ACR round up continued – Long term filgotinib data fails to reveal thrombotic concern

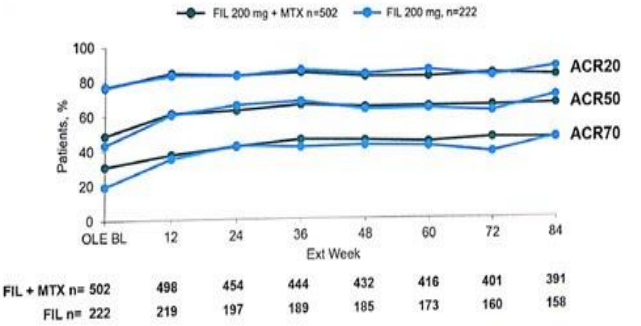
- As mentioned in our previous alert, in addition to Xeljanz and Olumiant, Abbvie and Gilead are developing JAK inhibitors upadacitinib and filgotinib. Both candidates have been positioned as JAK1 selective inhibitors although data reported by Lilly at ACR and described in our previous alert suggests upadacitinib may not be as selective as initially thought. Galapagos has previously and independently claimed this.
- Filgotinib data from the Phase 2b DARWIN studies have been extensively reported and further analysis was reported at ACR. We understand that Galapagos and Gilead are expending significant effort in investigating biomarkers of filgotinib response and two ACR presentations described biomarker changes in response to filgotinib treatment. One key advance would be the identification of predictive biomarkers but this remains elusive.
- Perhaps the most important data at ACR described long term filgotinib safety and efficacy in DARWIN 3. Interim 60wk data were reported at EULAR; 84wk data were reported at ACR (**1909**). Approx 94% patients who completed DARWIN 1 (filgotinib/MTX) or DARWIN 2 (filgotinib monotherapy) rolled into DARWIN 3. The vast majority of patients received 200mg qd or 100mg bid in combination with MTX, or 200mg qd monotherapy.
- Approx 70% patients entering DARWIN 3 completed 84wk treatment. Of the 723 patients receiving these doses, just 2 discontinued due to efficacy; 166 discontinued due to AEs
- In the context of heightened awareness of JAK related safety issues the analysis of AEs in DARWIN 3 is of particular interest (see below). Values are expressed per 100 pt yrs with absolute values in parentheses. Safety was similar to that previously reported and especial attention was drawn to DVT/PE. Just one patient presented with this AE (the same patient had both a VTE and PE) and when expressed in relation to exposure rates, incidence was 10-fold lower than across the Olumiant program (0.06 vs 0.5/100 pt yrs).
- In a recent study the incidence was 0.6/100 pt yrs in rheumatoid arthritis patients. This lends some credence to Lilly's argument that incidence of VTE/PE with Olumiant reflects that of the background population. This then begs the question of why is the incidence relatively low in filgotinib treated patients. This could reflect chance or difference in characteristics of patients enrolled to the filgotinib and Olumiant programs. An alternative explanation is that filgotinib lowers thrombotic risk, either indirectly by reducing joint inflammation or perhaps by reducing cardiov ascular inflammation directly. Olumiant could be devoid of this effect or alternatively the effect could be there but balanced by JAK2-mediated pro-thrombotic effects.
- Efficacy was durable over the 84wk and although data were as observed the low dropout rate, especially for treatment failure suggests durability is real. The inclusion of MTX appeared to have little effect on either safety or efficacy

Image: 84wk filgotinib data from DARWIN 3

DARWIN 3: Adverse Events of Special Interest (Per 100 PYE*)

	FIL + MTX			FIL			
Incidence rate (events)	100 mg BID n=251	100 mg QD† n=9	200 mg QD n=251	100 mg BID n=1	100 mg QD† n=8	200 mg QD n=221	Total N=739
Herpes Zoster	1.2 (7)	0	1.3 (8)	0	0	1.2 (6)	**1.2 (21)**
Active tuberculosis	0	0	0	0	0	0	**0**
Malignancy (excluding NMSC‡)	0.7 (4)	0	0.2 (1)	0	0	0.8 (4)	**0.5 (9)**
Treatment-emergent MACE*	0.3 (2)	0	0.7 (4)	0	0	0.4 (2)	**0.5 (8)**
Deep vein thrombosis‡	0.17 (1)‡	0	0	0	0	0	**0.06 (1)‡**
Pulmonary embolism‡	0.17 (1)‡	0	0	0	0	0	**0.06 (1)‡**
Anemia	2.5 (15)	0	1.2 (7)	0	0	2.1 (10)	**1.9 (32)**

DARWIN 3: ACR Response by Visit (Observed Case Analysis)



FIL + MTX n= 502	498	454	444	432	416	401	391
FIL n= 222	219	197	189	185	173	160	158

Dr Jon Goldhill
Pharma Information & Reports Ltd
UpdatesPlus/LeadDiscovery

www.leaddiscovery.co.uk
Maddomswood, Whatlington
E Sussex , TN31 5RA
England

Tel: +44 (0)1580 831877