Tuberculosis and Viral Hepatitis in Patients Treated with Certolizumab Pegol in Asia-Pacific Countries and Worldwide: Real-World and Clinical Trial Data

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**SUPPLEMENTARY INFORMATION**

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Supplementary Information regarding TB Screening

Prior to 2007, for TB screening of patients considering biologic treatment the cut-off for purified protein derivative [PPD] positivity ranged from ≥5 to ≥20 mm, especially in TB-vaccinated patients. From 2007 stricter screening rules were implemented: patients who tested positive for PPD, defined as a result of ≥5 mm, received isoniazid (INH) treatment for latent TB infection (LTBI). In addition, a patient TB risk questionnaire was administered every 6 months to help identify patients at risk and to increase physician awareness of potential TB symptoms/risk factors in defined patient groups, particularly in high TB incidence countries.[3](#_ENREF_3) This amendment was also enforced retrospectively for all patients already receiving CZP at the time of protocol amendment.[3](#_ENREF_3) Some later studies incorporated an Interferon Gamma Release Assay (IGRA) test (QuantiFERON TB GOLD) as part of TB screening.

**Supplementary Table S1.** Regions and countries included in the pooled safety analysis

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| --- | --- | --- |
| **Region** | **Countries included in theCZP clinical trial analysis** | **Countries included in thepost-marketing analysis** |
| Asia-Pacific (excluding Japan) | Australia, Hong Kong, New Zealand, Republic of Korea, Singapore | Australia, Hong Kong, Malaysia, New Caledonia, Republic of Korea |
| Japan | Japan | Japan |
| Eastern Europe | Belarus, Croatia, Georgia, Romania, Russia, Serbia, Ukraine | Romania, Russia |
| Central Europe | Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Slovakia, Slovenia | Bulgaria, Czech Republic, Hungary, Poland, Slovakia, Slovenia |
| Western Europe | Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, The Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, UK | Andorra, Austria, Belgium, Denmark, Finland, France, Greece, Germany, Ireland, Italy, The Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, UK |
| North America | Canada, US | Canada, US |
| Mexico | Mexico | Mexico |
| Latin America | Argentina, Brazil, Chile, Colombia | Argentina, Brazil, Chile, Colombia, Ecuador, French Guiana, Guadeloupe, Peru, Reunion |
| Rest of the World | Israel, Republic of South Africa | Bahrain, Cyprus, Egypt, Kuwait, Lebanon, Libya, Martinique, Qatar, Saudi Arabia, Turkey, UAE |

**Supplementary Table S2.** MedDRA Preferred Terms used for the selection of potential cases of TB, hepatitis B and hepatitis C

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| **MedDRA Preferred Terms** |
| **Tuberculosis** | **Hepatitis B and C** |
| Adrenal gland tuberculosisBone tuberculosisBovine tuberculosisCongenital tuberculosisConjunctivitis tuberculousCutaneous tuberculosisDisseminated tuberculosisEar tuberculosisEpididymitis tuberculousExtrapulmonary tuberculosisFemale genital tract tuberculosisImmune reconstitution inflammatory syndrome associated tuberculosisIntestinal tuberculosisJoint tuberculosisLymph node tuberculosisMale genital tract tuberculosisMeningitis tuberculousOesophageal tuberculosisOral tuberculosisPericarditis tuberculousPeritoneal tuberculosisProstatitis tuberculousPulmonary tuberculomaPulmonary tuberculosisRenal tuberculosisSalpingitis tuberculousSilicotuberculosisSpleen tuberculosisThyroid tuberculosisTuberculidTuberculoid leprosyTuberculoma of central nervous systemTuberculosisTuberculosis bladderTuberculosis gastrointestinalTuberculosis immunisationTuberculosis liverTuberculosis of central nervous systemTuberculosis of eyeTuberculosis of genitourinary systemTuberculosis of intrathoracic lymph nodesTuberculosis of peripheral lymph nodesTuberculosis ureterTuberculous abscess central nervous systemTuberculous endometritisTuberculous laryngitisTuberculous pleurisyTuberculous tenosynovitis | Viral hepatitis carrierHepatitis chronic persistentHepatitis chronic activeHepatitis C virus test positiveHepatitis C virus testHepatitis C core antibody positiveHepatitis C core antibodyHepatitis C antibodyHepatitis C antibody positiveHepatitis CChronic hepatitis CAcute hepatitis CHepatitis B virus testHepatitis B virus test positiveHepatitis B immunizationHepatitis B antigenHepatitis B antigen positiveHepatitis B e antigenHepatitis B e antigen positiveHepatitis B DNA assayHepatitis B DNA assay positiveHepatitis B DNA decreasedHepatitis B DNA increasedHepatitis B core antigenHepatitis B core antigen positiveHepatitis B core antibodyHepatitis B core antibody positiveHepatitis B antibodyHepatitis B antibody abnormalHepatitis B antibody positiveHepatitis BAcute hepatitis BChronic hepatitis BCongenital hepatitis B infection |

MedDRA: Medical Dictionary for Regulatory Activities; TB: tuberculosis.

Supplementary Table S3**.** Nationwide tuberculosis incidence rates in countries where CZP is approved (from the 2017 WHO Global TB Report)

| **Country** | **Population (millions)** | **TB incidence** |
| --- | --- | --- |
| **Number in thousands (95% CI)** | **Rate/100,000 population (95% CI), including HIV positive** |
| Andorra | <1 | <0.01 (<0.01–<0.01) | 6 (5.1–6.9) |
| Argentina | 44 | 11 (9.2–12.0) | 24 (21–28) |
| Australia | 24 | 1.5 (1.3–1.7) | 6.1 (5.2–7.1) |
| Austria | 9 | 0.71 (0.61–0.82) | 8.2 (7.0–9.5) |
| Bahrain | 1 | 0.18 (0.15–0.20) | 12 (11–14) |
| Belgium | 11 | 1.1 (0.97–1.3) | 10 (8.5–12) |
| Brazil | 208 | 87 (74–100) | 42 (36–48) |
| Bulgaria | 7 | 1.9 (1.5–2.4) | 27 (20–34) |
| Canada | 36 | 1.9 (1.6–2.2) | 5.2 (4.4–6.0) |
| Chile | 18 | 2.9 (2.5–3.4) | 16 (14–19) |
| Colombia | 49 | 16 (12–20) | 32 (25–41) |
| Costa Rica | 5 | 0.46 (0.35–0.58) | 9.5 (7.3–12) |
| Croatia | 4 | 0.52 (0.44–0.60) | 12 (10–14) |
| Cyprus | 1 | 0.066 (0.056–0.076) | 5.6 (4.8–6.5) |
| Czech Republic | 11 | 0.53 (0.45–0.61) | 5 (4.3–5.8) |
| Denmark | 6 | 0.35 (0.30–0.41) | 6.1 (5.3–7.1) |
| Dominican Republic | 11 | 6.4 (4.9–8.2) | 60 (46–77) |
| Ecuador | 16 | 8.2 (5.3–12) | 50 (33–72) |
| Egypt | 96 | 13 (12–15) | 14 (12–15) |
| El Salvador | 6 | 3.8 (2.9–4.8) | 60 (46–76) |
| Estonia | 1 | 0.22 (0.18–0.25) | 16 (14–19) |
| Finland | 6 | 0.26 (0.22–0.30) | 4.7 (4.0–5.4) |
| France† | 65 | 5 (4.4–5.6) | 7.7 (6.7–8.6) |
| French Guiana† | <1 | 5 (4.4–5.6) | 7.7 (6.7–8.6) |
| Germany | 82 | 6.6 (5.6–7.6) | 8.1 (6.9–9.3) |
| Greece | 11 | 0.49 (0.42–0.57) | 4.4 (3.7–5.1) |
| Guadeloupe† | <1 | 5 (4.4–5.6) | 7.7 (6.7–8.6) |
| Honduras | 9 | 3.6 (2.8–4.6) | 40 (30–50) |
| Hong Kong | 7 | 5.1 (4.3–5.9) | 69 (59–80) |
| Hungary | 10 | 0.86 (0.73–0.99) | 8.8 (7.5–10) |
| Iceland | <1 | <0.01 (<0.01–<0.01) | 2.1 (1.8–2.4) |
| Ireland | 5 | 0.34 (0.29–0.39) | 7.1 (6.1–8.2) |
| Israel | 8 | 0.29 (0.25–0.33) | 3.5 (3.0–4.1) |
| Italy | 59 | 3.7 (3.1–4.2) | 6.1 (5.3–7.1) |
| Jamaica | 3 | 0.13 (0.099–0.16) | 4.5 (3.4–5.7) |
| Japan | 128 | 20 (17–23) | 16 (14–18) |
| Kuwait | 4 | 0.96 (0.82–1.1) | 24 (20–27) |
| Latvia | 2 | 0.74 (0.63–0.85) | 37 (32–43) |
| Lebanon | 6 | 0.74 (0.64–0.86) | 12 (11–14) |
| Libya | 6 | 2.5 (1.6–3.7) | 40 (25–58) |
| Lithuania | 3 | 1.5 (1.3–1.8) | 53 (46–62) |
| Luxembourg | <1 | 0.033 (0.029–0.039) | 5.8 (5.0–6.7) |
| Malaysia | 31 | 29 (25–33) | 92 (79–107) |
| Malta | <1 | 0.058 (0.049–0.066) | 13 (11–15) |
| Martinique† | <1 | 5 (4.4–5.6) | 7.7 (6.7–8.6) |
| Mexico | 128 | 28 (21–35) | 22 (17–28) |
| The Netherlands | 17 | 1 (0.86–1.2) | 5.9 (5.1–6.9) |
| New Caledonia | <1 | 0.044 (0.037–0.050) | 16 (14–19) |
| New Zealand | 5 | 0.34 (0.29–0.39) | 7.3 (6.2–8.4) |
| Norway | 5 | 0.32 (0.27–0.37) | 6.1 (5.2–7.0) |
| Oman | 4 | 0.4 (0.34–0.46) | 9 (7.7–10) |
| Panama | 4 | 2.2 (1.7–2.8) | 55 (42–70) |
| Peru | 32 | 37 (28–47) | 117 (90–148) |
| Poland | 38 | 7.1 (6.0–8.2) | 18 (16–21) |
| Portugal | 10 | 2.1 (1.8–2.4) | 20 (17–23) |
| Qatar | 3 | 0.58 (0.50–0.67) | 23 (19–26) |
| Republic of Korea | 51 | 39 (36–42) | 77 (71–82) |
| Reunion† | <1 | 5 (4.4–5.6) | 7.7 (6.7–8.6) |
| Romania | 20 | 15 (13–17) | 74 (64–86) |
| Russia | 144 | 94 (61–135) | 66 (42–94) |
| Saudi Arabia | 32 | 3.3 (2.9–3.9) | 10 (8.9–12) |
| Serbia | 9 | 1.7 (1.4–2.0) | 19 (16–22) |
| Slovakia | 5 | 0.32 (0.28–0.37) | 5.9 (5.1–6.9) |
| Slovenia | 2 | 0.14 (0.12–0.16) | 6.5 (5.6–7.5) |
| Spain | 46 | 4.7 (4.0–5.5) | 10 (8.7–12) |
| Sweden | 10 | 0.81 (0.69–0.93) | 8.2 (7.0–9.5) |
| Switzerland | 8 | 0.66 (0.56–0.76) | 7.8 (6.7–9.1) |
| Taiwan ‡ | 24 | 11 | 46 |
| Tunisia | 11 | 4.3 (3.3–5.4) | 38 (29–48) |
| Turkey | 80 | 14 (12–16) | 18 (15–20) |
| UAE | 9 | 0.074 (0.063–0.085) | 0.79 (0.68–0.92) |
| UK | 66 | 6.5 (5.9–7.2) | 9.9 (8.9–11) |
| US | 322 | 10 (8.7–12) | 3.1 (2.7–3.6) |
| Venezuela | 32 | 10 (7.8–13) | 32 (25–41) |

†Data from France include data from 5 overseas departments (French Guiana, Guadeloupe, Martinique, Mayotte and Réunion). French incidence has been used for these overseas departments in this table. ‡Taiwan population data from National Statistics, Republic of China (Taiwan);[63](#_ENREF_63) TB incidence data from Lim et al. (2017).[34](#_ENREF_34) All other data from WHO Global Tuberculosis Report 2017.[13](#_ENREF_13) CI: confidence interval; HIV: Human immunodeficiency virus; TB: tuberculosis; UAE: United Arab Emirates; UK: United Kingdom; US: United States of America; WHO: World Health Organization.