years, and 6/10 cases were isolated pulmonary TB (table 1).

A total of 3278 patients had a PPD<5 mm and were considered PPD negative; the remaining 401 patients had no PPD test values recorded. Among patients with baseline PPD<5 mm, INH treatment (typically administered postbaseline) had little impact on TB incidence; 1/126 INH-treated patients (0.8%) versus 31/3152 non-INH-treated patients (1.0%)developed TB (figure 5). INH treatment of the PPD negative patient who went on to develop TB was initiated following a positive routine QuantiFERON test, performed 393 days after starting CZP treatment, and TB was reported 517 days later. The average time to TB onset in the 32 patients with PPD<5 mm at baseline was  $\sim$ 1.5 years after the first dose of CZP, the long latency suggestive of a new TB infection rather than LTBI reactivation. The majority of cases (22/32) were diagnosed as isolated pulmonary TB (table 1). Onset of TB in the two patients with RA with unknown PPD value occurred 142 and 200 days after the first dose of CZP; one patient had a history of positive PPD tests and was treated with INH for 141 days prior to administration of CZP, suggesting reactivation of LTBI.

Table 1 Incidence and type of active TB by PPD skin te	st subgroup for CZP-treat	ed patients with RA in the	pooled RA safety databas	e (N=4049)
	<b>Baseline PPD status</b>			
TB events	<5 mm (n=3278)	5–10 mm (n=219)	>10 mm (n=151)	PPD missing/unknown (n=401)
Positive TB cases				
n (%)	32*(1.0)	4 (1.8)	6 (4.0)	2† (0.5)
IR/100 PY (95% CI)	0.42 (0.29 to 0.59)	0.49 (0.13 to 1.25)	1.27 (0.47 to 2.77)	0.54 (0.07 to 1.95)
Time from start of CZP treatment to TB onset (days)				
Mean (SD)	552.5 (404.7)	519.3 (318.8)	473.7 (404.3)	171.0 (41.0)
Median	435.5	617.5	352.0	171.0
Q1–Q3	204.0-838.5	319.0–719.5	148.0-806.0	142.0-200.0
Minimum-maximum	50-1473	58-784	71-1113	142–200
Pulmonary TB cases	22	4	N	N
Non-pulmonary or disseminated TB cases	10	0	4	0
Positive TB cases/patients treated with INH (%)	1/126 (0.8)	0/153 (0.0)	0/89 (0.0)	1/19 (5.3)
Positive TB cases/patients not treated with INH (%)	31/3152 (1.0)	4/66 (6.1)	6/62 (9.7)	1/382 (0.3)
*One patient who developed TB received INH administration. INH †One patient with unknown PPD who developed TB was adminit onset of TB.	I treatment started 393 days stered INH treatment before s ide ID invidence refer N pure	after the first CZP dose was a study baseline; INH was admin mbor of postente: DDD murifie	dministered and 517 days be listered 141 days prior to the dimension devivative. DV patio	ore the onset of TB. irst CZP dose and 340 days before the otherse: BA the instead atheritie: TB
v, percentage or parterns, Ozi , certorizarriad pegol, init i, isoriitat tuberculosis.	יומי וווזי וווטמפורכפ ומופסי ואי וומ	אוווטפו טו אמופווא, ו ו ט, אמווופ	מ הוטופוון מפוואמוואכן דין, המופ	ווראכמוס, וות, וווכמווומנטום מותווונס, וים,

In the J-RAPID/HIKARI trials, 213/528 patients received INH at study baseline (no cases of TB were reported in these trials). No INH treatment for LTBI was administered to patients enrolled in psoriasis CZP trials (study 040/044), including a patient who developed disseminated TB. In the RAPID-PsA and RAPID-axSpA trials, a total of 26/393 and 25/315 patients, respectively, received INH treatment at study baseline. The single case of pulmonary TB reported in the RAPID-axSpA trial occurred in a PPD negative patient who did not receive treatment for LTBI. Onset of TB in the patient with axSpA, originally randomised to PBO for 24 weeks, was reported after 170 days of CZP exposure.

Overall, of the 46 cases of confirmed TB across CZP trials (44 in RA (20 in *original*, 22 in *intermediate* and 2 in *current* trials), 1 in psoriasis, 1 in axSpA), 34 were observed prior to the implementation of stricter screening rules (33 in RA, 1 in psoriasis) and predominantly occurred in patients who did not receive INH treatment.

#### Incidence of TB in relation to geographic location

The geographic distribution of CZP-treated patients in the pooled RA safety database was 19.8% from Western Europe, 20.0% from Central Europe, 12.4% from Eastern Europe, 41.3% from North America and 6.5% from the Rest of the World. United Nations statistics for the lower bound incidence of TB in the general population report a higher risk in Eastern and Central Europe (table 2). Consistent with this, the majority of TB cases observed with CZP originated in Eastern Europe (21 cases; IR 1.02/100 PY (0.63 to 1.56)) and Central Europe (18 cases; IR 0.58/100 PY (0.34 to 0.92)). 29/32 TB cases in patients with RA with PPD<5 mm at baseline were reported in patients from Eastern or Central Europe. Nevertheless, the rate of TB in patients with RA was far below the expected rate observed in the general population in each respective country (table 2). Three TB cases were confirmed in Western Europe (2 in Germany, 1 in the UK) along with single cases in North America (US) and the Rest of the World (Argentina) (table 2). The single cases of TB in the psoriasis and axSpA trials were in France and Argentina, respectively.

Of note, for *current* RA trials, the number of patients recruited from Central Europe and Eastern Europe was 0 and 40 patients, respectively, and may have contributed to the reduced rates of TB observed in patients with RA after protocol amendment. The majority of patients with RA in *current* trials were recruited from North America (1319/1682 patients).

#### DISCUSSION

Since the introduction of stricter screening rules for LTBI in CZP clinical trials (cut-off for PPD positivity of  $\geq$ 5 mm and a TB questionnaire including 13 questions relating to symptoms and risk factors for TB, in addition to chest X-rays), and mandating INH monotherapy for

Tablement in the structure of the structure of contracts and structure of the structu	Tentom         Tentom         Number         Number<	TB incidence rate in general population         TB incidence rate in general population         Patients (n)         <5 mr	Baseline	PPD status (n)		groups	n CZP treatment	
Oreal         AT         Dial         Dial <thdiai< th=""> <thdial< th="">         Dial         <thdia< th=""><th>Operation         400         270         201         0.47         0.47         0.41         0.47         0.41         0.43         0.43         0.43         0.43         0.43         0.43         0.43         0.43         0.43         0.43         0.43         0.43         0.43         0.44         &lt;</th><th>Overall         4049         3278           Western Europet         7.9         800         464           Austria         6.9         125         40           Belgium         8.5         19         18           Finden         4.9         8.5         19         18           Finden         4.9         8.5         19         18           France         7.7         6.9         2.4         4           France         7.7         6.9         2.0         18           France         7.7         6.9         2.0         14           France         7.5         8         2.0         14           France         7.7         6.3         2.0         17           Sweden         6.3         14,0         132         2.4         4           Sweden         6.3         14,0         132         4         4           UK         14,0         120         314         2.20         44           Latvia         5.6         4,7         314         2.20         44           Latvia         16.0         132         116         118           Storakia</th><th>ate in tion Patients (n) &lt;5 mm</th><th>≥5 mm</th><th>missing/ unknown</th><th>IR/100 PY (95% CI)</th><th>Number of events (in patients with PPD&lt;5 mm)</th><th>INH-treated, no active TB (no TB/INH treated)</th></thdia<></thdial<></thdiai<>	Operation         400         270         201         0.47         0.47         0.41         0.47         0.41         0.43         0.43         0.43         0.43         0.43         0.43         0.43         0.43         0.43         0.43         0.43         0.43         0.43         0.44         <	Overall         4049         3278           Western Europet         7.9         800         464           Austria         6.9         125         40           Belgium         8.5         19         18           Finden         4.9         8.5         19         18           Finden         4.9         8.5         19         18           France         7.7         6.9         2.4         4           France         7.7         6.9         2.0         18           France         7.7         6.9         2.0         14           France         7.5         8         2.0         14           France         7.7         6.3         2.0         17           Sweden         6.3         14,0         132         2.4         4           Sweden         6.3         14,0         132         4         4           UK         14,0         120         314         2.20         44           Latvia         5.6         4,7         314         2.20         44           Latvia         16.0         132         116         118           Storakia	ate in tion Patients (n) <5 mm	≥5 mm	missing/ unknown	IR/100 PY (95% CI)	Number of events (in patients with PPD<5 mm)	INH-treated, no active TB (no TB/INH treated)
Mastern Europet         7.9         800         461         4.2         2.84         0.23 (0.05 to 0.69)         3 (2)         9 (1)           Ansitin         8.5         1.9         1.9         1.0         0.1         0.1         0.1           Regun         8.5         1.9         1.0         0.1         0.1         0.1         0.1           Regun         5.5         1.0         1.0         0.1         0.1         0.1         0.1           Remary         7.1         0.0         0.1         0.1         0.1         0.1         0.0           Remary         7.1         0.0         0.1         0.1         0.1         0.1         0.1           Remary         5.3         0.1         1.0         0.1         0.1         0.1         0.1           Remary         5.3         0.1         0.1         0.1         0.1         0.1         0.1           Remary         5.3         2.0         0.5         2.2         0.5         0.1         0.1         0.1           Remary         5.3         0.1         0.3         0.0         0.1         0.1         0.1         0.1           Remary         2.3 <td>Western Europer         7.9         000         4.64         4.2         2.94         0.23         0.03         3</td> <td>Western Europet         7.9         800         464           Austria         6.9         125         40           Belgium         8.5         19         8           France         7.7         69         24           France         7.7         69         24           France         7.7         69         24           France         7.5         8         4           Tendend         5.8         20         18           Sweden         6.3         32         20         18           Sweden         6.3         32         20         14           VK         14,0         73         4         4           Sweden         6.3         32         20         18           UK         14,0         120         32         26           Sweden         6.3         314         220         4           UK         14,0         132         118           UK         14,0         132         118           Slovakia         5.9         52         44         4           Latvia         19,0         314         22         52      &lt;</td> <td>4049 3278</td> <td>370</td> <td>401</td> <td>0.47 (0.34 to 0.64)</td> <td>44 (32)</td> <td>385/387</td>	Western Europer         7.9         000         4.64         4.2         2.94         0.23         0.03         3	Western Europet         7.9         800         464           Austria         6.9         125         40           Belgium         8.5         19         8           France         7.7         69         24           France         7.7         69         24           France         7.7         69         24           France         7.5         8         4           Tendend         5.8         20         18           Sweden         6.3         32         20         18           Sweden         6.3         32         20         14           VK         14,0         73         4         4           Sweden         6.3         32         20         18           UK         14,0         120         32         26           Sweden         6.3         314         220         4           UK         14,0         132         118           UK         14,0         132         118           Slovakia         5.9         52         44         4           Latvia         19,0         314         22         52      <	4049 3278	370	401	0.47 (0.34 to 0.64)	44 (32)	385/387
Abilitia         63         125         40         1         64         -         0(-)         000           Pellolini         13         13         14         14         1         14         1         14         1         14         1         16         1         16         1         16         1         16         1         16         1         10         10         10         10         10         10         10         10         10         10         10         10         10         10         10         10         10 <td>Attila         6         1         64         -         0<!--</td--><td>Austria         6.9         125         40           Belgum         8.5         19         18           Finland         7.7         8         8           Finland         7.7         69         24           Finland         7.5         8         4           Finland         7.5         8         4           France         7.7         69         24           Gemany         7.5         8         4           Italy         5.5         4         4           Spain         5.5         4         4           Spain         6.3         20         18           UK         14.0         132         28           Stain         28.0         92         4           UK         14.0         132         28           Bulgaria         28.0         32         28           Latvia         40.0         132         314         23           Latvia         49.0         132         143         11           Stovakia         5.9         70         25         18           Stovakia         5.0         133         133         116<!--</td--><td>800 464</td><td>42</td><td>294</td><td>0.23 (0.05 to 0.68)</td><td>3 (2)</td><td>19/19</td></td></td>	Attila         6         1         64         -         0 </td <td>Austria         6.9         125         40           Belgum         8.5         19         18           Finland         7.7         8         8           Finland         7.7         69         24           Finland         7.5         8         4           Finland         7.5         8         4           France         7.7         69         24           Gemany         7.5         8         4           Italy         5.5         4         4           Spain         5.5         4         4           Spain         6.3         20         18           UK         14.0         132         28           Stain         28.0         92         4           UK         14.0         132         28           Bulgaria         28.0         32         28           Latvia         40.0         132         314         23           Latvia         49.0         132         143         11           Stovakia         5.9         70         25         18           Stovakia         5.0         133         133         116<!--</td--><td>800 464</td><td>42</td><td>294</td><td>0.23 (0.05 to 0.68)</td><td>3 (2)</td><td>19/19</td></td>	Austria         6.9         125         40           Belgum         8.5         19         18           Finland         7.7         8         8           Finland         7.7         69         24           Finland         7.5         8         4           Finland         7.5         8         4           France         7.7         69         24           Gemany         7.5         8         4           Italy         5.5         4         4           Spain         5.5         4         4           Spain         6.3         20         18           UK         14.0         132         28           Stain         28.0         92         4           UK         14.0         132         28           Bulgaria         28.0         32         28           Latvia         40.0         132         314         23           Latvia         49.0         132         143         11           Stovakia         5.9         70         25         18           Stovakia         5.0         133         133         116 </td <td>800 464</td> <td>42</td> <td>294</td> <td>0.23 (0.05 to 0.68)</td> <td>3 (2)</td> <td>19/19</td>	800 464	42	294	0.23 (0.05 to 0.68)	3 (2)	19/19
Finden         65         19         18         1         0	Belgun         85         19         18         1         0	Belgium         8.5         19         18           Finland         4.9         8.5         19         18           Finland         4.9         351         24           France         7.7         69         24           France         7.7         69         24           Finland         7.5         8         4           Ireland         7.5         8         4           The Netherlands         5.5         20         18           Spain         12.0         32         29         26           Sweden         6.3         32         20         4           Spain         12.0         32         20         4           UK         14.0         132         4         4           Sweden         6.3         32         28         2           UK         14.0         132         314         220           UK         14.0         132         14         4           Lativa         49.0         77.0         25         53           Lativa         49.0         77.0         26         171           Stovakia         5.9 <td< td=""><td>125 40</td><td>-</td><td>84</td><td>1</td><td>(-) 0</td><td>0/0</td></td<>	125 40	-	84	1	(-) 0	0/0
Finand         49         8         2         2         3         -         0(-)         00           Fance         7         361         24         19         38         0.4         0(-)         00           Fance         7         361         24         19         38         0.4         0(-)         00           Fance         5         4         4         2         0         -         0(-)         20           Fance         5         4         4         2         0         -         0(-)         20         0(-)         20           Span         5         5         1         2         0         -         0(-)         20         0(-)         20           Span         12         2         2         0         0         2         0(-)         20         0(-)         20         0(-)         20         0(-)         20         0(-)         20         20         0(-)         20         20         0(-)         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20 <td>Finduct         49         8         6         0&lt;</td> <td>Finland         4.9         8         8         8         8         8         8         8         8         8         7.7         8         8         8         7         7         8         8         8         7         7         7         8         8         7         14         7         5         8         8         4         4         4         7         7         5         7         7         9         14         7         5         5         7         7         9         14         6         3         2         2         4         4         4         5         5         7         4         4         4         4         6         3         2         2         3         2         3         2         3         2         4</td> <td>19 18</td> <td>-</td> <td>0</td> <td>1</td> <td>(-) 0</td> <td>0/0</td>	Finduct         49         8         6         0<	Finland         4.9         8         8         8         8         8         8         8         8         8         7.7         8         8         8         7         7         8         8         8         7         7         7         8         8         7         14         7         5         8         8         4         4         4         7         7         5         7         7         9         14         7         5         5         7         7         9         14         6         3         2         2         4         4         4         5         5         7         4         4         4         4         6         3         2         2         3         2         3         2         3         2         4	19 18	-	0	1	(-) 0	0/0
Finole         77         69         24         2         43         -         0 <th< td=""><td>France         77         68         24         2         43         -</td><td>France         7.7         69         24           Germany         7.5         8         4           Ireland         7.5         8         4           Ireland         7.5         8         4           The Netherlands         5.6         4         4           Spain         12.0         32         20           Spain         12.0         32         28           Sweden         6.3         32         28           Sweden         6.3         32         28           Sweden         6.3         32         28           Storia         12.0         314         220           Hungary         16.0         72         314         24           Latvia         19.0         72         35         53           Latvia         49.0         132         24         41           Restoria         16.0         77.0         25         53           Latvia         5.9         70         25         53           Slovakia         5.3         503         413           Ukraine         77.0         132         144           Restoria         <td< td=""><td>8</td><td>0</td><td>0</td><td>1</td><td>(-) 0</td><td>0/0</td></td<></td></th<>	France         77         68         24         2         43         -	France         7.7         69         24           Germany         7.5         8         4           Ireland         7.5         8         4           Ireland         7.5         8         4           The Netherlands         5.6         4         4           Spain         12.0         32         20           Spain         12.0         32         28           Sweden         6.3         32         28           Sweden         6.3         32         28           Sweden         6.3         32         28           Storia         12.0         314         220           Hungary         16.0         72         314         24           Latvia         19.0         72         35         53           Latvia         49.0         132         24         41           Restoria         16.0         77.0         25         53           Latvia         5.9         70         25         53           Slovakia         5.3         503         413           Ukraine         77.0         132         144           Restoria <td< td=""><td>8</td><td>0</td><td>0</td><td>1</td><td>(-) 0</td><td>0/0</td></td<>	8	0	0	1	(-) 0	0/0
Germany         49         351         294         19         38         0.34 (0.04 to 1.22)         2 (2)         0.66           Table         5         8         4         4         3         0.44 (0.04 to 1.22)         2 (2)         0.61           Table         5         4         1         2         0         0.1         2 (2)         0.61           Table         5         2         0         5         1         -         0.1         2 (2)         0.61           Spain         12         2         2         0         0         0.10 (0.10 (0.12)         1 (0)         2 (0)         0.1         2 (0)         0.1         0.1         2 (0)         0.1         0.1         2 (0)         0.1	Gammay         43         331         244         13         33         0.34 (0.04 to 122)         2 (2)         0 (6)           Tele Nertherized         55         2         3         0.34 (0.04 to 122)         2 (1)         2 (2)         0 (6)           The Nertherized         55         2         4         4         0         0         0         2 (1)         2 (2)         0 (6)           The Nertherized         10         32         2 (2)         0 (3)         0 (1)         1 (1)         0 (1)         2 (2)         0 (1)         2 (2)         0 (1)	Germany         4.9         351         294           Ireland         7.5         8         4           Italy         5.5         20         18           The Netherlands         5.5         4         4           Spain         5.5         32         26           Sweden         6.3         32         26           UK         14.0         7.3         32         28           Sweden         6.3         32         28         4           Sweden         6.3         32         28         4           Sweden         6.3         32         28         4           UK         14.0         73         27         8           Czech Republic         4.7         314         220           Latvia         28.0         7         314         220           Latvia         16.0         72         314         413           Lithuania         58.0         314         413           Slovakia         5.9         46         7         414           Restern Europe         5.9         46         7         413           Croatia         19.0 <td< td=""><td>69 24</td><td>0</td><td>43</td><td>1</td><td>(-) 0</td><td>0/0</td></td<>	69 24	0	43	1	(-) 0	0/0
	Indication         7.5         8         4         4         0         -         0         -         22           Tex Minimuts         5.8         2.8         2.8         0         0         0         0         22           Tex Minimuts         5.8         2.8         2         0         0         0         0         0         22           Same         6.5         2.8         2.8         0	Ireland         7.5         8         4           Italy         5.8         20         18           The Netherlands         5.5         4         4           Spain         12.0         32         26           Spain         12.0         32         26           Spain         12.0         32         26           Sweden         6.3         32         26           Sweden         25.1         810         633           Uk         14.0         132         28           Latvia         28.0         314         220           Latvia         28.0         314         220           Latvia         28.0         314         220           Latvia         16.0         72         53           Latvia         19.0         72         53           Slovakia         5.9         73         41           Slovakia         5.9         73         413           Vorth Americat         13.0         143         11           Slovakia         3.6         157         157           Slovakia         5.9         70         256         143	351 294	19	38	0.34 (0.04 to 1.22)	2 (2)	6/6
The Network         58         20         13         2         0         -         0(-)         22           The Network         55         4         4         1         0         -         0(-)         22           Spain         5         4         4         5         1         -         0(-)         25           Spain         0.5         33         177         0         0.58         0.14         0(-)         55           Spain         25.1         810         633         177         0         0.58         0.14         0.1         44           Vic         314         200         94         0         0.56         0.14         0.0         0.1         44           Uk         47         0         0.56         0.01         0.0         0.1         0.0	Itely         S         2         0         -         0         -         22           The Methetands         5         2         2         0         -         0         -         0         -         22           Sam         12         3         12         3         1         0         -         0         -         0         -         0         -         0         -         0         -         0         -         0         -         0         -         0         -         0         -         0         -         0         -         0         -         0         0         - <td>Italy         5.8         20         18           The Netherlands         5.5         4         4         4           Spain         12.0         32         26         5           Sweden         6.3         32         28         28           Sweden         6.3         32         28         28           Sweden         25.1         810         633         28           Uk         14.0         132         28         4         4           Estonia         28.0         314         220         8           Lutviania         29.0         72         53         43           Latvia         49.0         72         54         44           Voltania         58.0         92         8         53           Poland         19.0         72         55         53           Latvia         59         70         72         53         111           Restarn Europe         46.8         503         413         11           Restarn Europe         46.8         503         413         11           Serbia         77.0         226         133         143</td> <td>8</td> <td>4</td> <td>0</td> <td>I</td> <td>(-) 0</td> <td>2/2</td>	Italy         5.8         20         18           The Netherlands         5.5         4         4         4           Spain         12.0         32         26         5           Sweden         6.3         32         28         28           Sweden         6.3         32         28         28           Sweden         25.1         810         633         28           Uk         14.0         132         28         4         4           Estonia         28.0         314         220         8           Lutviania         29.0         72         53         43           Latvia         49.0         72         54         44           Voltania         58.0         92         8         53           Poland         19.0         72         55         53           Latvia         59         70         72         53         111           Restarn Europe         46.8         503         413         11           Restarn Europe         46.8         503         413         11           Serbia         77.0         226         133         143	8	4	0	I	(-) 0	2/2
The Methedratics         55         4         4         0         -         0(-)         00           The Methedratics         55         3         7         0         -         0(-)         55           Sweden         63         17         0         0         0         0(-)         55           Sweden         63         17         0         0         0.0         0.0         0.0         0.0           Sweden         23         132         28         7         0         0.0         0.0         0.0           Bulgaria         280         281         132         28         13         0         0.0         <	The Netherlards 5.5 2.4 4 0 0 0 - 0 0 0 0 0 0 0 0 0 0 0 0 0 0	The Netherlands         5.5         4         4           Spain         12.0         32         26           Spain         12.0         32         26           UK         14.0         132         28           Sweden         6.3         32         28           UK         14.0         132         28           Central Europe         28.0         52         45           Bulgaria         28.0         52         45           Bulgaria         28.0         52         45           Extonia         20.0         25         13           Hungary         16.0         72         55         53           Latvia         49.0         72         55         53           Latvia         19.0         72         55         53           Slovakia         5.9         79         52         53           Croatia         13.0         132         116           Ukraine         77.0         132         113           Ustatia         5.0         167         111           Ustatia         5.1         1576         114           Ustatia         3.6 </td <td>20 18</td> <td>0</td> <td>0</td> <td>1</td> <td>(-) 0</td> <td>2/2</td>	20 18	0	0	1	(-) 0	2/2
Spain         120         22         2         1         -         0(-)         55           Widen         163         32         28         5         1         -         0(-)         55           UK         143         32         28         6         5         1         -         0(-)         55           UK         143         20         31         220         33         177         0         0.36 (0.11 to 12.9)         11(-)         00           Extend Europe         25.1         314         220         94         0         0.36 (0.01 to 2.79)         11(-)         00           Extend         43         314         220         94         0         0.36 (0.01 to 2.79)         10(10           Lawia         430         44         0         0         2.0         0.0         33         0.0           Lawia         930         122         53         11         0         0.0         20         0.0         0.0         0.0         0.0         0.0         0.0         0.0         0.0         0.0         0.0         0.0         0.0         0.0         0.0         0.0         0.0         0.0         <	Spain         120         32         26         1         -         0(-)         55           Swell         10         10         0	Spain         12.0         32         26           UK         14.0         132         28         0           UK         14.0         132         28         0           UK         14.0         132         28         63           Bulgaria         28.0         52         45           Caech Republic         4.7         314         220           Hungary         16.0         72         55         53           Latvia         49.0         72         55         53           Latvia         49.0         72         55         53           Poland         19.0         72         55         53           Slovakia         5.9         79         52         53           Croatia         19.0         73         79         52           Serbia         77.0         132         114         11           Ukraine         77.0         150         133         14           Ust         3.6         150         133         1552           Ust         3.6         1516         144         14           Ust         3.6         167         133     <	4 4	0	0	I	(-) 0	0/0
Sweden         6.3         32         0         0         2         -         0 (-)         00           UK         10         11         12         2         0         0.56         0.51         0.0         0.0           Bugard         251         11         0         0.56         0.51         0.15         0.15         0.0           Bugard         251         132         25         13         7         0         0.56         0.15         0.05         0.01         0.0           Central Europe         251         13         2         0         0.56         0.51         0.0	Sweden         63         32         0         32         0         30         0(-)         00           UK         23         10         33         17         0         0.58         0.11         10         44           Central Europe         23.1         10         0.58         0.77         0         0.58         0.11         0.0           Central Europe         23.1         13.4         220         34         7         0         0.58         0.61         0.0         0.0           Central Europe         23.0         13         12         22.0         34         7         0         0.58         0.0         0.0         0.0           Central Europe         20         13         1         20         0         0.58         0.0         0.00         0.0	Sweden         6.3         32         0           UK         14.0         6.3         22.8         28.3         28.0         63.3         28.0         63.3         28.0         52         45         52         45         52         45         52         45         52         45         52         45         52         45         52         45         52         45         53         53         53         44<	32 26	5	-	1	(-) 0	5/5
UK         140         132         28         635         0.035         0.016         1(0)         44           Exact Republic         4.1         5.2         4.5         7         0         0.36         0.016         0.37         0.01         0.016         0.01	UK         140         122         28         6         0.55 (0.116)         110)         44           Bugaria         28.1         10         63.3         17         0         0.56 (0.116)         110)         44           Bugaria         28.0         38.1         12         0         0.56 (0.116)         113)         150/15           Bugaria         28.0         28.0         13         7         0         0.56 (0.116)         113)         150/15           Estonia         20.0         256 (0.176)         21         0         0.56 (0.116)         113)         0.6           Hugary         16.0         23         17         0         0.56 (0.176)         0.7         0         0.7         0.0         0.6         0.6         0.6         0.6         0.6         0.6         0.6         0.6         0.6         0.6         0.7         0         0.7         0         0         0.7	UK         14.0         132         28           Bulgaria         25.1         810         633           Bulgaria         28.0         52         45           Central Europe         25.1         810         633           Estonia         20.0         25         18           Estonia         20.0         25         18           Latvia         49.0         72         53           Latvia         49.0         72         53           Latvia         58.0         92         83           Poland         19.0         72         53           Stovakia         5.9         73         413           Storatia         13.0         132         118           Storatia         77.0         132         14           Russia         77.0         159         139           Orotatia         13.0         167         141           Russia         77.0         159         139           Ukraine         77.0         159         139           Ustaine         77.0         159         144           Ustaine         77.0         159         141	32 0	0	32	1	(-) 0	0/0
Cartral Europe         25.1         810         633         177         0         0.58         0.116.279         11(1)         0.50/151           Careth Flexuola         280         25         45         7         0         0.58         0.116.279         1(1)         0.0           Careth Flexuola         200         25         18         7         0         0.58         0.117         0.0           Larvia         400         25         18         19         0         2.10         0.51         0.0           Larvia         400         25         18         19         0         2.34         5         7         0         0.56         0.1         1010           Larvia         430         17         0         0         2.34         0.1         107         2.07         0.0           Pointurai         380         9         0         0         2.34         0.0         2.02         2.0         0.0         0.0           Pointurai         380         132         13         1         0         2.00         2.01         0.0         0.0         0.0         0.0         0.0         0.0         0.0         0.0	$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Central Europe         25.1         810         633           Bulgaria         28.0         52         45           Czech Republic         4.7         52         45           Estonia         20.0         25         18           Estonia         20.0         25         18           Hungary         16.0         72         53           Latvia         49.0         72         58.0           Poland         19.0         72         53           Slovakia         5.9         73         52           Slovakia         5.9         73         71           Russia         77.0         132         111           Russia         77.0         132         144           North Americat         3.6         155         144           Usatian         77.0         156         144           Usatian         3.6         157         16	132 28	ω	96	0.35 (0.01 to 1.94)	1 (0)	4/4
Bulgaria         280         32         45         7         0         0.50 (0.01 to 2.79)         1 (1)         0 0           Bulgaria         280         32         34         220         94         0         0.56 (0.11 to 2.79)         1 (1)         0 0           Hungary         160         27         28         18         7         0         2.10 (0.25 to 7.9)         2 (1)         0 0           Hungary         160         27         28         18         7         0         2.10 (0.25 to 7.9)         1 (1)         0 0           Hungary         160         27         28         18         7         0         2.10 (0.25 to 1.5)         2 (1)         10/10           Poind         190         122         118         14         0         0.55 (0.07 to 2.0)         2 (1)         20/20           Poind         130         132         118         14         0         0.55 (0.07 to 2.0)         2 (1)         20/20           Poind         130         130         130         130         137         217           Poind         130         130         130         130         137         216         133/13           Conalia<	Budgaria         280         52         74         0         0.56 (0.01 to 2.79)         1 (1)         0 00           Hungary         160         25         18         7         0         2.06 (0.11 to 2.79)         1 (1)         06           Hungary         160         25         18         7         0         2.00 (1.25 to 7.59)         2 (1)         0.00           Hungary         160         25         13         0         0         1.010         0.6         1.010         0.6           Hungary         160         25         13         0         0         2.00 (12.5 to 7.59)         1 (1)         0.6         1.010         0.6           Hungary         160         22         113         14         0         0.20 (0.01 to 2.51)         1 (1)         0.6         1 (1)         0.6         1 (1)         0.6         1 (1)         0.6         1 (1)         0.6         1 (1)         0.6         1 (1)         0.6         1 (1)         0.6         1 (1)         0.6         1 (1)         0.6         1 (1)         0.6         1 (1)         0.6         0.6         0.6         0.6         0.6         0.6         0.6         0.6         0.6         0.6	Bulgaria         28.0         52         45           Czech Republic         4.7         314         220           Estonia         20.0         25         18           Hungary         16.0         72         53           Latvia         49.0         72         53           Latvia         49.0         72         53           Latvia         58.0         92         83           Poland         19.0         72         52           Slovakia         5.9         73         52           Slovakia         5.9         73         52           Slovakia         5.9         73         52           Slovakia         5.9         73         413           Croatia         13.0         144         11           Russia         77.0         226         171           Serbia         20.0         156         144           North Americat         3.6         155         144           Serbia         77.0         226         144           Usatian         3.6         156         144           Usatian         5.7         263         216	810 633	177	0	0.58 (0.34 to 0.92)	18 (13)	150/151
Czech Republic         4.7         314         220         94         0         0.36 (0.12 to 0.84)         5 (2)         76/7           Hungary         16         100         2         18         7         0         210 (0.25 to 7.59)         211         10/10           Latvia         680         22         18         9         0         234 (0.46 to 6.54)         3 (3)         0/0           Latvia         580         92         183         19         0         234 (0.46 to 6.54)         3 (3)         0/0           Planaria         580         92         183         19         0         1.36 (0.71 2.00)         2 (1)         0/6           Storakia         5,9         72         0         2.24 (0.46 to 6.54)         3 (3)         0/0           Storakia         5,9         73         0         1.41         11         2         2         0/1         3 (3)         10/1           Storakia         5,0         7,10         2.26         171         55         0         10/10         2         10/1         10/10         2         2         2         10/10         2         2         10/10         2         2         2         10/	Czech Republic         4.7         314         220         94         0         0.38 (0.12 to 0.04)         5 (2)         7677           Hungary         600         72         53         19         0         2.10 (0.25 to 7.59)         2 (1)         66           Lanvia         800         72         53         19         0         2.10 (0.25 to 7.59)         2 (1)         00           Lanvia         800         132         118         14         0         0.36 (0.17 to 2.00)         2 (0)         0	Czech Republic         4.7         314         220           Estonia         20.0         25         18           Hungary         16.0         72         53           Latvia         49.0         72         53           Latvia         49.0         72         53           Latvia         49.0         92         83           Poland         19.0         132         118           Slovakia         5.9         73         52           Eastern Europe         46.8         5.9         73           Slovakia         5.9         73         413           Croatia         13.0         14         11           Russia         77.0         226         171           Serbia         20.0         159         139           Ukraine         77.0         226         171           Serbia         20.0         159         139           Ukraine         77.0         226         131           Ukraine         77.0         157         144           Uset of the WorldS         16.7         263         216           USA         3.6         157         144 </td <td>52 45</td> <td>7</td> <td>0</td> <td>0.50 (0.01 to 2.79)</td> <td>1 (1)</td> <td>0/0</td>	52 45	7	0	0.50 (0.01 to 2.79)	1 (1)	0/0
Estorial         200         25         18         7         0         2.10 (0.25 to 7.59)         2 (1)         66           Hungary         160         72         23         19         0         2.10 (0.25 to 7.59)         2 (1)         66           Linhuaria         580         32         19         0         2.24 (0.46 to 65.4)         3 (3)         77           Poland         190         122         23         0         1.30 (0.42 to 30.4)         5 (3)         77           Storatia         590         132         2118         14         0         0.55 (0.07 to 200)         2 (1)         31/31           Storatia         7.30         14         11         3         0         1.00 (0.46 to 18.2)         1 (1)         31/31           Storatia         7.30         14         11         3         0         1.00 (0.46 to 18.2)         1 (1)         2 (2)           Croatia         7.30         14         11         3         0         1.00 (0.46 to 18.2)         1 (1)         2 (2)           Storatia         7.70         228         0         1.00 (0.56 to 18.2)         1 (1)         2 (2)         2 (2)         2 (2)           Croatia	Estorial         200         25         18         7         0         2.10 (0.25 to 7.53)         2 (1)         66           Larvan         490         44         44         0         0         2.4 (0.46 to 6.54)         3 (3)         0 (-)         1010           Larvan         580         44         44         0         0         2.4 (0.46 to 6.54)         3 (3)         0 (-)         1010           Larvan         580         43         7         0         0.55 (0.07 to 200)         5 (5)         77           Storakia         59         70         0.55 (0.07 to 200)         0 (-)         3131         2020         0 (-)         3131         2020         0 (-)         3131         2020         2020         2010         2021         0 (-)         3131         2020         2010         000         2010         2021         0 (-)         3131         2020         2021         2010         2021         2010         2021         2010         2021         2010         2020         2010         2021         2010         2021         2010         2021         2010         2021         2010         2021         2010         2010         2010         2010         2010	Estonia       20.0       25       18         Hungary       16.0       72       53         Latvia       49.0       72       53         Latvia       49.0       72       53         Latvia       58.0       92       53         Poland       19.0       132       118         Slovakia       5.9       73       52         Eastern Europe       46.8       5.0       74         Slovakia       5.9       73       71         Slovakia       5.9       73       71         Slovakia       5.0       132       114         Russia       77.0       226       171         Serbia       20.0       104       92         Ukraine       77.0       156       144         North Americat       3.6       157       114         Usa       3.2       167       157       114         Usa       3.2       167       157       144         North Americat       3.6       155       144         Usa       3.2       167       156       144         Vastralia       5.7       210       132	314 220	94	0	0.36 (0.12 to 0.84)	5 (2)	76/77
Hungary16.07253190-10/10Latvia49.07253190000Lifthuaria58.0228890130 (145 to 510)2 (1)2020Poland19.01321181400.55 (107 to 2100)2 (1)2020Poland19.01321181400.55 (107 to 2100)2 (1)2020Stovakia5.97701.00 (105 to 10.82)1 (1)2020Estern Europe4.685034139001.00 (0.45 to 10.82)1 (1)2020Croatia13.01411301.00 (0.45 to 10.82)1 (1)2020Stribia77.014411300.00 (0.48 to 10.82)1 (0)2256Croatia77.015215201.00 (0.37 to 2.17)6 (3)4.444Vertine77.015315245760.00 (0.37 to 2.17)6 (3)Vertine77.01571119370.00 (0.37 to 2.17)6 (3)4.444Vertine77.01571119370.01 (0.70 (0.500)1 (0)10/10Uranic3.215711311310100.01 (0.00 to 0.33)1 (0)10/10Usin0.516711193700.06 (0.00 to 0.33)1 (0)10/10Usin1671111010 <td< td=""><td>Hungary16072531900Linkrvia49072531900Linkrvia890920224 (0.46 to 654)3 (3)00Linkrvia89012313313200Linkrvia8901221321181400.55 (0.77 to 200)2 (1)2020Poland19013211814000.55 (0.77 to 200)2 (1)2020Estern Europe468534132001.44 (0.654)3 (3)00Consist770231181411301.44 (0.654)3 (3)00Consist7702691411301.44 (0.654)3 (3)00Serbia20014111301.94 (0.654)1010202Consist13011411300.06 (0.00 to 0.23)1 (0)276Serbia20016712315500.06 (0.00 to 0.33)1 (0)276Serbia200167144136310.16 (0.00 to 0.33)1 (0)2656Caracta3167144136216100 (0.010 (0.0106)1 (1)1010Ukraine71012614136110100 (0.106)1 (1)1010Ukraine71012714136216100 (0.010 (0.0106)1 (1)1010</td><td>Hungary       16.0       72       53         Latvia       49.0       44       44         Lithuania       58.0       92       83         Poland       19.0       132       118         Slovakia       5.9       73       52         Slovakia       5.9       73       53         Slovakia       5.9       73       503         Slovakia       5.9       73       413         Slovakia       5.9       503       413         Slovakia       5.9       503       413         Slovakia       5.0       13.0       14         Russia       77.0       226       171         Serbia       20.0       104       92         Ukraine       77.0       226       133         North America‡       3.6       1673       1552         Canada       4.0       157       144         USA       3.2       167       144         Rest of the WorldS       16.7       263       216         USA       3.2       1552       131         Argentina       5.7       263       216         Katol</td><td>25 18</td><td>7</td><td>0</td><td>2.10 (0.25 to 7.59)</td><td>2 (1)</td><td>6/6</td></td<>	Hungary16072531900Linkrvia49072531900Linkrvia890920224 (0.46 to 654)3 (3)00Linkrvia89012313313200Linkrvia8901221321181400.55 (0.77 to 200)2 (1)2020Poland19013211814000.55 (0.77 to 200)2 (1)2020Estern Europe468534132001.44 (0.654)3 (3)00Consist770231181411301.44 (0.654)3 (3)00Consist7702691411301.44 (0.654)3 (3)00Serbia20014111301.94 (0.654)1010202Consist13011411300.06 (0.00 to 0.23)1 (0)276Serbia20016712315500.06 (0.00 to 0.33)1 (0)276Serbia200167144136310.16 (0.00 to 0.33)1 (0)2656Caracta3167144136216100 (0.010 (0.0106)1 (1)1010Ukraine71012614136110100 (0.106)1 (1)1010Ukraine71012714136216100 (0.010 (0.0106)1 (1)1010	Hungary       16.0       72       53         Latvia       49.0       44       44         Lithuania       58.0       92       83         Poland       19.0       132       118         Slovakia       5.9       73       52         Slovakia       5.9       73       53         Slovakia       5.9       73       503         Slovakia       5.9       73       413         Slovakia       5.9       503       413         Slovakia       5.9       503       413         Slovakia       5.0       13.0       14         Russia       77.0       226       171         Serbia       20.0       104       92         Ukraine       77.0       226       133         North America‡       3.6       1673       1552         Canada       4.0       157       144         USA       3.2       167       144         Rest of the WorldS       16.7       263       216         USA       3.2       1552       131         Argentina       5.7       263       216         Katol	25 18	7	0	2.10 (0.25 to 7.59)	2 (1)	6/6
Lativa         480         44         44         0         0         2.24 (0.46 to 6.54)         3 (3)         00           Inhuarita         580         92         83         9         0         1.30 (0.42 to 3.04)         5 (5)         77           Pondid         5.9         73         59         0         0.55 (0.07 to 2.00)         5 (5)         77           Storatia         5.9         73         90         0         1.50 (0.42 to 3.04)         5 (5)         77           Storatia         5.9         73         90         0         0.56 (0.07 to 2.00)         2 (1)         2020           Storatia         7.30         14         11         5         0         1.00 (0.48 to 1.83)         1 (1)         2 (2)           Coalia         7.10         159         171         5         0         1.00 (0.56 to 1.83)         1 (1)         7 (7)           Serbia         2.00         104         92         12         0         1.00 (0.76 to 0.83)         1 (1)         7 (7)           Washing         2.00         106         0.00 (0.48 to 1.83)         1 (1)         1 (1)         1 (1)         1 (1)           Serbia         2.00         133	$ \begin{array}{l c c c c c c c c c c c c c c c c c c c$	Latvia       49.0       44       44         Lithuania       58.0       92       83         Poland       19.0       132       118         Slovakia       5.9       79       52         Eastern Europe       46.8       5.9       73         Slovakia       5.9       73       413         Slovakia       5.9       73       413         Slovatia       13.0       14       17         Russia       77.0       226       171         North America‡       3.6       1673       1552         Ukraine       77.0       159       133         North America‡       3.6       157       141         Ukraine       77.0       159       133         Ukraine       77.0       157       141         Ukraine       77.0       157       141         Ust       3.2       1673       1552         Canada       4.0       157       141         Ust       3.2       1673       156         Ust       3.2       167       141         Rest of the World\$       16.7       210       132         Australi	72 53	19	0		0 (–)	10/10
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Liftuaria         650         92         83         9         0         130 (0.42 to 3.04)         5 (5)         77           Peland         59         73         22         130 (0.42 to 3.04)         5 (3)         77         3 (207 to 2.00)         2 (1)         3 (207 to 2.0)         2 (1)         3 (207 to 2.0)         2 (1)         3 (207 to 2.0)         3 (1)         3 (207 to 2.0)         3 (1)         3 (1)         3 (1)         3 (1)         3 (1)         3 (1)         3 (1)	Lithuania       58.0       92       83         Poland       19.0       132       118         Slovakia       5.9       79       52         Eastern Europe       46.8       5.9       70         Slovakia       5.9       70       132       118         Slovakia       5.9       70       172       111         Restern Europe       46.8       503       413         Croatia       13.0       13.0       14       171         Russia       77.0       226       171       92         Ukraine       77.0       226       171       92         Ukraine       77.0       1673       1552       144         Ust       3.6       157       156       144         Ust       3.2       1673       1552       167         USA       3.2       167       157       111         USA       3.2       1673       1552       167         USA       3.2       1673       156       144         Rest of the WorldS       16.7       263       216         Australia       5.7       213       131         Austral	44 44	0	0	2.24 (0.46 to 6.54)	3 (3)	0/0
Poland         190         132         118         14         0         0.55 (0.7 ho 2.00)         2 (1)         2 0(2)         3 1/31           Slovakia         5.9         5.3         27         0         -         -         0 (-)         3 1/31           Estern Europe         4.68         5.03         4.13         90         0         1.02 (0.63 to 1.62)         1 (0)         2 22           Russia         7.70         226         171         55         0         1.00 (0.46 to 1.82)         1 (0)         2 22           Russia         7.70         226         171         55         0         1.00 (0.46 to 1.82)         1 (0)         2 22           Noth Americat         3.6         171         55         0         1.00 (0.46 to 1.83)         1 (7)         7 9/79           Varaine         200         139         27         0         1.00 (0.46 to 1.83)         1 (7)         7 9/79           Noth Americat         3.6         141         3         0         0         0         2 22           Ustaine         2.0         1.00 (0.46 to 1.82)         1 (0)         2 20         2 4444           Noth Americat         3.6         1.11         3 6	Poland         190         132         118         14         0         0.55 (0.07 to 2.00)         2 (1)         2 0/20           Stovakia         5.9         73         52         27         0         -         0 (-)         31/31           Estern Europe         4.6         5.0         4.13         90         0         126 (6.07 to 2.60)         2 (1)         3 31/31           Croatia         13.0         14         11         5         0         1.94 (0.05 to 10.82)         1 (0)         27/9         27/9           Russia         77.0         139         104         92         12         0         1.00 (0.37 to 2.14)         1 (0)         27/9         27/9           Serbia         77.0         159         133         20         0         1.00 (0.37 to 2.14)         6 (1)         13/31           Unstand         77.0         159         131         3         0         0.06 (0.00 to 0.33)         1 (0)         27           Unstand         32         141         38         20         0.06 (0.00 to 0.33)         1 (0)         27           Ustand         32         141         38         0.06 (0.00 to 0.33)         1 (0)         27      <	Poland         19.0         132         118           Slovakia         5.9         79         52           Eastern Europe         46.8         503         413           Croatia         13.0         14         11           Russia         77.0         226         171           Serbia         20.0         104         92           Ukraine         77.0         226         171           Varaine         77.0         1673         1552           North America‡         3.6         1673         1552           Ukraine         77.0         159         139           North America‡         3.6         157         111           Usa         3.2         1673         1552           Canada         16.7         263         216           USA         3.2         167         141           Hest of the World§         16.7         263         216           Argentina         5.7         413         143           Australia         5.7         443         141           Kento         132         143         143           New Zealand         6.7         45	92 83	ი	0	1.30 (0.42 to 3.04)	5 (5)	7/7
Slovakia         5.9         79         5.2         27         0         -         0 (-)         31/31           Eastern Europe         468         503         413         90         0         1.02 (0.63 to 1.56)         21 (16)         135/135           Croatia         77.0         226         11         3         0         1.02 (0.63 to 1.632)         1 (0)         22           Russia         77.0         226         11         3         0         1.00 (0.45 to 1.032)         1 (0)         27           Serbia         200         100         41         3         0         1.00 (0.45 to 1.032)         1 (0)         27           North Americat         3.6         1167         133         20         0         1.00 (0.37 to 2.17)         6 (5)         44/44           North Americat         3.6         167         141         38         20         0.06 (0.00 to 0.30)         1 (0)         55/56           North Americat         3.6         1572         44         37         0.06 (0.00 to 0.30)         1 (0)         55/56           Carada         2.10         132         111         9         37         0.06 (0.00 to 0.30)         1 (0)         2 (0)	Slovakia5.9795.2270-0 (-)31/31Eastern Europe46.85031331413001.02 (0.63 to 1.56)21 (16)135/135Croatia77.02261715501.00 (0.48 to 1.82)10 (7)7979Russian77.02261715501.00 (0.48 to 1.82)10 (7)7979Serbia20.01041715501.00 (0.48 to 1.82)10 (7)7979Serbia20.0104157111500.06 (0.01 to 0.30)10 (7)7979Serbia20.015711192000.05 (0.01 to 0.30)10 (7)7979Serbia20.01571119370.05 (0.01 to 0.30)10 (7)7979Canada4.01571119370.05 (0.01 to 0.30)10 (7)5556Canada21.6144136310.11 (0.00 to 0.06)11 (1)10/10Ustatia5.71119370.11 (0.00 to 0.06)11 (1)22Australia5.7442200.19 (0.00 to 1.06)11 (1)22Australia5.7442200.19 (0.00 to 1.06)11 (1)10/10Australia5.74422220.60.01 (0.00 to 0.60)120Australia5.7442200.19 (0.00 to	Slovakia         5.9         79         52           Eastern Europe         46.8         503         413           Croatia         13.0         14         11           Russia         77.0         226         171           Serbia         20.0         104         92           Ukraine         77.0         226         171           Varaine         77.0         1673         1552           North America‡         3.6         1673         1552           Ukraine         77.0         159         139           North America‡         3.6         157         111           USA         3.2         1673         1552           USA         3.2         1673         1552           Argentina         21.0         132         141           Australia         5.7         263         216           Australia         5.7         43         12           Israel         6.7         45         37           Mexico         19.0         7         5           Inscel         6.7         45         7           Inscel         6.6         20         17 <td>132 118</td> <td>14</td> <td>0</td> <td>0.55 (0.07 to 2.00)</td> <td>2 (1)</td> <td>20/20</td>	132 118	14	0	0.55 (0.07 to 2.00)	2 (1)	20/20
Eastern Europe         46.8         503         413         90         0         1.02 (0.65 to 1.56)         21 (16)         135/135           Croatia         13.0         14         11         3         0         1.02 (0.65 to 1.65)         21 (16)         222           Croatia         13.0         14         11         3         0         1.09 (0.05 to 10.82)         1 (0)         770         222           Serbia         20.0         104         92         12         0         1.00 (0.45 to 10.82)         1 (0)         770         222           North Americat         3.6         1673         1552         45         76         0.05 (0.00 to 0.30)         1 (0)         770         74/44           North Americat         3.6         1411         36         37         0.05 (0.00 to 0.30)         1 (0)         55/66           Canada         4.0         157         1441         36         76         0.05 (0.00 to 0.30)         1 (0)         55/66           Argentina         21.0         132         131         1         1         101         0010           Satistical         5.7         2.83         216         16         0         101         001	Eastern Europe46.85034139001.02 (0.63 to 1.56)21 (16)135/135Croatia770226111301.04 (0.05 to 10.82)1 (0)22Russia7702261715501.04 (0.04 to 1.83)1 (1)27Serbia200104921200.098 (0.27 to 2.54)4 (4)1010Urkaine7701571132200.06 (0.04 to 0.33)1 (0)2556With Americat3.6157114136390.06 (0.00 to 0.33)1 (0)5556Canada3.2156144136390.06 (0.00 to 0.33)1 (0)5556Canada3.2156144136390.06 (0.00 to 0.33)1 (0)5556Canada5.713221614360.11 (0.00 to 0.03)1 (0)262Argentina5.11321122700.11 (0.00 to 0.06)1 (1)201Argentina5.1131000.11 (0.00 to 0.06)1 (1)202Argentina5.14.312200.11 (0.00 to 0.06)1 (1)201Argentina5.74.312200.11 (0.00 to 0.06)1 (1)202Argentina5.74.3122200.10 (0.00 to 0.06)1 (1)202Argentina5.11.422<	Eastern Europe       46.8       503       413         Croatia       13.0       14       11         Russia       77.0       226       171         Serbia       20.0       104       92         Ukraine       77.0       226       171         North America‡       3.6       1673       1552         North America‡       3.6       1673       1552         USA       3.2       167       141         Valatratia       5.7       43       14         Austratia       5.7       43       12         Israel       6.7       45       37         Mexico       19.0       7       5         New Zealand       6.6       20       17         Singapore       44.0       4       0	79 52	27	0	, , I	0 ()	31/31
Croatia         13.0         14         11         3         0         1.94 (0.05 to 10.82)         1 (0)         22           Russia         77.0         226         171         55         0         1.00 (0.48 to 183)         10 (7)         73/79           Serbia         20.0         157         1171         55         0         1.00 (0.48 to 183)         10 (7)         73/79           Serbia         20.0         153         133         20         0         1.00 (0.37 to 2.54)         4 (4)         10/10           Ukanicat         3.6         1673         1552         45         76         0.05 (0.00 to 0.33)         1 (0)         55/6           Canadda         4.0         157         111         9         37         -         0 (-1) (0)         55/6           Canadda         3.2         156         1441         36         0.06 (0.00 to 0.33)         1 (0)         56/56           Argentina         2.1         141         36         37         0.11 (0.00 to 1.06)         1 (1)         10/10           USA         3.2         143         1         1         0         1 (1)         0.06         0.010         0 (0)         1 (1)         0/10 <td>Croatia130141130144 (0.05 to 10.82)1 (0)22Russia7702261715501.00 (0.34 to 133)1 (7)777Russia7701591332201.00 (0.37 to 2.17)6 (3)4 (4)10/10Urraine7701591332201.00 (0.37 to 2.17)6 (3)4 (4)10/10North Americat3.61673157111937-00.06 (0.00 to 0.30)1 (0)55/6Canada4.0157111937-0.06 (0.00 to 0.33)1 (0)55/6Canada4.0157111937-0.06 (0.00 to 0.33)1 (0)45/46Rest of the WorldS16.7216144136390.01 (0.00 to 0.33)1 (0)45/46Argentina21.0132216144100.10 (0.00 to 0.33)1 (0)22Argentina21.0132216144200.10 (0.00 to 0.33)1 (0)22Argentina21.013214222-00.10 (0.00 to 0.33)1 (0)Argentina21.014200.10 (0.00 to 0.33)1 (0)222Argentina21.013214222-0 (-)0 (-)2Argentina6.74.814222222&lt;</td> <td>Croatia         13.0         14         11           Russia         77.0         226         171           Serbia         77.0         226         171           Serbia         20.0         104         92           Ukraine         77.0         159         139           North America‡         3.6         1673         1552           USA         3.2         1673         1552           Argentina         21.0         132         144           Australia         5.7         43         14           Australia         5.7         43         12           Israel         6.7         45         37           New Zealand         6.6         20         17           Singapore         44.0         4         0         0</td> <td>503 413</td> <td>06</td> <td>0</td> <td>1.02 (0.63 to 1.56)</td> <td>21 (16)</td> <td>135/135</td>	Croatia130141130144 (0.05 to 10.82)1 (0)22Russia7702261715501.00 (0.34 to 133)1 (7)777Russia7701591332201.00 (0.37 to 2.17)6 (3)4 (4)10/10Urraine7701591332201.00 (0.37 to 2.17)6 (3)4 (4)10/10North Americat3.61673157111937-00.06 (0.00 to 0.30)1 (0)55/6Canada4.0157111937-0.06 (0.00 to 0.33)1 (0)55/6Canada4.0157111937-0.06 (0.00 to 0.33)1 (0)45/46Rest of the WorldS16.7216144136390.01 (0.00 to 0.33)1 (0)45/46Argentina21.0132216144100.10 (0.00 to 0.33)1 (0)22Argentina21.0132216144200.10 (0.00 to 0.33)1 (0)22Argentina21.013214222-00.10 (0.00 to 0.33)1 (0)Argentina21.014200.10 (0.00 to 0.33)1 (0)222Argentina21.013214222-0 (-)0 (-)2Argentina6.74.814222222<	Croatia         13.0         14         11           Russia         77.0         226         171           Serbia         77.0         226         171           Serbia         20.0         104         92           Ukraine         77.0         159         139           North America‡         3.6         1673         1552           USA         3.2         1673         1552           Argentina         21.0         132         144           Australia         5.7         43         14           Australia         5.7         43         12           Israel         6.7         45         37           New Zealand         6.6         20         17           Singapore         44.0         4         0         0	503 413	06	0	1.02 (0.63 to 1.56)	21 (16)	135/135
Hussia         77.0         226         171         55         0         1.00 (0.48 to 1.83)         10 (7)         7979           Serbia         200         104         92         12         0         0.09 (0.27 to 2.54)         4 (4)         10/10           Ukraine         77.0         159         139         20         0         1.00 (0.37 to 2.17)         6 (5)         4444           North Americat         3.6         1673         1557         411         9         37         -         0.05 (0.00 to 0.30)         1 (0)         55/56           Canada         4.0         157         111         9         37         -         0.06 (0.00 to 0.30)         1 (0)         55/56           North Americat         3.2         1516         141         36         39         0.06 (0.00 to 0.30)         1 (0)         55/56           Nagentina         21.0         132         131         1         0         0.06 (0.00 to 0.30)         1 (0)         45/46           Argentina         5.7         43         1         0         0.06 (0.00 to 0.30)         1 (1)         1 0/10           Australia         5.7         43         14         2         2         2	Hussia77.02261715501.00 (0.48 to 1.83)10 (7)7979Serbia77.01391391200.09 (0.27 to 2.54)14 (4)10/10Ukraine77.01591392000.09 (0.27 to 2.54)4 (4)10/10Ukraine77.0157151245760.056 (0.00 to 0.30)10(1)55/56Canada4.0157114136390.06 (0.00 to 0.33)10(1)55/56Canada3.21516144136390.06 (0.00 to 0.33)10(1)55/56Canada21.0132131100.11 (0.00 to 0.03)10(1)26/26Argentina21.0132131100.11 (0.00 to 1.06)11(1)26/26Argentina21.01221221200.19 (0.00 to 1.06)11(1)26/26Argentina21.01212122200.19 (0.00 to 1.06)11(1)26/26Argentina21.0122200.19 (0.00 to 1.06)11(1)26/26Argentina21.01222000.19 (0.00 to 1.06)10/10Argentina21.01422200010/10Argentina21.0142222222Israel6.6011000110	Russia         77.0         226         171           Serbia         20.0         104         92           Ukraine         77.0         159         139           Ukraine         77.0         159         139           North America‡         3.6         1673         1552           Canada         4.0         157         111           USA         3.2         1673         1552           Canada         3.2         1673         1552           USA         3.2         167         141           Vacantala         3.2         167         141           Argentina         21.0         132         14           Australia         5.7         43         14           Chile         14.0         132         13           Australia         5.7         43         12           Israel         6.7         45         37           Mexico         19.0         7         5           New Zealand         6.6         20         17           Singapore         44.0         4         0	14 11	ო	0	1.94 (0.05 to 10.82)	1 (0)	2/2
Serbia         20.0         104         92         12         0         0.09 (0.27 to 2.54)         4 (4)         10/10           Ukraine         77.0         159         139         20         0         0.05 (0.00 to 0.30)         1 (0)         5556           Ukraine         77.0         157         157         1552         45         76         0.05 (0.00 to 0.30)         1 (0)         5556           Canada         4.0         157         111         9         37         -         0.05 (0.00 to 0.30)         1 (0)         5556           Res file         167         1516         1411         36         39         0.06 (0.00 to 0.30)         1 (0)         4/4/4           Variation         21.0         132         111         1         0         0.11 (0.00 to 0.60)         1 (1)         2/5/6           Argentina         21.0         132         131         1         0         0.11 (0.00 to 0.60)         1 (1)         2/5/6           Argentina         5.7         23         14         2         2/7         -         0.11 (0.00 to 0.106)         1 (1)         1 0/10           Australia         5.7         43         14         2         2/7	Serbia200104921200.99 (0.27 to 2.54)4 (4)10/10Ukraine77.015915345760.09 (0.27 to 2.54)4 (4)10/10Ukraine77.0159157111970.05 (0.00 to 0.30)1 (1)5556Canada3.21516141136390.06 (0.00 to 0.33)1 (1)5556Rest of the WorldS16.7263216144136310.11 (0.00 to 0.60)1 (1)Argentina21.0132131100.99 (0.00 to 1.06)1 (1)10/10Argentina21.0132131100.99 (0.00 to 1.06)1 (1)26/26Argentina21.01321121200.19 (0.00 to 1.06)1 (1)10/10Argentina21.013211212000922Australia5.745378000022New Zealand6.620110022New Zealand6.6453000110/10New Zealand6.64544000122Singapore44.04011110/10New Zealand6.645440122Singapore44.04012222Singapore44.0<	Serbia         20.0         104         92           Ukraine         77.0         159         139           North America‡         3.6         157         131           North America‡         3.6         157         141           USA         3.2         157         141           USA         3.2         16.7         156         1441           USA         3.2         16.7         216         1441           Argentina         21.0         132         131         216           Australia         5.7         43         14         12         12           Australia         5.7         45         37         14           Nexico         19.0         12         45         37           Mexico         19.0         7         45         37           New Zealand         6.6         2.0         17         5           Singapore         44.0         4         0         0	226 171	55	0	1.00 (0.48 to 1.83)	10 (7)	79/79
Ukraine         77.0         159         139         20         0         1.00 (0.37 to 2.17)         6 (5)         44/44           North Americat         3.6         1673         1572         45         76         0.05 (0.00 to 0.30)         1 (0)         55/56           Canada         4.0         157         111         9         37         -         0 (-)         10/10           USA         3.2         1516         1441         36         39         0.06 (0.00 to 0.33)         1 (0)         55/56           Rest of the World\$         16.7         216         144         36         39         0.06 (0.00 to 0.33)         1 (0)         45/46           Argentina         21.0         132         131         1         0         1 (1)         26/26           Argentina         21.0         132         131         1         0         1 (1)         26/26           Argentina         21.0         132         14         2         <	Ukraine         77.0         159         139         20         0         1.00 (0.37 to 2.17)         6 (5)         44/44           North Americat         3.6         1673         1552         45         76         0.05 (0.00 to 0.30)         1 (0)         55/56           Canada         4.0         157         111         9         37         -         0 (-)         10/10           Canada         16.7         1516         1441         36         39         0.06 (0.00 to 0.30)         1 (0)         45/46           Res the Worlds         16.7         263         216         16         31         0.11 (0.00 to 1.06)         1 (1)         26/56           Argentina         21.0         132         131         1         0         0.19 (0.00 to 1.06)         1 (1)         26/26           Argentina         5.7         43         14         2         27         -         0 (-)         2/2           Australia         5.7         43         14         2         2/7         -         0 (-)         2/2           Australia         5.7         45         37         8         0         0 (-)         2/2         2/2         2/2         2/2	Ukraine         77.0         159         139           North America‡         3.6         1673         1552           North America‡         3.6         157         111           USA         3.2         1516         1441           Canada         3.2         1516         1441           USA         3.2         16.7         263         216           Argentina         21.0         132         131         216           Australia         5.7         43         14           Chile         14.0         12         12         12           Australia         5.7         443         12         12           Australia         6.7         45         37           New Zealand         6.6         20         17           Singapore         44.0         4         0	104 92	12	0	0.99 (0.27 to 2.54)	4 (4)	10/10
North Americat         3.6         1673         1552         45         76         0.05 (0.00 to 0.30)         1 (0)         55/56           Canada         4.0         157         111         9         37         -         0 (-)         10/10           USA         3.2         1516         1441         36         37         -         0 (-)         10/10           USA         3.2         1516         1441         36         37         -         0 (-)         10/10           USA         3.2         1516         1441         36         39         0.06 (0.00 to 0.33)         1 (0)         55/56           Rest of the World\$         16.7         263         216         16         16         31         0.11 (0.00 to 0.60)         1 (1)         26/26           Argentina         21.0         132         131         1         2 </td <td>North Americat         3.6         1673         1552         45         76         0.05 (0.00 to 0.30)         1 (0)         55/56           Canada         4.0         157         111         9         37         -         0 (-)         10/10           USA         3.2         1516         1441         36         39         0.06 (0.00 to 0.33)         1 (0)         45/46           Rest file         16.7         21.3         14         1         0         0.11 (0.00 to 0.60)         1 (1)         26/26           Argentina         5.7         43         14         2         27         0         0.19 (0.00 to 1.06)         1 (1)         26/26           Argentina         5.7         43         14         2         27         0         0 (-)         2/2           Australia         5.7         43         14         2         27         0         0 (-)         2/2           Chile         14.0         12         12         12         12         2         2/2         2/2           Israel         6.7         45         3         0         0         0 (-)         2/2         2/2           Nexico         16.0</td> <td>North Americat         3.6         1673         1552           Canada         4.0         157         111           USA         3.2         1516         1441           Rest of the WorldS         16.7         263         216           Argentina         21.0         132         131           Australia         5.7         43         14           Chile         14.0         12         12           Australia         5.7         43         14           Chile         14.0         12         12           Israel         6.7         45         37           Mexico         19.0         7         5           New Zealand         6.6         20         17           Singapore         44.0         4         0</td> <td>159 139</td> <td>20</td> <td>0</td> <td>1.00 (0.37 to 2.17)</td> <td>6 (5)</td> <td>44/44</td>	North Americat         3.6         1673         1552         45         76         0.05 (0.00 to 0.30)         1 (0)         55/56           Canada         4.0         157         111         9         37         -         0 (-)         10/10           USA         3.2         1516         1441         36         39         0.06 (0.00 to 0.33)         1 (0)         45/46           Rest file         16.7         21.3         14         1         0         0.11 (0.00 to 0.60)         1 (1)         26/26           Argentina         5.7         43         14         2         27         0         0.19 (0.00 to 1.06)         1 (1)         26/26           Argentina         5.7         43         14         2         27         0         0 (-)         2/2           Australia         5.7         43         14         2         27         0         0 (-)         2/2           Chile         14.0         12         12         12         12         2         2/2         2/2           Israel         6.7         45         3         0         0         0 (-)         2/2         2/2           Nexico         16.0	North Americat         3.6         1673         1552           Canada         4.0         157         111           USA         3.2         1516         1441           Rest of the WorldS         16.7         263         216           Argentina         21.0         132         131           Australia         5.7         43         14           Chile         14.0         12         12           Australia         5.7         43         14           Chile         14.0         12         12           Israel         6.7         45         37           Mexico         19.0         7         5           New Zealand         6.6         20         17           Singapore         44.0         4         0	159 139	20	0	1.00 (0.37 to 2.17)	6 (5)	44/44
Canada         4.0         157         111         9         37         -         0 (-)         10/10           USA         3.2         1516         1441         36         39         0.06 (0.00 to 0.33)         1 (0)         45/46           USA         3.2         1516         1441         36         39         0.06 (0.00 to 0.33)         1 (0)         45/46           Rest of the World\$         16.7         263         216         16         31         0.11 (0.00 to 0.60)         1 (1)         26/26           Argentina         21.0         132         131         1         0         0.19 (0.00 to 1.06)         1 (1)         26/26           Australia         5.7         43         14         2         27         -         0 (-)         2/2           Chile         14.0         12         12         12         0         0         0         2/2           Israel         6.7         7         5         2         0         0         0         2/2         2/2           Israel         6.6         Mexico         190         7         5         0         0         0         2/2           New Zealand <td< td=""><td>Canada4.0157111937-0010/10USA3.21516144136390.06 (0.00 to 0.33)1145/46USA3.216.726321614136310.11 (0.00 to 0.60)1110/10Argentina21.0132131100.19 (0.00 to 1.06)1110/10Argentina21.01321214227-0-2/2Argentina21.0121212121200-0-2/2Australia6.74.31422.7-00-0-2/2Australia6.74.4122.7-0-0-2/2Australia6.74.575200-0-2/2Nexico19.075200-0-2/2Nexico19.075200-0-2/2New Zealand6.62017300-0-2/2New Zealand6.62017300-0-2/2New Zealand6.62017300-0-2/2Singapore44.067&lt;</td><td>Canada         4.0         157         111           USA         3.2         1516         1441           USA         3.2         16.7         216           Nest of the WorldS         16.7         263         216           Argentina         21.0         132         131           Australia         5.7         43         14           Chile         14.0         12         12           Listael         6.7         45         37           Mexico         19.0         7         5           New Zealand         6.6         20         17           Singapore         44.0         4         0</td><td>1673 1552</td><td>45</td><td>76</td><td>0.05 (0.00 to 0.30)</td><td>1 (0)</td><td>55/56</td></td<>	Canada4.0157111937-0010/10USA3.21516144136390.06 (0.00 to 0.33)1145/46USA3.216.726321614136310.11 (0.00 to 0.60)1110/10Argentina21.0132131100.19 (0.00 to 1.06)1110/10Argentina21.01321214227-0-2/2Argentina21.0121212121200-0-2/2Australia6.74.31422.7-00-0-2/2Australia6.74.4122.7-0-0-2/2Australia6.74.575200-0-2/2Nexico19.075200-0-2/2Nexico19.075200-0-2/2New Zealand6.62017300-0-2/2New Zealand6.62017300-0-2/2New Zealand6.62017300-0-2/2Singapore44.067<	Canada         4.0         157         111           USA         3.2         1516         1441           USA         3.2         16.7         216           Nest of the WorldS         16.7         263         216           Argentina         21.0         132         131           Australia         5.7         43         14           Chile         14.0         12         12           Listael         6.7         45         37           Mexico         19.0         7         5           New Zealand         6.6         20         17           Singapore         44.0         4         0	1673 1552	45	76	0.05 (0.00 to 0.30)	1 (0)	55/56
USA         3.2         1516         1441         36         39         0.06 (0.00 to 0.33)         1 (0)         45/46           Rest of the World\$         16.7         263         216         16         31         0.11 (0.00 to 0.60)         1 (1)         26/26           Argentina         21.0         132         131         1         0         0.19 (0.00 to 1.06)         1 (1)         26/26           Argentina         5.7         43         14         2         27         -         0.19 (0.00 to 1.06)         1 (1)         20/10           Australia         5.7         43         14         2         27         -         0 (-)         2/2           Chile         14.0         12         12         0         0         0 (-)         2/2           Israel         6.7         45         37         8         0         -         0 (-)         2/2           Nexico         19.0         7         5         2         0         0 (-)         0/-)         6/6           Mexico         19.0         7         5         2         0         0         0         0/-)         1/4           New Zealand         6.6	USA         3.2         1516         1441         36         39         0.06 (0.00 to 0.33)         1 (0)         45/46           Rest of the World\$         16.7         263         216         16         31         0.11 (0.00 to 0.60)         1 (1)         26/26           Argentina         5.7         43         14         2         27         -         0.19 (0.00 to 1.06)         1 (1)         10/10           Australia         5.7         43         14         2         27         -         0.19 (0.00 to 1.06)         1 (1)         10/10           Australia         5.7         43         14         2         27         -         0(-)         2/2           Australia         6.7         45         37         8         0         -         0(-)         2/2           Israel         6.7         45         37         8         0         -         0(-)         2/2           New zealand         6.6         17         3         0         -         0(-)         0/-)         4/4           New zealand         6.6         17         3         0         -         0(-)         0/-)         2/2           Inevico	USA       3.2       1516       141         Rest of the WorldS       16.7       263       216         Argentina       21.0       132       131         Australia       5.7       43       14         Chile       14.0       12       12         Israel       6.7       45       37         Mexico       19.0       7       5         New Zealand       6.6       2.0       17         Singapore       44.0       4       0	157 111	6	37	1	(-) 0	10/10
Rest of the World§         16.7         263         216         16         31         0.11 (0.00 to 0.60)         1 (1)         26/26           Argentina         21.0         132         131         1         0         0.19 (0.00 to 1.06)         1 (1)         10/10           Australia         5.7         43         14         2         27         -         0 (-)         2/2           Chile         14.0         12         12         0         0         0 (-)         2/2           Israel         6.7         45         37         8         0         -         0 (-)         2/2           Nexico         19.0         7         5         2         0         0 (-)         4/4           Nexico         19.0         -         0         0         -         0 (-)         5/2           Singapore         44.0         -         0         0         -         0 (-)         2/2	Rest of the World§         16.7         263         216         16         31         0.11 (0.00 to 0.60)         1 (1)         26/26           Argentina         21.0         132         131         1         0         0.19 (0.00 to 1.06)         1 (1)         10/10           Australia         5.7         4.3         1.4         2         2.7         0         0.19 (0.00 to 1.06)         1 (1)         10/10           Australia         5.7         4.3         1.4         2         2.7         0         0.19 (0.00 to 1.06)         1 (1)         10/10           Australia         5.7         4.5         37         8         0         0         0         0         2/2         2/2           Chile         14.0         7         5         2         0         0         0         2/2         2/2           New Zealand         6.6         0         0         0         0         0         0         0         2/2           New Zealand         6.6         0         0         0         0         0         0         0         0         1         4/4           New Zealand         6.6         0         0         0	Rest of the World§       16.7       263       216         Argentina       21.0       132       131         Australia       5.7       43       14         Chile       14.0       12       12         Israel       6.7       45       37         Mexico       19.0       7       5         New Zealand       6.6       20       17         Singapore       44.0       4       0	1516 1441	36	39	0.06 (0.00 to 0.33)	1 (0)	45/46
Argentina         21.0         132         131         1         0         0.19 (0.00 to 1.06)         1 (1)         10/10           Australia         5.7         43         14         2         27         -         0 (-)         2/2           Chile         14.0         12         12         12         0         0         0 (-)         2/2           Israel         6.7         45         37         8         0         -         0 (-)         2/2           Nexico         19.0         7         5         2         0         -         0 (-)         4/4           New Zealand         6.6         -         0         -         0 (-)         2/2           Singapore         44.0         -         0         0         -         0 (-)         2/2	Argentina         21.0         132         131         1         0         0.19 (0.00 to 1.06)         1 (1)         10/10           Australia $5.7$ $4.3$ $1.4$ $2$ $2.7$ $ 0(-)$ $2/2$ Chile $14.0$ $12$ $12$ $12$ $12$ $2/2$ $2/2$ Chile $6.7$ $45$ $37$ $8$ $0$ $ 0(-)$ $2/2$ Israel $6.7$ $45$ $37$ $8$ $0$ $ 0(-)$ $2/2$ New Zealand $6.6$ $20$ $17$ $3$ $0$ $ 0(-)$ $2/4$ New Zealand $6.6$ $20$ $17$ $3$ $0$ $ 0(-)$ $2/2$ New Zealand $6.6$ $20$ $17$ $3$ $0$ $ 0(-)$ $2/2$ New Zealand $6.6$ $0$ $ 0$ $ 0$ $ 2/2$ New Zealand	Argentina         21.0         132         131           Australia         5.7         43         14           Australia         5.7         43         14           Chile         14.0         12         12         12           Israel         6.7         45         37           Mexico         19.0         7         5           New Zealand         6.6         20         17           Singapore         44.0         4         0	263 216	16	31	0.11 (0.00 to 0.60)	1 (1)	26/26
Australia         5.7         43         14         2         27         -         0 (-)         22           Chile         14.0         12         12         0         0         -         0 (-)         2/2           Chile         14.0         12         12         0         0         -         0 (-)         2/2           Israel         6.7         45         37         8         0         -         0 (-)         5/6           Mexico         19.0         7         5         2         0         -         0 (-)         4/4           New Zealand         6.6         -         0         -         0 (-)         2/2         2/2           Singapore         44.0         4         0         0         -         0 (-)         2/2         2/2	Australia $5.7$ $43$ $14$ $2$ $27$ $ 0(-)$ $2/2$ Chile $14.0$ $12$ $12$ $12$ $12$ $0$ $0$ $0$ $2/2$ Israel $6.7$ $45$ $37$ $8$ $0$ $ 0$ $ 2/2$ Nexico $19.0$ $7$ $5$ $2$ $0$ $ 0$ $ 0$ $ 4/4$ New Zealand $6.6$ $20$ $17$ $3$ $0$ $ 0$ $ 4/4$ New Zealand $6.6$ $0$ $ 0$ $ 0$ $                              -$	Australia         5.7         43         14           Chile         14.0         12         12           Israel         6.7         45         37           Mexico         19.0         7         5           New Zealand         6.6         20         17           Singapore         44.0         4         0	132 131	-	0	0.19 (0.00 to 1.06)	1 (1)	10/10
Chile         14.0         12         12         0         0         2/2           Israel         6.7         45         37         8         0         -         0(-)         2/2           Mexico         19.0         7         5         2         0         -         0(-)         6/6           New Zealand         6.6         -         0         17         3         0         -         0(-)         4/4           New Zealand         6.6         -         0         0         -         0(-)         2/2           Singapore         44.0         -         0         0         -         0(-)         2/2	Chile         14.0         12         12         0         0         0         0         22           Israel $6.7$ $45$ $37$ $8$ 0 $-$ 0         0         0         6/6           Mexico         19.0 $7$ $5$ $2$ 0 $-$ 0 $-$ 6/6           New Zealand $6.6$ $20$ $17$ $3$ $0$ $ 0$ $ 4/4$ New Zealand $6.6$ $20$ $17$ $3$ $0$ $ 0$ $ 4/4$ New Zealand $6.6$ $0$ $ 0$ $ 0$ $ 4/4$ New Zealand $6.6$ $0$ $ 0$ $  4/4$ New Zealand $6.6$ $0$ $ 0$ $  4/4$ New Zealand $6.6$ $0$ $0$ $ 0$ $ 0$ $  0$ <td< td=""><td>Chile         14.0         12         12           Israel         6.7         45         37           Mexico         19.0         7         5           New Zealand         6.6         20         17           Singapore         44.0         4         0</td><td>43 14</td><td>0</td><td>27</td><td>1</td><td>(-) 0</td><td>2/2</td></td<>	Chile         14.0         12         12           Israel         6.7         45         37           Mexico         19.0         7         5           New Zealand         6.6         20         17           Singapore         44.0         4         0	43 14	0	27	1	(-) 0	2/2
Israel         6.7         45         37         8         0         -         0 (-)         6/6           Mexico         19.0         7         5         2         0         -         0 (-)         4/4           New Zealand         6.6         20         17         3         0         -         0 (-)         2/2           Singapore         44.0         4         0         0         -         0 (-)         2/2	Israel         6.7         45         37         8         0         -         0 (-)         6/6           Mexico         19.0         7         5         2         0         -         0 (-)         6/6           New Zealand         6.6         20         17         3         0         -         0 (-)         4/4           New Zealand         6.6         20         17         3         0         -         0 (-)         2/2           Singapore         44.0         4         0         0         -         0 (-)         2/2           *Based on UN statistics for the lower bound of incidence in 2012 per 100 000 population in individual countries within each geographic region. <sup>28</sup> 2/2         0/-         0/-         0/-         0/0         0/-         0/0         0/0         2/2         2/	Israel         6.7         45         37           Mexico         19.0         7         5           New Zealand         6.6         20         17           Singapore         44.0         4         0	12 12	0	0	1	(-) 0	2/2
Mexico         19.0         7         5         2         0         -         0 (-)         4/4           New Zealand         6.6         20         17         3         0         -         0 (-)         2/2           Singapore         44.0         4         0         0         -         0 (-)         2/2	Mexico19.07520-0 (-) $4/4$ New Zealand6.6201730-0 (-) $2/2$ Singapore44.04004-0 (-) $2/2$ *Based on UN statistics for the lower bound of incidence in 2012 per 100 000 population in individual countries within each geographic region. <sup>28</sup> 0 (-) $0/0$ $0/0$ *PPD test results missing for 294 patients, including the patient in the UK who developed TB.PPD test region. <sup>28</sup> $0 (-)$ $0/0$	Mexico         19.0         7         5           New Zealand         6.6         20         17           Singapore         44.0         4         0	45 37	8	0	1	(-) 0	6/6
New Zealand         6.6         20         17         3         0         –         0 (–)         2/2           Singapore         44.0         4         0         0         4         –         0/0	New Zealand       6.6       20       17       3       0       -       0 (-)       2/2         Singapore       44.0       4       0       0       4       -       0 (-)       0/0         *Based on UN statistics for the lower bound of incidence in 2012 per 100 000 population in individual countries within each geographic region. <sup>28</sup> 0 (-)       0/0       0/0         *PPD test results missing for 294 patients, including the patient in the UK who developed TB.       EPPD test results missing for 76 patients, including the patient who developed TB.       0       -       0       0/0       0/0	New Zealand         6.6         20         17           Singapore         44.0         4         0	7 5	N	0	1	(-) 0	4/4
Singapore         44.0         4         0         0         4         -         0 (-)         0/0           * Encodered in 101 of the final and of incidence in 2012 new 100 000 comulation in individual comption contribution and recommendia reaction 28         0 (-)         0/0         0/0	Singapore     44.0     4     0     0     4     -     0 (-)     0/0       *Based on UN statistics for the lower bound of incidence in 2012 per 100 000 population in individual countries within each geographic region. <sup>28</sup> 0 (-)     0/0       *PPD test results missing for 294 patients, including the patient in the UK who developed TB.     294 patients, including the patient who developed TB.	Singapore 44.0 4 0	20 17	ო	0	I	(-) 0	2/2
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	PPD test results missing for 294 patients, including the patient in the UK who developed TB. PPD test results missing for 76 patients, including the patient who developed TB. PPD test results missing for 76 patients, including the patient who developed TB. PPD test results missing for 76 patients, including the patient who developed TB.	*Based on LIN statistics for the lower hound of incidence in 2012 her 100 000 h	d of incidence in 2012 ner 100 000 nonul	Ilation in individu	ial countries wi	thin each deodraphic redio	n 28	
		TPPD test results missing for /6 patients, including the patient who developed	including the patient who developed 1B.					

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9 months in patients at risk, the IR of TB infection in CZP-treated patients with RA has decreased from 2.63/100 PY (*original* trials) to 0.18/100 PY (*current* trials). This rate is comparable to that reported for other monoclonal anti-TNF antibodies (IR ~0.3/100 PY)<sup>23–25</sup> and suggests beneficial effects of stricter LTBI screening prior to administering anti-TNFs in patients with IMID. A similar IR of 0.21/100 PY was reported for CZP-treated RAPID-axSpA patients (1 case), with no TB cases in RAPID-PSA patients to date.

Previous reports suggest that the risk of TB is elevated  $\sim 2-$  to 4-fold in patients with RA compared to the general population<sup>6</sup> <sup>7</sup> and that it further increased 1.6-25.1 times following anti-TNF therapy. <sup>1 3 6 26</sup> Over the past decade, there are signs of a global decrease in TB incidence among patients with anti-TNF,<sup>5</sup> but the IRs in some areas (eg, large cities) remain higher than the national rates.<sup>27</sup> Furthermore, the overall risk of TB may depend on many factors including the population exposed, clinical setting, comorbidities, concomitant medications and anti-TNF administered. Studies suggest that the majority of TB cases which develop soon after initiation of anti-TNF treatment are due to reactivation of LTBL<sup>2 3</sup> For CZP trials: 21/44 TB cases in patients with RA and two confirmed cases in patients with psoriasis and axSpA were reported during the first year of CZP treatment; implying that the cases were most likely due to reactivation of LTBI despite PPD negativity (<5 mm) at baseline, whereas in patients with onset of TB >1 year after the start of CZP therapy, yet testing PPD negative at baseline, it is likely to be a new TB infection.<sup>2 17</sup> No new cases of TB were reported in those who received INH as a result of a positive tuberculin skin test (PPD>5 mm), emphasising the benefits of more stringent screening of patients for LTBI and administration of LTBI therapy, regardless of vaccination status. Only two patients received INH treatment prior to TB diagnosis. The lower IR of TB in intermediate trials compared with original trials (0.30/100 PY vs 2.63/100 PY) suggests beneficial effects of treatment for LTBI in patients on long-term CZP treatment, even when administered sometime after the start of anti-TNF therapy. In current trials, recruitment of fewer patients from high TB incidence countries, changes in study design, introduction of a 6-monthly TB questionnaire to increase patient/ physician awareness (and facilitate appropriate management of TB) and recruitment of fewer biologically naïve patients<sup>5</sup> are likely to have contributed to reduced TB rates. During this study, only INH monotherapy was used for treatment of LTBI. However, no specific compliance check for patient adherence to 9 months of INH treatment was performed. The shorter regimen of INH and Rifampicin dual therapy (typically 3 months) was not used, even though this approach is associated with better treatment compliance.

The majority of TB cases in RA were reported from Central and Eastern Europe, consistent with the higher notification rates and risk of TB in these regions.<sup>27 28</sup>

A high proportion of these patients were PPD negative, in line with lower rates of PPD positivity than TB rates in TB endemic countries and high anergy rates for TB screening in patients with severe inflammatory diseases.<sup>29</sup> Glucocorticoid treatment may also lead to false negative PPD skin test results,<sup>28</sup> potentially resulting in inadequate LTBI treatment of at-risk patients. In contrast, prior BCG vaccination, sensitisation resulting from infection with environmental mycobacteria or an increase in non-TB mycobacteria may generate false positive test results.<sup>1 30</sup> Nevertheless, in most cases, routine BCG vaccination in newborns in TB endemic countries is unlikely to account for positive PPD skin tests during adulthood as reactivity declines during early childhood.<sup>31 32</sup> Consequently, frequent monitoring of patients in TB endemic countries may be required. Repeated PPD tuberculin skin tests are one approach, but potential booster effects could limit the interpretation of results.

In vitro interferon-y release assays (IGRAs; ie, QuantiFERON Gold or ELISPOT TB) data may provide an alternative LTBI screening method with improved specificity in BCG-vaccinated patients, reducing unnecessary administration of INH treatment for LTBI and its associated risks.<sup>33–35</sup> Although IGRAs can provide improved specificity,<sup>33–34</sup> they can also produce false positives.<sup>34</sup> Thus, reliance on a single screening test is not without problems and, in high TB endemic areas, the use of algorithms that combine the results of dual testing (PPD skin test and IGRAs) may provide greater benefits.<sup>35 36</sup> The lack of a gold standard for identifying BK infections does not allow an optimal evaluation of any TB screening method. In countries with low TB incidence or where BCG vaccination is generalised, using both tests may lead to an overuse of treatment for LTBI and use of IGRAs alone should be encouraged.<sup>18 33</sup> One limitation of the present paper is the lack of concomitant IGRAs data, not available at the start of the CZP programme.

A comparison of TB incidence in CZP trials with findings from other anti-TNF trials is limited by different inclusion/exclusion criteria, trial locations and other risk factors. Moreover, prior to the recent introduction of a specific Medical Dictionary for Regulatory Activities (MedDRA) preferred term for TB,<sup>37</sup> different sponsors may have reported positive PPD test results (LTBI), suspected TB or confirmed TB as a TB event.<sup>23 38 39</sup> A recent meta-analysis assessing the risk of TB in patients with IMID treated with biologicals or tofacitinib reported elevated TB rates across trials, with higher rates for CZP.<sup>40</sup> However, inclusion of suspected or LTBI cases from CZP trials and the recruitment of patients from high TB incidence countries is likely to have contributed to this finding. In general, data on the IR of TB from biological clinical trials that enrol patients from TB endemic countries are limited.<sup>40</sup> In CZP trials, non-TB mycobacteria may also be a confounding factor, but specific diagnostic tools allowing systematic screening are missing and no non-TB mycobacteria cases were

#### **RMD** Open

identified by the investigators. For the soluble TNF-receptor agent, reports evidenced a lower TB incidence,<sup>1</sup> <sup>2</sup> consistent with less stable inhibition of membrane-bound TNF and reduced effectiveness in the treatment of granulomatous inflammatory conditions such as Crohn's disease.

In summary, methods of screening for LTBI and decisions on whether to administer INH therapy can influence the incidence of TB in anti-TNF patients. In CZP trials, several cases of TB occurred in patients with negative PPD (<5 mm) at screening who did not receive INH treatment. However, the likelihood of developing TB was greatest in those with PPD  $\geq 5 \text{ mm}$  who did not receive treatment for LTBI. Physicians should be aware of the importance of adequate TB screening for biologicals patients, particularly in TB endemic countries and in discrete high TB incidence regions of countries with relatively low national TB rates. Increasing the stringency of TB assessments (eg, PPD positivity cut-off of  $\geq 5 \text{ mm}$ induration irrespective of vaccination status, alongside repeated/alternative screening tests) may reduce TB incidence in patients treated with anti-TNF and enable those receiving treatment for LTBI to continue biological therapy for their chronic autoimmune disease.

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10

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