WELCOME TO
CARE AT DDW 2018
FRAMED IN A CANADIAN PERSPECTIVE
JUNE 2, 2018 - WASHINGTON, DC
PRESENTED BY: CARE™
Ulcerative Colitis

Remo Panaccione, MD
University of Calgary
Calgary, Canada
The present and the future of therapy in ulcerative colitis

**Today**
- Non-targeted oral small molecules
  - corticosteroids
  - mesalazine
  - immunosuppressants
  - antibiotics
- Targeted biologics
  - anti-TNF-α
  - anti-integrin
  - anti-IL-12-23

**Tomorrow?**
- New targeted biologics
  - anti-β7
  - anti-IL-23A
- Targeted oral small molecules
  - JAK inhibitors
  - S1P₁ regulators
  - PDE4 inhibitors
- Cell therapy
  - adipocyte-derived stem cells
Selected Abstracts

Saturday, June 2

Sa1430 EFFECT OF VEDOLIZUMAB, INFliximab, AND ADAliMUMAb ON BILIARY INFLAMMATION IN INDIVIDUALS WITH PRIMARY SCLEROSING CHOLANGITIS AND INFLAMMATORY BOWEL DISEASE.
1200-200pm

Sa1753: TOFACITINIB ACHIEVES SYMPTOMATIC IMPROVEMENT WITHIN 3 DAYS IN MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS, REGARDLESS OF PRIOR TUMOUR NECROSIS FACTOR INHIBITOR TREATMENT STATUS: RESULTS FROM OCTAVE INDUCTION 1 & 2
1200-2pm

Sunday, June 3

277: COMPARATIVE SAFETY PROFILE OF VEDOLIZUMAB AND TUMOR NECROSIS FACTOR-ANTAGONIST THERAPY FOR INFLAMMATORY BOWEL DISEASE: A MULTICENTER CONSORTIUM PROPENSITY SCORE-MATCHED ANALYSIS
830-845 am

328: COMPARATIVE EFFECTIVENESS OF VEDOLIZUMAB AND TUMOR NECROSIS FACTOR-ANTAGONIST THERAPY IN ULCERATIVE COLITIS: A MULTICENTER CONSORTIUM PROPENSITY SCORE-MATCHED ANALYSIS.
1045-1100 am

Tuesday, June 5

813 APREMILAST FOR ACTIVE ULCERATIVE COLITIS: A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY.
800-815 am

905: EFFICACY AND SAFETY OF TOFACITINIB RETREATMENT FOR ULCERATIVE COLITIS AFTER TREATMENT INTERRUPTION: RESULTS FROM THE OCTAVE CLINICAL TRIALS
1100-1115 am
Vedolizumab for Health Outcomes in Inflammatory Bowel Diseases (VICTORY) Consortium

Over 10 IBD Centers across the United States

Largest real-world registry with over 1,000 VDZ-treated patients with UC or CD

Design

- 3-6 months
- De-identified

Data

Consortium

- Data re-coded
- Compiled
- Analyzed

Outcomes

- Effectiveness
- Safety
- Predictors
- Comparisons

CD, Crohn's disease; Ulcerative colitis; UC, ulcerative colitis; CD, Crohn's disease.

Comparative effectiveness of VDZ and TNF-antagonist therapy in UC: A multicenter consortium propensity score–matched analysis

**AIM:** To compare the effectiveness of VDZ to TNF-antagonist therapy for UC (data from the VICTORY consortium) using clinical and steroid-free remission and endoscopic healing at 12 months

**METHODS:**
- Propensity score matching accounted for age, sex, prior UC-related hospitalization within the previous year, disease extent, disease severity, steroid refractoriness or dependence, and prior TNF-antagonist failure
- 646 UC patients identified, 334 included after matching
- Propensity model AUC 0.73 for predicting VDZ vs. anti-TNF therapy

![Before matching](chart1.png)  ![After matching](chart2.png)
Comparative effectiveness of VDZ and TNF-antagonist therapy in UC: A multicenter consortium propensity score–matched analysis

RESULTS:

Cumulative rates of clinical and steroid-free remission and endoscopic healing at month 12

- **VDZ (n=167)**
- **TNF-antagonist (n=167)**

<table>
<thead>
<tr>
<th></th>
<th>VDZ</th>
<th>TNF-antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical remission</td>
<td>54</td>
<td>37</td>
</tr>
<tr>
<td>Steroid-free remission</td>
<td>49</td>
<td>38</td>
</tr>
<tr>
<td>Endoscopic healing</td>
<td>50</td>
<td>42</td>
</tr>
</tbody>
</table>

Patients, %
Comparative effectiveness of VDZ and TNF-antagonist therapy in UC: A multicenter consortium propensity score–matched analysis

RESULTS:

Cumulative rates of clinical and steroid-free remission and endoscopic healing at month 12
HR and 95% CI (VDZ vs. anti-TNF)

<table>
<thead>
<tr>
<th></th>
<th>Clinical remission</th>
<th>Steroid-free remission</th>
<th>Endoscopic healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>1.54 (1.08-2.18)</td>
<td>1.43 (0.79-2.60)</td>
<td>1.73 (1.10-2.73)</td>
</tr>
</tbody>
</table>

CONCLUSIONS:

• UC patients treated with VDZ had significantly higher 12-month cumulative rates of clinical remission and endoscopic healing, and numerically higher steroid-free remission rates, when compared with patients treated with TNF-antagonist

Clinical remission=complete resolution of UC-related symptoms; steroid-free=on steroids at baseline, tapered off, no repeat steroid prescription for 4 weeks; endoscopic healing=Mayo endoscopic subscore of 0 or 1. IM included azathioprine, 6-mercaptopurine, and methotrexate. Bold text indicates significance.
AIM: To compare the safety profile comparison of VDZ to TNF-antagonist therapy in patients with IBD (data from the VICTORY consortium)

RESULTS:
• Of 1,768 patients, after propensity score matching n=872 (VDZ=436; CD=538) patients were included
• Propensity score matching accounted for age, sex, prior disease-related hospitalization within the previous year, disease phenotype, disease severity, prior bowel surgery for CD, steroid refractoriness or dependence, and prior TNF-antagonist failure

Safety profile by treatment

Disease phenotype included stricturing or penetrating complication history for CD, disease extent for UC. Bold text indicates significance.

CD, Crohn’s disease; CI, confidence interval; IBD, inflammatory bowel disease; IM, immunomodulator; OR, odds ratio; SAE, serious adverse event; SI, serious infection; TNF, tumor necrosis factor; US, United States; VDZ, vedolizumab.
CONCLUSIONS:

- In clinical practice, rates of SI and SAEs were lower with VDZ than with TNF-antagonist therapy
- Concomitant immunosuppressive use was associated with an increased risk for both SI and SAE
- Rates of SI and SAEs were similar between VDZ and TNF-antagonist therapy when using concomitant immunosuppressive therapy
TOFACITINIB FOR INDUCTION AND MAINTENANCE OF MODERATE TO SEVERE ULCERATIVE COLITIS

- Moderate-to-severe patients (Mayo score 6–12)
- OCTAVE Induction 1: anti-TNF-exposed, % (placebo/tofa 10 mg): 53.3/53.4
- OCTAVE Induction 2: anti-TNF-exposed, % (placebo/tofa 10 mg): 58.0/54.5
- OCTAVE Sustain: anti-TNF-exposed, % (placebo/tofa 5 mg/tofa 10 mg): 46.5/45.5/51.3
  - Clinical remission: Mayo ≤2 with no subscore >1; Endoscopic remission: endoscopy subscore ≤1; For OCTAVE Sustain, baseline values were obtained at the time of entry into one of the induction trials (OCTAVE Induction 1 or 2); All P-values versus placebo. BID, twice daily.

TOFACITINIB ACHIEVES SYMPTOMATIC IMPROVEMENT WITHIN 3 DAYS IN MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS, REGARDLESS OF PRIOR TUMOUR NECROSIS FACTOR INHIBITOR TREATMENT STATUS: RESULTS FROM OCTAVE INDUCTION 1 & 2
TOFACITINIB ACHIEVES SYMPTOMATIC IMPROVEMENT WITHIN 3 DAYS IN MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS, REGARDLESS OF PRIOR TUMOUR NECROSIS FACTOR INHIBITOR TREATMENT STATUS: RESULTS FROM OCTAVE INDUCTION 1 & 2
Efficacy and safety of dose escalation to tofacitinib 10mg BID for patients with ulcerative colitis following loss of response on tofacitinib 5 mg BID maintenance therapy: results from OCTAVE OPEN

**Efficacy in the dose escalation subpopulation**

<table>
<thead>
<tr>
<th></th>
<th>Month 2</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical response</td>
<td>58.6</td>
<td>68.8</td>
</tr>
<tr>
<td>Mucosal healing</td>
<td>41.4</td>
<td>60.4</td>
</tr>
<tr>
<td>Remission</td>
<td>34.5</td>
<td>52.1</td>
</tr>
</tbody>
</table>

**Clinical response:** ≥3-point and 30% reduction from induction study baseline total Mayo score plus decrease ≥1 point in rectal bleeding subscore or absolute rectal bleeding subscore ≤1

**Mucosal healing:** Mayo endoscopic subscore of 0 or 1

**Remission:** total Mayo score ≤2 with no individual subscore >1, and rectal bleeding subscore of 0

Data are full analysis set, with non-responder imputation, based on local read of endoscopy. Two patients who received tofacitinib 5 mg BID are included (protocol violations). Patients were treated as non-responders after the time of discontinuation up to the visit they would have reached if they had stayed in the study. No imputation for missing data was applied for ongoing patients. N=58 patients included in efficacy analyses (based upon July 2016 data cut-off) includes two patients who qualified to receive tofacitinib 10 mg BID, but were assigned to treatment with tofacitinib 5 mg BID in OCTAVE Open; BID, twice daily; N, number of evaluable patients; n, number of patients with efficacy response.
APREMILAST FOR ACTIVE ULCERATIVE COLITIS: A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

Silvio Danese\textsuperscript{1}; Markus F. Neurath\textsuperscript{2}; Adam Kopoń\textsuperscript{3}; Salam F. Zakko\textsuperscript{4}; Timothy C. Simmons\textsuperscript{5}; Ronald Fogel\textsuperscript{6}; Judy Maccarone\textsuperscript{7}; Xiaojiang Zhan\textsuperscript{7}; Keith Usiskin\textsuperscript{7}; Denesh Chitkara\textsuperscript{7}

\textsuperscript{1}Istituto Clinico Humanitas, Milan, Italy; \textsuperscript{2}Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; \textsuperscript{3}Toruński Centrum Gastrologiczne Gastromed, Toruń, Poland; \textsuperscript{4}Connecticut Clinical Research Foundation of Bristol Hospital, Bristol, CT; \textsuperscript{5}West Gastroenterology Medical Group, Los Angeles, CA; \textsuperscript{6}Clinical Research Institute of Michigan, Chesterfield, MI; \textsuperscript{7}Celgene Corporation, Summit, NJ

Presented at: Digestive Disease Week\textsuperscript{©}; June 2–5, 2018; Washington, DC.
ClinicalTrials.gov: NCT02289417. This study was sponsored by Celgene Corporation.
CONVERSION OF cAMP TO AMP BY PDE4 INCREASES THE PRODUCTION OF PRO-INFLAMMATORY MEDIATORS

Leukocyte

APREMILAST: A NOVEL ORAL SMALL MOLECULE PDE4 INHIBITOR THAT WORKS INTRACELLULARLY TO MODULATE PRO- AND ANTI-INFLAMMATORY MEDIATORS

Pro-inflammatory mediators (e.g., TNF-α, IL-23)

Anti-inflammatory mediators (e.g., IL-10)

• The aim of this double-blind, placebo-controlled study is to evaluate the efficacy and safety of apremilast in subjects with active UC (defined as a TMS ≥6 to ≤11, with an MES ≥2) who failed ≥1 conventional therapy for UC and were naïve to biologic therapy.
• Patients were randomized (1:1:1) to receive apremilast 30 mg BID, apremilast 40 mg BID, or placebo BID for up to 12 weeks
• Endoscopy and histology scoring was done centrally
• Data from the 12-week, double-blind, placebo-controlled phase are being presented
• Blinded active treatment and extension phase are ongoing

TMS=Total Mayo Score; MES=Mayo Endoscopic Score.
### BASELINE SUBJECT DEMOGRAPHICS AND DISEASE CHARACTERISTICS

<table>
<thead>
<tr>
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<tr>
<td></td>
<td>n=58</td>
<td>n=57</td>
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</tr>
<tr>
<td>Age, mean, years</td>
<td>42.9</td>
<td>40.1</td>
<td>43.4</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>33 (57)</td>
<td>39 (68)</td>
<td>34 (62)</td>
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<tr>
<td>Duration of UC, mean, years</td>
<td>6.9</td>
<td>6.2</td>
<td>8.6</td>
</tr>
<tr>
<td>Disease in rectum and sigmoid only, n (%)</td>
<td>14 (24)</td>
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<td>Previous exposure to IMM, n (%)</td>
<td>17 (29)</td>
<td>18 (32)</td>
<td>16 (29)</td>
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<tr>
<td>Baseline TMS, mean</td>
<td>8.2</td>
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<tr>
<td>Baseline endoscopy subscore, mean</td>
<td>2.6</td>
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<td>2.6</td>
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IMM=immunosuppressant therapy (methotrexate, azathioprine, 6-mercaptopurine).
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IMM=immunosuppressant therapy (methotrexate, azathioprine, 6-mercaptopurine).
SUBJECT DISPOSITION THROUGH WEEK 12

Randomized N=170

- Placebo n=58
  - Did not complete treatment: Adverse event 3 (5.2%), Lack of efficacy 3 (5.2%), Withdrawal 1 (1.7%)
  - Completed placebo-controlled phase n=51 (87.9%)

- Apremilast 30 mg BID n=57
  - Did not complete treatment: Adverse event 3 (5.3%), Withdrawal 1 (1.8%)
  - Completed placebo-controlled phase n=53 (93%)

- Apremilast 40 mg BID n=55
  - Did not complete treatment: Adverse event 2 (3.6%), Withdrawal 1 (1.8%)
  - Completed placebo-controlled phase n=52 (94.5%)
PRIMARY END POINT: PROPORTION OF SUBJECTS ACHIEVING CLINICAL REMISSION BY TMS* AT WEEK 12 (ITT, NRI)

*TMS ≤2, with no individual subscore >1.

§Due to the stepdown testing procedure, the formal statistical test between apremilast 30 mg BID and placebo could not be performed. Nominal statistically significance at the 0.05 level is displayed.

ITT=intent to treat; NRI=non-responder imputation.
PROPORTION OF APREMILAST 30 MG BID SUBJECTS ACHIEVING ENDOSCOPIC SUBSCORE ≤1, CLINICAL REMISSION BY PMS*, AND CLINICAL RESPONSE§ BY TMS AT WEEK 12 (ITT, NRI)

*PMS ≤2 with no individual subscore >1.
§Decrease from baseline in the TMS ≥3 points and ≥30%, along with a reduction in the rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore ≤1.

PMS=Partial Mayo Score.
PROPORTION OF SUBJECTS ACHIEVING HISTOLOGICAL REMISSION (GEBOES <2) AT WEEK 12 (ITT, NRI)

Placebo

Apremilast 30 mg BID

Apremilast 40 mg BID

Δ=14.5%

Δ=12.5%

Δ=

P=0.1073

43.9%

P=0.1671

41.8%

n/N=

17/58

25/57

23/55

Proportion of Subjects Achieving Histological Remission

29.3%
EXPLORATORY END POINT: PROPORTION OF SUBJECTS ACHIEVING MUCOSAL HEALING (MES ≤1 AND GEBOES <2) AT WEEK 12 (ITT, NRI)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Proportion Achieving Mucosal Healing</th>
<th>Δ (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>15.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apremilast 30 mg BID</td>
<td>33.3%</td>
<td>17.8%</td>
<td>0.0326</td>
</tr>
<tr>
<td>Apremilast 40 mg BID</td>
<td>21.8%</td>
<td>6.3%</td>
<td>0.4805</td>
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## OVERVIEW OF TEAE THROUGH WEEK 12

<table>
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<tbody>
<tr>
<td></td>
<td>n=58</td>
<td>n=57</td>
<td>n=55</td>
</tr>
<tr>
<td>Subjects, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any TEAE</td>
<td>30 (51.7)</td>
<td>28 (49.1)</td>
<td>36 (65.5)</td>
</tr>
<tr>
<td>Any serious TEAE</td>
<td>2 (3.4)</td>
<td>0 (0.0)</td>
<td>1 (1.8)*</td>
</tr>
<tr>
<td>Any TEAE leading to drug withdrawal</td>
<td>4 (6.9)</td>
<td>0 (0.0)</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>Any TEAE leading to death</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>TEAEs in ≥5% of subjects, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral upper respiratory infection</td>
<td>1 (1.7)</td>
<td>5 (8.8)</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (6.9)</td>
<td>13 (22.8)</td>
<td>14 (25.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (8.6)</td>
<td>3 (5.3)</td>
<td>6 (10.9)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (1.7)</td>
<td>3 (5.3)</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>3 (5.2)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Back pain</td>
<td>1 (1.7)</td>
<td>0 (0.0)</td>
<td>3 (5.5)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>2 (3.4)</td>
<td>3 (5.3)</td>
<td>1 (1.8)</td>
</tr>
</tbody>
</table>

*Pancreatitis.

TEAE=treatment-emergent adverse event.
CONCLUSIONS

- Subjects with active UC treated with apremilast achieved clinically meaningful improvements in disease activity as compared with placebo.

- Subjects in the apremilast 30 mg treatment arm achieved statistically significant improvements in clinical remission, endoscopy, biomarkers of hsCRP and fecal calprotectin, and mucosal healing by endoscopy and histology compared with subjects in the placebo treatment arm.

- Subjects in the apremilast 40 mg treatment arm achieved statistically significant improvements in clinical response and biomarkers of hsCRP and fecal calprotectin compared with subjects in the placebo treatment arm.

- No new safety signals were detected with apremilast treatment in this study population.
• The landscape of treatment in ulcerative colitis is changing
  – Shift to leukocyte trafficking inhibitors such as vedolizumab which is safe and effective

• Oral small molecules will offer an attractive options from mild-severe UC
  – Pre and post-biologic positioning
  – Potential for intermittent dosing strategies
Thank you!

Enjoy Washington, DC and DDW 2018!