Supplemental Methods

Anti-Drug Antibodies

A drug-sensitive assay was performed by Progenika Biopharma (Derio, Spain)).(1) ADAs were determined by enzyme-linked immunosorbent assay (ELISA) using Promonitor-ANTI-IFX-1DV or Promonitor-ANTI-ADL-1DV, following package insert instructions, and Triturus® Analyzer for an automatic processing of 96 well ELISA plates. ADA concentrations are interpolated from corresponding standard curve generated with each assay. The lower limit of quantification is 5 AU/mL and 10 AU/mL for ANTI-IFX and ANTI-ADL respectively.

A drug-tolerant assay was performed by Labcorp (Calabasas, CA, USA). ADAs were quantified using Labcorp-developed electrochemiluminescence based immunoassays (ECLIA) with a lower limit of quantification of 22 ng/mL for infliximab and 25 ng/mL for adalimumab.[1] Labcorp's ADA assays' high drug tolerance is achieved by pre-treatment of samples that displaces circulating drug in patient serum that would otherwise cause falsely low or false negative ADA results. Furthermore, all ADA positive results are confirmed for drug-specificity by an additional analytic step.

ImproveCareNow registry

Study data was collected through the ICN Patient Registry and supplemented by trial-specific electronic case report forms. In 2007, ICN established a standardized, web-based clinical registry that enabled collection of standardized, IBD-specific data about processes and outcomes of care (e.g., disease characteristics, patient well-being, laboratory results, and medications). Participating collected routine clinical data at office visits and hospitalizations as part of the ICN registry described above.(2) In 2010, with AHRQ funding, ICN developed a modular, open-source, registry that can be linked to an electronic health record (EHR) to minimize the burden of manual data entry. This allows for a significant portion of registry data to be transferred electronically via a secure web portal to the registry, and stored for re-use in QI, chronic care delivery, and Comparative Effectiveness Research.(3)

Changes to the Original Study Protocol

Changes to the study protocol were made with input from study methodologists, the clinical committee, and parent co-investigators. Early in the study, we identified that eligibility criteria were too strict and that we were excluding some participants who site investigators would have considered candidates for combination therapy. We therefore broadened our eligibility criteria to allow our trial population to more closely represent the population of patients facing the treatment decision. We also lengthened the window of time allowed between initiation of the anti-TNF treatment and trial enrollment from 4 to 6 weeks as this was the window of time in which clinicians and families were often discussing the decision of whether to pursue anti-TNF combination or monotherapy. Another small change in the study protocol was made when we observed a few participants withdrew from the study within a day or two following randomization and before study medication was shipped from the pharmacy. As these patients reflect those that may change their mind before picking up a prescription from the pharmacy in the real world, we modified our protocol to utilize a modified intent-to-treat analysis only, including participants who received at least one shipment of medication from the study pharmacy.

We made a slight deviation to our planned analyses of ADA prior to beginning data analysis. We originally planned to compare the proportion of patients with positive ADA measured in the 2nd year of the trial; however, our final analyses included those with positive ADA between 6- and 12- months following randomization as well as in the 2nd year of follow-up. We made this change as 1) a positive ADA at an earlier timepoint is an important marker of immunogenicity, and 2) not all patients provided blood samples during the 2nd year of follow-up, particularly during the pandemic.

Other changes to the study protocol were made due to challenges with recruitment. Specifically, we shortened the minimum follow-up period to one rather than two years to allow more patients to be recruited prior to study closure. We also extended study follow-up for up to 3 years to collect additional data and allow more time for patients to experience primary study outcomes.

Sample Size

Our sample size calculation assumed treatment failure would occur in 50% of the monotherapy arm and in 35% of the combination arm. This was based on the two adult trials of anti-TNF combination versus monotherapy that observed 1-year treatment success rates of 40% and 56% in the monotherapy groups. (4, 5). We considered an absolute difference of 15% as the minimum clinically important difference, below which the benefits of combination therapy would not outweigh the risks. Assuming an exponential distribution for time to treatment failure, a total of 140 events would be required to achieve a power of 80% with a two-sided type I error rate of 0.05. After accounting for variable follow-up, we estimated a necessary sample size of 353 participants and a goal recruitment of 425 participants to allow exploration of heterogeneity of treatment effects.

Adverse Events and Serious Adverse Events.

Our study protocol defined serious adverse events (SAEs) as events that were, fatal, life-threatening, required or prolonged a hospital stay, resulted in persistent or significant disability or incapacity, a congenital anomaly or birth defect (in the offspring of a study participant), other important medical event**s** as determined by the site investigator. All adverse events not meeting any of the criteria for serious were regarded as non-serious AEs.

Supplemental Table 1a. Demographic and Clinical Characteristics of the Study Population – INFLIXIMAB ONLY

Demographics	All Patients		Combination Therapy (Active)		Monotherapy (Placebo)		P value
	n	% or SD	n	% or SD	n	% or SD	
Total Number of patients	**212**	**100%**	**110**	**52%**	**102**	**48%**	
Female (N, %)	81	38%	39	35%	42	41%	0.39
Mean age (SD)	13.7	2.6	13.6	2.5	13.7	2.8	0.89
Race (n, %)							
Asian	4	2%	2	2%	2	2%	0.94
Black / African American	27	13%	13	12%	14	14%	0.68
White	169	80%	88	80%	81	79%	0.92
Multi-race or Other	10	5%	5	4%	5	5%	0.90
Ethnicity (n, %)							
Hispanic or Latino	7	3%	5	5%	2	2%	0.45
Not Hispanic or Latino	203	97%	104	96%	99	98%	
Clinical Characteristics							
Mean Height, z-score (SD)	-0.28	1.08	-0.28	1.09	-0.28	1.07	0.99
Mean Weight, z-score (SD)	-0.27	1.13	-0.31	1.24	-0.23	1.02	0.58
Mean BMI, z-score (SD)	-0.18	1.17	-0.24	1.29	-0.12	1.04	0.48
Mean time from diagnosis in months (SD)	8.7	17.6	8.3	16.9	9.1	18.4	0.74
Disease Location – Lower GI (n, %)							
None	5	2%	5	5%	0	0%	
Ileum Only	46	23%	22	22%	24	24%	0.06
Colon Only	34	17%	13	13%	21	21%	
Ileocolonic	115	58%	61	60%	54	55%	
Upper GI – Proximal (n, %)	98	52%	51	54%	47	51%	0.67
Upper GI – Distal (n, %)	45	26%	22	25%	23	27%	0.76
Perianal disease at enrollment (n, %)	23	22%	12	22%	11	21%	0.93
History of perianal disease (n, %)	63	30%	29	27%	34	33%	0.31
Mean sPCDAI score at randomization	18.7	16.2	19.8	17.0	17.4	15.3	0.34
Physician Global Assessment at randomization							
Quiescent	42	23%	22	23%	20	23%	0.50
Mild	74	41%	35	37%	39	44%	
Moderate	58	32%	31	33%	27	31%	
Severe	8	4%	6	6%	2	2%	
Mean Baseline PROMIS Fatigue Score (SD)	48.1	14.7	47.5	14.7	48.7	14.8	0.56
Mean Baseline PROMIS Pain Score (SD)	47.6	14.5	46.9	14.5	48.3	14.5	0.48
Prior Treatment							

Prior azathioprine or mercaptopurine therapy (n, %)	23	11%	11	10%	12	12%	0.68
Prior methotrexate (n, %)	30	14%	17	15%	13	13%	0.59
Current Treatment							
Any Steroid at Randomization (n, %)	83	40%	45	41%	38	38%	0.67
Baseline Labs							
Mean Sed rate (ESR) highest within 42 days of randomization (SD)	18.9	18.6	21.7	20.9	15.8	15.3	0.03
Mean Alb worst within 42 days of randomization (SD)	3.8	0.6	3.8	0.5	3.8	0.6	0.28
Mean Hemoglobin (Hgb) lowest within 42 days of randomization (SD)	12.0	1.7	11.7	1.8	12.3	1.5	0.006
CRP at randomization greater than 2x upper limit of normal (n, %)	29	15%	18	19%	11	13%	0.22

Table 1b. Demographic and Clinical Characteristics of the Study Population – ADALIMUMAB ONLY

Demographics	**All Patients**		**Combination Therapy (Active)**		**Monotherapy (Placebo)**		**P value**
	n	**% or SD**	**n**	**% or SD**	**n**	**% or SD**	
Total Number of patients	**85**	**100%**	**46**	**54%**	**39**	**46%**	
Female (N, %)	23	27%	14	30%	9	23%	0.45
Mean age (SD)	14.4	2.6	14.1	2.5	14.8	2.6	0.24
Race (n, %)							
Asian	0	0%	0	0%	0	0%	--
Black / African American	5	6%	0	0%	5	13%	0.02
White	75	88%	43	93%	32	82%	0.18
Multi-race or Other	3	3%	3	7%	0	0%	0.50
Ethnicity (n, %)							
Hispanic or Latino	1	1%	0	0%	1	3%	0.45
Not Hispanic or Latino	82	99%	46	100%	36	97%	
Clinical Characteristics							
Mean Height, z-score (SD)	-0.15	1.06	-0.05	1.04	-0.27	1.09	0.35
Mean Weight, z-score (SD)	-0.19	1.07	-0.16	0.86	-0.22	1.30	0.82
Mean BMI, z-score (SD)	-0.23	1.18	-0.27	0.99	-0.18	1.39	0.75
Mean time from diagnosis in months (SD)	9.3	17.5	7.7	13.5	11.2	22.0	0.39
Disease Location – Lower GI (n, %)							
None	0	0%	0	0%	0	0%	
Ileum Only	21	26%	10	23%	11	29%	0.49
Colon Only	14	17%	6	14%	8	21%	
Ileocolonic	46	57%	27	63%	19	50%	
Upper GI – Proximal (n, %)	42	52%	23	52%	19	51%	0.93
Upper GI – Distal (n, %)	25	34%	14	36%	11	31%	0.68

Perianal disease at enrollment (n, %)	8	21%	5	22%	3	19%	1.0
History of perianal disease (n, %)	22	26%	14	30%	8	21%	0.30
Mean sPCDAI score at randomization	13.3	13.4	11.3	13.4	15.6	13.1	0.17
Physician Global Assessment at randomization							
Quiescent	27	36%	15	39%	12	32%	0.78
Mild	26	35%	13	34%	13	35%	
Moderate	22	29%	10	26%	12	32%	
Severe	0	0%	0	0%	0	0%	
Mean Baseline PROMIS Fatigue Score (SD)	46.4	16.4	47.3	17.4	45.3	15.2	0.61
Mean Baseline PROMIS Pain Score (SD)	45.2	13.6	45.5	14.6	44.7	12.6	0.81
Prior Treatment							
Prior azathioprine or mercaptopurine therapy (n, %)	13	15%	7	15%	6	15%	0.98
Prior methotrexate (n, %)	17	20%	9	20%	8	21%	0.91
Current Treatment							
Any Steroid at Randomization (n, %)	37	44%	19	41%	18	46%	0.65
Baseline Labs							
Mean Sed rate (ESR) highest within 42 days of randomization (SD)	17.6	17.9	16.2	12.2	19.0	22.3	0.55
Mean Alb worst within 42 days of randomization (SD)	3.9	0.6	4.0	0.6	3.9	0.6	0.90
Mean Hemoglobin (Hgb) lowest within 42 days of randomization (SD)	12.4	3.2	12.3	1.5	12.6	4.5	0.77
CRP at randomization greater than 2x upper limit of normal (n, %)	18	29%	9	29%	9	29%	1.0

Supplemental Table 2: Number of participants meeting a primary outcome and number of participants who experienced each component of the composite endpoint, stratified by treatment assignment and anti-TNF agent

	Adalimumab		Infliximab		Overall		
	Active	Placebo	Active	Placebo	Active	Placebo	Total
Number of Patients meeting ≥ 1 component of the primary outcome	**11**	**20**	**29**	**28**	**40**	**48**	**88**
Hospitalization (IBD-related) after week 25	1	1	7	7	8	8	**16**
Discontinuation of the anti-TNF agent for lack of effectiveness.	3	7	0	5	3	12	**15**
Discontinuation of the study drug for toxicity	3	1	6	6	9	7	**16**
Discontinuation of the anti-TNF agent for toxicity	2	2	3	3	5	5	**10**
Discontinuation of the study drug for lack of effectiveness	0	3	5	4	5	7	**12**
Abdominal Surgery for Active IBD after week 25	0	1	6	2	6	3	**9**
Use of (steroid) for a period of over 10 weeks cumulatively, beyond week 16	0	4	2	1	2	5	**7**
sPCDAI >=15 without non-IBD cause at 2+ consecutive visits beyond week 26	1	1	4	1	5	2	**7**
Failure to achieve remission (sPCDAI<15) by the week 26 visit	0	2	2	1	2	3	**5**
Failure to taper steroids by week 16	1	0	0	2	1	2	**3**
Number of Outcomes	**11**	**22**	**35**	**32**	**46**	**54**	**100**

Supplemental Table 3. Pre-specified subgroup analyses

Subgroup analysis	Interaction p	Group Name	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Race	0.67	White	0.63 (0.39-1.02)	Non-white	0.78 (0.34-1.81)		
Ethnicity	0.99	Hispanic	n/a	non-hispanic	0.59 (0.30-0.91)		
Time since diagnosis	0.49	<2 years	0.68 (0.44-4.51)	≥ 2 years	0.49 (0.10-1.67)		
Disease location	0.08	Ileum only	0.60 (0.01-0.55)	Colon only	0.07 (0.01-0.55)	Ileocolonic	0.78 (0.44-1.37)
CRP > 2X normal	0.33	Yes	0.50 (0.19-1.31)	No	0.86 (8.53-1.45)		
ESR > 18	0.02	Yes	0.33 (0.14-0.78)	No	1.15 (0.65-2.04)		
TNF dose change	0.55	Yes	0.73 (0.4201.27)	No	0.56 (0.29-1.07)		

Supplemental Table 4. Anti-Drug Antibodies (ADA) in Participants Treated with anti-TNF Monotherapy and Combination Therapy

Anti-TNF	Participants with sample for ADA measurement (monotherapy)	ADA positive N (%)	Participants with sample for ADA measurement (combination therapy)	ADA positive N (%)	OR (95% CI)
Infliximab	72	34 (47.2)	79	27 (34.0)	OR 0.72 (0.49-1.07)
Adalimumab	28	6 (21.4)	33	5 (15.2)	OR 0.71 (0.24-2.07)

Supplemental Table 5. Adverse Events (Serious and Non-Serious) reported in > 2% of study population

Event	All Patients (n=297)		Combination Therapy (Active) (n=156)		Monotherapy (Placebo) (n=141)	
	n	%	n	%	n	%
Infection	79	26%	45	28%	34	24%
Nausea / Vomiting	53	17%	35	22%	18	13%
Abdominal Discomfort	46	15%	24	15%	22	15%
Rash	36	12%	17	10%	19	13%
Headache	30	10%	12	7%	18	13%
Elevation of Liver Enzymes (AST, ALT)	29	9%	21	13%	8	6%
Fever	21	7%	13	8%	8	6%
Diarrhea	20	7%	7	4%	13	9%
Fatigue	16	5%	8	5%	8	6%
Anti-TNF Infusion Related Reaction	9	3%	4	2%	5	3%
Alopecia	8	3%	4	2%	4	3%
Dizziness	7	2%	3	2%	4	3%

Supplemental Table 6. Subjects with Lab Abnormalities

Abnormalities in Lab Values	All Patients (n=297)		Combination Therapy (Active) (n=156)		Monotherapy (Placebo) (n=141)	
	n	%	n	%	n	%
Elevated AST (2x ULN)	19	6%	15	9%	4	3%
Elevated ALT (2x ULN)	31	10%	21	13%	10	7%
Low WBC (< 3.5)	11	4%	6	4%	5	3%

Supplemental Table 7a. Serious Adverse Events Among Participants Assigned to Combination Therapy (n=27)

SAE Description	Number of events
Infection	5
Nausea / Vomiting	2
Tenosynovitis of right Ankle	1
Anti-TNF Infusion Reaction	1
Diarrhea	1
Intentional ingestion	1
PCD flare and pharyngitis (Group A Strep)	1
Headache	1
G tube placement	1
Major Depression	1
Back Pain	1
Colon perforation, colostomy creation	1
Crohn's exacerbation with ileitis and small bowel obstruction	1
Fever	1
Bowel obstruction	1
Suicide attempt	1
Tonsillectomy and adenoidectomy	1
Perirectal Abscess	1
Suicidal ideation, depression, anxiety	1
Nausea / Infection	1
Crohn's Disease w intestinal obstruction	1
Anemia	1

Supplemental Table 7b. Serious Adverse Events Among Participants Assigned to Monotherapy (n=29)

AE Description	Number of events
Abdominal Discomfort	6
Anti-TNF Infusion Reaction	2
Kidney Stone	2
Constiopation	1
Nausea / Vomiting	1
Bowel microperforation	1
Decreased stools, abdominal pain	1
Suicidal ideation	1
Abdominal pain, fecal impaction	1
Nausea/vomiting, abdominal pain	1
Ileocecectomy	1
Bloody diarrhea	1
Acute pancreatitis	1
Paranoia and mental status change	1
Acute cellulitis	1
PCD exacerbation	1
Acute Depression w/ suicidal ideation	1
Post-operative infection from ileocecectomy	1
Infection	1
Perianal Abscess	1
Facial Flushing	1
Facial Abscess	1

Supplemental Table 8: Anti-TNF Dosing, Dose Adjustment, and use of Therapeutic Drug Monitoring in Study Population

Measure	Infliximab	Adalimumab
Median initial maintenance dose (mg)	300	40
Median initial maintenance dose (mg)/kg	6.2	0.68
Median initial maintenance interval (weeks)	7.2	2
Proportion of participants with ≥ 1 recorded dose and/or interval change	53%	33%
Mean number of recorded dose changes	0.90	0.39
Median final maintenance dose (mg)	500	40
Median final maintenance dose (mg)/kg	8.5	0.63
Median final maintenance interval (weeks)	6.8	1.4
Proportion of patients with ≥ 1 standard of care therapeutic drug monitoring test in the first year since randomization	45%	40%

1. Marini JC, Sendecki J, Cornillie F, Popp JW, Jr., Black S, Blank M, et al. Comparisons of Serum Infliximab and Antibodies-to-Infliximab Tests Used in Inflammatory Bowel Disease Clinical Trials of Remicade®. Aaps j. 2017;19(1):161-71.
2. Crandall WV, Margolis PA, Kappelman MD, King EC, Pratt JM, Boyle BM, et al. Improved outcomes in a quality improvement collaborative for pediatric inflammatory bowel disease. Pediatrics. 2012;129(4):e1030-41.
3. Pratt J, Jeffers D, King EC, Kappelman MD, Collins J, Margolis P, et al. Implementing a Novel Quality Improvement-Based Approach to Data Quality Monitoring and Enhancement in a Multipurpose Clinical Registry. EGEMS (Wash DC). 2019;7(1):51.
4. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. The New England journal of medicine. 2010;362(15):1383-95.
5. Feagan BG, McDonald JW, Panaccione R, Enns RA, Bernstein CN, Ponich TP, et al. Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. Gastroenterology. 2014;146(3):681-8 e1.