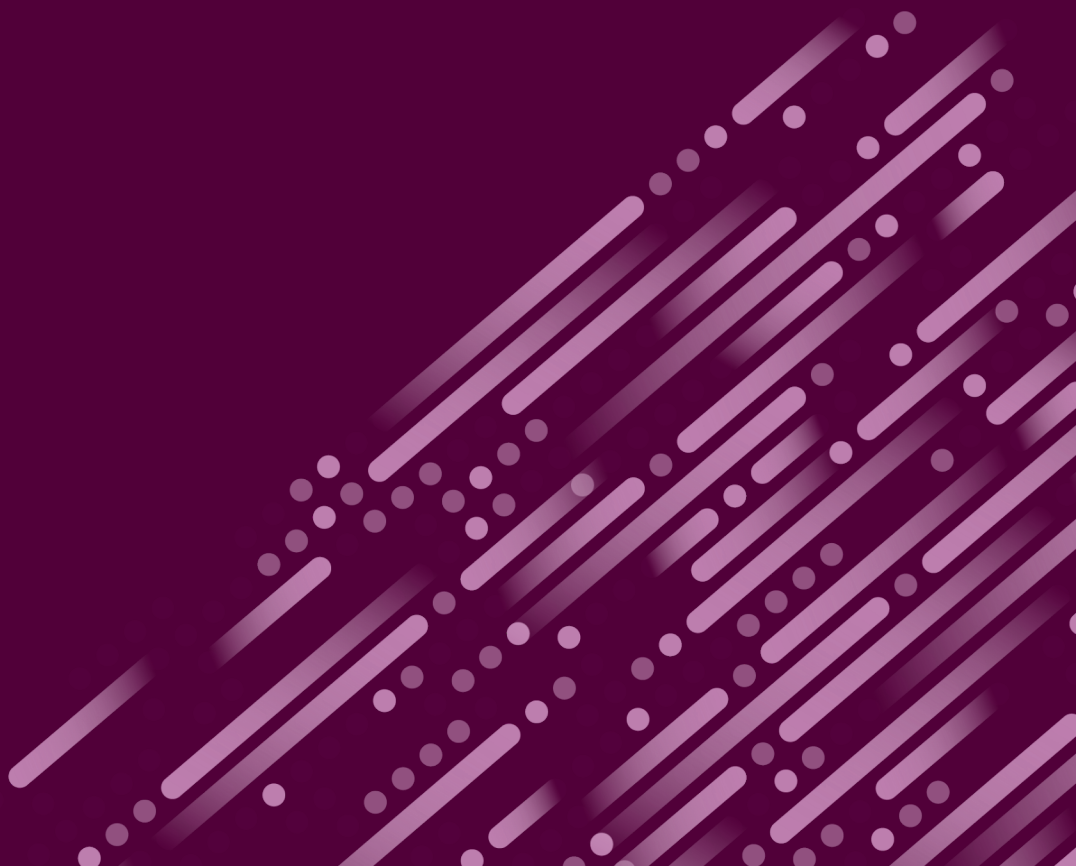
Pharma Intelligence
Informa

The 2021 American Academy of Dermatology (AAD) Conference



2021 AAD Conference

Day 1 Update - Friday April 23, 2021

The start of the 2021 AAD VMX Virtual Meeting marked the second time the conference was held virtually but was not without its technical difficulties. The On Demand feature of the meeting which was initially planned to be available at am was instead available in the late afternoon, and posters have not yet been uploaded.

The first day of AAD VMX 2021 also included the **Keynote** presentation given by best-selling author **Dani Shapiro**. *In the spring of 2016, through a genealogy website, Dani Shapiro received the stunning news that her father was not her biological father. Inheritance is a book about secrets secrets we keep from one another in the name of love. It speaks to our extraordinary moment, when science and technology have outpaced not only medical ethics but also the capacities of the human heart to contend with what we discover.*

Select highlights from our team of analysts are below:

2021 AAD Conference

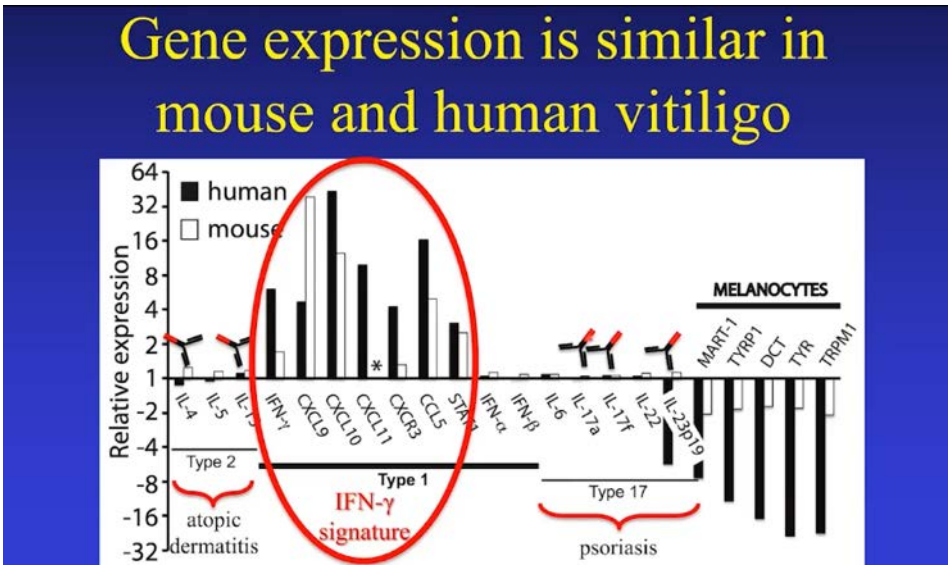
Day 1 Update - Friday April 23, 2021

S024: Marion B. Sulzberger, MD, Memorial Award and Lectureship: Vitiligo treatment from the Iron Age to the Age of Biologics: New hope for an ancient disease

During the plenary On-Demand session, Dr. John Harris from the University of Massachusetts Medical School presented on new and emerging treatments for vitiligo, a disease for which better treatments are needed. He indicated that vitiligo is quite common, affecting 3.25 million in the US and 74 million globally with 50 onset before the age of 20. Disease associations with vitiligo include type 1 diabetes, lupus, Hashimoto thyroiditis, pernicious anemia, and Addison's disease.

Dr. Harris emphasized the high psychological burden, low quality of life, and stigma associated with vitiligo, making it substantially more burdensome than just a cosmetic disease. Comparable to other dermatological diseases vitiligo patients were found to be the most willing to pay monthly or a one-time payment to cure their disease (Bae et al. JAAD 2020). Those with moderate to very severe scores on the Dermatology of Life Quality Index in vitiligo are similar to those in psoriasis (51 vs. 56 , respectively), however, while psoriasis has a good deal of available treatments, vitiligo does not.

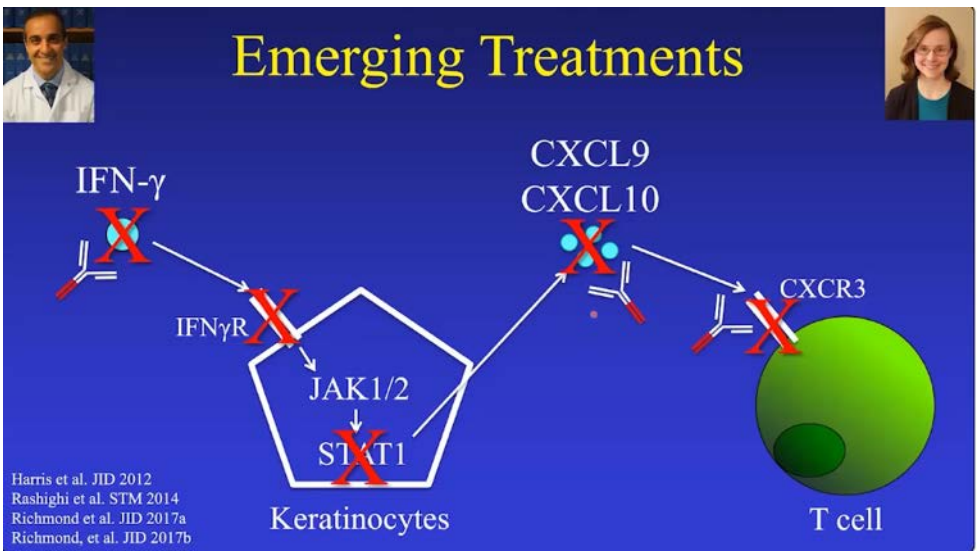
Based on early studies looking at gene expression in the skin in mouse and human vitiligo models, strong interferon (IFN)-gamma-driven responses were observed, with little to no Type 17 or Type 2 inflammation as seen with psoriasis and atopic dermatitis, respectively.



Knocking out members of the IFN-gamma signaling pathway including IFN-gamma, STAT1, CXCL , CXCL10, and CXCR3, successfully prevented disease in mouse models indicating that these signaling molecules were clearly important for driving disease. Utilizing antibodies against some of these molecules including JAK inhibitors were also able to prevent and reverse disease in these mouse models.

2021 AAD Conference

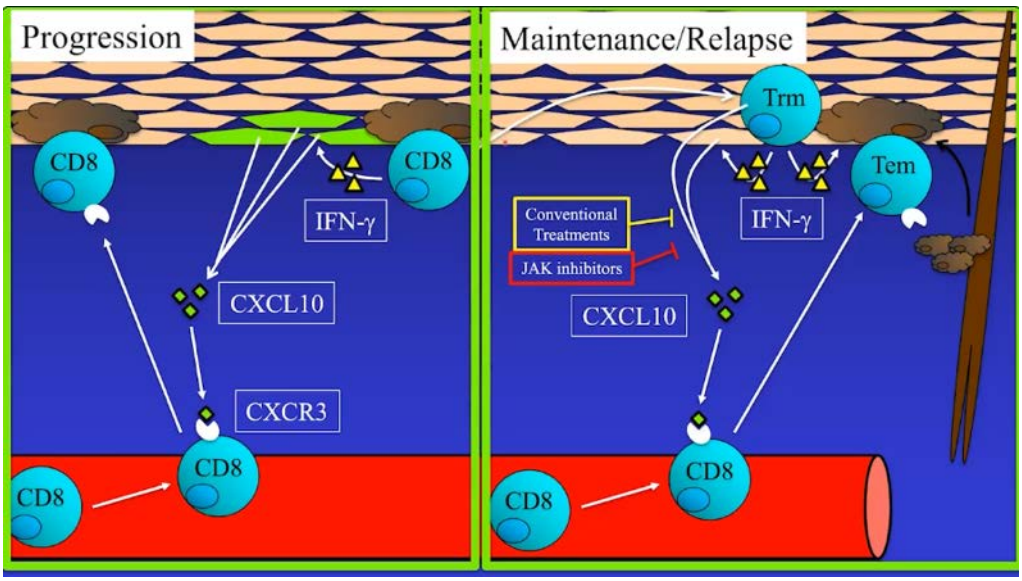
Day 1 Update - Friday April 23, 2021



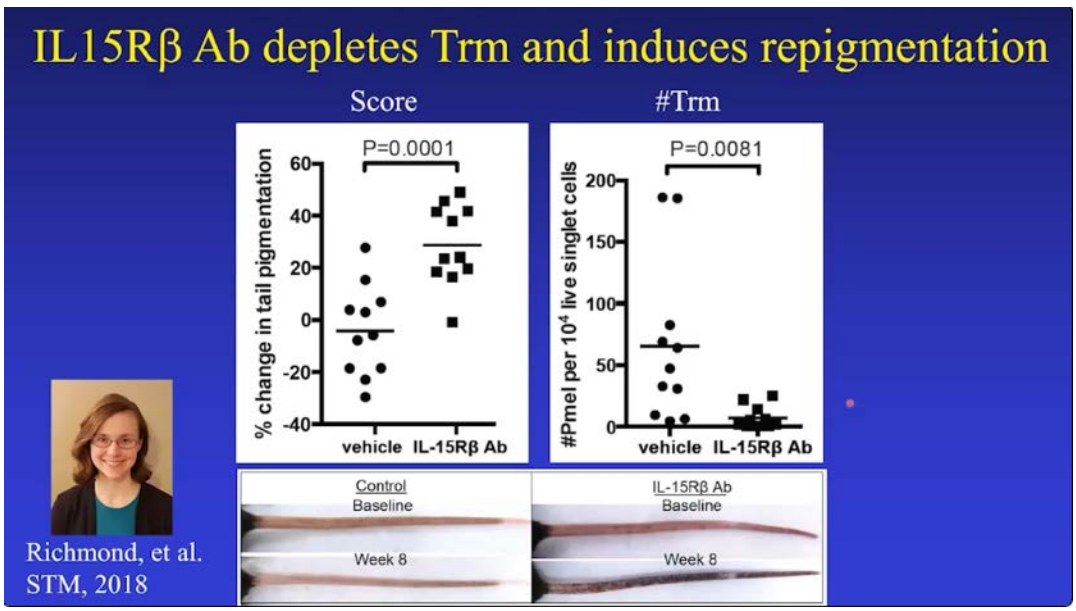
However, response durability of these JAKs is a concern with a 40 relapse rate occurring within the 1st year of stopping treatment. Further, vitiligo lesions recur in the same areas prior to treatment and initial research has shown that these lesions develop autoimmune memory. Conventional treatments and JAK inhibitors can turn off resident memory T-cell function in the epidermis but stopping treatment causes the reinitiating of those T-cells and disease.

2021 AAD Conference

Day 1 Update - Friday April 23, 2021



Dr. Harris's lab has initiated work to selectively deplete those resident memory T-cells in order to provide a durable treatment response and, found that inhibiting IL-15 receptor beta-chain with an antibody depleted resident memory T-cells in the skin and induced repigmentation.

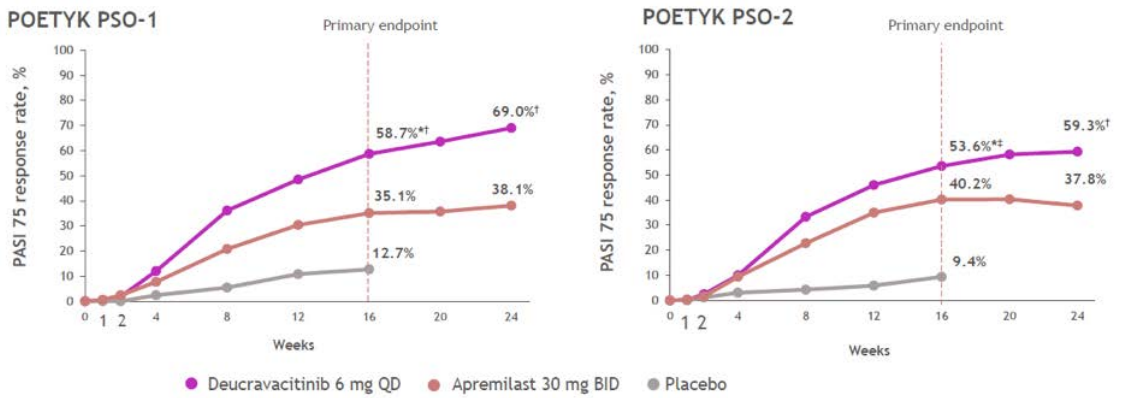


Future studies involve additional ways to block IL-15 signaling including blocking the cytokine for which Amgen has developed an antibody and is running an ongoing clinical trial in vitiligo. The other potential way to block IL-15 signaling involves inhibiting the IL-15 receptor beta chain, a strategy which Dr. Harris and his company, Villaris Therapeutics, are using to develop a potential drug with durable response.

S033: Efficacy and Safety of Deucravacitinib, an Oral, Selective Tyrosine Kinase 2 (TYK2) Inhibitor, Compared With Placebo and Apremilast in Moderate to Severe Plaque Psoriasis: Results From the Phase 3 POETYK PSO-1 Study

Though the late breaking abstract for Bristol Myers Squibb's (BMS) deucravactinib is scheduled for Saturday, the company presented in depth results from both POETYK PSO-1 and PSO-2 studies during a virtual investor event on Friday. The psoriasis trials that compared the oral TYK2 inhibitor deucravacitinib to PDE4 inhibitor, Otezla, met their primary endpoint with deucravacitinib showing superiority to placebo on the co-primary endpoints of PASI75 and sPGA 0/1 score at week 16. Additionally, significantly more deucravacitinib-treated patients achieved these endpoints compared to those treated with Otezla at week 16. Deucravacitinib also demonstrated superiority to Otezla on multiple key secondary endpoints.

Superior PASI 75 response at Week 16 and Week 24



Durable response for deucravacitinib pts achieving PASI 75 at Week 24: 82.5%/81.4% maintained response at Week 52

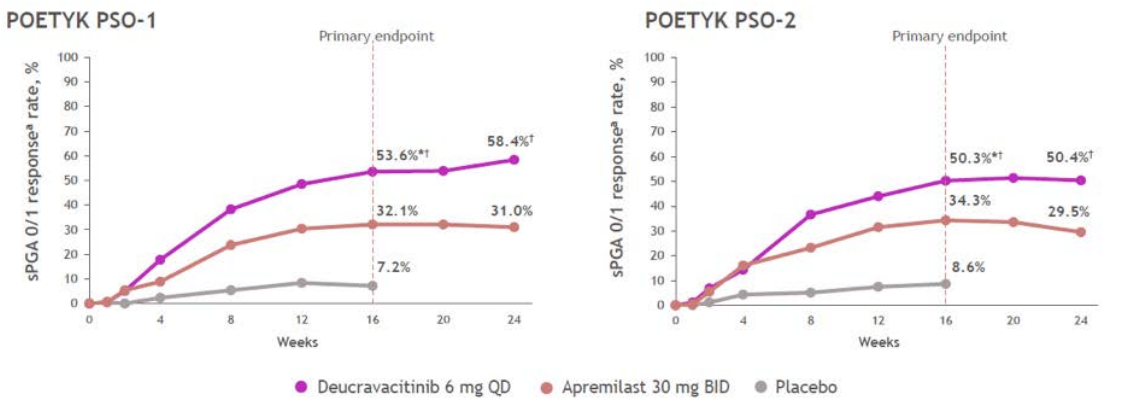
Bristol Myers Squibb

*P<0.0001 vs placebo. †P<0.0001 vs apremilast. ‡P=0.0003 vs apremilast
NRI = nonresponder imputation

Not for Product Promotional Use

9

Superior sPGA 0/1 response at both Week 16 and Week 24



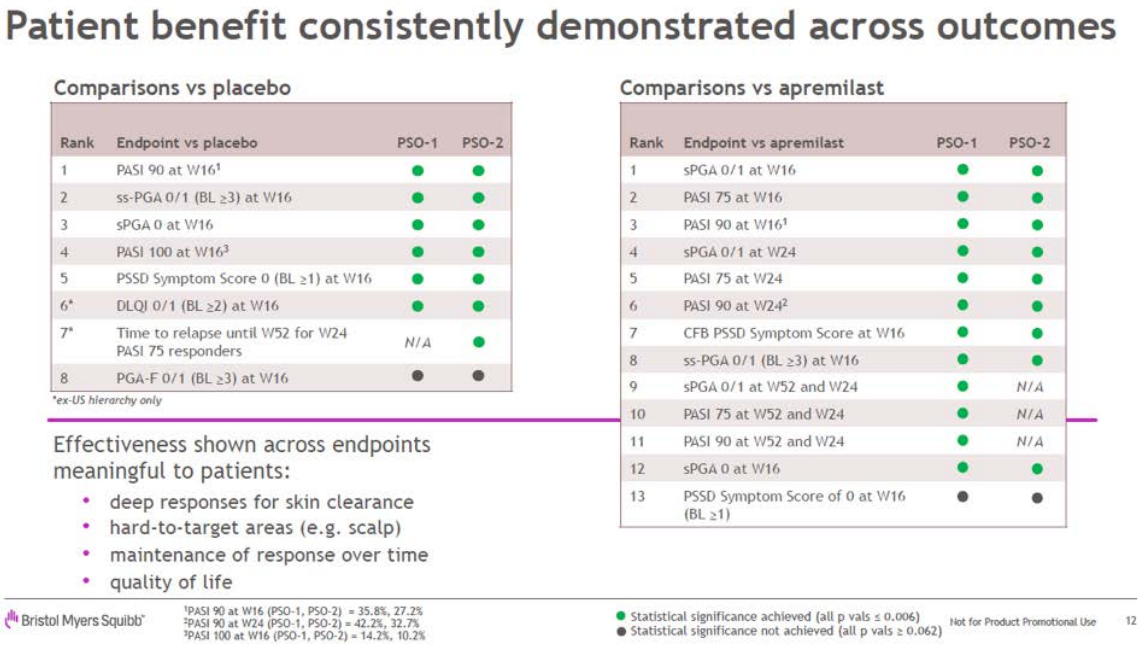
sPGA: static Physician Global Assessment

*Response defined as sPGA score of 0 or 1 with ≥2-point improvement from baseline.
*P<0.0001 vs placebo. †P<0.0001 vs apremilast.

Bristol Myers Squibb

Not for Product Promotional Use

10



Patient benefit consistently demonstrated across outcomes

Comparisons vs placebo

Rank	Endpoint vs placebo	PSO-1	PSO-2
1	PASI 90 at W16[1]	●	●
2	ss-PGA 0/1 (BL ≥3) at W16	●	●
3	sPGA 0 at W16	●	●
4	PASI 100 at W16[3]	●	●
5	PSSD Symptom Score 0 (BL ≥1) at W16	●	●
6*	DLQI 0/1 (BL ≥2) at W16	●	●
7*	Time to relapse until W52 for W24 PASI 75 responders	*N/A*	●
8	PGA-F 0/1 (BL ≥3) at W16	●	●

*ex-US hierarchy only

Comparisons vs apremilast

Rank	Endpoint vs apremilast	PSO-1	PSO-2
1	sPGA 0/1 at W16	●	●
2	PASI 75 at W16	●	●
3	PASI 90 at W16[1]	●	●
4	sPGA 0/1 at W24	●	●
5	PASI 75 at W24	●	●
6	PASI 90 at W24[2]	●	●
7	CFB PSSD Symptom Score at W16	●	●
8	ss-PGA 0/1 (BL ≥3) at W16	●	●
9	sPGA 0/1 at W52 and W24	●	*N/A*
10	PASI 75 at W52 and W24	●	*N/A*
11	PASI 90 at W52 and W24	●	*N/A*
12	sPGA 0 at W16	●	●
13	PSSD Symptom Score of 0 at W16 (BL ≥1)	●	●

Effectiveness shown across endpoints meaningful to patients:

- deep responses for skin clearance
- hard-to-target areas (e.g. scalp)
- maintenance of response over time
- quality of life

Bristol Myers Squibb

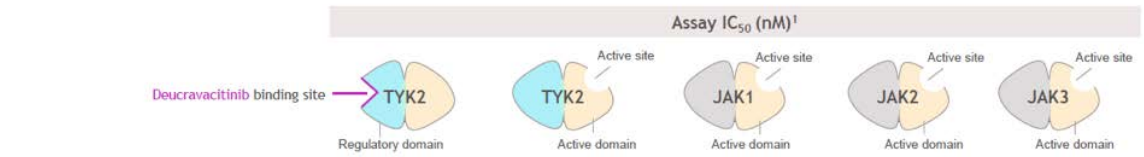
[1]PASI 90 at W16 (PSO-1, PSO-2) = 35.8%, 27.2%
[2]PASI 90 at W24 (PSO-1, PSO-2) = 42.2%, 32.7%
[3]PASI 100 at W16 (PSO-1, PSO-2) = 14.2%, 10.2%

● Statistical significance achieved (all p vals ≤ 0.006)
● Statistical significance not achieved (all p vals ≥ 0.062)

Not for Product Promotional Use 12

Mary Beth Harler, the company's Senior Vice President of Immunology and Fibrosis Development, emphasized several times the uniqueness of the mechanism in an attempt to differentiate their TYK2 inhibitor from the safety-plagued class of JAK inhibitors, to which TYK2 belongs. She highlighted a selectivity for TYK2's regulatory binding site, compared to JAK 1-3 inhibitors that bind the active site.

In-vitro data suggest differentiated profile versus JAK 1-3 inhibitors



	Inhibitor	TYK2 regulatory domain	TYK2 active domain	JAK1	JAK2	JAK3
1	Tofacitinib	nd	489	15	77	55
2	Baricitinib	nd	61	4	7	787
3	Filgotinib	nd	2600	363	2400	>10000
4	Upadacitinib	nd	4690	47	120	2304
5	PF-06700841	nd	23	17	77	6494
6	PF-06826647	nd	17	383	74	>10000
7	Deucravacitinib	0.2	>10000	>10000	>10000	>10000

IC_{50}=half-maximal inhibitory concentration; JAK=Janus kinase; nd=not determined; TYK=tyrosine kinase
Wrobleski ST et al. J Med Chem. 2019;62(20):8973-8995; Burke JR et al. Sci Transl Med. 2019;11(502); Winthrop KL. Nat Rev Rheumatol. 2017;13:234-243

Bristol Myers Squibb

Not for Product Promotional Use 7

The other key point she wanted to drive home was that they saw no venous thromboembolism (VTE) event, in an another attempt to further distance their TYK2 inhibitor from JAK inhibitors. Upon further questioning during the question and answer session, she noted that the VTE incidence rate was 0.21 per 100 patient years. In the Phase III program there were 2 VTE events, both on deucravacitinib and none on placebo or Otezla. One was deemed a serious adverse event, occurring in a patient who had an aortic dissection complicated by a pulmonary embolism. The second case was related to intravenous cannulation after which the patient had a minor thrombosis.

2021 AAD Conference

Day 1 Update - Friday April 23, 2021

Mary Beth Harler noted that they had an adjudicated committee review events across the Phase III studies and they saw no signal regarding VTE. These two events, however, do raise concern and may ultimately lead to a black box warning, despite BMS's best efforts to fight that in the label.

Favorable safety & improved tolerability, consistent with the mechanism

AE category, n[1], exposure-adjusted incidence rate (EAIR) events per 100 patient-years (PY)	POETYK integrated safety (PSO-1 and PSO-2), Wks 0-52		
	Placebo n=666 (total PY; 240.9)	Deucravacitinib n=1364 (total PY, 969.0)	Apremilast n=422 (total PY, 221.1)
Any AEs	347, 217.9	995, 229.2	299, 281.1
Serious AEs	14, 5.7	55, 5.7	9, 4.0
AEs leading to discontinuation	23, 9.4	43, 4.4	26, 11.6
Deaths	1*	2†	1‡
Most common AEs (≥5%) in any active treatment group, n, EAIR			
Nasopharyngitis	54, 22.9	229, 26.1	54, 25.9
Upper respiratory tract infection	33, 13.6	124, 13.4	27, 12.4
Headache	21, 8.6	80, 8.5	53, 26.0
Diarrhea	28, 11.6	69, 7.3	54, 26.5
Nausea	10, 4.1	20, 2.1	47, 22.9

Low rate of serious AEs, & fewer AEs leading to discontinuation vs apremilast & Pbo

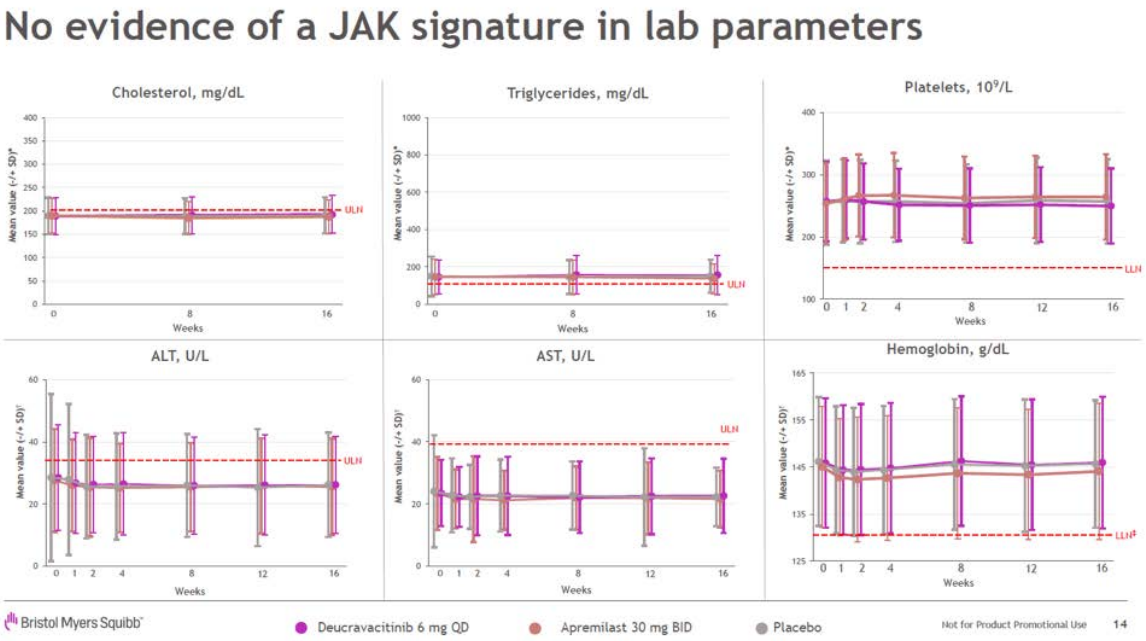
Bristol Myers Squibb

[1] Includes AEs between first dose and 30 days following last dose or rollover to long-term extension. *One 57-year-old female patient receiving placebo experienced sudden cardiac death due to hypertensive cardiovascular disease. †One patient discontinued deucravacitinib after 4 days of treatment due to prohibited medication (leflunomide) and died 9 days later due to sepsis and heart failure. One additional death between Week 16–52 due to hepatocellular carcinoma in a patient with a history of HCV infection and liver cirrhosis. ‡One patient discontinued apremilast due to lung cancer after 3 months and died 1 month later due to lung cancer and gastrointestinal bleed.

Not for Product Promotional Use

13

To additionally drill home the point that this selective TYK2 inhibitor is differentiated from other JAKs, BMS presented lab findings from the studies. Concerning signals on lipids, hemoglobin, liver enzymes, show up early and require ongoing monitoring for patients taking JAK inhibitors, which were not seen with deucravacitinib.



BMS executives also detailed the future plans for deucravacitinib in terms of development, in psoriatic arthritis, inflammatory bowel disease, and lupus, and in terms of potential launch in psoriasis. Upon launch in psoriasis, the company feels confident in gaining access to patients with open access plans positioning deucravacitinib to be the number one branded oral drug among both new patients and patients that switch. If successful across pipeline indications, BMS believes deucravacitinib has the potential to reach sales of over $4 billion in 2029.

Deucravacitinib has significant potential to be broadly applicable to a range of immune-mediated diseases

Indication	Relevant pathways inhibited via TYK2			Clinical Program Status / Expected Timing
Psoriasis	IL-12	IL-23		Filing pending
Psoriatic Arthritis	IL-12	IL-23		Beginning Ph3
Ulcerative Colitis	IL-12	IL-23		Ph2 POC 2H21
Crohn's Disease	IL-12	IL-23		Ph2 POC 2022
Lupus	IL-12	IL-23	Type I IFN	Ph2 POC 2022+

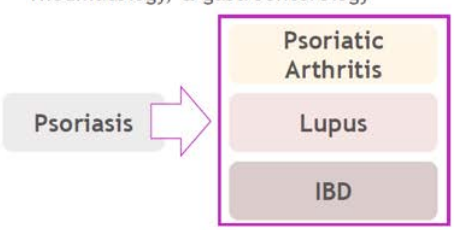
Bristol Myers Squibb

Not for Product Promotional Use 16

Deucravacitinib: potentially applicable to a broad range of immune-mediated diseases

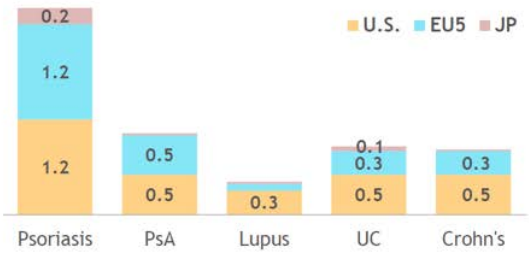
Future growth opportunities

Opportunity to grow the brand with new indications across dermatology, rheumatology, & gastroenterology



...for many patients with moderate-severe disease

Patient #s in millions**



2029 non risk-adjusted sales potential* >$4B

Source: Decision Resources Group; BMS Internal Analysis

Bristol Myers Squibb

*Non-risk adjusted revenue potential through 2029; subject to positive registrational trials and health authority approval
**Numbers indicate patients on any prescribed treatment (topical, systemic, advanced); Lupus includes Non-LN SLE treated patients with organ manifestation (90%) instead of moderate-severe treated population

Not for Product Promotional Use 22

2021 AAD Conference

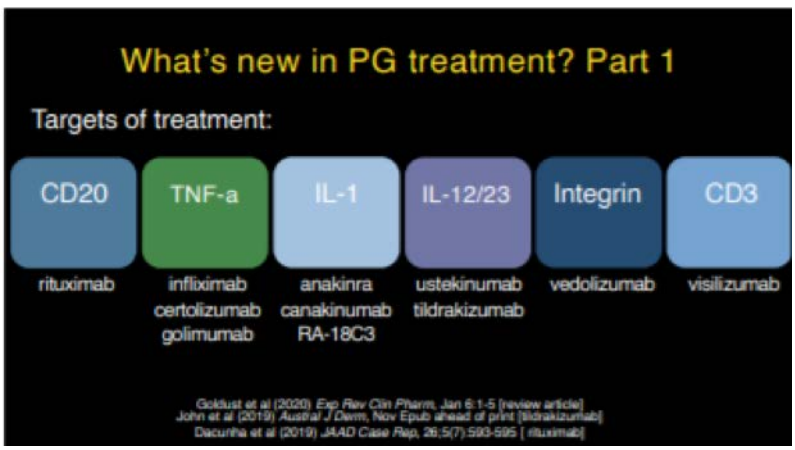
Day 1 Update - Friday April 23, 2021

Question and Answer Sessions

Despite the inability to access the on demand video content the first day, attendees still joined question and answer sessions without having seen the presentations. Among the most popular sessions were those on complex medical dermatology, the acne and rosacea symposium, off-label use of biologics and new medicines, and the COVID-19 symposium.

S001: Complex Medical Dermatology

Many of the questions from this session centered on the talk on pyoderma gangrenosum, with questions about colonoscopy requirements, X-rays for arthritis, and IL23 inhibitors being raised.



Additionally, Victoria Werth's discussion of cutaneous lupus erythematosus yielded several questions on lenalidomide treatment recommendations, coverages, REMS requirement, flares of systemic lupus erythematosus, and differences in the European guidelines. Questions about getting quinacrine re-approved were also addressed.

U008 - Off-label use of biologics and new medications

Adriane Levin and David Rosmarin gave an excellent discussion on off label use of biologics and JAK inhibitors. During this talk, they discussed the use of apremilast for patients with lichen planus, TNF-alpha inhibitors and JAK inhibitors for granulomas, ustekinumab for comorbid psoriasis and lupus, and dupilumab for alopecia, prurigo nodularis, and bullous pemphigoid. They also provided some tips on getting off label medications approved by insurance by citing the literature and clearly explaining what patients have already tried and failed, or using free samples or assistance programs for some, like Xeljanz and JAK inhibitors.

They also discussed their excitement around the efficacy of JAK inhibitors, believing they are more efficacious than Dupixent in atopic dermatitis, though the safety profile of Dupixent allows that drug to maintain first line status, with some room for to dermatology patients. It was noted that topical PDE4 inhbitor

roflumilast looks promising and hopefully does not have the site reaction seen with Eucrisa. They also lamented on the complexity of treating nail disease.