

Electronic Supplementary Material 1

Pregnancy outcomes in the tofacitinib safety databases for rheumatoid arthritis and psoriasis

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Table: List of studies from the RA and psoriasis clinical development programs

Study design	Registration number	Exposure time
<i>RA clinical trials</i>		
Phase 1	NCT01262118 [1]; NCT01484561 [2]	up to 12 weeks
Phase 2 RCT	NCT00147498 [3]; NCT00413660 [4]; NCT00550446 [5]; NCT00603512 [6]; NCT00687193 [7]; NCT01059864 [8]; NCT01164579 [9]; NCT00976599 [10]; NCT01359150 [11]	up to 24 weeks
Phase 3 RCT	NCT00960440 (ORAL Step) [12]; NCT00847613 (ORAL Scan) [13]; NCT00814307 (ORAL Solo) [14]; NCT00856544 (ORAL Sync) [15]; NCT00853385 (ORAL Standard) [16]; NCT01039688 (ORAL Start) [17]	up to 24 months
Long-term extension study	NCT00413699 (ORAL Sequel, ongoing ^a) [18]; NCT00661661 [18]	up to 6 years
<i>Psoriasis clinical trials</i>		
Phase 1	NCT01736696 [19]	2 weeks
Phase 2 RCT	NCT01710046 (Phase 2a) [20]; NCT00678210 (Phase 2b) [21]	12 weeks
Phase 3 RCT	NCT01276639 (OPT Pivotal 1) [22]; NCT01309737 (OPT Pivotal 2) [22]; NCT01241591 (OPT Compare) [23]; NCT01186744 (OPT Retreatment) [24]; NCT01519089 [25, 26]; NCT01815424	up to 56 weeks
Long-term extension study	NCT01163253 (ongoing ^a) [27]	up to 3 years

^aData as of April 2014, data collection and analyses for studies NCT00413699 and NCT01163253 are ongoing; therefore the study databases have not yet been locked (i.e. some values may change for the final, locked study databases)

RA, rheumatoid arthritis; RCT, randomized controlled trial

[NCT01519089: The results of this study have been submitted to and accepted by the *Journal of Dermatology*]

Reference List

1. Charles-Schoeman C, Fleischmann R, Davignon J, Schwartz H, Turner SM, Beysen C, et al. Potential mechanisms leading to the abnormal lipid profile in patients with rheumatoid arthritis versus healthy volunteers and reversal by tofacitinib. *Arthritis Rheumatol.* 2015;67:616-25.
2. Kremer JM, Kivitz AJ, Simon-Campos JA, Nasonov EL, Tony H, Lee SK, et al. Evaluation of the effect of tofacitinib on measured glomerular filtration rate in patients with active rheumatoid arthritis: results from a randomised controlled trial. *Arthritis Res Ther.* 2015;17:95.
3. Kremer JM, Bloom BJ, Breedveld FC, Coombs JH, Fletcher MP, Gruben D, et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: Results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. *Arthritis Rheum.* 2009;60:1895-905.
4. Kremer JM, Cohen S, Wilkinson BE, Connell CA, French JL, Gomez-Reino J, et al. A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. *Arthritis Rheum.* 2012;64:970-81.
5. Fleischmann R, Cutolo M, Genovese MC, Lee EB, Kanik KS, Sadis S, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an

- inadequate response to disease-modifying antirheumatic drugs. *Arthritis Rheum.* 2012;64:617-29.
6. Tanaka Y, Suzuki M, Nakamura H, Toyozumi S, Zvillich SH, Tofacitinib Study Investigators. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Arthritis Care Res (Hoboken)*. 2011;63:1150-8.
 7. Tanaka Y, Takeuchi T, Yamanaka H, Nakamura H, Toyozumi S, Zvillich S. Efficacy and safety of tofacitinib as monotherapy in Japanese patients with active rheumatoid arthritis: a 12-week, randomized, phase 2 study. *Mod Rheumatol*. 2015;25:514-21.
 8. McInnes IB, Kim HY, Lee SH, Mandel D, Song YW, Connell CA, et al. Open-label tofacitinib and double-blind atorvastatin in rheumatoid arthritis patients: a randomised study. *Ann Rheum Dis*. 2014;73:124-31.
 9. Conaghan P, Østergaard M, Wu C, van der Heijde D, Irazoque-Palazuelos F, Hrycaj P, et al. Effects of tofacitinib on bone marrow edema, synovitis, and erosive damage in methotrexate-naïve patients with early active rheumatoid arthritis (duration ≤ 2 years): results of an exploratory Phase 2 MRI study. *Arthritis & Rheumatology*. 2014;66:S519 abstract 1181.
 10. Boyle DL, Soma K, Hodge J, Kavanaugh A, Mandel D, Mease P, et al. The JAK inhibitor tofacitinib suppresses synovial JAK1-STAT signalling in rheumatoid arthritis. *Ann Rheum Dis*. 2015;74:1311-6.
 11. Winthrop KL, Silverfield J, Racewicz A, Neal J, Lee EB, Hrycaj P, et al. The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. *Ann Rheum Dis*. 2016;75:687-95.

12. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet*. 2013;381:451-60.
13. van der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. *Arthritis Rheum*. 2013;65:559-70.
14. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med*. 2012;367:495-507.
15. Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. *Ann Intern Med*. 2013;159:253-61.
16. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, García Mejjide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med*. 2012;367:508-19.
17. Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley J, Gruben D, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. *N Engl J Med*. 2014;370:2377-86.
18. Wollenhaupt J, Silverfield J, Lee EB, Curtis JR, Wood SP, Soma K, et al. Safety and efficacy of tofacitinib, an oral Janus kinase Inhibitor, for the treatment of rheumatoid arthritis in open-label, longterm extension studies. *J Rheumatol*. 2014;41:837-52.

19. Boy MG, Wang C, Wilkinson BE, Chow VF, Clucas AT, Krueger JG, et al. Double-blind, placebo-controlled, dose-escalation study to evaluate the pharmacologic effect of CP-690,550 in patients with psoriasis. *J Invest Dermatol.* 2009;129:2299-302.
20. Krueger J, Suarez-Farinas M, Fuentes-Duculan J, Cuteo I, Mallbris L, Tatulych S, et al. Pathologic immune pathways in psoriasis are rapidly attenuated by tofacitinib treatment. *Br J Dermatol.* 2014;171:e120-e121.
21. Papp KA, Menter A, Strober B, Langley RG, Buonanno M, Wolk R, et al. Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: a Phase 2b randomized placebo-controlled dose-ranging study. *Br J Dermatol.* 2012;167:668-77.
22. Papp KA, Menter MA, Abe M, Elewski B, Feldman SR, Gottlieb AB, et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: results from two, randomized, placebo-controlled, phase III trials. *Br J Dermatol.* 2015;173:949-61.
23. Bachelez H, van de Kerkhof PC, Strohal R, Kubanov A, Valenzuela F, Lee JH, et al. Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. *Lancet.* 2015;386:552-61.
24. Bissonnette R, Iversen L, Sofen H, Griffiths CEM, Foley P, Romiti R, et al. Tofacitinib withdrawal and retreatment in moderate-to-severe chronic plaque psoriasis: a randomized controlled trial. *Br J Dermatol.* 2015;172:1395-406.
25. Asahina A, Nagaoka M, Shibasaki Y, Isogawa N, Ohtsuki M. Domestic phase 3 study of tofacitinib in subjects with moderate to severe plaque psoriasis. Japanese Society for Psoriasis Research - 30th Annual meeting. 2015.

26. Asahina A, Ohtsuki M, Shibasaki Y, Toyozumi S, Nagaoka M. Domestic phase 3 study of tofacitinib in subjects with moderate to severe plaque psoriasis. European Academy of Dermatology and Venereology - 24th Congress. 2015.

27. Augustin M, Paul C, Valenza F, Azulay L, Langley RG, Leonardi C, et al. Tofacitinib in patients with chronic moderate to severe plaque psoriasis: 2-year efficacy and safety in an open-label long-term extension study. *British Journal of Dermatology*. 2015; 23rd World Congress of Dermatology Abstracts and Proceedings - Vancouver 2015.