Anti-Integrin Molecules – Advances in Vedolizumab Delivery

- A subcutaneous form of vedolizumab is approved for use in Japan and Europe for treatment of UC and CD; recently resubmitted for FDA approval for UC[1]
  - In 52-week maintenance trial for UC, following open-label IV induction, efficacy was similar to IV vedolizumab[2]
  - In a similarly-designed maintenance trial for CD, efficacy was similar to previously established values for IV vedolizumab[3]

ULCERATIVE COLITIS MAINTENANCE TRIAL[2]			
Endpoints (52 weeks)	**SC** (n = 106)	**IV** (n = 54)	**Placebo** (n = 56)
Clinical Remission (primary)	**46.2%***	**42.6%**	**14.3%**
Endoscopic Improvement	56.6%*	53.7%	21.4%
Durable Clinical Response	64.2%*	72.2%	28.6%

CROHN'S DISEASE MAINTENANCE TRIAL[3]		
Endpoints (52 weeks)	**SC** (n = 275)	**IV** (n = 134)
Clinical Remission (primary)	**46.2%†**	**42.6%**
Enhanced Clinical Response	64.2%	72.2%

- An oral formulation of a α4β7 integrin inhibitor is currently in phase 2 trials[4]

UPDATE: Subcutaneous vedolizumab was approved by the FDA September 27, 2023

*$P < 0.001$, relative to placebo groups. †$P = 0.008$ relative to IV group.

1. Takeda press release. April 27, 2023. Available at: https://www.takeda.com/newsroom/newsreleases/2023/takeda-announces-fda-acceptance-of-bla-resubmission-for-investigational-subcutaneous-administration-of-entyvio-vedolizumab-for-maintenance-therapy-in-moderately-to-severely-active-ulcerative-colitis/. Accessed October 2, 2023; 2. Sandborn WJ, et al. *Gastroenterology*. 2020;158(3):562-72.e12; 3. Vermiere S, et al. *J Crohns Colitis*. 2022;16(1):27-38; 4. Clinicaltrials.gov. NCT05291689 and NCT05611671.

IL-23 Inhibitors – Risankizumab Efficacy – CD and UC

- Following the development of the IL-12/IL-23 targeted antibody ustekinumab, developing new IL-23-targeted therapies for CD and UC has been a major focus of research
- Risankizumab is an IL-23 p19 antibody that is FDA-approved for CD[1]

	12-WEEK INDUCTION TRIALS[2]						52-WEEK MAINTENANCE TRIAL[3]		
	ADVANCE			MOTIVATE					
Co-Primary Endpoints	Risankizumab*		Placebo (n = 175)	Risankizumab*		Placebo (n = 187)	Risankizumab*		Placebo (n = 164)
	600 mg IV (n = 336)	1200 mg IV (n = 339)		600 mg IV (n = 191)	1200 mg IV (n = 191)		180 mg SC (n = 157)	360 mg SC (n = 141)	
CDAI Clinical Remission	45.2%	41.5%	24.6%	41.9%	40.3%	19.8%	55.4%	52.5%	40.9%
Stool Frequency and Abdominal Pain Remission	43.5%	41.0%	21.7%	34.6%	39.8%	19.3%	46.5%†	51.8%	39.6%
Endoscopic Response	40.2%	32.2%	12.0%	28.8%	34.0%	11.2%	47.1%	46.8%	22.0%

*$P \leq 0.007$ for difference between either risankizumab dose and placebo for all but one value. †P = NS

- Recently released data from 52-week phase 3 COMMAND trial for UC[4]
  - Met all primary and secondary endpoints

CDAI, Clinical Disease Activity Index; IL, interleukin; IV, intravenous; SC, subcutaneous. 1. SKYRIZI® (risankizumab-rzaa). Prescribing information. AbbVie Inc; 2022; 2. D'Haens G, et al. *Lancet*. 2022;399(10340):2015-30; 3. Ferrante M, et al. *Lancet*. 2022;399(10340):2031-46; 4. Abbvie press release. June 15, 2023. Available at: https://news.abbvie.com/news/press-releases/risankizumab-skyrizi-met-primary-and-key-secondary-endpoints-in-52-week-phase-3-maintenance-study-in-ulcerative-colitis-patients.htm#:~:text=The%20COMMAND%20study%20is%20a,to%20severely%20active%20ulcerative%20colitis. Accessed October 2, 2023.

IL-23 Inhibitors – Mirikizumab Efficacy – UC

- Mirikizumab is an IL-23 p19 antibody
- Significantly more effective than placebo in phase 3 trial[1]
- In April 2023, FDA found issues with manufacturing, but not efficacy or safety data[2]
  - Approved in Japan[1] and EU[3]
- Currently in phase 3 trial for CD[4]

12-WEEK INDUCTION TRIAL[1]

Endpoints	Mirikizumab* 300 mg IV (n = 868)	Placebo (n = 294)
Clinical Remission (Primary)	**24.2%**	**13.3%**
Clinical Response	63.5%	42.2%
Endoscopic Remission	36.3%	21.1
Histologic-Endoscopic Mucosal Improvement	27.1%	13.9%

52-WEEK MAINTENANCE TRIAL[1]

Endpoints	Mirikizumab* 200 mg SC (n = 365)	Placebo (n = 179)
Clinical Remission (Primary)	**49.9%**	**25.1%**
Maintenance of Clinical Remission	63.6%	36.9%
Endoscopic Remission	58.6%	29.1%
Histologic-Endoscopic Mucosal Remission	43.3%	21.8%
Glucocorticoid-free Clinical Remission	44.9%	21.8%
Bowel-Urgency Remission	42.9%	25.0%

UPDATE: Positive results of CD trial VIVID-1 reported October 12, 2023

*$P < 0.001$ for all endpoints. CDAI, IL, interleukin; IV, intravenous; SC, subcutaneous.

1. D'Haens G, et al. *N Engl J Med*. 2023;388(26):2444-55; 2. Lilly press release. April 27, 2023. Available at: https://investor.lilly.com/static-files/1df8cab7-5fa8-4eb4-b72d-a93efb1dac56. Accessed August 7, 2023; 3. European Medicines Agency. Accessed September 11, 2023. https://www.ema.europa.eu/en/medicines/human/EPAR/omvoh; 4. Clinicaltrials.gov. NCT03926130.

IL-23 Inhibitors – Mirikizimab and Risankizumab Safety

RISANKIZUMAB MAINTENANCE TRIAL in CD[1]			
Safety Endpoints	**Risankizumab**		**Placebo (n = 184)**
	180 mg SC (n = 179)	**360 mg SC (n = 179)**	
Severe adverse events	7%	12%	13%
Serious adverse events	12%	13%	13%
Discontinuation due to adverse events	2%	3%	3%
Serious infections	3%	4%	4%
Hepatic-related events	3%	4%	2%
Injection-site reactions	5%	6%	5%

MIRIKIZUMAB MAINTENANCE TRIAL in UC[2]		
Safety Endpoints	**Mirikizumab (n = 192)**	**Placebo (n = 389)**
Serious adverse events, excluding UC	3.3%	5.2%
Discontinuation due to adverse events	1.5%	8.3%
Serious infections	0.8%	1.6%
Depression	1%	0%
Hepatic-related events	3.1%	2.1%
Injection-site reactions	8.7%	4.2%

1. Ferrante M, et al. *Lancet*. 2022;399(10340):2031-46; 2. D'Haens G, et al. *N Engl J Med*. 2023;388(26):2444-55.