POS0091 OFF-TARGET PROFILING OF JANUS KINASE (JAK) INHIBITORS IN RHEUMATOID ARTHRITIS: A COMPUTER-BASED APPROACH FOR DRUG SAFETY STUDIES AND REPURPOSING

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Background: The JAK inhibitors (JAKi's) tofacitinib and baricitinib are new alternatives for treating rheumatoid arthritis. Safety concerns associated with JAKi's, such as the increased risk for thrombosis and viral infections, have emerged worldwide. The underlying explanatory mechanisms remain unknown, suggesting the elevated risk is likely due to underlying confounding or an off-target binding effect. Computational approaches can explore the potential for a small molecule drug to interact with previously unknown biological targets and identify potential safety-related concerns, and open doors for potential drug repurposing.
Objectives: To identify and characterize the off-target binding effects of baricitinib and tofacitinib, with a focus on targets related to thrombosis and viral infection
Methods: Potential targets of baricitinib and tofacitinib were predicted using two neural-network-based systems (TIGER[1] and SPiDER[2]). Targets were considered relevant if they had (1) a SPiDER confidence with p<0.05, or (2) a TIGER score >1. Selected targets related to the outcome of interest were experimentally evaluated at Eurofins Cerep (France-Celle L'Evescault, www.eurofins.com) if commercial available. Compounds were tested at (1) single concentration (30 µM) with technical replicates, using radioligand or enzymatic assays, or (2) multiple concentrations (30 µM highest concentration; dilution factor in a log-scale) with technical replicates, using calcium flux or inhibition of [cAMP] assays. Observed activity of ≥50% inhibition or stimulation on the target was considered active, between 25 to 50% inhibition (or a dissociation constant [Kd] from 1 to 10 µM) was considered as moderate activity, and lower than 25% was considered inactive. Dose-response curve were performed on active and moderate targets for IC_{50} / EC_{50} (half maximal inhibitory / effective concentration) determination.
Results: TIGER and SPiDER suggested a total of 99 off-target binding effects (baricitinib n=41; tofacitinib n=58), of which 17 targets had potential impact on thrombosis or viral infection (baricitinib n=5 and 4, respectively; tofacitinib n=5 and 3, respectively). Commercial testing was available on 11 targets (Adenosine Receptor A2A [AA2AR], Epidermal growth factor receptor, induclible NOS, PI3 Kinase (p110b/p85a), Phosphodiesterase 10A2 [PDE10A2] and Protein Kinase N2 [PKN2] for baricitinib; and Adenosine receptor A3, 15-Lipoxygenase [15-LO], PKN2, Transient receptor potential cation channel [TRPM6] and AA2AR for tofacitinib). Of these, 5 targets showed active or moderately active binding activity (baricitinib n=2; tofacitinib n=3), and were tested for dose-response curves. Test results confirmed ligand-binding activity with IC_{50} on nanomolar (PKN2), and micromolar ranges (PDE10A2 and TRPM6).
Conclusion: The results suggest both baricitinib and tofacitinib are promiscuous binders with effects on several families. Although it may lead to side effects, off-target binding also represents a potential opportunity for drug repurposing. Besides on-target effects, both drugs are under clinical investigation for the treatment of COVID-19 due to off-target interactions. The proposed pharmacological off-target effects of those with active binding include attenuation of pulmonary vascular remodeling, anti-fibrotic and anti-psychotic activities (PDE10A2), modulation of viral response (PKN2), and hypomagnesaemia (TRPM6), which is involved in cardiovascular diseases. This study supports tofacitinib and baricitinib as candidates for drug repurposing (e.g., in COVID-19, Hepatitis C virus, and pulmonary hypertension). We did not identify active off-target interactions linked to thrombosis to explain the elevated risk observed in clinical practice. Further research is required to elucidate the underlying patient-specific factors (confounders) that could explain this safety concern.

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POS0092 HERPES ZOSTER IN THE FILGOTINIB RHEUMATOID ARTHRITIS PROGRAM

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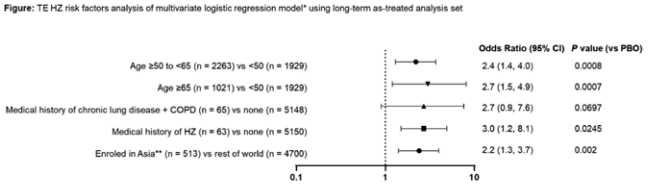
Background: The once daily, oral Janus kinase (JAK)-1 preferential inhibitor filgotinib (FIL) improved signs and symptoms of rheumatoid arthritis (RA) in phase (P)3 trials.[1-3] Patients (pts) with RA have increased herpes zoster (HZ) reactivation risk vs the general population. JAK inhibition is associated with increased infection incidence, including HZ.[4]
Objectives: To assess long-term safety of FIL across the global clinical program with respect to HZ.
Methods: Pts meeting 2010 ACR/EULAR RA criteria in a pooled analysis of P2 DARWIN 1–2 (D1–2), P3 FINCH 1–3 (F1–3), and long-term extension studies (D3, F4) were included. Placebo (PBO)-controlled as-randomised analysis included pts receiving FIL 100 mg (FIL100), FIL 200 mg (FIL200), or PBO up to week (W)12 (D1–2, F1–2); active-controlled as-randomised analysis included pts receiving FIL100, FIL200, adalimumab (ADA), or methotrexate (MTX) up to W52 (F1, F3). Long-term as-treated analysis included pts in all 7 studies receiving FIL100, FIL200, ADA, MTX, or PBO; data after re-randomisation were included and contributed to treatment received. Exposure-adjusted incidence rates (EAIR)/100 patient-years, calculated up to the last follow-up time or day, and differences with 95% confidence intervals (CIs) were calculated from the Poisson model. Logistic regression model was used for treatment-emergent (TE) HZ risk factor analysis and odds ratio (95% CI) and *P* value were provided.
Results: Table 1 shows TE HZ EAIRs in a pooled analysis. Rates of HZ were lower for FIL200 vs PBO during the 12W PBO-controlled period. At 52W, HZ rates were higher for FIL200/100 vs active control. Long-term HZ rates increased for FIL200 vs FIL100.

Table 1. EAIR of treatment-emergent herpes zoster

	N	Patient-years exposure	EAIR (95% CI)	EAIR diff (95% CI vs PBO/active control)
12W PBO-controlled				
FIL200	777	179.8	0.6 (0.1, 3.9)	–0.56 (–2.5, 1.3)
FIL100	788	181.6	1.1 (0.3, 4.4)	–0.02 (–2.2, 2.2)
PBO	781	178.4	1.1 (0.3, 4.5)	
Active-controlled, as-randomised[a]				
FIL200	475	439.7	1.4 (0.6, 3.0)	0.69 (–0.7, 2.1)
FIL100	480	443.4	0.9 (0.3, 2.4)	0.23 (–1.1, 1.5)
ADA	325	297.6	0.7 (0.2, 2.7)	
Active-controlled, as-randomised[a]				
FIL200	626	578.0	1.7 (0.9, 3.2)	0.65 (–0.8, 2.2)
FIL100	207	195.0	1.5 (0.5, 4.8)	0.46 (–1.6, 2.5)
MTX	416	372.2	1.1 (0.4, 2.9)	
Long-term as-treated[b]				
FIL200	2267	4047.7	1.8 (1.4, 2.3)	NC
FIL100	1647	2032.9	1.1 (0.8, 1.7)	NC

[a]up to W52. [b]data cut for LTE FINCH 4, Sept 19, 2019; DARWIN 3, April 26 2019.ADA, adalimumab; CI, confidence interval; EAIR, exposure-adjusted incidence rate; FIL, filgotinib; MTX, methotrexate; NC, not calculated; PBO, placebo; W week.

Figure 1 shows multivariate logistic regression model of TE risk factors.



Of 104 pts with TE HZ in long-term as-treated analysis set, 5 receiving FIL200 had history of HZ; EAIR (95% CI) was 8.7 (3.6–21.0). Of 8 pts with multiple events, 3 had events of differing severity for the same HZ episode.
EAIRs (95% CI) of TE HZ in Asia were: 3.7 (1.7–8.1) FIL200, n=197; 2.8 (1.3–6.3) FIL100, n=158; 0 ADA, n=40; 2.8 (0.4–19.6) MTX, n=43; and 3.4 (0.5–23.8) PBO, n=77 in long-term as-treated population. EAIRs (95% CI) in rest of the world were: 1.6 (1.2–2.1) FIL200, n=2070; 0.9 (0.6–1.5) FIL100, n=1489; 0.8 (0.2–3.1) ADA, n=285; 0.9 (0.3–2.9) MTX, n=373; and 0.7 (0.2–2.9) PBO, n=704 for all pts as-treated.

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Most TE HZ infections were mild to moderate and non-serious; 6 were serious; 2 were recurrences. No visceral TE HZ occurred across the FIL RA program; there was 1 case each of genital, disseminated, and ophthalmic HZ. The disseminated HZ occurred in a pt with prior HZ history. Lymphopenia was not associated with HZ during the PBO-controlled W12 period.

Conclusion: HZ was more common in both FIL groups vs ADA or MTX up to 52 weeks but comparable vs PBO during the 12-week placebo-controlled period. In multivariate analyses, prior history of HZ, Asian region, and age ≥50 years were associated with increased HZ risk.

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Rheumatoid arthritis - prognosis, predictors and outcome

POS0093

HETEROGENEITY IN ADVERSE EVENT ASSESSMENT BETWEEN COUNTRIES PARTICIPATING IN AN INTERNATIONAL COLLABORATION OF REGISTRIES OF RHEUMATOID ARTHRITIS PATIENTS USING JANUS KINASE INHIBITORS (THE JAK-POT STUDY)

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Background: Industry, regulators, and the rheumatology community have recognized the need for observational studies to monitor the safety of new anti-rheumatic agents. Registries provide a unique opportunity to understand the safety of newer therapies, but pharmacovigilance studies require large number of patients to evaluate rare drug-related adverse-events (AEs). Because JAK-inhibitors (JAKi) have only recently been approved for the treatment of rheumatoid arthritis, it makes sense to combine data from several registries in order to obtain a sufficiently large sample size to promote earlier detection of adverse events.

Objectives: The purpose of this analysis was to evaluate how AEs are assessed in the various registries in preparation for a collaborative pharmacovigilance analysis, and present preliminary results.

Methods: The "JAK-pot" collaboration includes 19 RA registries. The principal investigators of the participating registries were sent a structured questionnaire on AE assessment and 18 (94%) provided complete responses on the AE assessment procedures of their registries. We present simple descriptive statistics of the AE assessment procedures employed by the participating registries.

Results: The 19 registries represent 7186 patients initiating a JAKi (Table 1), who are on average 57 years old, with a mean disease duration 11 years, seropositive (83%), female (82%) and with moderate disease activity at treatment initiation.

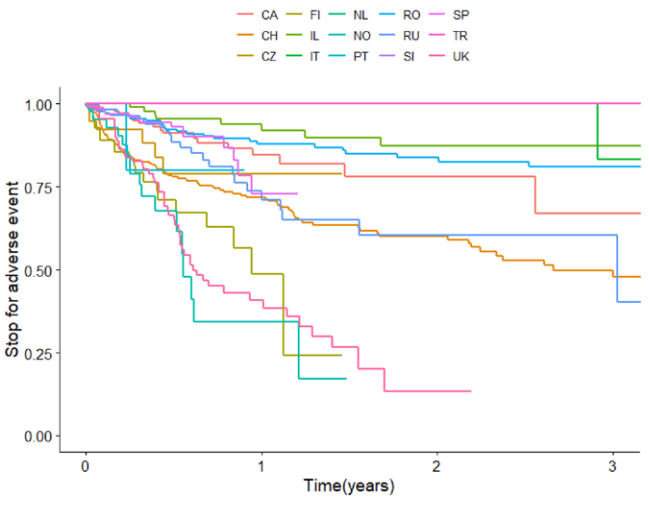
Table 1.

Country, registry	N° of patients on JAKi included
Austria, BIOREG	87
Belgium, TARDIS	2113
Canada, RHUMADATA	363
Czech Republic, ATTRA	197
Denmark, DANBIO	506
Finland, ROB-FIN	229
Germany, RABBIT	620
Italy, GISEA	244
Israel, I-RECORD	96
Netherlands, METEOR	4
Norway, NOR-DMARD	97
Portugal, REUMA.PT	44
Romania, RRBR	252
Russia, ARBITER	428
Slovenia, biorx.si	141
Spain, BIOBADASER	139
Switzerland, SCQM	738
Turkey, TURKBIO	404
UK, BSRBR	484

After ineffectiveness, AEs was the second most common reason for JAKi discontinuation (25.5%), with large differences between registries (Figure 1).

Of the participating registries, 2 registries do not collect AEs, while 16 (89%) assess incident AEs, by means of a pre-specified extraction form (3 registries), by free text (5 registries), by a combination of both (6 registries) and/or the use of linkage to external electronic records (3registries). AEs are coded using a predefined coding system by 11 registries (MeDRA (8), other (3)), but nearly all are recording the severity of the AE (15, 94%), AE related-death (15, 94%), or AE-related hospitalisation (15, 94%). AEs of special interest, such as serious infections (15, 94%), thromboembolic events (15, 94%), or shingles (9, 56%), are recorded by most registries. Incident AEs are linked by the treating physician to specific therapies in 11 registries (69%), while the other 5 registries extrapolate potential causal associations based on therapy start and stop dates. A pre-specified adjudication process for AEs is made only by 5 registries (31%).

Figure 1: Treatment discontinuation of JAKi for AEs in registries with individual patient-level information



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