Protocol Overview

- **M14-431:** A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of ABT-494 in Subjects with Moderately to Severely Active Crohn's Disease who have Inadequately Responded to or are Intolerant to Biologic Therapy
- **M14-433:** A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of ABT-494 in Subjects with Moderately to Severely Active Crohn's Disease who have Inadequately Responded to or are Intolerant to Conventional Therapies, but have not Failed Biologic Therapy
- **M14-430:** A Multicenter, Randomized, Double-Blind, Placebo-Controlled Maintenance and Long-Term Extension Study of the Efficacy and Safety of ABT-494 in Subjects with Crohn's Disease who Completed the M14-431 or M14-433 Studies

M14-431 and M14-433 Induction Studies

Primary Objective for M14-431/M14-433

The objective of Study M14-431 and M14-433 is to evaluate the efficacy and safety of upadacitinib compared to placebo as induction therapy in subjects with moderately and severely active CD.

Key Inclusion Criteria:

1. Male or female aged 18 – 75 years old.

2. Confirmed diagnosis of CD for at least 3 months prior to Baseline.

3. Simplified endoscopic score for CD (SES-CD) excluding the presence of narrowing component, ≥ 6 (or ≥ 4 for subjects with isolated ileal disease), confirmed by a central reader.

4. Average daily very soft/liquid stool frequency (SF) ≥ 4 and/or average daily abdominal pain (AP) score ≥ 2 at Baseline.

5. Demonstrated intolerance or inadequate response to one or more of the following categories of drugs :
    1. M14-431: biologic therapy (adalimumab, certolizumab, infliximab, natalizumab, ustekinumab and/or vedolizumab)
    2. M14-433: aminosalicylates, oral locally acting steroids, systemic steroids, immunomodulators (prior biologic use without failure or intolerance is allowed in up to 30% of subjects)

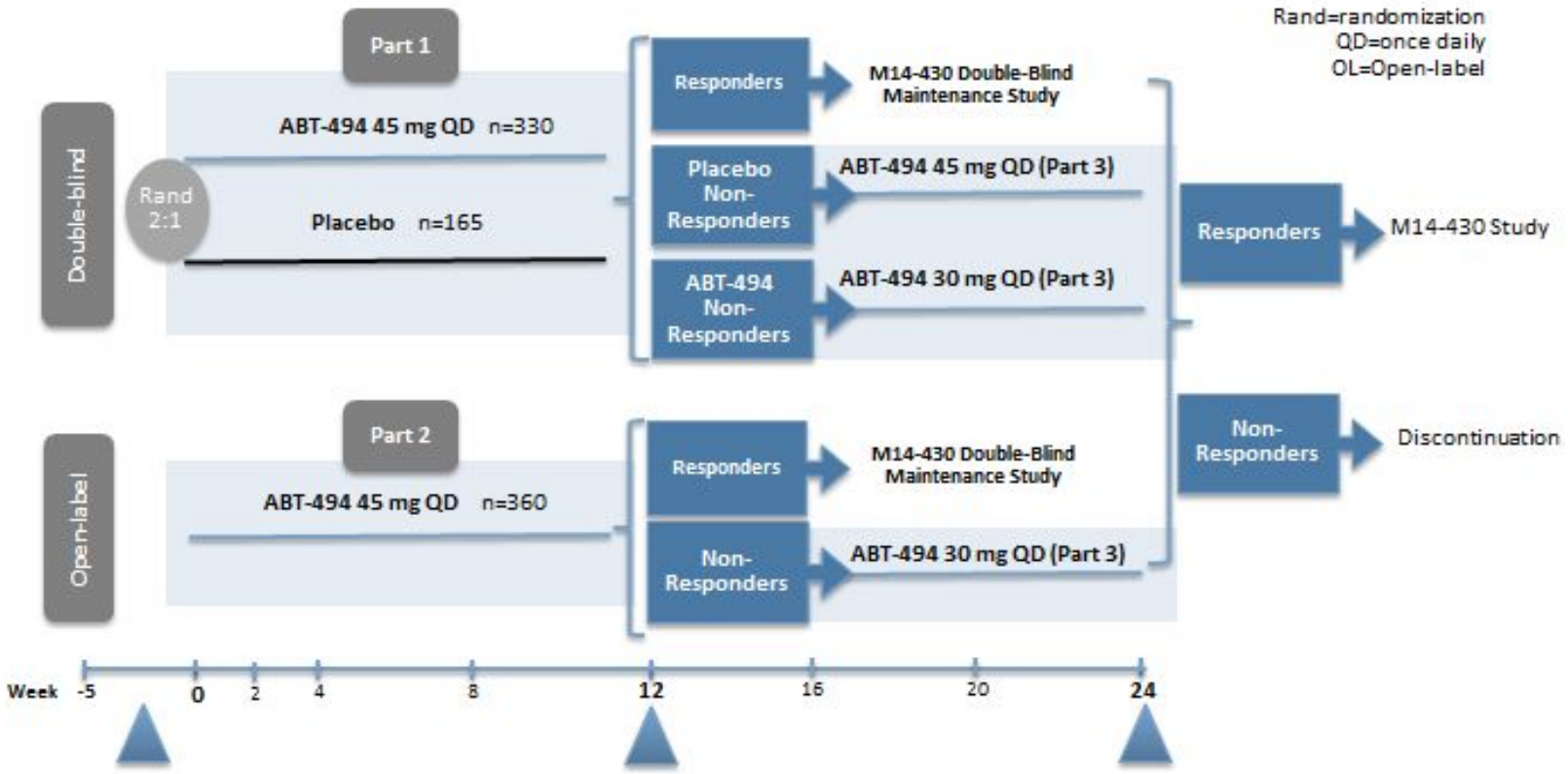
M14-431 and M14-433 Key Exclusion Criteria

Category	Exclusion Criteria	
Non-stable doses of concomitant medications	CD-related antibiotics	Oral steroids
	Oral aminosalicylates	Methotrexate
Concomitant or recent use of immunosuppressant or investigational therapies	IV anti-infectives	Biologic/Investigational drug use (5 half lives)
	Live vaccines	TPN
	Enema, FMT	
CD-Related	Diagnosis of UC/IC	Surgeries
	Known complications of CD: impassable or fixed bowel stenosis or strictures, symptomatic bowel strictures, fulminant colitis, toxic megacolon,	
Safety	Chronic or active infections	Screening lab abnormalities
	Malignancies	Pregnant/nursing females
	Diverticulitis	

Primary and Ranked Secondary Endpoints for M14-431 and M14-433

	Induction (M14-433 and M14-431)	
Primary	Clinical Remission at week 12 AND Endoscopic response at week 12	
Key Secondary and Exploratory Endpoints	<u>Secondary</u> Clinical Remission (CDAI) Enhanced clinical response Clinical response Endoscopic remission Clinical remission and endoscopic remission Clinical response and endoscopic response Steroid–free remission Steroid dose decrease <u>≥</u> 50% Steroid-free Fistula closure QoL questionnaires: CSS, IBDQ, FACIT-Fatigue, SF-36, EQ-5D-5L, WPAI, Hospitalizations Surgeries Fecal calprotectin Extra-intestinal manifestations CRP, AP and SF	<u>Exploratory</u> Mucosal healing Prognostic, Predictive, Surrogate Biomarkers

M14-431: Induction Study in Biologic Inadequate Responders



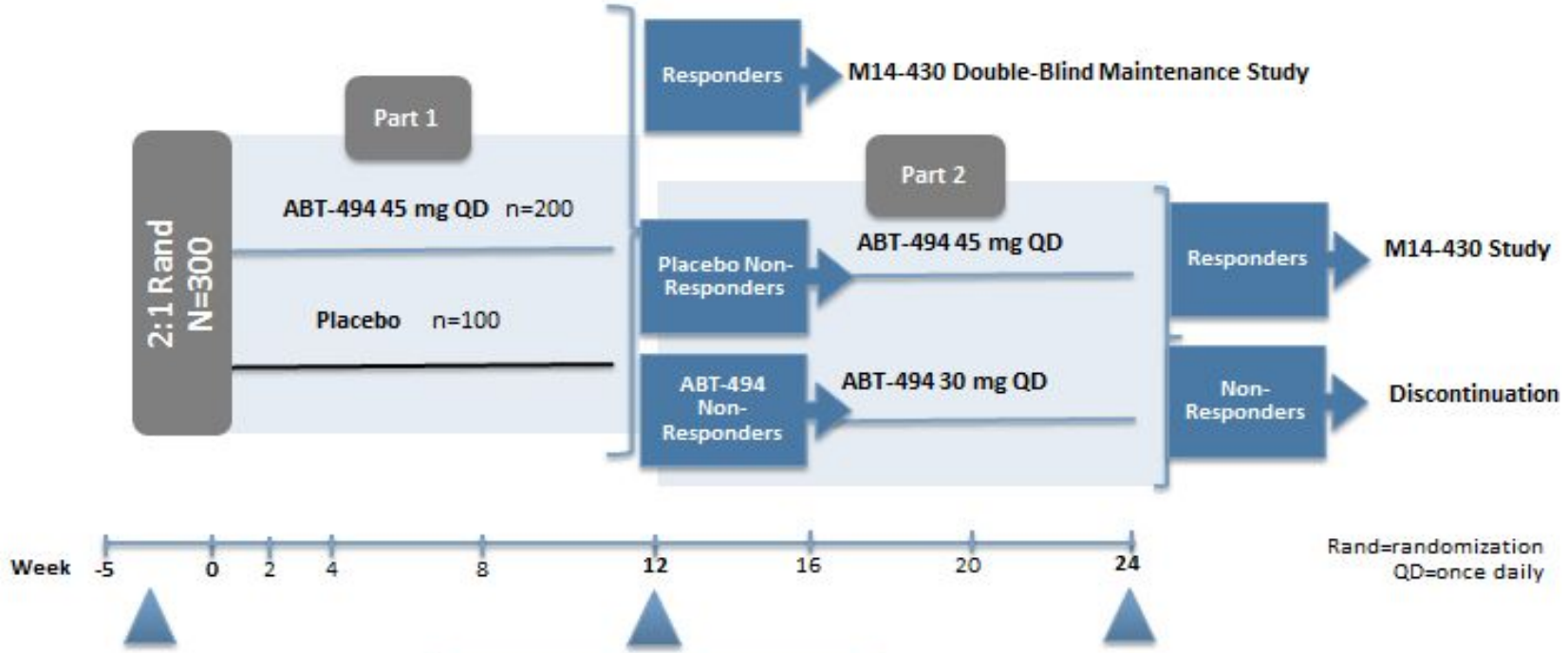
Colonoscopy

Co-Primary Endpoints:
Clinical Remission at wk 12 and
Endoscopic Response at wk 12

Stratification Factors:

1. Baseline steroid use
2. SES-CD ≥ or < 15
3. Number of prior biologics

M14-433: Induction Study in Biologic-naïve and Biologic-experienced patients (with no failure)



Concomitant medications

- All CD-related medications (aminosalicylates, methotrexate, CD-related antibiotics) held stable throughout the induction period.
- Corticosteroids: forced taper to stat at week 4

	Phase 2	Phase 3 Induction
Taper initiation	Week 2	Week 4
Schedule	Prednisone: decrease 5mg/d weekly until 10 mg/d, then decrease 2.5 mg/d weekly, until discontinuation Budesonide: decrease 3mg/d weekly	Prednisone : No changes Budesonide: decrease 3mg/d every 2 weeks
Allowed steroids	Any	Any
Protocol rules for efficacy assessments	Dose increases above BL value will be imputed as non-responders	(1) Dose increases above BL value up to week 9, or (2) any dose increase at or after week 10 will be considered as non-responders.
Dose changes, if there is loss of response	May be increased based on the investigator judgment about the subject's clinical status	May have their corticosteroid taper stopped or dose increased up to the dose used at Baseline, based on the investigator's judgment.

Example of Steroid Taper

Baseline Dose	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12
Prednisone or Prednisolone									
30	**25**	**20**	**15**	**10**	**7.5**	**5**	**2.5**	**Discontinue**	0
25	**20**	**15**	**10**	**7.5**	**5**	**2.5**	**Discontinue**	0	0
20	**15**	**10**	**7.5**	**5**	**2.5**	**Discontinue**	0	0	0
15	**10**	**7.5**	**5**	**2.5**	**Discontinue**	0	0	0	0
10	**7.5**	**5**	**2.5**	**Discontinue**	0	0	0	0	0
7.5	**5**	**2.5**	**Discontinue**	0	0	0	0	0	0
5	**2.5**	**Discontinue**	0	0	0	0	0	0	0
2.5	**Discontinue**	0	0	0	0	0	0	0	0

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M14-430 Maintenance and Long-Term Extension Study

Objectives of the Study

Sub-study 1: Randomized, double-blind, placebo-controlled maintenance

To evaluate the efficacy and safety of two doses of ABT-494 versus placebo as maintenance therapy in subjects with moderately to severely active Crohn's disease (CD) who responded to ABT-494 induction treatment in studies M14-431 or M14-433.

- M14-431: Who have inadequately responded to or are intolerant to biologic therapy
- M14-433: Who have inadequately responded to or are intolerant to conventional therapies, but have not failed biologic therapy

Sub-study 2: Long term extension (LTE)

To evaluate the efficacy and safety of one ABT-494 induction dose versus placebo in subjects with moderately and severely active Crohn's disease (CD) who participated in the phase 3 ABT-494 induction and maintenance studies M14-431 or M14-433

Key Inclusion

Substudy 1

- Subject achieved clinical response in Study M14-431 or M14-433.
- Subject completed Week 12 (in subjects who achieve response at Week 12) or Week 24 (in subjects who achieve response at Week 24) visit and procedures in Study M14-431 or M14-433.
- Note: Subjects completing Part 3/Cohort 3 of Study M14-431, who received open-label Extended Treatment, should enroll in Substudy 2.

Substudy 2

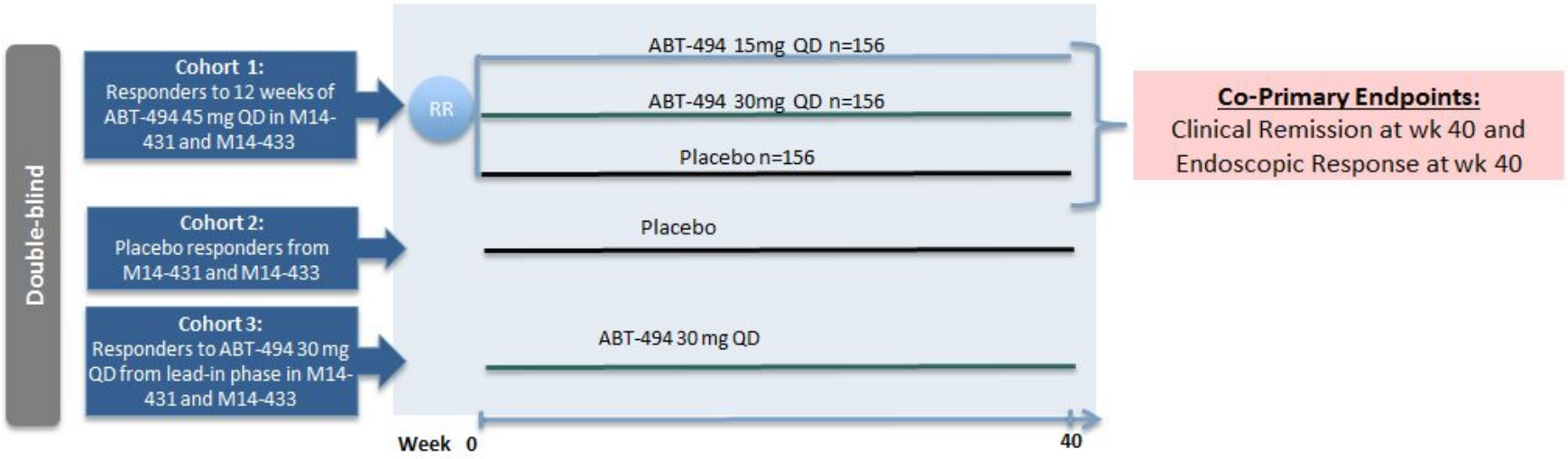
- Subject completed Week 40 of the maintenance period of Study M14-430 (Substudy 1). Completion includes the Week 40 endoscopy of Substudy 1.
- Subject achieved clinical response at Week 24 and completed Week 24 visit and procedures in Part 3/Cohort 3 of Study M14-431.

Key Exclusion

Substudy 1 and 2

- Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.
- Subject who has a known hypersensitivity to upadacitinib or its excipients, or had an AE during Study M14-431 or Substudy 1 of M14-430 that in the Investigator's judgment makes the subject unsuitable for this study.
- Subject with any active or chronic recurring infections based on the Investigator’s assessment that makes the subject an unsuitable candidate for the study. Subjects with ongoing infections undergoing treatment may be enrolled BUT NOT dosed until the infection treatment has been completed and the infection is cured, based on the Investigator’s assessment.
- Subjects with high grade colonic dysplasia or malignancy diagnosed at the endoscopy performed at the final visit of Study M14-431 (Week 24) or Substudy 1 of M14-430 (Week 40).

ABT-494 – M14-430 – Substudy 1 - Maintenance Study



Patient population:

1. Subjects who achieve clinical response at Week 12 of the induction study M14-431 or M14-433, or
2. Subjects who achieve clinical response at Week 24 after blinded lead-in treatment in study M14-431 or M14-433.

Disease activity required at study entry:

1. Clinical response : ≥ 30% decrease in average daily very soft/liquid stool frequency (SF) and/or ≥ 30% decrease in average daily abdominal pain (AP) score and both not worse than Baseline] and/or

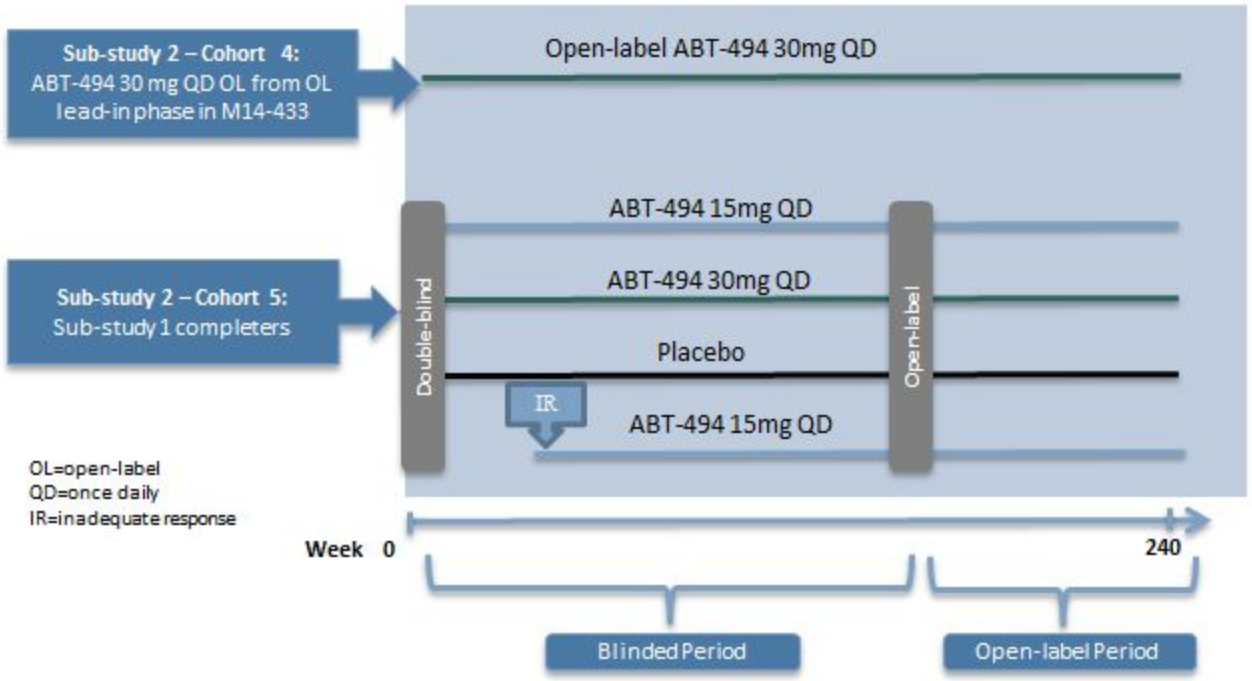
Stratification Factors:

1. Remission status
2. Endoscopy response status

Concomitant medications:

1. All CD-related concomitant medications held steady through induction
2. Continue steroid taper (for subjects on steroids at Baseline) initiated at Week 4 of the induction studies.

ABT-494 – M14-430 – Substudy 2 – Long-Term Extension Study



Patient population:

1. Subjects who achieve clinical response at Week 24 after open-label lead-in treatment in study M14-431, or
2. Subjects who complete M14-430 Substudy 1

Disease activity required at study entry:

1. Cohort 4: Clinical response and/or clinical remission
2. Cohort 5: Completion of Substudy 1

Concomitant medications:

1. All CD-related concomitant medications can be titrated or discontinued

Questions?