Pharmacokinetic boosting to enable a once-daily reduced dose of tofacitinib in patients with rheumatoid arthritis and psoriatic arthritis (the PRACTICAL study)

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Abstract

Background: Tofacitinib is a Janus Kinase (JAK) inhibitor used for the treatment of rheumatoid arthritis (RA) and psoriatic arthritis (PsA), dosed as 5 mg twice daily (BID). It is primarily metabolized by the cytochrome P-3A (CYP3A) enzyme, and therefore, the manufacturer recommends to halve the dose when using CYP3A-inhibiting co-medication. Combining half-dose tofacitinib with a registered CYP3A inhibitor (cobicistat) could reduce costs and improve patient experience.

Objectives: Primary: bioequivalence of tofacitinib 5 mg combined with cobicistat once daily (QD; intervention) to tofacitinib 5 mg BID (control). Secondary: safety, patient preference (7-point Likert scale at study end) and predicted differences in disease activity (DAS28-CRP and probability of ACR20 response) using a validated exposure-response model.

Design: Open-label, cross-over pharmacokinetic study.

Methods: We included patients with RA or PsA, treated with tofacitinib 5 mg BID for ≥14 days without co-medication affected by CYP3A inhibition. Pharmacokinetic sampling was performed at baseline and after 2-6 weeks of intervention treatment. Bioequivalence was defined as 90% CI of the average tofacitinib concentration (Cavg,ss; intervention to control) falling between 80% and 125%, assessed by non-linear mixed-effects modelling.

Results: Between 16 September 2019 and 15 January 2021, 30 patients were included, of whom 25 completed both PK measurements. The tofacitinib Cavg,ss was 85% (90% CI: 75–96%). No serious adverse events occurred. Patient preference was 56% for intervention versus 18% for control. No relevant differences in median predicted disease activity were found (DAS28-CRP: 0.03, 95% CI: −0.16 to 0.22; ACR20: −0.01, −0.07 to 0.05).

Conclusion: Due to slightly lower tofacitinib concentrations during intervention treatment, pharmacokinetic bioequivalence could not formally be established. However, pharmacokinetic boosting may be an attractive strategy for cost reduction of tofacitinib because of its safety, similar predicted pharmacodynamics and patient preference.

Registration: This study was registered on 29 May 2019 in the Netherlands Trial Register (register number: NL7766).

Keywords: rheumatoid arthritis, psoriatic arthritis, JAK-inhibitors, pharmacokinetics

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and decreases radiological progression in both conditions.\textsuperscript{2,3} Initially, tofacitinib was only available as 5 mg twice daily (BID), but more recently once-daily (QD) therapy with tofacitinib has become available by authorization of an 11 mg extended-release (XR) tablet. Interestingly, the approval of this XR tablet was entirely based on model-based prediction of the efficacy of this new formulation, using a small pharmacokinetic study and an existing exposure-response model.\textsuperscript{4}

However, tofacitinib treatment is associated with high costs. Yearly costs per patient for tofacitinib 5 mg BID varied between €13,000 in the European Union and €43,000 in the United States in 2018.\textsuperscript{5} Since its patent will not expire until 2028, innovative strategies are needed to provide effective but cost-effective treatment in the upcoming years.

For tofacitinib, an opportunity can be found in its metabolism, which is primarily executed by the cytochrome P450 isoenzyme 3A (CYP3A).\textsuperscript{6} Indeed, the manufacturer advises to halve the dose of tofacitinib when co-administered with a strong CYP3A-inhibiting drug, such as ketoconazole.\textsuperscript{6} Therefore, tofacitinib treatment could be decreased to 5 mg QD if deliberately combined with such an inhibitor, a strategy called ‘pharmacokinetic boosting’.

Pharmacokinetic boosting, by means of CYP3A inhibition, is a concept that is widely applied in human immunodeficiency virus (HIV) treatment to reduce pill burden and pharmacokinetic variability.\textsuperscript{7} Cobicistat is an approved pharmacokinetic booster used for HIV treatment. It strongly inhibits CYP3A metabolism in the intestines and the liver and is otherwise pharmacologically inactive.\textsuperscript{8} In the Netherlands, the cost of cobicistat is €1.09 per tablet, approximately one-twelfth of tofacitinib.\textsuperscript{9,10} As cobicistat has a well-tolerated safety profile,\textsuperscript{11} it can be a safe and efficacious drug to boost tofacitinib, and substituting tofacitinib BID for tofacitinib with cobicistat QD could lead to a significant cost reduction.

Apart from the near 50% cost reduction, boosted tofacitinib therapy could have other advantages. First, drug adherence could be improved as this is negatively associated with dose frequency.\textsuperscript{12} Moreover, it could have a positive impact on the interpatient pharmacokinetic variability because CYP3A significantly varies between humans,\textsuperscript{13} and the addition of a CYP3A inhibitor in combination with a reduced dose could thus stabilize tofacitinib exposure on a population level. A possible drawback includes interactions with other CYP3A substrates.

In summary, tofacitinib–cobicistat combination therapy can be an interesting strategy to reduce costs and improve patients’ experience with tofacitinib. As the results of the population pharmacokinetic analysis in patients with PsA were similar to those of patients with RA, these populations can be combined in a pharmacokinetic study.\textsuperscript{6} Therefore, the aim of our study was to investigate the bioequivalence of tofacitinib combined with cobicistat QD versus tofacitinib BID in patients with RA and PsA, and to explore the effects on modelled pharmacodynamics.

Methods

Study design

This was an open-label, non-randomized, within-group crossover study with the aim to investigate the bioequivalence of tofacitinib 5 mg (Xeljanz\textsuperscript{®}) with cobicistat 150 mg (Tybost\textsuperscript{®}) QD (intervention) and tofacitinib 5 mg BID (control), performed in the Sint Maartenskliniek (Ubbergen, The Netherlands). In addition to the bioequivalence study, the effect of pharmacokinetic boosting on treatment outcome was predicted using a validated pharmacokinetic-pharmacodynamic model. This model was previously used by the manufacturer to obtain marketing authorization for XR tofacitinib 11 mg, with the aim to predict efficacy based on pharmacokinetics only.\textsuperscript{4} The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.\textsuperscript{14}

Participants

We recruited patients (aged ≥16 years) from the outpatient rheumatology clinic of the Sint Maartenskliniek. Inclusion criteria were (1) a diagnosis of either RA or PsA (according to relevant classification criteria\textsuperscript{15–17} or a clinical diagnosis), and (2) current use of tofacitinib 5 mg BID for ≥2 weeks. If tofacitinib was used for >3 months, a sufficient clinical response was also required, defined as a Disease Activity Score 28 using C-reactive protein (DAS28-CRP) of <2.9 or a judgement of low disease activity by a rheumatologist. We excluded individuals with a known intolerance to cobicistat or with
co-medication affected by the CYP3A enzyme. Therefore, participants’ co-medication (including over-the-counter medication) was checked by a pharmacist before inclusion, using a predefined list of contra-indicated medication composed for this study (Supplementary Table 1). Some contra-indicated drugs could be replaced with a similar drug to enhance study participation, for example, replacing simvastatin with pravastatin (Supplementary Table 1). The use of (methyl) prednisolone, also affected by CYP3A, was accepted in a dose of \( \leq 10 \text{ mg} \) oral daily (prednisolone) or as an injection of \( \leq 120 \text{ mg} \) intramuscularly (methylprednisolone) during the study. Concomitant treatment with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate or leflunomide, or with non-steroidal anti-inflammatory drugs (NSAIDs) was also accepted. To exclude other CYP3A involvement, patients were asked at the start of each pharmacokinetic sampling day whether they had used grapefruit juice or Saint John’s Wort in the week prior.

Procedures

The study consisted of an inclusion visit to obtain informed consent and to collect patient characteristics, followed by two sampling days to measure tofacitinib concentrations of both treatment regimens (Figure 1). The first sampling day was planned at pharmacokinetic steady state after \( \geq 2 \) weeks’ use of tofacitinib 5 mg BID. After this sampling day, participants switched treatment to tofacitinib 5 mg and cobicistat 150 mg QD, ingested simultaneously. Then, after 2–6 weeks, another sampling day was performed. This time window was chosen to ensure that steady state of the new regimen was reached but to limit the exposure to a new medication regimen. Medication adherence was monitored throughout the study with pill count and a study medication diary. After this sampling day, the study ended for a participant.

At inclusion, we obtained data for demographics, disease and treatment characteristics and smoking history. On the sampling days, plasma samples were drawn pre-dose and at 0.5, 1, 2, 3, 4, 6, 9, 12, and 24 h post-dose (24-h intervention treatment only). We chose these time points to assess the area under the plasma concentration-time curve (AUC) of the full dosing interval on sufficient time points, in accordance with the European Medicines Agency (EMA). Samples were collected in 3 ml labelled lithium heparin tubes without gel and stored at \(-40^\circ\text{C}\). At the end of the study, tofacitinib concentrations were measured in batch with a validated bioanalytical assay.

Moreover, clinical and laboratory parameters, and adverse events (AEs) were collected at the sampling days. Clinical assessments included height (first sampling day only), weight, blood pressure, and DAS28-CRP and its components: swollen joint count (SJC), tender joint count (TJC), patient global assessment on disease activity [Visual Analogue Scale (VAS)], patient global assessment on pain (VAS pain) and physician global assessment on disease activity (VAS physician). Laboratory assessments included: erythrocyte sedimentation rate (ESR), CRP, alanine aminotransaminase (ALAT), total blood count and creatinine. AEs were asked by a research nurse or physician and registered using the Common Terminology Criteria for Adverse Events (CTCAE) version 5. Patient preference was measured at the second sampling day. Patients were asked to fill in a 7-point Likert scale for the question ‘Which medication regimen do you prefer?’ of which one end represented ‘very
strong preference for tofacitinib BID’, the middle ‘no preference’ and the other end ‘very strong preference for tofacitinib combined with cobicistat QD’.

Outcomes
The primary aim was to investigate the bioequivalence of the average tofacitinib concentration in steady state (C_{avg,ss}) of tofacitinib 5 mg and cobicistat 150 mg QD compared with tofacitinib 5 mg BID. The C_{avg,ss}, defined as the AUC divided by the dosing interval, was chosen as primary outcome for investigating bioequivalence as it best describes the clinical efficacy of tofacitinib. Bioequivalence was defined as the 90% confidence interval (CI) of the C_{avg,ss} geometric mean ratio (GMR) falling between 80% and 125%.

Secondary outcomes included DAS28-CRP (measured on both sampling days), AEs, patient preference (measured by a 7-point Likert scale on the last sampling day) and description of relevant pharmacokinetic parameters (clearance, bioavailability and volume of distribution).

DAS28-CRP and AEs were descriptively measured to timely assess safety and efficacy signals. Last, we predicted the effect of pharmacokinetic boosting on relevant pharmacodynamics on a population level, including the DAS28-CRP score and the American College of Rheumatology definition of 20% improvement of disease (ACR20 response).

Statistical analysis
Sample size calculation. The ‘Two One-Sided t-Tests (TOST) for (Bio)equivalence Studies’ package version 1.4-6 in R statistics v3.4.3 was used for the sample size calculation, with C_{avg,ss} as the primary end point for the study. We assumed a bioequivalence ratio of 1, standard bioequivalence margins and a known 27% coefficient of variance in AUC/C_{avg} based on the phase IIb dose-ranging study of tofacitinib. This led to a number of 28 patients needed to show bioequivalence with a 90% power and a significance level of 5%. To account for drop-out, we chose to include 30 patients.

Pharmacokinetic analysis. The pharmacokinetic analysis was performed by means of non-linear mixed-effects modelling. In short, we fitted a one-compartment pharmacokinetic model with zero-order oral absorption and first-order elimination previously developed by the manufacturer to the obtained rich pharmacokinetic data of this study. Pharmacokinetics were allometrically scaled to a standard body weight of 70 kg. The estimated glomerular filtration rate (eGFR) at baseline was investigated as a covariate for clearance. The effect of cobicistat co-administration was estimated as a binary covariate for clearance and bioavailability, as well as intra-individual variability on clearance.

From the pharmacokinetic model, the individual empirical Bayes estimate for the C_{avg,ss} of tofacitinib was obtained in the absence and presence of cobicistat and used to test equivalence on the primary end point, by means of a TOST procedure. The intervention regimen was considered pharmacokinetically bioequivalent to the control regimen if the 90% CI of the geometric mean ratio entirely fell between 80% and 125%, in accordance with the EMA guideline. Of note, we erroneously reported equivalence margins of 75–125% in the trial register; this was adjusted post hoc to comply with guidelines. Only the patients who completed both sampling days were included in the primary analysis so that both tofacitinib regimens could be compared.

Measured outcomes. Clinical efficacy in the study was evaluated with the mean difference in DAS28-CRP for both RA and PsA patients, measured on both sampling days. Safety was evaluated by descriptive analysis of the AEs using StataIC (version 13, StataCorp LLC, TX, USA), categorized by the CTCAE v5. Patient preference was evaluated by calculating the proportion of patients who preferred tofacitinib BID (Likert scale score 1–3), who had no preference (score 4) and who preferred tofacitinib with cobicistat QD (score 5–7). Only the patients who actually used the combination therapy were included in these secondary analyses.

Predicted clinical outcomes. For evaluation of the effect of pharmacokinetic boosting on DAS28-CRP and probability of ACR20 response improvement on a population level, we performed a Monte Carlo simulation (n=1000 in a cross-over study) of both outcomes at maximum efficacy, using the NONMEMV7.4 software package (ICON plc, Dublin, Ireland). In this simulation, we used the pharmacokinetic parameters from our study and the pharmacokinetic-pharmacodynamic model as described by Lamba et al., previously used for
model-informed development and registration of the XR formulation of tofacitinib. We predicted the median values and 95% CIs (2.5th–95th percentiles of the predicted clinical outcome measure including both interindividual variability as parameter uncertainty) of the DAS28-CRP score and the probability of ACR20 response for both study regimens. An increase of 0.6 in DAS28-CRP score and a 10% reduced probability of ACR20 were considered clinically relevant.\textsuperscript{21,24}

**Results**

**Inclusion**

Study inclusion took place between 16 September 2019 and 15 January 2021, and study measurements were performed up until 10 March 2021. Eighty-nine patients were assessed for eligibility, and 30 patients (34%) were included (Figure 2). Twenty-seven participants completed at least one sampling day and were included in the baseline and secondary analyses. Of the three excluded participants, two discontinued tofacitinib because of side effects, and the third withdrew informed consent because of fear of side effects of cobicistat. Of the 27 participants included in the baseline analyses, 2 could not be included in the primary analyses. One patient discontinued tofacitinib before the second sampling day could be performed due to COVID-19 lockdown. Patient preference was still collected because combination therapy was used by this patient. The second patient was excluded due to a protocol violation (tobafacinib and cobicistat QD administered in the evening instead of the morning).

The baseline characteristics of participants are displayed in Table 1. Median follow-up times were 14 days (range, 14–49 days, $n=26$) for the intervention regimen and 27 days (range, 1–171 days, $n=27$) for the control regimen. Eighty-two (22/27) percent of the participants were tofacitinib starters (use $\leq$ 3 months).

**Outcomes**

**Pharmacokinetic bioequivalence** The median tofacitinib $C_{avg,ss}$ was 19.0 ng/ml [interquartile range (IQR), 14.1–24.3] for tofacitinib 5 mg BID and 15.7 (14.0–19.3) for tofacitinib 5 mg with cobicistat 150 mg QD. The geometric mean ratio of tofacitinib $C_{avg,ss}$ for tofacitinib with cobicistat QD compared with tofacitinib BID was 85%, with its 90% CI being 75–96%. Thus, the bioequivalence criteria were not met (Figure 3).

**Measured clinical outcomes.** Disease activity measured by DAS28-CRP remained stable throughout this short-term study: the change between both sampling days was 0.04 (95% CI: −0.50 to 0.59, intervention to control, $n=26$; Table 2). No serious AEs occurred during the study. One patient had to temporarily discontinue tofacitinib with cobicistat because of heart failure, but these could be restarted without reoccurrence of symptoms after 3 weeks. The most frequently reported AEs during the intervention regimen were musculoskeletal, gastrointestinal and neurological (Supplementary Table 2). Both gastrointestinal and neurological AEs were reported more frequently during intervention than control treatment, for which nausea ($n=5$) and headache ($n=3$) were the most reported subcategories. Except for the known and small creatinine increase during cobicistat use,\textsuperscript{25} safety laboratory parameters did not differ between sampling days (Table 2). We concluded that therefore no major efficacy and safety concerns were observed after switch.

![Study flow chart.](image-url)
The majority of the patients (56%) preferred combination therapy of tofacitinib with cobicistat QD over tofacitinib BID, 18% preferred tofacitinib monotherapy and 26% had no preference (Figure 4).

**Pharmacokinetic parameters.** The parameters describing the pharmacokinetics of tofacitinib and the respective relative standard errors of estimates (RSE) were as follows: baseline apparent oral clearance (in absence of renal function) was 14.6 l/h (RSE 23%), which increased by 0.0531 l/h per ml/min increase in eGFR (RSE 54%). Baseline clearance decreased with 39.1% (RSE 10%) as a result of boosting. Relative oral bioavailability increased by 23% (RSE 6%) as a result of boosting. Volume of distribution was estimated to be 91.4 litres (RSE 7%). Duration of absorption could not be estimated due to very rapid absorption and limited sampling during the
absorption phase and was therefore fixed to 0.352 h, based on the population pharmacokinetic parameters of the manufacturer. The interindividual variability in clearance was estimated to be 31% (RSE 29%). The interindividual variability in relative bioavailability with and without pharmacokinetic boosting was 21% (RSE 73%) and 32.2% (RSE 30.9%), respectively.

**Predicted clinical outcomes.** The predicted median DAS28-CRP at maximum drug effect was 3.59 (95% CI, reflecting both interindividual

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**Figure 3.** Assessment of bioequivalence. Geometric mean ratio with 90% confidence interval of the tofacitinib C_{avg} (tofacitinib 5 mg BID compared with tofacitinib 5 mg and cobicistat 150 mg QD) represented as horizontal line. Equivalence margins are represented as vertical dotted lines at 80% and 125%.

**Table 2.** Efficacy and safety parameters on both sampling days.

| Parameter                      | TOFA BID (n=27) | TOFA + COBI QD (n=26) |
|--------------------------------|----------------|-----------------------|
| DAS28-CRP                      | 3.27 ± 1.41    | 3.18 ± 1.19           |
| DAS28-ESR                      | 3.27 ± 1.25 [n = 25] | 3.29 ± 1.36           |
| Swollen joint count (0–28)     | 1 (0–2)        | 0 (0–2)               |
| Tender joint count (0–28)      | 2 (0–5)        | 2 (0–3)               |
| VAS global (mm)                | 40 (20–60)     | 40 (20–60)            |
| VAS pain (mm)                  | 40 (30–60)     | 40 (28–60) [n = 24]   |
| VAS physician (mm)             | 40 (25–50)     | 30 (20–55) [n = 25]   |
| CRP (mmol/l)                   | 2 [1–10]       | 5 [2–13]              |
| ESR (mm/h)                     | 10 [5–27] [n = 25] | 15 [5–30]          |
| Haemoglobin (mmol/l)           | 8.4 (7.5–8.8)  | 8.5 (7.8–8.9)         |
| Leukocytes (10^9/l)            | 7.3 [5.7–8.4]  | 8.2 [6.2–9.3]         |
| Thrombocytes (10^9/l)          | 241 [203–270]  | 231 [207–308]         |
| Creatinine (µmol/l)            | 72 [59–87]     | 80 [74–92]            |
| ALAT (U/l)                     | 24 [17–31]     | 25 [17–30]            |

ALAT, alanine aminotransferase; COBI, cobicistat; CRP, C-reactive protein; DAS28, disease activity score based on 28 joints; ESR, erythrocyte sedimentation rate; TOFA, tofacitinib; VAS global, patient’s global assessment of disease activity on a visual analogue scale; VAS pain, patient’s global assessment of pain; VAS physician, physician’s global assessment of disease activity. Displayed as number (percentage), mean ± standard deviation or median (interquartile range). Percentages were calculated over the total number of participants unless indicated.
variability and variable uncertainty, 3.14–3.96) for tofacitinib with cobicistat QD versus 3.55 (3.06–3.95) for tofacitinib BID. The median difference in predicted DAS28-CRP was 0.03 (−0.16 to 0.22, intervention-control; Supplementary Figure 1A). The predicted ACR20 response was 64% (54–4%) for intervention versus 65% (54–75%) for control, leading to a difference of −0.01 (−0.07 to 0.05; Supplementary Figure 1B). These differences were not considered as clinically relevant differences because our predefined clinical relevance margins (an increase of 0.6 in DAS28-CRP score and a 10% reduced probability of ACR20) were not met.

**Discussion**

We found a slightly lower tofacitinib $C_{avg}$ for tofacitinib 5 mg with cobicistat 150 mg QD to tofacitinib 5 mg BID; therefore, pharmacokinetic bioequivalence could not be confirmed. However, because of the very comparable pharmacokinetics, no relevant differences in predicted DAS28-CRP and ACR20 response, and a clear patient preference, pharmacokinetic boosting seems to be an attractive strategy for cost-effective use of tofacitinib.

This study has several strengths. As it is a multiple-dose study conducted in patients with RA and PsA instead of healthy volunteers, both tolerability and patient preference data can be optimally generalized. Also, rich pharmacokinetic sampling was performed in this study so that the $C_{avg,ss}$ of tofacitinib could be adequately estimated. Other strengths include low drop-out and missing rates, again underscoring the high acceptability of tofacitinib with cobicistat. Finally, the used boosting drug, cobicistat, is safe, inexpensive and also available in non-high-income countries because of its co-administration with antiretroviral drugs.

There are some limitations that should be considered. First, it should be noted that this study was designed to assess pharmacokinetic bioequivalence and that clinical outcomes (disease activity) were only measured descriptively. Although we predict the minimal changes in pharmacokinetics are of negligible clinical impact, prospective evaluation is warranted. Second, the number of participants is just below the predefined sample size calculation, perhaps also driving the failure to prove bioequivalence. Third, the majority of patients in this study only recently (<1 month) started with tofacitinib. Combined with a short follow-up, this makes it difficult to study effects on disease activity. However, the predicted clinical efficacy seemed unaffected by the slightly lower exposure, as measured with a robust and validated pharmacokinetic-pharmacodynamic model. This model was previously used to obtain marketing authorization for the XR formulation of tofacitinib based on a pharmacokinetic study only, similar to our study.

All in all, we expect that this tofacitinib–cobicistat combination therapy can be of value in clinical practice. The phase IIb dosing study of tofacitinib showed effective response to 3 mg BID, but a dosage of 5 mg BID was chosen as standard because of a small difference in a secondary outcome (anaemia). Because of the potentially serious side effects of tofacitinib, such as risk on venous thromboembolism, it may be postulated that lower tofacitinib exposure is even preferable. Moreover, we found comparable clinical efficacy and safety, and the majority of patients preferring this combination regimen. With the advantages of a QD regimen, but around 40–50% lower costs than the XR formulation, we think this combination therapy is suitable to reduce costs of tofacitinib therapy.

A complicating factor of pharmacokinetic boosting may be unwanted drug–drug interactions with co-medication. During the screening phase of our study, the use of co-medication affected by CYP3A was the main reason for exclusion, especially cardiovascular drugs, used by a considerable number of patients.
part of patients with inflammatory arthritis. Therefore, use of cobicistat requires adequate assessment by the patient’s pharmacist. During the study, however, replacement of co-medication with non-CYP drugs to enable study participation was accepted by a notable proportion of patients (see Table 1), and that most patients were aware that they used a drug with a higher risk of interactions. In addition, since polypharmacy and drug–drug interactions with cobicistat are frequent in HIV patients, many lessons can be learned from this field, for example, by using a website designed for HIV treatment to assess drug–drug interactions when initiating cobicistat.26

Future research on this strategy should include a larger study with longer follow-up with disease activity as primary outcome. Also, the safety of the combination therapy should be monitored over a longer period of time, with a specific focus on musculoskeletal, gastrointestinal and neurological adverse events. Last, costs and quality of life should be assessed throughout the study so that formal cost-effectiveness analyses can be performed.

In conclusion, our study shows that pharmacokinetic boosting is not pharmacokinetically equivalent but shows similar predicted efficacy. Therefore, it remains an attractive and feasible strategy to reduce costs and dosing frequency of tofacitinib in RA and PsA.

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the local medical ethics committee (Commissie Mensgebonden Onderzoek region Arnhem-Nijmegen; 2018-4455) and the competent authority (CCMO; NL65634.091.18). All participants provided written informed consent.

**Consent for publication**

Not applicable.

**Author contributions**

**Céleste J.T. van der Togt:** Data curation; Formal analysis; Investigation; Project administration; Visualization; Writing – original draft.

**Lise M. Verhoef:** Conceptualization; Data curation; Formal analysis; Methodology; Validation; Writing – original draft.

**Bart J.F. van den Bemt:** Conceptualization; Methodology; Supervision; Writing – review & editing.

**Nathan den Broeder:** Conceptualization; Methodology; Writing – original draft.

**Rob ter Heine:** Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology; Resources; Software; Supervision; Writing – original draft.

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**Competing interests**

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Bart van den Bemt reports speaker payments for UCB, Pfizer, Sanofi-Aventis, Galapagos, Amgen and Eli Lilly outside the submitted work. Alfons den Broeder reports grants to the institution outside the current study from Abbvie, Galapagos, Pfizer, Novartis, Lilly, Sanofi and Gilead. The other authors declare no competing interests.

**Availability of data and materials**

Individual deidentified participants’ data with data syntaxes (includes syntaxes in StataIC and NONMEM) that underlie the results reported, the study protocol and the informed consent form...
can be shared upon request with publication to researchers with a methodologically sound proposal. Proposals should be directed to Alfons den Broeder, a.denbroeder@maartenskliniek.nl; to gain access, data requestors will need to sign a data access agreement.

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**Supplemental material**

Supplemental material for this article is available online.

**References**

1. Kerschbaumer A, Smolen JS, Nash P, *et al.* Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a systematic literature research. *RMD Open* 2020; 6: e001374.

2. Gratacós Masmitjà J, González Fernández CM, Gómez Castro S, *et al.* Efficacy of tofacitinib in the treatment of psoriatic arthritis: a systematic review. *Adv Ther* 2021; 38: 868–884.

3. Fleischmann R. A review of tofacitinib efficacy in rheumatoid arthritis patients who have had an inadequate response or intolerance to methotrexate. *Expert Opin Pharmacother* 2017; 18: 1525–1533.

4. Lamba M, Hutmacher MM, Furst DE, *et al.* Model-informed development and registration of a once-daily regimen of extended-release tofacitinib. *Clin Pharmacol Ther* 2017; 101: 745–753.

5. U.S. Government Committee on Ways and Means. A painful pill to swallow: U.S. vs. international prescription drug prices, [https://waysandmeans.house.gov/sites/democrats.waysandmeans.house.gov/files/documents/U.S.%20vs.%20International%20Prescription%20Drug%20Prices_0.pdf](https://waysandmeans.house.gov/sites/democrats.waysandmeans.house.gov/files/documents/U.S.%20vs.%20International%20Prescription%20Drug%20Prices_0.pdf) (accessed 7 February 2022).

6. Xeljanz. Summary of product characteristics, [https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf](https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf) (accessed 30 November 2021).

7. Larson KB, Wang K, Delille C, *et al.* Pharmacokinetic enhancers in HIV therapeutics. *Clin Pharmacokinet* 2014; 53: 865–872.

8. Tybost. Summary of the product characteristics, [https://www.ema.europa.eu/en/documents/product-information/tybost-epar-product-information_en.pdf](https://www.ema.europa.eu/en/documents/product-information/tybost-epar-product-information_en.pdf) (accessed 30 November 2021).

9. Zorginstituut Nederland. Tybost tablet filmomhuld 150 mg – Medicijnkosten. nl, [https://www.medicijnkosten.nl/medicijn%artikel=TYBOST+TABLET+FILMOMHULD+150MG%id=a1cf93d11d448c34135e4e97ad35334e](https://www.medicijnkosten.nl/medicijn%artikel=TYBOST+TABLET+FILMOMHULD+150MG%id=a1cf93d11d448c34135e4e97ad35334e) (accessed 30 November 2021).

10. Zorginstituut Nederland. Xeljanz tablet filmomhuld 5 mg – Medicijnkosten. nl, [https://www.medicijnkosten.nl/medicijn%artikel=XELJANZ+TABLET+FILMOMHULD+5MG%id=a1eef93d11d448c34135e4e97ad35334e](https://www.medicijnkosten.nl/medicijn%artikel=XELJANZ+TABLET+FILMOMHULD+5MG%id=a1eef93d11d448c34135e4e97ad35334e) (accessed 30 November 2021).

11. Mathias AA, German P, Murray BP, *et al.* Pharmacokinetics and pharmacodynamics of GS-9350: a novel pharmacokinetic enhancer without anti-HIV activity. *Clin Pharmacol Ther* 2010; 87: 322–329.

12. Coleman CI, Limone B, Sobieraj DM, *et al.* Dosing frequency and medication adherence in chronic disease. *J Manag Care Pharm* 2012; 18: 527–539.

13. de Wildt SN, Kearns GL, Leeder JS, *et al.* Cytochrome P450 3A: ontogeny and drug disposition. *Clin Pharmacokinet* 1999; 37: 485–505.

14. von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; 370: 1453–1457.

15. Arnett FC, Edworthy SM, Bloch DA, *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315–324.

16. Aletaha D, Neogi T, Silman AJ, *et al.* 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; 62: 2569–2581.

17. Taylor W, Gladman D, Helliwell P, *et al.* Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006; 54: 2665–2673.

18. EMA guideline on the investigation of bioequivalence, 2010. [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf)

19. Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, [https://ctep.cancer.gov/protocoldevelopment/electronic_
20. Fleischmann R, Cutolo M, Genovese MC, 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: 617–629.

21. Food and Drug Administration – Center for Drug Evaluation and Research. *Clinical pharmacology and biopharmaceutics review – tofacitinib*. Silver Spring, MD: Food and Drug Administration, 2011.

22. Anderson BJ and Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. *Annu Rev Pharmacol Toxicol* 2008; 48: 303–332.

23. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokinet Biopharm* 1987; 15: 657–680.

24. van der Maas A, Lie E, Christensen R, et al. Construct and criterion validity of several proposed DAS28-based rheumatoid arthritis flare criteria: an OMERACT cohort validation study. *Ann Rheum Dis* 2013; 72: 1800–1805.

25. Sherman EM, Worley MV, Unger NR, et al. Cobicistat: review of a pharmacokinetic enhancer for HIV infection. *Clin Ther* 2015; 37: 1876–1893.

26. University of Liverpool. Liverpool HIV drugs interaction checker. https://www.hiv-druginteractions.org/checker