Summary of Inflectra® (infliximab-dyyb) Approval Studies

Title & Citation	Summary
Park W, Hrycaj P, Jeka S, et al. **A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study.** Ann Rheum Dis. 2013;72(10):1605-12. (doi: 10.1136/annrheumdis-2012-203091)	• Phase I randomized, double-blind, multi-center, multi-national parallel-group study to compare the pharmacokinetics (PK), safety and efficacy of innovator infliximab (INX) and CT-P13, a biosimilar to INX, in patients with active ankylosing spondylitis (AS) • Patients were randomized to receive 5 mg/kg of CT-P13 (n=125) or INX (n=125). Primary endpoints were area under the concentration-time curve (AUC) at steady state and observed maximum steady state serum concentration (Cmax,ss) between weeks 22 and 30. Additional PK, efficacy endpoints, including 20% and 40% improvement response according to Assessment in Ankylosing Spondylitis International Working Group criteria (ASAS20 and ASAS40), and safety outcomes were also assessed. • Geometric mean AUC was 32 765.8 µgh/ml for CT-P13 and 31 359.3 µgh/ml for INX. Geometric mean Cmax,ss was 147.0 µg/ml for CT-P13 and 144.8 µg/ml for INX. The ratio of geometric means was 104.5% (90% CI 94% to 116%) for AUC and 101.5% (90% CI 95% to 109%) for Cmax,ss. ASAS20 and ASAS40 responses at week 30 were 70.5% and 51.8% for CT-P13 and 72.4% and 47.4% for INX, respectively. In the CT-P13 and INX groups more than one adverse event occurred in 64.8% and 63.9% of patients, infusion reactions occurred in 3.9% and 4.9%, active tuberculosis occurred in 1.6% and 0.8%, and 27.4% and 22.5% of patients tested positive for anti-drug antibodies, respectively. • he PK profiles of CT-P13 and INX were equivalent in patients with active AS. CT-P13 was well tolerated, with an efficacy and safety profile comparable to that of INX up to week 30.
Park W, Yoo DH, Miranda P, et al. **Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study.** Ann Rheum Dis. 2016;76(2):346-354 (doi: 10.1136/annrheumdis-2015-208783)	• Open-label extension study that recruited patients with AS who completed a 54-week, randomized controlled study comparing CT-P13 with RP (PLANETAS) to investigate the efficacy and safety of switching from infliximab reference product (RP) to its biosimilar or maintaining biosimilar treatment in patients with ankylosing spondylitis (AS). • CT-P13 (5 mg/kg) was administered intravenously every 8 weeks from week 62 to week 102. Efficacy end points included the proportion of patients achieving Assessment of SpondyloArthritis international Society (ASAS)20. Antidrug antibodies (ADAs) were measured using an electrochemiluminescent method. Data were analysed for patients treated with CT-P13 in the main PLANETAS study and the extension (maintenance group) and those who were switched to CT-P13 during the extension study (switch group). • Overall, 174 (82.9%) of 210 patients who completed the first 54 weeks of PLANETAS and agreed to participate in the extension were enrolled. Among these, 88 were maintained on CT-P13 and 86 were switched to CT-P13 from RP. In these maintenance and switch groups, respectively, ASAS20 response rates at week 102 were 80.7% and 76.9%. ASAS40 and ASAS partial remission were also similar between groups. ADA positivity rates were comparable (week 102: 23.3% vs 27.4%). Adverse events led to treatment discontinuation during the extension study in 3 (3.3%) and 4 (4.8%) patients, respectively. • This is the first study to show that switching from RP to its biosimilar CT-P13 is possible without negative effects on safety or efficacy in patients with AS. In the maintenance group, CT-P13 was effective and well tolerated over 2 years of treatment.

Title & Citation	Summary
Park W, Lee SJ, Yun J, Yoo DH. **Comparison of the pharmacokinetics and safety of three formulations of infliximab (CT-P13, EU-approved reference infliximab and the US-licensed reference infliximab) in healthy subjects: a randomized, double-blind, three-arm, parallel-group, single-dose, Phase I study.** Expert Rev Clin Immunol. 2015;11 Suppl 1:S25-31. (doi: 10.1586/1744666X)	• Double-blind, three-arm, parallel-group study to compare the pharmacokinetics (PK), safety and tolerability of biosimilar infliximab (CT-P13 [Remsima(®), Inflectra(®)]) with two formulations of the reference medicinal product (RMP) (Remicade(®)) from either Europe (EU-RMP) or the USA (US-RMP). • Healthy subjects received single doses (5 mg/kg) of CT-P13 (n = 71), EU-RMP (n = 71) or US-RMP (n = 71). The primary objective was to compare the PK profiles for the three formulations. Assessments of comparative safety and tolerability were secondary objectives. • Primary end points (Cmax, AUClast and AUCinf) were equivalent between all formulations (CT-P13 vs EU-RMP; CT-P13 vs US-RMP; EU-RMP vs US-RMP). All other PK end points supported the high similarity of the three treatments. Tolerability profiles of the formulations were similar. • The PK profile of CT-P13 is highly similar to EU-RMP and US-RMP. All three formulations were equally well tolerated.
Yoo DH, Racewicz A, Brzezicki J, et al. **A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study**. Arthritis Res Ther. 2015;18:82. (doi: 10.1186/s13075-016-0981-6.)	• Phase III double-blind study to to compare the 54-week efficacy, immunogenicity, safety, pharmacokinetics (PK) and pharmacodynamics (PD) of CT-P13(Remsima®, Inflectra®) and RP (reference product) in patients with active rheumatoid arthritis (RA). • Patients with active RA and an inadequate response to methotrexate (MTX) were randomized (1:1) to receive CT-P13 (3 mg/kg) or RP (3 mg/kg) at weeks 0, 2, 6 and then every 8 weeks to week 54 in combination with MTX (12.5-25 mg/week). Efficacy endpoints included American College of Rheumatology (ACR)20, ACR50 and ACR70 response rates, Disease Activity Score in 28 joints (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), European League Against Rheumatism (EULAR) response rates, patient-reported outcomes and joint damage progression. Immunogenicity, safety and PK/PD outcomes were also assessed. • Of 606 randomized patients, 455 (CT-P13 233, RP 222) were treated up to week 54. At week 54, ACR20 response rate was highly similar between groups (CT-P13 74.7 %, RP 71.3 %). ACR50 and ACR70 response rates were also comparable between groups (CT-P13 43.6 % and 21.3 %, respectively; RP 43.1 % and 19.9 %, respectively). DAS28, SDAI and CDAI decreased from baseline to week 54 to a similar extent with CT-P13 and RP. Radiographic progression measured by Sharp scores as modified by van der Heijde was also comparable. With both treatments, patient assessments of pain, disease activity and physical ability, as well as mean scores on the Medical Outcomes Study Short Form Health Survey (SF-36), improved markedly at week 14 and remained stable thereafter up to week 54. The proportion of patients positive for antidrug antibodies at week 54 was similar between the two groups: 41.1 % and 36.0 % with CT-P13 and RP, respectively. CT-P13 was well tolerated and had a similar safety profile to RP. PK/PD results were also comparable between CT-P13 and RP. • CT-P13 and RP were comparable in terms of efficacy (including radiographic progression), immunogenicity and PK/PD up to week 54. The safety profile of CT-P13 was also similar to that of RP.

Title & Citation	Summary
Yoo DH, Prodanovic N, Jaworski J, et al. **Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study**. Ann Rheum Dis. 2017;76(2):355-363. (doi: 10.1136/annrheumdis-2015-208786)	• Open-label extension study to assess the efficacy and safety of switching from the infliximab reference product (RP; Remicade) to its biosimilar CT-P13 (Remsima, Inflectra) or continuing CT-P13 in patients with rheumatoid arthritis (RA) for an additional six infusions. • Patients with RA who had completed the PLANETRA study received CT-P13 (3 mg/kg) was administered intravenously every 8 weeks from weeks 62 to 102. All patients received concomitant methotrexate. Endpoints included American College of Rheumatology 20% (ACR20) response, ACR50, ACR70, immunogenicity and safety. Data were analyzed for patients who received CT-P13 for 102 weeks (maintenance group) and for those who received RP for 54 weeks and then switched to CT-P13 (switch group). • Overall, 302 of 455 patients who completed the PLANETRA study enrolled into the extension. Of these, 158 had received CT-P13 (maintenance group) and 144 RP (switch group). Response rates at week 102 for maintenance versus switch groups, respectively, were 71.7% vs 71.8% for ACR20, 48.0% vs 51.4% for ACR50 and 24.3% vs 26.1% for ACR70. The proportion of patients with antidrug antibodies was comparable between groups (week 102: 40.3% vs 44.8%, respectively). Treatment-emergent adverse events occurred in similar proportions of patients in the two groups during the extension study (53.5% and 53.8%, respectively). • Comparable efficacy and tolerability were observed in patients who switched from RP to its biosimilar CT-P13 for an additional year and in those who had long-term CT-P13 treatment for 2 years.
Jørgensen KK, Olsen IC, Goll GL, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet 2017; 389: 2304–16. (doi: 10.1016/S0140-6736(17)30068-5)	• Randomized, non-inferiority, double-blind, phase 4 trial to examine switching from originator infliximab to the less expensive biosimilar CT-P13 regarding efficacy, safety, and immunogenicity. • Patients with informed consent were randomized in a 1:1 ratio to either continued infliximab originator or to switch to CT-P13 treatment, with unchanged dosing regimen. The primary endpoint was disease worsening during 52-week follow-up. 394 patients in the primary per-protocol set were needed to show a non-inferiority margin of 15%, assuming 30% disease worsening in each group. • 482 patients were enrolled and randomised (241 to infliximab originator, 241 to CT-P13 group; one patient was excluded from the full analysis and safety set for CT-P13) and 408 were included in the per-protocol set (202 in the infliximab originator group and 206 in the CT-P13 group). 155 (32%) patients in the full analysis set had Crohn's disease, 93 (19%) had ulcerative colitis, 91 (19%) had spondyloarthritis, 77 (16%) had rheumatoid arthritis, 30 (6%) had psoriatic arthritis, and 35 (7%) had chronic plaque psoriasis. Disease worsening occurred in 53 (26%) patients in the infliximab originator group and 61 (30%) patients in the CT-P13 group (per-protocol set; adjusted treatment difference –4·4%, 95% CI –12·7 to 3·9). The frequency of adverse events was similar between groups (for serious adverse events, 24 [10%] for infliximab originator vs 21 [9%] for CT-P13; for overall adverse events, 168 [70%] vs 164 [68%]; and for adverse events leading to discontinuation, nine [4%] vs eight [3%], respectively). • The NOR-SWITCH trial showed that switching from infliximab originator to CT-P13 was not inferior to continued treatment with infliximab originator according to a prespecified non-inferiority margin of 15%.