Journal of Crohn's and Colitis, 2020, S725–S736
doi:10.1093/ecco-jcc/jjaa014
Advance Access publication March 11, 2020
Supplement Article

Supplement Article

Clinical Pharmacology of Janus Kinase Inhibitors in Inflammatory Bowel Disease

Pavine L. C. Lefevre[a] and Niels Vande Casteele[a,b]

[a]Robarts Clinical Trials, Inc., London, ON, Canada [b]IBD Center, Department of Medicine, University of California San Diego, La Jolla, CA, USA

Corresponding author: Niels Vande Casteele, PharmD, PhD, University of California San Diego, School of Medicine, Division of Gastroenterology, IBD Center, 9,500 Gilman Drive #0956, La Jolla, CA 92093. Tel.: +1 858 345 5932; fax: +1 858 768 0645; email nvadecasteele@health.ucsd.edu

Abstract

Inflammatory bowel disease, including ulcerative colitis and Crohn's disease, are chronic inflammatory disorders of the gastrointestinal tract which are characterised, in part, by an imbalance in the production of several pro- and anti-inflammatory cytokines. Although various agents are effective for inducing and maintaining remission, approximately 20% of patients are treatment-refractory and require surgery. Parenterally administered monoclonal antibody-based biologics are associated with adverse effects resulting in treatment discontinuation and/or immunogenicity, leading to loss of response to therapy. Approximately 50% of patients who initially respond to treatment with tumour necrosis factor antagonists lose response to therapy within the 1st year of treatment. Incidence of immunogenicity tends to decrease over time, but once present can persist for years, even after treatment discontinuation. Nonimmunogenic oral small molecule therapies, including Janus kinase inhibitors, are currently being developed and have demonstrated efficacy in early phase clinical trials, which has already led to regulatory approval of tofacitinib for the treatment of patients with moderate-to-severe ulcerative colitis. Differentiation of T cells into T helper cells, which are mediators of the inflammatory response in inflammatory bowel disease, is mediated by the Janus kinase signal transducer and activator of the transcription signalling pathway. Absorption and distribution of Janus kinase inhibitors occurs at the site of action in the gastrointestinal tract, and newer compounds are being developed with limited systemic absorption, potentially reducing the risk of adverse effects. The current review describes the clinical pharmacology of approved Janus kinase inhibitors, as well as those in clinical development for the treatment of inflammatory bowel disease.

Key words: Janus kinases; signal transducer and activator of transcription; Janus kinase inhibitors; inflammatory bowel diseases

1. Introduction

The inflammatory bowel diseases [IBD] ulcerative colitis [UC] and Crohn's disease [CD] are chronic inflammatory disorders of the gastrointestinal [GI] tract characterised by alternating periods of relapse and remission. The prevalence of IBD in North America and Europe was reported to be as high as 249 and 505 per 100 000 persons, respectively.[1] A dysregulated mucosal immune response to intestinal microflora in a genetically predisposed host is presumed to underly the development of IBD, which is characterised by an imbalance in the production of several pro-inflammatory and anti-inflammatory cytokines.[2,3] Conventional therapy for IBD includes aminosalicylates, glucocorticoids, and immunomodulators.[4] Although various agents are effective for inducing and maintaining remission, about 20% of patients are treatment-refractory and require surgery.[5] Immunosuppressive therapy includes antibody-based biologics, which are administered parenterally and are often

associated with adverse effects [AEs] and/or loss of response to therapy, due to immunogenicity.[6] Approximately 50% of patients who initially respond to treatment with tumour necrosis factor antagonists lose response to therapy within the 1st year of treatment.[7] The annual risk for loss of response to infliximab and adalimumab in patients with Crohn's disease was reported to be 13% and 20%, respectively.[8,9] Incidence of immunogenicity tends to decrease over time, but once present can persist for years, even after treatment discontinuation.[10] The use of monoclonal antibodies is also associated with substantial intra-and interpatient variability in drug exposure, and frequently requires therapeutic drug monitoring with measurement of systemic drug concentrations to optimise treatment efficacy.[11]

Nonimmunogenic oral small molecule therapies are therefore currently being developed and tested clinically for the treatment of IBD.[12,13] As such, Janus kinase [JAK] inhibitors [JAKi] are promising drugs that have already demonstrated efficacy in treatment of IBD in early phase clinical trials,[14] and one JAKi, tofacitinib, has already received regulatory approval by the Food and Drug Administration [FDA] and European Medicines Agency [EMA] for treatment of patients with moderate-to-severe UC.[15,16] The JAK/signal transducer and activator of transcription [STAT] [JAK-STAT] signalling pathway is implicated in regulating innate and adaptive immunity, and haematopoiesis, as it participates in cell growth, survival, differentiation, and migration.[17] As such, the JAK-STAT signalling pathway is activated via cytokine binding in T cells and triggers their differentiation into T helper cells, which are mediators of the inflammatory response in IBD.[18] In addition, chronic inflammation in CD and UC is characterised by a response of cytokine production by helper T cells, and produced cytokines signal through the JAK-STAT signalling pathway to induce inflammatory response.[19]

The JAK family consists of four tyrosine kinase proteins [JAK1, JAK2, JAK3, and TYK2].[20] Members of the JAK family are constitutively associated with intracellular domains of type I or type II cytokine receptors.[17] Each receptor is composed of multiple subunits and each subunit associates with a JAK, with more or less selectivity.[21] Activation of JAKs is initiated by extracellular type I or type II cytokines binding to their cognate cytokine receptors, that are composed of distinct chains which dimerise upon binding of the cytokine. Dimerisation causes separation of the intracellular subunits of the cytokine receptors, which separates the receptor-associated JAKs apart from each other, thereby relieving inhibition and resulting in their activation.[21] The activated JAKs phosphorylate themselves as well as the intracellular portion of the receptor, and the latter, once phosphorylated, creates docking sites for STAT proteins. STAT proteins are then activated by phosphorylation by JAKs, and form homo- or heterodimers. Homo- or heterodimerised phosphorylated STATs then translocate to the nucleus where they bind to specific DNA sequences to regulate gene expression. Genome-wide association studies have demonstrated an association between polymorphisms encoding JAK-STAT proteins and exaggerated immune responses in patients with IBD.[22–24] Therefore, depending on the selectivity of JAKi for JAKs, different inflammatory pathways can be targeted.

In contrast to monoclonal antibodies used to treat IBD, JAKi are small molecules, which facilitates oral administration and drug adsorption and distribution at the site of action in the gastrointestinal [GI] tract.[25] These agents are typically rapidly absorbed and have short half-lives [within a few hours],[13] and are being developed to have limited systemic absorption, potentially reducing the risk of adverse events [AEs]. The targeted delivery of JAKi may also reduce intra- and interpatient drug exposure variability, particularly in the GI tract. This review describes the clinical pharmacology of approved JAKi as well as those in clinical development for the treatment of IBD [summarised in Table 1 and Table 2].

2. Tofacitinib

2.1. Chemistry and administration

Tofacitinib [CP-690,550][30] is a small molecule with a molecular weight of 312.4 g/mol and a molecular structure of $C_{16}H_{20}N_6O$.[31,32] An immediate release [IR] tablet formulation of tofacitinib citrate [tofacitinib IR] was developed for oral administration and was approved by the FDA and EMA for the treatment of UC [along with other inflammatory diseases, such as rheumatoid and psoriatic arthritis].[15,16] Recently, an extended release tablet

Table 1. Summary of clinical pharmacology parameters for JAK inhibitors currently used or developed for the treatment of inflammatory bowel diseases.

Drug	JAK Selectivity	PK Parameters	Metabolism [% of the dose metabolised, site, drug metabolising enzyme[s]]	Elimination [parent and metabolite compounds]
Tofacitinib	JAK1 > JAK3 > JAK2	T_{max} = 0.5–1 h $T_{1/2}$ ~3 h Bioavailability = 74%	65% Hepatic [CYP3A4 and CYP2C19]	Urine [80%] Faeces [20%]
Filgotinib	JAK1 > JAK2 > JAK3	T_{max} parent = 1–3 h $T_{1/2}$ parent ~ 5–6 h T_{max} metabolite = 3–5 h $T_{1/2}$ metabolite ~ 18–22 h	% Unknown Intestinal [CES2 [primarily]] Hepatic [CES1]	Urine [>80%]
TD-1473	JAK1 > JAK2/JAK3/TYK2	$T_{1/2}$ = 4–44 h	Unknown	Unknown
Upadacitinib	JAK1 > JAK2 > JAK3 > TYK2	T_{max} = 1–2 h $T_{1/2}$ ~ 4 h	34% Hepatic [CYP3A4 and CYP2D6]	Urine [43%] Faeces [53%]
PF-06700841	JAK1 > TYK2 > JAK2	Tmax = 1–1.5 h $T_{1/2}$ = 3.8–7.5	84% Hepatic [CYP3A4]	Urine [16%]
PF-06651600	JAK3	Unknown	% Unknown Hepatic [CYP450 and GST]	Unknown

JAK, Janus kinase; GST, glutathione-S-transferase; T_{max}, time at maximal concentration; $T_{1/2}$, elimination half-life.

formulation of tofacitinib [tofacitinib XR] was also approved for the treatment of UC.[15]

2.2. Target specificity

Tofacitinib is considered a pan-JAK inhibitor with inhibitory effects demonstrated on all JAK-mediated signalling pathways, albeit with varying selectivity.[33,34] A greater potency of tofacitinib was observed for JAK1/JAK3, with an observed half maximal inhibitory concentration [IC_{50}] of 33 nM and 76 nM for JAK1 and JAK3, respectively, and a 10-fold selectivity for JAK1 over JAK2 in human whole-blood assays.[33] Tofacitinib specificity for JAK1/JAK3 was also observed in human peripheral blood mononuclear cells [PBMCs], primarily in CD4 + T cells and natural killer [NK] cells, and in monocytes to a lesser extent.[34] Upon stimulation with the JAK1/JAK3-dependent cytokines interleukin [IL]-2, IL-4, IL-15, and IL-21, tofacitinib IC_{50} values ranged from 11 to 22 nM in CD4 + T cells and from 8 to 22 nM in NK cells.

2.3. Pharmacokinetics

Absorption of tofacitinib is rapid, with peak plasma concentrations achieved between 0.5 and 1 h following administration of single doses ranging from 0.3 to 100 mg in healthy subjects.[35,36] Tofacitinib has a linear and dose-proportional pharmacokinetic [PK] profile with a functional half-life of ~3 h in healthy subjects[35] and patients with UC.[26] Tofacitinib clearance is mediated by hepatic cytochrome P450 [CYP]-mediated metabolism [65%].[35] Primary and secondary hepatic metabolism occurs through CYP3A4 and CYP2C19, respectively, and results in fewer than 10% circulating metabolites.[35,36] Metabolites are not clinically significant, as their potency is predicted to be ≤10% of that observed for tofacitinib for inhibition of JAK1/JAK3.[35] Approximately 80% and 20% of tofacitinib and related metabolites are eliminated in the urine and faeces, respectively, in healthy subjects.[35] Absolute oral bioavailability of tofacitinib in healthy subjects was 74%, with total plasma clearance of 24.8 L/h.[37] An oral clearance [CL/F] of 34.9 L/h was observed in analysis of PK data collected in 16 phase 1 studies involving healthy subjects.[36]

Approval of tofacitinib XR was based on two phase 1 studies conducted in healthy subjects, which included a single- and multiple-dose relative bioavailability study and a food-effect study.[38] In the single-dose phase of the bioavailability study, subjects received either 11 mg tofacitinib XR once daily [QD] or 5 mg tofacitinib IR twice daily [BID] on Day 1. Subsequent dosing on Days 3 to 7 occurred in the multiple-dose phase. Bioequivalence of the XR and IR formulation was observed. Geometrical mean ratios of area under the curve [AUC_{∞} and maximum serum concentration [C_{max}] were contained within the 90% confidence intervals [CIs], and associated 90% CIs were within the equivalence interval of 80–125% following both single- and multiple-dose administration for the XR and IR formulations. In the food-effect study, healthy subjects received a single

Table 2. Population PK models, PK parameters and covariates for JAK inhibitors currently used or developed for the treatment of inflammatory bowel diseases.

Drug	PK model	Population PK parameters			Dosing regimen
		Parameters		Covariates	
Tofacitinib	One-compartment model with first order absorption and elimination in adult patients with UC[26]	CL/F [L/h] %CV [CL/F] V/F [L] Ka [/h] %CV [Ka] Tlag [h]	22.4 31.4 94.2 2.83 87.5 0.16	No covariates were identified to have an effect on tofacitinib exposure	Patients with UC administered with placebo or oral tofacitinib doses of 0.5, 3, 10, 15 mg BID for 8 weeks[26]
Filgotinib	Three-compartment model with first-order oral absorption and elimination in healthy subjects[27]	CL_p/F [L/h] %CV [CL_p/F] V_c/F [L] %CV [V_c/F] Q/F [L/h] V_p/F [L] CL_M/F [L/h] %CV [CL_M/F] V_M/F [L] %CV [V_M/F] Ka [/h]	3.97 8.0 3.08 52 2.002 4.72 1.004 20.3 4.36 4.7 -0.733	Decreased CL_p/F with body weight and sex was found to affect V_c/F [L]	Healthy male subjects administered either placebo or oral filgotinib single doses ranging from 10 mg to 200 mg and, subsequently, multiple doses of 25, 50, 100 mg BID or 200, 300, 450 mg QD for 10 days[27]
Upadacitinib	Two-compartment model with first-order absorption and elimination in healthy subjects[28]	CL/F [L/h] %CV [CL/F] Vc/F [L] %CV [Vc/F] Ka [1/h] %CV [Ka] Tlag [h] Vp/F [L] Q/F [L/h]	39.7 16 146 14 12.3 150 0.48 64.3 3.23	CL/F and Vc/F was decreased in females compared with males, CL/F was decreased with increased creatine clearance, Vc/F was decreased with increased body weight	Healthy subjects administered placebo or upadacitinib single doses of 1, 3, 6, 12, 24, 36 or 48 mg, or multiple doses of 3, 6, 12, and 24 mg BID for 14 days[29]

PK, pharmacokinetics; BID, twice daily; QD, once daily; CL/F, oral clearance; CLp/F, oral clearance for the parent compound; CL_M/F, oral clearance for the metabolite compound; CV, coefficient of variation; Ka, absorption rate constant; Q/F, oral intercompartmental clearance; $T_{1/2}$, half-life; UC, ulcerative colitis; V/F, oral volume of distribution; Vc/F, oral volume of distribution for the central compartment; Vp/F, oral volume of distribution for the peripheral compartment; V_M/F, oral volume of distribution for the metabolite compound; Tlag, absorption lag time.

11-mg dose of tofacitinib XR under fasting or fed [high-fat breakfast] conditions. Equivalence was observed for AUC_{∞} under the two conditions. Although tofacitinib XR C_{max} increased 27% with food intake, this increase was not considered clinically relevant.

A population PK analysis of tofacitinib IR was conducted in patients with UC and administered 0.5, 3, 10, or 15 mg of tofacitinib BID for 8 weeks, in a dose-ranging phase 2 trial.[26] The pharmacokinetic profile of tofacitinib was described by a one-compartment model with first-order absorption and elimination. Oral clearance, oral volume of distribution [V/F], and first order absorption rate constant [Ka] population parameters were estimated to be 22.4 ± 0.95 $L.h^{-1}$, 94.2 ± 2.35 L, and 2.83 ± 0.46 h^{-1} (mean ± standard error [SD]), respectively, with an absorption lag time of 0.16 h. Estimated interpatient variability [%CV] was 31.4% for CL/F and 87.5% for Ka. The tofacitinib population PK model developed in patients with UC showed no drug accumulation, as the average plasma drug concentration during a dosing interval at steady state [$C_{av,ss}$] over the nominal 12-h dosing interval dose-proportionally increased, and no significant change in exposure between baseline and Week 8 was described in the dose groups. Apparent clearance, baseline albumin concentration, total Mayo score, faecal calprotectin [FC], and C-reactive protein [CRP] concentrations were not found to be significant covariates for exposure, suggesting that tofacitinib $C_{av,ss}$ is not influenced by baseline disease activity. The observation that $C_{av,ss}$ and the minimum trough plasma concentration at steady state [$C_{trough,ss}$] at the end of the 12-h dosing interval increased, approximately in proportion with dose, was consistent with the linear and dose-proportional PK of tofacitinib observed in non-compartmental analysis conducted in healthy subjects.

An exposure-response model was also developed to determine the effects of tofacitinib on ex vivo markers of response [i.e., IL-6 mediated phosphorylation of STAT3 and IL-7 mediated phosphorylation of STAT5] in blood samples from healthy subjects administered tofacitinib 5 mg BID for 14 days.[39] In this study, tofacitinib reversibly inhibited IL-6 mediated phosphorylation of STAT3 and IL-7 mediated phosphorylation of STAT5 in a concentration-dependent manner. The estimated IC_{50} of tofacitinib was 119 nM for IL-6 mediated phosphorylation of STAT3 and 79.1 nM for IL-7 mediated phosphorylation of STAT5.

2.4. Pharmacodynamics

2.4.1. Efficacy

Tofacitinib IR was approved for the treatment of UC based on the results of the phase 3 OCTAVE programme, which included two identical induction studies [OCTAVE 1 and 2] and a maintenance trial [OCTAVE Sustain].[40,41] Patients enrolled in the induction studies were randomised to tofacitinib 10 mg BID or placebo for 8 weeks. Clinical remission [a total Mayo Clinic score ≤2, with no subscore >1 and a rectal bleeding subscore of 0] at 8 weeks occurred in 18.5% [OCTAVE 1] and 16.6% [OCTAVE 2] of patients randomised to tofacitinib versus 8.2% [OCTAVE 1] and 3.6% [OCTAVE 2] of patients randomised to placebo [$p = 0.007$ and $p < 0.001$ for the OCTAVE 1 and 2 primary outcome results], respectively. Week 8, responders [decrease from baseline in the total Mayo score >3 points and >30%, with an accompanying decrease in the rectal bleeding subscore of >1 point or an absolute rectal bleeding subscore of 0 or 1] were re-randomised to maintenance treatment with tofacitinib 10 mg or 5 mg or placebo BID for 52 weeks in the maintenance study.[41] After 52 weeks, clinical remission rates were significantly higher in patients re-randomised to treatment with 5 mg [34.3%] and 10 mg [40.6%] tofacitinib compared with those re-randomised to placebo [11.1%; $p < 0.001$ for both comparisons].

Although phase 2 clinical trials of tofacitinib for the treatment of CD were also conducted, similar efficacy was not observed in these patients compared with those with UC.[42] Clinical development for this indication was discontinued; however, modest associations were observed between higher doses of tofacitinib and Week 4 CRP and FC concentrations, suggesting a modulation of inflammatory activity.[42] It has also been suggested that high placebo response and remission rates, potentially arising from a combination of factors such as the use of concomitant medication [e.g., high proportion of patients using corticosteroids and slow prolonged taper during maintenance therapy], study design [e.g., site-investigator rather than blinded central reading of endoscopy for study enrolment], and the primary endpoint (e.g., Crohn's Disease Activity Index [CDAI] rather than patient-reported outcomes including objective markers of disease activity) may have obscured a potential treatment effect of tofacitinib in patients with CD.[14,43]

2.4.2. Safety

Influenza, nasopharyngitis, arthralgia, and headache were the most commonly reported AEs in the OCTAVE trial programme.[41] No overall difference in the rate of AEs between the recommended dosing regimens of tofacitinib (10 mg BID for 8 weeks [OCTAVE Induction 1 and 2 trials] and 5 mg or 10 mg BID for 52 weeks [OCTAVE Sustain trial]) and placebo were reported in the phase 3 randomised controlled trials included in the OCTAVE programme.[41] Infections occurred more frequently with tofacitinib treatment compared with placebo in the induction studies, including a small, but higher, risk for serious infections [1.3% versus 0% in OCTAVE 1 and 0.2% versus 0% in OCTAVE 2]. A higher rate of herpes zoster was observed in the 10 mg tofacitinib group [5.1%] compared with the 5 mg tofacitinib [1.5%] and the placebo group [0.5%] in the OCTAVE Sustain maintenance study.[41] Higher risk of herpes zoster was associated with age >65 years, Asian race, previous tumour necrosis factor inhibitor failure, and higher tofacitinib dose.[44] A dose-dependent risk of herpes zoster infection in patients with UC who received tofacitinib was reported in a recent integrated safety analysis of the aforementioned studies.[45] The risk of developing lymphoma or other malignancies in patients with UC was low and stable, based on analysis of the same pooled data the same analysis.[45] Recent post-marketing reports indicate a higher risk of thrombotic events in patients with rheumatoid arthritis [RA] on tofacitinib or other JAKi,[46] although these events are infrequent and may be related to the existence of underlying conditions.[47,48] The prescribing information for tofacitinib was modified to include two boxed warnings for an increased risk of pulmonary embolism and mortality with a 10 mg BID dose,[15] based on post-marketing data derived from patients with RA who were at least 50 years old and had at least one cardiovascular risk factor.[15] Furthermore, the current prescribing information for the treatment of patients with UC recommends the use of tofacitinib at the lowest dose and for the shortest duration possible to achieve/maintain a therapeutic response, such that treatment with 10 mg BID should not extend beyond the induction period, and maintenance dosing should not exceed 5 mg BID, except for loss of response.[15]

Changes in biochemical and laboratory parameters have been observed with tofacitinib treatment,[44,45,49] but none of these changes was shown to have a clinical impact, and all were reversible on therapy cessation. No foetal deaths or congenital malformations were observed in the clinical development programmes for RA, psoriasis, or IBD.[50,51] The safety of tofacitinib during pregnancy and breastfeeding has not been investigated, and is therefore not currently recommended in these patient populations.

2.5. Factors affecting pharmacokinetics

2.5.1. Drug interactions

Tofacitinib is metabolised via hepatic CYP3A4 and CYP2C19 enzymes; therefore, administration of tofacitinib with strong CYP3A4 inhibitors, such as ketoconazole, or co-administration with moderate CYP3A4 and strong CYP2C19 inhibitors, such as fluconazole, can lead to increased exposure to tofacitinib.[15] In healthy subjects, tofacitinib area under the curve [AUC] and Cmax values were increased by 79% and 27%, respectively, with fluconazole co-administration, and 103% and 16%, respectively, with ketoconazole co-administration.[52] This AUC change following co-administration of fluconazole or ketoconazole with tofacitinib is consistent with the reported involvement of CYP3A4 in approximately 50% of clearance, whereas the Cmax change is consistent with a calculated first-pass extraction ratio of approximately 0.2.[36] Adjustments of tofacitinib dose is therefore recommended if co-administration of strong CYP3A4 inhibitors, or moderate CYP3A4/strong CYP2C19 inhibitors, is required.[15] Phase 1 studies conducted in healthy subjects also demonstrated that co-administration of the CYP3A4 inducer rifampin decreased tofacitinib exposure, as shown by a decrease in tofacitinib $AUC_{0-\infty}$ and C_{max} of 84% and 74%, respectively.[53] The use of immunosuppressive drugs, such as azathioprine, tacrolimus, and cyclosporine, with tofacitinib can also affect tofacitinib exposure and increase risks associated with enhanced immunosuppression.[36] Co-administration of immunosuppressive drugs with tofacitinib is therefore not recommended.[36]

2.5.2. Renal impairment

The PK profile of tofacitinib in patients with normal [creatinine CL >80 mL/min], mild [creatinine CL >50 and ≤80 mL/min], moderate [creatinine CL ≥30 and ≤49 mL/min] or severe [creatinine CL <30 mL/min] renal impairment or with end-stage renal disease [ESRD] requiring dialysis was investigated in two phase 1 studies.[54] In both studies, patients were administered a single 10-mg dose of tofacitinib. Pharmacokinetic data were collected before and after dosing and/or haemodialysis [patients with ESRD only]. Tofacitinib C_{max} was comparable between patients with renal impairment or ESRD, and those with normal renal function. Relative to patients with normal renal function, the mean [90% confidence interval] tofacitinib $AUC_{0-\infty}$ ratios were 137% [97–195], 143% [101–202], and 223% [157–316] in patients with mild, moderate, and severe renal impairment, respectively. Terminal phase half-life increased with severity of renal impairment. The mean $AUC_{0-\infty}$ in patients with ESRD on a non-dialysis day was similar to that observed for patients with moderate renal impairment and approximately 40% higher than the mean $AUC_{0-\infty}$ for healthy subjects.

Dose adjustment for patients with moderate or severe renal impairment [including those with ESRD requiring dialysis] is therefore recommended for tofacitinib by both the FDA and the EMA.[15,16] Recommendations for tofacitinib dose adjustments are only recommended by the EMA for patients with severe renal impairment, whereas the FDA recommends these adjustments for both moderate and severe renal impairment.[15,16] For patients with renal impairment, the dose of tofacitinib IR should be reduced from 10 mg BID to 5 mg BID, or from 5 mg BID to 5 mg QD, and tofacitinib XR should be reduced from 22 mg QD to 11 mg QD or switched from 11 mg QD to 5 mg QD tofacitinib IR. Administration of adjusted doses of tofacitinib is recommended immediately following dialysis [when required] for patients with ESRD.

2.5.3. Hepatic impairment

The effect of mild [Child-Pugh score 5–6 points; Class A] and moderate [Child-Pugh score 7–9 points; Class B] hepatic impairment on the PK profile of tofacitinib was investigated in an open-label trial. All patients and healthy subjects in this trial received a single 10-mg dose of tofacitinib.[55] Both $AUC_{0-\infty}$ and C_{max} were comparable between patients with mild hepatic impairment and healthy subjects. However, increases [90% CI] of 65% [25–117] and 49% [12–97] for mean $AUC_{0-\infty}$ and $C_{max,}$ respectively, were observed in patients with moderate hepatic impairment compared with healthy subjects. The FDA and EMA recommend tofacitinib IR dose reductions from 10 mg BID to 5 mg BID, or from 5 mg BID to 5 mg QD for patients with moderate hepatic impairment.[15,16] Doses of tofacitinib XR should be reduced from 22 mg QD to 11 mg QD or switched from 11 mg QD to 5 mg QD of tofacitinib IR. There are no data on the effect of severe hepatic impairment on the PK of tofacitinib, and use of tofacitinib in this patient population is therefore not recommended by the FDA or EMA.

3. Filgotinib

3.1. Chemistry and administration

Filgotinib [or GLPG0634][33] is a small molecule with a molecular weight of 425.5 g/mol and a molecular formula of $C_{21}H_{23}N_5O_3S$.[32,56] A tablet formulation of filgotinib was developed for oral administration, and filgotinib is currently in clinical development for the treatment of patients with UC or CD.

3.2. Target specificity

In a cell-free enzyme assay, filgotinib inhibited JAK1 [IC_{50} = 10 nM] and, to a lesser extent, JAK2 [IC_{50} = 28 nM],but with greater potency than JAK3 [IC_{50} = 810 μM] or TYK2 [IC_{50} = 116 μM].[33] In human whole-blood assays, a greater potency [IC_{50} = 629 nM] and a 28-fold selectivity of filgotinib was observed for JAK1 over JAK2.[33] An active metabolite of filgotinib was found to have a similar selectivity [30-fold selectivity for JAK1 over JAK2] but with a reduced potency for JAK1 [IC_{50} = 11.9 μM], compared with the parent filgotinib.[57,58]

3.3. Pharmacokinetics

A non-compartmental PK analysis of filgotinib was conducted using data collected from two clinical trials in which healthy subjects received filgotinib as single dose of 10, 25, 50, 100. and 200 mg [trial 1], or repeated doses of 25, 50, and 100 mg BID or 200, 300, and 450 mg QD for 10 days [trial 2].[27] In trial 1 [single ascending doses] and trial 2 [multiple ascending doses], filgotinib was rapidly absorbed within 0.5 to 5.0 h [T_{max}]. Exposure to filgotinib was dose-proportionally increased within the single and multiple ascending dose ranges. Steady state for filgotinib exposure was reached after 48 h of repeated dosing, independently of administered dose and dosing regimen. Of note, filgotinib exposure also increased dose-proportionally for 100 mg BID and 200 mg QD, but the apparent terminal half-life [5–6 h] and the accumulation ratio were comparable between the two dosing regimens. Overall, the intrasubject variability of filgotinib exposure at steady state was low to moderate [16% to 44% when considering both C_{max} and AUC].

Filgotinib undergoes CYP-independent and extensive metabolism by carboxylesterases, resulting in an active metabolite.[57,58] In vitro studies revealed that this occurs primarily via metabolism by carboxylesterase-2[58] which is mainly expressed in the small intestine and colon, and to a lesser extent in the liver.[59] Elimination of

filgotinib and its major metabolite occurs predominantly in the urine [>80%].[58]

The active metabolite of filgotinib reached maximal exposure within 3 to 5 h, and increased in proportion to the single ascending doses as well as between repeated doses of 25 to 100 mg BID and 300 to 450 mg QD administered for 10 days.[27] Exposure of the filgotinib metabolite following 200-mg QD doses was similar to that observed following administration of 300 mg QD. The mechanism underlying this observation was unclear and could not be explained by a change in metabolite formation or elimination rates. The elimination half-life of filgotinib is 23 h following administration of single doses, and 22 to 27 h following repeated doses, leading to up to a 2.0- and 3.9-fold accumulation after administration of repeated doses of filgotinib 25 to100 mg BID and 200 to 450 mg o QD for 10 days, respectively.[27] Steady-state levels were reached within 4 days in the 50 to 200 mg repeated dose range. The metabolite concentrations were 16–20 fold higher than those of the parent compound with administration of the 50 to 200 mg daily doses.[27] Overall, the intrasubject variability of filgotinib metabolite exposure at steady state was low [below 26% when considering both C_{max} and AUC]. Dose-normalised exposure [$AUC_{0-\tau}$] and parent-metabolite ratio after 200 mg QD and 100 mg BID administration for 10 days were similar, thereby confirming the dose-proportional PKs of the metabolite. Considering the IC_{50} of filgotinib [IC_{50} = 629 nM or 267 ng/mL] and its major metabolite [IC_{50} = 11.9 nM or 4,529 ng/mL] for JAK1, and filgotinib exposure reported by Namour *et al*.,[27] the optimal therapeutic dose range of filgotinib would be between 50 mg BID and 200 mg QD. No food effect was reported on overall filgotinib or metabolite exposure.[60]

A population PK model for filgotinib and its active metabolite was also developed using data obtained from healthy subjects.[27] The dose-exposure profile of filgotinib and its metabolite was adequatey described by a three-compartment model, with an oral absorption and a linear elimination for filgotinib, and a linear elimination for the metabolite.[27] Final population parameters for the parent compound were -0.733 h^{-1} for Ka, 3.97 L/h for the oral parent clearance [CLp/F], and 3.08 L for the oral central volume of distribution [Vc/F]. For the metabolite, final population parameters were 1.04 L/h for the oral metabolite clearance [CL_M/F] and 4.36 L for the oral metabolite volume of distribution [V_M/F]. Body weight and sex were identified as significant covariates for filgotinib CL/F and V/F, respectively. Between-subject variance for the parent and metabolite CL/F was 0.102 and 0.0444, respectively. An exposure-response model was also developed to determine the effects of filgotinib on ex vivo markers responses [IL-6 induced STAT1 phosphorylation] in CD4+ cells isolated from blood samples collected from healthy subjects who received a single dose ranging from 10 to 200 mg, repeated doses of 25 to 100 mg BID, or 200 to 450 mg QD for 10 days.[27] In this study, filgotinib inhibited IL-6 induced STAT1 phosphorylation according to a sigmoid Emax model. Estimated IC_{50} for IL-6 induced STAT1 phosphorylation was 293 ng/mL for the parent compound and 1686 ng/mL for the metabolite.

3.4. Pharmacodynamics

3.4.1. Efficacy

The efficacy of filgotinib for treatment of CD was evaluated in the phase 2 FITZROY study in which patients with active symptoms [CDAI 220–450] and centrally confirmed endoscopically active CD (Simple Endoscopic Score [SES]-CD ≥7, or ≥4 in the case of isolated ileitis) were enrolled.[61] Patients were randomised to treatment with filgotinib 200 mg QD or placebo for 10 weeks. At Week 10, clinical remission [CDAI <150] was achieved in 47% of patients treated with filgotinib compared with 23% of patients treated with placebo (difference 24%, 95% confidence interval [CI] 9–39; p = 0.0077). Endoscopic and biomarker-related results also supported the efficacy of filgotinib for treatment of moderate-to-severe CD. Although numerically higher, the rate of endoscopic improvement [defined as a 50% reduction in the SES-CD score] at Week 10 was not significantly higher in patients treated with filgotinib compared with patients treated with placebo [25% versus 14%, respectively]. Normalisation of both CRP and FC concentrations were more frequently observed in patients treated with filgotinib, compared with patients treated with placebo. A large phase 3 clinical development programme of filgotinib for the treatment of CD [NCT02914561 and NCT02914600][14,62] and UC [NCT02914535 and NCT02914522][62,63] is ongoing, as are dedicated trials for patients with perianal fistulising [NCT03077412],[64] and small bowel CD [NCT03046056].[65]

3.4.2. Safety

In the phase 2 FITZROY study,[61] patients who responded to filgotinib at Week 10, based on CDAI clinical responder status, were re-randomised to treatment with filgotinib 100 mg or 200 mg QD, or placebo, for an observational period of 10 weeks. No differences in rates of serious treatment-emergent AEs were observed compared with placebo after 20 weeks of filgotinib therapy, although serious infections [i.e., urinary tract infections, nasopharyngitis, pneumonia, herpes zoster, and oral candidiasis] were observed in four of 152 patients [3%] in the filgotinib group compared with none in the placebo group.[61] One case of herpes zoster was reported in the filgotinib group as a serious infection. No effect on biochemical or laboratory parameters was observed with filgotinib treatment.

3.5. Factors affecting filgotinib pharmacokinetics

3.5.1. Drug interactions

Potential drug interactions affecting the PK and/or PD of filgotinib and its metabolite remain to be investigated. Theoretically, co-administration of drugs inhibiting or activating carboxylesterase-2[59] may affect the concentrations of filgotinib and its active metabolite.

3.5.2. Renal impairment

The PK profile of filgotinib was evaluated in a phase 1 study that included patients with normal, mild (estimated glomerular filtration rate [eGFR] 60–89 mL/min 1.73/m^2), moderate [eGFR: 30–59 mL/min 1.73/m^2] and severe [eGFR > 15 and ≤29 mL/min 1.73/ m^2] renal impairment. Patients received 100 mg filgotinib QD for 10 days.[66] Renal CL of filgotinib and its metabolite decreased with the severity of renal impairment; CL in patients with severe renal impairment [0.898 L/h] was 80% lower than that observed for subjects with normal renal function [4.45 L/h]. At steady state, AUC_{0-24h} was increased 1.54-fold for filgotinib and 2.74-fold for its metabolite in patients with severe renal impairment. Severity of renal impairment had no effect on C_{max} of filgotinib, whereas C_{max} for the metabolite was increased 2.17-fold in patients with severe renal impairment. Minimal effects on exposure [C_{max} and AUC_{0-24h}] to filgotinib or its metabolite were observed in patients with mild and moderate renal impairment; AUC_{0-24h} was increased 1.67-fold for the metabolite in patients with moderate renal impairment. Filgotinib dose adjustments may be considered in patients with moderate and severe renal impairment.

3.5.3. Hepatic impairment

One phase 1 clinical trial has been conducted to evaluate the effect of mild [Child-Pugh score 5–6 points; Class A], moderate [Child-Pugh score 7–9 points; Class B], and severe [Child-Pugh score 10–15 points; Class C] hepatic impairment on the PK profile of filgotinib. Patients received a single dose of 100 mg filgotinib. The AUCs for filgotinib and its metabolite were increased 1.6-fold and 1.2-fold, respectively, in patients with moderate hepatic impairment compared with healthy subjects.[67] No dose adjustment has been recommended for filgotinib for patients with mild or moderate hepatic impairment. No data for patients with severe hepatic impairment are currently available.

4. TD-1473

4.1. Chemistry and administration

TD-1473 [JNJ-8398] is a intestinally-restricted pan-JAK inhibitor that was developed for oral administration in patients with moderate-to-severe UC.[68] The molecular weight and structure of TD-1473 are currently not publicly available.

4.2. Target specificity

TD-1473 demonstrates inhibitory potencies similar to what has been reported for tofacitinib in cellular assays. In human PBMCs and colonic epithelial cell lines, TD-1473 inhibited cytokine-induced STAT phosphorylation with a $pIC_{50} \geq 6.7$ [or $IC_{50} \leq 200$ nM].[69] The of IC_{50} observed values for JAK1/JAK3 and TYK2 were reported to be in the range of 32–158 nM, with limited selectivity.[70] Of note, TD-1473 selectivity for JAK1 was shown to be >100 fold relative to TD-1473 off-target activity.[69]

4.3. Pharmacokinetics

Systemic exposure of TD-1473 [1 mg/kg] was approximately 1000-fold lower than that observed with tofacitinib [15 mg/kg] in a murine oxazolone-induced colitis model orally dosed with either of TD-1473 or of tofacitinib, confirming low systemic exposure [and potentially gut-restricted absorption] of TD-1473.[69]

Non-compartmental PK analyses of TD-1473 were conducted on PK data collected from healthy subjects randomised to receive a single TD-1473 dose ranging from 10 to 1000 mg or multiple ascending doses ranging from 10 to 300 mg over 14 days.[71] As expected, TD-1473 exhibited low systemic exposure, given that this molecule is intestinally-restricted. TD-1473 is characterised by a multiphasic and dose-proportional PK profile. Apparent mean terminal elimination half-life ranges from ~4 to 44 h. Accumulation ratios of C_{max} and $AUC_{0\text{-}24}$ from Day 1 to Day 14 ranged from 0.5 to 2.3 and 1.4 to 1.6, respectively, with minimal accumulation of TD-1473. Steady-state levels were achieved after ~9 days of dosing, and CL/F and V/F ranged from 5519 to 8662 L/h and 113 500 and 571 399 L, respectively. Less than 0.5% of TD-1473 was eliminated in the urine.

The PK profile of TD-1473 was also investigated in patients with moderate- to- severe active UC who received QD doses ranging from 20 to 270 mg.[70] Plasma exposure was low [C_{trough} ranged from 0.20 to 1.074 nM with ascending doses], specifically when compared with systemic tofacitinib exposure measured in patients with UC who received BID doses ranging from 0.5 to 15 mg [C_{trough} ranged from 0 to 20 ng/mL or 0 to 64 nM].[26] Colonic tissue concentrations of TD-1473 were expectedly higher than plasma [range from 10 to 160 nM with ascending doses] and were in the necessary range for JAK inhibition [IC_{50} = 32–158 nM for TD-1473-induced JAK1/JAK3 inhibition].[68]

Two clinical trials have been conducted to determine TD-1473 absorption, distribution, metabolism, and elimination in healthy subjects [NCT03408470] and food-effect and drug-drug interaction [NCT03555617]. Although these trials were completed in 2018, no data are currently publicly available.

4.4. Pharmacodynamics

4.4.1. Efficacy

The efficacy of TD-1473 for the treatment of moderate-to-severe active UC was investigated in one phase 1b study.[70] Patients received doses of TD-1473 ranging from 20 to 170 mg QD over 28 days. Trends for higher rates of mucosal healing and improvement ≥1 point on the Mayo Clinic rectal bleeding score and endoscopy subscore at Day 28 were observed in patients treated with TD-1473 compared with those treated with placebo.[70,72] A dose-related reduction in the Robarts Histological Index was observed in patients treated with 20 and 270 mg of TD-1473 for Day 28.[72] Although highly variable, overall concentrations of CRP and FC decreased in patients treated with TD-1473, compared with those treated with placebo.[70,72] Consistent with TD-1473's intestinal-restriction, clinical and histopathological outcomes following TD-1473 therapy were accompanied by molecular effects observed in colonic biopsies. Statistically significant reductions in the levels of phosphorylated colonic-STAT1 and STAT3 were observed in samples from patients treated with the highest TD-1473 dose [270 mg], and modifications in the tissue UC-transcriptomic signature were observed with TD-1473 treatment.[72]

Of note, a phase 3 study assessing the safety and efficacy of TD-1473 in patients with moderate-to-severe UC [Study RHEA, NCT03758443], a long-term safety study of TD-1473 in patients with moderate-to-severe UC [NCT03920254], and an efficacy and safety study of TD-1473 for treatment of patients with CD [study DIONE, NCT03635112] are currently ongoing.

4.4.2. Safety

No moderate, severe or serious treatment-emergent adverse events [TEAEs] were observed in healthy subjects randomised to receive a single TD-1473 dose ranging from 10 to 1000 mg or multiple ascending doses ranging from 10 to 300 mg over 14 days.[71] The incidence of TEAEs was higher in patients treated with placebo compared with patients treated with TD-1473 [40% versus 33% in the single-dose study and 88% versus 58% in the multiple-dose study]. No clinically relevant treatment-related effects on vital signs, clinical laboratory, or electrocardiogram parameters were reported in healthy subjects.[71] Similarly, no major safety concerns were observed in a phase 1b study involving patients with UC other than two serious TEAEs related to UC disease exacerbation [hospitalisation] in two patients, one each in the 20 mg and 80 mg treatment groups.[68,70] No cases of serious or opportunistic infection or signals for abnormalities in haematological or chemistry laboratory parameters were reported in this study.[68,70]

4.5. Factors affecting pharmacokinetics

There are no data currently available on potential drug interactions or the effect of renal or hepatic impairment on TD-1473 PK.

5. Upadacitinib

5.1. Chemistry and administration

Upadacitinib [ABT-494] has a molecular weight of 389.38 g/mol and a molecular formula of $C_{17}H_{19}F_3N_6O \bullet ½\ H2O$.[73] A tablet formulation of upadacitinib was developed for oral administration and

has received regulatory approval for the treatment of adults with moderately-to-severely active rheumatoid arthritis who have had an inadequate response or intolerance to treatment with methotrexate.[73,74] Upadacitinib is currently being evaluated in clinical trials for the treatment of adult patients with UC or CD.

5.2. Target specificity

Upadacitinib was engineered for increased selectivity for JAK1, using structural predictions indicating the potential for differential binding interactions outside the ATP-binding active site of JAK1 [in preference to JAK2 and JAK3].[75] In a cell-free enzyme assay, upadacitinib inhibited JAK1 with an IC_{50} of 43 nM and, to a minor extent, JAK2 [IC_{50} = 120 nM], but with greater potency than JAK3 [IC_{50} = 2.3 μM] or TYK2 [IC_{50} = 4.7 μM].[76] In cellular assays dependent on specific relevant cytokines [IL-6 for JAK1 activation, erythropoietin for JAK 2 activation, and IL-2, 4 and 15 for JAK3 activation], upadacitinib was approximately >60 fold more selective for JAK1 than for JAK2[75,77] and >100 fold more selective than for JAK3.[77] In human cell-based assays to measure upadaticinib-mediated inhibition of STAT phosphorylation, inhibition of JAK1/JAK1 [EC_{50} = 9 nM] and JAK1/JAK3 [EC_{50} = 5013 nM] signalling was potently greater than JAK2/JAK2 signalling [EC_{50} = 628 nM].[76] Upadaticinib specificity for JAK1/JAK3 was also observed in human PBMCs, primarily in CD4 + T cells and NK cells, and to a minor extent, in monocytes.[34] Upon stimulation with the JAK1/JAK3-dependent cytokines IL-2, IL-4, IL-15, and IL-21, upadacitinib IC_{50} values were 10, 18, 17, and 20 nM in CD4 + T cells and 27, 8, 40, and 24 nM in NK cells, respectively.

5.3. Pharmacokinetics

The PK profile of upadacitinib was investigated in a phase 1 clinical trial in which healthy subjects were administered single upadacitinib doses ranging from 1 to 48 mg and multiple ascending doses ranging from 3 to 24 mg given BID for 13 consecutive days.[29] Upadacitinib was rapidly absorbed after oral administration, with a T_{max} of 1 to 2 hours. Upadacitinib concentrations then decreased bi-exponentially, with a functional half-life of ~4 h.[29] Steady-state upadacitinib trough concentrations were achieved within 4 days, and minimal drug accumulation was detected across the 3 to 24 mg dose range when administered BID for 13 days. Upadacitinib's PK profile was dose-proportional over single doses ranging from 3 to 36 mg and multiple doses ranging from 3 to 24 mg BID.[29] Upadacitinib is subject primarily to hepatic metabolism [80%], mediated mostly by CYP3A4, and by CYP2D6 to a minor extent.[29] Approximately 24% and 38% of the drug is eliminated unchanged in urine and faeces, respectively.[29,73] No active metabolites of upadacitinib have been identified.[73]

Upadacitinib's PK profile in healthy subjects was well described by a two-compartment model with first-order absorption and elimination when using data from a phase 1 clinical trial.[28,29] Population parameters were estimated to be 0.48 h for absorption lag time, 12.3 h^{-1} for Ka, 210 L for apparent steady state V/F, and 39.7 L/h for CL/F. Significant covariates included sex [CL/F and Vc/F], creatinine clearance [CL/F], and body weight [Vc/F]. Inter-subject variability was 150% for Ka, 14% for V/F, and 16% for CL/V.[28] An exposure-response model was also developed in which the effects of varying doses of upadacitinib on ex vivo marker responses [IL-6 induced phosphorylated STAT3 and IL-7-induced phosphorylated STAT5] in blood samples were simulated.[39] Upadacitinib reversibly inhibited IL-6 induced phosphorylated STAT3 and IL-7 induced phosphorylated STAT5 in a concentration-dependent manner in this study. Estimated IC_{50} were of 60.7 nM for IL-6 induced phosphorylated STAT3 and 125 nM for IL-7-induced phosphorylated STAT5.

5.4. Pharmacodynamics

5.4.1. Efficacy

The efficacy of upadacitinib for the treatment of CD and UC was evaluated in two phase 2 clinical trials. The CD CELEST study randomised 220 patients with moderate-to-severe disease to treatment with an IR formulation of upadacitinib [3 mg, 6 mg, 12 mg, and 24 mg BID and 24 mg QD] or placebo for 16 weeks.[78,79] The co-primary endpoints included endoscopic remission [SES-CD ≤4 and ≥2 point reduction from baseline with no subscore >1] at Week 12 or Week 16, and clinical remission [Mayo Clinic stool frequency ≤1.5 and abdominal pain scores both ≤1 and both not worse than baseline] at Week 16. The rate of clinical remission was significantly higher in patients receiving upadacitinib 6 mg BID compared with placebo. Rates of endoscopic remission were significantly higher in patients receiving 3, 12, and 24 mg upadacitinib BID and 24 mg QD upadacitinib compared with placebo. A significant upadacitinib dose-response relationship was observed for the treatment outcome of endoscopic, but not clinical remission.[79] Early and significant effects of upadacitinib on clinical outcomes were demonstrated in the CELEST study.[80] Modified clinical remission (average daily liquid/very soft stool frequency [SF] ≤2.8 or daily abdominal pain score [AP] ≤1), and enhanced clinical response [≥60% reduction from baseline in SF or ≥35% reduction from baseline in AP and both not worse than at baseline or clinical remission] were observed in patients treated with upadacitinib as early as Week 4 and Week 8, respectively, compared with those treated with placebo, and both clinical endpoints were sustained in all upadacitinib dose groups for up to 16 weeks.[80] Significant decreases in mean CRP concentrations from baseline to Week 2 and in FC concentrations from baseline to Week 4, respectively were observed in the 12 and 24 mg upadacitinib treatment groups, and were sustained for up to 16 weeks. In Week 16 responders, dose-dependent increases in the rates of modified clinical remission and endoscopic remission were observed at Week 52 in the 3, 6, and 12 mg BID treatment arms.[81] Transcriptomic analyses of ileal or colonic biopsies, collected from patients enrolled in the CELEST study at Week 12 or 16, indicated that upadacitinib induces significant changes in the intestinal transcriptome of patients with CD, in comparison with patients with CD treated with placebo.[82] An exposure-response modelling analysis was conducted using data generated in the CELEST study.[83] Increasing estimates of upadacitinib exposure resulting from 18 to 24 mg BID dosing in patients with CD were associated with: improved efficacy [≥30% reduction from baseline in very soft/liquid SF and/or AP score, neither worse than baseline]; clinical remission [very soft/liquid SF ≤2·8 and AP score ≤1·0, neither worse than baseline, among patients with baseline very soft/liquid SF >4·0 or AP score >2·0] and CDAI <150 observed at Week 16; and with endoscopic response 25% [≥25% decrease in SES-CD from baseline], endoscopic response 50% [>50% decrease in SES-CD from baseline], or endoscopic remission [SES-CD ≤4 and ≥2 point reduction from baseline with no subscore >1] observed at Weeks 12 and 16.

ACHIEVE-UC was a dose-ranging [7.5 mg, 15 mg, 30 mg, 45 mg QD of an **XR** formulation of upadacitib], placebo-controlled 8-week study in 250 patients with moderate-to-severe UC.[84] The primary objective of this trial, a statistically significant upadacitinib dose-response relationship for achieving clinical remission at Week 8 compared with placebo, was achieved. The highest clinical remission rate was observed with 45 mg upadacitinib QD [19.6% in the 45 mg

upadacitinib QD group versus 0% in the placebo group]. In addition, the proportion of patients achieving endoscopic improvement, endoscopic remission, histological improvement, histological remission, and mucosal healing was statistically significantly higher in patients treated with 30 and 45 mg QD upadacitinib compared with patients treated with placebo.[85] Data generated in the ACHIEVE-UC study were used to conduct an exposure-response analysis.[86] A significant exposure-response relationship was observed between upadacitinib and the percentage of subjects achieving clinical response per adapted Mayo score, clinical remission per adapted and full Mayo score, endoscopic improvement, and endoscopic remission, observed at Week 8.[86]

5.4.2. Safety

Upadacitinib was well tolerated compared with placebo in healthy subjects administered single doses ranging from 1 to 48 mg or repeated ascending doses ranging from 3 to 24 mg BID for 14 days.[29] Reported AE frequency was comparable between subjects treated with upadacitinib and those treated with placebo. No serious infections, nor clinically significant changes in haematology, hepatobiliary, or renal laboratory metrics, were observed with 14 days of repeated upadacitinib dosing in healthy subjects.[29] No exposure-response relationships were observed at Week 16 for safety outcomes such as decreases in haemoglobin or lymphocytes, or for the occurrence of herpes zoster infections, pneumonia, or serious infections.[83] In the CELEST study, the rates of any AE were similar between patients treated with upadacitinib or placebo after over a 16-week induction period,[78,79] and for up to 52 weeks [although, this study lacked a placebo group, and two intestinal perforations were observed in patients treated with the highest upadacitinib dose [one each in the 24 mg BID and 24 mg QD groups].[79,81] In the UC-ACHIEVE phase 2 study, the overall incidence of AEs and AEs leading to discontinuation at Week 8was similar across upadacitinib treatment groups, and numerically higher in the placebo group.[84] Rates of serious AEs were 10.9%, 0%, 4.1%, 5.8%, and 5.4%, in which UC worsening was reported in 4.3%, 0%, 2.1%, 5.8%, and 1.8%, respectively, for placebo, 7.5, 15, 30, and 45 mg QD, respectively.

The positive efficacy signal and favourable tolerability and safety profile support further evaluation of upadacitinib in a phase 3 programme for the treatment of UC [NCT03006068, NCT03653026, and NCT02819635] and CD [NCT03345836, NCT03345823, NCT02782663, NCT03345849, NCT02365649].

5.5. Factors affecting pharmacokinetics

There are currently no data available on the effect of renal or hepatic impairment on the PK of upadacitinib.

5.5.1. Drug interactions

Given that upadacitinib undergoes hepatic metabolism primarily by CYP3A4,[73] co-administration of CYP3A4 inhibitors or inducers may affect systemic upadacitinib exposure. Two phase 1 studies were conducted to evaluate the effect of co-administration of ketoconazole [strong CYP3A4 inhibitor] 400 mg QD for 6 days and rifampin [strong CYP3A4 inducer] 600 mg QD for 9 days, on upadacitinib exposure in healthy subjects receiving daily doses of 3 mg upadacitinib.[87] Co-administration of ketoconazole increased upadacitinib C_{max} and AUC by 70% and 75%, respectively, whereas rifampin co-administration decreased upadacitinib C_{max} and AUC by approximately 50% and 60%, respectively. Caution is recommended for co-administration of CYP3A4 inhibitors, and co-administration CYP3A4 inducers is not recommended with upadacitinib.[73]

6. PF-06700841

6.1. Chemistry and administration

PF-06700841 is administered orally as a tablet and has a molecular weight of 389.40 and a molecular formula of $C_{18}H_{21}F_2N_7O$.[88]

6.2. Target specificity

PF-06700841 is a selective JAK1 and TYK2 inhibitor [IC_{50} 17 nM and 23 nM, respectively,] compared with an IC_{50} of 77 nM for JAK2, as assessed in a cell-free assay.[89]

6.3. Pharmacokinetics

The PK of PF-06700841 was assessed in a first-in-human study in healthy subjects and patients with plaque psoriasis. Time at maximal concentration [T_{max}] was achieved at ≤1 to 1.5 h following administration of single oral and multiple 10 to 175 mg doses of PF-06700841 QD, with high-fat meals delaying T_{max} by ~4 h.[90] Steady state was reached by Day 8 regardless of dose administered, and mean half-life ranged from 3.8 to 7.5 h after a single dose and from 4.9 to 10.7 h after multiple-dose administration. Proportional increases in AUC_{inf} and C_{max} were observed with doses up to 100 mg. Clearance was mediated primarily by hepatic metabolism [84%] and renal elimination [16%].

6.4. Pharmacodynamics

The efficacy and safety of PF-06700841 are currently being evaluated for the treatment of moderate-to-severe UC or CD along with a second compound, PF-06651600 [another JAKi discussed below] [NCT02958865 for UC and NCT03395184 for CD, respectively]. Concentrations of the biomarkers interferon gamma-induced protein 10 [IP-10; biomarker for inhibition of IFN signalling via JAK1 inhibition] and CRP [measured with a high-sensitivity assay] were reduced and returned to near baseline levels at the end of treatment in a first-in-human study involving healthy subjects and patients with plaque psoriasis.[90] No deaths or serious AEs were reported, and all AEs were mild or moderate in severity. Increases in serum creatinine were observed during the study and are related to the potential for PF-06700841 mediated inhibition of the renal transporter organic cation transporter 2 [OCT2], for which creatinine is a substrate. Six patients experienced this AE during the study, which led to discontinuation of PF-06700841, although no exacerbation of clinical symptoms was reported in these patients. Three upper respiratory tract and one herpes zoster infection were reported in patients treated with PF-06700841 during the study. None of these was considered treatment-related by the investigator; however, causality could not be definitely excluded.

Reticulocyte and neutrophil counts were reduced in healthy subjects and patients with psoriasis during treatment with multiple 100 mg and 175 mg doses of PF-06700841, and increased to baseline levels within 7 days after dosing.[90] A reduction in platelet count was also observed in patients with psoriasis treated with QD 100 mg PF-06700841. The observed decreases in reticulocyte and platelet counts are consistent with inhibition of the erythropoietin-JAK2 pathway.[18]

6.5. Factors affecting pharmacokinetics

There are currently no data available on the effect of renal or hepatic impairment on the PK of PF-06700841,

6.5.1. Drug interactions

Co-administration of CYP3A4 inhibitors and inducers may affect systemic exposure of PF-06700841, given that this molecule primarily undergoes CYP3A4-mediated hepatic metabolism.[89]

7. PF-06651600

7.1. Chemistry and administration

PF-06651600 is administered orally as a tablet and has a molecular weight of 285.34 and a molecular formula of $C_{15}H_{19}N_5O$.[91]

7.2. Target specificity

PF-06651600 is a selective JAK3 inhibitor with IC_{50} of 33.1 nM and with no activity [IC_{50} >10 000 nM] against JAK1, JAK2, and TYK2.[92] This selectivity for JAK3 over other JAK isoforms is achieved by irreversible covalent binding.

7.3. Pharmacokinetics

PF-06651600 is the first compound with acceptable PK/PD properties, whicht irreversibly inhibits JAK3 through covalent binding. The half-life for JAK3 turnover in vitro in human primary CD4 + T cells was in the 3–4 h range, suggesting that irreversible JAK3 binding would not lead to a significantly extended pharmacodynamic effect.[92]

7.4. Pharmacodynamics

As previously mentioned, PF-06651600 is currently being evaluated for efficacy and safety with PF-06700841 in patients with moderate-to-severe UC or CD. To date no information is available on the clinical safety and efficacy profile of PF-06651600.

7.5. Factors affecting pharmacokinetics

There are currently no date available on the effect of renal or hepatic impairment on the PK of PF-06651600.

7.5.1. Drug interactions

Metabolism of PF-06651600 is mediated by both CYP450 and glutathione-S-transferase [GST] enzymes.[92]

8. Discussion

Several JAKi have shown promise for induction and maintenance of remission in patients with moderate-to-severe UC and CD. This drug class may constitute a convenient alternative to monoclonal antibody therapy in patients with IBD, given that these compounds are orally bioavailable and characterised by low inter-subject PK variability. Similar to monoclonal antibodies, not all patients will respond to therapy, and some patients may experience serious AEs. Additionally, although data suggest that selected patients may benefit from higher doses, the trade-off in terms of safety risk associated with higher doses should be considered, as adverse events [such as infections, thrombotic events, and intestinal perforations] were reported in patients administered JAKi. Exposure to JAKi is increased in patients with renal or hepatic impairment and requires specific dose adjustment. Multiple questions remain regarding the mechanism of action of JAKi in IBD, the potential benefits of selective JAKi, and the extent to which drug exposure on a systemic and/or local level contributes to either safety or efficacy outcomes. Gut-restricted compounds with high tissue and low systemic drug exposure are in development and being evaluated. Prospective observational studies focusing on the clinical pharmacology of JAKi may help to identify a predictive biomarker signature for response that will aid in the selection of the optimal drug and dose for maximal overall benefit [efficacy versus safety] for patients with IBD.

Funding

NVC holds a Research Scholar Award from the American Gastroenterological Association

Conflict of Interest

PLCL has no conflict of interest to declare; NVC has received consulting fees from Janssen, Pfizer, Progenity, Prometheus, Takeda, and UCB, and grant/research support from R-Biopharm, Takeda, and UCB.

Acknowledgments

The authors would like to thank Lisa Shackelton, PhD [Robarts Clinical Trials] for technical review and editing, and Tran Nguyen [Robarts Clinical Trials] for editorial assistance with the manuscript.

References

1. Molodecky NA, Soon IS, Rabi DM, *et al.* Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012;**142**:46–54.e42; quiz e30.
2. Neurath MF. Cytokines in inflammatory bowel disease. *Nat Rev Immunol* 2014;**14**:329–42.
3. Park JH, Peyrin-Biroulet L, Eisenhut M, Shin JI. IBD immunopathogenesis: A comprehensive review of inflammatory molecules. *Autoimmun Rev* 2017;**16**:416–26.
4. Hemperly A, Sandborn WJ, Vande Casteele N. Clinical pharmacology in adult and pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 2018;**24**:2527–42.
5. Frolkis AD, Dykeman J, Negrón ME, *et al.* Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. *Gastroenterology* 2013;**145**:996–1006.
6. Hindryckx P, Novak G, Vande Casteele N, *et al.* Incidence, prevention and management of anti-drug antibodies against therapeutic antibodies in inflammatory bowel disease: a practical overview. *Drugs* 2017;**77**:363–77.
7. Pouillon L, Bossuyt P, Peyrin-Biroulet L. Considerations, challenges and future of anti-TNF therapy in treating inflammatory bowel disease. *Expert Opin Biol Ther* 2016;**16**:1277–90.
8. Gisbert JP, Panés J. Loss of response and requirement of infliximab dose intensification in Crohn's disease: a review. *Am J Gastroenterol* 2009;**104**:760–7.
9. Billioud V, Sandborn WJ, Peyrin-Biroulet L. Loss of response and need for adalimumab dose intensification in Crohn's disease: a systematic review. *Am J Gastroenterology* 2011;**106**:674–84.
10. Steenholdt C, Brynskov J, Thomsen OØ, *et al.* Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. *Gut* 2014;**63**:919–27.
11. Lefevre PLC, Shackelton LM, Vande Casteele N. Factors influencing drug disposition of monoclonal antibodies in inflammatory bowel disease: implications for personalized medicine. *BioDrugs* 2019;**33**:453–68.
12. Ma C, Battat R, Jairath V, Vande Casteele N. Advances in therapeutic drug monitoring for small-molecule and biologic therapies in inflammatory bowel disease. *Curr Treat Options Gastroenterol* 2019;**17**:127–45.

13. Pérez-Jeldres T, Tyler CJ, Boyer JD, *et al*. Targeting cytokine signaling and lymphocyte traffic via small molecules in inflammatory bowel disease: JAK inhibitors and s1pr agonists. *Front Pharmacol* 2019;**10**:212.
14. Ma C, Jairath V, Vande Casteele N. Pharmacology, efficacy and safety of JAK inhibitors in Crohn's disease. *Best Pract Res Clin Gastroenterol* 2019;**38-9**:101606.
15. FDA. *Xeljanz [package insert]*. New York, NY: Pfizer; 2018.
16. EMA. *Summary of Product Characteristics - Xeljanz*. https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf Accessed October 31, 2019.
17. Morris R, Kershaw NJ, Babon JJ. The molecular details of cytokine signaling via the JAK/STAT pathway. *Protein Sci* 2018;**27**:1984–2009.
18. Salas A, Hernandez-Rocha C, Duijvestein M, *et al*. JAK-STAT pathway targeting for the treatment of inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol* 2020. In press.
19. Boland BS, Vermeire S. Janus kinase antagonists and other novel small molecules for the treatment of Crohn's disease. *Gastroenterol Clin North Am* 2017;**46**:627–44.
20. Coskun M, Salem M, Pedersen J, Nielsen OH. Involvement of jak/stat signaling in the pathogenesis of inflammatory bowel disease. *Pharmacol Res* 2013;**76**:1–8.
21. Banerjee S, Biehl A, Gadina M, Hasni S, Schwartz DM. JAK-stat signaling as a target for inflammatory and autoimmune diseases: current and future prospects. *Drugs* 2017;**77**:521–46.
22. Anderson CA, Boucher G, Lees CW, *et al*. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. *Nat Genet* 2011;**43**:246–52.
23. Barrett JC, Hansoul S, Nicolae DL, *et al*.; NIDDK IBD Genetics Consortium; Belgian-French IBD Consortium; Wellcome Trust Case Control Consortium. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat Genet* 2008;**40**:955–62.
24. Franke A, Balschun T, Karlsen TH, *et al*. Replication of signals from recent studies of Crohn's disease identifies previously unknown disease loci for ulcerative colitis. *Nat Genet* 2008;**40**:713–5.
25. Olivera P, Danese S, Peyrin-Biroulet L. Next generation of small molecules in inflammatory bowel disease. *Gut* 2017;**66**:199–209.
26. Mukherjee A, Hazra A, Smith MK, *et al*. Exposure-response characterization of tofacitinib efficacy in moderate to severe ulcerative colitis: results from a dose-ranging phase 2 trial. *Br J Clin Pharmacol* 2018;**84**:1136–45.
27. Namour F, Diderichsen PM, Cox E, *et al*. Pharmacokinetics and pharmacokinetic/pharmacodynamic modeling of filgotinib [glpg0634], a selective JAK1 inhibitor, in support of phase IIb dose selection. *Clin Pharmacokinet* 2015;**54**:859–74.
28. Klünder B, Mohamed MF, Othman AA. Population pharmacokinetics of upadacitinib in healthy subjects and subjects with rheumatoid arthritis: analyses of phase I and II clinical trials. *Clin Pharmacokinet* 2018;**57**:977–88.
29. Mohamed MF, Camp HS, Jiang P, Padley RJ, Asatryan A, Othman AA. Pharmacokinetics, safety and tolerability of ABT-494, a novel selective JAK 1 inhibitor, in healthy volunteers and subjects with rheumatoid arthritis. *Clin Pharmacokinet* 2016;**55**:1547–58.
30. Changelian PS, Flanagan ME, Ball DJ, *et al*. Prevention of organ allograft rejection by a specific janus kinase 3 inhibitor. *Science* 2003;**302**:875–8.
31. PubChem. *Tofacitinib, cid=9926791,*. National Center for Biotechnology Information, 2019. https://pubchem.ncbi.nlm.nih.gov/compound/9926791. Accessed February 24, 2020.
32. Kim S, Chen J, Cheng T, *et al*. PubChem 2019 update: improved access to chemical data. *Nucleic Acids Res* 2019;**47**:D1102–9.
33. Van Rompaey L, Galien R, van der Aar EM, *et al*. Preclinical characterization of glpg0634, a selective inhibitor of JAK1, for the treatment of inflammatory diseases. *J Immunol* 2013;**191**:3568–77.
34. McInnes IB, Byers NL, Higgs RE, *et al*. Comparison of baricitinib, upadacitinib, and tofacitinib mediated regulation of cytokine signaling in human leukocyte subpopulations. *Arthritis Res Ther* 2019;**21**:183.
35. Dowty ME, Lin J, Ryder TF, *et al*. The pharmacokinetics, metabolism, and clearance mechanisms of tofacitinib, a janus kinase inhibitor, in humans. *Drug Metab Dispos* 2014;**42**:759–73.
36. FDA. *Clinical Pharmacology and Biopharmaceutics Review[s]: Application number: 203214orig1s000 [tofacitinib-xeljanz]*. 2011. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=2ahUKEwiS6Kb95ernAhXF854KHUyNAhkQFjAAegQIAhAB&url=https%3A%2F%2Fwww.accessdata.fda.gov%2Fdrugsatfda_docs%2Fnda%2F2012%2F203214Orig1s000ClinPharmR.pdf&usg=AOvVaw1gwyJ9oxxXkyQg2gLTBvn6.
37. Gupta P, Stock T, Wang R, *et al*. A phase 1 study to estimate the absolute oral bioavailability of tofacitinib [cp-690,550] in healthy subjects [abstract 1122902]. *J Clin Pharmacol* 2001;**51**:1348.
38. Lamba M, Wang R, Fletcher T, Alvey C, Kushner J 4th, Stock TC. Extended-release once-daily formulation of tofacitinib: evaluation of pharmacokinetics compared with immediate-release tofacitinib and impact of food. *J Clin Pharmacol* 2016;**56**:1362–71.
39. Mohamed MF, Beck D, Camp HS, Othman AA. Preferential inhibition of JAK1 relative to JAK3 by upadacitinib: exposure-response analyses of ex vivo data from 2 phase 1 clinical trials and comparison to tofacitinib. *J Clin Pharmacol* 2020;**60**:188–97.
40. Sandborn WJ, Ghosh S, Panes J, *et al*.; Study A3921063 Investigators. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. *N Engl J Med* 2012;**367**:616–24.
41. Sandborn WJ, Su C, Sands BE, *et al*.; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2017;**376**:1723–36.
42. Panés J, Sandborn WJ, Schreiber S, *et al*. Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two phase IIb randomised placebo-controlled trials. *Gut* 2017;**66**:1049–59.
43. Ma C, Lee JK, Mitra AR, *et al*. Systematic review with meta-analysis: efficacy and safety of oral janus kinase inhibitors for inflammatory bowel disease. *Aliment Pharmacol Ther* 2019;**50**:5–23.
44. Winthrop KL, Melmed GY, Vermeire S, *et al*. Herpes zoster infection in patients with ulcerative colitis receiving tofacitinib. *Inflamm Bowel Dis* 2018;**24**:2258–65.
45. Sandborn WJ, Panés J, D'Haens GR, *et al*. Safety of tofacitinib for treatment of ulcerative colitis, based on 4.4 years of data from global clinical trials. *Clin Gastroenterol Hepatol* 2019;**17**:1541–50.
46. Verden A, Dimbil M, Kyle R, Overstreet B, Hoffman KB. Analysis of spontaneous postmarket case reports submitted to the FDA regarding thromboembolic adverse events and JAK inhibitors. *Drug Saf* 2018;**41**:357–61.
47. Desai RJ, Pawar A, Weinblatt ME, Kim SC. Comparative risk of venous thromboembolism with tofacitinib versus tumor necrosis factor inhibitors: a cohort study of rheumatoid arthritis patients. *Arthritis Rheum* 2019;**71**:892–900. doi: 10.1002/art.40798.
48. Scott IC, Hider SL, Scott DL. Thromboembolism with janus kinase [jak] inhibitors for rheumatoid arthritis: how real is the risk? *Drug Saf* 2018;**41**:645–53.
49. Cohen SB, Tanaka Y, Mariette X, *et al*. Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. *Ann Rheum Dis* 2017;**76**:1253–62.
50. Clowse ME, Feldman SR, Isaacs JD, *et al*. Pregnancy outcomes in the tofacitinib safety databases for rheumatoid arthritis and psoriasis. *Drug Saf* 2016;**39**:755–62.
51. Mahadevan U, Dubinsky MC, Su C, *et al*. Outcomes of pregnancies with maternal/paternal exposure in the tofacitinib safety databases for ulcerative colitis. *Inflamm Bowel Dis* 2018;**24**:2494–500.
52. Gupta P, Chow V, Wang R, *et al*. Evaluation of the effect of fluconazole and ketoconazole on the pharmacokinetics of tofacitinib in healthy adult subjects. *Clin Pharmacol Drug Dev* 2014;**3**:72–7.
53. Lamba M, Wang R, Kaplan I, *et al*. The effect of rifampin on the pharmacokinetics of tofacitinib [cp-690,550] in healthy volunteers [abstract pi-73]. *Clin Pharmacol Ther* 2012;**91**:35.
54. Krishnaswami S, Chow V, Boy M, Wang C, Chan G. Pharmacokinetics of tofacitinib, a janus kinase inhibitor, in patients with impaired renal function and end-stage renal disease. *J Clin Pharmacol* 2014;**54**:46–52.
55. Lawendy N, Lamba M, Chan G, Wang R, Alvey CW, Krishnaswami S. The effect of mild and moderate hepatic impairment on the pharmacokinetics of tofacitinib, an orally active Janus kinase inhibitor. *Clin Pharmacol Drug Dev* 2014;**3**:421–7.

56. PubChem. *Filgotinib, cid=49831257*. National Center for Biotechnology Information. 2019. https://pubchem.ncbi.nlm.nih.gov/compound/Filgotinib. Accessed February 24, 2020.
57. Galien R, Vayssiere B, de Vos S, *et al*. Analysis of the JAK1 selectivity of glpg0634 and its main metabolite in different species, healthy volunteers and rheumatoid arthritis patients. *Arthritis Rheum* 2013;**65**:S209–S10.
58. Namour F, Desrivot J, Van der Aa A, Harrison P, Tasset C, van't Klooster G. Clinical confirmation that the selective JAK1 inhibitor filgotinib [glpg0634] has a low liability for drug-drug interactions. *Drug Metab Lett* 2016;**10**:38–48.
59. Wang D, Zou L, Jin Q, Hou J, Ge G, Yang L. Human carboxylesterases: a comprehensive review. *Acta Pharm Sin B* 2018;**8**:699–712.
60. Anderson K, Zheng H, Kotecha M, *et al*. The Relative bioavailability and effects of food and acid-reducing agents on filgotinib tablets in healthy subjects. *Clin Pharmacol Drug Dev* 2019;**8**:585–94.
61. Vermeire S, Schreiber S, Petryka R, *et al*. Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib [the Fitzroy study]: results from a phase 2, double-blind, randomised, placebo-controlled trial. *Lancet* 2017;**389**:266–75.
62. ClinicalTrials.gov. *Filgotinib in Long-term Extension Study of Adults With Crohn's Disease*. Bethesda, MD: National Library of Medicine (US). 2016. https://clinicaltrials.gov/ct2/show/NCT02914600. Accessed February 24, 2020.
63. ClinicalTrials.gov. *Filgotinib in the Induction and Maintenance of Remission in Adults With Moderately to Severely Active Crohn's Disease*. Bethesda, MD: National Library of Medicine (US). 2016. https://clinicaltrials.gov/ct2/show/NCT02914561. Accessed February 24, 2020.
64. ClinicalTrials.gov. *Efficacy and Safety of Filgotinib in the Treatment of Perianal Fistulizing Crohn's Disease*. Bethesda, MD: National Library of Medicine (US). 2017. https://clinicaltrials.gov/ct2/show/NCT03077412. Accessed February 24, 2020.
65. ClinicalTrials.gov. *Efficacy and Safety of Filgotinib in the Treatment of Small Bowel Crohn's Disease [SBCD]*. Bethesda, MD: National Library of Medicine (US). 2017. https://clinicaltrials.gov/ct2/show/NCT03046056. Accessed February 24, 2020.
66. Namour F, Fagard L, Van der Aa A, Harrison P, Xin Y, Tasset C. Influence of age and renal impairment on the steady state pharmacokinetics of filgotinib, a selective JAK1 inhibitor. *Br J Clin Pharmacol* 2018;**84**:2779–89.
67. Anderson K, Zheng H, Medzihradsky O, *et al*. Thu0117: Pharmacokinetics and short-term safety of filgotininb, a selective janus kinase 1 inhibitor, in subjects with moderate hepatic impairment In: Annual European Congress of Rheumatology, 2019; Madrid, Spain.
68. Sandborn WJ, Bhandari R, Leighton J, *et al*. P041 the gut-selective, orally administered, pan-JAK inhibitor td-1473 demonstrates favorable safety, tolerability, pharmacokinetic, and signal for clinical activity in subjects with moderately-to-severely active ulcerative colitis. *Gastroenterology* 2019;**156**:S29–S30.
69. Beattie D, Tsuruda P, Shen F, *et al*. P069 TD-1473, a novel, potent, and orally administered, GI-targeted, pan-janus kinase [JAK] inhibitor. *J Crohns Colitis* 2016;**10**:S123.
70. Sandborn WJ, Bhandari R, Leighton JA, *et al*. The intestinally restricted, orally administered, pan-JAK inhibitor TD-1473 demonstrates favorable safety, tolerability, pharmacokinetics, and signal for clinical activity in subjects with moderately-to-severely active ulcerative colitis. *United European Gastroenterol J* 2018;**6**:1588–9.
71. Ferslew B, Graham R, Sherman C, Nguyen D. P469 safety, tolerability, and pharmacokinetics of the intestine-restricted oral pan-janus kinase inhibitor TD-1473 after single and multiple oral doses in healthy subjects. *J Crohns Colitis* 2017;**11**:S317–S8.
72. Sandborn WJ, Nguyen D, Ferslew B, *et al*. Dop53 clinical, endoscopic, histological and biomarker activity following treatment with the gut-selective, pan-JAK inhibitor TD-1473 in moderately to severely active ulcerative colitis. *J Crohns Colitis* 2019;**13**:S060–S1. doi: 10.1093/ecco-jcc/jjy222.087.
73. FDA. *Rinvoq [package insert]*. Chicago, IL: Abbvie; 2019.
74. EMA. *EMA/CHMP/521392/2019: Summary of Opinion [Initial Authorisation] for Rinvoq [Upadacitinib]*. Committee for Medicinal Products for Human Use [CHMP], 2019.
75. Graff C, Schwartz A, Voss J, *et al*. *Characterization of ABT-494, a second generation JAK1 selective inhibitor*. In: *ACR/ARHP Annual Meeting*; Nov 14, 2014; Boston, MA.£.
76. FDA. *Non-clinical review[s]-application number: 211675orig1s000 [upadacitinib]*. 2019. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=2ahUKEwjHh6D4guvnAhUWhHIEHQ3kDawQFjAAegQIBBAB&url=https%3A%2F%2Fwww.accessdata.fda.gov%2Fdrugsatfda_docs%2Fnda%2F2019%2F211675Orig1s000PharmR.pdf&usg=AOvVaw2NU6E635Un-oyrONtyug-Q.
77. Parmentier JM, Voss J, Graff C, *et al*. In vitro and in vivo characterization of the JAK1 selectivity of upadacitinib [ABT-494]. *BMC Rheumatol* 2018;**2**:23.
78. Panaccione R, Atreya R, Ferrante M, *et al*. P601 upadacitinib improves steroid-free clinical and endoscopic endpoints in patients with Crohn's disease: Data from the CELEST study. *J Crohns Colitis* 2018;**12**:S412–S3.
79. Sandborn WJ, Feagan B, Panes J, *et al*. Safety and efficacy of ABT-494 [upadacitinib], an oral JAK1 inhibitor, as induction therapy in patients with Crohn's disease: Results from CELEST. In: Society for Surgery of the Alimentary Tract, 58th Annual Meeting; 2017; Chicago, IL, USA.
80. Schreiber S, Peyrin-Biroulet L, Boland BS, *et al*. Op022 rapidity of clinical and laboratory improvements following upadacitinib induction treatment: Data from the CELEST study. *J Crohns Colitis* 2018;**12**:S015. doi: 10.1093/ecco-jcc/jjx180.021.
81. Panes J, Sandborn WJ, Loftus Jr EV, *et al*. P273 efficacy and safety of upadacitinib maintenance treatment for moderate to severe Crohn's disease: Results from the CELEST study. *J Crohns Colitis* 2018;**12**:S238–S9.
82. Aguilar D, Planell N, Panes J, *et al*. P843 upadacitinib-induced endoscopic improvement is associated with modulation of pathways involved in Crohn's disease pathogenesis. *J Crohns Colitis* 2018;**12**:S542 -S3. doi: 10.1093/ecco-jcc/jjx180.970.
83. Mohamed MF, Klunder B, Lacerda AP, Othman AA. Exposure-response analyses for upadacitinib efficacy and safety in the Crohn's disease CELEST study and bridging to the extended-release formulation. *Clin Pharmacol Ther* 2019, Oct 8. doi: 10.1002/cpt.1668. [Epub ahead of print.]
84. Sandborn WJ, Ghosh S, Panes J, *et al*. Op195 efficacy and safety of upadacitinib as an induction therapy for patients with moderately-toseverely active ulcerative colitis: Data from the phase 2b study u-achieve. *United European Gastroenterol J* 2018;**6**.
85. Sandborn WJ, Schreiber S, Lee SD, *et al*. Op14 improved endoscopic outcomes and mucosal healing of upadacitinib as an induction therapy in adults with moderately to severely active ulcerative colitis: data from the u-achieve study. *J Crohns Colitis* 2018;**13**:S009. doi: 10.1093/ecco-jcc/jjy222.013.
86. Minocha M, Engelhardt B, Stodtmann S, Zhou W, Othman AA. P0347 exposure-response analyses of upadacitinib [ABT-494] efficacy in subjects with moderately to severely active ulcerative colitis - analyses of a phase 2 dose ranging induction study. *United European Gastroenterol J* 2018;**6**:P0347.
87. Mohamed MF, Jungerwirth S, Asatryan A, Jiang P, Othman AA. Assessment of effect of cyp3a inhibition, cyp induction, oatp1b inhibition, and high-fat meal on pharmacokinetics of the JAK1 inhibitor upadacitinib. *Br J Clin Pharmacol* 2017;**83**:2242–8.
88. PubChem. *Pf-06700841, cid=135087198*. National Center for Biotechnology Information; 2019. https://pubchem.ncbi.nlm.nih.gov/compound/135087198. Accessed February 24, 2020.
89. Fensome A, Ambler CM, Arnold E, *et al*. Dual inhibition of TYK2 and JAK1 for the treatment of autoimmune diseases: discovery of [[S]-2,2-difluorocyclopropyl][[1 R,5 S]-3-[2-[[1-methyl-1 H-pyrazol-4-yl]amino] pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]methanone [PF-06700841]. *J Med Chem* 2018;**61**:8597–612.
90. Banfield C, Scaramozza M, Zhang W, *et al*. The safety, tolerability, pharmacokinetics, and pharmacodynamics of a TYK2/JAK1 inhibitor [pf-06700841] in healthy subjects and patients with plaque psoriasis. *J Clin Pharmacol* 2018;**58**:434–47.
91. PubChem. *Pf-06651600,cid=118115473*. National Center for Biotechnology Information; 2019. https://pubchem.ncbi.nlm.nih.gov/compound/pf-06651600. Accessed February 24, 2020.
92. Telliez JB, Dowty ME, Wang L, *et al*. Discovery of a JAK3-selective inhibitor: functional differentiation of jak3-selective inhibition over pan-jak or jak1-selective inhibition. *ACS Chem Biol* 2016;**11**:3442–51.