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Continuous Clinical Response Is Associated With a Change of Disease Course in Patients With Moderate to Severe Ulcerative Colitis Treated With Golimumab

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GLOSSARY

Continuous Clinical Response Is Associated With a Change of Disease Course in Patients With Moderate to Severe Ulcerative Colitis Treated With Golimumab

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Background: Responders to induction treatment sustain continuous clinical response (CCR) through 1 year in about 50% of patients in PURSUIT-M trial with golimumab maintenance in ulcerative colitis (UC). This post hoc analysis of PURSUIT-M describes the 1-year clinical, endoscopic, quality of life (QoL), and biomarker and 4-year clinical outcome in patients with sustained response to golimumab therapy for UC.

Methods: We compared clinical, endoscopic, QoL, and calprotectin outcomes in CCR and non-CCR patients through 54 weeks in PURSUIT-M. Persistence on golimumab therapy and clinical response at 4 years was assessed for CCR and non-CCR patients. The relationship of colectomy with CCR status was determined.

Results: Among patients receiving golimumab maintenance, greater proportions of patients with vs without CCR at week 54 achieved clinical remission (67.1% vs 1.9%), corticosteroid-free remission (61.6% vs 1.9%), endoscopic remission (Mayo endoscopy score 0 [47.9% vs 1.3%]), and normal QoL (inflammatory bowel disease questionnaire score ≥170 [75.0% vs 24.4%]). CCR but not non-CCR patients maintained normalized calprotectin levels during maintenance. Among patients who entered the long-term extension study, a greater proportion of patients with vs without CCR maintained PGA 0 through week 216 (58% vs 42%). Colectomy was performed in 47 induction nonresponders and in 13 induction responders. None of the patients going onto colectomy achieved CCR through 54 weeks in PURSUIT-M.

Conclusions: Continuous clinical response is associated with favorable short- and long-term clinical, endoscopic, QoL, and biomarker responses that may result in changing the course of disease and may prevent colectomy in patients with moderate to severe UC treated with golimumab.

Key Words: continuous clinical response, golimumab, ulcerative colitis, endoscopic healing, colectomy

Received for publications February 21, 2018; Editorial Decision May 22, 2018.

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Conflicts of interest: WR has received research funding from Abbott Laboratories, Abbvie, Aesca, Centocor, Falk Pharma GmbH, Immundiagnsotik, and MSD; WR has served as a speaker for Abbott Laboratories, Abbvie, Aesca, Aptalis, Centocor, Celltrion, Danone Austria, Elan, Falk Pharma GmbH, Ferring, Immundiagnostik, Mitsubishi Tanabe Pharma Corporation, MSD, Otsuka, PDL, Pharmacosmos, Schering-Plough, Shire, Takeda, Therakos, Vifor, and Yakult; WR has served as a consultant for Abbott Laboratories, Abbvie, Aesca, Amgen, AM Pharma, Astellas, Astra Zeneca, Avaxia, Bioclinica, Biogen IDEC, Boehringer-Ingelheim, Bristol-Myers Squibb, Cellerix, Chemocentryx, Celgene, Centocor, Celltrion, Covance, Danone Austria, Elan, Falk Pharma GmbH, Ferring, Galapagos, Genentech, Gilead, Grünenthal, ICON, Index Pharma, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, MedImmune, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Nestle, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Robarts Clinical Trial, Schering-Plough, Second Genome, Setpointmedical, Takeda, Therakos, Tigenix, UCB, Vifor, Zyngenia, and 4SC; and WR has served as an advisory board member for Abbott Laboratories, Abbvie, Aesca, Amgen, AM Pharma, Astellas, Astra Zeneca, Avaxia, Biogen IDEC, Boehringer-Ingelheim, Bristol-Myers Squibb, Cellerix, Chemocentryx, Celgene, Centocor, Celltrion, Danone Austria, Elan, Ferring, Galapagos, Genentech, Grünenthal, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, MedImmune, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Nestle, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Schering-Plough, Second Genome, Setpointmedical, Takeda, Therakos, Tigenix, UCB, Zyngenia, and 4SC. J-FC has received research funding from AbbVie, Second Genome, and Takeda and personal fees from Janssen and Pfizer. PG has received research funding from Janssen, Abbvie, and Ferring and consultancy from Janssen, Abbvie, Takeda, Merck, Pfizer, Celltrion, Danone, and Ferring. PR has received research funding from Abbott, Janssen, Merck, Merck Serono, UCB, Millennium/Takeda, Genentech/Hoffman LaRoche, Neovacs, Bristol-Myers Squibb, Robarts, Tillotts, Pfizer, and Falk Pharma and consultancy from Abbott, Janssen, Merck, MerckSerono, UCB, Millennium/Takeda, Genentech/Hoffman LaRoche, Neovacs, Bristol-Myers Squibb, Robarts, Tillotts, Pfizer, and Falk Pharma. WJS has received research funding from, has served as a consultant for, and has received honoraria and travel support from Janssen. DT has no disclosures relevant to this work. FC and AK are employees of and shareholders in MSD Switzerland. SH, GP, and RY are employees of and shareholders in Merck & Co., Inc. CM and HZ are employees of and shareholders in Johnson & Johnson.

Supported by: This study was funded by Merck & Co., Inc., Kenilworth, NJ, USA. PURSUIT-M was sponsored by Janssen Research & Development, LLC, Spring House, PA, USA.

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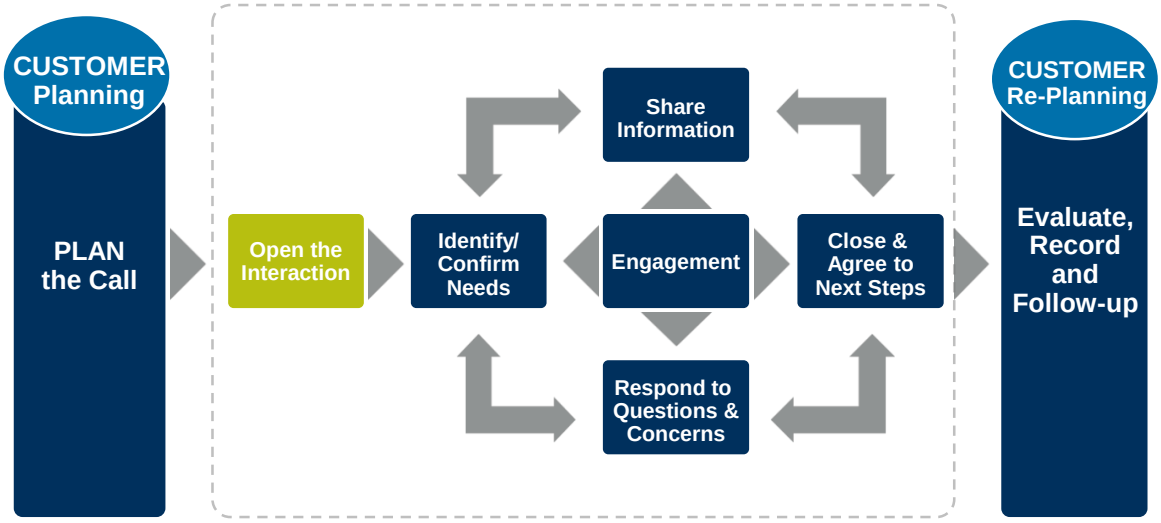
doi: 10.1093/ibd/izy229
Published online 6 july 2018

Abstract

The abstract provides a summary of the study and describes the background, methods, results, and author conclusions. The abstract can be an effective starting point as you introduce this post hoc analysis of the PURSUIT maintenance (PURSUIT-M) trial to customers.

Open the Interaction



Suggested Verbalization:

*"Doctor, I'd like to share with you the results of the post hoc analysis of the PURSUIT-M trial, which compared clinical, **endoscopic***, quality-of-life, and **calprotectin*** outcomes in continuous clinical response (CCR) patients and non-CCR patients through week 54 in the trial."*

*The definition of this word may be found in the glossary.

GLOSSARY

INTRODUCTION

The STRIDE consensus initiative of the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) on outcome measures in inflammatory bowel disease (IBD) clinical trials concluded that patient-reported normalization of stool frequency and absence of rectal bleeding together with endoscopic healing (Mayo endoscopy score of 0–1 or 0) is the target of UC treatment.[1] The STRIDE consensus furthermore considers the restoration of patient-reported normal quality of life (QoL) as an overarching goal of IBD therapy. Patients' expectation of UC treatment is a normal quality of life, achieved by sustained symptom control (remission) with durable response to medical therapy, while avoiding hospitalization and surgery.[2]

Episodes of uncontrolled mucosal inflammation result in a relapsing disease course of UC.[3] There is growing evidence that uncontrolled inflammation of the bowel mucosa in UC results in bowel damage that may require colectomy.[4,5] In a large prospective UC cohort study including 285 UC patients who started infliximab, the 5-year relapse rate and colectomy rate were 61% and 20%, respectively, and predictors of relapse-free and colectomy-free survival included short-term complete clinical response and endoscopic healing.[6] Early and continuous control of mucosal inflammation with clinical and endoscopic remission ("deep remission") is an important goal of medical therapy in UC and may result in long-term clinical benefit with prevention of colectomy.

The randomized, double-blind, placebo-controlled PURSUIT maintenance (PURSUIT-M) trial of golimumab for UC introduced continuous clinical response (CCR) as the primary efficacy endpoint specifically constructed to measure the continuous control of disease activity among patients with response to golimumab induction.[7] In PURSUIT-M, CCR was defined as a clinical response that was maintained without treatment failure through 54 weeks (Supplementary Table 1) using partial Mayo score assessments every 4 weeks (Q4W) and full Mayo score assessments at weeks 30 and 54; endoscopy was also performed at any time a clinical flare was noted (on the partial Mayo score) to confirm a loss of response. The CCR endpoint can thus be considered a very strict measure of continuous control of UC disease activity based on both symptoms and endoscopic healing after successful induction of response.

This post hoc analysis of the PURSUIT-M trial describes the clinical, endoscopic, and quality-of-life benefits that are associated with continuous clinical response through 54 weeks in PURSUIT-M, the change of calprotectin level and the need for colectomy in patients with and without CCR, and the effect of achieving CCR on the long-term (4 years) disease course of moderate to severe UC.

METHODS

This was a post hoc analysis of PURSUIT-M (protocol number C0524T18; ClinicalTrials.gov, NCT00488631; EudraCT, 2006-003399-37), a randomized, double-blind, placebo-controlled, multicenter phase 3 trial. PURSUIT-M was conducted in accordance with Good Clinical Practice and the principles of the Declaration of Helsinki and was approved by each site's institutional review board or ethics committee. Patients provided written informed consent before participating in the study.

Patients

As described previously,[7] patients were eligible for PURSUIT-M after completing golimumab induction in PURSUIT-SC (ClinicalTrials.gov, NCT00487539)[8] or PURSUIT-IV (ClinicalTrials.gov, NCT00488774)[9] trials, which enrolled patients with moderate to severe UC (Mayo score 6–12 and endoscopic subscore ≥2) who had an inadequate response to or were intolerant to oral 5-aminosalicylates, oral corticosteroids, or immunosuppressives or who were corticosteroid-dependent.

PURSUIT-M

In PURSUIT-M, 464 responders to golimumab subcutaneous or intravenous induction regimens at week 6 were randomized to 50 mg or 100 mg subcutaneous golimumab or placebo maintenance through week 54 (the randomized population of PURSUIT-M) (Fig. 1). Responders to placebo induction regimens (N = 129) were continued on placebo during maintenance, and nonresponders to placebo or golimumab induction regimens (N = 230 and N = 405, respectively) were not randomized and received 100 mg golimumab during maintenance (the nonrandomized population of PURSUIT-M) (Fig. 1). In the randomized population with responders to golimumab induction, clinical response through week 54 was the primary endpoint of PURSUIT-M and was defined as a continuous clinical response (CCR) to golimumab or placebo maintenance without treatment failure.[7] Clinical remission, corticosteroid-free clinical remission, endoscopic healing, and QoL (IBDQ score) were secondary endpoints of PURSUIT-M.[7] But these were not assessed in the CCR vs the non-CCR patient subpopulations and will, therefore, be described in this article. Patients who had a clinical flare (Supplementary Table 1) at any time during the study received endoscopy to confirm (or rule out) a loss of the clinical response. In addition to loss of response, patients who had protocol-prohibited concomitant UC medication changes, a partial or total colectomy or an ostomy, discontinued treatment owing to lack of efficacy, or golimumab dose adjustment before week 54 were considered to be in treatment failure (ie, non-CCR) (Supplementary Table 1).

PURSUIT Long-Term Extension

Patients were eligible for a 3-year, open-label, long-term extension (LTE) of PURSUIT-M if the investigators felt that continued benefit from golimumab treatment was most likely. Overall, 120 of 154 and 116 of 154 responders to golimumab induction completed week 54 on 50 mg and 100 mg golimumab maintenance, respectively; 101 and 102 patients entered the LTE on 50 mg and 100 mg golimumab Q4W, respectively. Two hundred patients continued receiving golimumab Q4W, and

Introduction

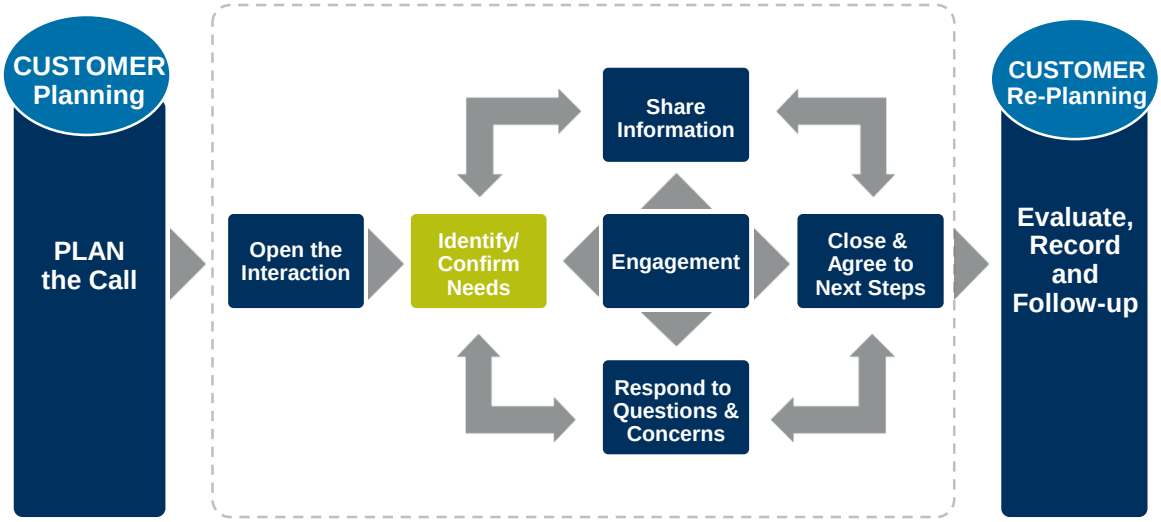
The Introduction provides a concise account of the background of the research question and defines the objectives of the work.

The Introduction in Reinisch, et al. discusses the relationship between episodes of uncontrolled **mucosal*** inflammation and a relapsing disease course in UC. The authors identify early and continuous control of mucosal* inflammation with clinical and **endoscopic remission*** as an important goal of medical therapy in UC, potentially resulting in long-term clinical benefit with prevention of **colectomy***.

The Introduction concludes by discussing the PURSUIT-M trial of golimumab for UC and its introduction of the primary efficacy endpoint of continuous clinical response (CCR). CCR, defined as a **clinical response*** maintained at every 4-week assessment without treatment failure through 54 weeks, was a unique measure specifically constructed in this trial to measure the continuous control of UC disease activity among patients who responded to golimumab induction of clinical response.*

*The definition of this word may be found in the glossary.

Identify/Confirm Needs



Suggested Verbalization:

"Doctor, there is growing evidence that episodes of uncontrolled mucosal inflammation in UC may lead to a relapsing disease course that results in bowel damage that may require colectomy*. Early and continuous control of mucosal* inflammation with clinical and endoscopic remission* is identified as an important target of medical therapy in UC, potentially leading to long-term clinical benefit, prevention of colectomy*, and restoration of normal quality of life."*

*The definition of this word may be found in the glossary.

Execution

Patients' Unmet Needs/Physicians' Expectations

Patients with UC seek continuous control of symptoms. Physicians aim to withdraw corticosteroids completely in their patients with corticosteroid-dependent disease.

- SIMPONI is the only biologic proven to deliver CCR, maintaining clinical response* at every 4-week assessment for 54 weeks in the PURSUIT-M clinical trial
- SIMPONI delivered major clinical outcomes at week 54, as confirmed by CCR versus non-CCR UC patient data on **mucosal healing***, discontinuation of corticosteroids, **clinical remission***, and quality-of-life
- SIMPONI delivered long-term disease control, maintaining no or mild disease activity in 72% of week 54 CCR patients through 4 years†
- CCR is a unique measure that addresses unmet needs, focusing on patients' and physicians' demand for long-lasting disease control

*The definition for this word may be found in the glossary.
†Disease activity was based on Physician Global Assessment (PGA)—a 5- or 6-point scoring system used by clinicians to assess disease severity and guide therapeutic decisions.

Methods

The Methods section provides a detailed description of the methods used to answer a research question. In the Methods section of Reinisch, et al. investigators describe how they conducted these post hoc analyses of the PURSUIT-M trial by:

- Comparing the clinical, endoscopic*, quality-of-life, and calprotectin* outcomes associated with continuous clinical response through week 54 in the PURSUIT-M trial of CCR versus non-CCR patients
- Determining the relationship of colectomy* and CCR status
- Assessing persistence on golimumab therapy and clinical response* at 4 years for CCR and non-CCR patients

*The definition of this word may be found in the glossary.

Study Design—PURSUIT-M

PURSUIT-M was a randomized, double-blind, placebo-controlled, multicenter phase 3 study.
In a randomized trial, study participants are randomly assigned to a treatment group. In the case of PURSUIT-M, participants were randomized to one of three treatment arms: 50 mg or 100 mg of subcutaneous golimumab or placebo (“withdrawal group”)—named as such because the patients in the placebo arm of this maintenance study were in clinical response* to golimumab after participating in companion induction studies (i.e., “withdrawal” of golimumab after response to induction).

*The definition of this word may be found in the glossary.

Patients—PURSUIT-M

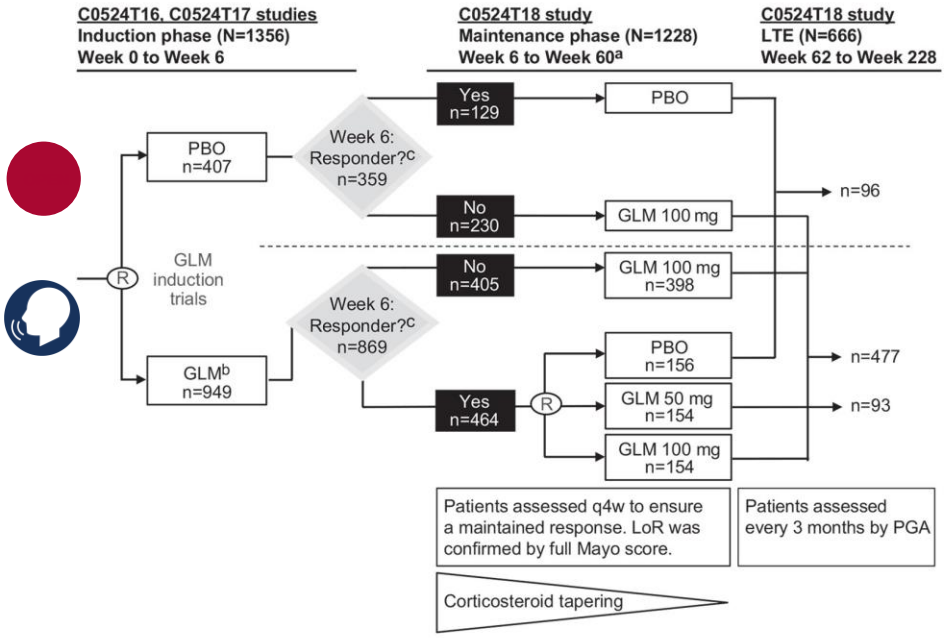
Patients eligible for PURSUIT-M had completed golimumab induction regimens in the PURSUIT-subcutaneous (SC) or PURSUIT-intravenous (IV) studies and had demonstrated clinical response* to golimumab induction at week 6.

*The definition of this word may be found in the glossary.

Study Design—PURSUIT-Long-Term Extension (LTE)

PURSUIT-LTE was a 3-year, open-label, long-term extension of PURSUIT-M. This long-term extension included patients identified by the investigators as most likely to derive continued benefit from golimumab treatment.

GLOSSARY



[a]Week 60 from start of treatment = Week 54 of C0524T18 (PURSUIT-Maintenance) trial
[b]Various tested doses
[c]Week-6 Responder = defined by Clinical Response on full Mayo score
R, randomization; PBO, placebo; GLM, golimumab; q4w, every 4 weeks; LoR, loss of response

FIGURE 1. Patient flow in PURSUIT-M.

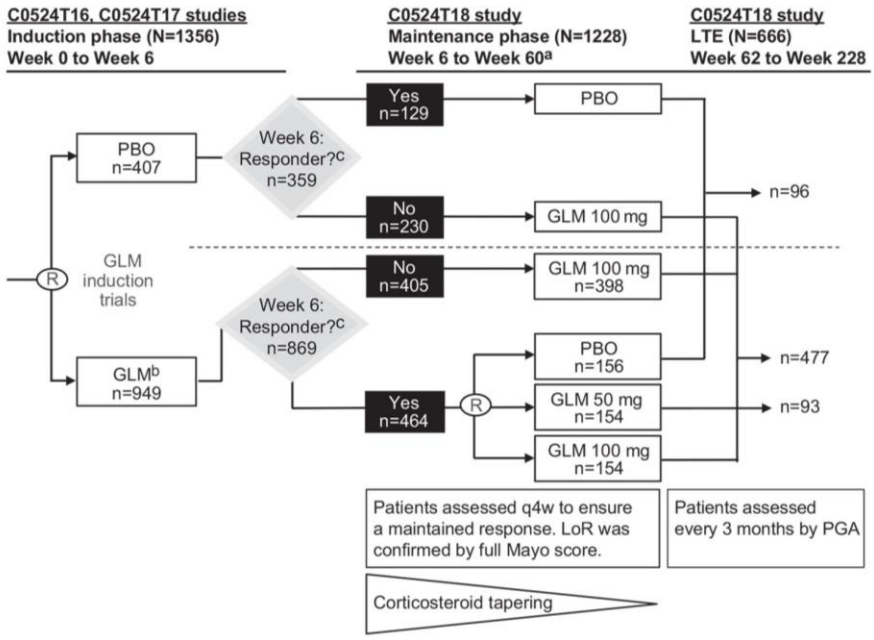
of those, 195 were considered responders by Physician Global Assessment (PGA 0 or 1) at the start of LTE and were included in the LTE efficacy analysis.[10] Patients who were on golimumab 50 mg maintenance in the main study and who, in the opinion of the investigators, experienced disease worsening were permitted to receive a 1-time dose increase to 100 mg golimumab. Patients receiving golimumab 100 mg in the main study were not eligible for a dose increase. In addition, 104 patients on subcutaneous placebo maintenance in the randomized population and another 365 patients of the nonrandomized population entered the LTE at week 56. During the LTE, change of concomitant medications was allowed at the discretion of the investigator. Disease activity was assessed by PGA every 3 months. Loss of response was defined as an increase of at least 2 PGA points (on a 0–3 scale). The 2-year results of the LTE study of PURSUIT-M were recently published.[10] The last golimumab dose of the LTE was given at week 212, and final safety analysis was at week 228.

Post Hoc Analyses

In post hoc analyses, 2 subgroups were defined by the primary efficacy endpoint in PURSUIT-M: "CCR patients" who achieved continuous clinical response and "non-CCR patients" who did not achieve continuous clinical response through 54 weeks of PURSUIT-M. To assess the clinical, endoscopic, and QoL benefits associated with continuous clinical response, the rates of clinical remission, corticosteroid-free clinical remission (among patients receiving corticosteroids at baseline of induction), endoscopic healing (including separate analyses for patients with Mayo endoscopy subscore 0–1 or subscore 0), and inflammatory bowel disease questionnaire (IBDQ) score ≥170 (considered normal QoL) were analyzed at week 54 alone, and at both weeks 30 and 54, comparing CCR and non-CCR patients. The odds ratios (OR, 95% confidence interval [CI]) of achieving major clinical endpoints, endoscopic healing, and normal QoL were also calculated for CCR and non-CCR patients.

Calprotectin levels were measured at start (week 0) and end (week 6) of PURSUIT induction and at week 30 and week 54 of maintenance in the randomized population of PURSUIT-M. Calprotectin levels over time during induction and maintenance were assessed for CCR and non-CCR patients.

All colectomy cases in the randomized and nonrandomized populations of PURSUIT (N = 1228) were collected and reviewed through 54 weeks of follow-up. The early response to golimumab or placebo induction regimen and continuous clinical response to maintenance through week 54 (CCR) were assessed for all colectomy cases.



[a]Week 60 from start of treatment = Week 54 of C0524T18 (PURSUIT-Maintenance) trial
[b]Various tested doses
[c]Week-6 Responder = defined by Clinical Response on full Mayo score
R, randomization; PBO, placebo; GLM, golimumab; q4w, every 4 weeks; LoR, loss of response

FIGURE 1. Patient flow in PURSUIT-M.

As shown in this flow chart, 464 patients who responded to golimumab subcutaneous or intravenous induction regimens at week 6 in PURSUIT induction trials were randomized to receive 50 mg or 100 mg subcutaneous golimumab or placebo through week 54 in the PURSUIT-M trial. Patients who responded to placebo induction regimens (n =129) continued to receive placebo during maintenance. Conversely, non-responders to placebo or golimumab induction regimens (n = 230 and n = 405, respectively) did not undergo randomization and received 100 mg golimumab during maintenance.

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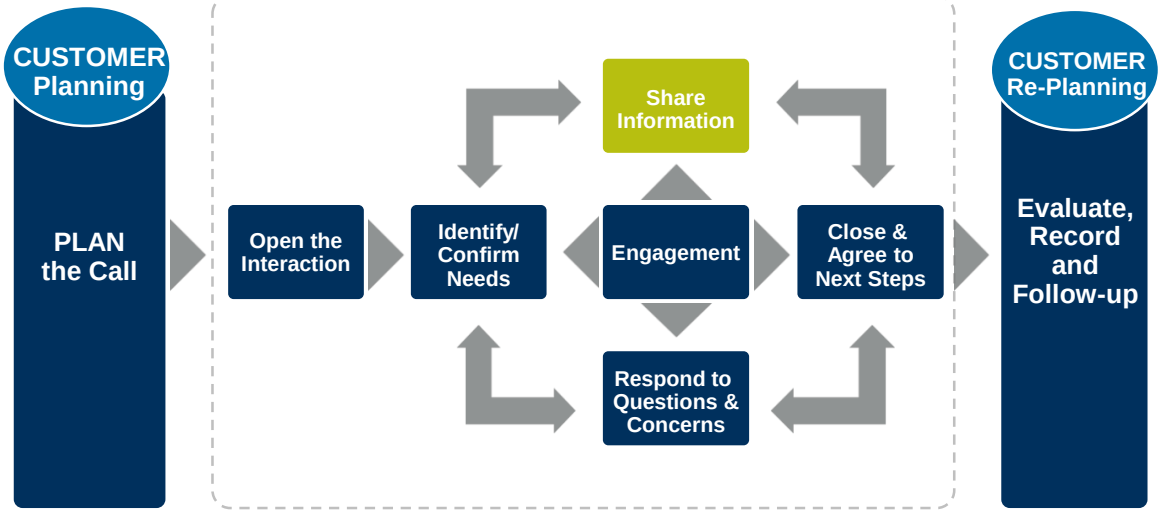


Suggested Verbalization:

"The randomized population of PURSUIT-M consisted of 464 patients who responded to golimumab subcutaneous or intravenous regimens at week 6 and were randomized to receive 50 mg or 100 mg subcutaneous golimumab or placebo through week 54.

"The 129 patients who responded to placebo induction regimens continued to receive placebo during the maintenance phase. The 230 nonresponders to placebo and 405 nonresponders to golimumab induction regimens were not randomized and received 100 mg golimumab during maintenance."

Patient Subgroups

Two patient subgroups were identified in the post hoc analyses based on the primary efficacy endpoint in PURSUIT-M:

- CCR patients: those who achieved continuous clinical response
- Non-CCR patients: those who did not achieve continuous clinical response through week 54

Calprotectin*

Levels of calprotectin* were measured at the start (week 0) and the end (week 6) of the PURSUIT induction phase and at week 30 and week 54 of the maintenance phase in the randomized population of PURSUIT-M.

Calprotectin* is a water-soluble, calcium- and zinc-binding protein found in the **cytosol*** of **neutrophils***. During active intestinal inflammation, neutrophils* migrate from the circulation to the intestinal mucosa*. The inflammatory process causes neutrophils*, and therefore, calprotectin*, to leak into the **lumen***, with subsequent excretion in feces. Thus, calprotectin* is considered a fecal biomarker of gastrointestinal inflammation.

*The definition of this word may be found in the glossary.

GLOSSARY

To assess the effect of CCR on the long-term disease course of moderate to severe UC, we compared the proportion of CCR patients with non-CCR patients with PGA 0 or 0–1 state (no or mild disease, respectively) through the 3-year LTE study (total follow-up of 4 years).

RESULTS

Clinical, Endoscopic, and Quality-of-Life Benefits Associated With Early and Continuous Clinical Response in PURSUIT-M

At week 6, 51.0% of moderate to severe UC patients responded to 200 mg (week 0) and 100 mg (week 2) subcutaneous golimumab induction. Through week 54, 47.0% and 49.7% of patients achieved CCR on 50 mg and 100 mg golimumab maintenance, respectively. The percentages of patients who were in clinical remission at both weeks 30 and 54 on 50 mg and 100 mg maintenance were 23.2% and 27.8%, respectively (compared with 15.6% on placebo maintenance).[7] A greater proportion of CCR patients than non-CCR patients achieved clinical remission (golimumab maintenance, 67.1% vs 1.9%; golimumab withdrawal, 68.8% vs 0.9%; Fig. 2A), corticosteroid-free remission (Fig. 2B), endoscopic healing (Mayo endoscopy score 0–1; Fig. 2C), endoscopic remission (Mayo endoscopy score 0; Fig. 2D), and an IBDQ score ≥170 (Fig. 2E). Similarly, greater proportions of CCR patients than non-CCR patients also achieved major clinical, endoscopic, and QoL endpoints as measured at both weeks 30 and 54 (Fig. 3). The odds of achieving major clinical, endoscopic, and QoL endpoints at week 54 based on achieving continuous clinical

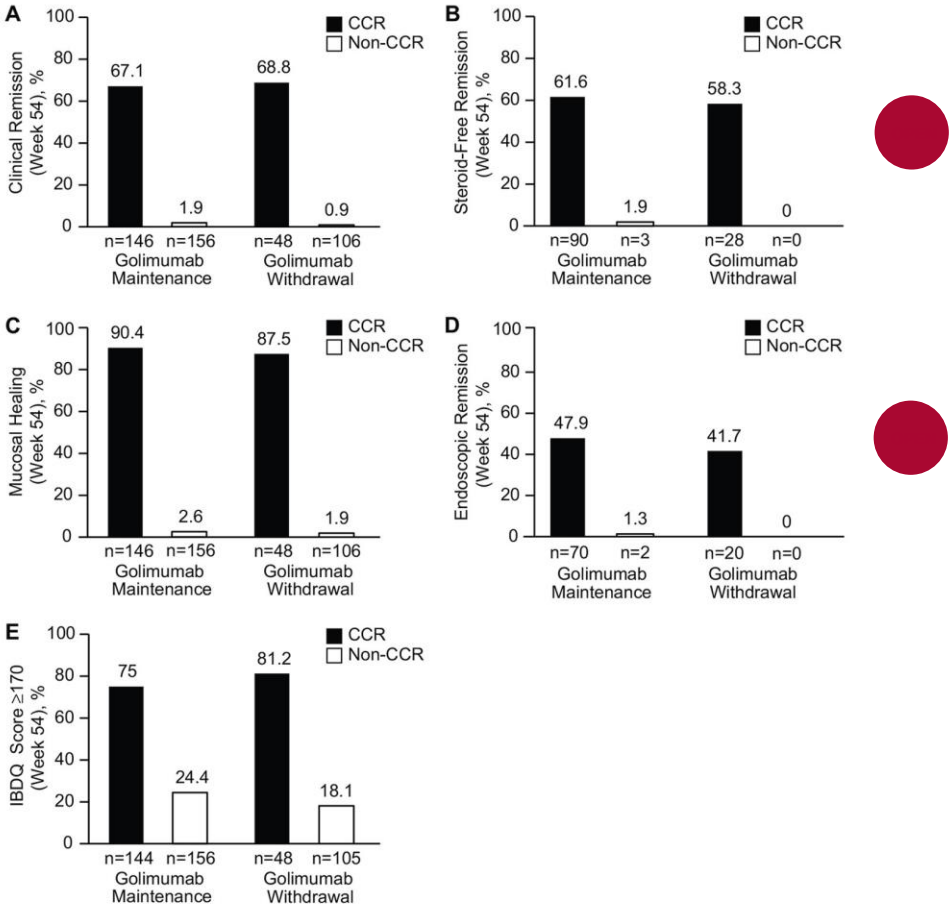


FIGURE 2. Proportions of patients who, at week 54, achieved clinical remission (A), corticosteroid-free remission (B), endoscopic healing (C), Mayo endoscopy subscore 0 (D), and IBDQ score >170 (E). IBDQ, Inflammatory Bowel Disease Questionnaire.

Objective

The objective of the post hoc analyses was to assess the effect of CCR on the long-term disease course of moderate-to-severe UC by comparing the proportion of CCR patients and non-CCR patients with Physician Global Assessment (PGA) 0 (no disease) or 0–1 state (mild disease) through the 3 year long-term extension study (total follow-up of 4 years).

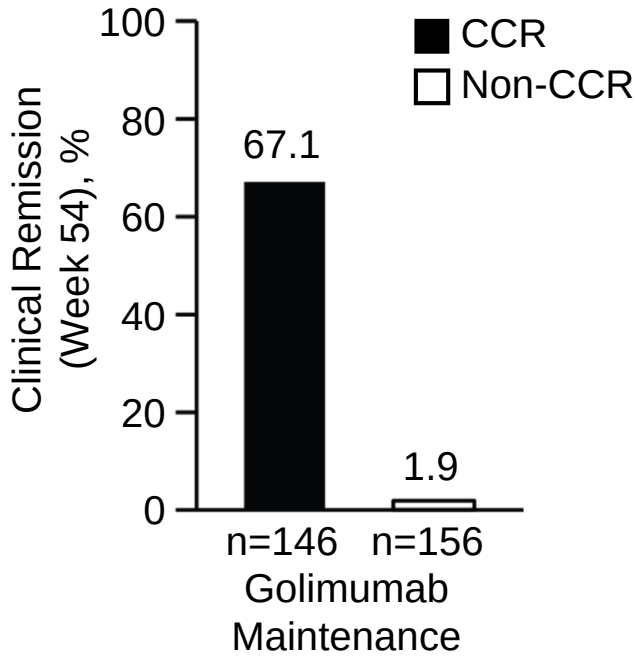
Results

The Results section provides a summary of the important findings of the research. In Reinisch et al. the Results section starts with a discussion of the clinical, endoscopic*, and quality-of-life benefits associated with early and continuous clinical response in the PURSUIT-M trial. The study investigators report that a greater proportion of CCR versus non-CCR patients achieved the following:

- Clinical remission* (golimumab maintenance, 67.1% versus 1.9%; golimumab withdrawal, 68.8% versus 0.9%)
- Corticosteroid-free remission
- Endoscopic* healing (Mayo endoscopy score 0–1)
- Endoscopic remission* (Mayo endoscopy score 0)
- IBDQ score ≥170

*The definition of this word may be found in the glossary.

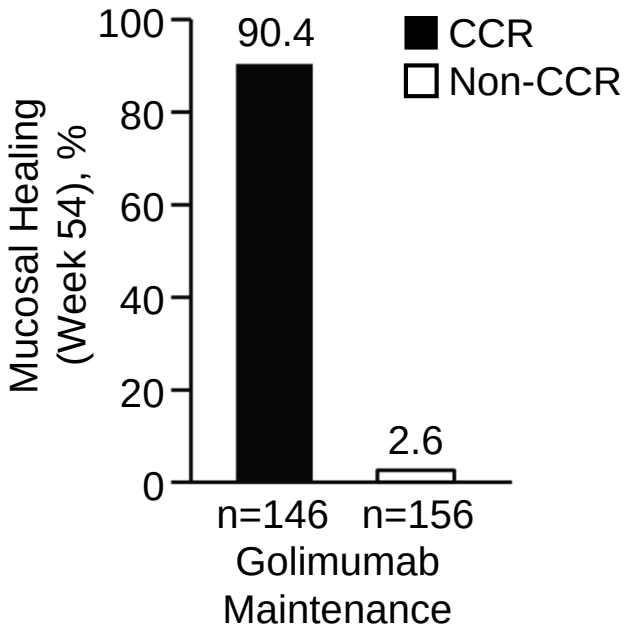
Results—Clinical Remission*



At week 54, 67.1% (n = 146) of patients in CCR achieved clinical remission* compared with 1.9% (n = 156) of non-CCR patients.

*The definition of this word may be found in the glossary.

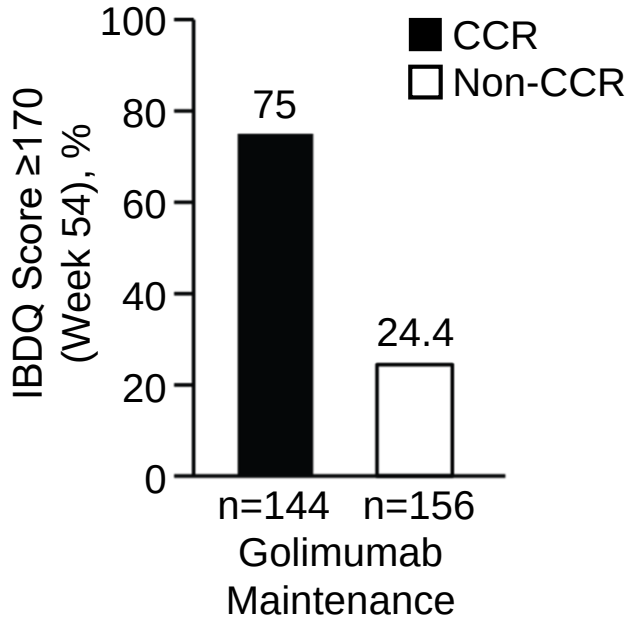
Results—Mucosal Healing*



At week 54, 90.4% (n = 146) of patients in CCR achieved mucosal healing* compared with 2.6% (n = 156) of non-CCR patients.

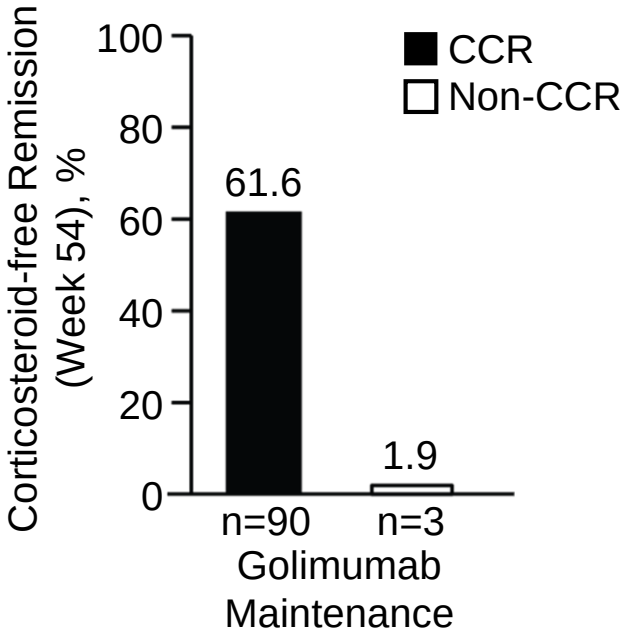
*The definition of this word may be found in the glossary.

Results—Quality-of-Life Score



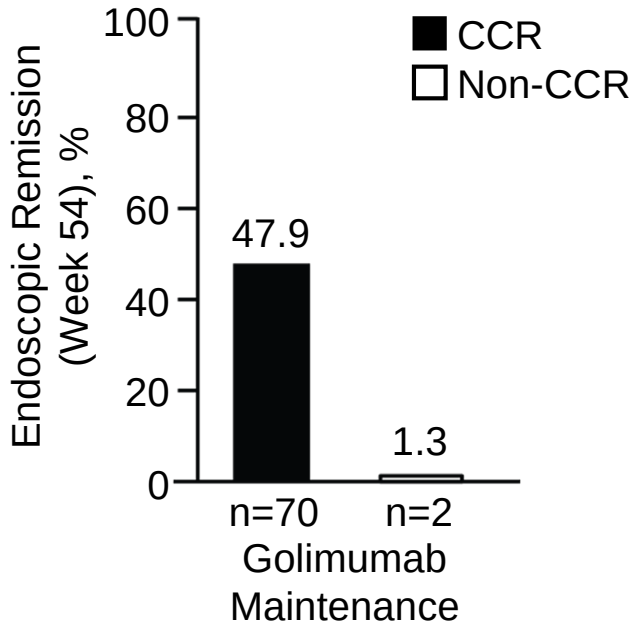
At week 54, 75.0% (n = 144) of patients in CCR achieved a normalized quality-of-life score (and Inflammatory Bowel Disease Questionnaire (IBDQ) score (≥170)) compared with 24.4% (n = 156) of non-CCR patients.

Results—Corticosteroid-free Remission



At week 54, 61.6% (n = 90) of patients in CCR achieved corticosteroid-free remission compared with 1.9% (n = 3) of non-CCR patients.

Results—Endoscopic Remission*



At week 54, 47.9% (n = 70) of patients in CCR achieved endoscopic remission* compared with 1.3% (n = 2) of non-CCR patients.

*The definition of this word may be found in the glossary.

Execution

SIMPONI Can Be Differentiated Through CCR

CCR in UC patients through the first year of therapy was associated with:

- A change of disease course
- Better clinical outcomes, including:
  - ✓ Clinical remission*
  - ✓ Mucosal healing*
  - ✓ Steroid-free remission
- Improvements in quality of life
- Long-term disease control

*The definition of this word may be found in the glossary.

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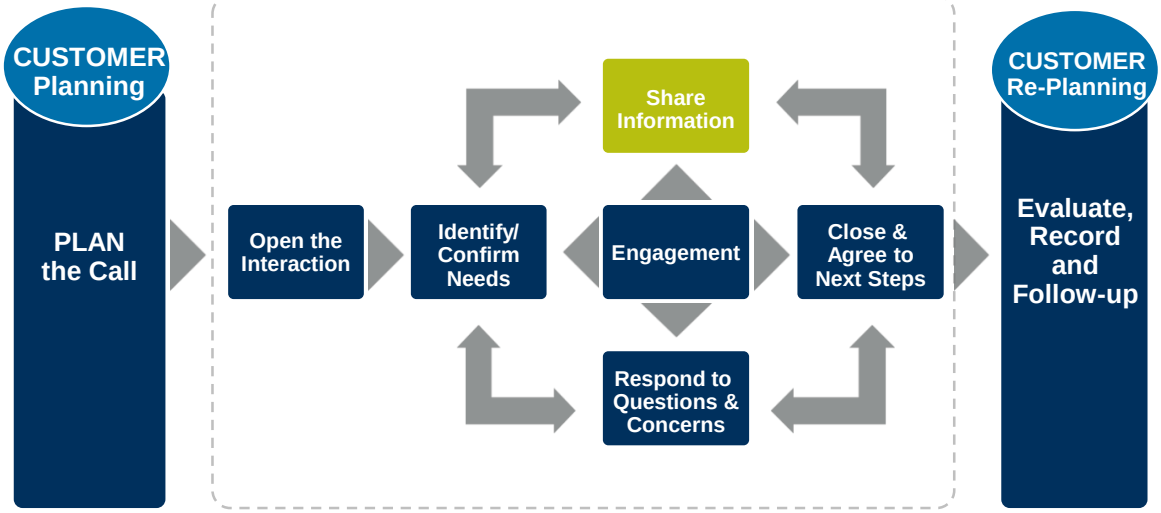

Suggested Verbalization:

"Doctor, PURSUIT-M study results suggest CCR is associated with a change of disease course in patients with moderate to severe UC treated with golimumab. This post hoc analysis showed that a greater proportion of CCR patients than non-CCR patients achieved clinical remission, corticosteroid-free remission, endoscopic* healing, endoscopic remission*, and an IBDQ score of ≥170. Greater proportions of CCR patients versus non-CCR patients also achieved major clinical, endoscopic*, and quality-of-life endpoints at weeks 30 and 54."*

*The definition of this word may be found in the glossary.

GLOSSARY

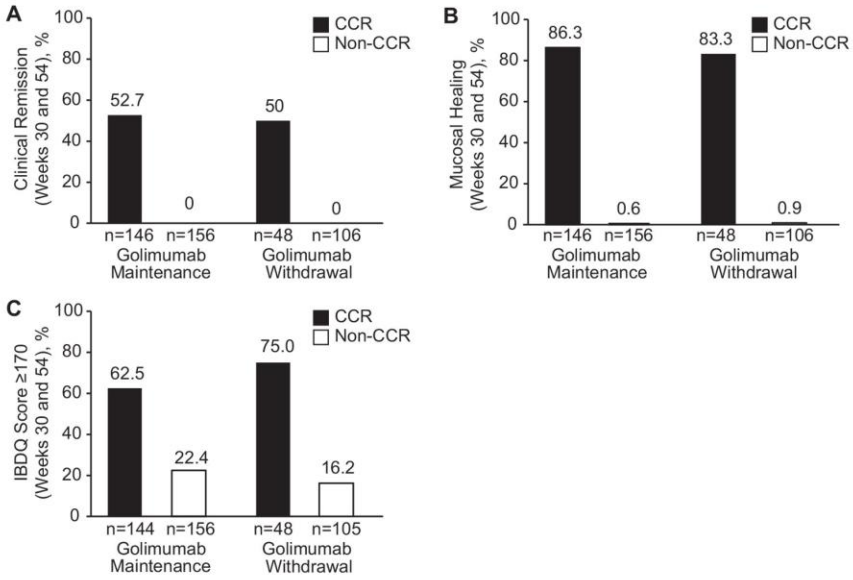

FIGURE 3. Proportion of patients who, at both weeks 30 and 54, achieved clinical remission (A), endoscopic healing (B), and IBDQ score >170 (C). IBDQ, Inflammatory Bowel Disease Questionnaire.

response in patients on golimumab maintenance are summarized in Table 1. The odds of achieving clinical remission, mucosal healing, endoscopic remission, and normal QoL (IBDQ ≥170) are 104.1, 358.3, 70.9, and 9.3, respectively. None of the non-CCR patients achieved corticosteroid-free remission at week 54. The results for CCR vs non-CCR patients on golimumab withdrawal (placebo maintenance) were quite similar, although no patients on placebo maintenance achieved endoscopic remission at week 54 (Table 1). Disease duration, extent of disease, Mayo score, severity of UC, c-reactive protein (CRP), and presence or absence of extra-intestinal manifestations at baseline did not separate the CCR and non-CCR patients.

Forty-seven patients (47 of 1228; 3.8%) needed colectomy during PURSUIT-M. The majority of colectomies were done in patients who did not respond to induction regimens (34 of 635, 5.4%), whereas 13 colectomies were done in responders to induction (13 of 593, 2.2%). Disease duration was longer in patients who responded to induction and required colectomy vs those without colectomy. Other baseline disease characteristics showed a trend for more extensive disease, more active UC, higher CRP, and more frequent extra-intestinal manifestations.

None of the 13 patients who responded to induction and required colectomy achieved CCR through week 54 in PURSUIT-M.

Calprotectin in CCR and Non-CCR Patients

At baseline of induction, the median calprotectin level was 594.0 µg/g and 478.0 µg/g in CCR patients randomized to golimumab and placebo maintenance, respectively (Table 2). Baseline median calprotectin values for non-CCR patients in these groups were 818.0 µg/g and 624.0 µg/g, respectively. During induction (weeks 0–6) and maintenance (weeks 6–54), the median calprotectin level was reduced in CCR patients but not in non-CCR patients (Table 2). Interestingly, in CCR patients randomized to placebo maintenance (golimumab withdrawal), the median calprotectin level increased from week 6 (84.0 µg/g) through week 30 (141.0 µg/g) and week 54 (203 µg/g) of placebo maintenance (Fig. 4).

Ulcerative Colitis Course of Disease in CCR and Non-CCR UC Patients

Two hundred three patients entered the LTE while on continuous golmumab therapy (101 on 50 mg and 102 on 100 mg golimumab), and 200 of 203 continued golimumab at the start of LTE; 195 of 200 patients were assessed using the Mayo PGA score every 3 months. At the start of the LTE, 136 of 195 patients (70%) were defined as CCR patients, whereas 59 of 195 (30%) had lost response during the first year of golimumab maintenance treatment in PURSUIT-M (non-CCR patients). A Physician Global Assessment of 0–1 (no or mild disease activity) was sustained through the LTE in 98 of 136 (72%) CCR patients and in 35 of 59 (59%) non-CCR patients (intention to treat [ITT]). A PGA 0 (no disease activity) state was sustained through the LTE in 79 of 136 (58%) CCR patients and in 25 of 59 (42%) non-CCR patients (ITT) (Fig. 5).

Results—Colectomy*

All cases of colectomy* in the randomized and nonrandomized patient populations of PURSUIT-M (N = 1228) were collected and reviewed though 54 weeks of follow-up. The study investigators reported that:

- Of the 47 colectomies* (among 1228 patients) performed during PURSUIT-M, 34 were in patients who did not respond to induction therapy, while 13 colectomies* were performed in responders to induction therapy
- Colectomies* were more frequent in patients who did not respond to induction therapy (5.4% [n = 34/635]), than in induction responders (2.2% [n =13/593])
- None of the 13 patients who responded to induction and required colectomy* achieved CCR through week 54

*The definition of this word may be found in the glossary.

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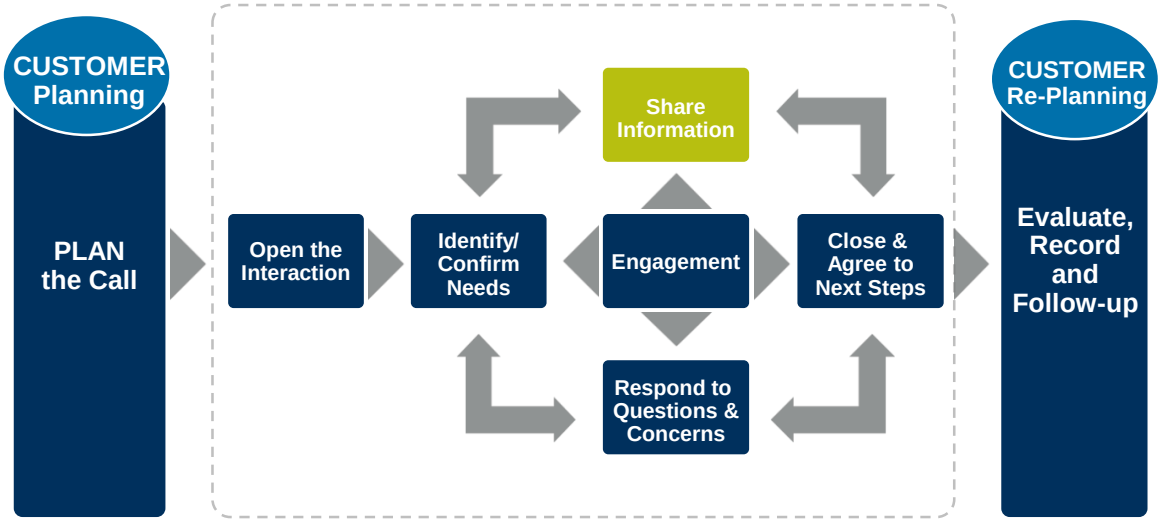
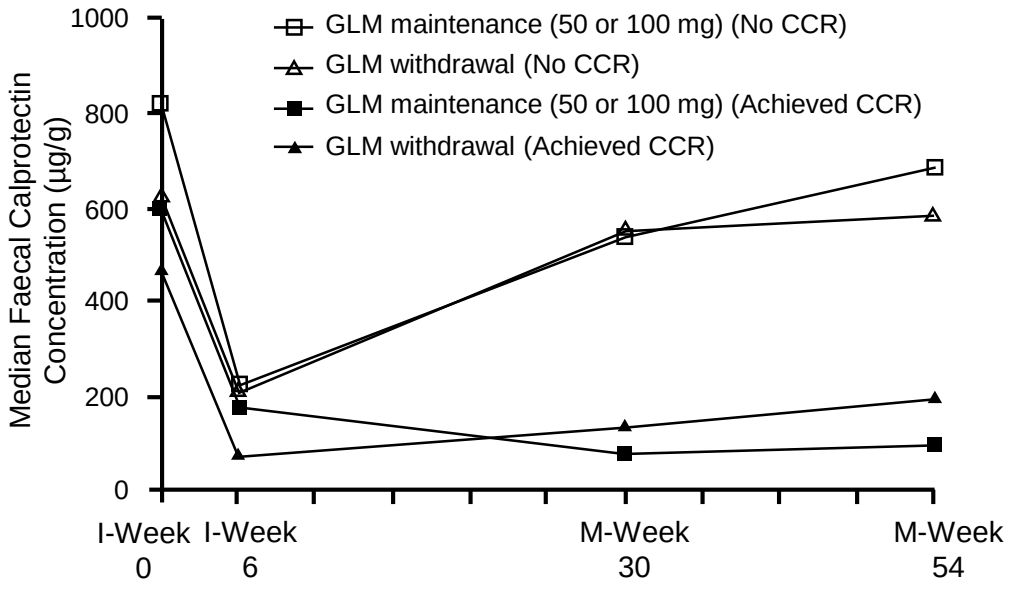


Suggested Verbalization:

"Doctor, in the PURSUIT-M trial, colectomies were more frequent in patients who did not respond to induction therapy than in induction responders."*

*The definition of this word may be found in the glossary.

Results—Median Calprotectin* Levels by CCR Status



During induction (weeks 0–6) and maintenance therapy (weeks 6–54), the median calprotectin* levels were reduced from baseline in CCR patients but not in non-CCR patients.

*The definition of this word may be found in the glossary.

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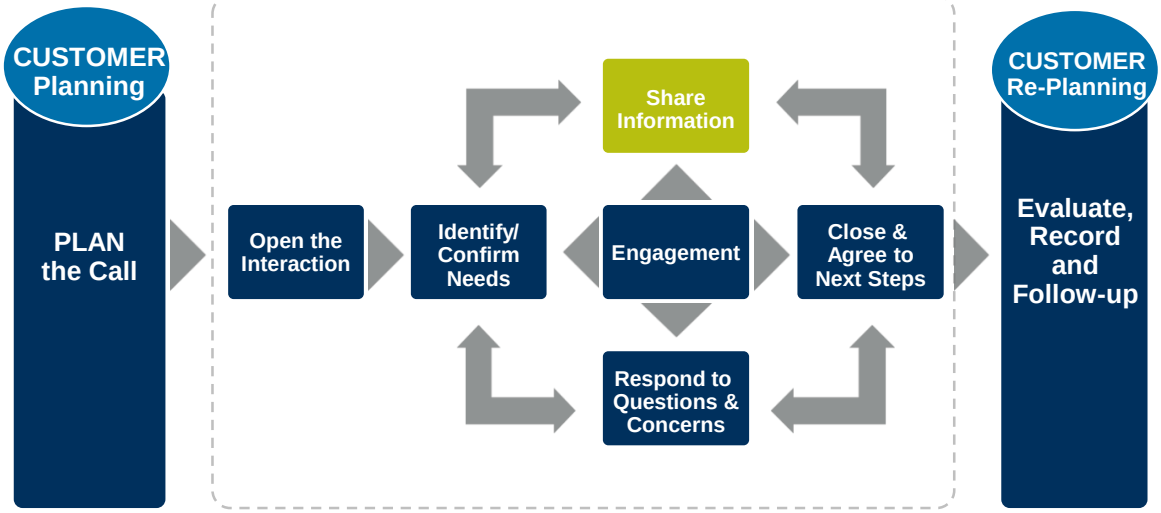

Suggested Verbalization:

"Doctor, during both induction and maintenance, there was a reduction in median calprotectin levels in CCR patients but not in non-CCR patients. In the study, CCR was also associated with sustained low levels of calprotectin* compared with elevated levels in non-CCR patients."*

*The definition of this word may be found in the glossary.

Results—Disease Course

The effect of CCR on long-term disease course in UC was analyzed in a 3-year, open-label extension of the PURSUIT-M trial (with a total follow-up of 4 years). Investigators determined that:

- 72% (n = 98/136) of CCR patients sustained PGA 0–1 (no or mild disease activity) through the long-term extension compared with 59% (n = 35/59) of non-CCR patients
- 58% (n = 79/136) of CCR patients sustained PGA 0 (no disease activity) through the long-term extension compared with 42% (n = 25/59) of non-CCR patients

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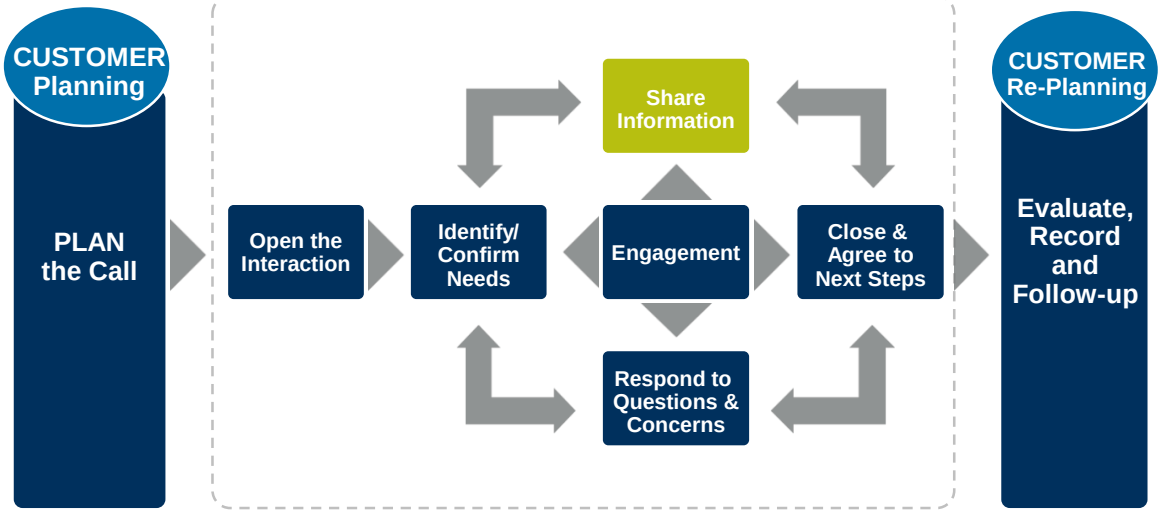

Suggested Verbalization:

"Doctor, 72% of CCR patients sustained PGA 0–1 through the long-term extension compared with 59% of non-CCR patients. In addition, 58% of CCR patients sustained PGA 0 through the long-term extension compared with 42% of non-CCR patients. These data indicate that CCR is associated with better long-term disease control through 3 years (4 years total) compared to non-CCR in UC patients."

GLOSSARY

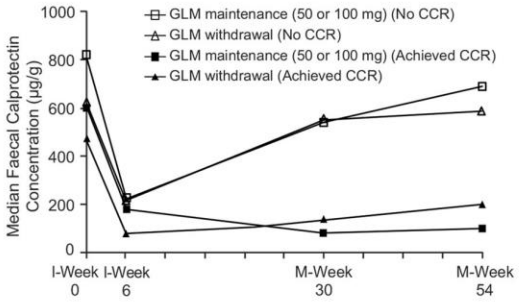

FIGURE 4. Fecal calprotectin levels by CCR status and treatment (all randomized patients in PURSUIT-M). GLM, golimumab; I-Week, induction week; M-Week, maintenance week. Patients who had a missing value at M-Week 0 had their last available I-Week 0 value carried forward; patients who had a prohibited change in UC medication, an ostomy or colectomy, a dose adjustment, or discontinued study agent due to lack of therapeutic effect before the M-Week 54 visit had their I-Week 0 value carried forward from the time of the event onward; patients who had a missing fecal calprotecin value at a timepoint had their last available value carried forward to that timepoint.

DISCUSSION

Continuous clinical response without treatment failure (CCR) as defined in PURSUIT-M is associated with major clinical, endoscopic, QoL, and long-term clinical benefit in patients with moderate to severe UC treated with golimumab. Normal stool frequency and resolution of rectal bleeding are targets of UC therapy.[1] These patient-reported outcomes are assessed by the partial Mayo score in PURSUIT-M. Endoscopy at week 30 and 54 added an objective outcome measure to the CCR definition. Clinical remission and corticosteroid-free remission was achieved in 67.1% and 61.6% of patients achieving CCR with golimumab maintenance. Corticosteroid-free remission is the treatment target proposed by European Crohn's and Colitis Organisation (ECCO) guidelines for UC.[11] Endoscopic remission is recommended as the best objective outcome measure in UC because achieving normal mucosa may be associated with change of the disease course in UC.[12] The predictive role of mucosal healing for colectomy-free survival was first established in the Inflammatory Bowel South-Eastern Norway (IBSEN) study cohort with long-term follow-up.[13] In the Active Ulcerative Colitis Trials (ACT) trials with infliximab in UC, the 1-year colectomy-free survival rate was significantly better in patients who achieved mucosal healing at week 8 (P = 0.0004 for Mayo endoscopy score 0–1 vs 2–3).[14] An association of CCR with mucosal healing might be expected because the definition of CCR included endoscopic assessment of response at weeks 30 and 54; mucosal healing and endoscopic remission are thus found in a high proportion of CCR patients (90.4% and 47.9%, respectively). We suggest that CCR is an accurate measure to tightly monitor clinical and endoscopic activity and helps in selecting those patients who are more likely to achieve

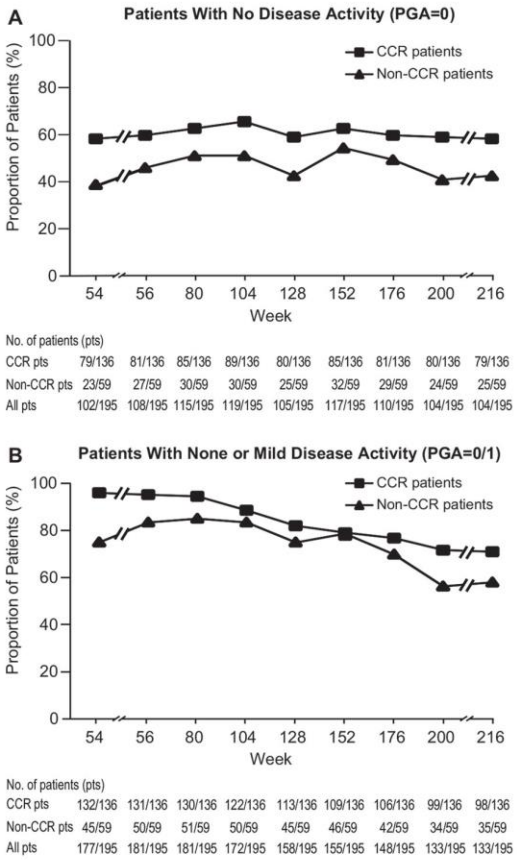

FIGURE 5. Proportion of golimumab-randomized patients who were treated in the long-term extension and who had a PGA of 0 or 0–1, presented by CCR status. Data are presented as ITT.

a long-term change of UC disease course. Normal QoL as the overarching treatment goal of the STRIDE consensus was observed in the majority of CCR patients. The long-term benefit associated with CCR in UC was further substantiated in 195 patients who entered the 3-year extension of PURSUIT-M and continued golimumab therapy. Data from the 1-year extension showed that 56.4% and 80.5% of patients sustained PGA 0 or PGA 0–1, respectively, at week 104 (ITT analysis).[10] The majority of patients entering the LTE were CCR patients (70% CCR vs 30% non-CCR). This confirms that the treating physician may have relied on the CCR state when deciding to continue treatment beyond 54 weeks, seeing that the protocol criterion for continuation was defined as "if the investigators felt that continued benefit from golimumab treatment was most likely." Sustained PGA 0 state was observed in 58% and 42% of CCR and non-CCR patients, respectively, at the end of the LTE (delta

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Discussion—Results Summary

The Discussion section provides a concise and relevant interpretation of the results in the context of existing knowledge on the topic.

The authors open the Discussion section in Reinisch, et al. by stating that: “CCR as defined in PURSUIT-M is associated with major clinical, endoscopic*, QoL, and long-term clinical benefit in patients with moderate to severe UC treated with golimumab.”

*The definition of this word may be found in the glossary.

Discussion—CCR as a Measure of Disease Activity

In PURSUIT-M, normal quality of life (IBDQ score ≥170) was observed in the majority of CCR patients. The long-term benefit of CCR was further demonstrated in the long-term extension. The authors suggest that CCR may be used as a measure to tightly monitor clinical and endoscopic* activity and to help in selecting patients who are more likely to achieve a long-term change of UC disease course.

*The definition of this word may be found in the glossary.

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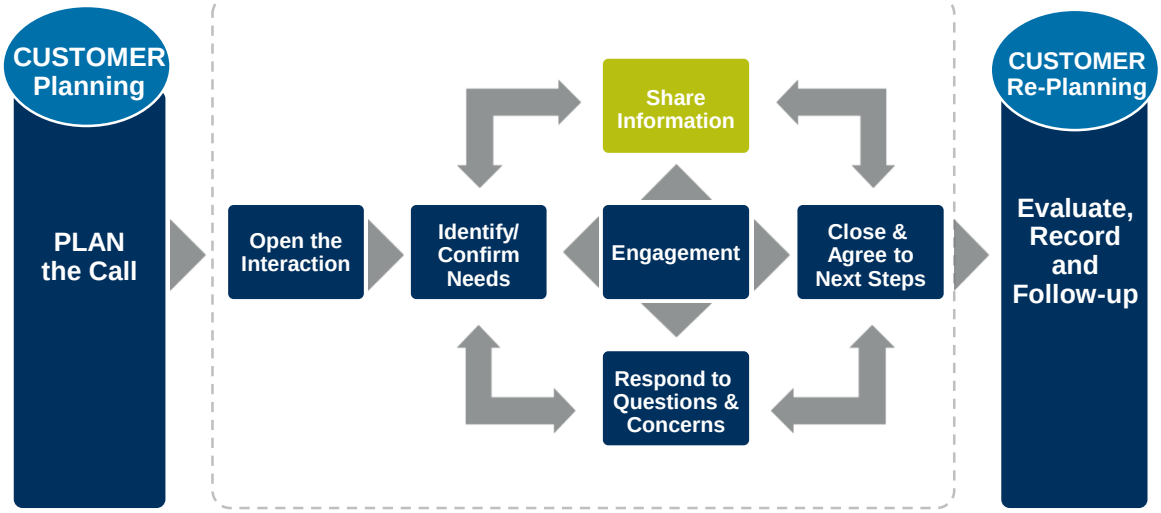

Suggested Verbalization:

"Doctor, at the end of the long-term extension, sustained PGA 0 state was seen in 58% and 42% of CCR and non-CCR patients, respectively. PGA 0-1 was sustained in 72% and 59% of CCR and non-CCR patients, respectively. The observed difference in PGA scores in these patient groups (13%–16%) was considered clinically meaningful."

"These results suggest that achieving CCR compared with not achieving CCR was associated with better long-term sustained clinical outcomes through up to 4 years."

GLOSSARY

of 16%; ITT), and PGA 0–1 was sustained in 72% and 59% of CCR and non-CCR patients, respectively (delta of 13%; ITT). The observed difference in PGA scores in CCR vs non-CCR patients (13%–16%) can be considered clinically meaningful. Therefore, we conclude that CCR compared to non-CCR patients not only show better clinical, endoscopic, and QoL outcomes at 1 year but also show better long-term sustained clinical outcome through up to 4 years.

Decrease of calprotectin in CCR patients, but not in non-CCR patients, underscores the biological response observed in CCR patients. The calprotectin profile of CCR patients supports the high degree of endoscopic healing and remission observed in these patients. Endoscopy remains the established objective measure of disease activity in UC. Still, biomarkers such as calprotectin may be useful for monitoring response to therapy and early detection of disease worsening. We previously showed that the fecal calprotectin level of responders to induction at week 6 is an independent predictor of CCR in PURSUIT-M.[15] The calprotectin results presented here support the use of the calprotectin biomarker as an adjunctive objective measure in UC.[1]

The majority of colectomies (34 of 47) in PURSUIT-M were done in patients not responding to induction therapy. None of the 13 induction responders requiring colectomy achieved CCR in the first year of maintenance therapy. Our results suggest that achieving CCR during the first year of golimumab therapy changes the disease course of UC and that continuous control of disease activity (CCR) and inflammation may prevent colectomy in moderate to severe UC patients followed in PURSUIT-M.

However, CCR is not a practical disease monitoring method inasmuch as it required Q4W partial Mayo scores and, therefore, a Q4W clinic visit in PURSUIT-M. How can we apply the findings of this study and rely on CCR to tightly monitor UC disease activity in clinical practice? Lewis et al[16] and Jairath et al[17] showed that the combined patient-reported stool frequency and rectal bleeding scores of the partial Mayo score (referred to as PRO2) are as accurate as partial Mayo score for treatment response assessment in moderate to severe UC. We can thus rely on Q4W PRO2 assessment, and this monitoring method becomes practical and attractive with the use of remote monitoring. Smart phone applications allowing patients to remotely monitor their disease activity with PROs have been introduced recently.[18–20] These improvements of tight monitoring should result in better control of disease activity in patients with UC.

Our study has some limitations. First, it is based on post hoc analyses of PURSUIT-M and is therefore limited by its exploratory nature. Second, the association of major clinical, endoscopic, and QoL endpoints with CCR was evaluated by combining the 50 mg and 100 mg maintenance treatment groups; however, this approach is justified by the similar proportions of patients who achieved CCR in the 50 mg and 100 mg arms of the PURSUIT-M trial (47.0% and 49.7%, respectively).

In conclusion, these post hoc analyses of PURSUIT-M show that continuous clinical response is associated with short- and long-term improvement in major clinical, endoscopic, QoL, biomarker, and colectomy outcomes and may be considered a treatment target in UC. Ongoing research aims at translating the PURSUIT-M CCR tight control measure into a practical tight monitoring tool with use of remotely collected PROs and biomarkers aimed at avoiding clinic visits and endoscopy in UC patients.

SUPPLEMENTARY DATA

Supplementary data is available at *Inflammatory Bowel Diseases* online.

ACKNOWLEDGEMENTS

The authors thank Brian G. Feagan, Jewel Johanns, and Richard Strauss for their contributions to the PURSUIT-M trial. The authors also wish to thank Ben Scott, PhD, of Scott Medical Communications, LLC (funded by Merck & Co., Inc., Kenilworth, NJ, USA) and Alan Meehan, PhD (Merck & Co., Inc., Kenilworth, NJ, USA) for writing assistance and Jennifer Pawlowski (Merck & Co., Inc., Kenilworth, NJ, USA) for preparing this paper for publication.

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Discussion—Colectomy*

The majority of the colectomies* (34 of 47) performed in PURSUIT-M were in patients who did not respond to induction therapy. None of the 13 induction responders who needed colectomy* achieved CCR in the first year of maintenance therapy.

The results of this post hoc analysis suggest that achieving CCR during the first year of therapy with golimumab may result in changing the disease course of UC and may prevent colectomy* in patients with moderate to severe UC.

*The definition of this word may be found in the glossary.

Conclusion

The authors conclude that the post hoc analyses demonstrate that CCR is associated with both short- and long-term improvement in major clinical, endoscopic*, quality-of-life, biomarker, and colectomy* outcomes. Thus, CCR may be considered a treatment target in UC.

*The definition of this word may be found in the glossary.

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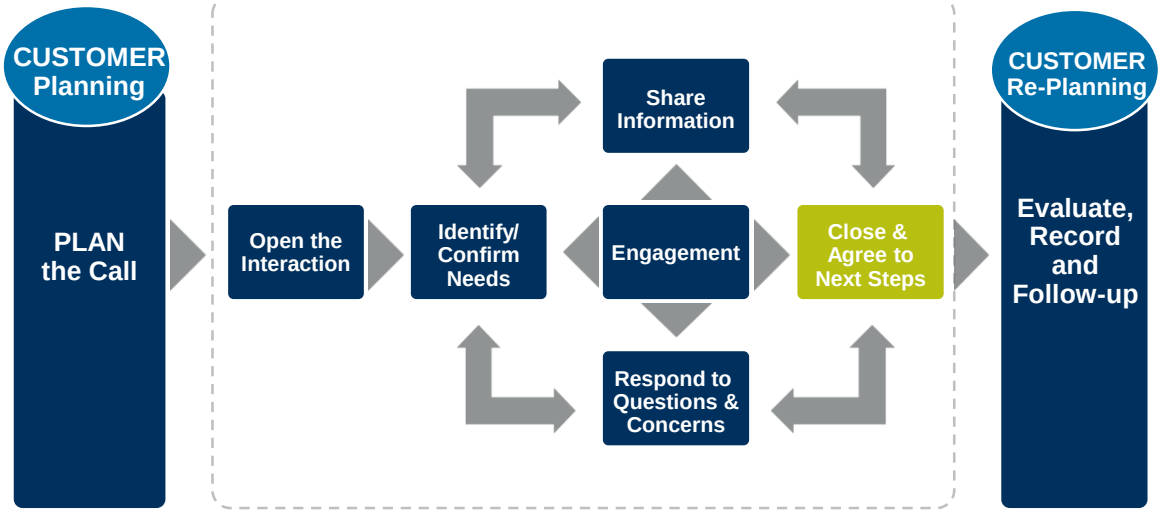

Suggested Verbalization:

"Doctor, in conclusion, CCR is associated with favorable short- and long-term clinical, endoscopic, quality-of-life, and biomarker responses that may result in changing the disease course of UC and may prevent colectomy* in patients with moderate to severe UC treated with golimumab."*

*The definition of this word may be found in the glossary.

Glossary

calprotectin: a water-soluble, calcium- and zinc-binding protein that appears in the cytosol of neutrophils

clinical remission: defined as a Mayo score of ≤2 points, with no individual subscore of >1

clinical response: defined as a decrease from the baseline value (observed in PURSUIT-IV or PURSUIT-SC) in the Mayo score by 30% or more and 3 or more points, with either a decrease in the rectal bleeding subscore of 1 or more or a rectal bleeding subscore of 0/1

colectomy: excision of part or all of the colon

cytosol: the fluid of cytoplasm, a watery solution consisting of ions and nutrients

endoscopic: pertaining to endoscopy, or inspection of body organs or cavities with an endoscope

endoscopic remission: defined as a Mayo endoscopy subscore of 0

lumen: the interior space within an artery, vein, intestine, or tube

mucosa: a mucous membrane or tissue lining the hollow organs and cavities of the body

mucosal healing: defined as a Mayo endoscopy subscore of 0 or 1

neutrophil: a granular white blood cell; represents the most common type (55% to 70%) of white blood cell; neutrophils play a central role in inflammation and are responsible for much of the body's defense against infection

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Note to countries: Local markets to ensure the insertion of the approved local short balance/indication (i.e., ISI) for SIMPONI along with any other requirements regarding the access and presentation of SSI.

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