THE LANCET

ARTICLES | VOLUME 399, ISSUE 10341, P2113-2128, JUNE 04, 2022

Upadacitinib as induction and maintenance therapy for moderately to severely active ulcerative colitis: results from three phase 3, multicentre, double-blind, randomised trials

報告者：江新平 藥師
指導藥師：盧莘蓓 藥師

2022/10/19

Outline

- **Background**
  UC and JAK inhibitors
- **Clinical Trial**
- **Discussion**
- **Appraisal**
  CASP RCT checklist

Background

Ulcerative Colitis- Epidemiology

- **Geography**
  The highest incidences have been reported in northern Europe (24.3/100,000), Canada (19.2/100,000), and Australia (17.4/100,000). Prevalence rates are highest in Europe (505/100,000), Canada (248/100,000), and the USA (214/100,000).
  在台灣盛行率(prevalence)為 12/100000,每年新確診之個案約為350人，近年盛行率與發生率有增加趨勢。
- **Age**
  The peak age of disease onset is between ages 30 to 40 years of age.
- **Sex**
  Slight male predominance in ulcerative colitis.

Ungaro, R.(2017). Ulcerative colitis. The Lancet, 389(10080), 1756-1770

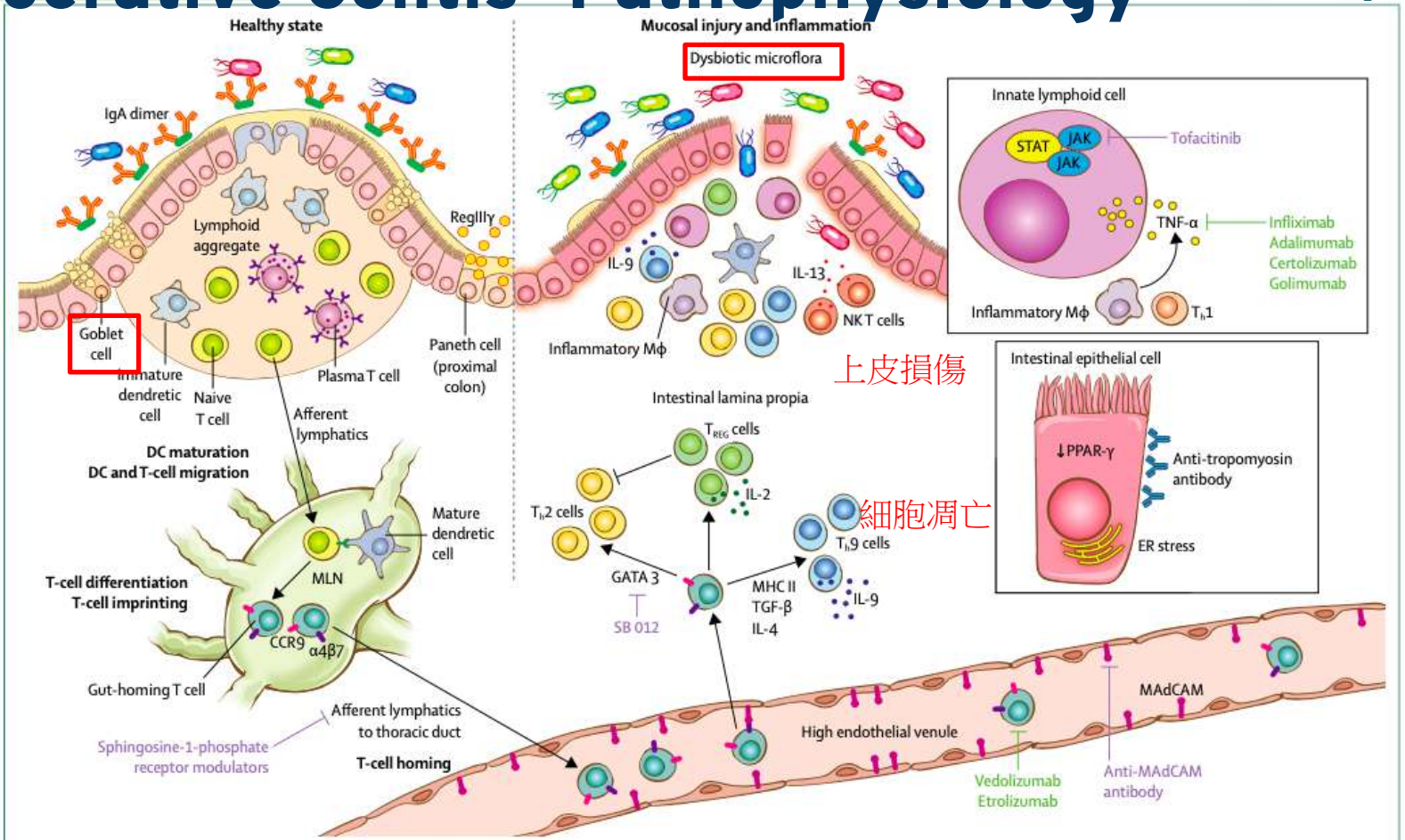
Ulcerative Colitis- Risk Factors

- **Genetic factors**
  Family history of inflammatory bowel disease and first-degree relatives have four times the risk of developing the disease.

- **Environmental factors**
  1. Incidence is higher in developed countries than in developing countries, in urban than in rural areas.
  2. Former cigarette smoking is one of the strongest risk factors, while active smokers are less likely to develop ulcerative colitis compared with former and non-smokers.

- **Drugs**
  Oral contraceptives, hormone replacement therapy, and NSAID increase risk of ulcerative colitis.

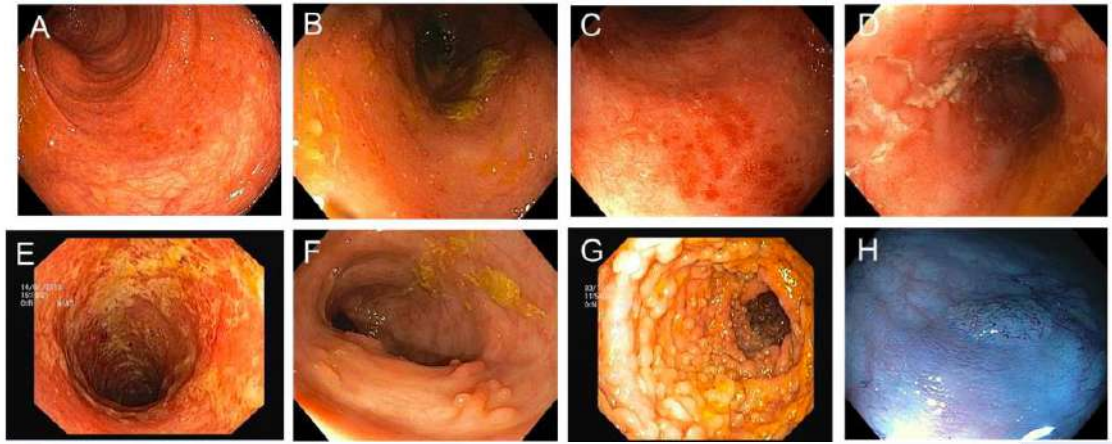
Ulcerative Colitis- Pathophysiology



Ungaro, R.(2017). Ulcerative colitis. The Lancet, 389(10080), 1756-1770

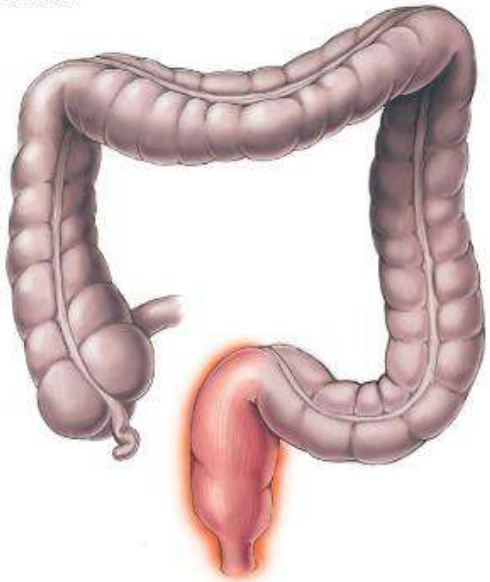
Diagnosis

- **Symptoms**
  Rectal bleeding, diarrhea, urgency, tenesmus (裡急後重), abdominal pain, fever (severe cases).
- **Endoscopic findings**
  Loss of vascular pattern, erythema, granularity, friability, erosions, ulcerations, spontaneous bleeding.



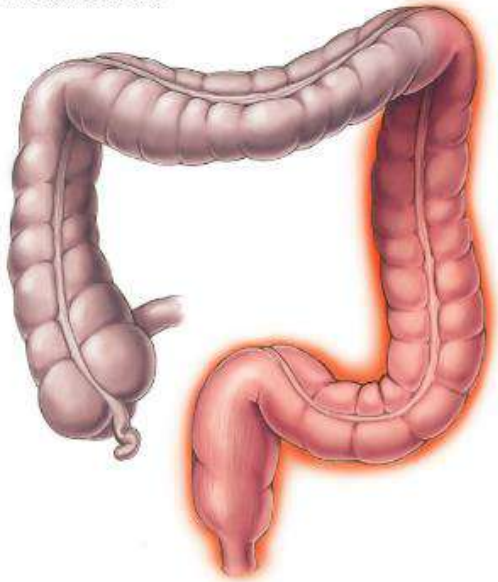
Phenotypes-Inflammatory Bowel Disease

Proctitis



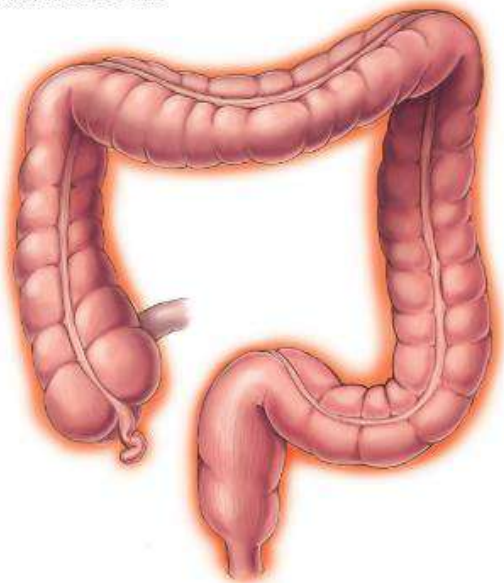
30–60% of patients
Symptoms
Rectal bleeding, tenesmus, urgency

Left-sided colitis

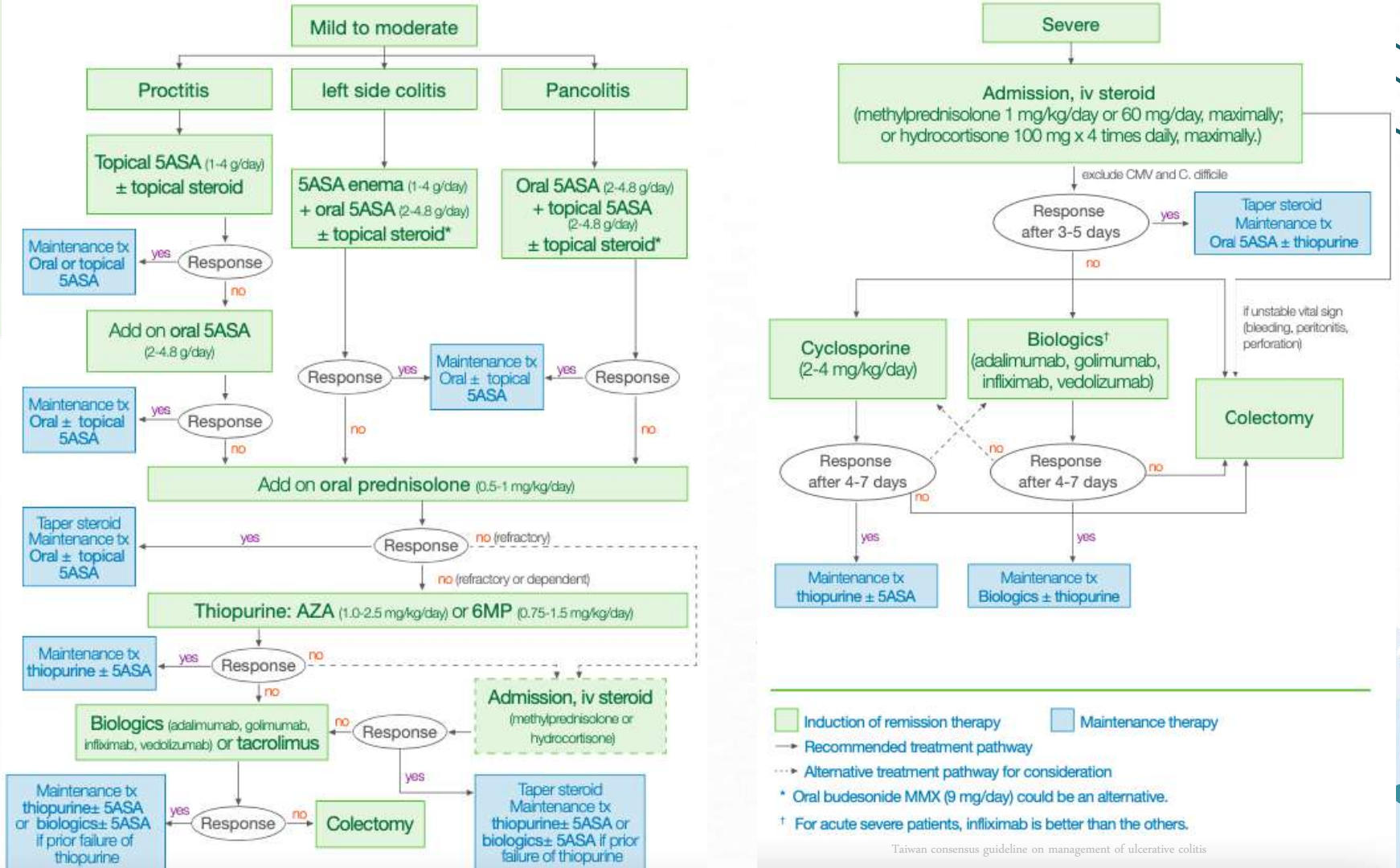


16–45% of patients
Symptoms
Proctitis plus diarrhoea, abdominal cramping

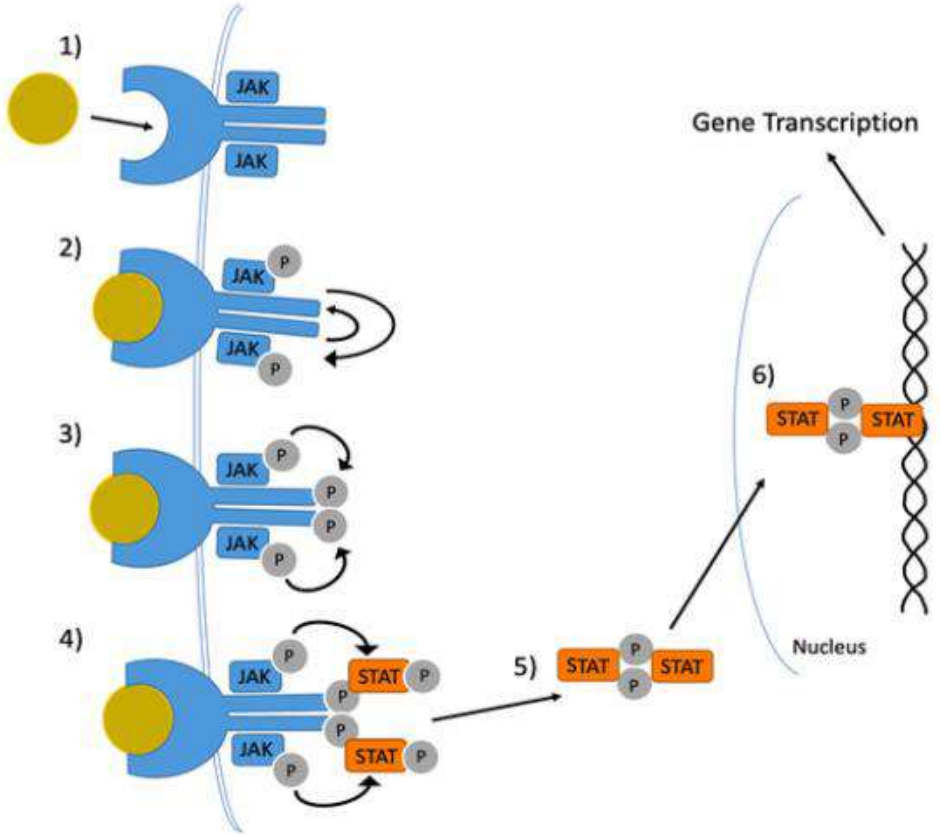
Extensive colitis

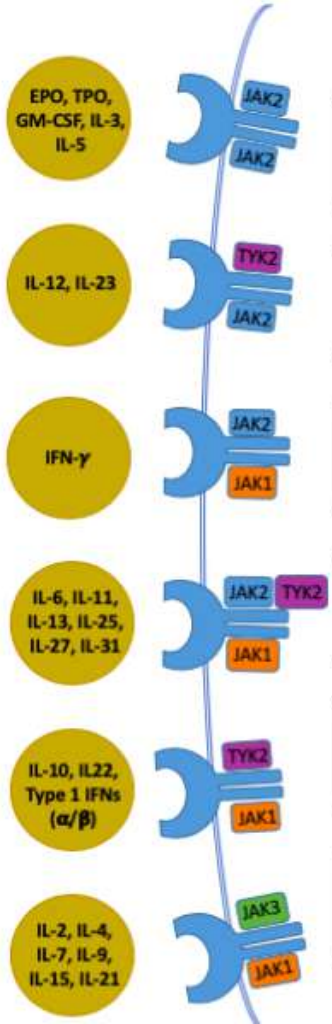


15–35% of patients
Symptoms
Left-sided colitis plus constitutional symptoms, fatigue, and fever


Mild to moderate
Proctitis
left side colitis
Pancolitis
Topical 5ASA (1-4 g/day) ± topical steroid
5ASA enema (1-4 g/day) + oral 5ASA (2-4.8 g/day) ± topical steroid*
Oral 5ASA (2-4.8 g/day) + topical 5ASA (2-4.8 g/day) ± topical steroid*
Maintenance tx Oral or topical 5ASA
yes
Response
no
Add on oral 5ASA (2-4.8 g/day)
Response
yes
Maintenance tx Oral ± topical 5ASA
yes
Response
Maintenance tx Oral ± topical 5ASA
yes
Response
no
no
no
Add on oral prednisolone (0.5-1 mg/kg/day)
Taper steroid Maintenance tx Oral ± topical 5ASA
yes
Response
no (refractory)
no (refractory or dependent)
Thiopurine: AZA (1.0-2.5 mg/kg/day) or 6MP (0.75-1.5 mg/kg/day)
Maintenance tx thiopurine ± 5ASA
yes
Response
no
no
Admission, iv steroid (methylprednisolone or hydrocortisone)
Biologics (adalimumab, golimumab, infliximab, vedolizumab) or tacrolimus
no
Response
yes
Maintenance tx thiopurine± 5ASA or biologics± 5ASA if prior failure of thiopurine
yes
Response
no
Colectomy
Taper steroid Maintenance tx thiopurine± 5ASA or biologics± 5ASA if prior failure of thiopurine
Severe
Admission, iv steroid (methylprednisolone 1 mg/kg/day or 60 mg/day, maximally; or hydrocortisone 100 mg x 4 times daily, maximally.)
exclude CMV and C. difficile
Response after 3-5 days
yes
Taper steroid Maintenance tx Oral 5ASA ± thiopurine
no
if unstable vital sign (bleeding, peritonitis, perforation)
Cyclosporine (2-4 mg/kg/day)
Biologics† (adalimumab, golimumab, infliximab, vedolizumab)
Colectomy
Response after 4-7 days
no
Response after 4-7 days
no
no
yes
yes
Maintenance tx thiopurine ± 5ASA
Maintenance tx Biologics ± thiopurine
Induction of remission therapy
Maintenance therapy
Recommended treatment pathway
Alternative treatment pathway for consideration
* Oral budesonide MMX (9 mg/day) could be an alternative.
† For acute severe patients, infliximab is better than the others.

Janus Kinase Inhibitor





	JAK1	JAK2	JAK3	TYK2
Myelopoiesis Erythropoiesis Thrombopoiesis Growth Mammary development		✓		
Innate immunity Inflammation Th17 cell differentiation and proliferation		✓		✓
Inflammation Anti-viral Anti-mycobacterial	✓	✓		
Inflammation B cell proliferation T cell homeostasis Granulopoiesis Naïve T cell differentiation	✓	✓		✓
Inflammation Anti-tumour Anti-viral	✓			✓
Inflammation Cellular differentiation Lymphoid cell maturation	✓		✓	

學名(商品名)	機轉	劑量	核准適應症	Black Box Warning
Tofacitinib (Xeljanz®)	Non-Selective JAK inhibitor	5mg,10mg 膜衣錠 11mg持續性藥效錠	• 類風濕性關節炎 • 乾癬性關節炎 • **潰瘍性結腸炎**	• **Serious Infections** (tuberculosis, opportunistic infection, herpes zoster) • **Malignancies** • **Major Adverse Cardiovascular Events** • **Thrombosis** (pulmonary embolism, deep venous thrombosis and arterial thrombosis)
Baricitinib (Olumiant®)	JAK1, JAK2 inhibitor	2mg,4mg膜衣錠	• 類風濕性關節炎 • 異位性皮膚炎 • COVID-19	
Upadacitinib (Rinvoq®)	JAK1 inhibitor	15mg持續性藥效錠	• 類風濕性關節炎 • 乾癬性關節炎 • 僵直性脊椎炎	

Clinical Trial

Upadacitinib as induction and maintenance therapy for moderately to severely active ulcerative colitis: results from three phase 3, multicentre, double-blind, randomised trials

Silvio Danese, Séverine Vermeire*, Wen Zhou, Aileen L Pangan, Jesse Siffledeen, Susan Greenbloom, Xavier Hébuterne, Geert D'Haens, Hiroshi Nakase, Julian Panés, Peter D R Higgins, Pascal Juillerat, James O Lindsay, Edward V Loftus Jr, William J Sandborn, Walter Reinisch, Min-Hu Chen, Yuri Sanchez Gonzalez, Bidan Huang, Wangang Xie, John Liu, Michael A Weinreich, Remo Panaccione*

Lancet 2022; 399: 2113–28

Published Online
May 26, 2022
https://doi.org/10.1016/
S0140-6736(22)00581-5

P (Patients)	**Patients aged 16–75 years with moderately to severely active ulcerative colitis**
I (Intervention)	• **Upadacitinib 45mg (induction)** • **Upadacitinib 15mg, 30mg (maintenance)**
C (Comparison)	**Placebo**
O (Outcome)	**Efficacy and safety**

Study Design

A phase 3, multicentre, randomised, double-blind, placebo-controlled clinical programme consisted of two replicate induction studies and a maintenance study.

Induction Studies	U-ACHIEVE substudy 2 [UC1] U-ACCOMPLISH [UC2]
Maintenance Study	U-ACHIEVE substudy 3 [UC3]

Patients Inclusion Criteria

1. ≥16 and ≤75 years of age

2. Diagnosis of ulcerative colitis for ≥90 days to baseline, confirmed by colonoscopy.

3. Active UC with an Adapted Mayo score of 5–9 points and endoscopic subscore of 2 or 3.

4. Inadequate response to, loss of response to, or intolerance to at least one of the following treatments including:
   -Oral aminosalicylates
   -Corticosteroids
   -Immunosuppressants
   -Biologic therapies

Adapted Mayo score of 5–9 points

- 0-2: clinical remission
- 3-5: mild
- 6-10: moderate
- 11-12: severe

Table 1. Mayo Scoring System for Assessment of Ulcerative Colitis Activity.*

Stool frequency†
- 0 = Normal no. of stools for this patient
- 1 = 1 to 2 stools more than normal
- 2 = 3 to 4 stools more than normal
- 3 = 5 or more stools more than normal

Subscore, 0 to 3

Rectal bleeding‡
- 0 = No blood seen
- 1 = Streaks of blood with stool less than half the time
- 2 = Obvious blood with stool most of the time
- 3 = Blood alone passes

Subscore, 0 to 3

Findings on endoscopy
- 0 = Normal or inactive disease
- 1 = Mild disease (erythema, decreased vascular pattern, mild friability)
- 2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)
- 3 = Severe disease (spontaneous bleeding, ulceration)

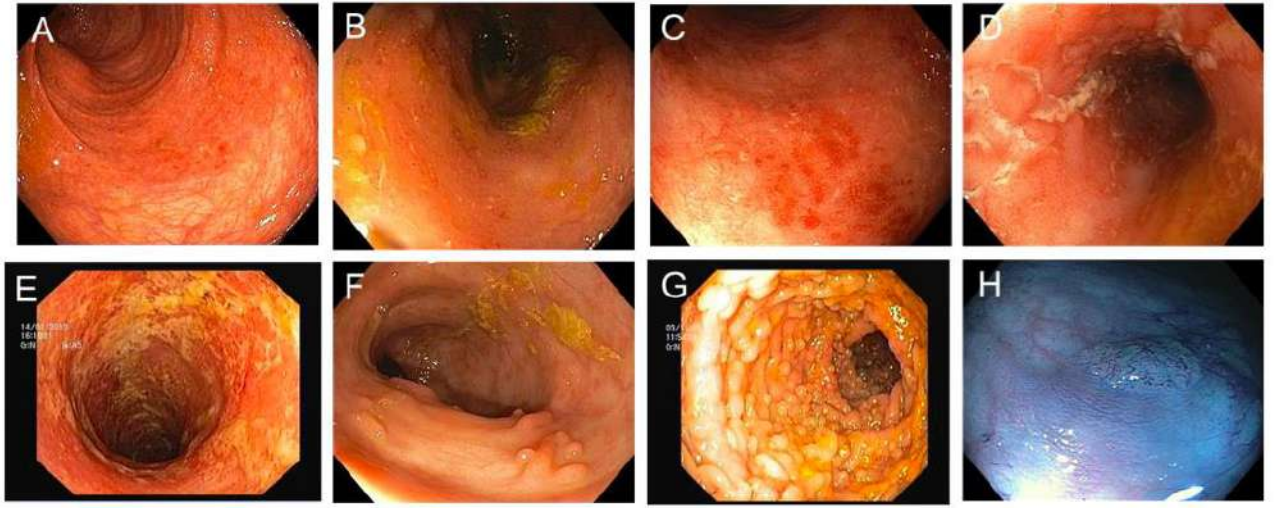
Subscore, 0 to 3

Physician's global assessment§
- 0 = Normal
- 1 = Mild disease
- 2 = Moderate disease
- 3 = Severe disease

Subscore, 0 to 3

Endoscopic subscore of 2 or 3

Endoscopy Findings	
Normal or inactive disease	0
Mild (erythema, decreased vascular pattern, mild friability)	1
Moderate (marked erythema, absent vascular pattern, friability, erosions)	2
Severe (spontaneous bleeding, ulceration)	3



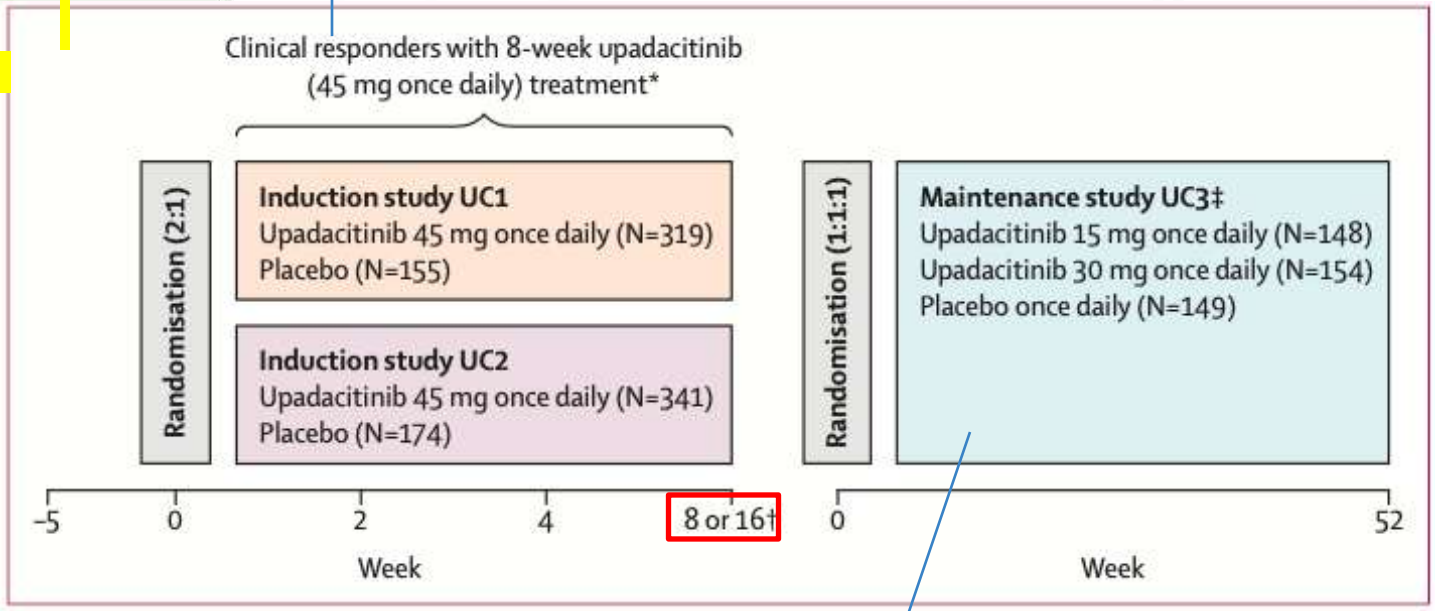
A. Mild disease with erythema and decreased vascular pattern consistent with Mayo score of 1. B. Moderate disease with loss of vascular pattern and erosions consistent with Mayo score of 2. C. Erythematous mucosa, erosions and absent vascular pattern consistent with Mayo score of 2. D. Severe disease with deep ulcerations demonstrative of Mayo score of 3. E. Severe diffuse ulcerations consistent with Mayo score of 3. F. Scattered pseudopolyps in inactive ulcerative colitis. G. Dense pseudopolyps making dysplasia surveillance difficult. H. Chromoendoscopy following application of dye spray demonstrating dysplastic lesion. *Images courtesy of Dr. Jerome Waye.*

Patients Exclusion Criteria

1. Crohn's disease or indeterminate colitis
2. Fulminant colitis and/or toxic megacolon
3. Disease limited to the rectum (ulcerative proctitis)
4. Active infection
5. Previous exposure to JAK inhibitors

Method

defined as a decrease from baseline in the Adapted Mayo score ≥2 points and ≥30% from baseline, plus a decrease in rectal bleeding score [RBS]≥1 or an absolute RBS≤ 1



Section 6. UC3 maintenance study - primary and non-primary analysis patient population

Primary Analysis Population (N=451) First 451 randomized patients who achieved clinical response per adapted Mayo score following 8-week induction treatment of upadacitinib 45 mg OD, 1:1:1 randomized to 52-week treatment of upadacitinib 15 mg, 30 mg OD, or placebo in maintenance study		
Phase 2b (U-ACHIEVE Substudy 1)	UC1	UC2
N= 21	N= 278	N= 152

Outcome Assessment

SFS: Stool Frequency Score
RBS: Rectal Bleeding Score

Induction Studies (UC1, UC2)

Primary endpoint

- ✓ Clinical remission at week 8
  (Adapted Mayo score ≤2, with SFS ≤1 and not greater than baseline, RBS=0, and endoscopic subscore ≤1 without friability)

Key secondary endpoints

- ✓ Endoscopic improvement (endoscopic score ≤1 without friability)
- ✓ Clinical response per Adapted Mayo score (a decrease in Adapted Mayo score of ≥2 points and ≥30% from baseline, and a decrease in the RBS of ≥1 point or an absolute RBS of ≤1)

Outcome Assessment

SFS: Stool Frequency Score
RBS: Rectal Bleeding Score

Maintenance Studies (UC3)

Primary endpoint

- ✓ Clinical remission at week 52
  (Adapted Mayo score ≤2, with SFS ≤1 and not greater than baseline, RBS=0, and endoscopic subscore ≤1 without friability)

Key secondary endpoints

- ✓ Endoscopic improvement (endoscopic score ≤1 without friability)
- ✓ Clinical response per Adapted Mayo score (a decrease in Adapted Mayo score of ≥2 points and ≥30% from baseline, and a decrease in the RBS of ≥1 point or an absolute RBS of ≤1)
- ✓ Corticosteroid-free clinical remission (corticosteroid- free for ≥90 days prior to week 52)

Statistical Analysis

Induction Studies (UC1, UC2)

- Enrolment of 308 patients in the upadacitinib 45 mg group and 154 in the placebo group was expected to provide more than **95% power** to detect the **13% target difference** in the primary endpoint between treatment groups using the **two-sided Fisher's exact test at a 0.05** significance level.

Statistical Analysis

Maintenance Studies (UC3)

- Enrolment of 150 patients per treatment group was expected to provide more than **95% power** to detect the anticipated **28% treatment difference** in the primary endpoint between an upadacitinib dose (15 or 30 mg) and placebo using the two-sided Fisher's exact test at a **0.025 significance** level with multiplicity adjustment.

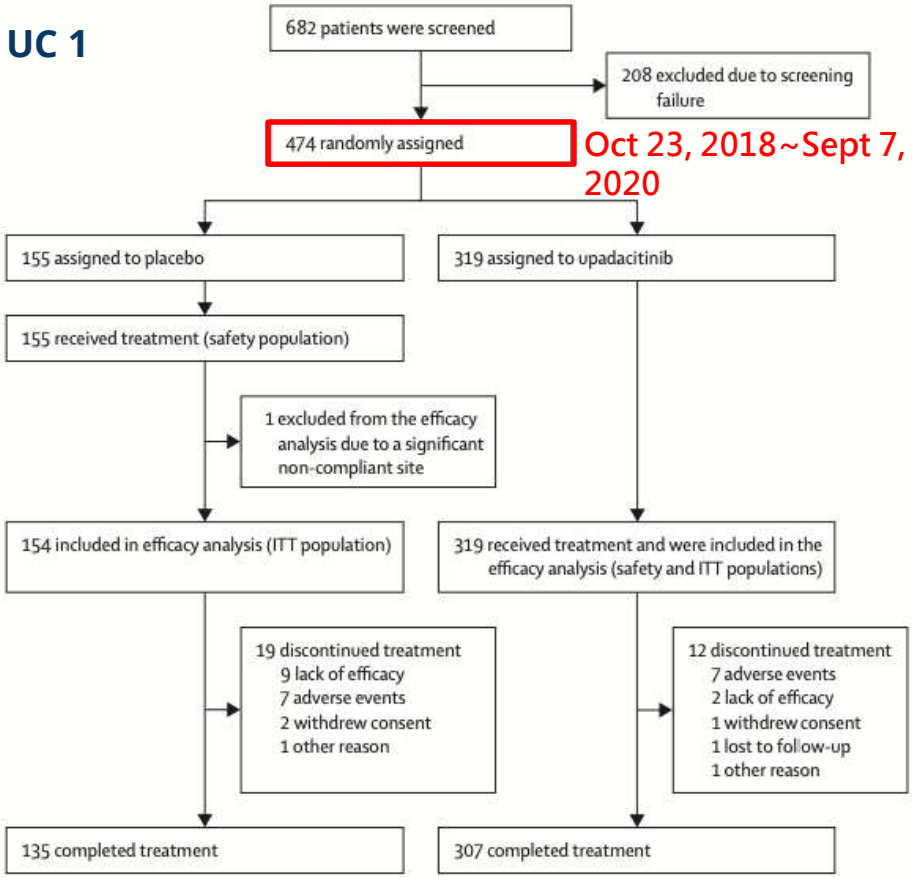
Statistical Analysis

COVID-19 pandemic

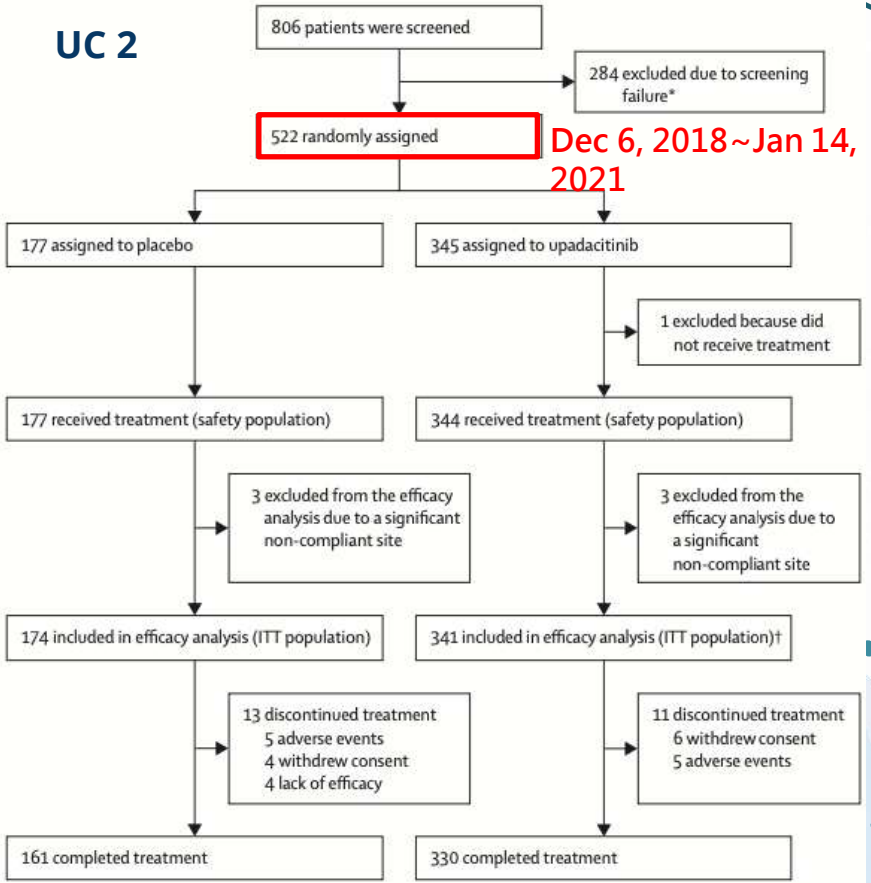
- Completion of in-person study visits and sample collection were affected, leading to missing data.
- **Non-responder imputation** incorporating **multiple imputation** to handle missing data due to COVID-19 (NRI-C) was used for the categorical endpoints which were analysed using the **Cochran–Mantel–Haenszel test** adjusted by stratification factors.

Results- Flow of Patients Induction Studies

UC 1

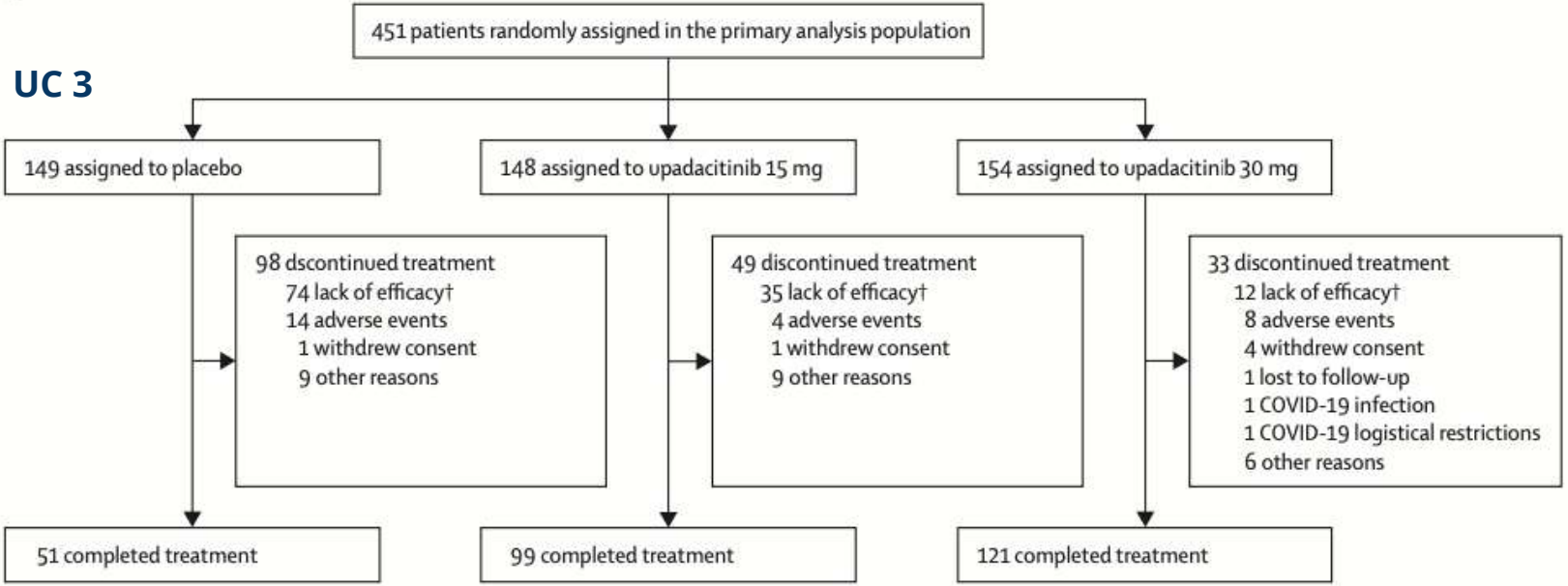


UC 2



Results- Flow of Patients Maintenance Studies

UC 3



Primary Analysis Population (N=451) First 451 randomized patients who achieved clinical response per adapted Mayo score following 8-week induction treatment of upadacitinib 45 mg OD, 1:1:1 randomized to 52-week treatment of upadacitinib 15 mg, 30 mg OD, or placebo in maintenance study		
Phase 2b (U-ACHIEVE Substudy 1)	UC1	UC2
N= 21	N= 278	N= 152

Results- Baseline characteristics

Induction Studies (UC1,UC2)

	UC1		UC2	
	Placebo (n=154)	Upadacitinib 45 mg once daily (n=319)	Placebo (n=174)	Upadacitinib 45 mg once daily (n=341)
Sex				
Female	57 (37%)	121 (38%)	67 (39%)	127 (37%)
Male	97 (63%)	198 (62%)	107 (61%)	214 (63%)
Race				
White	100 (65%)	206 (65%)	124 (71%)	234 (69%)
Black or African American	4 (3%)	12 (4%)	6 (3%)	11 (3%)
Asian	46 (30%)	95 (30%)	41 (24%)	94 (28%)
American Indian or Alaska Native	2 (1%)	0	1 (1%)	0
Native Hawaiian and other Pacific Islander	0	1 (<1%)	1 (1%)	0
Multiple	2 (1%)	5 (2%)	1 (1%)	2 (1%)
Age, years	44·5 (23·0)	43·0 (23·0)	42·0 (24·0)	40·0 (24·0)
Weight, kg	70·0 (26·5)	69·3 (24·6)	71·5 (24·3)	71·2 (21·4)
Disease duration, years	6·0 (10·0)	6·6 (9·6)	4·9 (7·4)	5·6 (7·5)
Disease extent				
Left-sided	74 (48%)	158 (50%)	88 (51%)	164 (48%)
Extensive or pancolitis	80 (52%)	161 (50%)	86 (49%)	176 (52%)
Faecal calprotectin, mg/kg	1902 (2651)	1780 (3728)	1552 (2507)	1655 (2415)
High sensitivity CRP, mg/L	4·7 (12·5)	4·1 (8·1)	4·7 (10·0)	3·8 (8·0)

	UC1		UC2	
	Placebo (n=154)	Upadacitinib 45 mg once daily (n=319)	Placebo (n=174)	Upadacitinib 45 mg once daily (n=341)
Immunosuppressant (methotrexate) use	3 (2%)	2 (1%)	3 (2%)	1 (<1%)
Aminosalicylates use	103 (67%)	220 (69%)	120 (69%)	233 (68%)
Corticosteroid use				
Yes	61 (40%)	124 (39%)	72 (41%)	120 (35)
Baseline dose,* mg	20·0 (10·0)	20·0 (12·5)	20·0 (15·0)	20·0 (15)
Previous [illegible]logical therapy failure				
Yes	78 (51%)	168 (53%)	89 (51%)	172 (50%)
No				169 (50%)
Numb				
1				64 (19%)
2				67 (20%)
3				34 (10%)
≥4	4 (3%)	11 (3%)	3 (2%)	8 (2%)
Adapted Mayo score				
≤7	94 (61%)	195 (61%)	103 (59%)	205 (60%)
>7	60 (39%)	123 (39%)	71 (41%)	135 (40%)
Mean (SD)	7·0 (1·2)	7·0 (1·2)	7·0 (1·2)	7·0 (1·2)
Endoscopic subscore				
3	104 (68%)	223 (70%)	121 (70%)	233 (68%)
Mean (SD)	2·7 (0·47)	2·7 (0·46)	2·7 (0·46)	2·7 (0·47)

Corticosteroids dose are converted to equivalent daily dosage of prednisone in mg; the maximum dose allowed was 30 mg .

Results- Baseline characteristics Maintenance Studies

	Placebo (n=149)	Upadacitinib 15 mg once daily (n=148)	Upadacitinib 30 mg once daily (n=154)
Sex			
Female	64 (43%)	53 (36%)	68 (44%)
Male	85 (57%)	95 (64%)	86 (56%)
Race			
White	93 (62%)	97 (66%)	101 (66%)
Black or African American	6 (4%)	7 (5%)	3 (2%)
Asian	42 (28%)	44 (30%)	48 (31%)
American Indian or Alaska Native	0	0	0
Native Hawaiian and other Pacific Islander	1 (1%)	0	1 (1%)
Multiple	7 (5%)	0	1 (1%)
Age, years	40·0 (21·0)	40·0 (22·0)	41·0 (7·0)
Weight, kg	70·0 (21·2)	71·5 (25·6)	68·8 (29·0)
Disease duration, years	6·2 (8·6)	6·4 (10·6)	6·0 (9·7)
Disease extent			
Left-sided	79 (53%)	66 (45%)	68 (44%)
Extensive or pancolitis	70 (47%)	82 (55%)	86 (56%)
Faecal calprotectin, mg/kg	1991 (3193)	1718 (2502)	1465 (1750)
High sensitivity CRP, mg/L	4·3 (8·0)	3·8 (10·0)	4·1 (7·1)

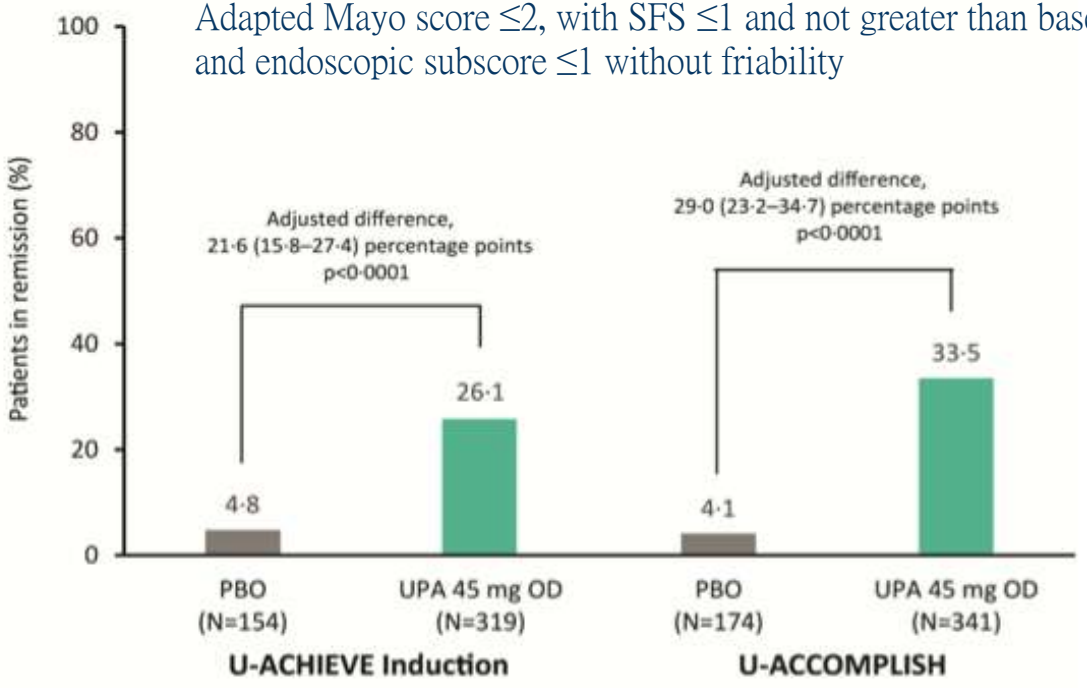
Results- Baseline characteristics Maintenance Studies

	Placebo (n=149)	Upadacitinib 15 mg once daily (n=148)	Upadacitinib 30 mg once daily (n=154)
Immunosuppressant (methotrexate) use	0	1 (<1%)	1 (<1%)
Aminosalicylates use	99 (66%)	99 (67%)	106 (69%)
Corticosteroid use			
Yes	60 (40%)	55 (37%)	57 (37%)
Baseline dose†, mg	15·0 (10·0)	15·0 (15·0)	20·0 (10·0)
Previous biological therapy failure			
Yes	81 (54%)	71 (48%)	73 (47%)
No	68 (46%)	77 (52%)	81 (53%)
Number of previous biological treatments			
1	30 (20%)	30 (20%)	34 (22%)
2	34 (23%)	32 (22%)	24 (16%)
3	16 (11%)	10 (7%)	16 (10%)
≥4	4 (3%)	1 (<1%)	3 (2%)
Adapted Mayo score			
≤7	87 (58%)	89 (60%)	88 (58%)
>7	62 (42%)	59 (40%)	64 (42%)
Mean (SD)	7·0 (1·2)	7·0 (1·2)	7·1 (1·3)
Endoscopic subscore			
3	98 (66%)	100 (66%)	108 (70%)
Mean (SD)	2·7 (0·48)	2·7 (0·47)	2·7 (0·48)

Results- Primary & Secondary Endpoints

Induction Studies (UC1, UC2)

A Clinical remission (adapted Mayo)*

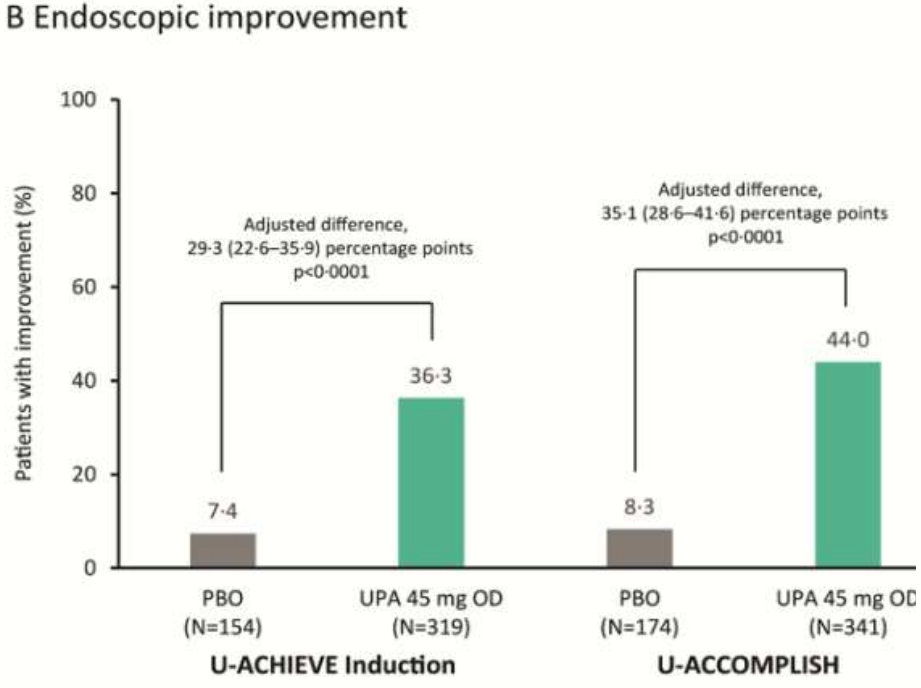


UC1 UC2

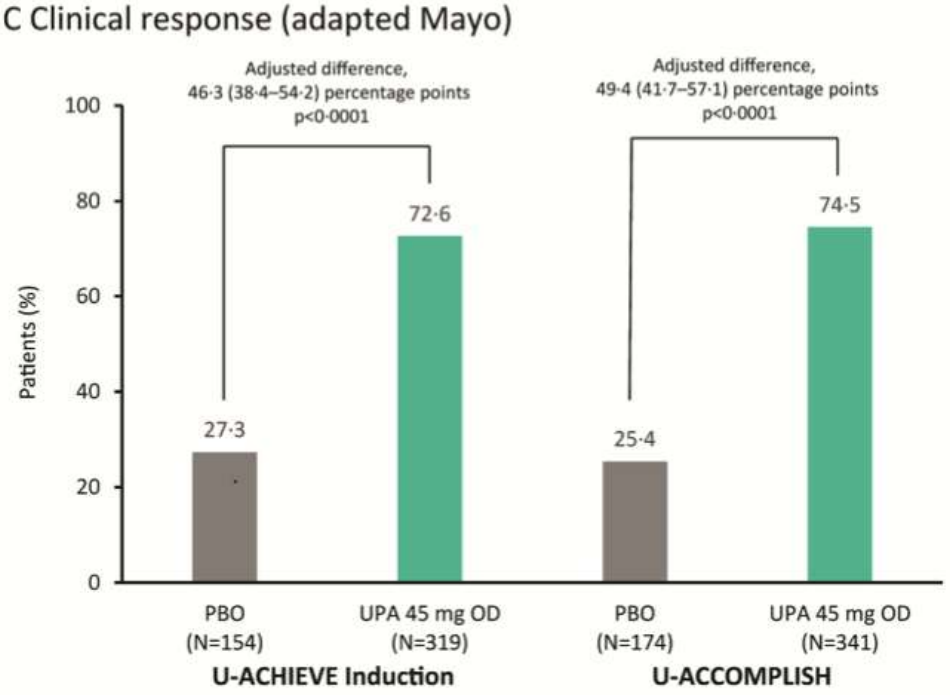
Results- Primary & Secondary Endpoints

Induction Studies (UC1, UC2)

A decrease in Adapted Mayo score of ≥2 points and ≥30% from baseline, and a decrease in the RBS of ≥1 point or an absolute RBS of ≤1



UC1 UC2

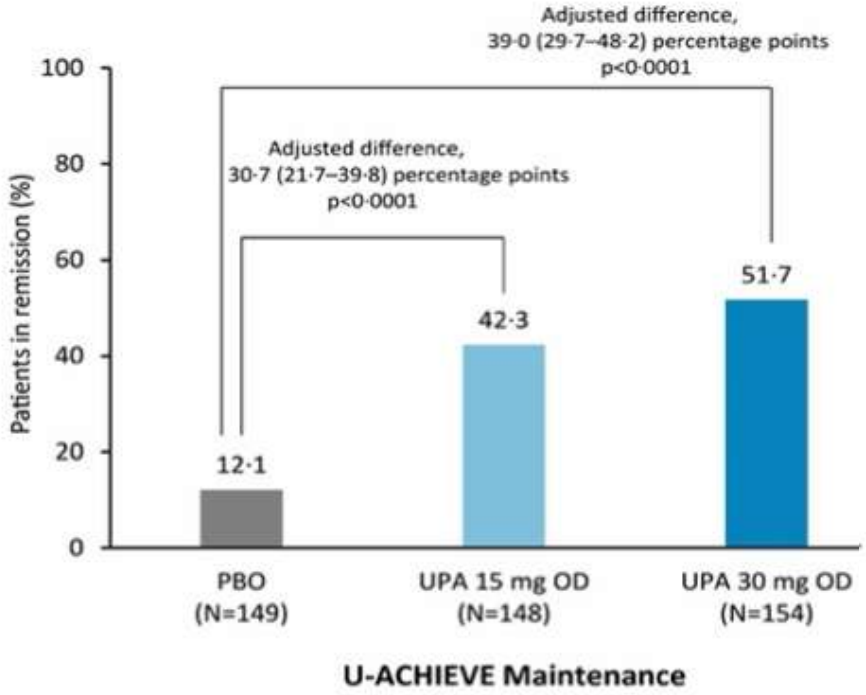


UC1 UC2

Results- Primary & Secondary Endpoints

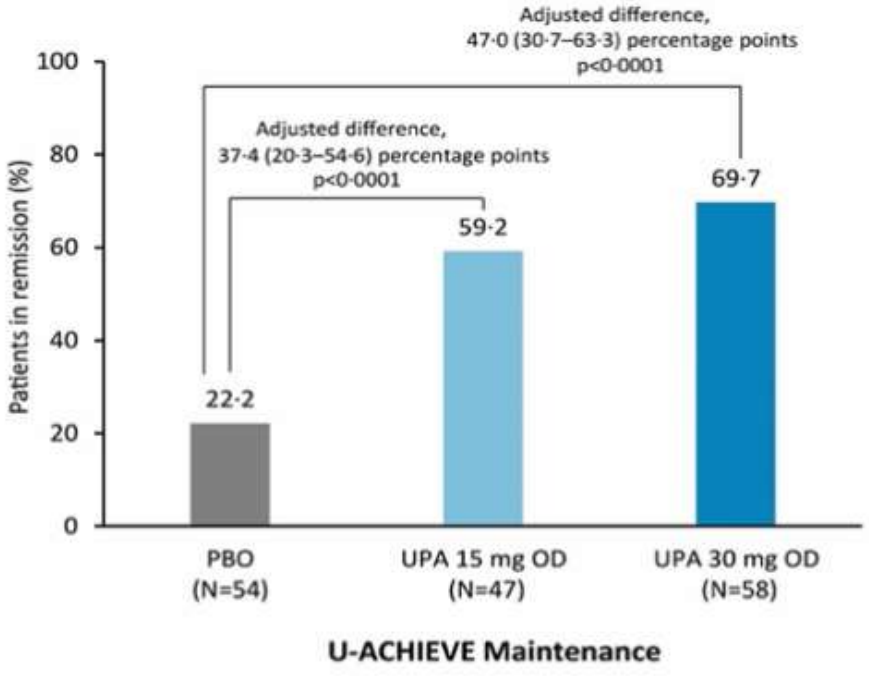
Maintenance Studies (UC3)

A Clinical remission (adapted Mayo)*



UC3

B Maintenance of clinical remission (adapted Mayo)†

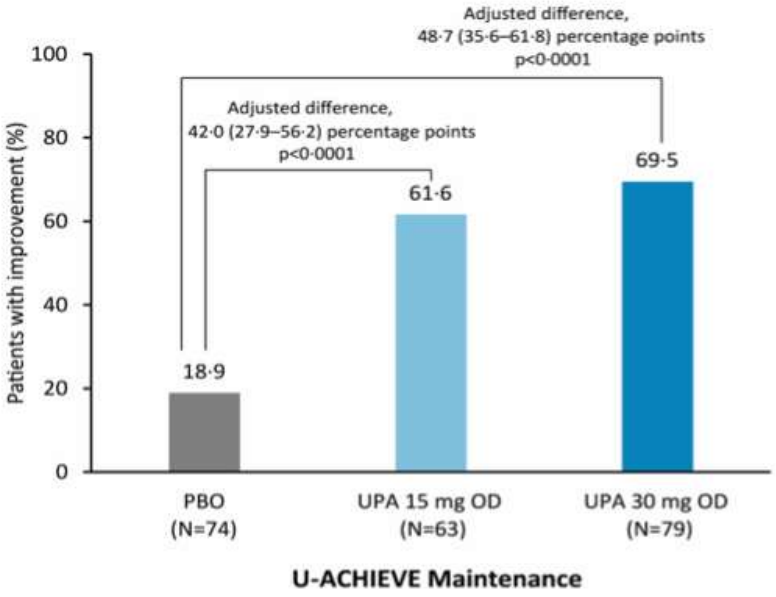


UC3

Results- Primary & Secondary Endpoints

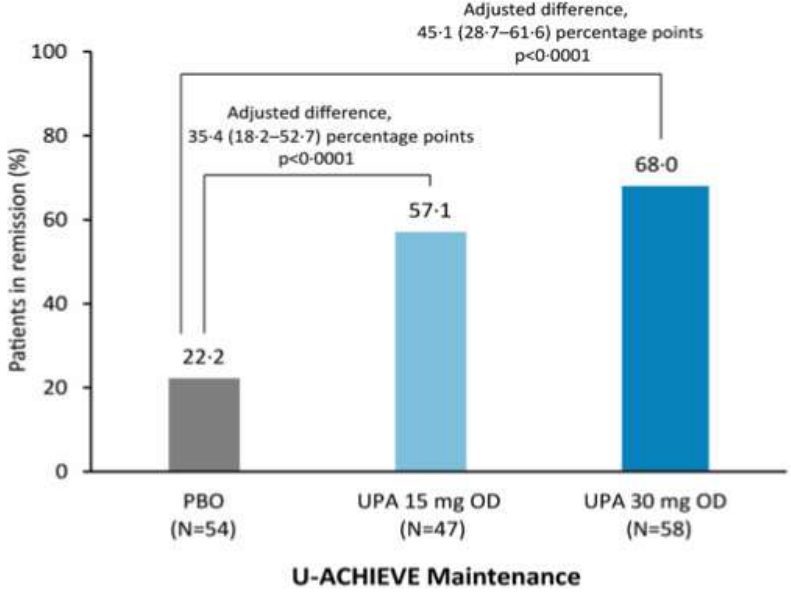
Maintenance Studies (UC3)

C Maintenance of endoscopic improvement‡



UC3

D Corticosteroid-free clinical remission (adapted Mayo)† at week 52



UC3

Results- Safety Induction Studies (UC1, UC2)

	UC1			UC2		
	Placebo (N=155)	Upadacitinib 45 mg once daily (N=319)	Treatment difference (95% CI)	Placebo (N=177)	Upadacitinib 45 mg once daily (N=344)	Treatment difference (95% CI)
Adverse events	96 (62%); 883·1	180 (56%); 898·0	-5·5 (-14·9 to 3·9)	70 (40%); 638·5	182 (53%); 738·5	13·4 (4·4 to 22·3)
Serious adverse events	9 (6%); 62·1	8 (3%); 16·3	-3·3 (-7·4 to 0·8)	8 (5%); 45·6	11 (3%); 20·9	-1·3 (-4·9 to 2·3)
Adverse events leading to discontinuation	14 (9·0) [66·6]	6 (2%); 14·3	-7·2 (-11·9 to -2·4)	9 (5%); 57·0	6 (2%); 19·0	-3·3 (-6·9 to 0·2)
Death*	0	0	0	0	0	0
Most frequent adverse events (reported by ≥5% of patients in any treatment group across studies)						
Nasopharyngitis	6 (4%)	15 (5%)	..	4 (2%)	13 (4%)	..
CPK elevation	3 (2%)	16 (5%)	..	2 (1%)	16 (5%)	..
Worsening of ulcerative colitis	21 (14%)	3 (<1%)	..	8 (5%)	6 (2%)	..
URTI	6 (4%)	8 (3%)	..	1 (1%)	7 (2%)	..
Acne	1 (1%)	15 (5%)	..	3 (2%)	24 (7%)	..
Arthralgia	7 (5%)	5 (2%)	..	3 (2%)	5 (1%)	..
Headache	4 (3%)	13 (4%)	..	9 (5%)	8 (2%)	..
Anaemia	9 (6%)	8 (3%)	..	4 (2%)	14 (4%)	..

No deaths were reported

CPK: Creatine phosphokinase

Results- Safety Induction Studies (UC1, UC2)

Black Box Warning

	UC1			UC2		
	Placebo (N=155)	Upadacitinib 45 mg once daily (N=319)	Treatment difference (95% CI)	Placebo (N=177)	Upadacitinib 45 mg once daily (N=344)	Treatment difference (95% CI)
Adverse event of special interest						
Serious infection	2 (1%); 8·9	5 (2%); 10·2	0·3 (−2·0 to 2·5)	1 (1%); 7·6	2 (1%); 3·8	0 (−1·3 to 1·4)
Opportunistic infection (excluding tuberculosis and herpes zoster)	0	1 (<1%); 2·0	0·3 (−0·3 to 0·9)	0	2 (1%); 3·8	0·6 (−0·2 to 1·4)
Herpes zoster†	0	1 (<1%); 4·1	0·3 (−0·3 to 0·9)	0	2 (1%); 3·8	0·6 (−0·2 to 1·4)
Malignancy excluding NMSC‡	0	0	0	0	0	0
NMSC	0	0	0	0	0	0
Renal dysfunction	0	0	0	0	0	0
Hepatic disorder	7 (5%); 53·2	9 (3%); 30·6	−1·7 (−5·4 to 2·0)	1 (<1%); 11·4	10 (3%); 26·6	2·3 (0·3 to 4·4)
Adjudicated gastrointestinal perforation‡	0	0	0	1 (1%); 3·8	0	−0·6 (−1·7 to 0·5)
Adjudicated MACE‡§	0	0	0	0	0	0
Adjudicated VTE¶	0	0	0	1 (1%); 3·8	0	−0·6 (−1·7 to 0·5)
Anaemia†	14 (9%); 66·6	10 (3%); 22·4	−5·9 (−10·8 to −1·0)	4 (2%); 15·2	15 (4%); 30·5	2·1 (−1·0 to 5·2)
Neutropenia†	1 (1%); 4·4	16 (5%); 34·7	4·4 (1·7 to 7·1)	0	15 (4%); 30·5	4·4 (2·2 to 6·5)
Lymphopenia†	1 (1%); 4·4	10 (3%); 24·5	2·5 (0·2 to 4·8)	1 (1%); 7·6	6 (2%); 15·2	1·2 (−0·6 to 2·9)
CPK elevation	3 (2%); 13·3	16 (5%); 36·7	3·1 (−0·2 to 6·3)	2 (1%); 7·6	16 (5%); 34·3	3·5 (0·8 to 6·2)

Results- Safety Maintenance Studies (UC3)

	Placebo (n=149)	Upadacitinib 15 mg once daily (n=148)	Treatment difference (95% CI)*	Upadacitinib 30 mg once daily (n=154)	Treatment difference (95% CI)*
Treatment-emergent adverse events					
Adverse events	113 (76%); 492·2	115 (78%); 304·2	2·4 (–7·0 to 11·8)	121 (79%); 304·9	3·1 (–6·2 to 12·3)
Serious adverse events	19 (13%); 27·5	10 (7%); 9·2	–6·1 (–13·0 to 0·7)	9 (6%); 6·7	–6·8 (–13·5 to –0·1)
Adverse events leading to discontinuation	17 (11%); 20·6	6 (4%); 5·9	–7·4 (–13·6 to –1·3)	10 (6%); 7·4	–4·8 (–11·4 to 1·8)
Death†	0	0	0	0	0
Most frequent adverse events (reported by ≥5% of patients in any treatment group across studies)					
Nasopharyngitis	15 (10%)	18 (12%)	..	22 (14%)	..
CPK elevation	3 (2%)	9 (6%)	..	13 (8%)	..
Worsening of ulcerative colitis	45 (30%)	19 (13%)	..	11 (7%)	..
URTI	6 (4%)	7 (5%)	..	9 (6%)	..
Acne	6 (4%)	4 (3%)	..	6 (4%)	..
Arthralgia	15 (10%)	9 (6%)	..	5 (3%)	..
Headache	6 (4%)	4 (3%)	..	5 (3%)	..
Anaemia	6 (4%)	7 (5%)	..	1 (<1%)	..

No deaths were reported

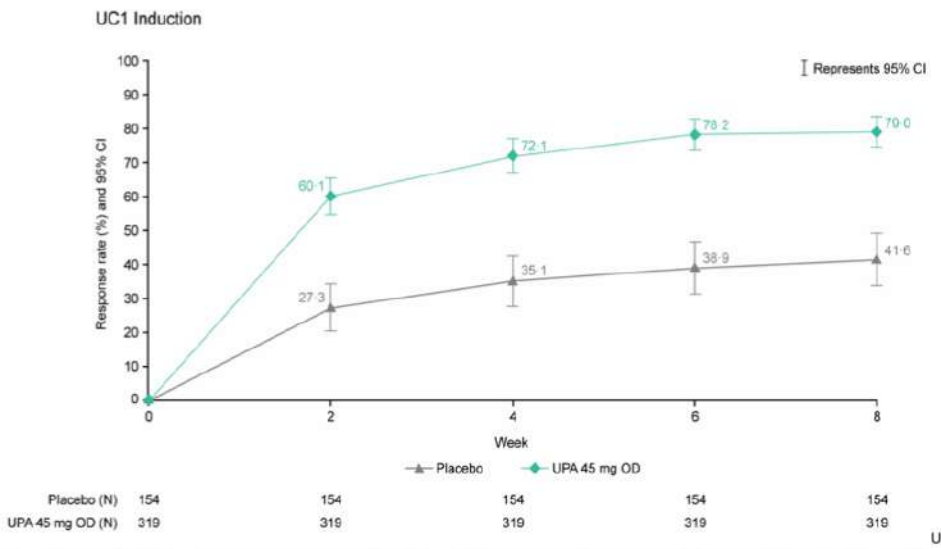
Results- Safety Maintenance Studies (UC3)

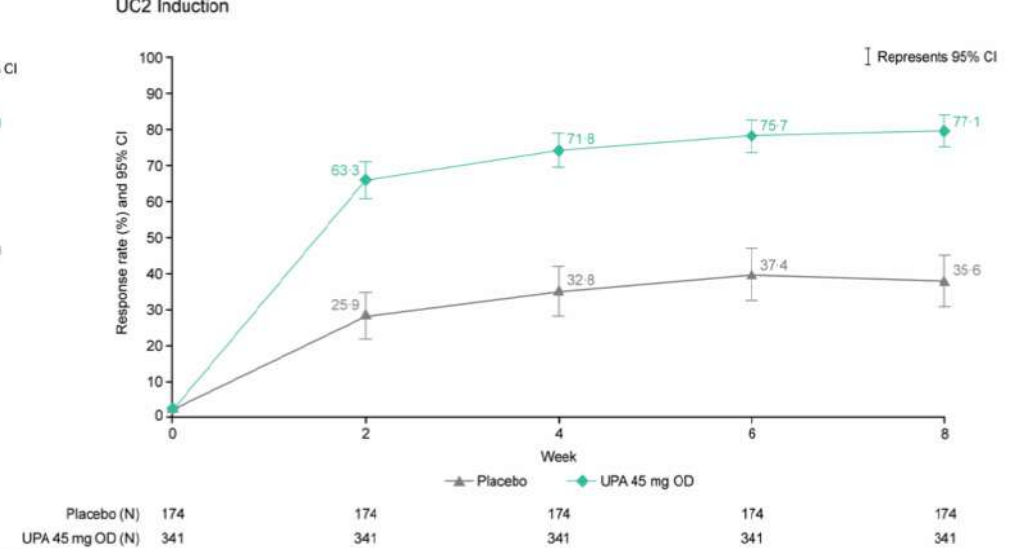
Black Box Warning

Adverse event of special interest	Placebo (n=149)	Upadacitinib 15 mg once daily (n=148)	Treatment difference (95% CI)*	Upadacitinib 30 mg once daily (n=154)	Treatment difference (95% CI)*
Serious infection	6 (4%); 6·9	5 (3%); 4·2	−0·7 (−5·3 to 3·8)	4 (3%); 3·0	−1·4 (−5·8 to 3·0)
Opportunistic infection (excluding tuberculosis and herpes zoster)	0	1 (1%); 0·8	0·6 (−1·6 to 2·9)	0	0
Herpes zoster‡	0	6 (4%); 5·0	4·2 (0·5 to 7·8)	6 (4%); 4·4	3·8 (0·3 to 7·3)
Malignancy excluding NMSC§	1 (<1%); 1·1	1 (<1%); 0·8	0 (−2·7 to 2·6)	2 (1%); 1·5	0·6 (−2·3 to 3·5)
NMSC	0	0	0	2 (1%); 1·5	1·3 (−1·2 to 3·9)
Renal dysfunction	1 (<1%); 1·1	1 (<1%); 0·8	−0·1 (−2·7 to 2·5)	1 (<1%); 0·7	0 (−2·6 to 2·5)
Hepatic disorder	3 (2%); 5·7	10 (7%); 16·8	4·8 (−0·1 to 9·7)	8 (5%); 7·4	3·2 (−1·3 to 7·8)
Adjudicated gastrointestinal perforation§	1 (1%); 2·3	0	−0·7 (−3·0 to 1·6)	0	−0·7 (−3·0 to 1·6)
Adjudicated MACE§¶	1 (1%); 1·1	0	−0·7 (−2·9 to 1·6)	0	−0·7 (−2·9 to 1·6)
Adjudicated VTE‖	0	0	0	2 (1%); 1·5	1·3 (−1·2 to 3·9)
Anaemia‡	9 (6%); 12·6	7 (5%); 5·9	−1·2 (−6·5 to 4·1)	3 (2%); 2·2	−4·1 (−8·7 to 0·5)
Neutropenia‡	2 (1%); 2·3	4 (3%); 4·2	1·4 (−2·3 to 5·0)	9 (6%); 8·9	4·5 (0·1 to 8·9)
Lymphopenia‡	2 (1%); 3·4	3 (2%); 2·5	0·7 (−2·7 to 4·1)	3 (2%); 3·0	0·7 (−2·7 to 4·0)
CPK elevation	3 (2%); 3·4	9 (6%); 7·5	3·9 (−0·8 to 8·7)	13 (8%); 11·1	6·4 (1·2 to 11·5)

NMSC: Non-melanoma skin cancer

Discussion





- **Efficacy**
  In both induction studies, upadacitinib 45 mg onset of action was rapid, with statistically significantly more patients **achieving clinical response** in this group than in the placebo at **week 2.**

- **Strength**
  Excluded the PGA from Mayo score due to its subjectiveness.
  A more stringent criterion RBS of 0, compared with previous studies which used RBS of 1 or less to define clinical remission.

Limitations

- **Short follow-up period**
  8-week induction and 52 week maintenance therapeutic regimen with limited patient exposure, which might **limit detection and interpretation of adverse events with low incidences** (eg, malignancy).

- **Lack of dose adjustment during maintenance treatment**
  Patients could not return to upadacitinib 45 mg or increase to 30 mg if the 15 mg dose was ineffective.

Appraisal

CASP RCT Checklist

Section A:

Is the basic study design valid for a randomised controlled trial?

1. Did the study address a clearly focused research question?
   ☑ Yes ☐ No ☐ Can't tell

- P: Patients aged 16–75 years with moderately to severely active ulcerative colitis
- I: Upadacitinib 45mg (induction)
  Upadacitinib 15mg, 30mg (maintenance)
- C: Placebo
- O: Efficacy and safety

2. Was the assignment of participants to interventions randomised?
   ☑ Yes ☐ No ☐ Can't tell

All patients were randomly assigned using web-based interactive response technology.

3. Were all participants who entered the study accounted for at its conclusion?
   ☑ Yes ☐ No ☐ Can't tell

The efficacy analyses in the two induction studies were based on the intent-to-treat population, which included all randomised patients who received at least one dose of treatment.

Section B:

Was the study methodologically sound?

4. Were the participants/ investigators/ people analyzing outcome ‘blind’?

   ☑ Yes ☐ No ☐ Can’t tell

Study investigators, study site personnel, and patients were **masked** to treatment allocation throughout the study (except in the open-label extension periods). The upadacitinib and placebo tablets were identical in appearance.

5. Were the study groups similar at the start of the randomised controlled trial?

   ☑ Yes ☐ No ☐ Can’t tell

Patient demographics and disease characteristics were generally **balanced** across treatment groups in both induction studies and the maintenance study.

Section B:

Was the study methodologically sound?

6. Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?

   ✓ Yes ☐ No ☐ Can't tell

- At baseline ,a **wash out period** of 8 weeks was required for patients with previous use of TNF drugs and vedolizumab, and 12 weeks for ustekinumab.
- During induction, **concomitant ulcerative colitis-related medications** (oral corticosteroids not exceeding the equivalent dose of prednisone 30 mg daily, antibiotics, aminosalicylates, or methotrexate) were **kept at a stable dose**. Concomitant use of **biologics and immunosuppressants other than methotrexate** was **prohibited**.
- During maintenance, rescue therapy could be provided to treat worsening of ulcerative at the investigator's discretion.

Section C

What are the results?

7. Were the effects of intervention reported comprehensively?
   ✓ Yes ☐ No ☐ Can't tell

8. Was the precision of the estimate of the intervention or treatment effect reported?
   ✓ Yes ☐ No ☐ Can't tell

9. Do the benefits of the experimental intervention outweigh the harms and costs?
   ☐ Yes ☐ No ✓ Can't tell

Enrolment of 308 patients in the upadacitinib 45 mg group and 154 in the placebo group was expected to provide more than **95% power** to detect the **13% target difference.** Enrolment of 150 patients per treatment group was expected to provide more than **95% power** to detect the anticipated **28% treatment difference.**

Short follow-up period
Lack of cost-effectiveness analysis
每年花費：

Adalimumab (Humira)	314,784 NTD
Golimumab (Simponi)	362,280 NTD
Upadacitinib (Rinvoq)	378,112 NTD

Section D

Can the result help locally?

10. Can the results be applied to your local population?

☑ Yes ☐ No ☐ Can't tell

	UC1		UC2	
	Placebo (n=154)	Upadacitinib 45 mg once daily (n=319)	Placebo (n=174)	Upadacitinib 45 mg once daily (n=341)
Sex				
Female	57 (37%)	121 (38%)	67 (39%)	127 (37%)
Male	97 (63%)	198 (62%)	107 (61%)	214 (63%)
Race				
White	100 (65%)	206 (65%)	124 (71%)	234 (69%)
Black or African American	4 (3%)	12 (4%)	6 (3%)	11 (3%)
Asian	46 (30%)	95 (30%)	41 (24%)	94 (28%)
American Indian or Alaska Native	2 (1%)	0	1 (1%)	0
Native Hawaiian and other Pacific Islander	0	1 (<1%)	1 (1%)	0
Multiple	2 (1%)	5 (2%)	1 (1%)	2 (1%)

	Placebo (n=149)	Upadacitinib 15 mg once daily (n=148)	Upadacitinib 30 mg once daily (n=154)
Sex			
Female	64 (43%)	53 (36%)	68 (44%)
Male	85 (57%)	95 (64%)	86 (56%)
Race			
White	93 (62%)	97 (66%)	101 (66%)
Black or African American	6 (4%)	7 (5%)	3 (2%)
Asian	42 (28%)	44 (30%)	48 (31%)
American Indian or Alaska Native	0	0	0
Native Hawaiian and other Pacific Islander	1 (1%)	0	1 (1%)
Multiple	7 (5%)	0	1 (1%)

Section 1. Number of randomised patients by country

Country	UC1 Induction (N=474)	UC2 Induction (N=522)	UC3 Maintenance (N=451)
Taiwan	3	15	10

Section D

Can the result help locally?

11. Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?

☐ Yes ☐ No ✔ Can't tell

THANK YOU