The Effect of Mirikizumab on Fecal Calprotectin and C-Reactive Protein in Phase 3 Studies of Patients With Moderately to Severely Active Ulcerative Colitis

MP284

Britta Siegmund,[1] Bruce E. Sands,[2] Karen Hamrick Samaan,[3] Xingyuan Li,[3] Nathan Morris,[3] Theresa Hunter Gibble,[3] Isabel Redondo,[3] Trevor Lissoos,[3] Geert R. D'Haens[4]

[1]Charité – Universitätsmedizin Berlin, Berlin, Germany; [2]Icahn School of Medicine at Mount Sinai, New York, USA; [3]Eli Lilly and Company, Indianapolis, USA; [4]Amsterdam University Medical Center, Amsterdam, The Netherlands

BACKGROUND

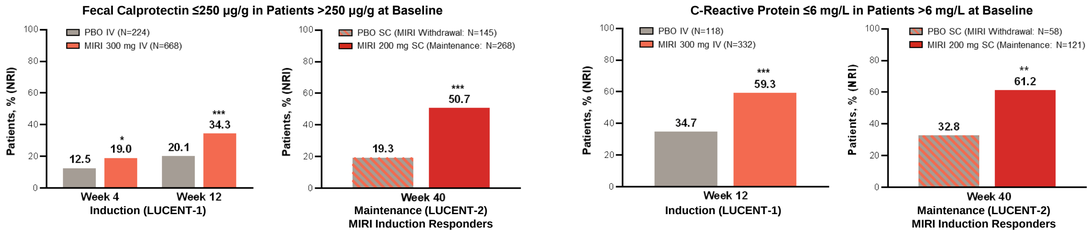
- Mirikizumab, a p19-directed anti–interleukin (IL)-23 antibody, demonstrated efficacy and was well tolerated in Phase 3 induction (LUCENT-1; NCT03518086)[1] and maintenance (LUCENT-2; NCT03524092)[2] studies in patients with moderately to severely active ulcerative colitis
- Fecal calprotectin and C-reactive protein are biomarkers widely used by clinicians as a measure of inflammatory disease activity in patients with ulcerative colitis
  - Fecal calprotectin >250 µg/g is associated with the presence of ulcerative colitis endoscopic mucosal inflammatory activity[3,4]
  - Normalization of fecal calprotectin and/or C-reactive protein is an intermediate target for the management of ulcerative colitis[5]

OBJECTIVE

- To explore the effect of mirikizumab on the inflammatory biomarkers fecal calprotectin and C-reactive protein in the LUCENT-1 and LUCENT-2 studies

KEY RESULTS

Mirikizumab-Treated Patients Achieved Statistically Significant Reduction in Fecal Calprotectin and C-Reative Protein vs. Placebo During Induction That Was Sustained in Maintenance Treatment



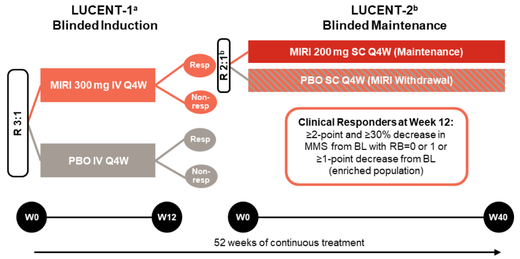
* p<0.05; ** p<0.01; *** p<0.001 vs. PBO; Cochran-Mantel-Haenszel test adjusted by stratification factors

CONCLUSIONS

- Patients with ulcerative colitis treated with mirikizumab in the 12-week LUCENT-1 induction study showed significantly greater improvements from baseline in fecal calprotectin and C-reactive protein vs. placebo
  - Median biomarker levels suggest more patients treated with mirikizumab vs. placebo achieved normalized fecal calprotectin and C-reactive protein within 12 weeks
- In the LUCENT-2 maintenance study, normalization of fecal calprotectin and C-reactive protein levels was sustained throughout treatment in the mirikizumab induction responder group who continued mirikizumab maintenance treatment
  - Median fecal calprotectin, after 52 weeks of continuous treatment with mirikizumab in the responder group, fell to a level known to be correlated with both endoscopic and histologic healing[6,7]
- Mirikizumab-treated patients were more likely to achieve fecal calprotectin ≤250 µg/g and C-reactive protein ≤6 mg/L vs. placebo during induction and maintenance treatment
- Reduction in inflammatory biomarkers with mirikizumab treatment demonstrates response to therapy and indicates improvement in disease activity

METHODS

Study Design



[a] LUCENT-1 was a Phase 3, randomized, parallel-arm, double-blind, PBO-controlled induction trial of MIRI in patients with moderately to severely active ulcerative colitis; [b] LUCENT-2 was a Phase 3, double-blind, randomized, withdrawal maintenance study in patients who responded to MIRI induction therapy in LUCENT-1. Figure is not the full LUCENT-2 program, only the patient cohort who were MIRI responders during induction and randomized to maintenance treatment are presented here. Clinical responders to induction MIRI therapy at Week 12 of LUCENT-1 were randomized to receive maintenance MIRI therapy or PBO for 40 weeks (52 weeks of treatment). Randomization in LUCENT-2 was stratified by induction remission status, biologic failure status, baseline corticosteroid use, and global region

Assessments and Statistical Analyses

- Change from baseline in fecal calprotectin and C-reactive protein levels was compared between the mirikizumab and placebo arms using analysis of covariance
  - Baseline for both LUCENT-1 and LUCENT-2 refers to the values collected before the initiation of study treatment in LUCENT-1
  - C-reactive protein levels were available at baseline and Week 12 but not at Week 4
  - Missing values at designated time points were imputed using last observation carried forward, except that missing values after patient discontinuation due to an adverse event were imputed using baseline observation carried forward
- Proportions of patients achieving fecal calprotectin ≤250 µg/g or C-reactive protein ≤6 mg/L were compared between the mirikizumab and placebo arms using a Cochran-Mantel-Haenszel test
  - Missing data were treated as non-response

Key Eligibility Criteria: LUCENT-1

- Age ≥18 and ≤80 years
- Moderately to severely active ulcerative colitis
  - Modified Mayo Score of 4-9, with an endoscopic subscore of 2-3
- Inadequate response, loss of response, or intolerance to:
  - ≥1 corticosteroid, immunomodulator, biologic therapy, or Janus kinase inhibitor for ulcerative colitis
- No previous exposure to anti–IL-12/23p40 or anti–IL-23p19 antibodies
- No previous failure of ≥3 different biologic therapies

RESULTS

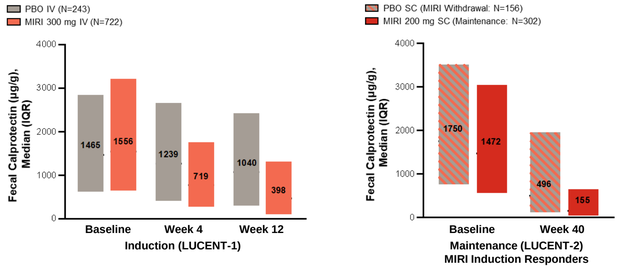
Baseline[a] Demographics and Disease Characteristics

	LUCENT-1 (mITT)		LUCENT-2 (mITT MIRI Induction Responders)	
	PBO IV (N=294)	MIRI 300 mg IV (N=868)	PBO SC (MIRI Withdrawal) (N=179)	MIRI 200 mg SC (N=365)
Age, years, mean (SD)	41.3 (13.8)	42.9 (13.9)	41.2 (12.8)	43.4 (14.2)
Male	165 (56.1)	530 (61.1)	104 (58.1)	214 (58.6)
Disease duration, years, mean (SD)	6.9 (7.0)	7.2 (6.7)	6.7 (5.6)	6.9 (7.1)
Disease location				
Left-sided colitis	188 (64.2)	544 (62.7)	119 (66.5)	234 (64.1)
Pancolitis	103 (35.2)	318 (36.6)	59 (33.0)	128 (35.1)
MMS category				
Moderate [score 4-6]	138 (47.1)	404 (46.5)	77 (43.0)	181 (49.6)
Severe [score 7-9]	155 (52.9)	463 (53.3)	102 (57.0)	184 (50.4)
Endoscopic Mayo subscore, severe [score 3]	200 (68.3)	574 (66.1)	106 (59.2)	235 (64.4)
Bowel urgency severity (UNRS), mean (SD)	6.2 (2.2)	6.1 (2.2)	6.2 (1.9)	6.0 (2.2)
Baseline corticosteroid use	113 (38.4)	351 (40.4)	68 (38.0)	135 (37.0)
Baseline immunomodulator use	69 (23.5)	211 (24.3)	39 (21.8)	78 (21.4)
Prior biologic or tofacitinib failure	118 (40.1)	361 (41.6)	64 (35.8)	128 (35.1)

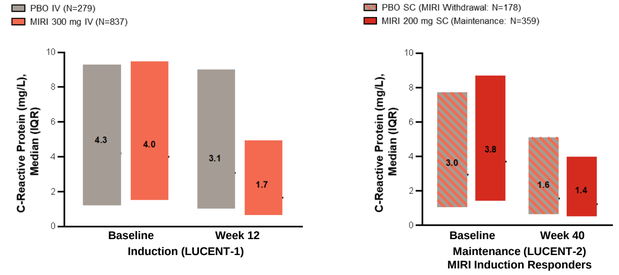
Data are presented as n (%) unless stated otherwise

[a] Baseline refers to Week 0 of LUCENT-1

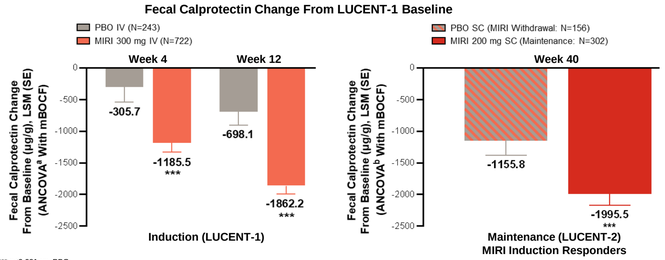
Median Fecal Calprotectin Was Reduced With MIRI vs. PBO During Induction and Responder Maintenance



Median C-Reactive Protein Was Reduced With MIRI vs. PBO During Induction and Responder Maintenance



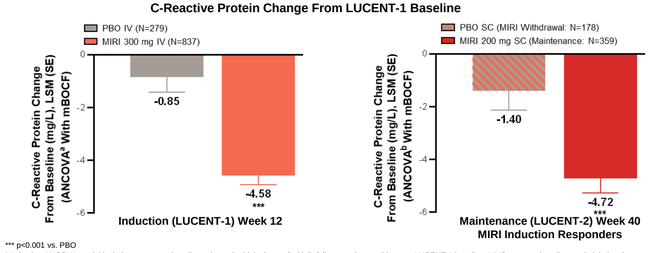
LSM Reduction in Fecal Calprotectin Was Greater With MIRI vs. PBO During Induction and Responder Maintenance



*** p<0.001 vs. PBO

[a] Induction ANCOVA model includes treatment, baseline value, prior biologic or tofacitinib failure, corticosteroid use at LUCENT-1 baseline, MMS group at baseline, and global region; [b] Maintenance ANCOVA model includes treatment, baseline value, prior biologic or tofacitinib failure, corticosteroid use at LUCENT-1 baseline, global region, and clinical remission status at LUCENT-1 Week 12

LSM Reduction in C-Reactive Protein Was Greater With MIRI vs. PBO During Induction and Responder Maintenance



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ABBREVIATIONS

ANCOVA=analysis of covariance; BL=baseline; IQR=interquartile range; IV=intravenous; LSM=least squares mean; mBOCF=modified baseline carried forward; MIRI=mirikizumab; mITT=modified Intent-to-Treat; MMS=Modified Mayo Score; Non-resp=non-responder; NRI=non-responder imputation; PBO=placebo; Q4W=every 4 weeks; R=randomization; RB=rectal bleeding; Resp=responder; SC=subcutaneous; SD=standard deviation; SE=standard error; UNRS=Urgency Numeric Rating Scale; W=Week

DISCLOSURES

- **B. Siegmund** has served as a consultant and/or speaker for: AbbVie, Arena Pharmaceuticals, Bristol Myers Squibb, Boehringer Ingelheim, CED Service GmbH, Celgene, Dr. Falk Pharma, Eli Lilly and Company, Ferring Pharmaceuticals, Galapagos NV, Janssen, Novartis, Pfizer, Prometheus Therapeutics and Diagnostics, and Takeda; **B. E. Sands** has served as a consultant and/or speaker for: AbbVie, Abivax, Adiso Therapeutics, Alimentiv, Amgen, Arena Pharmaceuticals, Artizan Biosciences, Artugen Therapeutics, AstraZeneca, Bacainn Therapeutics, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Calibr, Celltrion, ClostraBio, Cytoki Pharma, Connect Biopharma, Eli Lilly and Company, Enterx Bio, Evommune, Fresenius Kabi, Galapagos NV, Genentech, Gilead Sciences, GlaxoSmithKline, Gossamer Bio, Imhotex, Immunic Therapeutics, InDex Pharmaceuticals, Inotrem, Innovation Pharmaceuticals, Ironwood Pharmaceuticals, Janssen, Kaleido Biosciences, Kallyope, MiroBio, Morphic Therapeutic, MRM Health, OSE Immunotherapeutics, Pfizer, Progenity, Prometheus Therapeutics and Diagnostics, Protagonist Therapeutics, Q32 Bio, RedHill Biopharma, Sun Pharma, Surrozen, Synlogic, Target RWE, Takeda, Teva, Theravance Biopharma, TLL Pharmaceutical, USWM Enterprises, Ventyx Biosciences, Viela Bio, and VTA Labs; **K. Hamrick Samaan**, **X. Li**, **N. Morris**, **T. Hunter Gibble**, **I. Redondo**, and **T. Lissoos** are employees and shareholders of Eli Lilly and Company; **G. R. D'Haens** has served as an advisor for: AbbVie, Ablynx, Active Biotech, AgomAb Therapeutics, Allergan, AlphaBiomics, Amakem, Amgen, AM-Pharma, Applied Molecular Therapeutics, Arena Pharmaceuticals, AstraZeneca, Avaxia Biologics, Biogen, Boehringer Ingelheim, Bristol Myers Squibb/Celgene, Celltrion, Cosmo Pharmaceuticals, Dr. Falk Pharma, DSM Pharmaceuticals, Echo Pharmaceuticals, Eli Lilly and Company, enGene, Exelixis Biosciences, Ferring Pharmaceuticals, Galapagos NV, GenentechRoche, Gilead Sciences, GlaxoSmithKline, Gossamer Bio, Immunic Therapeutics, Johnson & Johnson, Kinta Therapeutics, Lycera, Medimetrics, Medtronic, Merck Sharp & Dohme, Mitsubishi Pharma, Mundipharma, Nextbiotics, Novo Nordisk, Otsuka, Pfizer, PhotoPills, ProciseDx, ProDigest, Progenity, Promethera Laboratories/Nestlé, Protagonist Therapeutics, RedHill Biopharma, Robarts Clinical Trials, Salix Pharmaceuticals, Samsung Bioepis, Sandoz, Seres Therapeutics/Nestec/Nestlé, Setpoint, Shire, Takeda, Teva, TiGenix, Tillotts Pharma AG, Topivert, Versant, and Vifor Pharma; and received speaker fees from: AbbVie, Biogen, Ferring Pharmaceuticals, Galapagos NV/Gilead Sciences, Johnson & Johnson, Merck Sharp & Dohme, Mundipharma, Norgine, Pfizer, Samsung Bioepis, Shire, Millenium/Takeda, Tillotts Pharma AG, and Vifor Pharma
- Medical writing assistance was provided by Linda Donnini, PhD, of ProScribe – Envision Pharma Group, and was funded by Eli Lilly and Company

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Study was sponsored by Eli Lilly and Company

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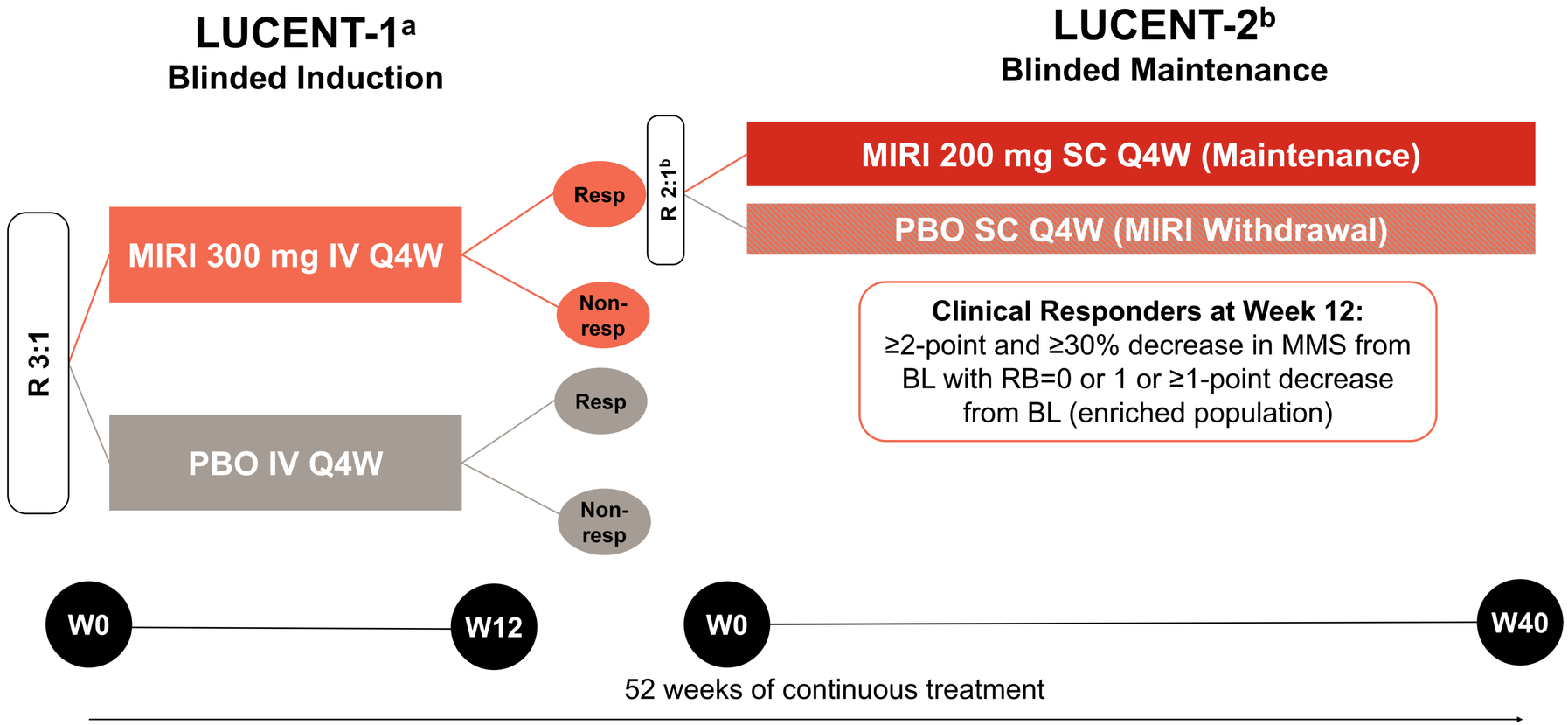
Study Design



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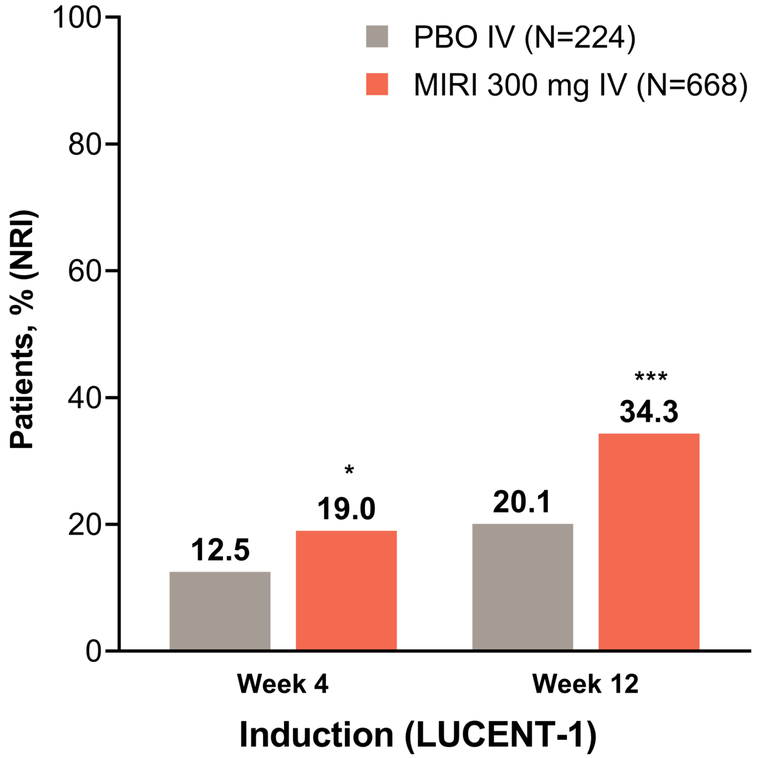
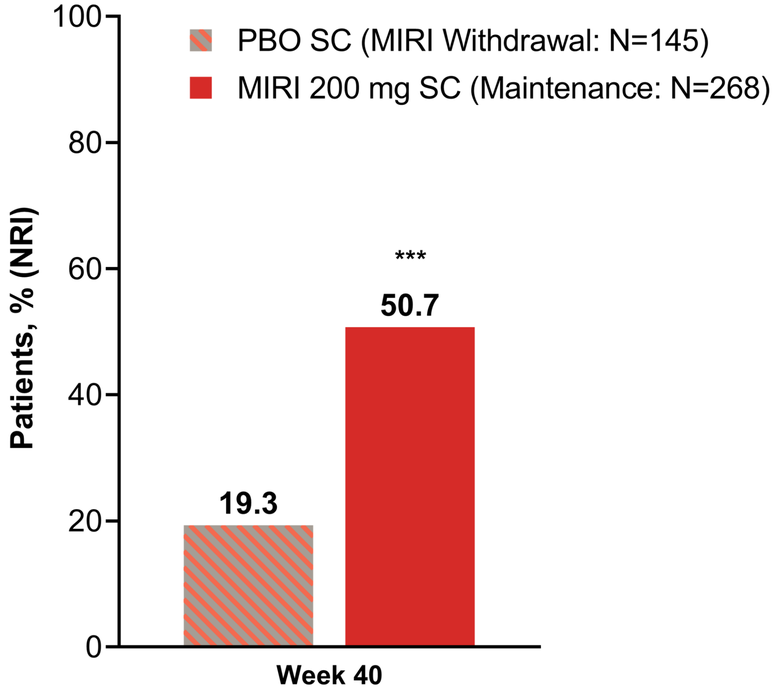
Mirikizumab-Treated Patients Achieved Statistically Significant Reduction in Fecal Calprotectin and C-Reative Protein vs. Placebo During Induction That Was Sustained in Maintenance Treatment (1/2)

Fecal Calprotectin ≤250 µg/g in Patients >250 µg/g at Baseline



Induction (LUCENT-1)



Maintenance (LUCENT-2)
MIRI Induction Responders

* p<0.05; *** p<0.001 vs. PBO; Cochran-Mantel-Haenszel test adjusted by stratification factors

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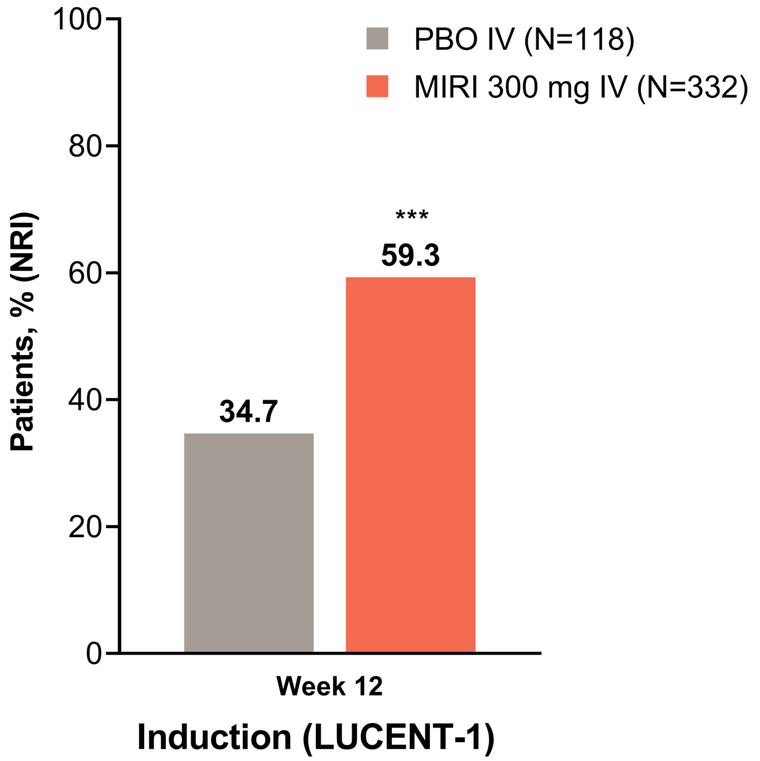
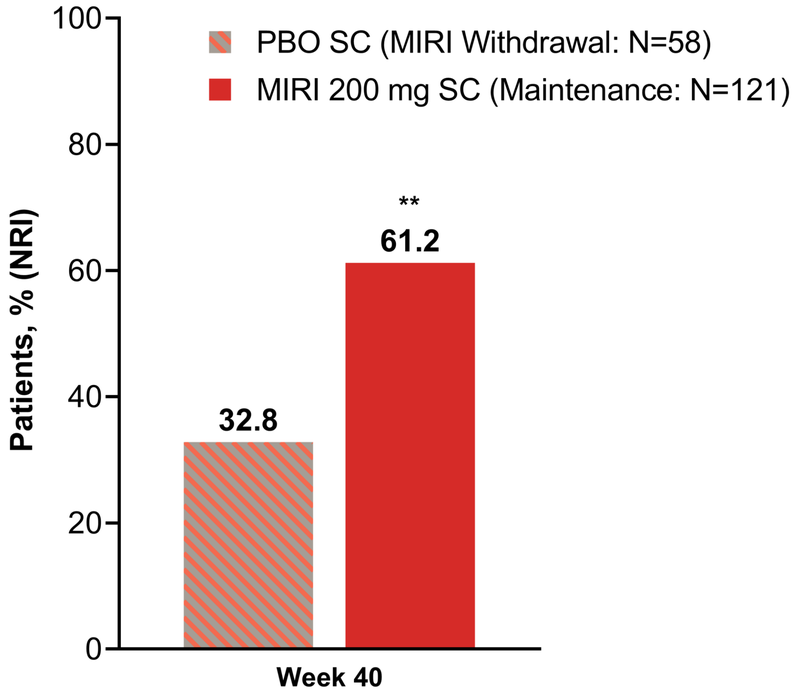
Mirikizumab-Treated Patients Achieved Statistically Significant Reduction in Fecal Calprotectin and C-Reative Protein vs. Placebo During Induction That Was Sustained in Maintenance Treatment (2/2)

C-Reactive Protein ≤6 mg/L in Patients >6 mg/L at Baseline



Induction (LUCENT-1)



Maintenance (LUCENT-2 MIRI Induction Responders)

** p<0.01; *** p<0.001 vs. PBO; Cochran-Mantel-Haenszel test adjusted by stratification factors

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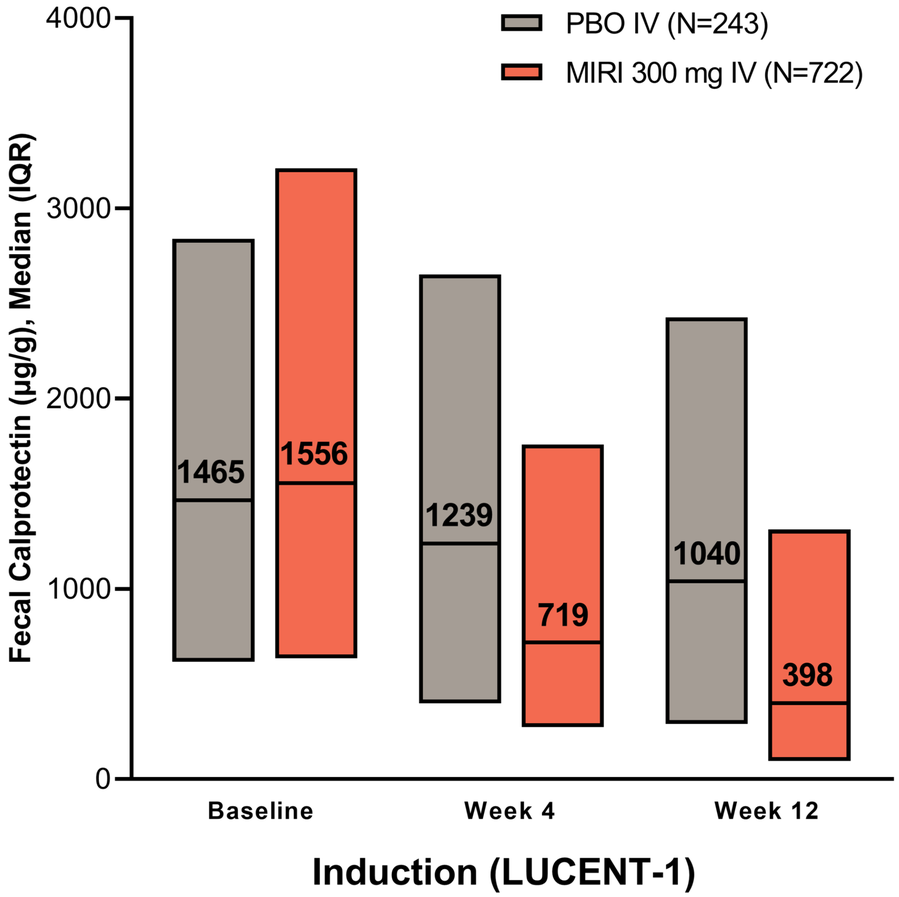
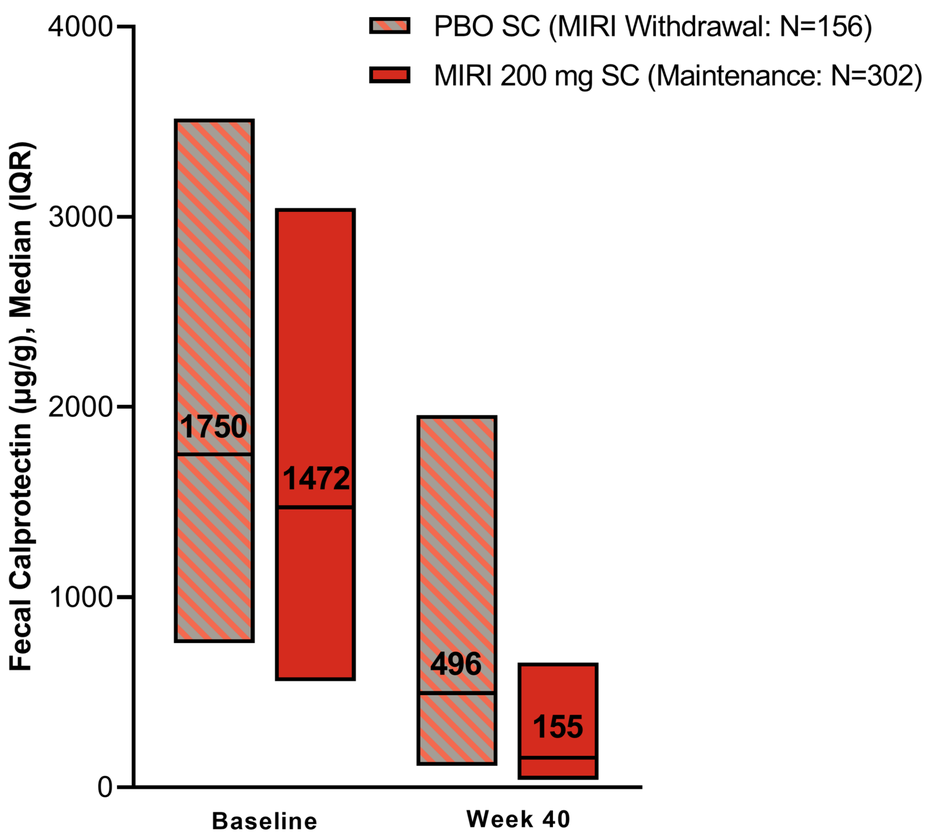


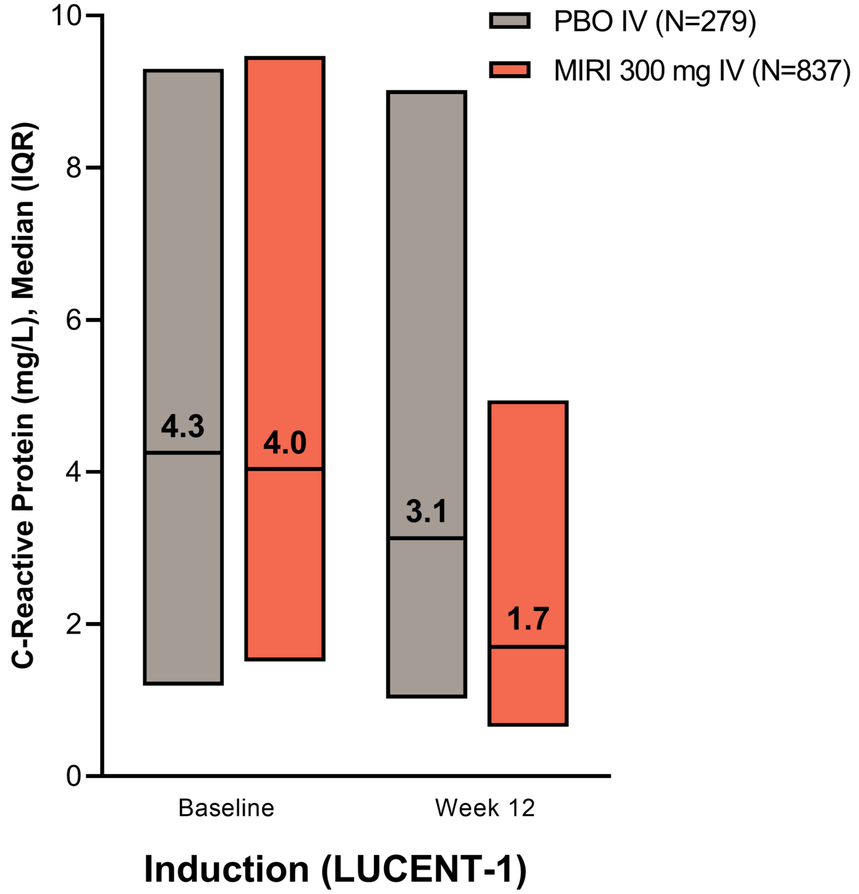
Induction (LUCENT-1)



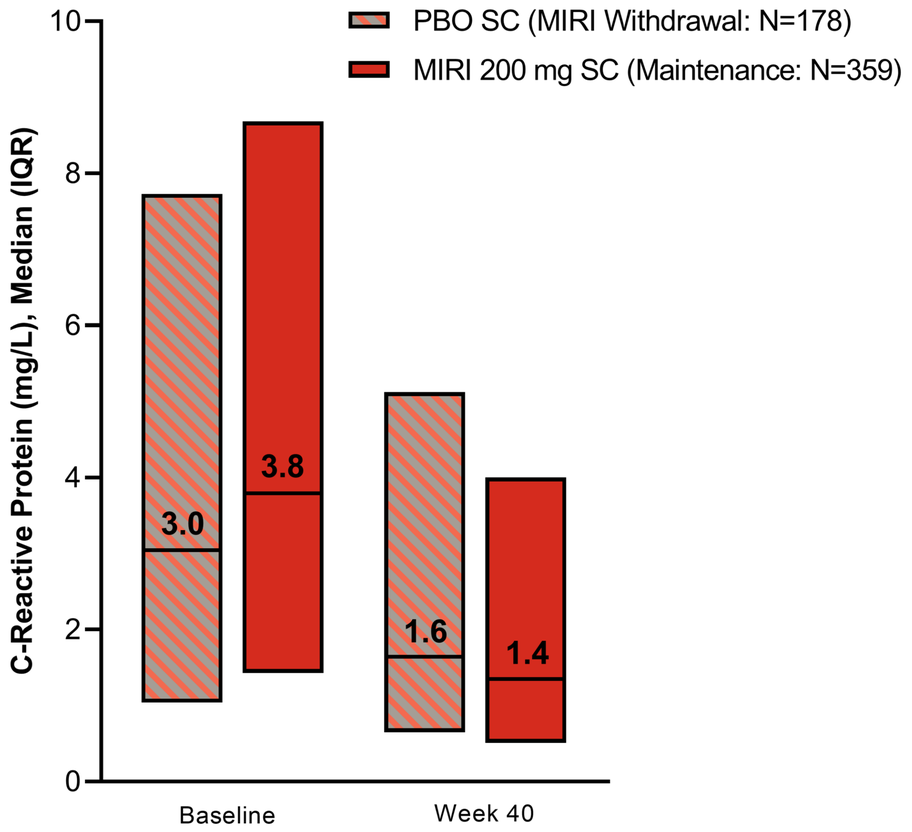
Maintenance (LUCENT-2)
MIRI Induction Responders

IQR=interquartile range; IV=intravenous; LSM=least squares mean; MIRI=mirikizumab; PBO=placebo; SC=subcutaneous

Median C-Reactive Protein Was Reduced With MIRI vs. PBO During Induction and Responder Maintenance



Induction (LUCENT-1)



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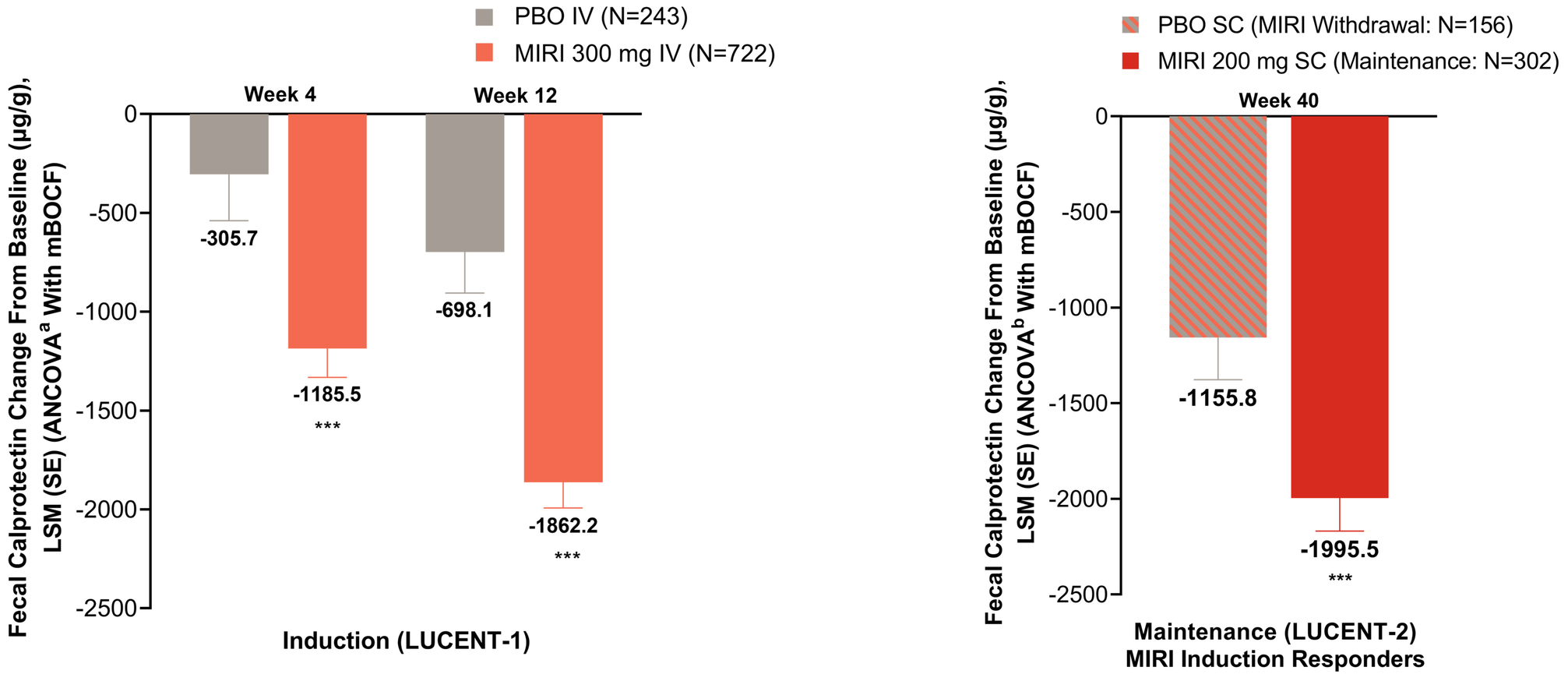
LSM Reduction in Fecal Calprotectin Was Greater With MIRI vs. PBO During Induction and Responder Maintenance

Fecal Calprotectin Change From LUCENT-1 Baseline



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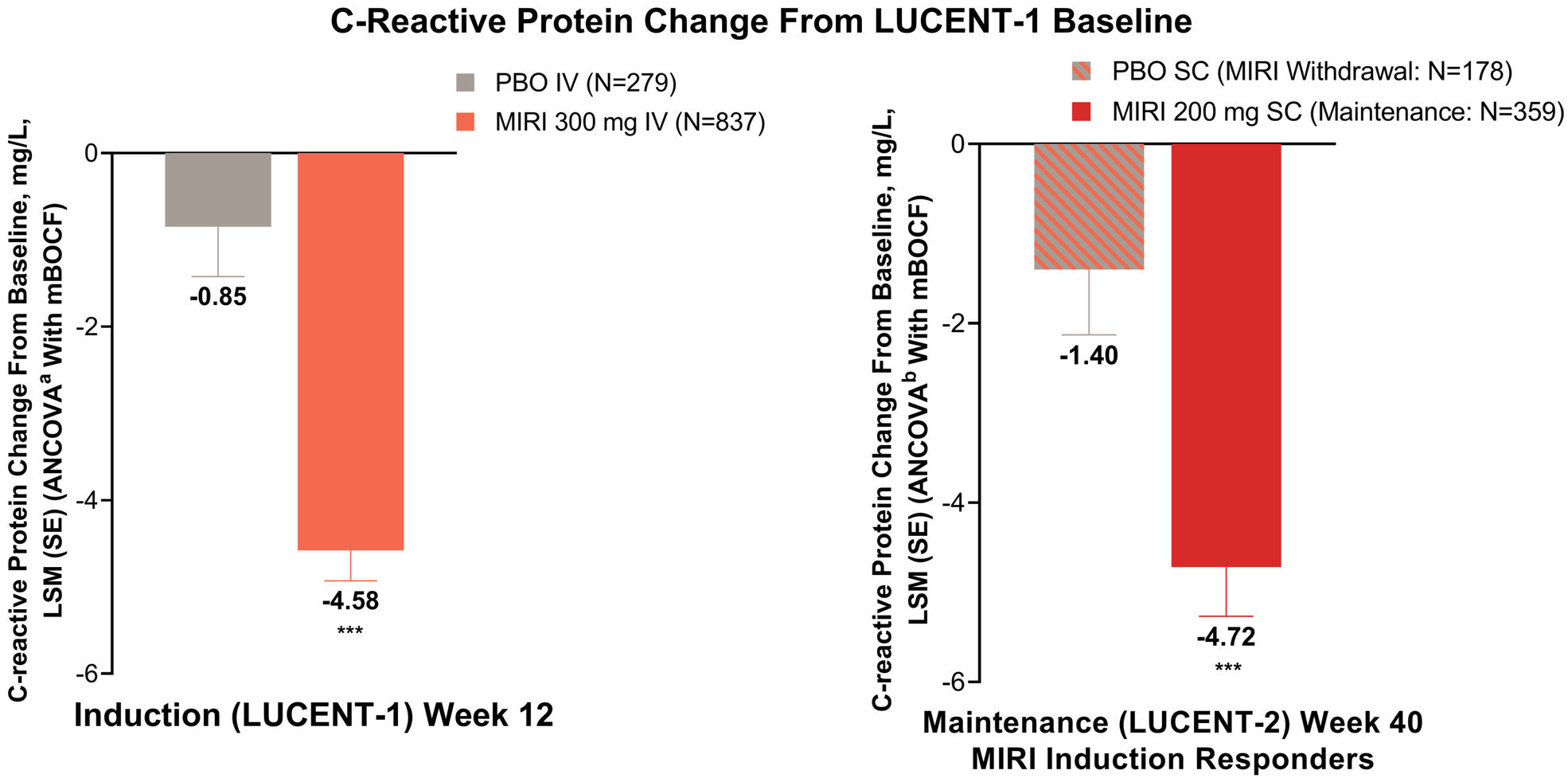
ANCOVA=analysis of covariance; IV=intravenous; LSM=least squares mean; mBOCF=modified baseline observation carried forward; MIRI=mirikizumab; MMS=Modified Mayo Score; PBO=placebo; SC=subcutaneous; SE=standard error

LSM Reduction in C-Reactive Protein Was Greater With MIRI vs. PBO During Induction and Responder Maintenance



*** p<0.001 vs. PBO

[a] Induction ANCOVA model includes treatment, baseline value, prior biologic or tofacitinib failure, corticosteroid use at LUCENT-1 baseline, MMS group at baseline, and global region; [b] Maintenance ANCOVA model includes treatment, baseline value, prior biologic or tofacitinib failure, corticosteroid use at LUCENT-1 baseline, global region, and clinical remission status at LUCENT-1 Week 12

ANCOVA=analysis of covariance; IV=intravenous; LSM=least squares mean; mBOCF=modified baseline observation carried forward; MIRI=mirikizumab; MMS=Modified Mayo Score; PBO=placebo; SC=subcutaneous; SE=standard error

CONCLUSIONS

- Patients with ulcerative colitis treated with mirikizumab in the 12-week LUCENT-1 induction study showed significantly greater improvements from baseline in fecal calprotectin and C-reactive protein vs. placebo
  - Median biomarker levels suggest more patients treated with mirikizumab vs. placebo achieved normalized fecal calprotectin and C-reactive protein within 12 weeks
- In the LUCENT-2 maintenance study, normalization of fecal calprotectin and C-reactive protein levels was sustained throughout treatment in the mirikizumab induction responder group who continued mirikizumab maintenance treatment
  - Median fecal calprotectin, after 52 weeks of continuous treatment with mirikizumab in the responder group, fell to a level known to be correlated with both endoscopic and histologic healing[6,7]
- Mirikizumab-treated patients were more likely to achieve fecal calprotectin ≤250 µg/g and C-reactive protein ≤6 mg/L vs. placebo during induction and maintenance treatment
- Reduction in inflammatory biomarkers with mirikizumab treatment demonstrates response to therapy and indicates improvement in disease activity

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DISCLOSURES

- **B. Siegmund** has served as a consultant and/or speaker for: AbbVie, Arena Pharmaceuticals, Bristol Myers Squibb, Boehringer Ingelheim, CED Service GmbH, Celgene, Dr. Falk Pharma, Eli Lilly and Company, Ferring Pharmaceuticals, Galapagos NV, Janssen, Novartis, Pfizer, Prometheus Therapeutics, and Takeda; **B. E. Sands** has served as a consultant and/or speaker for: AbbVie, Abivax, Adiso Therapeutics, Alimentiv, Amgen, Arena Pharmaceuticals, Artizan Biosciences, Artugen Therapeutics, AstraZeneca, Bacainn Therapeutics, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Calibr, Celltrion, ClostraBio, Cytoki Pharma, Connect Biopharma, Eli Lilly and Company, Entera Bio, Evommune, Fresenius Kabi, Galapagos NV, Genentech, Gilead Sciences, GlaxoSmithKline, Gossamer Bio, Imhotex, Immunic Therapeutics, InDex Pharmaceuticals, Inotrem, Innovation Pharmaceuticals, Ironwood Pharmaceuticals, Janssen, Kaleido Biosciences, Kallyope, MiroBio, Morphic Therapeutic, MRM Health, OSE Immunotherapeutics, Pfizer, Progenity, Prometheus Therapeutics, Protagonist Therapeutics, Q32 Bio, RedHill Biopharma, Sun Pharma, Surrozen, Synlogic, Target RWE, Takeda, Teva, Theravance Biopharma, TLL Pharmaceutical, USWM Enterprises, Ventyx Biosciences, Viela Bio, and VTA Labs; **K. Hamrick Samaan**, **X. Li**, **N. Morris**, **T. Hunter Gibble**, **I. Redondo**, and **T. Lissoos** are employees and shareholders of: Eli Lilly and Company; **G. R. D'Haens** has served as an advisor for: AbbVie, Ablynx, Active Biotech, AgomAb Therapeutics, Allergan, AlphaBiomics, Amakem, Amgen, AM-Pharma, Applied Molecular Therapeutics, Arena Pharmaceuticals, AstraZeneca, Avaxia Biologics, Biogen, Boehringer Ingelheim, Bristol Myers Squibb/Celgene, Celltrion, Cosmo Pharmaceuticals, Dr. Falk Pharma, DSM Pharmaceuticals, Echo Pharmaceuticals, Eli Lilly and Company, enGene, Exeliom Biosciences, Ferring Pharmaceuticals, Galapagos NV, Genentech/Roche, Gilead Sciences, GlaxoSmithKline, Gossamer Bio, Immunic Therapeutics, Johnson & Johnson, Kintai Therapeutics, Lycera, Medimetrics, Medtronic, Merck Sharp & Dohme, Mitsubishi Pharma, Mundipharma, Nextbiotics, Novo Nordisk, Otsuka, Pfizer, PhotoPills, ProciseDx, ProDigest, Progenity, Prometheus Laboratories/Nestlé, Protagonist Therapeutics, RedHill Biopharma, Robarts Clinical Trials, Salix Pharmaceuticals, Samsung Bioepis, Sandoz, Seres Therapeutics/Nestec/Nestlé, Setpoint, Shire, Takeda, Teva, TiGenix, Tillotts Pharma AG, Topivert, Versant, and Vifor Pharma; and received speaker fees from: AbbVie, Biogen, Ferring Pharmaceuticals, Galapagos NV/Gilead Sciences, Johnson & Johnson, Merck Sharp & Dohme, Mundipharma, Norgine, Pfizer, Samsung Bioepis, Shire, Millenium/Takeda, Tillotts Pharma AG, and Vifor Pharma

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ABBREVIATIONS

ANCOVA=analysis of covariance; BL=baseline; IQR=interquartile range; IV=intravenous; LSM=least squares mean; mBOCF=modified baseline carried forward; MIRI=mirikizumab; mITT=modified Intent-to-Treat; MMS=Modified Mayo Score; Non-resp=non-responder; NRI=non-responder imputation; PBO=placebo; Q4W=every 4 weeks; R=randomization; RB=rectal bleeding; Resp=responder; SC=subcutaneous; SD=standard deviation; SE=standard error; UNRS=Urgency Numeric Rating Scale; W=Week