JAK Inhibitors: Upadacitinib and UC

Janus kinases (JAKs) – part of signal transduction pathway for activation of inflammatory cytokines[1]

- JAK inhibitors are small-molecule drugs taken orally
- First JAK inhibitor for IBD – tofacitinib, which has preferential binding for $JAK_{1,3}$ receptors[2]
- Upadacitinib is a JAK inhibitor that binds most closely to JAK_1 receptors[1]
  - FDA-approved for both UC and CD[3]

UPATACITINIB INDUCTION AND MAINTENANCE TRIALS FOR ULCERATIVE COLITIS[1]

Efficacy Endpoints	WEEK 12 - INDUCTION				WEEK 52 - MAINTENANCE		
	UC-1		UC-2				
	Upadacitinib* (45 mg, n = 322)	Placebo (n = 154)	Upadacitinib* (45 mg, n = 341)	Placebo (n = 174)	Upadacitinib* (15 mg, n = 148)	Upadacitinib* (30 mg, n = 154)	Placebo (n = 149)
Clinical remission (primary)	**26%**	**5%**	**33%**	**4%**	**42%**	**52%**	**15%**
Clinical response (new or maintained)	73%	27%	74%	25%	63%	77%	19%
Endoscopic improvement	36%	7%	44%	8%	49%	62%	14%
Endoscopic improvement – histologic remission	30%	6%	36%	6%	50%	35%	12%
No bowel urgency	48%	21%	54%	26%	56%	64%	17%
No abdominal pain	47%	23%	54%	24%	46%	55%	21%

*$P \leq 0.0001$ for all primary and secondary endpoints in study.

1. Danese S, et al. *Lancet.* 2022;399(10341):2113-28; 2. Sandborn WJ, et al. *NEJM*. 2017;376(18):1723-36; 3. RYNVOQ® (upadacitinib). Prescribing information. AbbVie Inc; 2023.

JAK Inhibitors – Upadacitinib and CD

- First JAK-inhibitor therapy for CD[1]

UPADACITINIB INDUCTION AND MAINTENANCE TRIALS FOR CROHN'S DISEASE[2]							
Efficacy Endpoints	**WEEK 12 - INDUCTION**				**WEEK 52 - MAINTENANCE**		
	U-EXCEL		**U-EXCEED**				
	Upadacitinib* (45 mg, n = 322)	Placebo (n = 154)	Upadacitinib* (45 mg, n = 341)	Placebo (n = 174)	Upadacitinib* (15 mg, n = 148)	Upadacitinib* (30 mg, n = 154)	Placebo (n = 149)
CDAI clinical remission (primary)	**49.5%**	**29.1%**	**38.9%**	**21.1%**	**37.3%**	**47.6%**	**15.1%**
Endoscopic response (co-primary)	**45.5%**	**13.1%**	**34.6%**	**3.5%**	**27.6%**	**40.1%**	**7.3%**
Clinical response	56.6%	37.3%	50.5%	27.5%	41.4%	51.2%	15.2%
Glucocorticosteroid-free CDAI clinical remission	42.9%	15.7%	34.3%	11.7%	36.7%	46.4%	14.5%

*$P \leq 0.0001$ for all endpoints.
CDAI, Crohn's Disease Activity Index; JAK, Janus kinase.
1. FDA approves Rinvoq. May 18, 2023. Available at: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-first-oral-treatment-moderately-severely-active-crohns-disease#:~:text=FDA%20has%20approved%20Rinvoq%20(upadacitinib,to%20severely%20active%20Crohn's%20disease. Accessed August 11, 2023; 2. Loftus EV Jr, et al. *N Engl J Med*. 2023;388(21):1966-80.

Upadacitinib Safety

UPADACITINIB MAINTENANCE TRIAL FOR ULCERATIVE COLITIS[1]			
Efficacy Endpoints	**WEEK 52 - MAINTENANCE**		
	Upadacitinib (15 mg, n = 148)	Upadacitinib (30 mg, n = 154)	Placebo (n = 149)
Serious adverse event	7%	6%	13%
Discontinuation due to adverse event	4%	6%	11%
Serious infection	3%	3%	4%
Malignancy	<1%	<1%	1%
Hepatic disorder	7%	5%	2%
Neutropenia	3%	6%	1%
Creatine phosphokinase	6%	8%	2%

UPADACITINIB MAINTENANCE TRIAL FOR CROHN'S DISEASE[2]			
Safety Endpoints	**WEEK 52 – MAINTENANCE**		
	Upadacitinib* (15 mg, n = 148)	Upadacitinib* (30 mg, n = 154)	Placebo (n = 149)
Severe adverse event	25.0%	18.6%	35.5%
Serious adverse event	25.0%	21.0%	37.4%
Discontinuation due to adverse event	12.8%	8.4%	7.5%
Serious infection	6.1%	7.8%	8.4%
Hepatic disorder	7.4%	10.2%	2.8%
Malignancy	0.7%	1.2%	0

1. Danese S, et al. *Lancet*. 2022;399(10341):2113-28; 2. Loftus EV Jr, et al. *N Engl J Med.* 2023;388(21):1966-80.

Filgotinib in UC

- Filgotinib binds most closely to JAK_1 receptor
- Results from phase 2b/3 trials[1]:

FILGOTINIB INDUCTION AND MAINTENANCE TRIALS FOR ULCERATIVE COLITIS										
Efficacy Endpoints	**WEEK 10 – INDUCTION TRIALS**						**WEEK 58 – MAINTENANCE TRIAL**			
	A: Biologic-naive			**B: Biologic-experienced**						
	Filgotinib 100 mg (n = 277)	**Filgotinib*** 200 mg (n = 245)	**Placebo** (n = 137)	**Filgotinib** 100 mg (n = 285)	**Filgotinib*** 200 mg (n = 262)	**Placebo** (n = 142)	**Filgotinib** 100 mg (n = 238)	**Placebo** (n = 279)	**Filgotinib*** 200 mg (n = 238)	**Placebo** (n = 279)
Clinical remission – primary	19.1%	**26.1%**	**15.3%**	9.5%	**11.5%**	**4.2%**	23.8%	13.5%	**37.2%**	**11.2%**
MCS remission	17.0%	24.5%	12.4%	6.0%	9.5%	4.2%	22.7%	13.5%	34.7%	9.2%
Endoscopic remission	5.8%	12.2%	3.6%	2.1%	3.4%	2.1%	13.4%	7.9%	15.6%	6.1%
Histological remission	23.8%	35.1%	16.1%	13.7%	19.8%	8.5%	27.9%	18.0%	38.2%	13.3%
Sustained clinical remission	--	--	--	--	--	--	8.7%	7.9%	18.1%	5.1%
Corticosteroid-free remission	--	--	--	--	--	--	13.6%	5.4%	27.2%	6.4%

- Efficacy sustained up to 4 years in long term extension trial[2]

*Response to 200 mg filgotinib significantly greater than to placebo, except for endoscopic remission in Induction Group B.
JAK, Janus kinase; MCS, Mayo Clinic Score.
1. Feagan B, et al. *Lancet*. 2021;397(10292):2372-84; 2. Feagan B, et al. Presented at 18th Congress of ECCO; March 1-4, 2023; Abstract OP35.

Filgotinib Safety

FILGOTINIB MAINTENANCE TRIAL FOR ULCERATIVE COLITIS					
Safety Endpoints	**WEEK 58 – MAINTENANCE TRIAL**				
	Placebo* (n = 93)	**Placebo†** (n = 91)	**Placebo‡** (n = 99)	**Filgotinib** 100 mg (n = 179)	**Filgotinib** 200 mg (n = 202)
Serious adverse events	4.3%	7.7%	0	4.5%	4.5%
Discontinuation due to adverse events	3.2%	4.4%	2.0%	5.6%	3.5%
Serious infections	1.1%	2.2%	0	1.7%	1.0%
Malignancy	0	0	0.6%	0	0.5%
Lymphocytes <500/mm^3	1.1%	1.1%	1.0%	1.7%	2.5%
Creatine kinase >5x ULN	1.1%	1.1%	2.1%	1.1%	4.0%

*Responded to placebo during induction. †Responded to filgotinib 100 mg during induction. ‡Responded to filgotinib 200 mg during induction.
ULN, upper limit of normal.
Feagan B, et al. *Lancet*. 2021;397(10292):2372-84.