15 October 2020
EMA/584443/2020
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: Humira

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/000481/II/0198

Marketing authorisation holder (MAH) AbbVie Deutschland GmbH & Co. KG

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Table of contents

List of abbreviations

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
AAA	anti-adalimumab antibody
AE	adverse event
AESI	adverse events of special interest
AZA	azathioprine
CD	Crohn's disease
CI	confidence interval
CL/F	apparent clearance or apparent oral clearance
CSR	clinical study report
DB	double-blind
DNA	deoxyribonucleic acid
ELISA	enzyme-linked immunosorbent assay
ERA	enthesitis-related arthritis
Ew	every week
FMS	Full Mayo Score
HS	hidradenitis suppurativa
IBD	inflammatory bowel disease
ICN	ImproveCareNow
IgG1	immunoglobulin G1
I-HD	induction high dose
IMM	immunosuppressant
IPAA	ileal pouch-anal anastomosis
I-SD	induction standard dose
ITT	intent-to-treat
IV	intravenous
JIA	juvenile idiopathic arthritis
MedDRA	Medical Dictionary for Regulatory Activities
M-HD	maintenance high dose
mITT	modified intent-to-treat
MPA	Medical Products Agency
M-PL	Maintenance placebo

M-SD	maintenance standard dose
NRI	non-responder imputation
OL	open-label
OLE	open-label extension
OR	odds ratio
JIA	polyarticular juvenile idiopathic arthritis
PMS	Partial Mayo Score
Ps	psoriasis
PUCAI	Paediatric Ulcerative Colitis Activity Index
PY	patient-year
QOL	quality of life
RA	rheumatoid arthritis
RBS	rectal bleeding subscore
SAE	serious adverse event
SOC	system organ class
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF	tumour necrosis factor
UC	ulcerative colitis
WPAI	Work Productivity and Activity Impairment Questionnaire

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AbbVie Deutschland GmbH & Co. KG submitted to the European Medicines Agency on 8 April 2020 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of moderately to severely active ulcerative colitis in paediatric patients for HUMIRA; as a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC for 40mg/0.8mL, 40mg/0.4mL and 80mg/0.8mL presentations are updated. Furthermore, sections 5.1 and 5.2 of the SmPC for 20mg/0.2mL are updated. The Package Leaflet is updated in accordance. Version 15.0 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	8 April 2020
Start of procedure:	25 April 2020
CHMP Rapporteur Assessment Report	21 June 2020
PRAC Rapporteur Assessment Report	21 June 2020
PRAC members comments	1 July 2020
PRAC Outcome	9 July 2020
CHMP members comments	13 July 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 July 2020
Request for supplementary information (RSI)	23 July 2020
CHMP Rapporteur Assessment Report	15 September 2020
PRAC Rapporteur Assessment Report	15 September 2020
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	01 October 2020
CHMP members comments	05 October 2020
Updated CHMP Rapporteur Assessment Report	08 October 2020
Opinion	15 October 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Ulcerative colitis (UC) is one of the two primary forms of idiopathic inflammatory bowel disease (IBD). It is a chronic, relapsing inflammatory disease of the rectum and/or large intestine characterized by inflammation and ulceration of the mucosal and submucosal intestinal layers. The hallmark clinical symptoms include bloody diarrhoea associated with rectal urgency and tenesmus.

The clinical course of UC is marked by exacerbation and remission of symptoms and may eventually require a restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) in up to 30% of patients. The most severe intestinal manifestations of UC are toxic megacolon, perforation, and massive haemorrhage. Furthermore, UC may be accompanied by extra-intestinal manifestations such as arthritis, dermatological conditions, uveitis, and primary sclerosing cholangitis (which can progress to liver failure requiring transplantation, and is associated with an increased risk of colorectal, bile duct, and gallbladder cancers).

The general clinical and histopathological features of UC as well as the drug effects are similar in adults and children. Both patient populations share the same clinical hallmark symptoms: inflammation being limited to large intestine and rectum, the occurrence of extra-intestinal manifestations, and the clinical course which usually alternates between exacerbation and remission and may lead to colectomy. There is also substantial overlap of gene expression profiles from disease tissues in both paediatric and adult UC patients suggesting strong similarity of molecular pathways. In addition, treatment paradigms are essentially similar for both populations, and pharmacological therapies such as aminosalicylates, corticosteroids, immunosuppressants (IMMs), and the anti-tumour necrosis factor (TNF) infliximab have shown efficacy in adult and paediatric patients with UC. However, there are differences in the phenotypic presentation and progression of the disease. While the vast majority of adults with UC have limited or left-sided colitis, pancolitis is more common in children. Ulcerative colitis often presents as a more severe disease in children. Severity of disease correlates with the likelihood of colectomy; 10-year colectomy rates in adults are 15% to 25% compared to 30% to 40% in paediatric patients.

The burden of colectomy is high in paediatric UC; among children presenting with moderate or severe disease, 9% had surgery within 1 year and 26% within 5 years. The cumulative likelihood of colectomy is generally similar between adults and children (in children 6% after 1year, 29% after 20years).

Age of Onset, Incidence, and Prevalence

Ulcerative colitis onset can occur at any age, but it is rare in infants and relatively infrequent in early childhood. The overall (adult and paediatric) incidence of UC has been reported as 1.2 to 20.3 cases per 100,000 persons/year. Incidence of paediatric IBD (Crohn's disease [CD] and UC) has been increasing worldwide. Evidence suggests that the incidence of early-onset IBD, including UC, is increasing in younger age groups. Recent studies provide incidence estimates for children under 5years old in European countries, including up to 1.0 per 100,000 for females in the UK, 0.7 per 100,000 in Hungary, and 2.22 per 100,000 in Germany. Among older children, estimated incidence rates are higher. In France, the estimated incidence of UC is 0.6 per 100,000 person-years among children aged 0 to 9 years old and 4.1 per 100,000 person-years among children aged 10 to 16. Corresponding estimates in Finland are 3.1 per 100,000 person-years for children 0 to 9 years, 15.4 per 100,000 person-years for 10 to 15 years, and finally 40.4 per 100,000 person years for 15 to 19 years old. Similar increases in incidence with increases in age was also seen in Germany, Italy, the UK, and Hungary.

There are some published prevalence estimates of UC for a few European countries, although the bulk of the recently published literature reports estimated incidence rates as opposed to prevalence estimates. Unsurprisingly, prevalence increases with increasing age. The highest published prevalence estimate was from Denmark, with an estimated 83.4 cases per 100,000 people under 16 years old. The lowest prevalence estimate is from Germany, which was 23.74 cases per 100,000 children 18 years old or younger.

In a commercially insured US population of over 12.5 million people for the period 2008–2009, the prevalence of paediatric UC (<20 years of age) was estimated as 34 (95% confidence interval [CI] 32 – 36) per 100,000 persons. The prevalence of paediatric UC increased with age.

More recently, in an observational retrospective cross-sectional study conducted in 2 claims databases in the US, the pooled prevalence in 2016 per 100,000 was 21.6 for UC (95% CI, 20.3– 22.8) for paediatric patients (2 to 17 years of age). This real-world data study reported a 152% increase in prevalence for UC from 2007 to 2016 (8.6 to 21.6), which was attributed mainly to increases in the 10 to 17-year-old subgroup.

With this variation, the MAH seeks to add the following indication to the product information for Humira (adalimumab):

Humira is indicated for the treatment of moderately to severely active ulcerative colitis in paediatric patients (from 5 years of age) who have had an inadequate response to conventional therapy including corticosteroids and/or 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

The proposed dosing regimen of adalimumab for patients from 5 to 17 years of age with UC is based on body weight.

- *For patients < 40 kg, the induction dose is 80 mg at Week 0 and 40 mg at Week 2, followed by a maintenance dose of 40 mg every other week (eow) starting at Week 4.*
- *For patients ≥ 40 kg, the induction dose is 160 mg at Week 0 and 80 mg at Week 2, followed by a maintenance dose of 80 mg eow starting at Week 4. The maintenance doses of 40 mg eow and 80 mg eow are considered equivalent to 20 mg every week (ew) and 40 mg ew doses, respectively.*

Continued therapy beyond 8 weeks should be carefully considered in patients not showing signs of response within this time period. Patients who experience a disease flare after beginning maintenance therapy may benefit from a one-time re-induction dose of 80 mg (< 40 kg) or 160 mg (≥ 40 kg), followed by maintenance dosing.

Management

The pharmacological treatment of UC in childhood is largely the same as in adulthood. Conventional pharmaceutical therapies do not completely abate the inflammatory process and have significant side effects. Conventional therapies for the induction of remission include anti-inflammatory agents (5-aminosalicylic acid [5-ASA] derivatives and corticosteroids) and the immunomodulatory agent cyclosporine. 5-aminosalicylic acid derivatives as well as immunomodulatory agents (azathioprine [AZA]or 6-mercaptopurine [6-MP]) have been used for the maintenance of remission. Safety issues associated with the use of thiopurines include bone marrow suppression, malignancies including lymphoma, and serious infections including progressive multifocal leukoencephalopathy. Corticosteroids are not effective for the maintenance of remission. In addition to the induction and maintenance of clinical remission, absence of adverse effects on linear growth and maturation is demanded from therapy of paediatric UC. Similar to adults, corticosteroid dependence is frequent, but long-term corticosteroids are absolutely contraindicated because they do not maintain remission and have a negative effect on linear growth and bone mineralization.

Infliximab (a chimeric monoclonal anti-TNF-α antibody) is approved in Europe for the treatment of paediatric patients with severe UC and in the US for the treatment of paediatric patients with moderate to severe UC based on the results of an open-label (OL) study in 60 subjects. However, infliximab is an intravenous (IV) therapy, may pose a burden to paediatric patients. For adult UC, vedolizumab and tofacitinib were approved globally and in the US and European Union (EU) respectively, and ustekinumab was approved in the US and EU recently, but none have been approved for paediatric UC patients. Hence, additional treatment options that offer induction and maintenance of remission to a clinically meaningful number of patients, an acceptable safety profile, and more convenient dosing regimens than currently approved therapies are needed for paediatric UC patients.

2.1.2. About the product

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system. It consists of 1330 amino acids and has a molecular weight of approximately 148

kilodaltons. Adalimumab is composed of fully human heavy and light chain variable regions, which confer specificity to human TNF, and human IgG1 heavy chain and kappa light chain sequences. Adalimumab binds with high affinity and specificity to soluble TNF-α but not to lymphotoxin-α (TNF-β).

Tumour necrosis factor is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in pathologic inflammation. Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF. After treatment with adalimumab, levels of acute phase reactants of inflammation (C-reactive protein and erythrocyte sedimentation rate) and serum cytokines rapidly decrease.

Adalimumab was first approved for the treatment of patients with rheumatoid arthritis (RA) in the US in December 2002 and in the EU in September 2003. In addition, adalimumab is approved for the treatment of patients with early RA, polyarticular juvenile idiopathic arthritis (pJIA) (2 years of age and older), psoriatic arthritis, ankylosing spondylitis, CD (adult and paediatric), UC (adult), plaque psoriasis (Ps) (adult), hidradenitis suppurativa (HS)(adult and adolescent), and non-infectious uveitis (adult and paediatric) in the EU, US, and the rest of the world. Adalimumab is also approved for the treatment of patients with non-radiographic axial spondyloarthritis (nr-axSpA), paediatric enthesitis-related arthritis (ERA), and paediatric plaque Ps in the EU and many other countries, as well as for intestinal Behcet's disease in Japan and several other countries outside of the EU. Most recently, adalimumab has been approved for the treatment of generalized pustular Ps in Japan.

The estimated cumulative postmarketing patient exposure since the International Birth Date (31 December 2002) through 31 December 2019 is approximately 7.8 million PYs.

Adalimumab has been evaluated in 49,693 subjects in MAH-sponsored clinical trials and patient registries through 31 December 2019.

2.2. Non-clinical aspects

No new non clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

In accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human use (EMEA/CHMP/SWP/4447/00), proteins are unlikely to result in a significant risk to the environment. Hence, the CHMP agreed that no environmental risk assessment studies were needed.

2.2.2. Conclusion on the non-clinical aspects

Given that the pharmaco-toxicological profile of adalimumab has been well established, the CHMP agreed that no non-clinical data were needed to support this application.

2.3. Clinical aspects

2.3.1. Introduction

Adalimumab is a fully human antibody that binds specifically to Tumour Necrosis Factor (TNF)-α and neutralizes the biological function of TNF-α. Adalimumab also modulates biological responses that are induced or regulated by TNF-α. After treatment with adalimumab, levels of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines rapidly decrease. Adalimumab is approved for use in the treatment of several immunological diseases including but not limited to rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult and paediatric Crohn's disease, adult and paediatric uveitis, adult and adolescent hidradenitis suppurativa, plaque psoriasis and adult ulcerative colitis (UC).

In this submission, the MAH seeks to add a new indication for Humira (adalimumab) for the treatment of paediatric patients 5 to 17 years of age with moderately to severely active UC. This application is supported by data from 2 Phase 3 clinical studies:

- a randomized, controlled study (Study M11-290);
- an open-label (OL) long-term study (Study M10-870) for subjects who participated in, and successfully completed Study M11-290.

Study M11-290 is a post-marketing commitment to the United States (US) Food and Drug Administration (FDA). This submission also aims to fulfil the agreed European Union (EU) Paediatric Investigation Plan (PIP) (EMEA-000366-PIP02-09-M06, Decision P/0174/2019).

Proposed Indication and Dose

Humira is indicated for the treatment of moderately to severely active ulcerative colitis in paediatric patients (from 5 years of age) who have had an inadequate response to conventional therapy including corticosteroids and/or 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

The proposed dosing regimen of adalimumab for patients from 5 to 17 years of age with UC is based on body weight. For patients < 40 kg, the induction dose is 80 mg at Week 0 and 40 mg at Week 2, followed by a maintenance dose of 40 mg every other week (eow) starting at Week 4. For patients ≥ 40 kg, the induction dose is 160 mg at Week 0 and 80 mg at Week 2, followed by a maintenance dose of 80 mg eow starting at Week 4. The maintenance doses of 40 mg eow and 80 mg eow are considered equivalent to 20 mg every week (ew) and 40 mg ew doses, respectively. Continued therapy beyond 8 weeks should be carefully considered in patients not showing signs of response within this time period. Patients who experience a disease flare after beginning maintenance therapy may benefit from a one-time re-induction dose of 80 mg (< 40 kg) or 160 mg (≥ 40 kg), followed by maintenance dosing.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study number	Title	Country	Study completion date
M11-290	A Multicenter, Randomized, Double-Blind Study of the Human Anti-TNF Monoclonal Antibody Adalimumab in Pediatric Subjects with Moderate to Severe Ulcerative Colitis	Austria, Belgium, Canada, Spain, United Kingdom, Israel, Poland, Slovakia, United States	Last Subject Last Visit: 28 August 2019
M10-870	A Multi-Center, Open-Label Study of the Human Anti-TNF Monoclonal Antibody Adalimumab to Evaluate Long-Term Safety and tolerability of Repeated Administration of Adalimumab in Pediatric Subjects with Ulcerative Colitis Who Completed the Study M11-290	Poland, Slovakia, United Kingdom, United States	Data cut-off date: 28 August 2019 Study Status: Ongoing

2.3.2. Pharmacokinetics

The pharmacokinetic (PK) and immunogenicity of adalimumab were evaluated in paediatric subjects with moderate to severe UC in a Phase 3 study (Study M11-290).

Population PK of adalimumab was also assessed in paediatric UC subjects using a non-linear mixed effects modelling approach.

The PK and immunogenicity of adalimumab are well characterized in paediatric subjects in the approved indications of juvenile idiopathic arthritis (JIA; specifically, the categories of polyarticular JIA [pJIA] and enthesitis-related arthritis [ERA]), paediatric psoriasis (Ps), and paediatric Crohn's disease (CD)).

Methods

Bioanalytical methods

Bioanalytical methods for adalimumab and anti-adalimumab antibody (AAA) were provided with previous submissions. No additional biopharmaceutic or analytical studies are included in this application.

Descriptive pharmacokinetic analysis for study M11-290

Analysis of adalimumab

Serum adalimumab concentrations were summarized at each time point using descriptive statistics. For induction period, serum adalimumab concentrations were analyzed by induction dose group, prior anti-TNF use, Baseline HACA status, and PMS remission status at Week 8. For maintenance period, summaries of serum adalimumab concentrations were compared by maintenance dose group and remission status at Week 52 per Full Mayo Score (FMS) in those subjects who were responders per PMS at Week 8. Data listings were generated for individual subjects. For the calculation of summary statistics and plots, concentration values below lower limit of quantitation (LLOQ) were set to zero.

Analysis of immunogenicity

The number and percentage of subjects who developed AAA were determined. The impact of AAA status on serum adalimumab concentrations, efficacy (both coprimary efficacy points) and safety were assessed.

Population pharmacokinetic analysis

A cross-indication popPK analysis was performed. The analysis is described under the section Pharmacokinetics in target population.

Pharmacokinetics in target population - study M11-290

A total of 100 paediatric UC subjects (93 in main study and 7 in Japan sub-study) were included in the PK summary and population PK modelling, as well as exposure-response/simulation analyses. The mean age was 14 years and the mean body weight was 55 kg. Blood samples were obtained for the measurement of adalimumab concentrations at Baseline, Weeks 2, 4, 16, 26 and at 52/ET and for the measurement of AAA at Baseline, Weeks 16, 26 and 52/ET.

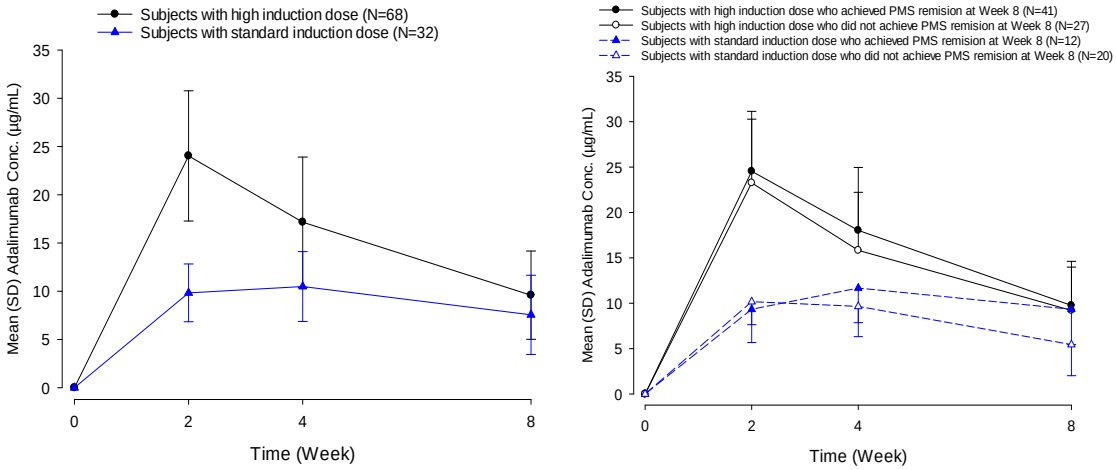
Summary of adalimumab concentrations versus time for the first 8 weeks by induction dose group and infliximab/HACA status were compared. The mean adalimumab concentrations appeared similar in anti-TNF-naïve and anti-TNF-experienced subjects in both induction dose groups. Adalimumab concentrations appeared to be lower in HACA+ subjects (N = 3) than in HACA– subjects for the high induction dose group. However, adalimumab concentrations in HACA+ subject (N = 1) were similar to the mean adalimumab concentrations in HACA– subjects for the standard induction dose group.

A summary of adalimumab concentrations by induction dose and maintenance dose are presented in Table 1. Results show that the mean adalimumab concentration were 24.0 µg/mL and 17.2 µg/mL in subjects receiving high induction dose at Weeks 2 and 4 compared to 9.83 µg/mL and 10.5 µg/mL in subjects receiving standard induction dose. Mean adalimumab concentrations appeared to be slightly higher in subjects who achieved PMS remission at Week 8 than those who did not in both treatment groups (Figure 1).

Table 1 Summary of Serum Adalimumab Concentrations **(µg/mL)** Stratified by Induction and Maintenance Doses

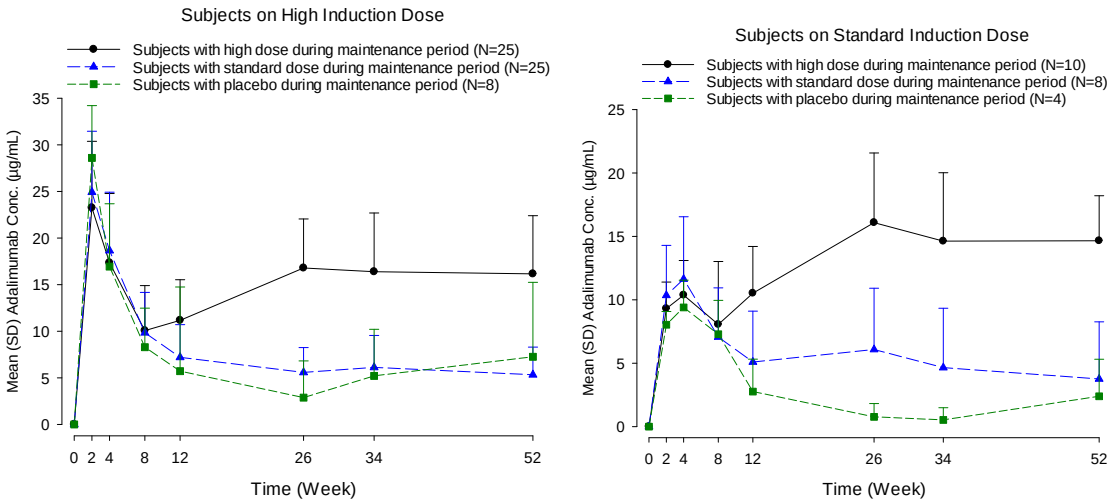
Maintenance Period Treatment	Mean ± SD (Range), N							
	Week							
	0	2	4	8	12	26	34	52
Subjects on High Induction Dose during Induction Period								
High Maintenance Dose (N = 25)	0 ± 0 (0 – 0), 25	23.3 ± 7.14 (4.47 – 34.0), 25	17.4 ± 7.42 (3.34 – 28.5), 25	10.1 ± 4.84 (1.02 – 19.2), 25	11.2 ± 4.37 (3.22 – 20.4), 25	16.8 ± 5.25 (8.32 – 27.3), 24	16.4 ± 6.30 (5.15 – 28.4), 24	16.2 ± 6.24 (5.98 – 27.6), 23
Standard Maintenance Dose (N = 25)	0 ± 0 (0 – 0), 25	24.9 ± 6.55 (14.1 – 36.1), 25	18.7 ± 6.27 (4.03 – 30.3), 25	9.84 ± 4.33 (3.11 – 19.1), 25	7.19 ± 3.51 (2.46 – 13.9), 25	5.58 ± 2.66 (0.063 – 10.5), 22	6.12 ± 3.43 (0 – 13.2), 22	5.33 ± 2.97 (0 – 11.9), 20
Placebo (N = 8)	0 ± 0 (0 – 0), 8	28.6 ± 5.62 (20.8 – 37.7), 8	16.9 ± 6.74 (4.34 – 27.3), 8	8.29 ± 4.18 (2.74 – 13.3), 8	5.72 ± 9.03 (0 – 27.5), 8	2.88 ± 3.94 (0 – 10.5), 7	5.20 ± 5.00 (0 – 10.7), 7	7.25 ± 8.00 (0 – 21.2), 7
Subjects on Standard Induction Dose during Induction Period								
High Maintenance Dose (N = 10)	0 ± 0 (0 – 0), 9	9.30 ± 2.10 (5.19 – 11.9), 9	10.4 ± 2.72 (6.37 – 15.4), 9	8.06 ± 4.97 (2.25 – 18.9), 10	10.5 ± 3.69 (5.64 – 17.1), 10	16.1 ± 5.50 (8.18 – 25.8), 9	14.6 ± 5.39 (2.60 – 19.7), 9	14.7 ± 3.55 (8.85 – 20.4), 9
Standard Maintenance Dose (N = 8)	0 ± 0 (0 – 0), 8	10.4 ± 3.94 (3.21 – 17.6), 8	11.6 ± 4.92 (6.44 – 19.6), 8	7.06 ± 3.89 (1.73 – 12.3), 8	5.09 ± 4.02 (0.195 – 11.3), 8	6.07 ± 4.85 (0 – 12.9), 5	4.65 ± 4.69 (0 – 11.5), 5	3.75 ± 4.51 (0 – 11.0), 5
Placebo (N = 4)	0 ± 0 (0 – 0), 4	8.03 ± 1.04 (7.11 – 9.40), 4	9.40 ± 2.16 (6.96 – 11.5), 4	7.29 ± 2.67 (3.75 – 10.1), 4	2.76 ± 2.56 (0.114 – 5.23), 3	0.765 ± 1.05 (0 – 2.30), 4	0.524 ± 0.966 (0 – 1.97), 4	2.39 ± 2.92 (0 – 5.96), 4

Figure 1 Mean (SD) Adalimumab Concentrations vs Time by Induction Dose (Left Panel) and PMS Remission Status at Week 8 (Right Panel) During Induction Period



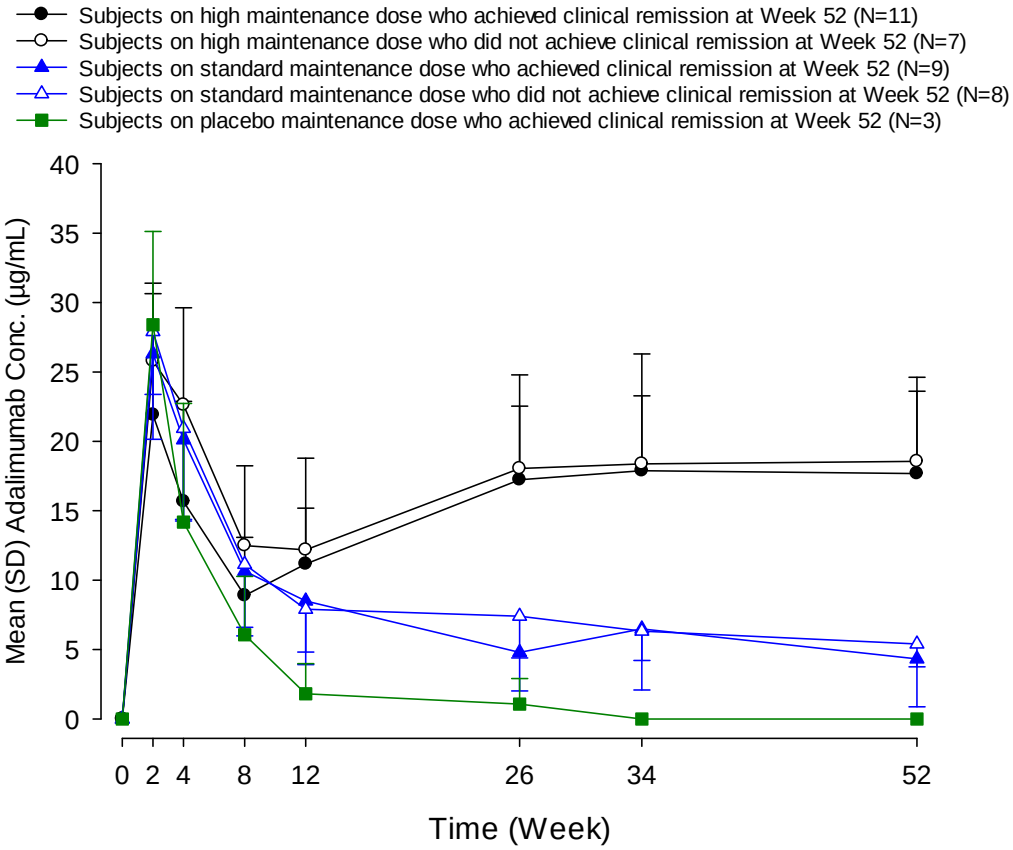
At Week 8, subjects who demonstrated a clinical response per PMS were allowed to continue in the maintenance period of the study. Starting from Week 26, the mean adalimumab steady state concentrations reached approximately 15 – 17 µg/mL and 4 – 6 µg/mL for high maintenance dose and standard maintenance dose, respectively (Figure 2). For subjects who were randomized to placebo treatment in maintenance period, their measurable adalimumab levels were due to receipt of adalimumab due to disease flare.

Figure 2 Comparison of Serum Adalimumab Concentrations vs Time by Induction and Maintenance Doses for Subjects who Continued in Maintenance Period



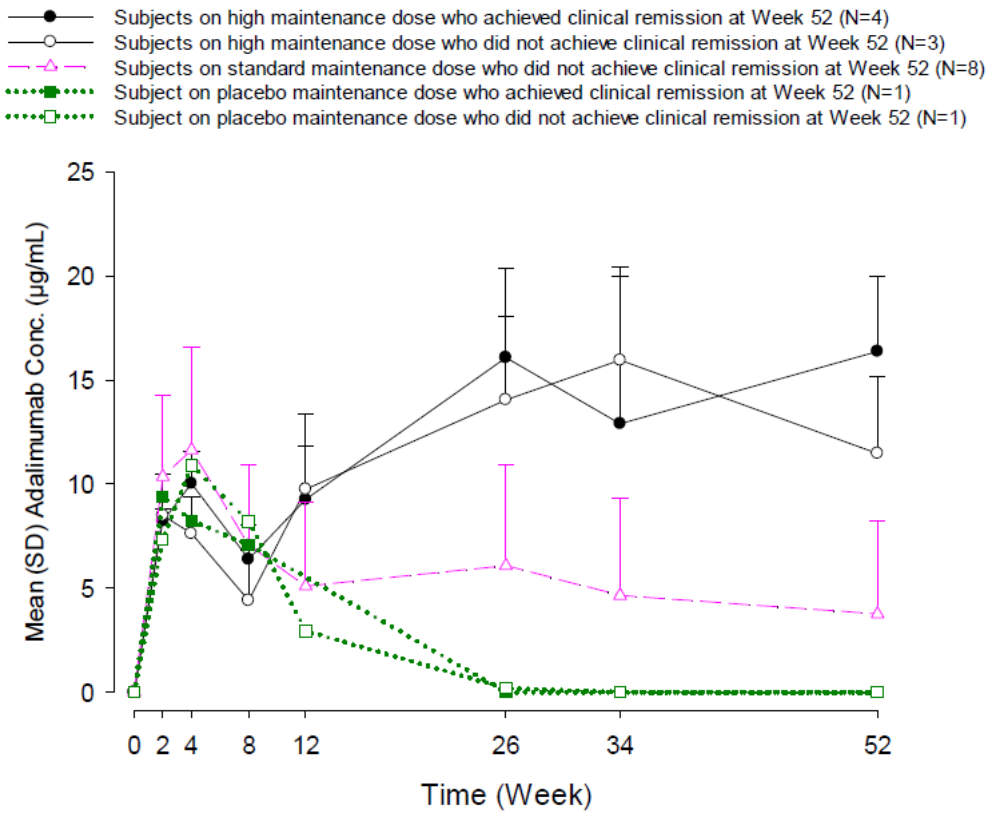
For subjects receiving either high dose or standard dose in maintenance period without disease flare, mean adalimumab concentrations were comparable regardless of their clinical remission status at Week 52 per full Mayo Score. For subjects who were on placebo during maintenance period without disease flares, all 3 of them achieved clinical remission at Week 52 per full Mayo score (Figure 3).

Figure 3 Comparison of Serum Adalimumab Concentrations vs Time by Maintenance Doses and Week 52 Remission Status for Subjects on High Induction Dose Who Continued in Maintenance Period



For subjects on high dose in maintenance period without disease flare, the mean adalimumab concentrations were similar with large variability among subjects by Week 52 remission status per full Mayo score. For subjects on standard dose (N = 8) in maintenance period without disease flare, none of them achieved Week 52 clinical remission per full Mayo score. For subjects (N = 2) who were on placebo in maintenance period without disease flares, one subject achieved Week 52 remission per full Mayo score and the other did not. Both had similar adalimumab concentrations (Figure 4).

Figure 4 Comparison of Serum Adalimumab Concentrations vs Time by Maintenance Doses and Week 52 Remission Status for Subjects on Standard Induction Dose Continued in Maintenance Period



Population pharmacokinetic analysis

Data inclusion

The population PK model development included paediatric Study M11-290 (UC), Study M06-806 (Crohn's disease [CD]), Study M04-717 (Psoriasis [Ps]), Study DE038 (polyarticular juvenile idiopathic arthritis [pJIA]), Study M11-328 (Enthesis-Related Arthritis [ERA]) and Study M10-444 (pJIA).

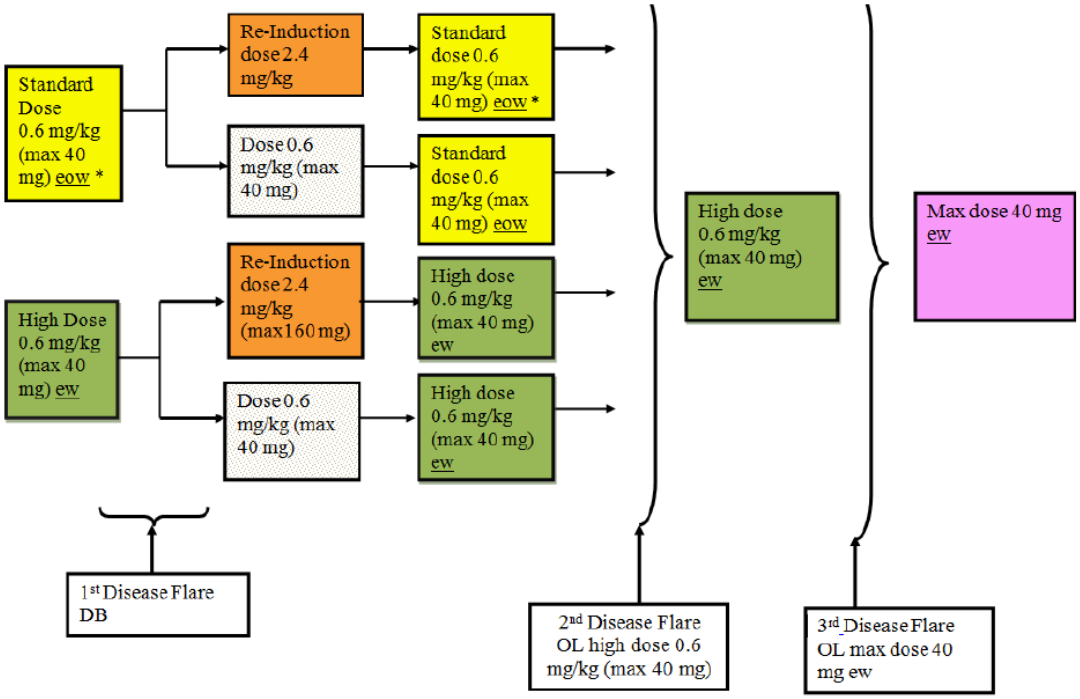
Study M11-290

All subjects who received at least one dose of adalimumab treatment and who had at least one adalimumab concentration measurement between first and last adalimumab dose plus 30 days were included in the analyses. Doses and concentrations were included up to a maximum of 52 weeks, starting with the first adalimumab dose. Only doses that reported in the database with available dates were used. Adalimumab doses given later than one day after the last concentration measurement were excluded from the model. Concentrations measured before the first active dose or after the last active dose + 30 days were excluded. Concentrations that did not have a blood collection date were excluded. For concentrations with available collection date but missing collection time, the measurements were included, and the time was set to 12:00 AM. Actual dosing times were used in the analyses where available. When data times were not available, a dosing time of 8:00 AM was assumed.

All concentrations below limit of quantitation (BLQ) in the PK dataset were set to LLOQ/2.

Demographics and Dosing Information

Figure 5 Study Design Schematic for Dose Escalation After Amendment 4 (Study M11-290)



* Subjects received the matching placebo at the alternate week.

There were 101 paediatric subjects (93 in main study and 8 in Japan sub-study) with UC enrolled in Study M11-290. One subject in the Japan sub-study did not have any adalimumab, AAA, infliximab and HACA results. Therefore, the subject was excluded in the PK and immunogenicity summary calculations and analyses. A summary of all subjects' disposition information on dosing assignments in induction and maintenance period, as well as disease flare status, is listed in Table 2.

The dose levels in the study are summarised below, the study design of M11-290 is further described in the clinical efficacy section. All doses were administered as subcutaneous injections.

- Induction phase: 2.4 mg/kg (max 160 mg) week 1 and 2, high dose 1.2 mg/kg (max 80 mg) or no dose for standard dose week 3, and 0.6 mg/kg (max 40 mg) week 4.
- Maintenance phase: standard dose 0.6 mg/kg [max 40 mg] eow, high dose 0.6 mg/kg [max 40 mg] ew.

Subjects with a disease flare were allowed to receive a re-induction dose. A subject was allowed to receive treatment for disease flare 3 times before being withdrawn from the study.

The summary demographic data for all subjects in study M11-290 are shown in Table 3.

Table 2 Summary of Subjects' Disposition Information by Treatment (Study M11-290)

Induction	**N**	**Week 8 PMS Responder (N)**	**Maintenance**	**N**
High Dose (Including DB and OL)	68	58	High Dose	25
			Standard Dose	25
			Placebo	8
Standard Dose	32	22	High Dose	10
			Standard Dose	8
			Placebo	4

Table 3 Baseline Demographics (Study M11-290)

		Mean ± SD (min - max)		
		All Subjects (N = 100)	**Main Study (N = 93)**	**Japan Sub-Study (N = 7)**
Age (yr)		14.1 ± 2.91 (5 - 17)	14.1 ± 2.99 (5 - 17)	14.3 ± 1.50 (12 - 16)
Weight (kg)		55.4 ± 17.6 (15 - 110)	55.9 ± 18.1 (15 - 110)	48.0 ± 5.07 (39 - 54)
Height (cm)		162 ± 16.7 (105 - 193)	163 ± 17.1 (105 - 193)	158 ± 8.99 (142 - 172)
		N (%)		
Sex	Male	49 (49%)	42 (45%)	7 (100%)
	Female	51 (51%)	51 (55%)	0 (0%)
Race	White	88 (88%)	88 (95%)	0 (00%)
	Asian	8 (8%)	1 (1%)	7 (100%)
	Other	4 (4%)	4 (4%)	0 (0%)

Other = black or multi-race

A total of 630 subjects were included in the population pharmacokinetic analyses of Studies M11-290, M06-806, M04-717, DE038, M11-328, and M10-444. Summaries of demographic factors and AAA *distribution for subjects included in the population pharmacokinetic analysis are presented in Table 4.*

Table 4 Demographics and of Subjects Included in Population Pharmacokinetic Analyses

Characteristics		**DE038 (N = 171)**	**M04-717 (N = 110)**	**M06-806 (N = 191)**	**M10-444 (N = 12)**	**M11-328 (N = 46)**	**M11-290 (N = 100)**	**All Subjects (N = 630)**
Age (years)	N	171	110	191	12	46	100	630
	Mean (SD)	11.27 (3.53)	12.98 (3.77)	13.61 (2.49)	2.50 (0.67)	12.91 (2.92)	14.07 (2.91)	12.67 (3.57)
	Median	11.00	14.00	14.00	2.00	13.00	15.00	13.00
	Min, Max	4.00, 17.00	5.00, 18.00	6.00, 17.00	2.00, 4.00	6.00, 18.00	5.00, 17.00	2.00, 18.00
Body Weight (kg)	N	171	110	191	12	46	100	630
	Mean (SD)	42.15 (18.79)	51.39 (20.48)	45.24 (15.33)	13.07 (1.49)	49.39 (16.40)	55.38 (17.65)	46.78 (18.75)
	Median	40.00	51.50	43.00	13.00	44.00	53.60	46.00
	Min, Max	13.00, 99.00	15.00, 108.00	19.00, 120.00	11.00, 16.00	21.00, 90.00	15.00, 110.00	11.00, 120.00
Sex	Male	36 (21.05%)	48 (43.64%)	107 (56.02%)	1 (8.33%)	31 (67.39%)	49 (49.00%)	272 (43.17%)
	Female	135 (78.95%)	62 (56.36%)	84 (43.98%)	11 (91.67%)	15 (32.61%)	51 (51.00%)	358 (56.83%)
Race	White	157 (91.81%)	99 (90.00%)	169 (88.48%)	11 (91.67%)	35 (76.09%)	88 (88.00%)	559 (88.73%)
	Black	3 (1.75%)		11 (5.76%)	1 (8.33%)	1 (2.17%)	3 (3.00%)	19 (3.02%)
	Asian	2 (1.17%)	5 (4.55%)	3 (1.57%)		1 (2.17%)	8 (8.00%)	19 (3.02%)
	Other/Unknown	9 (5.26%)	6 (5.45%)	8 (4.19%)		9 (19.57%)	1 (1.00%)	33 (5.24%)
Disease Indication	RA	171 (100.00%)	--	--	12 (100.00%)	46 (100.00%)	--	229 (36.35%)
	Ps	--	110 (100.00%)	--	--	--	--	110 (17.46%)
	CD	--	--	191 (100.00%)	--	--	--	191 (30.32%)
	UC	--	--		--	--	100 (100.00%)	100 (15.87%)
AAA	No	133 (77.78%)	85 (77.27%)	185 (96.86%)	12 (100.00%)	41 (89.13%)	97 (97.00%)	553 (87.78%)
	Yes	38 (22.22%)	25 (22.73%)	6 (3.14%)		5 (10.87%)	3 (3.00%)	77 (12.22%)

Model development

The starting PK model was a one-compartment model. The model complexity was increased until no improvement of the model fit could be achieved anymore or until the models could not be estimated. In the next model, building step covariates were tested to improve the model using the forward inclusion backward elimination procedure. The likelihood ratio test was used for hypothesis testing to discriminate among alternative models. Graphical methods were employed to assess model goodness of fit.

From the previously developed cross-indication paediatric PK model for adalimumab (as described in procedure EMEA/H/C/0481/II/0134) and several adult and paediatric studies of adalimumab, it was known that both AAA and concomitant MTX medication impact the exposure of adalimumab. Therefore,

both AAA and MTX were tested on apparent clearance (CL/F) of adalimumab and subsequently included as covariates if significant before other covariates were tested. The following additional covariates were tested on:

- CL/F: Baseline body weight, baseline body surface area, baseline age, baseline albumin, baseline high sensitivity C-reactive protein (hsCRP), baseline AST, baseline ALT, indication, race;
- Apparent volume of distribution (V2/F) and first-order absorption rate constant (Ka): baseline body weight, baseline body surface area, baseline age, indication, race.

In the final paediatric PK model, adalimumab pharmacokinetics were characterized using a one-compartment model with linear absorption. Overall, adalimumab apparent oral clearance (CL/F) in paediatric subjects with UC was comparable to that in other paediatric populations after accounting for identified covariates. Inter-subject-variability (ISV) in adalimumab CL/F and apparent volume of distribution of central compartment (V2/F) were estimated to be 47% and 19%, respectively (Table 5). Shrinkage in the distribution of individual ISV were 5.5% and 39% for CL/F and V2/F, respectively. Significant model covariates were AAA development, MTX coadministration, baseline albumin serum concentration, and baseline body surface area on CL/F as well as baseline body surface area, UC indication, and CD indication on V2/F. The estimated PK parameter values are shown in Table 5 and were in good agreement with the medians of the parameter values estimated in a bootstrap analysis (not shown).

Table 5 Parameter Estimates of the Final Pharmacokinetic Model

PK Parameter	**Population Estimate (SEE)**	**% RSE**	**95% Confidence Interval**
CL/F (L/day)	0.253 (0.006)	2.37	0.241 – 0.265
V_2/F (L)	4.99 (0.136)	2.73	4.72 – 5.25
KA (1/day)	0.673 (0.046)	6.76	0.584 – 0.763
AAA on CL/F (Starting Week 3)	7.24 (0.354)	4.89	6.55 – 7.94
MTX on CL/F	0.834 (0.038)	4.57	0.759 – 0.908
Albumin on CL/F	–1.14 (0.144)	12.6	–1.42 – –0.860
BSA on CL/F	1.33 (0.072)	5.40	1.19 – 1.47
BSA on V_2/F	1.63 (0.069)	4.23	1.49 – 1.77
UC relative to RA, PS on V_2/F	1.46 (0.084)	5.79	1.29 – 1.62
CD relative to RA, PS on V_2/F	1.20 (0.056)	4.69	1.09 – 1.31
Parameter (ISV)	**Population Estimate (% CV)**	**% RSE**	**95% Confidence Interval**
ISV on CL/F	0.202 (47.4)	7.04	0.174 – 0.230
ISV on V_2/F	0.035 (18.8)	25.1	0.018 – 0.052
Parameter (RUV)	**Population Estimate (SEE)**	**% RSE**	**95% Confidence Interval**
Proportional Error	0.200 (0.006)	3.20	0.187 – 0.212
Additive Error (µg/mL)	1.34E-04 (1.92E-05)	14.4	9.60E-05 – 1.71E-04

BSA = body surface area; ISV = inter-subject variability; CD = Crohn's disease; RSE = relative standard error of estimate; RUV = residual unexplained variability; SEE = standard error of estimate; UC = ulcerative colitis

Figure 6 Goodness-Of-Fit Plots of Final Pharmacokinetic Model.

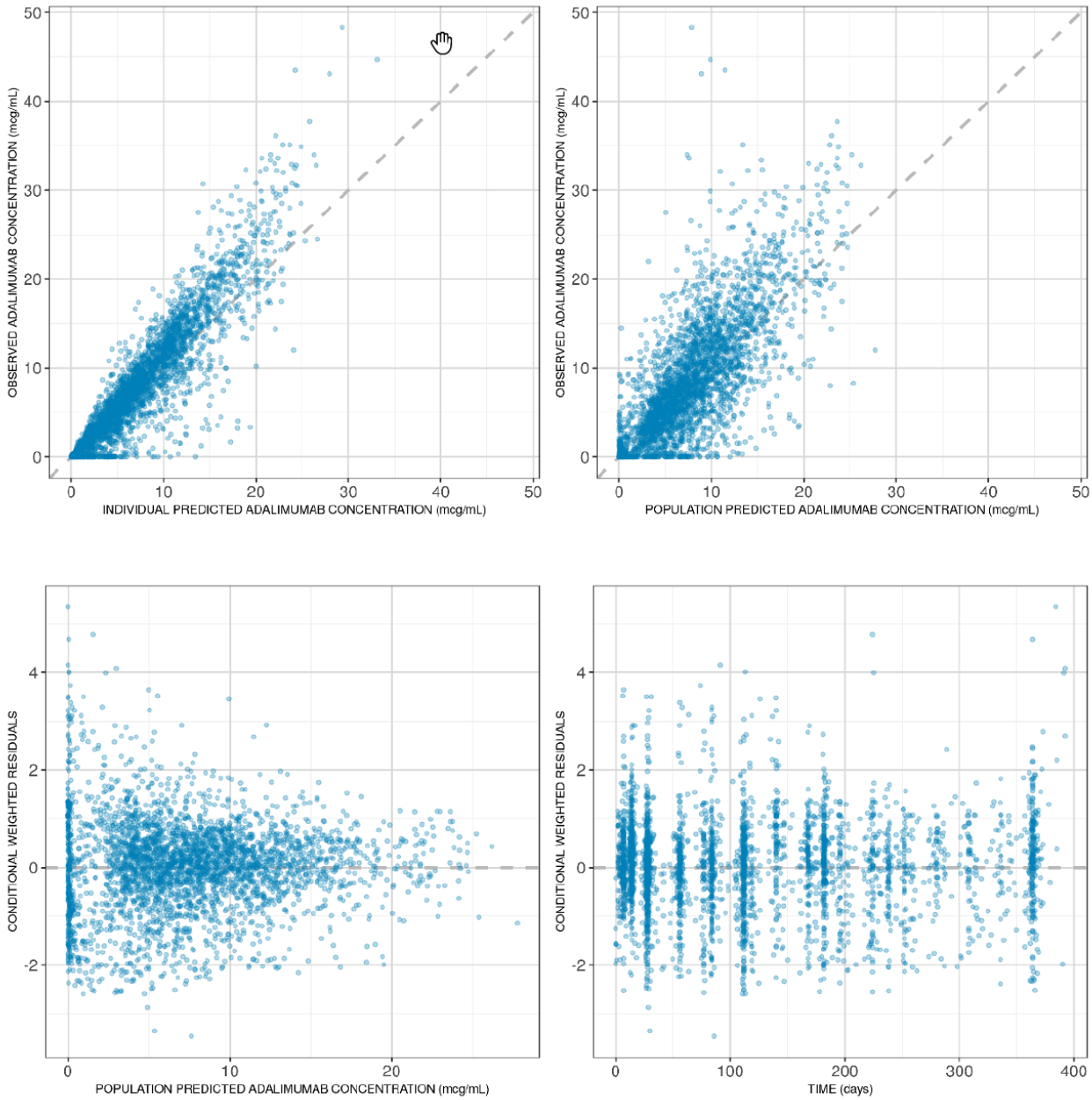
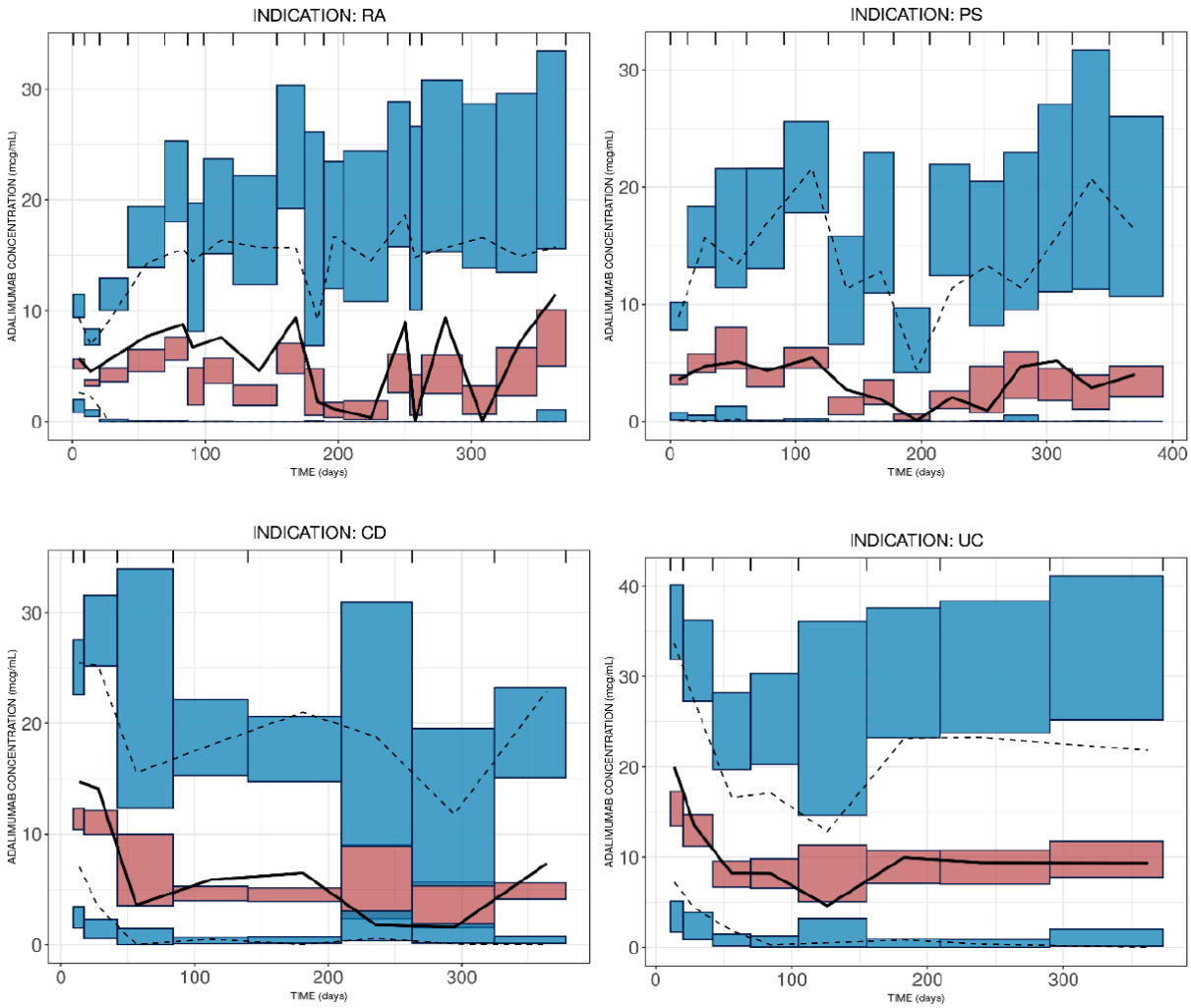


Figure 7 Visual Predictive Checks of Final Pharmacokinetic Model Stratified by Indication

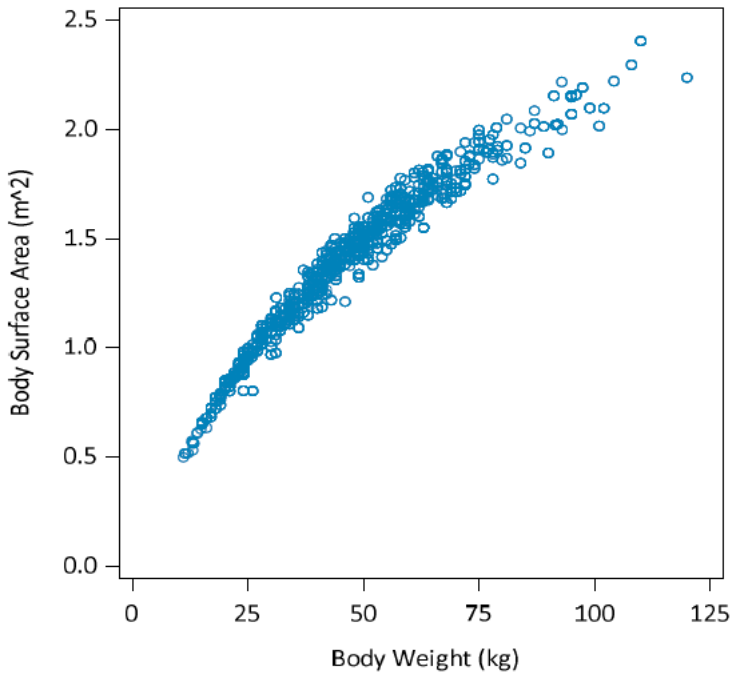


The shaded blue areas represent the 90% prediction interval of the 5th and 95th percentiles of simulated concentrations, the red areas represent the 90% prediction interval of the 50th percentile of simulated concentrations, the solid black line represents median of observed concentrations and dashed black lines represent the 5th and 95th percentile of the observed concentrations.

Simulations of exposure to inform dose selection

The final PK model was used to conduct PK simulations for paediatric UC to evaluate fixed-dose regimens and compare expected concentrations to those using the body weight-based dosing regimens used in the paediatric UC Study M11-290. The fixed-dose regimens were compared to the body weight-based dosing regimens with standard and high induction doses as well as to the adult Phase 3 exposures to determine an appropriate fixed-dosing regimen similar to body weight-based dosing (Figure 8).

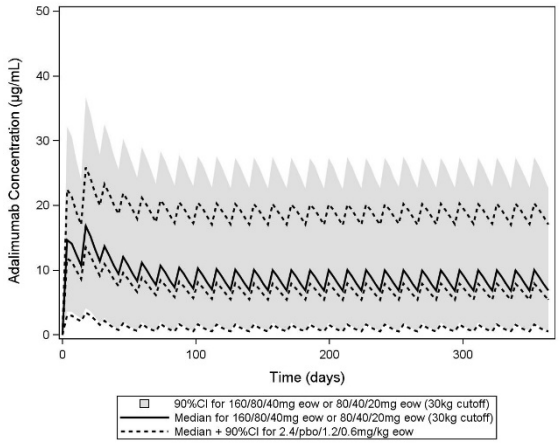
Figure 8 Baseline Body Surface Area Versus Baseline Body Weight (All Subjects Included in Population PK Analysis)



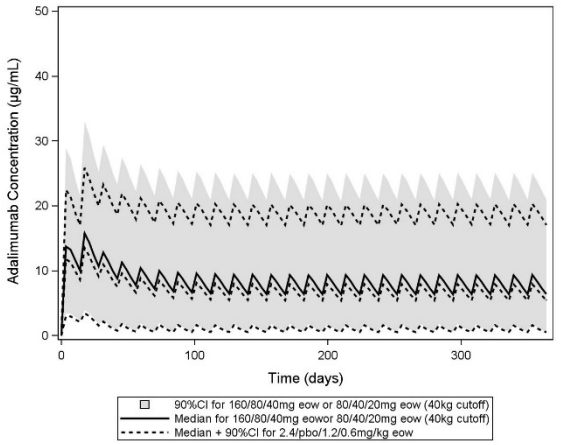
Overall, results of PK modelling and simulation demonstrated that fixed-dose and body weight-based dosing (mg/kg) regimens give largely overlapping concentration-time profiles for paediatric UC subjects under eow maintenance dosing (Figure 9) or ew maintenance dosing (Figure 10) subsequent to induction dosing. Simulated serum adalimumab concentrations were comparable between the fixed-dose scenarios that were evaluated (30 or 40 kg cut-off for 160/80 mg at Week 0, 80/40 mg at Week 2, and 40/20 mg eow or ew starting at Week 4) and the body weight-based dosing used in Study M11-290 in the maintenance portion of dosing (eow or ew dosing), respectively.

Figure 9 Simulated Serum Adalimumab Concentrations (Median and 90% Confidence Interval) in Paediatric UC Subjects Receiving Either Fixed-Dose or Body Weight-Based Dose (Induction/eow Maintenance Dose)

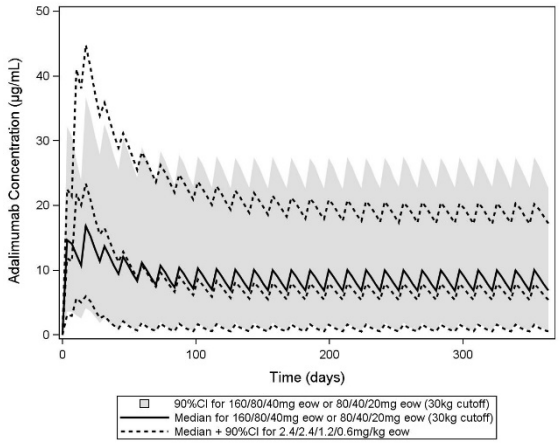
BW-based dose using standard induction and standard maintenance and FD eow using 30 kg cut-off



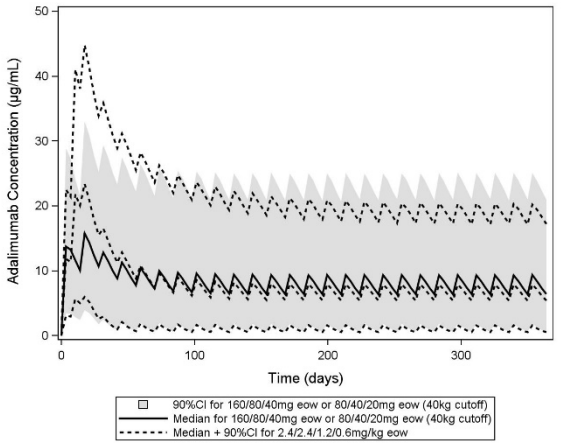
BW-based dose using standard induction and standard maintenance and FD eow using 40 kg cut-off



BW-based dose using high induction and standard maintenance and FD eow using 30 kg cut-off



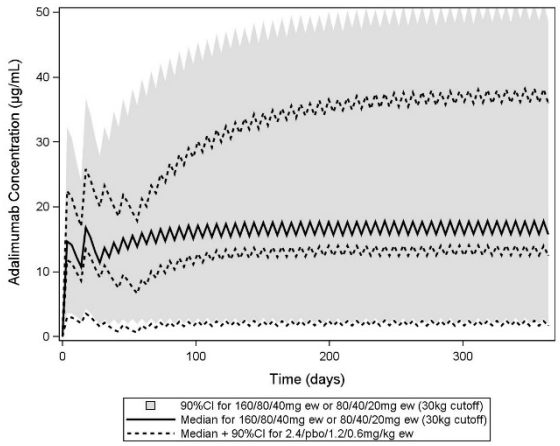
BW-based dose using high induction and standard maintenance and FD eow using 40 kg cut-off



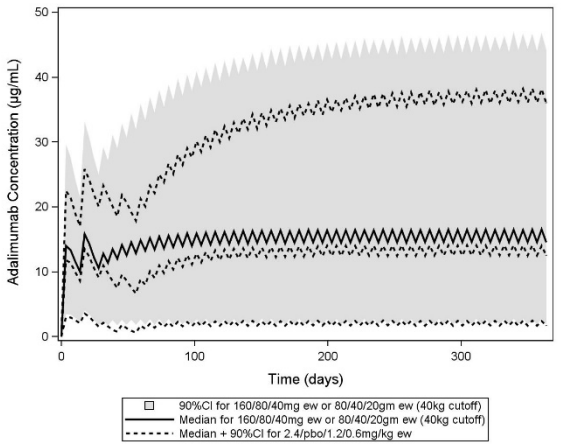
BW = body weight; CI = confidence interval, eow = every other week; FD = fixed dose; UC = ulcerative colitis

Figure 10 Simulated Serum Adalimumab Concentrations (Median and 90% Confidence Interval) in Paediatric UC Subjects Receiving Either Fixed-Dose or Body Weight-Based Dose (Induction/ew Maintenance Dose)

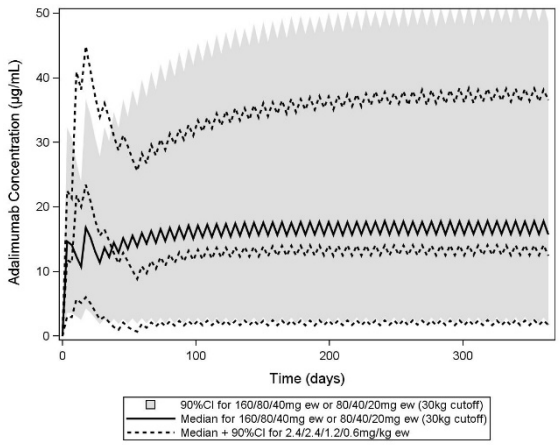
BW-based dose using standard induction and high maintenance and FD ew using 30 kg cut-off



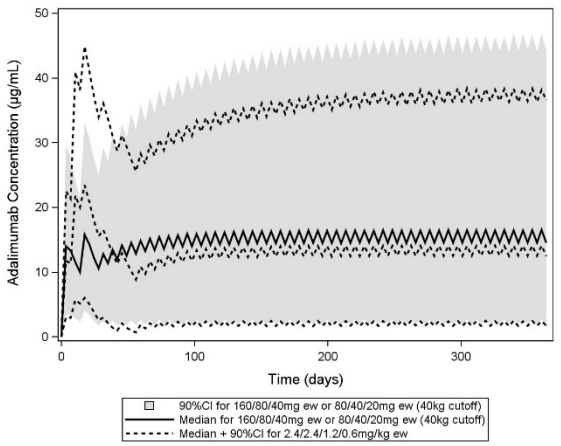
BW-based dose using standard induction and high maintenance and FD ew using 40 kg cut-off



BW-based dose using high induction and high maintenance and FD ew using 30 kg cut-off



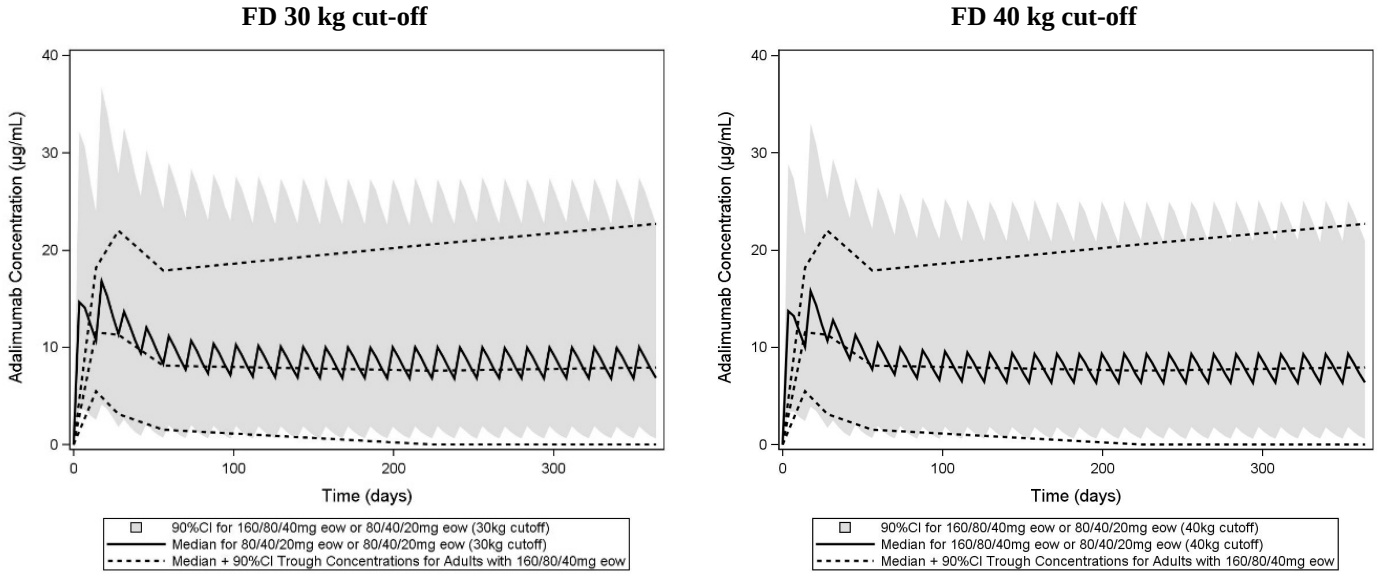
BW-based dose using high induction and high maintenance and FD ew using 40 kg cut-off



BW = body weight; CI = confidence interval, ew = every week; FD = fixed dose; UC = ulcerative colitis

The predicted concentrations at early time points following the fixed-dose regimen (160/80 mg at Week 0, 80/40 mg at Week 2, and 40/20 mg eow or ew starting at Week 4 using 30 or 40 kg cut-off) were similar to concentrations at early time points under the standard induction dose from Study M11-290 and slightly lower when compared to the concentrations at early time points under the high induction dose from Study M11-290. However, simulated serum adalimumab concentrations at early time points under the fixed-dose scenarios (30 or 40 kg weight cut-off) were similar to the adalimumab concentrations observed at early time points in adult subjects with UC from Study M06-827 (Figure 11).

Figure 11 Simulated Serum Adalimumab Concentrations in Paediatric UC Subjects Fixed-Dose Regimens (Standard Induction/eow Maintenance Dosing) with 30 kg or 40 kg Body Weight Cut-off Compared to Observed Concentrations in Adult UC Subjects (Study M06-827)



BW = body weight; CI = confidence interval, eow = every other week; FD = fixed dose UC = ulcerative colitis

To further evaluate the potential fixed-dose options with 30 kg or 40 kg body weight cut-off, serum adalimumab concentrations from each dosing regimen were compared across different body weight categories. The distribution of the simulated Week 52 trough serum adalimumab concentrations by body weight categories and dosing regimen are shown in

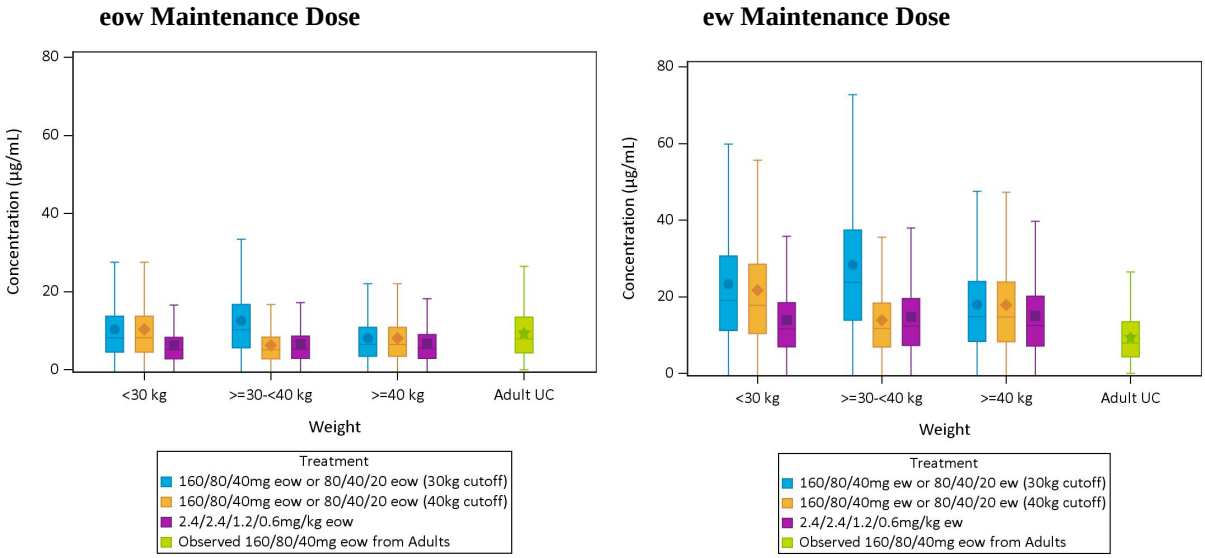
Figure 12, left (eow maintenance dosing) and

Figure 12, right (ew maintenance dosing).

For maintenance period, the simulation results showed that a body weight 40 kg cut-off predicted to provide adalimumab concentrations similar to the body weight-based doses used in Study M11-290 (for both eow or ew maintenance dosing) including those subjects with body weight between 30 to 40 kg (

Figure 12).

Figure 12 Distribution of Simulated Week 52 Serum Adalimumab Trough Concentrations by Body Weight Categories and Dosing Regimen (Induction/eow Maintenance Dose [Left Panel] and ew Maintenance Regimen [Right Panel]) And Observed Adalimumab Trough Concentrations from Adult UC Subjects under eow Dosing (Study M06-827)



Upon request from CHMP, the MAH provided simulated exposures for the low weight group of ≥15kg and <25kg or ≥25kg.

The simulation approach relied on re-sampling subjects from the observed population to retain realistic correlation structures for all covariates. Two weight bins were created for subjects, including subjects ≥ 15 kg to < 25 kg and subjects ≥ 25 kg, in order to assess the simulated exposure levels down to 15 kg. It is noted that in the weight bin from 15 kg to 25 kg, the paediatric UC dataset only contained data for six subjects. Thus, to continue using this approach, the dataset was enriched using data from the other paediatric indications (Crohn's disease [CD], psoriasis [Ps], and enthesitis-related arthritis [ERA]). From the combined dataset, all subjects in the 15 kg to 25 kg bin were retained for the simulation dataset and combined with all subjects above 25 kg from the M11-290 study. For all subjects, the indication and methotrexate covariates were set to UC and no concomitant use, respectively. The distribution of the covariates across the studies were comparable.

Based on the final population PK model, the resulting virtual populations were used to simulate adalimumab concentration-time profiles considering the following dosing regimens (1–7):

1. Studied high induction/high maintenance dosing regimen: 2.4/2.4/1.2 mg/kg at Week 0/1/2 and 0.6 mg/kg every week (ew) maintenance starting at Week 4
2. Studied high induction/standard maintenance dosing regimen: 2.4/2.4/1.2 mg/kg at Week 0/1/2 and 0.6 mg/kg every other week (eow) maintenance starting at Week 4
3. Studied standard induction/high maintenance dosing regimen: 2.4/placebo/1.2 mg/kg at Week 0/1/2 and 0.6 mg/kg ew maintenance starting at Week 4
4. Studied standard induction/standard maintenance dosing regimen: 2.4/placebo/1.2 mg/kg at Week 0/1/2 and 0.6 mg/kg eow maintenance starting at Week 4
5. Assessed fixed-dosing regimen: 160/80 mg at Week 0, 80/40 mg at Week 2 and 40/20 mg eow maintenance starting at Week 4 (40 kg cut-off)

6. Assessed fixed-dosing regimen: 160/80 mg at Week 0, 80/40 mg at Week 2 and 40/20 mg ew maintenance starting at Week 4 (40 kg cut-off)
7. Final proposed fixed-dosing regimen: 160/80 mg at Week 0, 80/40 mg at Week 2 and 80/40 mg eow maintenance starting at Week 4 (40 kg cut-off)

One hundred replicates of each regimen for each subject in the dataset were simulated using the final population PK model and drawing new between-subject variability (BSV) terms in each replicate.

The resulting simulated concentration-time profiles were summarized into two weight bins (≥ 15 kg to < 25 kg vs ≥ 25 kg). The adalimumab concentration-time profiles for subjects with either ≥ 15 kg to < 25 kg or ≥ 25 kg following different dosing regimens are shown in Figure 13. A direct comparison between proposed dosing regimen and studied high induction/high maintenance dosing regimen for subjects with ≥ 15 to < 25 kg and subjects with ≥ 25 kg are shown in

Figure 14 and Figure 15, respectively. In addition, the average adalimumab concentrations from Week 0 to 8 ($C_{avg,8}$) for subjects with body weight ≥ 15 to < 25 kg or ≥ 25 kg are summarized in Table 6. The $C_{avg,8}$ was computed as area under the concentration-time curve (AUC) from Week 0 to 8 divided by 56 days. The median trough adalimumab concentrations at Weeks 2, 4, 8, and 52 are summarized in Table 7 (for simulation Regimens 1, 3, 6, and 7).

Figure 13 Simulated Adalimumab Concentraions Over Time for Subjects With Body Weight ≥ 15 to < 25 kg or ≥ 25 kg by Different Dosing Regimens

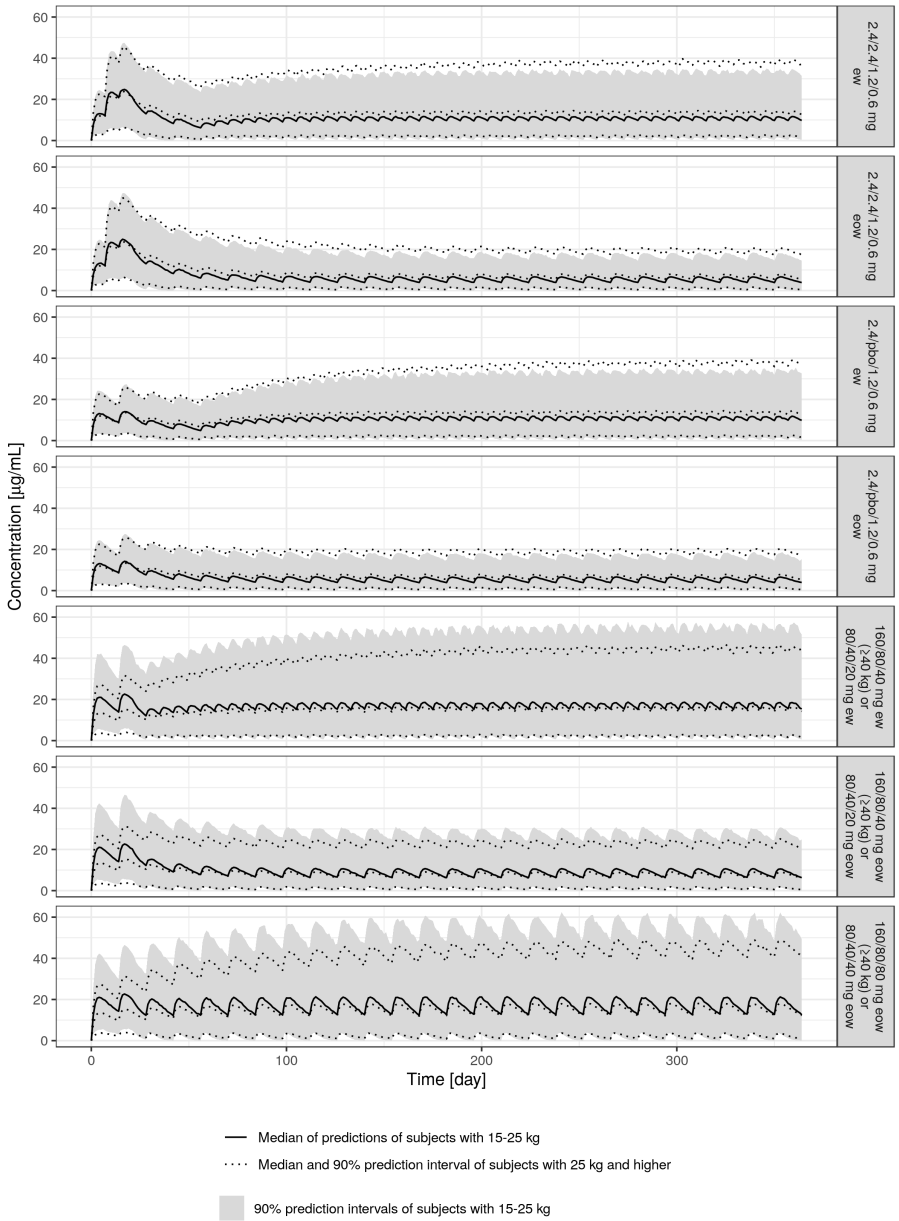


Figure 14 Simulated Adalimumab Concentrations Over Time for Subjects With Body Weight ≥ 15 to < 25 kg Given Proposed Dosing Regimen or Studied High Induction/High Maintenance Dosing Regimen

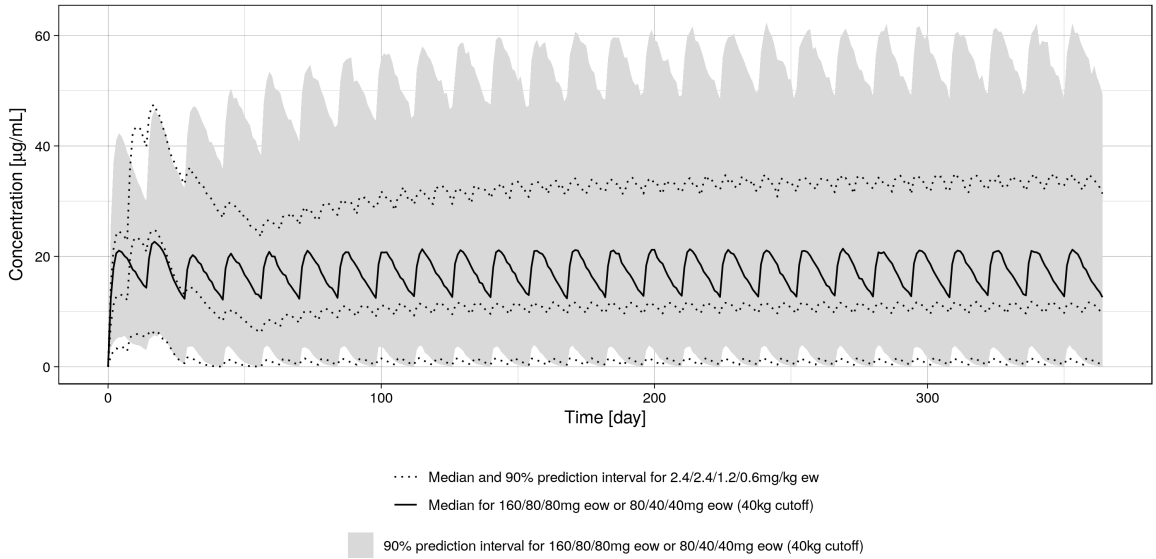


Figure 15 Simulated Adalimumab Concentrations Over Time for Subjects With Body Weight ⩾ 25 kg Given Proposed Dosing Regimen or Studied High Induction/High Maintenance Dosing Regimen

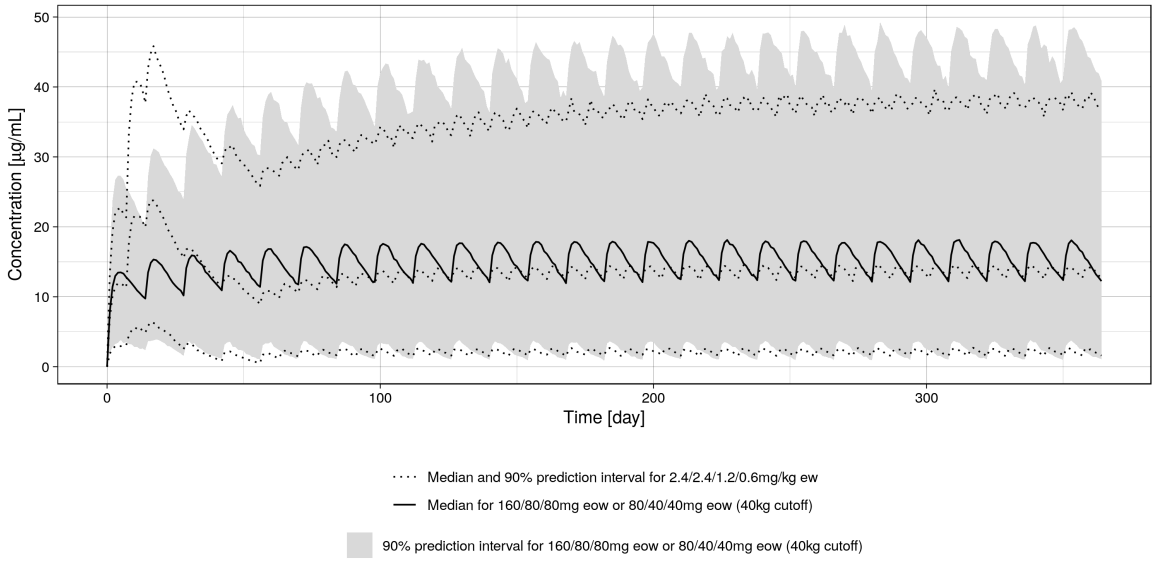


Table 6 Average Adalimumab Concentration From Week 0 to 8 for Subjects With Body Weight ≥ 15 kg to < 25 kg or ≥ 25 kg by Different Dosing Regimens

		Body Weight	
Regimen No.	**Dosing Regimens**	**15 kg to < 25 kg**	**≥ 25 kg**
1	2.4/2.4/1.2/0.6 mg ew	15.3 (7.70, 23.4)	16.3 (9.14, 23.3)
2	2.4/2.4/1.2/0.6 mg eow	15.3 (7.69, 23.3)	16.4 (9.09, 23.2)
3	2.4/pbo/1.2/0.6 mg ew	9.92 (4.93, 15.0)	10.5 (5.87, 14.9)
4	2.4/pbo/1.2/0.6 mg eow	9.96 (4.83, 15.0)	10.4 (5.81, 14.9)
5	160/80/40 mg eow (≥ 40 kg) or 80/40/20 mg eow (< 40 kg)	15.8 (7.86, 26.4)	11.9 (6.40, 19.0)
6	160/80/40 mg ew (≥ 40 kg) or 80/40/20 mg ew (< 40 kg)	17.5 (8.73, 29.3)	13.1 (7.18, 20.8)
7	160/80/80 mg eow (≥ 40 kg) or 80/40/40 mg eow (< 40 kg)	18.3 (8.94, 30.4)	13.8 (7.45, 21.8)

eow =every other week; ew = every week; pbo = placebo.

Table 7 Median (90% Prediction Interval) Trough Adalimumab Concentration Over Time for Subjects With Body Weights Either ≥ 15 kg to < 25 kg or ≥ 25 kg by Different Dosing Regimens (Simulation Regimen 1, 3, 6, and 7)

Dosing Regimens	**Regimen 1**		**Regimen 3**		**Regimen 6**		**Regimen 7**	
	2.4/2.4/1.2/0.6 mg ew		**2.4/pbo/1.2/0.6 mg ew**		**160/80/40 mg ew (≥ 40 kg) or 80/40/20 mg ew (< 40 kg)**		**160/80/80 mg eow (≥ 40 kg) or 80/40/40 mg eow (< 40 kg)**	
	Body Weight							
Time (Weeks)	**15 kg to < 25 kg**	**≥ 25 kg**	**15 kg to < 25 kg**	**≥ 25 kg**	**15 kg to < 25 kg**	**≥ 25 kg**	**15 kg to < 25 kg**	**≥ 25 kg**
2	20.8 (5.47, 39.8)	19.9 (4.87, 37.7)	8.86 (1.79, 17.7)	8.67 (2.11, 16.9)	13.9 (2.83, 30.1)	9.61 (2.22, 20.2)	14.3 (3.03, 30.0)	9.74 (2.39, 20.4)
4	13.0 (0.637, 33.1)	15.5 (2.53, 33.9)	7.78 (0.329, 19.5)	9.12 (1.54, 20.1)	12.0 (0.526, 32.4)	10.3 (1.64, 24.0)	12.3 (0.500, 32.4)	10.2 (1.51, 23.8)
8	6.20 (0.0261, 23.6)	8.95 (0.547, 25.8)	4.88 (0.0208, 16.8)	6.60 (0.590, 18.1)	14.3 (0.682, 42.2)	12.6 (1.63, 30.6)	12.4 (0.0635, 38.3)	11.4 (1.07, 30.3)
52	9.77 (0.378, 31.4)	12.7 (1.59, 37.0)	9.86 (0.356, 32.6)	12.8 (1.76, 36.5)	15.4 (0.557, 51.5)	14.2 (1.56, 43.1)	12.6 (0.0577, 49.3)	12.2 (1.07, 40.9)

eow =every other week; ew = every week; pbo = placebo.

2.3.3. PK/PD modelling

Exposure-response modelling was performed to investigate the relationship of adalimumab in paediatric subjects with UC using logistic regression models for the coprimary endpoints of clinical remission per PMS at Week 8 and clinical remission per FMS at Week 52 for Week 8 responders per PMS. Furthermore, a Markov exposure-response model was developed for clinical remission per PMS collected from baseline to Week 52. The demographics and covariate distributions of all subjects included in the Markov model and logistic regressions are shown in Table 8.

Table 8 Demographics and Baseline Characteristics of Subjects Included in Markov Analyses, Logistic Regressions, and Exposure-Response Simulations (Study M11-290)

Characteristics		All Subjects (N = 100)	Maintenance (Markov Analysis) (N = 80)	Week 8 Logistic Regression Analysis (N = 91)	Week 52 Logistic Regression Analysis (N = 68)
Age (years)	N	100	80	91	68
	Mean (SD)	14.07 (2.91)	13.89 (3.11)	14.00 (2.98)	13.84 (3.17)
	Median	15.00	15.00	15.00	15.00
	Min, Max	5.00, 17.00	5.00, 17.00	5.00, 17.00	5.00, 17.00
Body Weight (kg)	N	100	80	91	68
	Mean (SD)	55.38 (17.65)	55.88 (18.41)	56.23 (18.18)	56.30 (18.87)
	Median	53.60	55.70	55.00	57.00
	Min, Max	15.00, 110.00	15.00, 110.00	15.00, 110.00	15.00, 110.00
Sex	Male	49 (49.00%)	40 (50.00%)	44 (48.35%)	33 (48.53%)
	Female	51 (51.00%)	40 (50.00%)	47 (51.65%)	35 (51.47%)
Race	White	88 (88.00%)	71 (88.75%)	81 (89.01%)	61 (89.71%)
	Black	3 (3.00%)	3 (3.75%)	3 (3.30%)	2 (2.94%)
	Asian	8 (8.00%)	6 (7.50%)	7 (7.69%)	5 (7.35%)
	Other	1 (1.00%)	--	--	--
Concomitant MTX Treatment	No	99 (99.00%)	79 (98.75%)	90 (98.90%)	67 (98.53%)
	Yes	1 (1.00%)	1 (1.25%)	1 (1.10%)	1 (1.47%)
Baseline Partial Mayo Score	N	100	80	91	68
	Mean (SD)	5.59 (1.16)	5.62 (1.11)	5.65 (1.15)	5.60 (1.11)
	Median	5.40	5.50	5.60	5.50
	Min, Max	3.40, 8.80	3.40, 8.80	3.40, 8.80	3.40, 8.80
Baseline Mayo Score	N	100	80	91	68
	Mean (SD)	7.77 (1.20)	7.74 (1.12)	7.80 (1.19)	7.74 (1.13)
	Median	7.60	7.60	7.60	7.60
	Min, Max	6.00, 10.80	6.00, 10.80	6.00, 10.80	6.00, 10.80
Concomitant Azathioprine Treatment	No	39 (39.00%)	29 (36.25%)	35 (38.46%)	22 (32.35%)
	Yes	61 (61.00%)	51 (63.75%)	56 (61.54%)	46 (67.65%)
Concomitant 6-mercaptopurine Treatment	No	98 (98.00%)	79 (98.75%)	91 (100.00%)	68 (100.00%)
	Yes	2 (2.00%)	1 (1.25%)	--	--
Concomitant 5-Amino Salicylic Acid Treatment	No	99 (99.00%)	79 (98.75%)	91 (100.00%)	67 (98.53%)
	Yes	1 (1.00%)	1 (1.25%)	--	1 (1.47%)

Logistic Regression Exposure-Response Analyses on Efficacy

Adalimumab observed serum concentrations at Weeks 8 and 52 were used as the exposure measure for the logistic regression analyses of clinical remission per PMS at Week 8 and clinical remission per PMS at Week 52 for Week 8 responders per PMS, respectively.

The coprimary efficacy endpoints were modelled as binary variables. The endpoint definitions were:

- Clinical response per PMS: Decrease in PMS ≥ 2 and ≥ 30% from Baseline
- Clinical remission per PMS: PMS ≤ 2 and no sub score > 1
- Clinical remission per MS: MS ≤ 2 and no sub score > 1

The probabilities of response were modelled using the equation:

$$P(Y_i = 1) = \frac{e^{placebo+slope*C_P+pref*covariate}}{e^{placebo+slope*C_P+pref*covariate}+1}$$

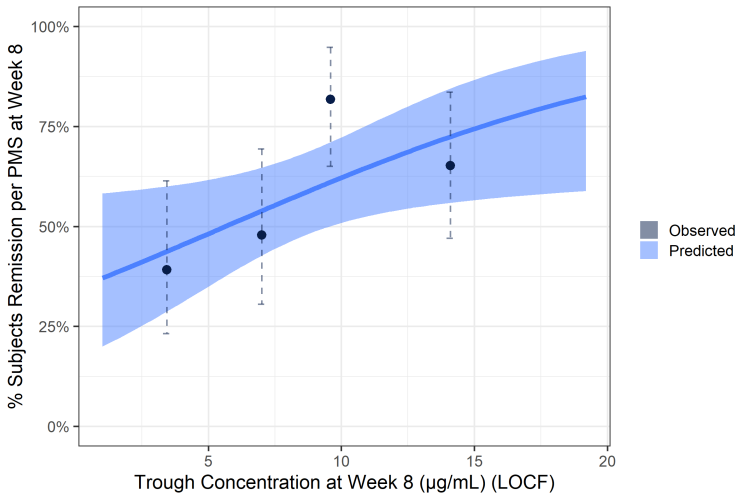
where C_P is the exposure metric, and Yi represents the occurrence (or lack thereof) of an event in the ith subject. P(Yi = 1) is the probability of observation Y from subject i being equal to 1, with 1 indicating that the endpoint is achieved or an event occurred. Placebo describes the probability of an observation in the absence of drug while slope describes the strength of the drug effect.

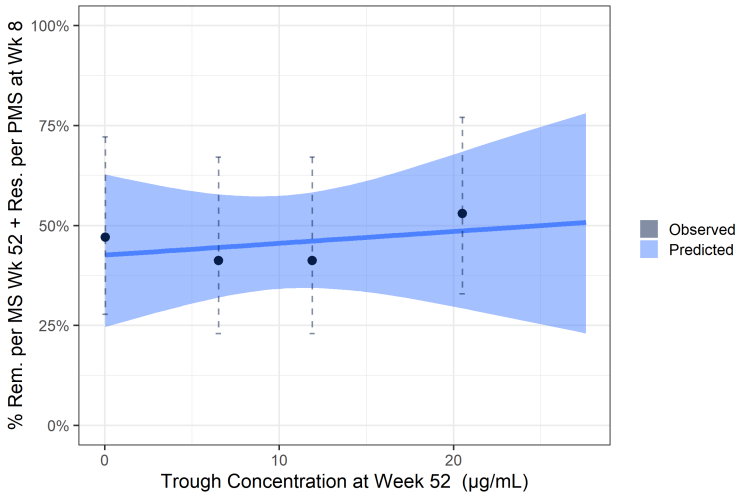
Covariates were tested by adding linear terms as shown above in the equation with PREF being the estimated covariate parameter. Tested covariates were sex, age, race, baseline body weight, baseline hsCRP, baseline MS, and concomitant medication with methotrexate, mycophenolate mofetil, azathioprine, 6-mercaptopurine, or 5-amino salicylic.

The logistic regression analyses for the coprimary endpoints were performed using software R 3.5.2.

A logistic regression analysis showed an exposure-response relationship between adalimumab concentration and % subjects with remission per PMS at Week 8 and a slight relationship for % subjects who responded at Week 8 per PMS and achieved clinical remission at Week 52 per full Mayo score in paediatric subjects with UC (Figure 16 and Table 9). Adalimumab drug effect was found to be a significant predictor for clinical remission per PMS at Week 8 with higher concentrations leading to higher remission. Observed remission rates at Week 8 appeared to reach a plateau at the third quartile, while there was a slight increase in remission rate at Week 52 with increasing adalimumab concentrations.

Figure 16 Logistic Regressions of Observed Coprimary Endpoints vs Observed Trough Concentration in Pediatric UC (Study M11-290); Remission per PMS at Week 8 (Top) and Remission per Full Mayo Score at Week 52 (Bottom)





Note: Blue lines show estimated model fits; the blue-shaded areas represent the 95% confidence intervals of the estimated models; the black dots show quartiles of the observed responses; and the dashed error bars correspond to 95% confidence intervals derived from a binomial distribution.

Table 9 Summary of Parameter Estimates in Paediatric UC

Endpoint	Parameter	Estimate	95% CI
Remission per PMS at Week 8	Intercept	–0.644	–1.60 – 0.308
	Slope for Concentration	0.114	0.0120 – 0.216
Remission per FMS at Week 52 among Responders per PMS at Week 8	Intercept	–0.298	–1.12 – 0.524
	Slope for Concentration	0.0119	–0.0538 – 0.0776

CI = confidence interval; FMS = full Mayo score; PMS = partial Mayo score

Efficacy simulations were performed to evaluate different fixed dosing regimens in paediatric UC subjects [

Figure 17 (clinical remission at Week 8) and Figure 18 (clinical remission at Week 52)]. The simulation results showed that the probability of achieving efficacy endpoints were overlapping for all dosing regimens (fixed-dose regimen of 160/80 mg at Week 0, 80/40 mg at Week 2 followed by eow or ew [using a 30 or 40 kg body weight cut-off]) and the body weight-based (mg/kg) eow or ew dosing, respectively, used in Study M11-290) across the different body weight categories for paediatric UC. The small differences in the probability of achieving efficacy endpoints between dosing regimens within and across body weight categories are expected based on the different doses and resulting exposures (adalimumab concentrations), along with the modest exposure-response relationship.

Figure 17 Probability of Achieving Remission per PMS at Week 8 in Subjects Receiving Either Fixed Dose or Body Weight-Based Dose Based on Simulated Adalimumab Concentrations and Logistic Regression (Fixed Dose with eow Maintenance Dose [Left] or Fixed Dose with ew Maintenance Dose [Right] Compared with Standard or High Induction Doses Used in Study M11-290)

eow Maintenance Dose **ew Maintenance Dose**

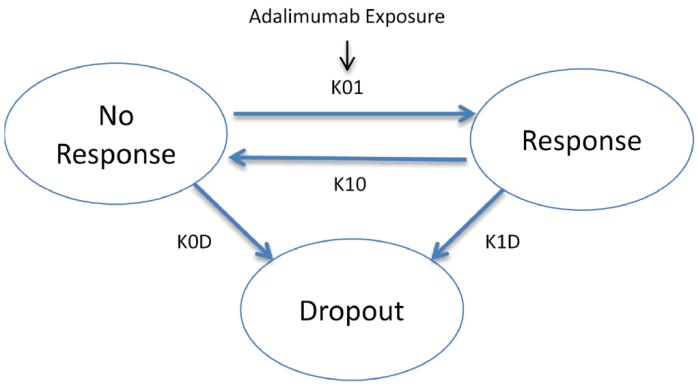
Figure 18 Probability of Achieving Remission per FMS at Week 52 in Subjects with Response per PMS at Week 8 Receiving Either Fixed Dose or Body Weight-Based Dose Based on Simulated Adalimumab Concentrations and Logistic Regression (High Induction Followed by eow Maintenance Dose [Left] and ew Maintenance Dose [Right])

eow Maintenance Dose **ew Maintenance Dose**

Markov Exposure-Response Modelling for Clinical Remission per PMS

To show similarity of efficacy between 80 mg eow and 40 mg ew maintenance dosing, a continuous time Markov exposure-response modelling approach was utilized, which took into account the time course of response with adalimumab treatment. The Markov model employed described the relationship between actual adalimumab serum exposures Cp on achievement of clinical remission per PMS in Study M11-290. Only the Week 8 responders per PMS who entered the maintenance period of Study M11-290 were considered for model building to avoid modelling study design artefacts such as the forced dropout for non-responders per PMS at Week 8. A total of 80 subjects who entered the maintenance phase were included in the modelling.

The time course of clinical remission was modelled via transitions between model states, which were characterized by respective transition rate constants K_{ij}. The rate constant K01 describes the transition from no response to response, the rate constant K10 the transition from response to no response, the rate constant K0D the transition from no response to dropout, and the rate constant K1D the transition from response to dropout. A model schematic is illustrated below:



Transition rates were then translated into time-dependent transition probabilities Pij. Due to the time-continuous implementation, rapid changes of disease states were enabled. The Markov property implies that future states only depend on the current state, therefore accounting for serial correlation in data. This stochastic process was described by the Kolmogorov forward equations.

$$\frac{dP_{ij}}{dt} = \sum_{k \neq j} K_{kj} P_{ik}(t) - \sum_{k \neq j} K_{jk} P_{ij}(t),$$

yielding a system of differential equations for the probabilities of going from state i to state j. Drug effect on transition rate constants K01 was incorporated using an Emax model as:

$$K_{01} = Placebo\ rate * \left(1 + \frac{E_{max} \cdot C_P}{C_p + EC_{50}}\right)$$

Where Cp denotes the exposure metric used. Emax describes the maximum drug effect on rate constant K01, with concentration that provides half the maximal response (EC50) being the concentration at which half maximal effect on K01 is achieved.

The parameter estimates of the model are shown in Table 10. The dropout rate K1D for dropout from response was estimated to be very low and could not be estimated precisely. The model was rerun fixing rate K1D to the point estimate. When comparing K1D with the dropout rate K0D from no response, one can see that K1D was estimated to be much lower compared to K0D indicating that the dropout is informative where mostly non-responders leave the study. Visual predictive checks were performed and

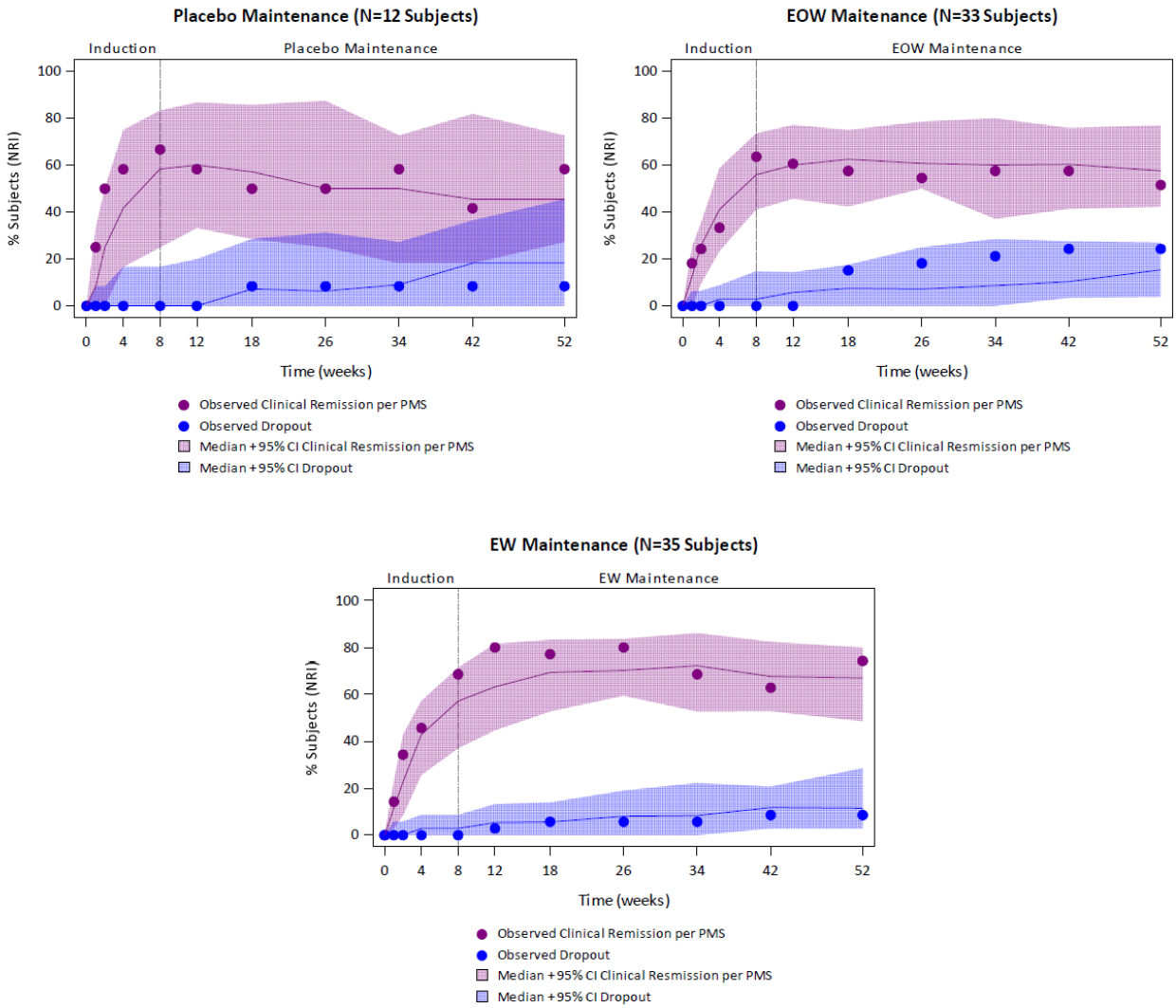
showed that the model adequately described the observed clinical remission per PMS and dropout in Study M11-290 (Figure 19).

Table 10 Parameter Estimates for Clinical Remission Per PMS (Markov Model)

Parameter	Population Estimate (SEE)	% RSE	95% Confidence Interval
K_{01} (1/day)	0.00417 (0.00508)	122	0.000915 - 0.0190
K_{10} (1/day)	0.00640 (0.000931)	14.5	0.00483 - 0.00847
K_{0D} (1/day)	0.00127 (0.000392)	30.8	0.000721 - 0.00224
K_{1D} (1/day)	1.88E-12 (Fixed)	--	--
E_{max}	11.2 (23.2)	207	1.64 - 77.1
EC_{50} (µg/mL)	25.7 (119)	462	2.09 – 315

RSE = relative standard error of estimate; SEE = standard error of estimate

Figure 19 Visual Predictive Check of Markov Model for Clinical Remission Per PMS Over Time Stratified by Dosing Regimen (Study M11-290)



Exposure-Safety Analysis in Paediatric Subjects

The range of concentrations expected with the proposed fixed-dose regimen, based on population PK simulations, has been previously observed in paediatric subjects across several indications of adalimumab. The relationship between adalimumab concentrations and the risk of adverse events is shown in Figure 20 for paediatric UC subjects and Figure 21 for paediatric CD subjects. In addition, data from previous adalimumab development programs in adults includes doses up to 10 mg/kg intravenous for 6 months and 3 mg/kg for up to 2 years, plus doubling of approved subcutaneous doses in multiple indications (RA, Ps and CD), showing a similar safety profile across doses and exposures.

Figure 20 Relationship Between Observed Adalimumab Concentrations and Adverse Events in Paediatric UC Subjects Through Week 52 (Study M11-290)

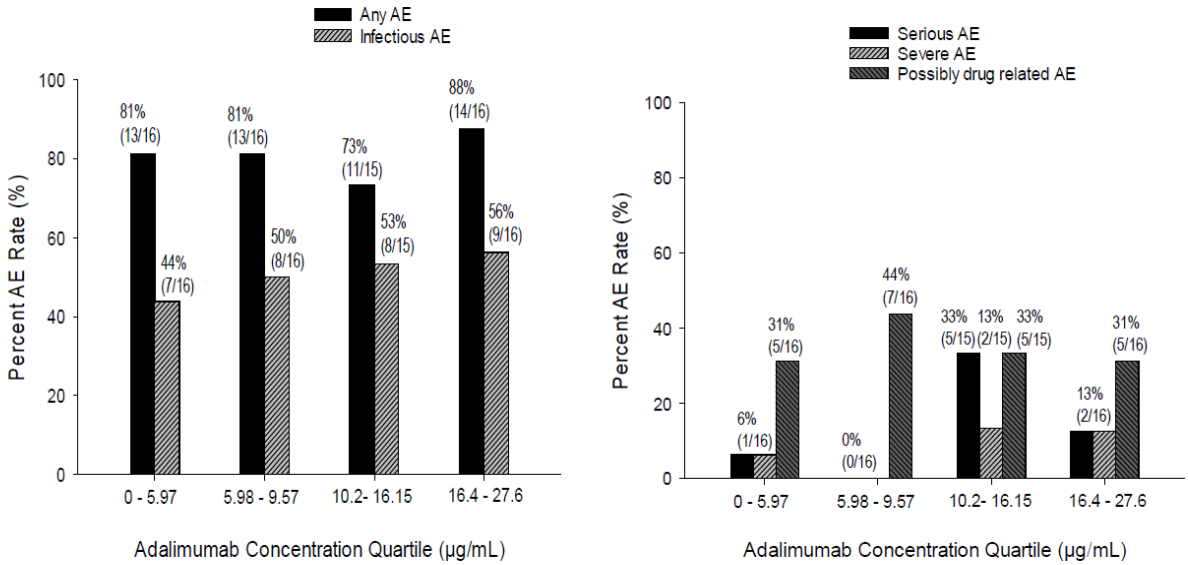
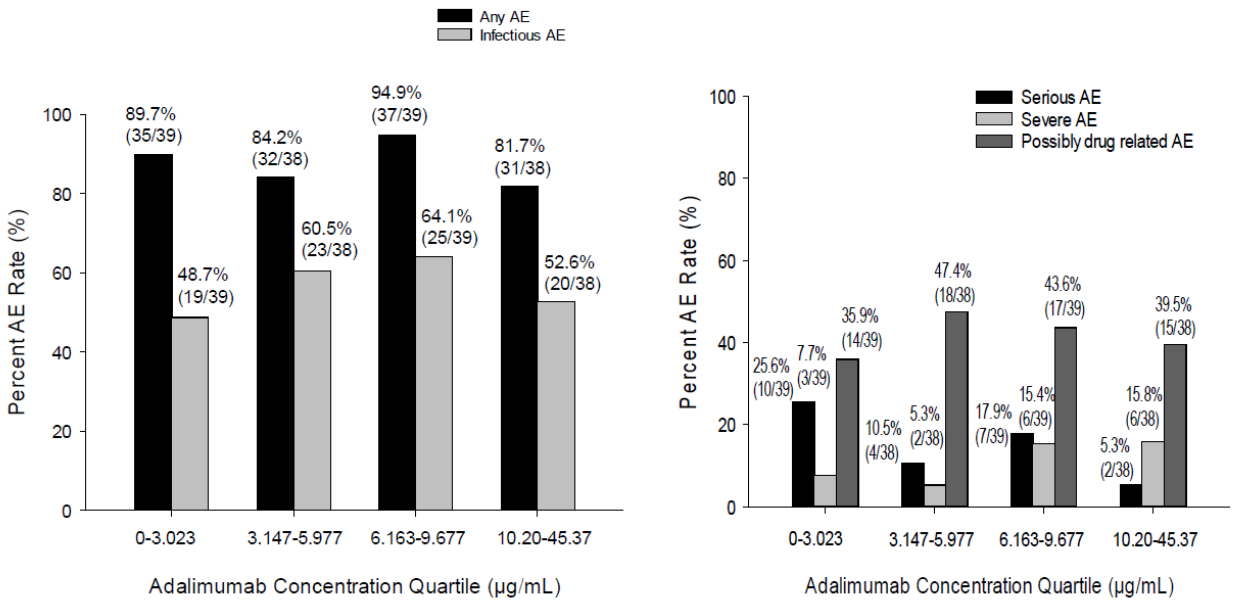


Figure 21 Relationship Between Adalimumab Concentrations and Adverse Events in Paediatric CD Subjects During Double-Blind Maintenance Phase (Week 4 to 52)



2.3.4. Discussion on clinical pharmacology

The PK and immunogenicity of adalimumab were evaluated in paediatric subjects with moderate to severe UC in a Phase 3 study (Study M11-290). Population PK of adalimumab was also assessed in paediatric UC subjects using a non-linear mixed effects modelling approach.

The pharmacokinetic results showed that the mean adalimumab concentrations were 24.0 µg/mL and 17.2 µg/mL in subjects on high induction dose at Weeks 2 and 4, respectively, compared to 9.83 µg/mL and 10.5 µg/mL in subjects on standard induction dose. Starting from Week 26, the mean adalimumab steady-state concentrations reached approximately 15 - 17 µg/mL and 4 - 6 µg/mL for subjects on high maintenance dose and standard maintenance dose, respectively.

The overall AAA+ rate was 3% (3/100) using the current ELISA AAA assay. In general, as previously identified, serum adalimumab concentrations were lower in AAA+ subjects compared to those in AAA– subjects.

A paediatric cross-indication population PK analysis was performed to describe PK in UC patients and other paediatric indications. The model was subsequently used to simulate exposure levels given the proposed flat dose posology. The final PK model was largely similar to a previous cross-indication popPK model, with the addition of different volume of distribution estimates for UC and CD populations. The visual predictive checks indicate that the variability for the UC patient population is over-estimated and hence simulated UC exposures can be expected to be somewhat higher than observed values. However, as this caveat would lead to a conservative decision, the popPK model is agreed by CHMP for this application.

The expected exposure levels are studied in previously approved dosing regimens for other Humira indications. When comparing the 40 mg ew and 80 mg eow regimens the main difference is that the fluctuations (i.e peak to trough concentration ratio) is larger for the 80 mg eow, however the average concentration is expected to be largely the same.

A concern was raised during the evaluation regarding the expected exposures for the most light-weight UC patients as the dosing strategy in the induction phase is considerably higher than other approved indications such as the pJIA for example. Hence, the MAH was asked to provide simulated exposure levels down to 15 kg. The MAH provided simulated exposure levels, with highlight on subjects >15 to ≤25 kg. It is noted that the expected exposure in the smallest children are exceeding previously accepted adalimumab exposure levels. For the most light-weight the flat-dose regimen will result in higher exposures, during maintenance treatment, than the dosing regimen used in the paediatric UC study. The 80/40/40 eow dosing regimen in small children is the dosing regimen that would result in the highest exposures; those exposures have not previously been reached by any approved Humira dosing regimen. The 80 mg eow maintenance dosing regimen is approved (as an alternative dosing regimen) for CD patients from 6 years; however, as the largest deviation between the flat dosing from the body-weight dosing is apparent at the lowest body-weight, the proposed dosing regimen is not considered acceptable to CHMP under the age of 6 years. Therefore, the MAH agreed to restrict the indication for the use in children as of 6 years of age.

The MAH provided exposure simulations where a re-induction dose has been introduced during the maintenance phase to present the expected exposure levels after such dose. Similarly, the expected exposure subsequent a (flat-dose) re-induction dose exceeds previously accepted exposure levels for adalimumab, both in previous indications and in the present paediatric UC study. Hence, the recommendation of a re-induction dose was not supported by CHMP. Therefore, the MAH agreed to remove this claim from the SmPC (see also Discussion on clinical efficacy).

Exposure-efficacy analyses were performed both for PMS (week 8) and FMS (week 52), as well as a longitudinal Markov analysis for PMS. For the exposure-response analyses, observed adalimumab concentrations were used and due to the sampling schedule, the exposure metric was C_{trough}. For the logistic regression analysis at week 8, there was a clear trend with increasing probability of response with increasing exposure. In the FMS analysis, the confidence interval for the Slope parameter (i.e. drug effect) overlap zero, hence indicating that there is no relationship between adalimumab concentration and clinical remission at week 52. This relationship, however, is most likely diluted by the fact that only responders at week 8 are carried forward to the maintenance phase and as such a weak exposure-response relationship is not unexpected at week 52. A continuous time Markov exposure-response model was developed, which take into account the time course of response with adalimumab treatment. Such modelling approach could have provided supportive information to describe the clinical response over time. However, the parameter estimates for the drug effect (Emax and EC50) are estimated with very high uncertainty and as such, using the model to distinguish between the ew and eow dosing regimens are not considered reliable by CHMP. Therefore, no conclusion can be made from this analysis.

Graphical analysis was presented for exposure-safety endpoints. The exposure-safety results from study M11-290 indicate that there is a trend of increasing rate of infections with increasing exposure, no other adverse events indicated a relationship with exposure. This behaviour was similar in the paediatric CD population, which also displayed a wider exposure range more comparable to the exposure range expected from the flat dose regimens proposed. The MAH has provided a summary of adalimumab exposure-safety across several paediatric indications (UC, JIA, Ps, and CD) and no trends of increasing AEs with increasing adalimumab concentration could be detected.

2.3.5. Conclusions on clinical pharmacology

The PK and PK/PD has been sufficiently characterised in paediatric patients. The expected adalimumab exposure, given the proposed flat-dose regimen, has been accepted in previous indications of Humira in children 6 years and above.

The initially proposed indication was for children 5 years and older. However, since the exposure levels in the smallest children exceeded studied exposure levels, the available data did not support dosing recommendations in children lower than 6 years of age. The indication was therefore restricted to children 6 years and above.

In addition, a re-induction dose was initially proposed in case of disease flare. However, the expected exposure subsequent a re-induction dose exceeded previously accepted exposure levels for adalimumab, the re-induction dose was therefore removed from the SmPC.

2.4. Clinical efficacy

In this submission, the MAH seeks to add a new indication for Humira (adalimumab) for the treatment of paediatric patients 5 to 17 years of age with moderately to severely active UC. This application is supported by data from 2 Phase 3 clinical studies:

- a randomized, controlled study (Study M11-290)
- an open-label (OL) long-term study (Study M10-870) for subjects who participated in, and successfully completed, Study M11-290. Study M11-290 is a post-marketing commitment to the US FDA. This submission also aims to fulfil the agreed EU PIP (EMEA-000366-PIP02-09-M06, Decision P/0174/2019).

The indication and dose initially proposed in the application are:

Humira is indicated for the treatment of moderately to severely active ulcerative colitis in paediatric patients (from 5 years of age) who have had an inadequate response to conventional therapy including corticosteroids and/or 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

The proposed dosing regimen of adalimumab for patients from 5 to 17 years of age with UC is based on body weight. For patients < 40 kg, the induction dose is 80 mg at Week 0 and 40 mg at Week 2, followed by a maintenance dose of 40 mg every other week (eow) starting at Week 4. For patients ≥ 40 kg, the induction dose is 160 mg at Week 0 and 80 mg at Week 2, followed by a maintenance dose of 80 mg eow starting at Week 4. The maintenance doses of 40 mg eow and 80 mg eow are considered equivalent to 20 mg every week (ew) and 40 mg ew doses, respectively. Continued therapy beyond 8 weeks should be carefully considered in patients not showing signs of response within this time period. Patients who experience a disease flare after beginning maintenance therapy may benefit from a one-time re-induction dose of 80 mg (< 40 kg) or 160 mg (≥ 40 kg), followed by maintenance dosing.

2.4.1. Dose response study

No dedicated dose response studies were performed. Exposure-response relationships were evaluated based on the M11-290 data, further described in the PK/PD modelling section.

2.4.2. Main studies

The MAH submitted two main studies; study M11-290 is a Phase 3, multicenter, randomized, double-blind (DB) trial. This study is part of the Paediatric Investigation Plan (PIP) in the EU and a postmarketing commitment associated with the US Food and Drug Administration's (FDA's) approval of the adult UC indication. Study M10-870 is a Phase 3, multi-center, OL study designed to evaluate the long-term maintenance of clinical response, safety and tolerability of adalimumab in pediatric subjects with UC who participated in, and successfully completed, Protocol M11-290 through Week 52.

Since there were issues in recruitment of paediatric patients with UC in Study M11-290, major changes to the protocol were made during the study, these changes were agreed by PDCO and implemented as agreed modifications to the PIP (

Table 11).

Table 11 PIP modifications regarding Study M11-290 are summarized in the table below.

Date	Type of Interaction	Purpose and Outcome
16 February 2011 Decision P/63/2011, 18 February 2011	PIP modification (EMEA-000366-PIP02-09-M01)	Administrative modification: to link the existing indications (RA, JIA, CD, psoriasis, psoriatic arthritis and ankylosing spondylitis) and agreed PIP measures/conditions into the UC PIP decision.

22 February 2013 Decision P/0137/2013, 21 June 2013	PIP modification (EMEA-000366-PIP02-09-M02)	To replace the previously agreed study design (multicenter, randomized, double-blind, three arm lower and higher dose, placebo-controlled trial to evaluate the efficacy, safety and pharmacokinetics of adalimumab in children from 4 to less than 18 years of age with moderately to severely active ulcerative colitis) with a new study design (Study M11-290). Study M11-290 reconciled the requirements of the EMA's pediatric committee (PDCO) and FDA in order to conduct a single global study within a reasonable timeframe. Co-primary endpoints used the Mayo score (since FDA did not accept the PUCAI as the primary endpoint and PDCO acknowledged the importance of endoscopy). Sample size was re-calculated based on the revised co-primary endpoints. PUCAI-based endpoints were analyzed as secondary endpoints. Active induction therapy was provided to all subjects with external comparisons to the adult UC placebo data and a randomization to placebo in initial responders.
28 January 2014 Decision P/0162/2014, 13 June 2014	PIP modification (EMEA-000366-PIP02-09-M03)	To change to the date of study initiation.
02 March 2015 Decision P/0131/2015, 12 June 2015	PIP modification (EMEA-000366-PIP02-09-M04)	To mitigate the effects of the placebo arm on enrolment by reducing the length of time (from Week 20 to Week 12) before a subject could receive escape therapy due to a disease flare and by lowering the threshold for qualification of disease flare from two consecutive visits to one visit. Further reduced the complexity of study procedures (including removal of stool sample collection and reducing blood sampling).
24 July 2017 Decision P/0342/2017, 10 November 2017	PIP modification (EMEA-000366-PIP02-09-M05)	To remove the internal placebo control arm from the maintenance period and use an external placebo arm instead. As a result of this change, the test strategy for the Week 52 co-primary endpoint and certain ranked secondary endpoints was modified to compare to the external placebo. In addition, to cease randomization to the DB induction treatment and have all subsequent subjects who entered the study received the high induction dose given OL. The statistical analyses were also updated to reflect this change and the sample size was modified based on the design changes. This PIP modification was discussed during a teleconference on 05 October 2017, between AbbVie the European Medicines Agency (EMA), Scientific Advice Working Party (SAWP), PDCO, Swedish Medical Products Agency (MPA) and the FDA. The PIP modification was also discussed on 11 Oct 2017 between the PDCO and the EMA's Committee for Medicinal Products for Human Use (CHMP). The outcome was fully endorsed by the CHMP.

19 December 2018 Decision P/0174/2019, 15 May 2019	PIP modification (EMEA-000366-PIP02-09-M06)	PIP modification to update the statistical analyses and ranking of the endpoints based on the results of the meta-analysis. The description of the control group was changed to reflect the external placebo control and the sample size was also updated based on the results of the meta-analysis.

Study M11-290: A Multicenter, Randomized, Double-Blind Study of the Human Anti-TNF Monoclonal Antibody Adalimumab in Pediatric Subjects with Moderate to Severe Ulcerative Colitis

Methods

Study M11-290 is a Phase 3, multicenter, randomized, double blind (DB) trial designed to evaluate the efficacy and safety of adalimumab in paediatric subjects with moderate to severe UC who have failed therapy with corticosteroids and/or immunosuppressant (IMM).

A sub-study conducted in Japanese patients, results from this sub-study were not included in the submitted analysis.

Prior to Amendment 4, enrolled subjects were randomized 3:2 at Baseline to 1 of 2 DB adalimumab induction doses, induction high dose (I-HD) or induction standard dose (I-SD). At Week 8, subjects demonstrating a clinical response per Partial Mayo Score (PMS) are randomized to the following groups in a 2:2:1 ratio: adalimumab maintenance standard dose (M-SD), adalimumab maintenance high dose (M-HD), or placebo. Subjects continue their blinded treatment during the maintenance period until Week 52.

After Amendment 4, enrolled subjects receive adalimumab induction high dose open-label (I-HD-OL). At Week 8, subjects demonstrating a clinical response per PMS are randomized and stratified by Week 8 remission status per PMS in a 1:1 ratio to 1 of 2 adalimumab maintenance treatment groups, M-SD or M-HD. Subjects continue their blinded treatment during the maintenance period until Week 52

Prior to Amendment 4, internal placebo was chosen as the control group during maintenance period. Over the course of study, there were significant recruitment difficulties (the primary reason being objection to the placebo group in the maintenance period) despite efforts to reduce subject burden and study complexity. As a result, after Amendment 4, per agreement with the regulatory agencies, randomization to the internal placebo group was ceased, and external placebo derived from a meta-analysis of placebo-controlled studies in adult subjects with moderate to severe UC who had failed

conventional therapy was used as comparator for the confirmatory analysis of co-primary and ranked secondary efficacy endpoints instead.

The duration of the study is up to 66 weeks, which includes a screening period of up to 28 days, an 8-week induction period and a 44-week DB maintenance period and a 70-day follow-up phone call. Upon completion of the study, subjects were to have the option to enrol into an OLE study (Study M10-870 Main) where they were to continue to receive OL adalimumab.

Figure 22 Study M11-290 Study design prior to Amendment 4

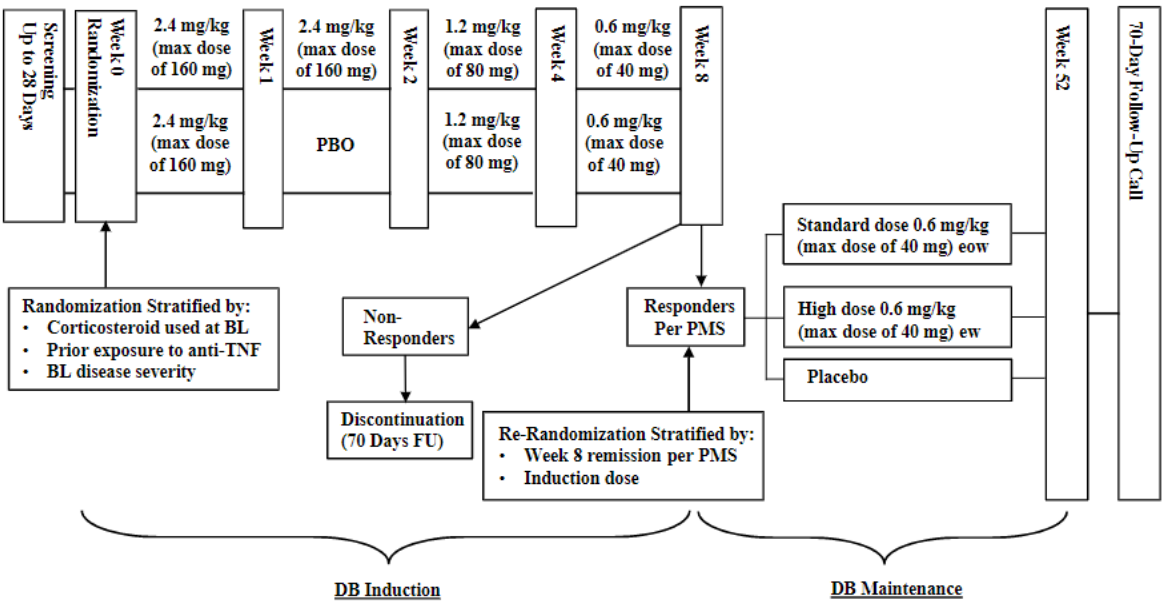
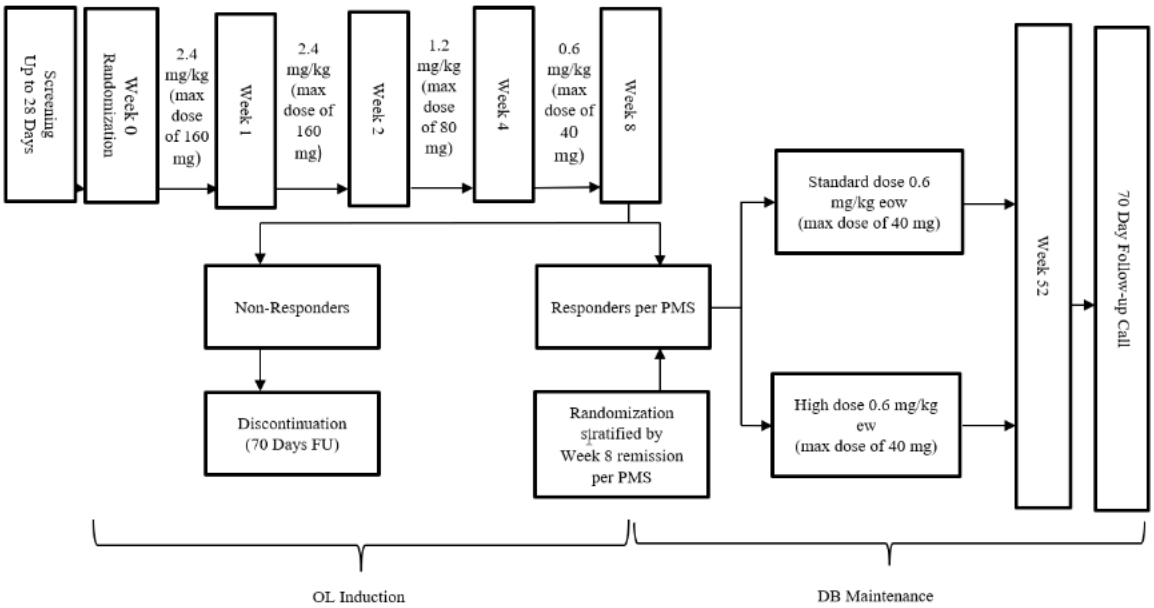


Figure 23 Study M11-290 Study design after Amendment 4



Flares

Criteria for disease flare were as follows:

- Subjects with a Week 8 PMS of 0 to 2 who presented with a PMS at least 3 points greater than their Week 8 score.
- Subjects with a Week 8 PMS of 3 to 4 who presented with a PMS at least 2 points greater than their Week 8 score.
- Subjects with a Week 8 PMS of 5 to 6 who presented with a PMS at least 1 point greater than their Week 8 score.

Subjects were expected to remain on blinded therapy throughout the 44-week maintenance period. However, subjects with a disease flare could be re-randomized to receive the following blinded treatment at or after Week 12:

Subjects who were randomized to M-SD were to be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or adalimumab (0.6mg/kg [maximum of 40 mg]) at the visit. Afterwards, all subjects were to resume receiving the standard dose (adalimumab 0.6 mg/kg [maximum of 40mg] eow) within the original dosing schedule.

Subjects who were randomized to M-HD were to be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or adalimumab (0.6mg/kg [maximum of 40 mg]) at the visit. The following week, all subjects were to resume receiving the high dose (adalimumab 0.6 mg/kg [maximum of 40 mg] ew) within the original dosing schedule.

Subjects who were randomized to placebo prior to Amendment 4 were to be re-randomized to receive either adalimumab re-induction dose (adalimumab 2.4 mg/kg [maximum of 160 mg]) or to receive adalimumab (0.6 mg/kg [maximum of 40mg]) at the visit. Afterwards, all subjects were to receive the standard dose (adalimumab 0.6mg/kg [maximum of 40 mg] eow) within the original dosing schedule

If a subject continued to meet the definition of disease flare (2nd time) following at least a 4-week course of blinded therapy since the subject had been re-randomized for the disease flare, they could have been switched to OL adalimumab ew at 0.6 mg/kg [maximum of 40 mg]. If a subject was re-randomized at Week 12 to receive either re-induction dose (adalimumab 2.4 mg/kg [maximum of 160 mg]) or to receive adalimumab (0.6 mg/kg [maximum of 40mg]), then the earliest that subject could have been evaluated to determine if they meet the criteria for disease flare for switch to OL (adalimumab 0.6 mg/kg [maximum of 40 mg]) weekly dosing was at Week 16.

If a subject continued to meet the definition of disease flare (3rd time) following a 4-week course of OL adalimumab ew at 0.6mg/kg (maximum of 40 mg), they could have been switched to receive adalimumab OL 40 mg ew (maximum dose, not weight-based). Subjects with persistent disease flare while on adalimumab 40 mg ew (maximum dose) could have been withdrawn from the study at the investigator's discretion. During OL rescue therapy, subjects who were responders and had been in remission for at least 8 consecutive weeks may have had their dosage decreased from ew to eow. If subjects demonstrated disease flare after dose de-escalation, subjects also had an opportunity to re-escalate their dose back to adalimumab ew dosing

External placebo group

In order to derive robust external placebo assumptions for the co-primary and ranked secondary endpoints, a thorough literature search of placebo-controlled clinical studies in subjects with moderate to severe UC who had failed conventional therapy was performed. Studies M06-826 and M06-827 in adults were the only available data sources with PMS data at Week 8. Studies GEMINI 1 and OCTAVE Sustain in adults were the only studies with a similar subject population (i.e. failure or intolerance to prior corticosteroids or IMMs), study design (i.e. randomized withdrawal), and endpoint definitions for derivation of external placebo rates for the Week 52 endpoints in Study M11-290.

Study participants

Paediatric subjects with moderate to severe UC (Mayo score of 6 to 12 points and endoscopy sub score of 2 to 3) from 4 to less than 18 years old, who have failed therapy with corticosteroids and/or immunosuppressant (IMM) and meet all of the inclusion criteria and none of the exclusion criteria were eligible for enrolment.

Diagnosis and Main Criteria for Inclusion/Exclusion

Main Inclusion

1. Subjects from the ages of 4 to 17 prior to baseline dosing.

2. Subjects with a diagnosis of UC for at least 12 weeks prior to screening confirmed by endoscopy with biopsy. A colonoscopy will be performed during the screening period unless the subject underwent a colonoscopy within 12 months prior to Screening and appropriate documentation is available (to confirm the diagnosis without evidence of dysplasia, colon cancer or infection). In this case the screening endoscopy may be either a colonoscopy or a flexible sigmoidoscopy. If the subject underwent an endoscopy within 56 days of Baseline, and a video recording of the endoscopy is available, the video recording may be used and no additional endoscopy be performed during the Screening period. If no appropriate documentation for confirmation of the diagnosis is available as per the investigator's judgment a diagnostic biopsy must also be performed. Biopsies to rule out dysplasia, colon cancer and infection may be taken at the investigator's discretion.

3. Active ulcerative colitis with a Mayo Score of 6 – 12 points and endoscopy subscore of 2 – 3 (confirmed by central reader) despite concurrent treatment with at least one of the following (oral corticosteroids or immunosuppressants or both as defined below):

- Oral prednisone of ≥ 2 mg/day or equivalent, but not exceeding 40 mg/day, or oral budesonide ≥ 3 mg/day, but not exceeding 9 mg/day, with a stable dose for at least 7 days prior to Baseline; and/or
- At least a consecutive 28-day course of azathioprine or 6-MP or methotrexate (MTX) prior to Baseline, with a stable dose prior to Baseline of azathioprine ≥ 1.5 mg/kg/day or 6-MP ≥ 1 mg/kg/day (rounded to the nearest available tablet or half tablet formulation) or a documented 6-TGN level of 230 – 450 pmol/8 × 10^8 RBC on the current dosing regimen or MTX ≥ 15mg/m^2 body surface area/week, or a dose that is the highest tolerated by the subject (e.g., due to leukopenia, elevated liver enzymes, nausea) during that time.
  Note: If subjects are on both oral corticosteroid and immunosuppressants BOTH of the drugs need to meet the above criteria; and/or
- Concurrent therapy with corticosteroids or immunosuppressants (azathioprine, 6-MP or MTX) is not required for subjects who were previously treated during the past 1 year and have confirmed documentation of failure to respond, or were previously treated during the past 5 years and have confirmed documentation indicating lack of tolerability.

4. Parent or guardian has voluntarily signed and dated an informed consent form.

5. Subjects must be able and willing to self-administer SC injections or have a qualified person available to administer SC injections.

6. Subject has a negative TB Screening Assessment. If a subject has a positive (≥ 5 mm induration) PPD test and/or IGRA test at Screening, a CXR (PA and lateral view) must be performed for evaluation of active TB disease. If the subject has evidence of a latent TB infection, the subject must initiate and complete a minimum of 2 weeks (or per local guidelines, whichever is longer) of an ongoing course of TB prophylaxis or have documented completion of a full course of TB prophylaxis, prior to Baseline.

7. If female, subject who is either not of childbearing potential, defined as pre-menstrual, or is of childbearing potential and is practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug.

8. Subject is judged to be in good health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, physical examination, chest x-ray (CXR), and a 12-lead electrocardiogram (ECG) performed during Screening.

Main Exclusion:

1. Subject with Crohn's disease (CD) or indeterminate colitis (IC).

2. Current diagnosis of fulminant colitis and/or toxic megacolon.

3. Subjects with disease limited to the rectum (ulcerative proctitis) during the screening endoscopy.

4. Therapeutic enema or suppository within 14 days prior to the Screening endoscopy and during the remainder of the Screening Period.

5. History of colectomy or subtotal colectomy (with ostomy) or is planning bowel surgery.

6. Received cyclosporine, tacrolimus, or mycophenolate mofetil, within 30 days prior to Baseline.

7. Female subjects who are breast-feeding or considering becoming pregnant during the study.

8. Positive pregnancy test at Screening or Baseline.

9. History of clinically significant drug or alcohol abuse in the last 12 months.

10. Subjects on azathioprine or 6-mercaptopurine (6-MP) or MTX and subjects:

- Have not been on stable doses of these medications for at least 28 days prior to Baseline; or
- Have discontinued these medications within 28 days of Baseline.

11. Subjects on oral aminosalicylates who:

- Have not been on stable doses of these medications for at least 14 days prior to Baseline; or
- Have discontinued use of aminosalicylates within 14 days of Baseline.

12. Subjects on growth hormone who have not been on a stable dose for at least 4 weeks prior to Baseline.

13. Subjects on oral corticosteroids who:

- Have not been on stable doses of these drugs for at least 7 days prior to Baseline; or
- Discontinued use of oral corticosteroid within 14 days of Baseline; or
- Have been taking both budesonide and prednisone (or equivalent) simultaneously.

14. Received intravenous corticosteroids within 5 days prior to Screening or during the Screening Period.

15. Subject who has previously used infliximab or any anti-TNF agent within 56 days of Baseline.

16. Subject who has previously used infliximab or any anti-TNF agent and has not clinically responded at any time ("primary non-responder") unless subject experienced a treatment limiting reaction.

17. Previous treatment with adalimumab or previous participation in an adalimumab clinical study.

18. Positive Clostridium difficile (C. difficile) stool assay during the Screening Period.

19. Currently receiving total parenteral nutrition (TPN).

20. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.

21. History of invasive infection (e.g., listeriosis and histoplasmosis), human immunodeficiency syndrome (HIV).

22. History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and any other condition which would put the subject at risk by participation in the study.

23. Subjects with any active viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study.

24. Subject with a positive result for the Hepatitis B surface antigen (HBs Ag) or any HBV DNA PCR result that meets or exceeds detection sensitivity will be excluded.

25. Chronic recurring infections or active TB.

26. Subject has been treated with any investigational drug of chemical or biologic nature or any investigational procedure (including previous faecal transplantation) within 30 days or 5 half-lives (whichever is longer) of the drug prior to the Baseline Visit.

27. Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline Visit or oral anti-infectives within 14 days prior to the Baseline Visit.

28. Prior exposure to biologics that have a potential or known association with PML (i.e., natalizumab or efalizumab or rituximab).

29. Known hypersensitivity to adalimumab or its excipients.

30. Evidence of dysplasia or history of malignancy (including lymphoma and leukaemia) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix. If the Screening endoscopy shows evidence of dysplasia or malignancy, subject may not be enrolled in the study.

31. Screening laboratory and other analyses show any of the following abnormal results:

- ECG – with clinically significant abnormalities;
- Aspartate transaminases (AST) or alanine transaminase (ALT) > 1.75 × the upper limit of the reference range;
- Total bilirubin ≥ 3 mg/dL;
- Serum creatinine > 1.6 mg/dL;
- Clinically significant abnormal screening laboratory results as evaluated by the Investigator.

32. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

Treatments

Prior to Amendment 4, subjects randomized to I-HD group receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.

Subjects randomized to I-SD group receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and matching placebo at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.

At Week 8, subjects randomized to M-SD group receive 0.6 mg/kg (maximum dose of 40 mg) every other week (eow), and subjects randomized to M-HD group receive 0.6mg/kg (maximum dose of 40 mg) every week (ew).

After Amendment 4, enrolled subjects (I-HD-OL group) receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week4 and Week 6. At Week 8, subjects received either M-SD or M-HD.

Objectives

The objective of the study was to demonstrate the efficacy and safety, and to assess the pharmacokinetics of adalimumab administered subcutaneously in paediatric subjects with moderate-to-severe UC.

Outcomes/endpoints

Co-primary efficacy endpoints:

1. The proportion of subjects who achieve clinical remission at Week 8 as measured by PMS (defined as a PMS ≤ 2 and no individual subscore > 1);

2. The proportion of subjects who responded at Week 8 per PMS and achieve clinical remission at Week 52 as measured by Mayo score (defined as a Mayo Score ≤ 2 and no individual subscore > 1).

Ranked secondary efficacy endpoints:

1. Proportion of subjects in Mayo clinical response at Week 52 in Week 8 responders per PMS;

2. Proportion of subjects who achieve mucosal healing at Week 52 as measured by Mayo endoscopy subscore (defined as ≤ 1) in Week 8 responders per PMS;

3. Proportion of subjects who achieve Mayo clinical remission at Week 52 in Week 8 remitters per PMS;

4. Proportion of subjects receiving corticosteroid at Baseline who have discontinued corticosteroid prior to Week 52 and are in Mayo clinical remission at Week 52 in Week 8 responders per PMS.

Additional exploratory secondary analyses:

- Proportion of subjects in PMS clinical remission at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in Paediatric Ulcerative Colitis Activity Index (PUCAI) remission (defined as < 10) at Week 8;
- Proportion of subjects in PUCAI response (defined as a decrease in PUCAI ≥ 20 points from Baseline) at Week 8;
- Proportion of subjects in PUCAI remission (defined as < 10) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in PUCAI response (defined as a decrease in PUCAI ≥ 20 points from Baseline) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and are in PUCAI remission at Week 52 in Week 8 responders per PMS;
- Change from Baseline in total IMPACT III Quality of Life scores over time for subjects at least 9 years old at Baseline;
- Change from Baseline in WPAI scores over time;

- Change from Baseline in "z" scores for height (observed height velocity [cm/yr] – mean height velocity for age and sex [cm/yr]/SD of the mean) at Week 26 and Week 52;
- Change from Baseline in BMI at Week 26 and Week 52;
- Change from Baseline in "z" scores for weight-for-age at Week 26 and Week 52;
- Proportion of subjects at appropriate Tanner stage at Week 26 and Week 52 compared to Baseline
- Proportion of subjects in PMS response over time;
- Proportion of subjects in PMS remission over time;
- Proportion of subjects in PUCAI response over time;
- Proportion of subjects in PUCAI remission over time;
- Change from Baseline in number of daily stool over time;
- Change from Baseline in albumin and total protein at different time points
- Change from Baseline in haemoglobin, haematocrit, red blood cell count at different time points;
- Change from Baseline in hs-CRP levels at different time points;
- Proportion of subjects with extraintestinal manifestations (EIM) at Week 26 and Week 52 compared to Baseline;
- Proportion of subjects with Mayo endoscopy sub score of 0 or 1 (without friability) at Week 52;
- Proportion of subjects being hospitalized during the study;
- Proportion of subjects undergoing colectomy during the study;
- Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and completed Week 52;
- Correlation between PMS and PUCAI at different time points;
- Proportion of subjects in a 9 point Mayo (without SFS) clinical remission (defined as ≤ 2 and no individual sub score > 1) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in a 9 point Mayo (without PGA) clinical remission (defined as ≤ 2 and no individual sub score > 1) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in a 9-point Mayo (without rectal bleeding sub score (RBS)) clinical remission (defined as ≤ 2 and no individual sub score > 1) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in a 6 point Mayo (without SFS and endoscopy sub score) clinical remission (defined as ≤ 1) at Week 8;
- Proportion of subjects in a 6 point Mayo (without PGA and endoscopy sub score) clinical remission (defined as ≤ 1) at Week 8;
- Proportion of subjects in a 6 point Mayo (without RBS and endoscopy sub score) clinical remission (defined as ≤ 1) at Week 8;
- Change from Baseline in Mayo Score at Week 52;
- Change from Baseline in PMS over time;
- Change from Baseline in PUCAI over time;
- Change from Baseline in endoscopy sub score at Week 52
- Change from Baseline in SFS over time;
- Change from Baseline in RBS over time;
- Change from Baseline in PGA over time.

Table 12 Definitions of Key Efficacy Endpoints

Term	Definition
Full Mayo Score (FMS)	Composite score of UC disease activity based on the subscores of stool frequency (0 – 3), rectal bleeding (0 – 3), physician's global assessment (0 – 3) and endoscopic subscore (0 – 3). This score ranges from 0 – 12 points with higher scores representing more severe disease.
Partial Mayo Score (PMS)	Composite score of UC disease activity based on the subscores of stool frequency, rectal bleeding, and physician's global assessment and DOES NOT include the endoscopic subscore. This score ranges from 0 – 9 points with higher scores representing more severe disease.
Clinical response per PMS	Decrease in PMS ≥ 2 points and ≥ 30% from Baseline
Clinical remission per PMS	PMS ≤ 2 and no individual subscore > 1
Mucosal healing	Endoscopy subscore of 0 or 1
Clinical remission per FMS	Mayo score ≤ 2 and no individual subscore > 1
Corticosteroid-free remission per FMS	Subjects receiving systemic corticosteroids (UC-related or non-UC-related) at Baseline who discontinued systemic corticosteroids prior to Week 52 and achieved Mayo clinical remission
Clinical response per FMS	Decrease in Mayo Score ≥ 3 points and ≥ 30% from Baseline
Pediatric Ulcerative Colitis Activity Index (PUCAI)	Sum of six subscores of PUCAI with a maximum total score of 85: abdominal pain (no pain = 0, pain can be ignored = 5, pain cannot be ignored = 10), rectal bleeding (none = 0, small amount with < 50% of stools = 10, small amount with most stools = 20, large amount with > 50% of stool content = 30), stool consistency of most stools (formed = 0, partially formed = 5, completely unformed = 10), number of stools per 24 hours (0 to 2 = 0, 3 to 5 = 5, 6 to 8 = 10, > 8 = 15), nocturnal stools (no = 0, yes = 10), activity level (no limitation = 0, occasionally limited = 5, severe restriction = 10). Higher scores represent more severe disease.
PUCAI remission	PUCAI < 10
PUCAI response	A decrease in PUCAI ≥ 20 points from Baseline.

Sample size

Originally planned sample size:

Table 13 Sample size based on Week 8 and Week 52 co-Primary Endpoints

Endpoints	External Placebo Upper 95% CI	Assumption for High ADA Group	Power	N in High ADA Group	Randomization Ratio	Total Induction Phase Sample Size
Week 8 PMS Remission Rate	19.25%[a]	30%	85%	135	Induction High:Standard 3:2 = 135:90	225

Endpoints	Internal Placebo	Assumption for High ADA Group	Power	N in High ADA Group	Randomization Ratio	Total Maintenance Phase Sample Size
Week 52 FM Remission Rate	15%	45%	80%	62	Maintenance High:Standard:Placebo 2:2:1 = 62:62:31	155[b]

PMS = partial Mayo score; FM = full Mayo score

a. The upper limit of 95% CI for placebo from adult UC studies. Sample size calculation is based on a one group chi-square test.

b. Sample size calculation is based on a two-sided Fisher's exact test at a 0.05 significance level. 225 subjects at baseline are required assuming 70% response rate at Week 8.

Changes to the sample size calculation:

The sample size was changed in amendment 5 to 93 patients in total. The ordering of the secondary endpoints was changed. A 48% remission rate per PMS at Week 8 for the combined standard and high adalimumab induction dose groups was assumed. A 52% remission rate per PMS at Week 8 for the high adalimumab induction dose group was assumed.

Randomisation

Subjects were initially to be randomized 3:2 between standard induction dose or high induction dose. At Week 8, subjects demonstrating a clinical response were to be re-randomized in a 2:2:1 ratio to adalimumab maintenance standard dose, adalimumab maintenance high dose or placebo, respectively. The randomization was stratified by Week 8 remission status per PMS (defined as a PMS ≤ 2 and no individual subscore > 1) and induction dose.

Randomization to DB induction treatment was discontinued and open-label high induction dose was instead used for all subsequently enrolled subjects after amendment 4. Randomization to the internal placebo arm from the maintenance period was discontinued after amendment 4.

Blinding (masking)

Subjects were to continue their blinded treatment during the maintenance period until Week 52.

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team) the Investigator, study site personnel and the subject were to remain blinded to each subject's treatment throughout the blinded period of the study. The IVRS/IWRS was to provide access to blinded subject treatment information in the case of medical emergency.

Statistical methods

Analysis methods

Efficacy analyses are performed on the ITT population for the Week 8 efficacy endpoints and on the mITT population for the Week 52 efficacy endpoints, unless otherwise noted. Testing of the co-primary and ranked secondary endpoints were to be done on the ITT-E (for Week 8 efficacy endpoints) and mITT-E population (for Week 52 efficacy endpoints). Endpoints that are of the binary type were to be analyzed as proportions by treatment group including 95% CIs. Endpoints that are of the continuous type were to be analyzed as changes from baseline and reported by treatment group including 95% CIs.

Analysis sets

Seven study populations will be used for analyses in this study. These are:

Intent-To-Treat (ITT) population: The ITT population includes all subjects who received at least one dose of the study medication during induction period. ITT subjects were to be analyzed as randomized/enrolled.

ITT-E population: The ITT-E population was to be a subpopulation of the ITT population, where subjects who have received open-label high induction dose are excluded. The ITT-E is the primary population for the confirmatory induction period efficacy analyses.

Modified ITT (mITT) population: The mITT population consists of all Week 8 PMS responders who were randomized at Week 8 and received at least one dose of the study medication during maintenance period. mITT subjects were to be analyzed as randomized at the beginning of maintenance phase.

mITT-E population: The mITT-E population was to be a subpopulation of the mITT population, where subjects who have received Placebo are excluded. The mITT-E is the primary population for the confirmatory maintenance period efficacy analyses.

Re-Randomized (RR) population: Consists of all subjects who were re-randomized due to a disease flare and received at least one dose of the study medication after the rerandomization. RR subjects will be analyzed as randomized at the beginning of maintenance phase.

Safety population: Includes all subjects who received at least one dose of the study drug. The safety population was to be analyzed (separately for induction and maintenance phase) as treated, according to treatment the subject actually received. The safety population was to be used for safety analyses.

Per Protocol (PP) populations: The PP populations was only to be used for sensitivity analyses of the co-primary and ranked secondary endpoints.

External Placebo Control

In order to derive external placebo assumptions for the co-primary and ranked secondary endpoints, a literature search of placebo-controlled clinical studies in subjects with moderate to severe UC who had failed conventional therapy was performed.

Studies M06-826 and M06-827 in adults were the only available data sources with PMS data at Week 8. Studies GEMINI 1 and OCTAVE Sustain in adults were the only studies with a similar subject population (i.e., failure or intolerance to prior corticosteroids or IMMs), study design (i.e., randomized withdrawal), and endpoint definitions for derivation of external placebo rates for the Week 52 endpoints in Study M11-290.

For all co-primary and ranked secondary endpoints where available, separate estimates for anti-TNF naïve placebo patients and anti-TNF experienced placebo patients were derived. The estimates for anti-TNF naïve placebo patients and anti-TNF experienced placebo patients were then combined as a weighted

mean according to the assumed proportion of anti-TNF naïve and experienced subjects as per the Study M11-290 protocol, i.e., 0.75 × rate in anti-TNF naïve + 0.25 × rate in anti TNF experienced subjects.

Missing data

Missing Data Handling

In general, missing Baseline and safety data were not imputed.

Baseline Value is Missing:

Subjects were excluded from analysis of change from Baseline if Baseline evaluation is missing.

Missing Efficacy and Outcome Evaluations:

Missing values was only to be imputed for study periods which a subject has actually entered, e.g., if a subject is a non-responder at Week 8 and thus discontinues from the study after induction period, this subject's missing data would only be imputed up to Week 8.

Non-responder Imputation (NRI): The NRI approach is used for all binary efficacy variables. These variables can take values of 'Response' (i.e., response, remission or mucosal healing) or 'Non-response' (i.e., non-response, non-remission or no mucosal healing) or may be missing for any reason including discontinuation from study. According to the NRI method all missing values were considered as 'Non-Response'. Subjects re-randomized due to disease flare were considered as 'Non-Responders' at and after their 1st re-randomization. The confirmatory efficacy analyses used NRI approach to impute the missing values. Additionally, only for sensitivity analyses on the mITT population, a modified NRI (mNRI) approach to impute the missing values was used. For mNRI method, subjects re-randomized due to disease flare were considered as 'Non-Responders' at and after the switch to the open-label therapy (2nd disease flare).

Last Observation Carried Forward (LOCF):

For categorical and continuous efficacy variables the following rules was used for LOCF approach:

- Baseline and pre-baseline values were not to be used to impute the missing post-baseline values, and
- Missing values after baseline were to be imputed using the last non-missing values after baseline and prior to the missing value.
- For subjects who were re-randomized due to disease flare, the last non-missing value before or at the re-randomization after 1st disease flare were carried forward.

The LOCF analysis was performed as sensitivity analysis.

For patients with disease flare and at least one non-missing post-Baseline endoscopy, last observation carried forward (LOCF) rules were refined to carry forward the last non-missing PMS prior to disease flare combined with the last non-missing post-Baseline prior to disease flare or the Baseline endoscopy subscore if the only non-missing post-Baseline endoscopy was after disease flare for the calculation of Mayo Score at Week 52.

Observed Cases (OC): Observed case analysis was performed on data until 1st re-randomization of subjects with a disease flare as a sensitivity analysis.

Multiple Imputation (MI): Visits were imputed in order, where later visits were imputed based upon all previous visits, baseline, treatment group, demographics and other key baseline characteristics. Subjects who discontinued due to lack of efficacy or received rescue medication were forced in as non-responders. The MI analysis was performed as sensitivity analysis.

A description of how Missing Items on Questionnaire Scales was handled was also provided in the SAP.

Other sensitivity analyses of interest

In order to utilize the 12 internal placebo subjects' data, a sensitivity analysis of the second co-primary endpoint was performed in R using Bayesian borrowing. After deriving informative prior distributions for clinical remission rates at Week 52 from historical data for adalimumab and for placebo subjects, posterior probabilities for the difference between adalimumab and placebo subjects in clinical remission rates were calculated considering prior anti-TNF experience.

Subgroup analyses
The subgroups listed below were used for the analyses of co-primary and ranked secondary endpoints including calculation of 95% confidence intervals (CIs).

- Sex (male, female)
- Age (< 13 years, ≥ 13 years)
- Ethnicity (white, non-white)
- Geographic region (North America, Western Europe, Eastern Europe)
- Disease severity per Baseline Mayo Score (≤ 9, > 9)
- Prior exposure to anti-TNF (yes, no)
- Baseline systemic corticosteroid use (yes, no)
- Baseline IMM use (yes, no)
- Weight (< 40 kg, ≥ 40 kg)
- Pancolitis (yes, no)
- Disease duration (≤ Baseline-median, > Baseline-median)
- Baseline high-sensitivity C-reactive protein (hs-CRP) (≤ Baseline-median, > Baseline-median)
- Fecal calprotectin (≤ Baseline-median, > Baseline-median)
- Induction treatment group (I-HD, I-SD, I-HD-OL) [only for Mayo clinical Remission at Week 52 in the mITT population]
- Week 8 remission status per PMS (yes, no) [only for Mayo clinical remissionat Week 52 in the mITT population]

Multiplicity
In the co-primary and ranked secondary endpoints adalimumab dose groups were tested against external placebo in a sequentially rejective multiple test procedure with a familywise type I error of 5%.

A graphical presentation of the multiple testing procedure was provided in the SAP.

Interim analyses
Interim analyses were not planned or performed. An Independent Data Monitoring Committee (IDMC) was established for the study to independently monitor and assess safety and primary efficacy data from the study. No changes to the study were requested by the IDMC.

Changes to the statistical analysis

The study has been subjected to major changes (amendments 4 and 5), including ceasing randomization to DB induction treatment and switching to open-label high induction dose for all subsequently enrolled subjects, as well as ceasing randomization to the internal placebo arm from the maintenance period, reducing the number of planned subjects, and modifying study endpoints and statistical analyses accordingly.

A description of the timing of amendments and the study status at each change was provided in appendix A in the overview. Part of this table is presented below. In the complete table subjects are also reported per study week.

Table 14 Subject disposition per protocol amendment in Study M11-290

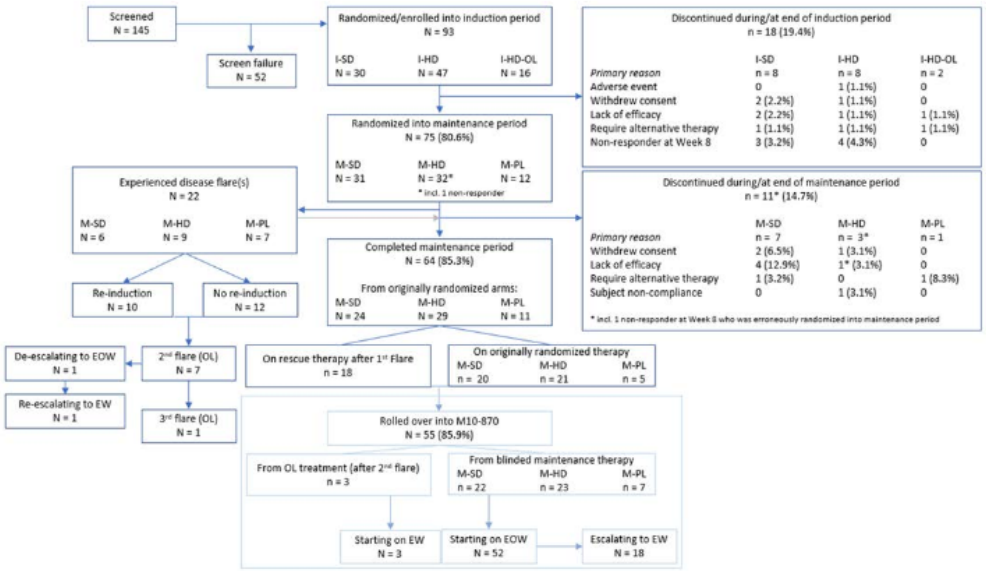
Protocol Amendment	1	2	3	4	5
Subjects that had discontinued/completed the study at the time of Protocol Amendment approval	0	0	5	48	23
Subjects newly enrolled while this Protocol Amendment was the most current version (i.e., on/after approval of this Protocol Amendment up to approval of next Protocol Amendment)	0[a]	20[a]	49[a]	24[a]	0
I-HD	0	13	27	7	0
I-SD	0	7	22	1	0
I-HD-OL	NA	NA	NA	16	0
Subjects ongoing at the time of Protocol Amendment approval	0	0	15	16	17
Week 8	NA	NA	1	1	2
M-HD	NA	NA	0	0	1
M-SD	NA	NA	1	1	1
M-PL	NA	NA	0	0	0

Results

Participant flow

Of the 93 subjects enrolled in main portion of Study M11-290, 64 completed Week 52 of the study.

Table 15 Number and proportion of patients who were screened, randomized, discontinued, flared or changed treatment in study M11-290



EOW = every other week treatment; EW = every week treatment; I-HD = induction high dose group; I-HD-OL = induction high dose group open-label; I-SD = induction standard dose group; M-HD = maintenance high dose group; M-PL = maintenance placebo group; M-SD = maintenance standard dose group; OL = open label.
Note: Percentages are calculated relative to the (sub-)population-N of the respective period.

Table 16 Subject Disposition

	ITT (N = 93) n (%)	ITT-E (N = 77) n (%)	mITT (N = 74) n (%)	mITT-E (N = 62) n (%)	RR (N = 22) n (%)	Safety (N = 93) n (%)
Completed Week 52	--	--	64	53	18	64
M-PL	--	--	11	0	6	11
I-SD	--	--	4	0	2	4
I-HD	--	--	7	0	4	7
M-SD						
I-SD	--	--	5	5	0	5
I-HD/I-HD-OL	--	--	19	19	4	19
I-HD	--	--	13	13	3	13
I-HD-OL	--	--	6	6	1	6
M-HD						
I-SD	--	--	9	9	3	9
I-HD/I-HD-OL	--	--	20	20	5	20
I-HD	--	--	14	14	4	14
I-HD-OL	--	--	6	6	1	6
Discontinued in induction period	18 (19.4)	16 (20.8)	--	--	--	18 (19.4)
I-SD						
Primary reason	8 (8.6)	8 (10.4)	--	--	--	8 (8.6)
Withdrew consent	2 (2.2)	2 (2.6)	--	--	--	2 (2.2)
Lack of efficacy	2 (2.2)	2 (2.6)	--	--	--	2 (2.2)
Requires alternative (or prohibited) therapy	1 (1.1)	1 (1.3)	--	--	--	1 (1.1)
Non-Responder at Week 8	3 (3.2)	3 (3.9)	--	--	--	3 (3.2)
I-HD						
Primary reason	8 (8.6)	8 (10.4)	--	--	--	8 (8.6)
Adverse event	1 (1.1)	1 (1.3)	--	--	--	1 (1.1)
Withdrew consent	1 (1.1)	1 (1.3)	--	--	--	1 (1.1)
Lack of efficacy	1 (1.1)	1 (1.3)	--	--	--	1 (1.1)
Requires alternative (or prohibited) therapy	1 (1.1)	1 (1.3)	--	--	--	1 (1.1)

	ITT (N = 93) n (%)	ITT-E (N = 77) n (%)	mITT (N = 74) n (%)	mITT-E (N = 62) n (%)	RR (N = 22) n (%)	Safety (N = 93) n (%)
Non-Responder at Week 8	4 (4.3)	4 (5.2)	--	--	--	4 (4.3)
I-HD-OL						
Primary reason	2 (2.2)	--	--	--	--	2 (2.2)
Lack of efficacy	1 (1.1)	--	--	--	--	1 (1.1)
Requires alternative (or prohibited) therapy	1 (1.1)	--	--	--	--	1 (1.1)
Discontinued in maintenance period	--	--	10 (13.5)	9 (14.5)	4 (18.2)	11 (11.8)
M-PL						
Primary reason	--	--	1 (1.4)	0	1 (4.5)	1 (1.1)
Requires alternative (or prohibited) therapy	--	--	1 (1.4)	0	1 (4.5)	1 (1.1)
M-SD						
Primary reason	--	--	7 (9.5)	7 (11.3)	2 (9.1)	7 (7.5)
Withdrew consent	--	--	2 (2.7)	2 (3.2)	0	2 (2.2)
Lack of efficacy	--	--	4 (5.4)	4 (6.5)	1 (4.5)	4 (4.3)
Requires alternative (or prohibited) therapy	--	--	1 (1.4)	1 (1.6)	1 (4.5)	1 (1.1)
M-HD						
Primary reason	--	--	2 (2.7)	2 (3.2)	1 (4.5)	3 (3.2)
Withdrew consent	--	--	1 (1.4)	1 (1.6)	0	1 (1.1)
Lack of efficacy	--	--	0	0	0	1 (1.1)
Subject non-compliance	--	--	1 (1.4)	1 (1.6)	1 (4.5)	1 (1.1)

I-HD = induction high dose group; I-HD-OL = induction high dose open-label group; I-SD = induction standard dose group; ITT = intent-to-treat population; M-HD = maintenance high dose group; mITT = modified intent-to-treat population; M-PL = maintenance placebo group; M-SD = maintenance standard dose group; RR = rerandomized population

Table 17 Subjects who flared

Treatment	W/ Re-Induction Dose n (%) [A]	W/O Re-Induction Dose n (%) [A]	Switched to OL 0.6 mg/kg EW n (%) [A]	Switched to OL 40 mg EW n (%) [A]	With Dose De-Escal. EW to EOW n (%) [A]	With Dose De-Escal./ Re-Escal. EW to EOW to EW n (%) [A]
Overall (N=22)	N*=10 (45.5)	N*=12 (54.5)	N*=7 (31.8)	N*=1 (4.5)	N*=1 (4.5)	N*=1 (4.5)
M-PL	4 (40.0)	3 (25.0)	3 (42.9)	1 (100)	0	0
I-SD	1 (10.0)	1 (8.3)	0	0	0	0
I-HD	3 (30.0)	2 (16.7)	3 (42.9)	1 (100)	0	0
M-SD + M-HD total	6 (60.0)	9 (75.0)	4 (57.1)	0	1 (100)	1 (100)
M-SD	3 (30.0)	3 (25.0)	1 (14.3)	0	0	0
I-SD	0	0	0	0	0	0
I-HD/I-HD-OL	3 (30.0)	3 (25.0)	1 (14.3)	0	0	0
I-HD	2 (20.0)	2 (16.7)	0	0	0	0
I-HD-OL	1 (10.0)	1 (8.3)	1 (14.3)	0	0	0
M-HD	3 (30.0)	6 (50.0)	3 (42.9)	0	1 (100)	1 (100)
I-SD	1 (10.0)	2 (16.7)	1 (14.3)	0	0	0
I-HD/I-HD-OL	2 (20.0)	4 (33.3)	2 (28.6)	0	1 (100)	1 (100)
I-HD	2 (20.0)	3 (25.0)	1 (14.3)	0	1 (100)	1 (100)
I-HD-OL	0	1 (8.3)	1 (14.3)	0	0	0

I-SD = induction standard dose group; I-HD = induction high dose group; I-HD-OL = induction high dose open-label group; M-PL = maintenance placebo group; M-SD = maintenance standard dose group; M-HD = maintenance high dose group.
[A] Percentages in the 'Overall' line are relative to total N. All other percentages are relative to the respective N* in that column.

Recruitment

A total of 93 subjects enrolled in the study at 19 sites in Austria, Belgium, Canada, Spain, United Kingdom, Israel, Poland, Slovakia, and the US.

First Subject First Visit:13 October 2014

Last Subject Last Visit: 28 August 2019

Conduct of the study

Protocol amendments:

The original protocol (27 June 2013, 0 subjects) had 5 amendments and 3 administrative changes. The amendments and number of subjects (screened under each amendment) who were subsequently enrolled were as follows:

Amendment 1 (06 September 2013, 2 subjects).

Major changes included: revised the time points of blood sampling measurements for adalimumab concentrations and anti-adalimumab antibodies; revised exclusion criteria and prohibited therapy to clarify that rectal medication for bowel preparation prior to endoscopy was permitted; revised exclusion criteria and concomitant therapy in terms of the number of days that subjects needed to be on stable dose of oral aminosalicylates prior to Baseline; revised study procedures to clarify the process of adjudication to evaluate subject's eligibility for the study and to clarify that subjects who prematurely discontinue from the study before or at Week 26 do not have to undergo an endoscopy at the Premature Discontinuation Visit; ePRO and data collection process details were added.

Amendment 2 (02 April 2014, 26 subjects).

Major changes included: added information about a Japan sub-study with inclusion of approximately 20 subjects; revised steroid tapering requirements; replaced inadequate response criteria with disease flare criteria; clarified Inclusion Criterion 2 regarding the diagnosis of UC confirmed by endoscopy; revised Inclusion Criterion 3 regarding methotrexate (MTX) dosing requirement; added information of antibiotics use in prior therapy and concomitant therapy.

Amendment 3 (28 August 2015, 51 subjects).

Major changes included: revised steroid tapering requirements to allow tapering schedule based on investigator's discretion; revised time point to allow increasing dose of corticosteroid after corticosteroid taper was initiated; revised time point allowing initiation of treatment with corticosteroids, IMMs or aminosalicylates; revised disease flare criteria and time point that rescue therapy based on disease flare could be initiated; updated Inclusion Criterion 2 to clarify the requirement for endoscopy during the Screening period; revised Inclusion Criterion 3 to add guidance on use of 6-TGN levels and revised the required timeline for previous treatment with corticosteroids or IMMs; clarified Exclusion Criterion 24 regarding Hepatitis B; added fecal transplantation within 30 days prior to the Baseline visit to Exclusion Criterion 26; added vedolizumab to the list of prohibited medications; removed stool sample collection for fecal calprotectin and microbiota; removed the collection of serum bone markers; added information about the use of Non-responder imputation (NRI). Administrative Change 3 (22 May 2015) was incorporated into Amendment 3 though it was not specified as such.

Amendment 4 (02 November 2017, 14 subjects [of note, 2 of the 51 subjects screened under Amendment 3 and were subsequently enrolled under Amendment 4]).

Major changes included: ceased randomization to DB induction treatment and enrollment into the standard induction dose group (all subsequent subjects who enter the study were to receive open-label high induction dose); ceased randomization to the internal placebo arm from the maintenance period and modified study endpoints and statistical analyses to reflect said change; reduced the number of planned subjects from approximately 225 (and approximately 20 subjects in the Japan Substudy) to approximately 85 subjects (and up to approximately 20 subjects in the Japan Substudy).

Amendment 5 (20 November 2018, 0 subjects).

Major changes included: modified statistical analyses and ranking of study endpoints; reflected final sample size of 93 subjects (and up to approximately 9 subjects in the Japan Substudy).

Table 18 Protocol Deviations (All Randomized/Enrolled Subjects)

		I-SD/M			I-HD/HD-OL/M				
Protocol deviation	**I-SD/- (N = 8)**	**M-PL (N = 4)**	**M-SD (N = 8)**	**M-HD (N = 10)**	**I-HD/HD-OL/- (N = 10)**	**M-PL (N = 8)**	**M-SD (N = 23)**	**M-HD (N = 22)**	**Total (N = 93)**
Subjects who had at least one protocol deviation	0	1 (25.0)	0	4 (40.0)	1 (10.0)	3 (37.5)	6 (26.1)	5 (22.7)	20 (21.5)
Subject entered into the study even though did not satisfy entry criteria	0	0	0	1 (10.0)	0	1 (12.5)	1 (4.3)	1 (4.5)	4 (4.3)
Inclusion criteria #6 violated	0	0	0	1 (10.0)	0	1 (12.5)	0	1 (4.5)	3 (3.2)
Exclusion criteria #24 violated	0	0	0	0	0	0	1 (4.3)	0	1 (1.1)
Subject received wrong treatment or incorrect dose	0	1 (25.0)	0	2 (20.0)	1 (10.0)	2 (25.0)	4 (17.4)	4 (18.2)	14 (15.1)
Subject received excluded concomitant treatment	0	0	0	0	0	0	1 (4.3)	0	1 (1.1)
Subject developed withdrawal criteria during the study and was not withdrawn	0	0	0	1 (10.0)	0	0	0	0	1 (1.1)

I-SD = induction standard dose group; I-HD = induction high dose group; I-HD-OL = induction high dose open-label group; M-PL = maintenance placebo group; M-SD = maintenance standard dose group; M-HD = maintenance high dose group

Note: All randomized/enrolled subjects = includes all patients randomized to a treatment or enrolled under amendment 4 into the OL treatment group. Screening Failures are excluded.
Both I-SD/- and I-HD/HD-OL/- indicate subjects who discontinued as non-responders from the study at Week 8.
Inclusion criteria: #6: Subjects had an indeterminate TB Screening test.
Exclusion criteria: #24: Subject was enrolled prior to Hepatitis B test results being available.

Baseline data

The MAH states that subject demographic characteristics were generally balanced between treatment groups during Induction and Maintenance. Evaluating across treatment groups, the subject population was predominantly in the categories of ≥ 13 years and ≥ 12 years, White, in Eastern Europe, had no prior exposure to anti-TNF, and had Baseline IMM use. Baseline disease characteristics were generally balanced between treatment groups and consistent with a paediatric subject population with moderate to severe UC.

Table 19 Demographic Characteristics (ITT/Safety Population)

Variable	I-SD (N = 30) n (%)	I-HD (N = 47) n (%)	I-SD+I-HD (N = 77) n (%)	I-HD-OL (N = 16) n (%)	Total (N = 93) n (%)
Sex					
Female	15 (50.0)	23 (48.9)	38 (49.4)	13 (81.3)	51 (54.8)
Male	15 (50.0)	24 (51.1)	39 (50.6)	3 (18.8)	42 (45.2)
Age (year)					
n	30	47	77	16	93
Mean (SD)	14.7 (2.73)	13.8 (3.16)	14.1 (3.01)	13.6 (2.96)	14.1 (2.99)
Median	15.5	15.0	15.0	13.5	15.0
Min, Max	6, 17	5, 17	5, 17	7, 17	5, 17
Age Group 1 (year)					
< 13	4 (13.3)	16 (34.0)	20 (26.0)	5 (31.3)	25 (26.9)
≥ 13	26 (86.7)	31 (66.0)	57 (74.0)	11 (68.8)	68 (73.1)
Age Group 2 (year)					
< 12	3 (10.0)	12 (25.5)	15 (19.5)	4 (25.0)	19 (20.4)
≥ 12	27 (90.0)	35 (74.5)	62 (80.5)	12 (75.0)	74 (79.6)
Race					
White	28 (93.3)	45 (95.7)	73 (94.8)	15 (93.8)	88 (94.6)
Black	1 (3.3)	2 (4.3)	3 (3.9)	0	3 (3.2)
Asian	1 (3.3)	0	1 (1.3)	0	1 (1.1)
Multiple	0	0	0	1 (6.3)	1 (1.1)
Geographic region					
North America	2 (6.7)	8 (17.0)	10 (13.0)	3 (18.8)	13 (14.0)
Western Europe	3 (10.0)	4 (8.5)	7 (9.1)	1 (6.3)	8 (8.6)
Eastern Europe	25 (83.3)	35 (74.5)	60 (77.9)	12 (75.0)	72 (77.4)

Prior exposure to anti-TNF					
Yes	6 (20.0)	8 (17.0)	14 (18.2)	1 (6.3)	15 (16.1)
No	24 (80.0)	39 (83.0)	63 (81.8)	15 (93.8)	78 (83.9)
Baseline systemic corticosteroid use[a]					
Yes	13 (43.3)	22 (46.8)	35 (45.5)	9 (56.3)	44 (47.3)
No	17 (56.7)	25 (53.2)	42 (54.5)	7 (43.8)	49 (52.7)
Baseline immunosuppressants (IMM) use					
Yes	21 (70.0)	29 (61.7)	50 (64.9)	5 (31.3)	55 (59.1)
No	9 (30.0)	18 (38.3)	27 (35.1)	11 (68.8)	38 (40.9)
Weight (kg)					
< 40	3 (10.0)	9 (19.1)	12 (15.6)	3 (18.8)	15 (16.1)
40 - < 60	17 (56.7)	20 (42.6)	37 (48.1)	9 (56.3)	46 (49.5)
≥ 60	10 (33.3)	18 (38.3)	28 (36.4)	4 (25.0)	32 (34.4)

I-HD = induction high dose group; I-HD-OL = induction high dose open-label group; I-SD = induction standard dose group; ITT = intent-to-treat population; Min = minimum; Max = maximum; SD = standard deviation; TNF = tumor necrosis factor

a. True Baseline systemic corticosteroid use is displayed. One subject was randomized in the stratum "No," but actually had Baseline systemic corticosteroid use documented.

Note: Percentages calculated on non-missing values.

Table 20 Baseline disease Characteristics (ITT/Safety Population)

Variable	I-SD (N = 30)	I-HD (N = 47)	I-HD-OL (N = 16)	Total (N = 93)
Duration of UC (year)				
N	30	47	16	93
Mean (SD)	1.9 (1.65)	2.6 (2.59)	2.0 (2.13)	2.3 (2.25)
Median	1.1	1.8	1.3	1.5
Min, Max	0.3, 5.3	0.4, 11.4	0.3, 9.0	0.3, 11.4
Site of UC - n (%)				
Left sided UC	10 (33.3)	22 (46.8)	5 (31.3)	37 (39.8)
Extensive UC/pancolitis	20 (66.7)	25 (53.2)	11 (68.8)	56 (60.2)
Mayo Score				
N	30	47	16	93
Mean (SD)	7.9 (1.21)	7.8 (1.28)	7.8 (1.08)	7.8 (1.21)
Median	7.9	7.6	7.4	7.8
Min, Max	6.0, 10.0	6.0, 10.8	6.0, 9.6	6.0, 10.8
Partial Mayo Score				
N	30	47	16	93
Mean (SD)	5.7 (1.14)	5.6 (1.24)	5.6 (1.05)	5.6 (1.17)
Median	5.8	5.4	5.3	5.6
Min, Max	4.0, 8.0	3.6, 8.8	4.0, 7.6	3.6, 8.8
PUCAI total score				
N	30	47	16	93
Mean (SD)	39.8 (18.58)	41.6 (16.20)	43.4 (13.87)	41.4 (16.52)
Median	40.0	42.5	45.0	45.0
Min, Max	0.0, 72.5	15.0, 80.0	25.0, 72.5	0.0, 80.0
IMPACT III total score				
N	27	44	15	86
Mean (SD)	110.9 (22.27)	110.0 (24.03)	107.4 (19.25)	109.8 (22.50)
Median	105.0	113.0	111.0	111.5

Min, Max	78.0, 155.0	63.0, 159.0	76.0, 144.0	63.0, 159.0
WPAI - absenteeism (%)				
N	20	29	8	57
Mean (SD)	12.8 (16.72)	12.5 (19.75)	23.1 (29.27)	14.1 (20.26)
Median	0.0	7.9	13.4	7.9
Min, Max	0.0, 50.0	0.0, 100.0	0.0, 71.1	0.0, 100.0
WPAI - presenteeism (%)				
N	20	30	8	58
Mean (SD)	44.5 (26.05)	44.0 (28.48)	42.5 (23.75)	44.0 (26.62)
Median	45.0	45.0	45.0	45.0
Min, Max	0.0, 80.0	0.0, 100.0	0.0, 80.0	0.0, 100.0
WPAI - work impairment (%)				
N	20	29	8	57
Mean (SD)	49.7 (28.94)	50.4 (26.68)	50.8 (30.64)	50.2 (27.52)
Median	57.8	54.3	48.6	55.6
Min, Max	0.0, 86.0	0.0, 100.0	0.0, 94.2	0.0, 100.0
WPAI - activity impairment (%)				
N	30	47	16	93
Mean (SD)	42.0 (26.57)	47.0 (26.61)	53.1 (29.60)	46.5 (27.09)
Median	50.0	40.0	50.0	50.0
Min, Max	0.0, 80.0	0.0, 100.0	0.0, 100.0	0.0, 100.0
hs-CRP [mg/L]				
N	28	41	16	85
Mean (SD)	7.6 (26.76)	4.9 (8.66)	3.7 (8.70)	5.6 (16.78)
Median	1.2	1.4	1.3	1.3
Min, Max	0.1, 142.6	0.1, 35.2	0.1, 35.9	0.1, 142.6

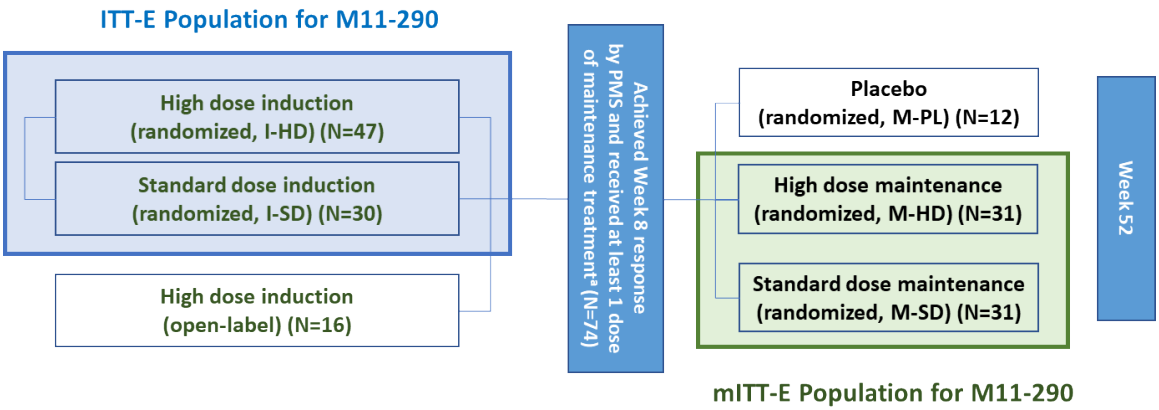
hs-CRP = high-sensitivity C-reactive protein; I-HD = induction high dose group; I-HD-OL = induction high dose open-label group; I-SD = induction standard dose group; ITT = intent-to-treat population; Max = maximum; Min = minimum; PUCAI = Pediatric Ulcerative Colitis Activity Index; SD = standard deviation; UC = ulcerative colitis; WPAI = Work Productivity and Activity Impairment Questionnaire

Numbers analysed

Table 21 Study M11-290 Key Analysis Sets

Analysis Sets	Study Population
Intent-To-Treat (ITT) population N = 93	All subjects who received at least one dose of the study medication during induction period.
ITT-E population N = 77	A subpopulation of the ITT population, where subjects who received open-label high induction dose were excluded. This was the primary population for the confirmatory analysis of the Week 8 co-primary endpoint.
Modified ITT (mITT) population N = 74	All Week 8 PMS responders who were randomized at Week 8 and received at least one dose of the study medication during maintenance period. Of note, one Week 8 PMS non-responder who was erroneously randomized into maintenance period was, per definition, not included in this population.
mITT-E population N = 62	A subpopulation of the mITT population, where subjects who received Placebo were excluded. This was the primary population for the confirmatory analysis of the Week 52 co-primary endpoint and ranked secondary endpoints.

Figure 24 Key Analysis Sets for the Primary Efficacy Analysis of Study M11-290



Note: One additional patient without response by PMS was randomized and included in the maintenance period safety analyses.

Outcomes and estimation

The first co-primary endpoint of clinical remission per PMS (defined as ≤ 2 and no individual subscore > 1) at Week 8 was achieved by 59.6% of subjects randomized to the adalimumab I-HD group and 43.3% of subjects randomized to the I-SD group (NRI) (Table 22). A statistically significantly greater proportion of subjects in the combined adalimumab I-HD and I-SD group as well as the I-HD group achieved clinical remission as measured by PMS at Week 8 compared with the external placebo control. A high proportion of subjects in the adalimumab I-HD-OL group (11/16 [68.8%]) also achieved clinical remission as measured by PMS at Week 8.

The second co-primary endpoint clinical remission per Mayo Score (defined as a Mayo Score ≤ 2 and no individual subscore > 1) at Week 52 in PMS responders at Week 8 was achieved by 45.2% of subjects in

the adalimumab M-HD group and 29.0% of subjects in the M-SD group (NRI) (Table 22). A statistically significantly greater proportion of subjects in the combined adalimumab M-HD and M-SD group as well as M-HD group who were Week 8 responders per PMS achieved clinical remission as measured by Mayo Score at Week 52 compared with the external placebo control. Four of 12 subjects (33.3%) in the M-PL group who were Week 8 responders per PMS achieved clinical remission as measured by Mayo Score at Week 52.

Table 22 Study M11-290 Co-Primary Endpoints Results

Endpoint	Treatment Groups	n (%)	95% Confidence Interval[a]	*P* value[b]
Clinical Remission per PMS at Week 8 (NRI, ITT-E Population; 1st Co-Primary Endpoint)	I-HD + I-SD (N = 77)	41 (53.2)	(41.52, 64.71)	< 0.001[c]
	I-HD (N = 47)	28 (59.6)	(44.27, 73.63)	< 0.001[c]
	I-SD (N = 30)	13 (43.3)	(25.46, 62.57)	0.001
Clinical Remission per FMS at Week 52 in Week 8 Responders per PMS (NRI, mITT-E Population; 2nd Co-Primary Endpoint)	M-HD+M-SD (N = 62)	23 (37.1)	(25.16, 50.31)	< 0.001[c]
	M-HD (N = 31)	14 (45.2)	(27.32, 63.97)	< 0.001[c]
	M-SD (N = 31)	9 (29.0)	(14.22, 48.04)	0.125

FMS = Full Mayo Score; I-HD = induction high dose group; I-SD = induction standard dose group; ITT = intent-to-treat population; M-HD = maintenance high dose group.; mITT = modified intent-to-treat population; M-SD = maintenance standard dose group; NRI = non-responder imputation; PMS = Partial Mayo Score

a) Clopper-Pearson confidence interval for proportion in remission.

b) Nominal P values from a 1-sample 2-sided chi-square test.

c) Statistical significance per pre-specified sequentially rejective multiple test procedure.

Note: Clinical remission per PMS= PMS ≤ 2 and no individual subscore > 1. Clinical remission per FMS = FMS ≤ 2 and no individual subscore > 1

ITT-E = Subpopulation of the ITT population, where subjects who received open-label high induction dose were excluded. mITT-E = Subpopulation of the mITT population, where subjects who received placebo were excluded. One subject was erroneously randomized into M-HD and received a maintenance dose but was not a responder at Week 8. This subject is not part of mITT-E per definition but is part of the ADA set -E for integrated analyses.

External placebo rate for statistical comparison = 19.83% for 1st co-primary endpoint, 18.37% for 2nd co-primary endpoint.

Non-responder imputation: Missing data was imputed as not having met the endpoint. Subjects re-randomized due to disease flare were considered as not having met the endpoint at and after their 1stdisease flare.

Ranked Secondary outcomes

- First ranked secondary endpoint: Mayo clinical response (defined as a decrease in Mayo Score ≥ 3 points and ≥ 30% from baseline) at Week 52 in Week 8 responders per PMS.

Over 60% of subjects in both adalimumab maintenance treatment groups achieved Mayo clinical response (

Table 23).

A statistically significantly greater proportion of subjects in the combined adalimumab M-HD and M-SD group as well as both the M-HD and M-SD groups individually who were Week 8 responders per PMS achieved Mayo clinical response at Week 52 compared with the external placebo control.

Four of 12 subjects (33.3%) in the M- PL group who were Week 8 responders per PMS achieved clinical response as measured by Mayo Score at Week 52.

- Second ranked secondary endpoint: Mucosal healing at Week 52 as measured by Mayo endoscopy subscore (defined as ≤ 1) in Week 8 PMS responders

Mucosal healing was achieved by 51.6% of subjects who were randomized to the adalimumab M-HD group and 38.7% of subjects in the M-SD group (

Table 23).

A statistically significantly greater proportion of subjects in the combined adalimumab M-HD and M-SD group as well as the M-HD group who were Week 8 responders per PMS achieved mucosal healing at Week 52 as measured by Mayo endoscopy subscore compared with the external placebo control.

Four of 12 subjects (33.3%) in the M-PL group who were Week 8 responders per PMS achieved mucosal healing at Week 52 as measured by Mayo endoscopy subscore.

- Third ranked secondary endpoint: Clinical remission per Mayo Score at Week 52 among subjects in clinical remission per PMS at Week 8

Clinical remission per Mayo score at Week 52 was reported by 45.5% of subjects in the adalimumab M-HD group and 42.9% of subjects in the M-SD group (

Table 23).

A statistically significantly greater proportion of subjects in the combined adalimumab M-HD and M-SD group as well as the M-HD group who were Week 8 remitters per PMS achieved Mayo clinical remission at Week 52 compared with the external placebo control.

Three of 8 subjects (37.5%) in the M-PL group who were Week 8 remitters per PMS achieved Mayo clinical remission at Week 52.

- Fourth ranked secondary endpoint: Proportion of subjects receiving systemic corticosteroids [UC related or non-UC related] at Baseline who discontinued systemic corticosteroids prior to Week 52 and were in Mayo clinical remission at Week 52 in Week 8 responders per PMS)

A numerically greater proportion of subjects in the combined adalimumab M-HD and M-SD group (31.0%) who were receiving corticosteroids at Baseline and were Week 8 responders per PMS were able to discontinue corticosteroids prior to Week 52 and achieved Mayo clinical remission at Week 52 compared with the external placebo control (

Table 23).

Two of 5 subjects (40.0%) in the M- PL group who were receiving corticosteroids at Baseline and were Week 8 responders per PMS were able to discontinue corticosteroids prior to Week 52 and achieved Mayo clinical remission at Week 52.

Table 23 Study M11-290 Ranked Secondary Endpoint Results

Endpoint	Treatment Groups	n (%)	95% Confidence Interval[a]	*P* value[b]
Clinical Response per FMS at Week 52 in Week 8 Responders per PMS (NRI, mITT-E Population; 1st Ranked Secondary Endpoint)	M-HD + M-SD (N = 62)	40 (64.5)	(51.34, 76.26)	< 0.001[c]
	M-HD (N = 31)	21 (67.7)	(48.63, 83.32)	< 0.001[c]
	M-SD (N = 31)	19 (61.3)	(42.19, 78.15)	< 0.001[c]
Mucosal Healing at Week 52 in Week 8 Responders per PMS (NRI, mITT-E Population; 2nd Ranked Secondary Endpoint)	M-HD + M-SD (N = 62)	28 (45.2)	(32.48, 58.32)	< 0.001[c]
	M-HD (N = 31)	16 (51.6)	(33.06, 69.85)	< 0.001[c]
	M-SD (N = 31)	12 (38.7)	(21.85, 57.81)	0.025
Clinical Remission per FMS at Week 52 in Week 8 Remitters per PMS (NRI, mITT-E Population; 3rd Ranked Secondary Endpoint)	M-HD + M-SD (N = 43)	19 (44.2)	(29.08, 60.12)	< 0.001[c]
	M-HD (N = 22)	10 (45.5)	(24.39, 67.79)	< 0.001[c]
	M-SD (N = 21)	9 (42.9)	(21.82, 65.98)	< 0.001
Corticosteroid-Free Clinical Remission per FMS at Week 52 in Week 8 Responders per PMS (NRI, mITT-E Population; 4th Ranked Secondary Endpoint)	M-HD + M-SD (N = 29)	9 (31.0)	(15.28, 50.83)	0.381
	M-HD (N = 16)	5 (31.3)	(11.02, 58.66)	0.502
	M-SD (N = 13)	4 (30.8)	(9.09, 61.43)	0.573

FMS = Full Mayo Score; M-HD = maintenance high dose group; mITT = modified intent-to-treat; M-SD = maintenance standard dose group; NRI = non-responder imputation; PMS = Partial Mayo Score

a. Clopper-Pearson confidence interval for proportion in remission/response.

b. Nominal *P* values from a 1-sample 2-sided chi-square test.

c. Statistical significance per pre-specified sequentially rejective multiple test procedure.

Note: Clinical response per FMS = decrease in Mayo Score ≥ 3 points and ≥ 30% from Baseline. Mucosal healing (centrally assessed) = Mayo endoscopy subscore as ≤ 1. Clinical remission per FMS = FMS ≤ 2 and no individual subscore > 1). Corticosteroid-free remission per FMS = Subjects receiving systemic corticosteroids (UC related or non-UC related) at Baseline who discontinued systemic corticosteroids prior to Week 52 and were in Mayo clinical remission.

mITT-E = Subpopulation of the mITT population, where subjects who received placebo were excluded. One subject was erroneously randomized into M-HD and received a maintenance dose but was not a responder at Week 8. This subject is not part of mITT-E per definition but is part of the ADA set -E for integrated analyses.

External placebo rate for statistical comparison = 26.10% for 1st ranked secondary endpoint, 22.03% for 2nd ranked secondary endpoint, 14.79% for 3rd ranked secondary endpoint, 24.08% for 4th ranked secondary endpoint (95% confidence interval upper limits of point estimates from meta-analysis).

Non-responder imputation: Missing data was imputed as not having met the endpoint. Subjects re-randomized due to disease flare were considered as not having met the endpoint at and after their 1st disease flare.

Other outcomes

When the original protocol for Study M11-290 was finalized in 2013, the primary endpoint definitions were aligned with the requirements from all relevant regulatory agencies and the scientific community. European Medicines Agency's recently updated "Guideline on the Development of New Medicinal Products

for the Treatment of Ulcerative Colitis" as of 2018, which mainly focuses on studies in adults, now requests cessation of rectal bleeding for the definition of remission. Although the pre-specified and previously agreed upon primary endpoint definitions in Study M11-290 do not specifically entail a RBS of 0, the available efficacy results provide evidence of clinically meaningful improvement of RBS over time. At Week 8 RBS improved from Baseline by 0.86 and 1.07 points in subjects on the I-SD and I-HD dose regimens, respectively. In addition, at Week 52, RBS improved from Baseline by 1.48 and 1.36 points in subjects on the M-SD and M-HD doses, respectively. Furthermore, RBS data corroborated the clinical remission rates per PMS at Week 8 and per FMS at Week 52.

Clinical remission per PUCAI at Week 8 was achieved by 46.8% and 33.3% of subjects in the adalimumab I-HD and I-SD groups, respectively. PUCAI response at Week 52 in Week 8 PMS responders was achieved by 51.6% and 58.1% of subjects in the adalimumab M-HD and M-SD groups, respectively. PUCAI remission at Week 52 in Week 8 PMS responders was reported by 58.1% and 45.2% of subjects in the adalimumab M-HD and M-SD groups, respectively. Corticosteroid-free PUCAI clinical remission at Week 52 in subjects receiving corticosteroids at Baseline and Week 8 PMS responders was reported by 43.8% and 38.5% of subjects in the adalimumab M-HD and M-SD groups, respectively.

Overall, these clinical outcomes were accompanied by UC-related hospitalization rates of < 20% and very low colectomy rates (1.1%) in the adalimumab-treated subjects. The QOL for the adalimumab-treated subjects as well as work productivity and activity impairment for their caregivers also showed clinically meaningful improvements as early as Week 8 compared to Baseline during the study as measured by IMPACT III and Work Productivity and Activity Impairment Questionnaire (WPAI).

Clinically meaningful improvement in height velocity was reported for subjects who received either of the adalimumab maintenance doses through the study. While subjects demonstrated some evidence of reduced linear growth rate at Baseline (mean z-score of –0.843), subjects experienced an increase of height velocity subsequent to adalimumab treatment by a change from baseline in mean z score of 0.798 and 1.154 at Weeks 26 and 52, respectively. Clinically relevant improvement in body mass index at Weeks 26 and 52 was achieved by subjects who received the adalimumab high maintenance dose as a change from Baseline of 0.490 mg/kg2 and 0.566 mg/kg2, respectively.

Re-Induction Following Disease Flare

Among adalimumab-treated subjects who experienced their first disease flare during Maintenance, little to no difference was observed in the proportion of subjects with clinical response and clinical remission per FMS at Week 52 in Week 8 responders per PMS with re-induction dose compared to without re-induction dose, although a numerically greater proportion of subjects who received a re-induction dose (33.3%) demonstrated clinical response at Week 52 compared to subjects without re-induction (22.2%). However, the number of subjects for each subgroup is too small to be conclusive.

Table 24 FMS Response and FMS remission at Week 52 in Week 8 responders who flared- with and without Re-induction dose

	With Re-Induction Dose				
Endpoint Endpoint Met	M-SD	M-HD	Total	M-PL	Total
FMS Response at Week 52 in Week 8 PMS Responders	N=3	N=3	N=6	N=4	N=10
Yes	1 (33.3)	1 (33.3)	2 (33.3)	1 (25.0)	3 (30.0)
No	2 (66.7)	2 (66.7)	4 (66.7)	3 (75.0)	7 (70.0)
95% Confidence Interval [A]	(0.84, 90.57)	(0.84, 90.57)	(4.33, 77.72)	(0.63, 80.59)	(6.67, 65.25)
FMS Remission at Week 52 in Week 8 PMS Responders	N=3	N=3	N=6	N=4	N=10
Yes	0	0	0	1 (25.0)	1 (10.0)
No	3 (100)	3 (100)	6 (100)	3 (75.0)	9 (90.0)
95% Confidence Interval [A]	(0.00, 70.76)	(0.00, 70.76)	(0.00, 45.93)	(0.63, 80.59)	(0.25, 44.50)

Endpoint Endpoint Met	Without Re-Induction Dose M-SD	 M-HD	 Total	 M-PL	 Total
FMS Response at Week 52 in Week 8 PMS Responders	N=3	N=6	N=9	N=3	N=12
Yes	1 (33.3)	1 (16.7)	2 (22.2)	1 (33.3)	3 (25.0)
No	2 (66.7)	5 (83.3)	7 (77.8)	2 (66.7)	9 (75.0)
95% Confidence Interval [A]	(0.84, 90.57)	(0.42, 64.12)	(2.81, 60.01)	(0.84, 90.57)	(5.49, 57.19)
FMS Remission at Week 52 in Week 8 PMS Responders	N=3	N=6	N=9	N=3	N=12
Yes	0	0	0	0	0
No	3 (100)	6 (100)	9 (100)	3 (100)	12 (100)
95% Confidence Interval [A]	(0.00, 70.76)	(0.00, 45.93)	(0.00, 33.63)	(0.00, 70.76)	(0.00, 26.46)

Ancillary analyses

For the subgroup analysis, a higher proportion of prior anti-TNF naïve subjects achieved the co-primary efficacy endpoints compared to subjects with prior anti-TNF. When analysing subgroups by geographic regions, a higher proportion of subjects in Eastern Europe achieved the co-primary efficacy endpoints compared to subjects in North America and Western Europe; however, the number of subjects for the Western countries subgroups are too small to be conclusive.

Study M10-870: A Multi-Center, Open-Label Study of the Human Anti-TNF Monoclonal Antibody Adalimumab to Evaluate Long-Term Safety and Tolerability of Repeated Administration of Adalimumab in Paediatric Subjects with Ulcerative Colitis Who Completed the Study M11-290

Methods

Study M10-870 is a Phase 3, multi-centre, OL study designed to evaluate the long-term maintenance of clinical response, safety and tolerability of adalimumab in paediatric subjects with UC.

All subjects receive OL therapy beginning at the baseline visit (Week 52 visit from the Study M11-290) as follows:

- Subjects who enrolled into the study from blinded treatment in Study M11-290 receive OL adalimumab 0.6 mg/kg (maximum of 40 mg) every other week (eow).
- Subjects who received OL adalimumab in Study M11-290 maintain the same dose in Study M10-870.

The duration of the study is up to 298 weeks, which includes a 288-week OL maintenance period and a 70-day follow-up phone call. The submitted clinical study report (CSR) is an interim report for Study M10-870 with a data cut-off date of 28 August 2019 and covers the Main Study, which includes all subjects enrolled outside of Japan. A separate interim CSR is being prepared for the Japan Substudy, which includes only the subjects enrolled at sites in Japan.

Study participants

Paediatric subjects with UC who participated in, and successfully completed, Protocol M11-290 through Week 52 were eligible to enrol as long as they met all of the Study M10-870 inclusion criteria and none of the exclusion criteria.

Key eligibility criteria for Study M10-870 included: subject must have successfully enrolled in and completed Protocol M11-290 through Week 52; and the subject is judged to be in good medical condition, as determined by the Principal Investigator based upon results of clinical and laboratory evaluations done throughout the preceding ulcerative colitis Study M11-290.

Key exclusion criteria for Study M10-870 included: subject is considered by the Investigator, for any reason, to be an unsuitable candidate for continuing therapy in the Study M10-870; subject with Crohn's disease or indeterminate colitis; subject who is planning surgical bowel resection at any time point while enrolled in the study; known hypersensitivity to adalimumab or its excipients; or current diagnosis of fulminant colitis and/or toxic megacolon.

Treatments

All subjects received open-label therapy as follows beginning at the Baseline Visit in Study M10-870: subjects who enrolled into the study from blinded treatment in Study M11-290 received open label 0.6 mg/kg (maximum of 40 mg) eow of adalimumab; or subjects who received open label adalimumab in Study M11-290 maintained the same dose in Study M10-870. Subjects who experienced disease flare received either of the following: subjects who were on 0.6 mg/kg (maximum dose of 40 mg, weight based) eow of adalimumab could receive 0.6 mg/kg (maximum of 40mg, weight based) every week (ew); or subjects who were on 0.6 mg/kg ew of adalimumab could receive 40 mg ew (maximum dose) of adalimumab.

The duration of Treatment was up to 288 weeks of OL treatment.

Objectives

The objective of the study is to evaluate the long-term safety, tolerability, and maintenance of clinical response, of repeated administration of adalimumab in paediatric subjects with UC who participated in, and successfully completed, Protocol M11-290 through Week 52.

Outcomes/endpoints

There were no primary or secondary efficacy variables for this study.

The efficacy variables were:

- the proportion of subjects who achieve clinical remission as measured by Partial Mayo Score (PMS) (defined as a PMS ≤ 2 and no individual subscore > 1) overtime;
- the proportion of subjects who achieve clinical response as measured by PMS (defined as a decrease in PMS ≥ 2 points and ≥ 30% from Study M11-290-Baseline) over time;
- the proportion of subjects who achieve PUCAI remission (defined as < 10) over time;
- the proportion of subjects who achieve PUCAI response (defined as a decrease in PUCAI ≥ 20 points from Study M11-290 Baseline);
- change from Baseline in total IMPACT III Quality of Life score and subscores over time for subjects at least 9 years old at Baseline;
- change from Baseline in Work Productivity and Activity Impairment Questionnaire (WPAI) scores over time;
- change from Baseline in "z" scores for height over time;

- change from Baseline in body mass index over time
- change from Baseline in "z" scores for weight-for-age over time;
- change from Baseline in albumin and total protein over time;
- change from Baseline in hemoglobin, hematocrit, red blood cell count over time;
- change from Baseline in hs-CRP levels over time;
- the proportion of subjects at appropriate Tanner stage over time;
- the proportion of subjects in Mayo Score clinical response over time (for subjects with available Mayo Score);
- the proportion of subjects in Mayo Score clinical remission over time (for subjects with available Mayo Score);
- the proportion of subjects who achieve mucosal healing over time as measured by Mayo endoscopy subscore (defined as ≤ 1, for subjects with available Mayo Score)
- the proportion of subjects in 9 point Mayo score (without physician global assessment [PGA]) clinical remission over time (for subjects with available Mayo Score)
- and the proportion of subjects in 6-point Mayo Score (without PGA and endoscopy subscore) clinical remission over time (for subjects with available Mayo Score)

Sample size

Subjects who successfully completed Study M11-290 through Week 52 were potentially eligible to participate in this study. A total of 55 subjects were enrolled.

Randomisation

Not applicable

Blinding (masking)

Not applicable

Statistical methods

Efficacy and Safety: the Full Analysis Set was used for all analyses and included all subjects who received at least one dose of adalimumab in Study M10-870.

Results

Participant flow

Table 25 Subject Disposition (FAS)

Status	Adalimumab
Enrolled	55
Treated	55
Completed Study[a]	0
Discontinued	14 (25.5)
Adverse event	2 (3.6)
Withdrew consent	2 (3.6)
Lost to follow-up	1 (1.8)
Lack of efficacy	10 (18.2)
Requires alternative (or prohibited) therapy	1 (1.8)
Subject non-compliance	1 (1.8)
Primary Reason for Discontinuation	14 (25.5)
Adverse event	0
Withdrew consent	2 (3.6)
Lost to follow-up	1 (1.8)
Lack of efficacy	9 (16.4)
Requires alternative (or prohibited) therapy	1 (1.8)
Subject non-compliance	1 (1.8)

FAS = full analysis set

a. The study is currently ongoing.

Recruitment

A total of 55 subjects were enrolled and randomized at 11 sites in Poland, Slovakia, the United Kingdom, and the US.

The first subjects started the study in November 2015; as of the cut-off date of 28 August 2019, no subjects completed the study as the study was still ongoing.

A total of 3 subjects received adalimumab 0.6 mg/kg (maximum dose of 40mg) ew (hereafter referred to as the ew dose) at Baseline and 52 subjects received adalimumab 0.6 mg/kg (maximum dose of 40 mg) eow (hereafter referred to as the eow dose) at Baseline.

Of these subjects, 18 subjects had at least 1 dose escalation from the eow dose to the ew dose; no subjects had dose de-escalation from the ew dose to the eow dose; and no subjects had dose re-escalation from the eow dose to the ew dose.

The rate of discontinuation was 25.5%. The primary reason for discontinuation reported by most subjects was lack of efficacy.

Conduct of the study

Protocol amendments

The original protocol (07 May 2015, 2 subjects [2 Main Study; 0 Japan Substudy]) had 3 amendments and 1 administrative change. The amendments and number of subjects enrolled under each amendment were as follows:

- Amendment 1 (17 August 2015, 27 subjects [25 Main Study; 2 Japan Substudy]). Major changes included:
    - Added criteria for reduction or discontinuation of concomitant medications;
    - Further clarified the treatment of subjects with persistently uncontrolled disease during the study;

- Excluded active viral infection (exclusion Criterion 6);
- Excluded subjects with fulminant colitis and/or toxic megacolon (exclusion Criterion 11);
- Added vedolizumab to the list of prohibited medications; and
- Removed stool samples collection for faecal calprotectin.

- Amendment 2 (09 June 2017, 30 subjects [28 Main Study; 2 Japan Substudy]). Major changes included:
  - Extended the study duration from 106 weeks to 298 weeks;
  - Removed the further collection of pharmacokinetic, immunogenicity and serologic marker samples; and
  - Extended the duration between study visits beyond Week 120 to every 6 months, added a phone contact at 3-month intervals between scheduled visits, and the frequency of specific study procedures such as collection of high-sensitivity C-reactive protein (hs-CRP) was reduced.
- Amendment 3 (30 July 2019, 0subjects). Major changes included:
  - Added interim analysis, and
  - Corrected the time points for urinalysis.

Table 26 Protocol Deviations (FAS)

Protocol Deviations	Adalimumab (N = 55)
Subjects who had at least one protocol deviation	5 (9.1)
Subject entered into the study even though did not satisfy entry criteria	0
Subject received wrong treatment or incorrect dose	5 (9.1)
Subject received excluded concomitant treatment	0
Subject developed withdrawal criteria during the study and was not withdrawn	0

FAS = full analysis set

Baseline data

At Baseline for Study M10-870, the majority of subjects were white (94.5%) and female (54.5%) with an overall mean age of 14.7 years. At Baseline, subjects had a mean duration of UC of 3.6 years. Baseline characteristics for subjects in Study M10-870 Main were generally consistent with inactive or mild UC disease (mean Mayo score 2.1, mean PMS 1.2) after these subjects had been treated with adalimumab for up to 52 weeks in Study M11-290 prior to entering Study M10-870.

Outcomes and estimation

Clinical remission and response per PMS (**Table 27**) and PUCAI (CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward

Note: Clinical remission per Partial Mayo Score was defined as PMS ≤ 2 and no individual subscore > 1.

Baseline is defined as the last non-missing value before the baseline visit date (i.e., at or before the Week 52 visit form Study M11-290 Main) and prior to the first dose of Study M10-870 Main.

Last observation carried forward: Missing data was imputed by carrying forward the last non-missing post-baseline observation. For interim analyses, missing values was imputed up to the timepoint a patient could have potentially reached at the data cutoff for analyses.

Due to the ongoing status of the study, not all subjects could have reached each study timepoint, therefore the overall N decreases.

Table 28) seemed sustained for subjects receiving adalimumab through Week 168.

As the study is ongoing, the number of subjects at each timepoint decreased over time, making conclusions at later timepoints less robust.

The quality of life of subjects receiving adalimumab and the work productivity of their caregivers seem to be sustained as measured by IMPACT III and WPAI assessments from Baseline through Weeks 120 and 72, respectively.

Table 27 Proportion of Subjects Who Achieved Clinical Remission per Partial Mayo Score Over Time in Study M10-870 (FAS; LOCF)

	Adalimumab		
Timepoint	**N**	**n (%)**	**95% CI**
Baseline	55	43 (78.2)	(64.99, 88.19)
Week 4	52	44 (84.6)	(71.92, 93.12)
Week 8	52	40 (76.9)	(63.16, 87.47)
Week 12	49	41 (83.7)	(70.34, 92.68)
Week 24	46	31 (67.4)	(51.98, 80.47)
Week 36	43	31 (72.1)	(56.33, 84.67)
Week 48	38	25 (65.8)	(48.65, 80.37)
Week 60	37	27 (73.0)	(55.88, 86.21)
Week 72	33	23 (69.7)	(51.29, 84.41)
Week 84	32	20 (62.5)	(43.69, 78.90)
Week 96	28	14 (50.0)	(30.65, 69.35)
Week 108	25	13 (52.0)	(31.31, 72.20)
Week 120	23	10 (43.5)	(23.19, 65.51)
Week 144	16	7 (43.8)	(19.75, 70.12)
Week 168	9	4 (44.4)	(13.70, 78.80)
Week 192	3	1 (33.3)	(0.84, 90.57)

CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward

Note: Clinical remission per Partial Mayo Score was defined as PMS ≤ 2 and no individual subscore > 1.

Baseline is defined as the last non-missing value before the baseline visit date (i.e., at or before the Week 52 visit form Study M11-290 Main) and prior to the first dose of Study M10-870 Main.

Last observation carried forward: Missing data was imputed by carrying forward the last non-missing post-baseline observation. For interim analyses, missing values was imputed up to the timepoint a patient could have potentially reached at the data cutoff for analyses.

Due to the ongoing status of the study, not all subjects could have reached each study timepoint, therefore the overall N decreases.

Table 28 Proportion of Subjects with Remission per PUCAI Over Time in Study M10-870 (FAS; LOCF)

	Adalimumab		
Timepoint	**N**	**n (%)**	**95% CI**
Baseline	55	40 (72.7)	(59.04, 83.86)
Week 4	52	44 (84.6)	(71.92, 93.12)
Week 8	52	39 (75.0)	(61.05, 85.97)
Week 12	49	40 (81.6)	(67.98, 91.24)
Week 24	46	30 (65.2)	(49.75, 78.65)
Week 36	43	30 (69.8)	(53.87, 82.82)
Week 48	38	24 (63.2)	(45.99, 78.19)
Week 60	37	25 (67.6)	(50.21, 81.99)
Week 72	33	24 (72.7)	(54.48, 86.70)
Week 84	32	22 (68.8)	(49.99, 83.88)
Week 96	28	16 (57.1)	(37.18, 75.54)
Week 108	25	15 (60.0)	(38.67, 78.87)
Week 120	23	13 (56.5)	(34.49, 76.81)
Week 144	16	9 (56.3)	(29.88, 80.25)
Week 168	9	4 (44.4)	(13.70, 78.80)
Week 192	3	1 (33.3)	(0.84, 90.57)

CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; PUCAI = Pediatric Ulcerative Colitis Activity Index

Note: PUCAI clinical remission was defined as a total PUCAI score < 10.

Baseline is defined as the last non-missing value before the baseline visit date (i.e., at or before the Week 52 visit form Study M11-290 Main) and prior to the first dose of Study M10-870 Main.

Last observation carried forward: Missing data was imputed by carrying forward the last non-missing post-baseline observation. For interim analyses, missing values was imputed up to the timepoint a patient could have potentially reached at the data cutoff for analyses.

Due to the ongoing status of the study, not all subjects could have reached each study timepoint, therefore the overall N decreases.

Ancillary analyses

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Title: A Multicenter, Randomised, Double-Blind Study of the Human Anti-TNF Monoclonal Antibody Adalimumab in Pediatric Subjects with Moderate to Severe Ulcerative Colitis		
Study identifier	M11-290 (EudraCT Number: 2013-003032-77) Main Study	
Design	Phase 3, multicentre, randomised, double-blind (DB) trial designed to evaluate the efficacy and safety, and to assess the pharmacokinetics of subcutaneously administered adalimumab in paediatric subjects aged 4 to less than 18 years with moderate to severe ulcerative colitis (UC; defined as a Mayo Score of 6 to 12 points and endoscopy subscore of 2 to 3), who have failed therapy with corticosteroids and/or immunosuppressant. Prior to protocol Amendment 4, enrolled subjects were randomised 3:2 at baseline to 1 of 2 DB adalimumab induction doses, induction high dose (I-HD) or induction standard dose (I-SD). Randomisation was stratified by baseline disease severity (Mayo Score ≤ 9, > 9), prior exposure to anti-TNF (infliximab), and corticosteroid use at baseline. After Amendment 4, enrolled subjects received adalimumab induction high dose open label (I-HD-OL). Ongoing subjects randomized prior to Amendment 4 continued their blinded treatment during the induction period until Week 8. Prior to protocol Amendment 4, subjects demonstrating a clinical response per Partial Mayo Score (PMS; defined as a decrease in PMS ≥ 2 points and ≥ 30% from baseline) at Week 8 were stratified by Week 8 remission status per PMS (remission defined as a PMS ≤ 2 and no individual subscore > 1) and induction dose, then randomised in a 2:2:1 ratio to adalimumab maintenance standard dose (M-SD), adalimumab maintenance high dose (M-HD), or placebo (M-PL). After Amendment 4, subjects demonstrating a clinical response per PMS at Week 8 were stratified by Week 8 remission status per PMS and randomised in a 1:1 ratio to 1 of 2 adalimumab maintenance treatment groups, M-SD or M-HD. Subjects continued their blinded treatment during the maintenance period until Week 52 unless they experienced ≥ 2 disease flares and received open label rescue therapy after the second flare. Prior to protocol Amendment 4, internal placebo was chosen as the control group during the maintenance period per regulatory requirement. After Amendment 4, in agreement with the regulatory agencies, randomisation to the internal placebo group was ceased, and external placebo rates were used as comparators for co-primary and ranked secondary efficacy endpoints instead. The external placebo rates were identified from a meta-analysis of relevant publicly available clinical trials.	
	Duration of DB induction phase or OL induction phase: Duration of DB maintenance phase: Duration of OL extension (M10-870):	8 weeks 44 weeks 288 weeks OL maintenance
Hypothesis	Superiority: For co-primary induction endpoint: I-SD + I-HD vs external placebo rate; I-HD vs external placebo rate; and I-SD vs external placebo rate For maintenance endpoints: M-SD + M-HD vs external placebo rate; M-HD vs external placebo rate; and M-SD vs external placebo rate.	

Treatments groups	Induction high dose (I-HD)	adalimumab, n = 47 randomised Baseline: 2.4 mg/kg (maximum 160 mg) Week 1: 2.4 mg/kg (maximum 160 mg) Week 2: 1.2 mg/kg (maximum 80 mg) Week 4: 0.6 mg/kg (maximum 40 mg) Week 6: 0.6 mg/kg (maximum 40 mg)
	Induction standard dose (I-SD)	adalimumab, n = 30 randomised Baseline: 2.4 mg/kg (maximum 160 mg) Week 1: matching placebo Week 2: 1.2 mg/kg (maximum 80 mg) Week 4: 0.6 mg/kg (maximum 40 mg) Week 6: 0.6 mg/kg (maximum 40 mg)
	Induction high dose-open-label (I-HD-OL)	adalimumab, n = 16 enrolled Baseline: 2.4 mg/kg (maximum 160 mg) Week 1: 2.4 mg/kg (maximum 160 mg) Week 2: 1.2 mg/kg (maximum 80 mg) Week 4: 0.6 mg/kg (maximum 40 mg) Week 6: 0.6 mg/kg (maximum 40 mg)
	Maintenance high dose (M-HD)	adalimumab, n = 32 randomised 0.6 mg/kg (maximum 40 mg) every week
	Maintenance standard dose (M-SD)	adalimumab, n = 31 randomised 0.6 mg/kg (maximum 40 mg) every other week with matching placebo on the alternate week
	Maintenance placebo (M-PL) (DB induction subjects only)	placebo, n = 12 randomised

Endpoints and definitions	Co-primary endpoints: 1. Proportion of subjects who achieve clinical remission at Week 8 as measured by PMS 2. Proportion of subjects who achieved clinical remission at Week 52 as measured by FMS in Week 8 responders per PMS	Clinical remission per PMS defined as PMS ≤ 2 and no individual subscore > 1 Clinical remission per Full Mayo Score (FMS) defined as Mayo Score ≤ 2 and no individual subscore > 1 Clinical response per PMS defined as a decrease in PMS ≥ 3 points and ≥ 30% from baseline
	1st ranked secondary endpoint: Proportion of subjects who achieve clinical response per FMS at Week 52 in Week 8 responders per PMS	Clinical response per FMS defined as a decrease in Mayo Score ≥ 3 points and ≥ 30% from baseline and Clinical response per PMS defined as above
	2nd ranked secondary endpoint: Proportion of subjects who achieve mucosal healing at Week 52 in Week 8 responders per PMS	Mucosal healing defined as Mayo endoscopy subscore ≤ 1 Clinical response per PMS defined as above
	3rd ranked secondary endpoint: Proportion of subjects who achieve clinical remission per FMS at Week 52 in Week 8 remitters per PMS	Clinical remission per FMS defined as above Clinical remission per PMS defined as above
	4th ranked secondary endpoint: Proportion of subjects receiving corticosteroid at baseline who have discontinued corticosteroid prior to Week 52 and are in clinical remission per FMS at Week 52 in Week 8 responders per PMS	Corticosteroid-free clinical remission defined as receiving systemic corticosteroids (UC-related or non-UC related) at baseline and discontinuing systemic corticosteroids prior to endpoint assessment and being in clinical remission at Week 52 per FMS defined as above Clinical response per PMS defined as above
Database lock	Interim database lock: 25 Oct 2019	
Results and Analysis		
Analysis description		
Analysis populations and time point description	Week 8, Intent to treat (ITT)-E population (n = 77): Subpopulation of the ITT population (all subjects who received at least one dose of study medication during induction period; n = 93), where subjects who received I-HD-OL (n = 16) were excluded. Week 52, Modified ITT-E (mITT-E) population (n = 62): Subpopulation of the mITT population (all Week 8 responders per PMS who were randomised at Week 8 and received at least one dose of study medication during the maintenance period; n=74), where subjects who received placebo (n = 12) were excluded. One subject who was erroneously randomised to the M-HD treatment group had received a maintenance dose but was not a responder at Week 8. This subject was excluded from the mITT-E population per definition but was included in the safety population.	
	Primary Analysis	
Effect estimate per	Co-primary endpoints	

comparison	Endpoint	Treatment Group	Proportion n (%)	95% Confidence Interval (CI)[a] *P*-value[b] vs external placebo rate[c]
	Proportion of subjects achieving clinical remission per PMS at Week 8	I-SD + H-SD	41/77 (53.2)	(41.52, 64.71) < 0.001 vs 19.83%
		I-HD	28/47 (59.6)	(44.27, 73.63) < 0.001 vs 19.83%
		I-SD	13/30 (43.3)	(25.46, 62.57) 0.382 vs 19.83%
	Proportion of subjects with clinical remission per FMS at Week 52 in Week 8 responders per PMS	M-SD + H-SD	23/62 (37.1)	(25.16, 50.31) < 0.001 vs 18.37%
		M-HD	14/31 (45.2)	(27.32, 63.97) < 0.001 vs 18.37%
		M-SD	9/31 (29.0)	(14.22, 48.04) 0.382 vs 18.37%
	Secondary Analysis			
Effect estimate per comparison	Ranked Secondary Endpoints:			
	Endpoint	Treatment Group	Proportion n (%)	95% Confidence Interval (CI)[a] *P*-value[b] vs external placebo rate[c]
	Proportion of subjects with clinical response per FMS at Week 52 in Week 8 responders per PMS	M-SD + H-SD	40/62 (64.5)	(51.34, 76.26) < 0.001 vs 26.10%
		M-HD	21/31 (67.7)	(48.63, 83.32) < 0.001 vs 26.10%
		M-SD	19/31 (61.3)	(42.19, 78.15) 0.008 vs 26.10%
	Proportion of subjects with mucosal healing at Week 52 in Week 8 responders per PMS	M-SD + H-SD	28/62 (45.2)	(32.48, 58.32) < 0.001 vs 22.03%
		M-HD	16/31 (51.6)	(33.06, 69.85) < 0.001 vs 22.03%
		M-SD	12/31 (38.7)	(21.85, 57.81) 0.382 vs 22.03%
	Proportion of subjects with clinical remission per FMS at Week 52 in Week 8 remitters per PMS	M-SD + H-SD	19/43 (44.2)	(29.08, 60.12) < 0.001 vs 14.79%
		M-HD	10/22 (45.5)	(24.39, 67.79) < 0.001 vs 14.79%
		M-SD	9/21 (42.9)	(21.82, 65.98) 0.292 vs 14.79%
	Proportion of subjects with corticosteroid-free	M-SD + H-SD	9/29 (31.0)	(15.28, 50.83) 0.382 vs 24.08%

	clinical remission per FMS at Week 52 in Week 8 responders per PMS	M-HD	5/16 (31.3)	(11.02, 58.66) 1.000 vs 24.08%
		M-SD	4/13 (30.8)	(9.09, 61.43) 1.000 vs 24.08%
Notes	[a] Clopper-Pearson CI for proportion in remission/response. [b] Adjusted P values from a sequentially rejective multiple test procedure, testing co-primary and ranked secondary endpoints first for I-SD/I-HD combined and then for individual adalimumab dose groups against the respective external placebo rate, controlling familywise Type I error of 5% in a strong sense. [c] External placebo rates for statistical comparisons (upper limit of 95% CI of point estimates from meta-analysis). Note: Non-responder imputation (NRI) method was used to impute missing values for binary efficacy endpoints. Missing data was imputed as not having met the endpoint. Subjects re-randomized due to disease flare were considered as not having met the endpoint at and after their 1st disease flare.			

Analysis performed across trials (pooled analyses and meta-analysis)

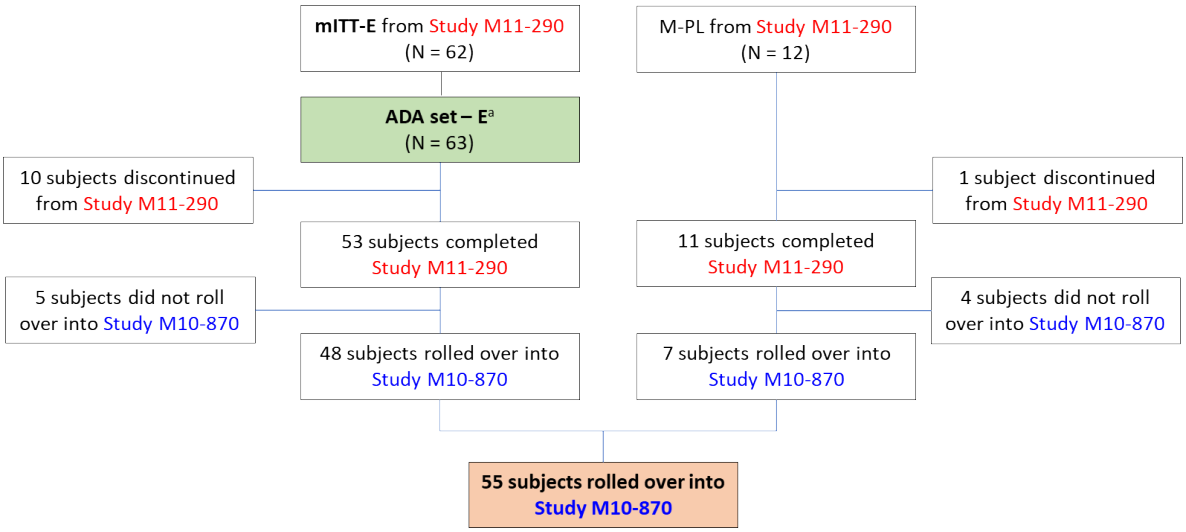
Analyses on integrated efficacy data from Studies M11-290 and M10-870 prespecified in the SAP have been presented. The adalimumab set for efficacy ("ADA set – E") consists of 63 subjects who received at least 1 dose of adalimumab during the maintenance period of Study M11-290 and who were not randomized to placebo during the maintenance period (

Table 29). Among the ADA set – E, a total of 53 subjects completed Study M11-290, and of those, 48 subjects enrolled in the ongoing Study M10-870. As of the data cut-off date of 28 August 2019, 36 subjects are ongoing in Study M10-870 in the ADA set – E and none has completed as the study is ongoing. A total of 22 subjects discontinued adalimumab in the ADA set – E, and most were due to the primary reason of lack of efficacy (14 subjects). Similar trends were observed in the re-randomised with re-induction analysis set for efficacy ("RR with Re-Ind Set – E") though the number of subjects in that analysis set are too small to be conclusive.

Table 29 Integrated Analysis Sets

Analysis Sets	Studies Included	Study Population and Treatment Period	Treatment Groups and Treatment Group Comparisons
Adalimumab (ADA) Analysis Set for Efficacy ("ADA set - E") N = 63	M11-290 M10-870	**Study Population:** Includes all subjects who received at least one dose of adalimumab during the maintenance period of Study M11-290. Subjects who were randomized to Placebo for the maintenance phase of Study M11-290 are excluded. **Treatment Period:** Includes double-blind and open-label data collected during treatment with ADA in Study M11-290 and Study M10-870. The "ADA set – E" allows for an assessment of efficacy data based on all subjects consistently exposed to adalimumab beyond induction dosing, from first dose of adalimumab in Study M11-290 through last available observation during the treatment with adalimumab in Study M11-290/M10-870 or up to the cut-off date for the Study M10-870 snapshot, whichever is earlier.	**Treatment Group:** Adalimumab **Pairwise Comparisons:** No pairwise comparisons
Adalimumab (ADA) Analysis Set for the Induction Period ("ADA set - Ind") N = 93	M11-290	**Study Population:** Includes all subjects who received at least one dose of adalimumab during the induction period of Study M11-290. **Treatment Period:** Includes data collected during treatment with ADA in induction period of Study M11-290.	**Treatment Group:** Adalimumab **Pairwise Comparisons:** No pairwise comparisons
Re-Randomized with Re-Induction Analysis Set for Efficacy ("RR with Re-Ind Set - E") N = 6	M11-290 M10-870	**Study Population:** Includes all subjects in the "ADA set – E" who (due to 1st disease flare in maintenance period of Study M11-290) were re-randomized to receive re-induction dose. **Treatment Period:** Includes double-blind and open-label data collected during treatment with ADA in Study M11-290 and Study M10-870.	**Treatment Group:** Adalimumab **Pairwise Comparisons:** No pairwise comparisons

Figure 25 Key Analysis Sets for Integrated Analysis



a. ADA set – E = mITT-E plus 1 patient without response by PMS who was erroneously randomized to the maintenance period of Study M11-290 and received M-HD until the error was detected and the subject was discontinued.

Note: Bolded subject populations indicate key analysis sets for efficacy.

Table 30 Proportion of Adalimumab-Treated Subjects with Clinical Remission per FMS Over Time (LOCF, ADA Set – E)

Visit	N	n (%)	95% Confidence Interval[a]
Week 52	53	25 (47.2)	(33.30, 61.36)
Week 100	33	16 (48.5)	(30.80, 66.46)
Week 148	24	13 (54.2)	(32.82, 74.45)
Week 244	4	2 (50.0)	(6.76, 93.24)

FMS = full Mayo Score; LOCF = last observation carried forward

b. Clopper-Pearson confidence interval for proportion in remission.

Note: Baseline is defined as the last non-missing value prior to the first dose of study drug in Study M11-290.
Last observation carried forward: Missing data is imputed by carrying forward the last non-missing post-Baseline observation up to Week 8, Week 52 or the cutoff date depending on the study periods actually entered. Missing values are only imputed up to the timepoint a patient could have potentially reached at the data cutoff.
Clinical remission per FMS is defined as Mayo Score ≤ 2 and no individual subscore > 1.

Table 31 Proportion of Adalimumab-Treated Subjects with Clinical Remission per PMS Over Time (LOCF, ADA Set – E)

Visit	N	n (%)	95% Confidence Interval[a]
Week 1	62	10 (16.1)	(8.02, 27.67)
Week 2	63	18 (28.6)	(17.89, 41.35)
Week 4	63	23 (36.5)	(24.73, 49.60)
Week 8	63	43 (68.3)	(55.31, 79.42)
Week 12	63	44 (69.8)	(56.98, 80.77)
Week 18	63	42 (66.7)	(53.66, 78.05)
Week 26	63	44 (69.8)	(56.98, 80.77)
Week 34	63	40 (63.5)	(50.40, 75.27)
Week 42	63	40 (63.5)	(50.40, 75.27)
Week 52	63	39 (61.9)	(48.80, 73.85)
Week 56	47	41 (87.2)	(74.26, 95.17)
Week 60	45	35 (77.8)	(62.91, 88.80)
Week 64	42	35 (83.3)	(68.64, 93.03)
Week 76	39	26 (66.7)	(49.78, 80.91)
Week 88	36	27 (75.0)	(57.80, 87.88)
Week 100	33	22 (66.7)	(48.17, 82.04)
Week 112	32	24 (75.0)	(56.60, 88.54)
Week 124	28	20 (71.4)	(51.33, 86.78)
Week 136	27	17 (63.0)	(42.37, 80.60)
Week 148	24	13 (54.2)	(32.82, 74.45)
Week 160	22	12 (54.5)	(32.21, 75.61)
Week 172	21	10 (47.6)	(25.71, 70.22)
Week 196	14	7 (50.0)	(23.04, 76.96)
Week 220	9	4 (44.4)	(13.70, 78.80)
Week 244	4	1 (25.0)	(0.63, 80.59)

LOCF = last observation carried forward; PMS = partial Mayo Score

c. Clopper-Pearson confidence interval for proportion in remission.

Note: Baseline is defined as the last non-missing value prior to the first dose of study drug in Study M11-290.
Last observation carried forward: Missing data is imputed by carrying forward the last non-missing post-Baseline observation up to Week 8, Week 52 or the cutoff date depending on the study periods actually entered. Missing values are only imputed up to the timepoint a patient could have potentially reached at the data cutoff.
Clinical remission per PMS is defined as PMS ≤ 2 points and no individual subscore > 1.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In this submission, the MAH initially sought a new indication for Humira (adalimumab) for the treatment of paediatric patients 5 to 17 years of age with moderately to severely active UC. This application is supported by data from 2 Phase 3 clinical studies: a randomized, controlled study (Study M11-290) and an open-label (OL) long-term study (Study M10-870) for subjects who participated in, and successfully completed, Study M11-290. Study M11-290 is a post-marketing commitment to the US FDA. This

submission also aims to fulfill the agreed European Union (EU) Paediatric Investigation Plan (PIP) (EMEA-000366-PIP02-09-M06, Decision P/0174/2019).

Study M11-290 is a Phase 3, multicenter, randomized, DB trial with an 8 week- induction period followed by a 44 weeks maintenance period. It was initially planned as an induction-maintenance/withdrawal study with a placebo part but due to recruitment problems, several changes were done during the study and this was discussed and accepted by EMA/PDCO/FDA. The major changes affecting the study design were implemented in amendment 4 and therefore the study design is presented before and after amendment 4.

Before amendment 4, the study participants were randomised (3:2) to receive either an induction high dose (I-HD) or an induction standard dose (I-SD). At week 8, subjects demonstrating a clinical response per Partial Mayo Score (PMS) were re-randomized in a 2:2:1 ratio to receive either maintenance standard dose (M-SD), maintenance high dose (M-HD) or maintenance placebo dose (M-PL).

After amendment 4, the lower dose in the induction phase (i.e. the I-SD part) was omitted. Instead, all patients received open label high dose induction dose (I-HD-OL). In addition, at week 8, the re-randomisation of patients to a placebo group was ceased and subjects demonstrating a clinical response per PMS were instead re-randomized in a 1:1 ratio to receive either M-SD or M-HD.

Two different induction regimens were studied: High dose (I-HD): adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1 or Standard dose (I-SD): adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and matching placebo at Week 1. Both doses were followed by 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.

Two different maintenance regimens were studied (from week 8 and onwards): Standard dose (M-SD): Adalimumab 0.6 mg/kg (maximum dose of 40 mg) every other week (eow) or High dose (M-HD): Adalimumab 0.6 mg/kg (maximum dose of 40 mg) every week (ew). The study was not designed to compare the two different doses used, neither for induction therapy nor for maintenance therapy.

Subjects were to continue their blinded treatment during the maintenance period until week 52. In case of disease flare (defined in three different ways depending on the received PMS score at week 8) the patients were randomized to receive a bolus dose of adalimumab either 2.4 mg/kg (or maximum 160 mg) or 0.6 mg/kg (or maximum 40 mg). Thereafter, the patients returned to their original treatment, with exception for the placebo group, who received M-SD treatment.

The study is divided in an induction phase and a maintenance phase. This is in line with the EMA guideline (CHMP/EWP/18463/2006 Rev.1) which states that *"combined trial designs for induction and maintenance of remission can be accepted. Nevertheless, the design has to be adapted to allow interpretation of results in both phases and an element of dose-comparison may be built into a maintenance phase considering that the dose may not be the same for achieving as for maintaining remission. Dose-finding aspects in long-term treatment should be addressed".*

Since recruitment to the internal placebo group was ceased after amendment 4, the presented efficacy endpoints rely on external placebo data derived from an adult population. The MAH had initially proposed to include results from the adult external placebo group in Section 5.1 of the SmPC. A central assumption in these comparisons is that placebo remission rates are at the same level for adults and children. Also, they require that the studies are conducted in a comparable manner. The submitted application does not provide support of these assumptions. The CHMP considers therefore hard to make any conclusions about the effect in children from these comparisons, and the corresponding p-values should not be used to make claims about the efficacy. The MAH provided some additional argumentations for keeping this in the SmPC. However, the issue that the treated group and comparison group are from fundamentally different populations remains, and it is therefore not acceptable to include the results of the comparison in the

SmPC. Upon request from the CHMP, the MAH agreed to remove the efficacy comparison with the adult control group from the SmPC.

The inclusion and exclusion criteria of the study adequately defined paediatric patients with moderate to severe UC (Mayo score of 6 to 12 points and endoscopy sub score of 2 to 3) from 4 to less than 18 years old, who have failed therapy with corticosteroids and/or immunosuppressant (IMM). Patient were to have had previous failed conventional therapy.

The study has two co-primary endpoints, clinical remission at Week 8 as measured by PMS and clinical remission at week 52 (in patients receiving PMS response at week 8) measured by FMS. The PMS evaluates clinical symptoms such as stool frequency and rectal bleeding and includes a physician's global score. The FMS includes in addition an endoscopic evaluation which is endorsed by CHMP. Four ranked secondary endpoints were analysed at week 52, where proportion of subjects receiving systemic corticosteroids at Baseline who discontinued systemic corticosteroids prior to Week 52 and were in Mayo clinical remission at Week 52 in Week 8 responders per PMS was one of them.

The data in this study has been collected over several years due to inclusion difficulties. A new EMA guideline on the development of new medicinal products for the treatment of Ulcerative Colitis has been released in January 2019. This guidelines states that: "*The aim of UC treatment in children should be achieving remission without affecting growth and maturation. Symptomatic remission and endoscopic MH should be used as co-primary endpoints. The primary endpoint of maintenance trials should be sustained relapse-free corticosteroid-free remission (defined as maintaining both, symptomatic remission, and endoscopic MH).* In addition, it is mentioned at least in the general part of this guideline that for defining clinical remission it is recommended to use a sub score of 0 for RBS. Since there is no validated paediatric patient reported outcome measurement for the evaluation of symptoms for the time being, the use of the PUCAI as a surrogate for symptomatic remission is suggested in the guidelines.

Although the MAH does not use the more stringent definition of PMS and FMS remission (ie RBS 0), the chosen endpoints and exploratory analysis are acceptable to CHMP. The MAH analyses PUCAI as an exploratory outcome. Height, weight, BMI, Tanner stage were also analysed as exploratory outcomes.

Study M10-870 is a Phase 3, multi-centre, open-label study designed to evaluate the long-term maintenance of clinical response, safety and tolerability of adalimumab in paediatric subjects with ulcerative colitis. Subjects who successfully completed Study M11-290 through Week 52 were potentially eligible to participate in this study. The duration of the study is up to 298 weeks, which includes a 288-week OL maintenance period and a 70-day follow-up phone call. The study is currently ongoing and at the data cut-off date of 28 August 2019, no patients had completed the study.

All subjects received open-label therapy as follows: subjects who enrolled into the study from blinded treatment in Study M11-290 received open label 0.6 mg/kg (maximum of 40 mg) eow of adalimumab; or subjects who received open label adalimumab in Study M11-290 maintained the same dose in Study M10-870. Subjects who experienced disease flare received either of the following: subjects who were on 0.6 mg/kg (maximum dose of 40 mg, weight based) eow of adalimumab could receive 0.6 mg/kg (maximum of 40 mg, weight based) every week (ew); or subjects who were on 0.6 mg/kg ew of adalimumab could receive 40 mg ew (maximum dose) of adalimumab.

The study M10-870 has no primary or secondary endpoints but several exploratory endpoints.

Efficacy data and additional analyses

Study M11-290:

In the main study, a total of 93 subjects enrolled in the study at 19 sites in Austria, Belgium, Canada, Spain, United Kingdom, Israel, Poland, Slovakia, and the US.

In the ITT/Safety population, 73.1% were >13 years of age, with a mean age of 14.1 years, mean disease duration of 2.3 years and 54.8% were females.

The majority of the patients had concomitant immunotherapy (59.1%), 47.3% had concomitant corticosteroids at baseline and 16.1% had previously been exposed to TNF-inhibitors. At baseline, 60.2% of the patients had extensive disease/pancolitis and mean baseline Mayo score and Partial Mayo score were 7.8 and 5.6 respectively reflecting the intended population with an active moderate to severe disease despite conventional therapy. Baseline disease characteristics were generally well balanced between the two treatment groups receiving I-SD and I-HD.

In the mITT population (i.e all Week 8 PMS responders who were randomized at Week 8 and received at least one dose of the study medication during maintenance period) demographics were similar to the patients in the ITT population in respect of gender, age and disease duration. For the mITT population, PMS score at week 8 were low (total median (min, max) PMS at week 8 were 1.6 (0.0, 5.0)) as expected and did not differ between the treatment groups. Upon request from CHMP, additional demographics were presented per age-group (<or≥13 years). There were numerically more females in the <13 years age group than in the ≥13 years age group, otherwise the group did not differ in respect of disease severity or previous use of TNF-inhibitors.

Of the 93 patients included in the study, 64 patients (68.8%) completed the 52 weeks. During the induction phase (week 0-8), 47 patients were randomized to the I-HD group, 30 patients to the I-SD group and 16 patients received I-HD open label. In total 18 of the patients (19.4%) discontinued the study during the induction phase. The proportion of patients who discontinued the study were numerically higher in the I-SD group 8/30 (26.7%) than in the I-HD group 8/47 (17.0%). The main reason for discontinuation in all groups were being non responders at week 8. The number of patients screened were 145 and the number of patients who flared more than once were 7.

For the 74 patients that continued to maintenance treatment, 31 patients were randomized to M-HD, 31 patients to M-SD and 12 patients to Placebo (M-PL). During the maintenance period, 22 patients (29.7%) were rerandomized due to flare. Additional information provided by the MAH upon CHMP's request showed that PMS values at the time of the flare were rather high, with a PMS between 3.6 and 7.4 at the time of the flare. No changes in corticosteroid treatment seemed to have occurred in any of the patients at the time of the flare. The flares occurred between approximately 1 and 7.8 month after start of maintenance treatment in the three groups, with no apparently differences between the groups. It is noted that the proportion of patients who flared was numerically higher in the M-HD group (n=9, 29%) compared with the M-SD group (n=6, 19%) although the numbers are too small to make any firm conclusion. Of the 22 patients who flared, no one achieved FMS remission at week 52, regardless of re-induction therapy or not. Of the 10 patients who received a re-induction dose, all patients (100%) had an initial PMS response at first visit after the re-induction dose (mean 38.0 days after flare) and a third of them (33.3%) achieved clinical remission per PMS at week 52. Although the response in the population without reinduction dose were numerically lower (66.7% PMS response at first visit after flare and 11.1% in PMS remission at week 52) it should be noted that the number of patients in the respective groups are small. Only three patients in the M-HD group received a re-induction dose and only one patient achieved a beneficial effect from the re-induction dose. The numbers are too low to draw any firm conclusion but the fact that none of the patient reached the co-primary endpoint at week 52 (FMS remission) regardless of re-induction treatment does not justify the proposed suggestion of a re-induction dose. In addition, the

re-induction dose will lead to exposure outside the previously studied exposure range for Humira (see also Discussion on clinical pharmacology). Upon request from CHMP, the MAH removed the suggested dose re-induction in patients with flares.

At week 8 after the induction phase, clinical remission per PMS was achieved in 59.6% of the patients receiving the higher induction dose (I-HD) and in 43.3% of the patients receiving the standard induction dose (I-SD). In the group receiving I-HD-OL, 68.8% of the patients reached clinical remission. Although only an exploratory statistical comparison was made between the doses, it is noted that a numerically higher proportion of patients receiving the higher induction dose reached clinical remission. This supports the MAH's suggested posology using the higher dose for induction therapy. This is also in line with the approved posology for induction therapy in adults with the same indication. To further explore the supposed differences between the two doses, although no formal statistical analysis can be done, the MAH provided tabulations of not only the patients receiving blinded I-SD and blinded I-HD, but also the patients receiving blinded I-HD and open label I-HD combined. The proportion of patients with PMS remission at week 8 was 61.9% in the I-HD/I-HD-OL group and 43.3% in the I-SD group. The nominal p-value for this exploratory comparison was 0.09. It is noted that the study was not powered to detect any difference between the two doses of adalimumab.

Compared to the external placebo rate (19.83%), I-HD was statistically significantly better, although the relevance of this comparison is not endorsed (see statistical methodology discussed above). It is noted that the external placebo group for this comparison is derived from the MAH's own studies in adult population with the same indication (studies M06-826 and M06-827).

At week 52, clinical remission per FMS were reached by 14 patients (45.2%) in the maintenance high dose group (M-HD) and 9 patients (29.0%) in the maintenance standard dose group (M-SD). Although no statistical comparison was made regarding the internal placebo it is noted that 4 patients (33.3%) in the placebo group received clinical remission per FMS. Compared to the external placebo rate (18.37%), derived from an adult population, statistically significant better effect was seen only in the higher dose. This finding could imply that the higher dose is needed for adequate mucosal healing. The same result was seen when analysing the second ranked secondary endpoint where mucosal healing at Week 52 as measured by Mayo endoscopy sub score (defined as ≤ 1) in Week 8 PMS responders was achieved by 51.6% of subjects who were randomized to the adalimumab M-HD group and 38.7% of subjects in the M-SD group.

Posology

Although no formal comparison between doses is made in this study, the MAH suggests using the higher maintenance dose in the paediatric population. The MAH proposes a higher maintenance dose for the paediatric UC indication than what is approved as standard dose for the adult UC population and for the other paediatric indications (although a dose increase to the currently proposed dose is possible in both adult UC and the paediatric Crohn's population). To further explore the suggested posology, the MAH was asked to discuss the results in the light of the results received in the studies of adalimumab treated adult population (M06-826 and M06-827). The MAH explained that in the adult UC studies M06-826 and M06-827, only the standard maintenance dose of 40 mg adalimumab eow was evaluated for the primary efficacy analysis. In the adult study M06-827, the 2nd co-primary endpoint FMS remission at week 52 were reached by 17.3% in the Adalimumab group compared with 8.5% in the placebo group (although this study evaluated all patients randomized to active drug versus placebo at baseline (i.e. in contrast to the paediatric population, the placebo group has never received active induction treatment) and not only, as in the paediatric population, PMS responders at week 8). In addition, 27.7% and 30.8% of the adult UC population in the respective study required escalation to ew dosing during the maintenance period. This could, as stated by the MAH, indicate that also a substantial proportion of the adults would benefit from a higher dose and this is also reflected in the SmPC were the dose can be escalated to 40 mg ew for

the adult population. The MAH also argued that paediatric patients often present with a more severe disease than adults and that the presented study results from M11-290 point towards a generally better efficacy outcome in the M-HD population without indicating any worsening of the safety profile, supporting therefore the suggested posology.

The MAH provided also a justification of the selection for doses used in Study M11-290 and the subsequent proposal of a flat dose regimen. The justification is supported including the use of model-based PK-matching approach to support the flat-dose regimen. The data provide exposures generally comparable between the studied body weight-based high induction/high maintenance regimen and the proposed two-tiered fixed dosing regimen in paediatric UC patients for the induction and maintenance doses. The methodology to support a switch to a flat-dose regimen has been accepted in previous paediatric variations for Humira. The MAH's argumentation is therefore endorsed by CHMP and the dosing recommendations are as follows:

Patient Weight	Induction Dose	Maintenance Dose Starting at Week 4*
< 40 kg	• 80 mg at Week 0 (given as two 40 mg injections in one day) and • 40 mg at Week 2 (given as one 40 mg injection)	• 40 mg every other week
≥ 40 kg	• 160 mg at Week 0 (given as four 40 mg injections in one day or two 40 mg injections per day for two consecutive days) and • 80 mg at Week 2 (given as two 40 mg injections in one day)	• 80 mg every other week

* Paediatric patients who turn 18 years of age while on Humira should continue their prescribed maintenance dose.

The MAH has provided data showing mean RBS improvement from Baseline by 0.86 and 1.07 points in subjects on the I-SD and I-HD dose regimens, respectively and RBS improved from Baseline at Week 52 by 1.48 and 1.36 points in subjects on the M-SD and M-HD doses, respectively. Upon request, the MAH provided data on numbers and proportions of patients reaching a rectal bleeding score of 0 at week 8 and week 52 and in both treatment doses the proportions were >50% which are acceptable to CHMP.

Clinical remission per PUCAI at Week 8 was achieved by 46.8% and 33.3% of subjects in the adalimumab I-HD and I-SD groups, respectively. PUCAI response at Week 52 in Week 8 PMS responders was achieved by 51.6% and 58.1% of subjects in the adalimumab M-HD and M-SD groups, respectively. PUCAI remission at Week 52 in Week 8 PMS responders was reported by 58.1% and 45.2% of subjects in the adalimumab M-HD and M-SD groups, respectively. The MAH included information about the exploratory endpoint PUCAI in 5.1 of the SmPC upon recommendation from CHMP since it is suggested as a measure of clinical symptoms in paediatric patients in the EMA guidelines.

The QOL for the adalimumab-treated subjects as well as work productivity and activity impairment for their caregivers also showed meaningful improvements as early as Week 8 compared to Baseline during the study as measured by IMPACT III and WPAI. At week 52, subjects randomized to the M-SD and M-HD treatment regimens achieved mean changes from baseline in Activity Impairment of -19.0 and -32.9 percentage points, in Impairment While Working of -26.1 and -24.5 percentage points, in Overall Work Impairment of -27.7 and -24.8 percentage points, and in Work Time Missed of -5.8 and -7.9 percentage points at Week 52, respectively. The MAH justified that the mean changes in WPAI were above the minimum clinically important difference (MCID) of WPAI established as a change of 7 percentage points[1].

[1] Sandborn WJ, Reilly MC, Brown MCJ, et al. Minimally Important Difference for WPAI:CD Scores: Defining Relevant Impact on Work Productivity in Active Crohn's Disease: 962. Am J Gastroenterol. 2007;102:S472.

Even though established in patients with CD, this MCID has been extrapolated to patients with UC in a systemic review of psychometric evaluation in WPAI to evaluate the ability to detect change and the responsiveness to treatment[2]. In addition, this threshold has also been used in patients with UC to demonstrate the treatment effect on clinical meaningful improvement of WPAI[3]. CHMP endorsed the provided justification and considers the improvements measured by IMPACT III and WPAI as clinically meaningful. Section 5.1 of the SmPC is updated accordingly.

Study M10-870

The submitted clinical study report is an interim report, covering the main study (excluding Japan). A total of 55 patients is included in the study. This study is currently ongoing, and none of subject enrolled has yet completed the study. Only three subjects received adalimumab 0.6 mg/kg (maximum dose of 40 mg) ew (M-HD) at baseline, the other 52 patients received adalimumab 0.6 mg/kg (maximum dose of 40 mg) eow (M-SD). Of these, 18 subjects (34.6%) had at least 1 dose escalation from the eow dose to the ew dose; no subjects had dose de-escalation from the ew dose to the eow dose. The rate of discontinuation was 25.5% and the primary reason for discontinuation reported by most subjects was lack of efficacy.

2.4.4. Conclusions on the clinical efficacy

Despite difficulties to enrol patients during the conduct of the pivotal study M11-290, resulting in change of the study design omitting the original placebo group, the study managed to include 93 paediatric patients with active moderate to severe ulcerative colitis.

The results indicate clinically significant effects both in reducing symptoms and mucosal healing. The comparison towards the external placebo group received from an adult population relies on a central assumption that placebo remission rates are at the same level for adults and children. Also, they require that the studies are conducted in a comparable manner. However, the submitted application does not provide support of these assumptions. It is therefore hard to make any conclusions about the effect in children from these comparisons, and the corresponding p-values cannot be used to make claims about the efficacy. At the CHMP's request, those values were not included in the SmPC.

The study was not designed to compare the two different doses used, neither for induction therapy nor for maintenance therapy. However, the results seem to indicate a better response in the patients receiving the higher induction dose and also with the higher maintenance dose. Such results would not be expected without active treatment in a population who is non responders to standard of care, and thus, a drug effect is undoubtedly shown.

The MAH proposes a higher maintenance dose for the paediatric UC indication than what is approved as standard dose for the adult UC population and for the other paediatric indications (although a dose increase to the currently proposed dose is possible in both adult UC and the paediatric Crohn's population). This is acceptable to the CHMP for patients 6 years and older (see also discussions on clinical pharmacology).

The benefit of the suggested one-time re induction dose was not supported by the data submitted; therefore, the MAH agreed to remove it from the SmPC.

The following indication is agreed by CHMP:
Humira is indicated for the treatment of moderately to severely active ulcerative colitis in paediatric

[2] Yarlas A, Maher SM, Bayliss MS, et al. Psychometric validation of the work productivity and activity impairment questionnaire in ulcerative colitis: results from a systematic literature review. J Patient Rep Outcomes. 2018;2(1):62.
[3] Travis S, Feagan BG, Peyrin-Biroulet L, et al. Effect of adalimumab on clinical outcomes and health-related quality of life among patients with ulcerative colitis in a clinical practice setting: results from InspirADA. J Crohns Colitis. 2017;11(11):1317-25.

patients (from 6 years of age) who have had an inadequate response to conventional therapy including corticosteroids and/or 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

2.5. Clinical safety

Introduction

Adalimumab was approved for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) in April 2012 in the European Union (EU) and September 2012 in the US. Adalimumab is approved for several paediatric indications: Juvenile idiopathic arthritis (from 2 years), Paediatric plaque psoriasis (from 4 years), Paediatric Crohn's disease (from 6 years) and Paediatric Uveitis (from 2 years).

With this variation, the MAH seeks to add a new indication for the treatment of paediatric patients 5 to 17 years of age with moderately to severely active ulcerative colitis. This application is supported by data from 2 Phase 3 clinical studies: a randomized, controlled study (Study M11-290) and an open-label (OL) long-term study (Study M10-870) for subjects who participated in, and successfully completed, Study M11-290.

For an overview of the study design and treatment regimens, please refer to the clinical efficacy section.

Study M11-290 had an 8-week double-blind (DB) induction period and a 44-week DB maintenance period. Study M10-870 (extension study of Study M11-290) has a 288-week maintenance period, with subjects receiving OL adalimumab beginning at the baseline visit (Week 52 visit from Study M11-290).

The analysis sets are described below.

Safety data was summarized across all treatment groups ("any adalimumab") for the analysis sets. No statistical comparisons were made.

Table 32. Analysis sets

Analysis Sets	Studies Included	Study Population and Treatment Period	Treatment Groups and Treatment Group Comparisons
Any Adalimumab Analysis Set ("Any ADA Set")	M11-290 M10-870	**Study Population:** Includes all subjects who received at least 1 dose of adalimumab in Study M11-290 or Study M10-870. **Treatment Period:** Includes double-blind and open label data collected during treatment with ADA in Study M11-290 and Study M10-870.	**Treatment Groups:** Any adalimumab **Pairwise Comparisons:** No pairwise comparisons
Re-Randomized with Re-Induction Analysis Set ("RR with Re-Ind Set")	M11-290 M10-870	**Study Population:** Includes all subjects who (due to 1st disease flare in maintenance period of Study M11-290) were re-randomized to receive a re-induction dose. **Treatment Period:** Includes double-blind and open label data collected during treatment with ADA in Study M11-290 and Study M10-870.	**Treatment Groups:** Any adalimumab **Pairwise Comparisons:** No pairwise comparisons

ADA = adalimumab

Patient exposure

The mean duration of adalimumab exposure for the 93 subjects who received at least 1 dose of adalimumab in Study M11-290 or Study M10-870 (Any ADA Set) was 569.6 days (median 427.0 days, range 28 – 1736 days), for a total of 145.0 patient-years (PYs) of exposure.

The mean age of the studied patients was 14.1 years (range 5-17). The majority (~80%) was older than 12 years, and only 19 of the patients were below 12 years of age (5, 6, 7 (n=2), 8 (n=2), 9 (n=3), 10 (n=3), 11 (n=7)) (Table 33).

Table 33. Key Demographic Characteristics (Any ADA Set)

Demographic Characteristic	Any Adalimumab (N = 93)
Sex - n (%)	
Female	51 (54.8)
Male	42 (45.2)
Age (years)	
n	93
Mean (SD)	14.1 (2.99)
Median	15.0
Min, Max	5, 17
Age group 1 (years) - n (%)	
< 13 years	25 (26.9)
≥ 13 years	68 (73.1)
Age group 2 (years) - n (%)	
< 12 years	19 (20.4)
≥ 12 years	74 (79.6)
Race - n (%)	
White	88 (94.6)
Black	3 (3.2)
Asian	1 (1.1)
American Indian/Alaska Native	0
Other	0
Multiple	1 (1.1)
Ethnicity - n (%)	
Hispanic or Latino	4 (4.3)
Japanese	0
No ethnicity	89 (95.7)
Geographic region - n (%)	
North America	13 (14.0)
Western Europe	8 (8.6)
Eastern Europe	72 (77.4)
Disease severity per baseline Mayo Scorea - n (%)	
≤ 9	76 (81.7)
> 9	17 (18.3)
Prior exposure to anti-TNF - n (%)	
Yes	15 (16.1)
No	78 (83.9)
Baseline systemic corticosteroid useb - n (%)	
Yes	44 (47.3)
No	49 (52.7)
Baseline immunosuppressants use - n (%)	
Yes	55 (59.1)
No	38 (40.9)

Demographic Characteristic	Any Adalimumab (N = 93)
Body weight (kg)	
n	93
Mean (SD)	55.9 (18.14)
Median	55.0
Min, Max	15.0, 110.0
Body mass index (kg/m2)	
n	93
Mean (SD)	20.6 (4.12)
Median	20.0
Min, Max	12.1, 32.7

TNF = tumor necrosis factor

a. True baseline Mayo Score is displayed. One subject was randomized in the stratum '> 9', but actually had a baseline Mayo Score ≤ 9 (value was corrected by the site after randomization).

b. True baseline systemic corticosteroid use is displayed. One subject was randomized in the stratum 'No', but actually had baseline systemic corticosteroid use documented.

Note: Percentages calculated on non missing values.

Adverse events

Induction phase – Study M11-290

The adverse events in the induction phase of study M11-290 are presented shown in Table 34.

Table 34. Overview of TEAEs and Deaths During Induction (Safety Population)

Subjects with:	I-SD (N = 30) n (%)	I-HD (N = 47) n (%)	I-HD-OL (N = 16) n (%)	Total (N = 93) n (%)
Any TEAE	17 (56.7)	23 (48.9)	12 (75.0)	52 (55.9)
Any serious AE (SAE)	5 (16.7)	4 (8.5)	1 (6.3)	10 (10.8)
Any severe TEAE	4 (13.3)	1 (2.1)	0	5 (5.4)
Any TEAEs leading to discontinuation of study drug	2 (6.7)	1 (2.1)	0	3 (3.2)
Any TEAEs with reasonable possibility of being related to study drug[a]	4 (13.3)	7 (14.9)	1 (6.3)	12 (12.9)
Any SAEs with reasonable possibility of being related to study drug[a]	2 (6.7)	1 (2.1)	1 (6.3)	4 (4.3)
Any TEAEs leading to Death	0	0	0	0
All deaths	0	0	0	0

AE = adverse event; I-HD = induction high dose group; I-HD-OL = induction high dose open-label group; I-SD = induction standard dose group; SAE = serious adverse event; TEAE = treatment-emergent adverse event

a. As assessed by investigator.

Note: Treatment-emergent adverse events are defined as events with an onset date on or after the first dose date of the study drug in the induction period and up to 70 days after the last dose date of the study drug in the induction period and prior to the first dose date of the study drug in the maintenance period if applicable.
Subjects are counted once in each row, regardless of the number of events they may have had.
Treatment-emergent adverse events with unknown relationship were counted as "reasonable possibility of being related."
Treatment-emergent adverse events with unknown severity were counted as "severe."

The most frequently reports AEs are presented in Table 35.

Table 35. Adverse Events Reported in ≥ 5% of Subjects by PT - Induction (Safety Population)

MedDRA 22.0 Preferred Term	I-SD (N = 30) n (%)	I-HD (N = 47) n (%)	I-HD-OL (N = 16) n (%)	Total (N = 93) n (%)
Any adverse event	17 (56.7)	23 (48.9)	12 (75.0)	52 (55.9)
Headache	4 (13.3)	5 (10.6)	4 (25.0)	13 (14.0)
Anaemia	3 (10.0)	3 (6.4)	1 (6.3)	7 (7.5)
Colitis ulcerative	4 (13.3)	2 (4.3)	1 (6.3)	7 (7.5)
Nasopharyngitis	2 (6.7)	2 (4.3)	1 (6.3)	5 (5.4)

I-HD = induction high dose group; I-HD-OL = induction high dose open-label group; I-SD = induction standard dose group; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term

Note: Treatment-emergent adverse events are defined as events with an onset date on or after the first dose date of the study drug in the induction period and up to 70 days after the last dose date of the study drug in the induction period and prior to the first dose date of the study drug in the maintenance period if applicable.
Subjects are counted once in each row, regardless of the number of events they may have had.

Maintenance phase – Study M11-290

An overview of AEs during the maintenance phase is provided in Table 36.

Table 36. Overview of TEAEs and Deaths During Maintenance up to First Disease Flare (Safety Population)

Subjects with:	M-SD (N = 31) n (%)	M-HD (N = 32) n (%)	ADA (N = 63) n (%)	M-PL (N = 12) n (%)
Any TEAE	20 (64.5)	22 (68.8)	42 (66.7)	10 (83.3)
Any SAE	4 (12.9)	5 (15.6)	9 (14.3)	1 (8.3)
Any severe TEAE	3 (9.7)	1 (3.1)	4 (6.3)	0
Any TEAEs leading to discontinuation of study drug	2 (6.5)	0	2 (3.2)	0
Any TEAEs with reasonable possibility of being related to study drug[a]	8 (25.8)	10 (31.3)	18 (28.6)	5 (41.7)
Any SAEs with reasonable possibility of being related to study drug[a]	0	1 (3.1)	1 (1.6)	1 (8.3)
Any TEAEs leading to Death	0	0	0	0
All deaths	0	0	0	0

ADA = adalimumab; M-PL = maintenance placebo group; M-SD = maintenance standard dose group; M-HD = maintenance high dose group; TEAE = treatment-emergent adverse event; SAE = serious adverse event

a. As assessed by investigator.

Note: Treatment-emergent adverse events are defined as events with an onset date on or after the first dose date of the study drug in the maintenance period and prior to re-randomization due to first disease flare if applicable and up to 70 days after the last dose date of the study drug in the maintenance period. The events with an onset date on or after the first dose date in Study M10-870 are excluded.
Subjects are counted once in each row, regardless of the number of events they may have had.
Treatment-emergent adverse events with unknown relationship were counted as "reasonable possibility of being related."
Treatment-emergent adverse events with unknown severity were counted as "severe."

Study M10-870 (long-term extension)

The objective of the study was to evaluate the long-term safety, tolerability, and maintenance of clinical response, of repeated administration of adalimumab in paediatric subjects with UC who participated in, and successfully completed, study M11-290 through Week 52.

An overview of AEs is shown in Table 37 and of the most common AEs in Table 38.

Table 37. Overview of Treatment-Emergent Adverse Events and Deaths

Subjects With Treatment-Emergent	Adalimumab (N = 55) n (%)
Adverse event	36 (65.5)
Serious AE	8 (14.5)
Severe AE	2 (3.6)
AEs leading to discontinuation of study drug	2 (3.6)
AEs rated as possibly related to study drug by the investigator (reasonable possibility)[a]	11 (20.0)
SAEs rated as possibly related to study drug by the investigator (reasonable possibility)[a]	2 (3.6)
AEs leading to death	0

AE = adverse event; FAS = full analysis set; SAE = serious adverse event

a. As assessed by the investigator.

Table 38. Treatment-Emergent Adverse Events Reported in ≥ 5% of Subjects by Preferred Term (FAS)

Subjects With Treatment-Emergent	Adalimumab (N = 55) n (%)
Adverse event	36 (65.5)
Colitis ulcerative	11 (20.0)
Upper respiratory tract infection	6 (10.9)
Headache	5 (9.1)
Anaemia	4 (7.3)
Arthralgia	4 (7.3)
Mycobacterium tuberculosis complex test positive	4 (7.3)
Bronchitis	3 (5.5)
Gastritis	3 (5.5)
Nasopharyngitis	3 (5.5)

FAS = full analysis set

Any adalimumab dataset (studies M11-290 and M10-870)

Overall, the majority of adalimumab-treated subjects (86%) experienced ≥ 1 TEAE (Table 39).

Table 39. Overview of Treatment-Emergent Adverse Events Through 28 August 2019 (Any ADA Set)

	Any Adalimumab	
	(N = 93) n (%)	(PYs = 145.0) Events (E/100 PYs)
Subjects with any treatment-emergent		
Adverse event (AE)	80 (86.0)	465 (320.7)
Serious AE	26 (28.0)	44 (30.3)
Severe AE	12 (12.9)	18 (12.4)
AEs leading to discontinuation of study drug	7 (7.5)	9 (6.2)
AEs rated as possibly related to study drug by the investigator (reasonable possibility)[a]	37 (39.8)	79 (54.5)
SAEs rated as possibly related to study drug by the investigator (reasonable possibility)[a]	8 (8.6)	10 (6.9)
AEs leading to death	0	0
All deaths	0	0

PYs = patient-years

a. As assessed by investigator.

Note: Subjects are counted once in each row, regardless of the number of events they may have had. AEs with unknown relationship were counted as 'reasonable possibility of being related'. AEs with unknown severity were counted as 'severe'.

Adverse events were most frequently reported in the Any ADA Set in the SOCs of Infections and Infestations, Gastrointestinal Disorders, and Nervous System Disorders. Colitis ulcerative, headache, anaemia, upper respiratory tract infection, nasopharyngitis, and pharyngitis were the most frequently reported (> 10% of subjects) TEAEs.

Table 40. Adverse Events Reported in ≥ 5% of Subjects by Preferred Term Through 28 August 2019 (Any ADA Set)

MedDRA 22.0 Preferred Term	Any Adalimumab n (%)
Colitis ulcerative	29 (31.2)
Headache	23 (24.7)
Anaemia	15 (16.1)
Upper respiratory tract infection	14 (15.1)
Nasopharyngitis	11 (11.8)
Pharyngitis	11 (11.8)
Oropharyngeal pain	7 (7.5)
Urinary tract infection	7 (7.5)
Abdominal pain	6 (6.5)
Abdominal pain upper	6 (6.5)
Arthralgia	5 (5.4)
Bronchitis	5 (5.4)
C-reactive protein increased	5 (5.4)
Mycobacterium tuberculosis complex test positive	5 (5.4)
Nausea	5 (5.4)
Pyrexia	5 (5.4)
Rash	5 (5.4)

MedDRA = Medical Dictionary for Regulatory Activities

Note: Subjects are counted once in each row, regardless of the number of events they may have had.

Re-induction data-set

This dataset included all subjects exposed to adalimumab who were re-randomized, due to 1st disease flare in maintenance period of Study M11-290, to receive a re-induction dose. Subject data is included from first dose of adalimumab in Study M11-290 through last available observation in Study M11-290/Study M10-870.

Although the number of subjects in the RR with Re-Ind Set was small, the MAH states that the TEAEs for this analysis set were consistent with those for the Any ADA Set. Most subjects (90%) in the RR with Re-Ind Set experienced at least 1 TEAE (Table 41, Table 42). Three subjects (30%) in the RR with Re-Ind Set reported a SAE (1 subject had colitis ulcerative; 1 subject had a large intestine polyp; and 1 subject had colitis ulcerative, a large intestine polyp, bronchitis, asthma, and growth failure). There was no temporal relationship between administration of a re-induction dose and occurrence of any of the SAEs, except that 1 event of colitis ulcerative was reported on the same day as the re-induction dose and was deemed as having no reasonable possibility of relationship by the investigator. In addition, nonserious cytomegalovirus enterocolitis was reported in a subject approximately 3 months after receiving the re-induction dose. No subject in the RR with Re-Ind Set discontinued study drug due to an AE, and no deaths were reported.

In accordance with the study population and the underlying disorder, most subjects in the RR with Re-Ind Set reported AEs of the Infections and Infestations (80%) and Gastrointestinal Disorders (60%) SOCs. The most frequently reported AEs (> 1 subject) overall were colitis ulcerative (5 subjects), headache (4 subjects), upper respiratory tract infection (3 subjects), urinary tract infection, viral upper respiratory tract infection, nasopharyngitis, pharyngitis, large intestine polyp, epistaxis (2 subjects each).

Table 41. Overview of Treatment-Emergent Adverse Events and All Deaths through 28 August 2019 Ex-Japan Sites (RR with Re-Ind Set)

	Any Adalimumab (N=10) n (%)
Subjects with any treatment-emergent	
Adverse event (AE)	9 (90.0)
Serious AE	3 (30.0)
Severe AE	2 (20.0)
AEs leading to discontinuation of study drug	0
AEs rated as possibly related to study drug by the investigator (reasonable possibility)#	5 (50.0)
SAEs rated as possibly related to study drug by the investigator (reasonable possibility)#	1 (10.0)
AEs leading to death	0
Infections	8 (80.0)
Serious infections	1 (10.0)
Legionella infections	0
Diverticulitis	0
Opportunistic infections excluding oral candidiasis and tuberculosis (TB)	1 (10.0)
Oral candidiasis	0
Tuberculosis	1 (10.0)
Active tuberculosis	0

Note: TEAEs are defined as any event with onset on or after the first dose of ADA treatment in Study M11-290 and up to 70 days after the last study drug injection or up to the cut-off date, whichever comes first. For subjects who received placebo during the maintenance period of Study M11-290, the TEAE collection period ends 70 days after last induction dose of ADA and re-starts with their next ADA dose, if applicable.
Subjects are counted once in each row, regardless of the number of events they may have had.
AEs with unknown relationship were counted as 'reasonable possibility of being related'.
AEs with unknown severity were counted as 'severe'.
RR with Re-Ind = Re-Randomized with Re-Induction.
As assessed by investigator.

Table 42. Overview of Treatment-Emergent Adverse Events and All Deaths through 28 August 2019 per 100 Patient-Years (PYS) Ex-Japan Sites (RR with Re-Ind Set)

	Any Adalimumab (N=10) (PYS=16.2) Events (E/100PY)
Any treatment-emergent	
Adverse event (AE)	76 (469.1)
Serious AE	7 (43.2)
Severe AE	3 (18.5)
AEs leading to discontinuation of study drug	0
AEs rated as possibly related to study drug by the investigator (reasonable possibility)#	7 (43.2)
SAEs rated as possibly related to study drug by the investigator (reasonable possibility)#	1 (6.2)
AEs leading to death	0
Infections	22 (135.8)
Serious infections	1 (6.2)
Legionella infections	0
Diverticulitis	0
Opportunistic infections excluding oral candidiasis and tuberculosis (TB)	1 (6.2)

Note: TEAEs are defined as any event with onset on or after the first dose of ADA treatment in Study M11-290 and up to 70 days after the last study drug injection or up to the cut-off date, whichever comes first. For subjects who received placebo during the maintenance period of Study M11-290, the TEAE collection period ends 70 days after last induction dose of ADA and re-starts with their next ADA dose, if applicable.
RR with Re-Ind = Re-Randomized with Re-Induction; E/100PY = Events per 100 patient-years.
AEs with unknown relationship were counted as 'reasonable possibility of being related'.
AEs with unknown severity were counted as 'severe'.
As assessed by investigator.

Serious adverse event/deaths/other significant events

Serious adverse events

During Induction, a total of 10 subjects (10.8%) experienced SAEs. The most frequently reported SAEs were colitis ulcerative (5 subjects [5.4%]). The proportion of subjects with SAEs was higher in the I-SD group (5 subjects [16.7%]) than the I-HD group (4 subjects [8.5%]).

During Maintenance up to the first disease flare, a total of 10 subjects (13.3%) experienced SAEs. The most frequently reported SAEs were colitis ulcerative (3 subjects [4.0%]). Similar proportions of subjects in the M-SD (12.9%) and M-HD (15.6%) groups experienced SAEs although the incidence rates of SAEs

were consistently higher with the standard dose regimen than the high dose regimen during Induction (159.1 E/100 PYs vs 56.3 E/100 PYs) and Maintenance (44.6 E/100 PYs vs 28.3 E/100 PYs), respectively.

In the any adalimumab dataset, a total of 26 of 93 subjects (28.0%) experienced ≥ 1 treatment-emergent SAE. Anaemia and colitis ulcerative were the only SAEs reported by >5% of subjects.

Table 43. Treatment-Emergent Serious Adverse Events through 28 August 2019 by System Organ Class and Preferred Term (Any ADA Set)

MedDRA 22.0 System Organ Class **Preferred Term**	**Any Adalimumab** **(N = 93)** **n (%)**
Any adverse event	26 (28.0)
Blood and lymphatic system disorders	5 (5.4)
Anaemia	5 (5.4)
Blood loss anaemia	1 (1.1)
Cardiac disorders	1 (1.1)
Pericarditis	1 (1.1)
Gastrointestinal disorders	14 (15.1)
Colitis ulcerative	11 (11.8)
Dyspepsia	1 (1.1)
Enteritis	1 (1.1)
Large intestine polyp	2 (2.2)
Pancreatitis	1 (1.1)
Rectal haemorrhage	1 (1.1)
Hepatobiliary disorders	1 (1.1)
Cholecystitis	1 (1.1)
Infections and infestations	6 (6.5)
Bronchitis	1 (1.1)
Gastroenteritis	2 (2.2)
Meningitis aseptic	1 (1.1)
Pharyngitis	1 (1.1)
Urinary tract infection	1 (1.1)
Injury, poisoning and procedural complications	2 (2.2)
Hand fracture	1 (1.1)
Upper limb fracture	1 (1.1)
Wrist fracture	1 (1.1)
Musculoskeletal and connective tissue disorders	1 (1.1)
Growth failure	1 (1.1)
Nervous system disorders	1 (1.1)
Headache	1 (1.1)
Loss of consciousness	1 (1.1)
Reproductive system and breast disorders	1 (1.1)
Ovarian cyst	1 (1.1)
Respiratory, thoracic and mediastinal disorders	1 (1.1)
Asthma	1 (1.1)

MedDRA 22.0 System Organ Class Preferred Term	Any Adalimumab (N = 93) n (%)
Skin and subcutaneous tissue disorders	1 (1.1)
Erythema nodosum	1 (1.1)

MedDRA = Medical Dictionary for Regulatory Activities

Note: Subjects are counted once in each row, regardless of the number of events they may have had.

Deaths

There were no deaths in the studies.

Adverse events of special interest

AESIs were reported in the following categories through the 28 August 2019 cut-off date: infections, serious infections, opportunistic infections excluding oral candidiasis and TB, latent TB, allergic reactions including angioedema/anaphylaxis, pancreatitis, new or worsening psoriasis, hematologic disorders including pancytopenia, and injection site reaction.

Table 44. Subjects with Adverse Events of Special Interest through 28 August 2019 by System Organ Class and Preferred Term (Any ADA Set)

MedDRA 22.0 System Organ Class Preferred Term	Any Adalimumab (N = 93) n (%)
Subjects with any treatment-emergent	
Infections	50 (53.8)
Serious infections	6 (6.5)
Legionella infections	0
Diverticulitis	0
Opportunistic infections excluding oral candidiasis and tuberculosis (TB)	1 (1.1)
Oral candidiasis	0
Tuberculosis	5 (5.4)
Active tuberculosis	0
Latent tuberculosis	5 (5.4)
Parasitic infections	0
Reactivation of Hepatitis B	0
Progressive multifocal leukoencephalopathy (PML)	0
Malignancies	0
Lymphoma	0
Hepatosplenic T-cell lymphoma (HSTCL)	0
Non-melanoma skin cancer (NMSC)	0
Melanoma	0
Leukemia	0
Malignancy other than lymphoma, HSTCL, leukemia, NMSC or melanoma	0
Allergic reactions including angioedema/anaphylaxis	6 (6.5)
Lupus-like reactions and systemic lupus erythematosus	0
Vasculitis	0
Cutaneous vasculitis	0
Non-cutaneous vasculitis	0
Sarcoidosis	0
Autoimmune Hepatitis	0

MedDRA 22.0 System Organ Class Preferred Term	Any Adalimumab (N = 93) n (%)
Myocardial infarction (MI)	0
Cerebrovascular accident (CVA)	0
Congestive heart failure (CHF)	0
Pulmonary embolism	0
Interstitial lung disease	0
Intestinal perforation	0
Pancreatitis	1 (1.1)
Stevens-Johnson syndrome	0
Erythema multiforme	0
Worsening or new onset of psoriasis	2 (2.2)
Demyelinating disorder	0
Amyotrophic lateral sclerosis	0
Reversible posterior leukoencephalopathy syndrome (RPLS)	0
Hematologic disorders including pancytopenia	15 (16.1)
Liver failure and other liver events	0
Humira administration related medication error	0
Injection site reaction	8 (8.6)

ADA = adalimumab; MedDRA = Medical Dictionary for Regulatory Activities

Infections

Infections were the most frequently reported category of AESIs (53.8% of subjects). Serious infectious AEs occurred in 6.5% of the patients (bronchitis, gastroenteritis, aseptic meningitis, pharyngitis, urinary tract infection). Upper respiratory tract infection, pharyngitis, and nasopharyngitis were the most frequently reported infections. No serious infections led to discontinuation of the study drug.

One nonserious opportunistic infection (cytomegalovirus enterocolitis) was severe and considered by the investigator to have a reasonable possibility of being related to study drug; the event resolved in 25 days. Five subjects had a positive TB test result during their routine annual screening; all events were mild, without clinical symptomatology of TB infection, and none led to a change in study drug dose or premature discontinuation. Chemoprophylaxis medication was prescribed to 4 subjects who remained in the study; 1 subject was lost to follow-up before initiating TB prophylaxis.

The occurrence of serious infections per dose in study M11-290 is shown in Table 45.

Table 45. Treatment-Emergent Serious Infections during Maintenance Period, study M11-290

Subjects with Treatment-Emergent Serious Infections during Maintenance Period
by System Organ Class and Preferred Term
Ex-Japan Sites
(Safety Population - Patients with at Least One Dose of Study Drug in Maintenance Period)

MedDRA 22.0 System Organ Class Preferred Term	M-SD (N=31) n (%)	M-HD (N=32) n (%)	Total-ADA (N=63) n (%)	M-PL (N=12) n (%)	Total (N=75) n (%)
Any adverse event	2 (6.5)	3 (9.4)	5 (7.9)	0	5 (6.7)
Infections and infestations	2 (6.5)	3 (9.4)	5 (7.9)	0	5 (6.7)
Gastroenteritis	2 (6.5)	0	2 (3.2)	0	2 (2.7)
Meningitis aseptic	0	1 (3.1)	1 (1.6)	0	1 (1.3)
Pharyngitis	0	1 (3.1)	1 (1.6)	0	1 (1.3)
Urinary tract infection	0	1 (3.1)	1 (1.6)	0	1 (1.3)

M-PL = maintenance placebo group, M-SD = maintenance standard dose group, M-HD = maintenance high dose group.
Note: Subjects are counted once in each row, regardless of the number of events they may have had.

Program Source Code: /parepbk/SDA/Humira/UC/M11-290/CSR/X/Main/14.3/PCMB_RUN/m11290-aesum-mt.sas

Allergic reactions

Allergic reactions occurred in 6 subjects; all were mild. One subject had an attack of asthma, which the investigator considered probably allergy-related, with cough; the event led to hospitalization and resolved in 4 days although the asthma remained intermittent. Two subjects had injection site urticaria that was considered by the investigator to have a reasonable possibility of being related to study drug. None of the AEs required interruption or discontinuation of study drug.

Pancreatitis

One subject had pancreatitis that was moderate, considered by the investigator to have a reasonable possibility of being related to study drug, led to hospitalization, and resolved in 15 days. The subject had a history of pancreatitis secondary to UC flare prior to study entry.

Haematologic disorders

Anaemia was the only hematologic disorder reported (15 of 93 subjects [16.1%]); in the majority of these subjects, the anaemia was mild or moderate and resolved. Five subjects had serious anaemia that required hospitalization; 1 of these subjects discontinued study drug due to the anaemia. In 3 of these subjects, the anaemia was severe; anaemia was not considered by the investigator to have a reasonable possibility of being related to study drug for these subjects. Three of the 5 subjects with serious anaemia had a prior medical history of anaemia.

Laboratory findings

According to the MAH, mean changes in haematology, clinical chemistry, and urinalysis parameter values were small and not considered clinically significant.

In the Any ADA Set, few potentially clinically significant liver function laboratory values were reported. One subject with a history of cholecystitis had elevated liver tests including transaminases > 5 × upper limit of normal 9 days after the subject had stopped receiving study drug; 1 subject had an isolated ALT value > 3 × upper limit of normal. No other subjects had an ALT or AST value > 3 × upper limit of normal as of the cut-off date.

Immunological events

Three subjects became AAA+ during the study. The overall AAA+ rate was 3% (3/100). None of these patients had a disease flare during the study. According to the MAH, immunogenicity did not appear to have a significant impact on the safety.

Safety in special populations

Adverse events by age

Adverse events by age group are provided in Table 46.

Table 46. Overview of Treatment-Emergent Adverse Events and All Deaths through 28 August 2019 per 100 Patient-Years (PYS) by Age

	Any Adalimumab — Age Categories	
	< 13 Years (N=25) (PYS=46.5) Events (E/100PY)	>= 13 Years (N=68) (PYS=98.5) Events (E/100PY)
Any treatment-emergent		
Adverse event (AE)	156 (335.5)	309 (313.7)
Serious AE	12 (25.8)	32 (32.5)
Severe AE	2 (4.3)	16 (16.2)
AEs leading to discontinuation of study drug	1 (2.2)	8 (8.1)
AEs rated as possibly related to study drug by the investigator (reasonable possibility)#	17 (36.6)	62 (62.9)
SAEs rated as possibly related to study drug by the investigator (reasonable possibility)#	2 (4.3)	8 (8.1)
AEs leading to death	0	0
Infections	55 (118.3)	62 (62.9)
Serious infections	1 (2.2)	5 (5.1)
Legionella infections	0	0
Diverticulitis	0	0
Opportunistic infections excluding oral candidiasis and tuberculosis (TB)	0	1 (1.0)

Note: TEAEs are defined as any event with onset on or after the first dose of ADA treatment in Study M11-290 and up to 70 days after the last study drug injection or up to the cut-off date, whichever comes first. For subjects who received placebo during the maintenance period of Study M11-290, the TEAE collection period ends 70 days after last induction dose of ADA and re-starts with their next ADA dose, if applicable.
ADA = Adalimumab; E/100PY = Events per 100 patient-years.
AEs with unknown relationship were counted as 'reasonable possibility of being related'.
AEs with unknown severity were counted as 'severe'.
As assessed by investigator.

Adverse events by weight

Adverse events by weight are provided in Table 47.

Table 47. Overview of Treatment-Emergent Adverse Events and All Deaths through 28 August 2019 per 100 Patient-Years (PYS) by Weight

	Any Adalimumab — Weight	
	< 40 kg (N=15) (PYS=30.8) Events (E/100PY)	>= 40 kg (N=78) (PYS=114.2) Events (E/100PY)
Any treatment-emergent		
Adverse event (AE)	84 (272.7)	381 (333.6)
Serious AE	12 (39.0)	32 (28.0)
Severe AE	2 (6.5)	16 (14.0)
AEs leading to discontinuation of study drug	1 (3.2)	8 (7.0)
AEs rated as possibly related to study drug by the investigator (reasonable possibility)#	14 (45.5)	65 (56.9)
SAEs rated as possibly related to study drug by the investigator (reasonable possibility)#	1 (3.2)	9 (7.9)
AEs leading to death	0	0
Infections	20 (64.9)	97 (84.9)
Serious infections	2 (6.5)	4 (3.5)
Legionella infections	0	0
Diverticulitis	0	0
Opportunistic infections excluding oral candidiasis and tuberculosis (TB)	0	1 (0.9)

Note: TEAEs are defined as any event with onset on or after the first dose of ADA treatment in Study M11-290 and up to 70 days after the last study drug injection or up to the cut-off date, whichever comes first. For subjects who received placebo during the maintenance period of Study M11-290, the TEAE collection period ends 70 days after last induction dose of ADA and re-starts with their next ADA dose, if applicable.
ADA = Adalimumab; E/100PY = Events per 100 patient-years.
AEs with unknown relationship were counted as 'reasonable possibility of being related'.
AEs with unknown severity were counted as 'severe'.
As assessed by investigator.

Extrinsic factors

According to the MAH, extrinsic factor analyses performed for TEAEs by prior exposure to anti-TNFs, baseline systemic corticosteroids, baseline immunosuppressants, and disease severity per Mayo score did not show any significant differences, with the exception that:

- the percentage of subjects with SAEs, with serious infections, and with hematologic disorders was larger in subjects with prior exposure to anti-TNFs than without (46.7% versus 24.4%, respectively, for SAEs; 20.0% versus 3.8%, respectively, for serious infections; 26.7% versus 14.1%, respectively for hematologic disorders);
- subjects on systemic corticosteroids at Baseline experienced higher incidences of AEs leading to discontinuation of study drug (11.4% versus 4.1%), serious infections (11.4% versus 2.0%), and latent TB (9.1% versus 2.0%) compared with subjects without concomitant corticosteroids at Baseline, respectively; and
- subjects on concomitant immunosuppressants at Baseline reported more hematologic disorders compared with subjects without use of immunosuppressants (21.8% versus 7.9%, respectively).

Pregnancy and lactation

No pregnancies were reported in Study M11-290 or Study M10-870 as of the 28 August 2019 cut-off date.

Discontinuation due to adverse events

Adverse events leading to discontinuation of study drug occurred in 7 of 93 subjects (7.5%). These included anaemia, pericarditis, ulcerative colitis and enteritis.

Post marketing experience

The proposed indication for paediatric UC is further supported by data from the ImproveCareNow (ICN) registry, claims database data, literature data, safety data from other approved indications for Humira in paediatric populations, and pharmacovigilance data.

Real World Evidence

The safety of Humira in UC paediatric population is supported by supplemental real-world data from a number of other sources. One data source is a retrospective, longitudinal, observational cohort study of 133 patients with UC who were treated with adalimumab at ICN network of paediatric gastroenterology care centres in the US up to November 2016. In addition, 4 reports are available on the use of adalimumab in 51 paediatric patients with UC, most of whom had prior exposure to infliximab: 1) a retrospective analysis reports from an Italian registry (Aloi 2018[4]) and 2) report from a single United Kingdom (UK) center (Volonaki 2015[5]), 3) a prospective audit report from clinical centers in the UK (Merrick 2018[6]), and 4) an individual patient report (Cameron 2015[7]). In summary, the ICN registry and these reports, encompassing a total of 184 patients, suggest that clinically meaningful proportions of paediatric patients with UC who were primarily refractory to previous treatment benefitted from use of

[4] Aloi M, Bramuzzo M, Arrigo S, et al. Efficacy and safety of adalimumab in pediatric ulcerative colitis: a real-life experience from the SIGENP-IBD Registry. J Pediatr Gastroenterol Nutr. 2018;66(6):920-5.
[5] Volonaki E, Mutalib M, Kiparissi F, et al. Adalimumab as a second-line biological therapy in children with refractory ulcerative colitis. Eur J Gastroenterol Hepatol. 2015;27(12):1425-8.
[6] Merrick VM, Mortier K, Williams LJ, et al. Real-life anti-tumor necrosis factor experience in more than 500 patients: high co-immunosuppression rates but low rates of quantifying treatment response. J Pediatr Gastroenterol Nutr. 2018;66(2):274-80.
[7] Cameron FL, Wilson ML, Basheer N, et al. Anti-TNF therapy for paediatric IBD: the Scottish national experience. Arch Dis Child. 2015;100(4):399-405.

adalimumab over durations up to and beyond 1 year. No deaths, malignancies, or TB were reported. The available published studies are limited by their noninterventional and mainly retrospective nature, the lack of randomization, and a less stringent data collection approach compared to Phase 3 studies, such as Study M11-290 and Study M10-870, which may have resulted in underreporting of safety events. However, according to the MAH, the observed safety profile in these published sources is consistent with the established safety experience with adalimumab in the treatment IBD, the underlying disease and patient population, and the use of prior and concomitant UC-related medications.

Safety Data for Other Approved Paediatric Indications for Humira

A recent publication reported an analysis of the safety of adalimumab in paediatric patients with juvenile idiopathic arthritis (JIA; polyarticular JIA and paediatric enthesitis-related arthritis), psoriasis, and CD from 7 global, randomized, and OL MAH-sponsored clinical trials of adalimumab and the OL extensions conducted between September 2002 and December 31, 2015 (Horneff 2018[8]). A total of 577 patients were included, for a total of 1440.7 PYs of adalimumab exposure. Across the indications, the most frequently reported adverse events were injection site pain, upper respiratory tract infections, headache, and nasopharyngitis (44.8, 24.3, 19.9, and 17.3 E/100 PYs, respectively). Serious infections (4.0 E/100 PYs) were the most frequent serious AEs; serious infection rates were 2.7, 0.8, and 6.6 E/100 PYs, respectively, across patients with JIA, psoriasis, and CD. The conclusion was that the safety profile of adalimumab across paediatric indications was similar to the respective adult indications taking differences between study populations into account; no new safety signals were identified with adalimumab treatment.

Pharmacovigilance Data

A registry (Study P10-262 [STRIVE]) in patients with polyarticular or polyarticular-course JIA is ongoing, with an accumulation of 2204.5 patient-years of adalimumab exposure as of 01 June 2019. To date, the benefit-risk profile of adalimumab in patients with polyarticular JIA remains positive.

The overall safety profile of adalimumab in paediatric patients (from 6 years of age) with moderately to severely active CD, some with more than 7 years of exposure, has been consistent with the known safety profile of adalimumab in adults with CD. As of December 2019, a total of 192 paediatric patients with CD have been exposed to adalimumab (522.1 PYs) in MAH-sponsored clinical studies. A long-term noninterventional registry in paediatric patients with moderately to severely active CD (Study P11-292 [CAPE]) is ongoing, with 887 patients enrolled in the Humira Registry Group with an accumulation of 1641.5 patient-years of adalimumab exposure as of 31 May 2019. No new safety signals have been identified for paediatric patients with CD.

Treatment with adalimumab to date has been safe and well-tolerated for paediatric patients with moderately to severely active CD. Overall, the long-term MAH-sponsored paediatric studies (Study P10-262 in JIA [completed 10th year] and Study P11-292 in paediatric CD [completed 5th year]) have shown that the majority of the most frequently reported treatment-related AEs, including SAE, AESI, and AEs that resulted in discontinuation of registry drug are either consistent with the safety profile described in the currently approved prescribing information for Humira or associated with the disease of interest.

Cumulatively, there were a total of 49,693 unique patients on treatment in MAH-sponsored clinical studies (including registries) of approved and unapproved indications through 31 December 2019. These include clinical studies with RA, JIA, paediatric ERA, ankylosing spondylitis, spondyloarthritis, non-radiographic axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric psoriasis, CD, paediatric CD, UC, hidradenitis suppurativa, uveitis, intestinal Behçet's disease, pustular psoriasis, and pyoderma gangrenosum. The estimated cumulative postmarketing patient exposure from all indications from 31

[8] Horneff G, Seyger MMB, Arikan D, et al. Safety of adalimumab in pediatric patients with polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis, psoriasis, and Crohn's disease. J Pediatr. 2018;201:166-75.

December 2002 (International Birth Date) to 31 December 2019 is 7.8 million patient-treatment years. To date, comprehensive data across all Humira postmarketing, observational registries continue to show that the benefit-risk profile of Humira in patients of the approved indications remains favourable.

Real-World Multi-Database Study in Patients in the United States

To augment the published and registry-based information on AEs in real-world paediatric UC populations, the MAH conducted analyses of safety in adalimumab-treated patients with UC < 18 years of age in 2 US-based administrative claims databases, Optum Clinformatics® (data from 01 January 2013 through 30 June 2019) and IBM MarketScan® commercial (data from 01 January 2013 through 30 June 2019). Patients included in the analyses had a filled prescription claim for adalimumab and met criteria for UC diagnosis prior to the date of the first adalimumab claim (index date), were < 18 years of age, and had a minimum of 180 days of insurance eligibility on the date of the first adalimumab claim. In each claims database, relevant AEs included UC-related inpatient admissions, intestinal resection procedures, hospitalized infections (TB and herpes infections separated out), and malignancies (nonmelanoma skin cancer separated out). On-treatment person-time (follow-up period) was defined as the day after index through the consecutive days covered by adalimumab prescription claims, censoring at the event of interest, treatment termination (30 day gap allowed), age 18, end of insurance eligibility, death or end of data. Median follow-up duration was 108 – 138 days, depending on database and outcome.

Demographic characteristics of patients included in the 2 claims database analyses were similar and comparable to the respective characteristics of subjects in Study M11-290 (Table 12). Although the number of subjects in both adalimumab-treated cohorts was small and median follow-up durations were short, the results of relevant AEs (number and percent of subjects, number of AEs per 100 PYs; Table 13) reported for each cohort were consistent with the underlying paediatric UC and no new safety information was identified.

Table 48. Baseline Demographic Characteristics for Adalimumab-Treated Paediatric Patients with Ulcerative Colitis (Claims-Based Real-World Cohorts)

Characteristic	Clinformatics Database (N = 176)	MarketScan Database N = 439
Age, mean (SD)	14.28 (2.69)	14.41 (2.85)
Age, median (IQR)	15.00 (13.00, 16.00)	15.00 (13.00, 17.00)
Gender, n (%)		
Female	89 (50.6)	207 (47.2)
Male	87 (49.4)	232 (52.8)

IQR = interquartile range; SD = standard deviation

Note: Data is from the date of first adalimumab prescription claim (index).

Table 49. Adverse Events in Adalimumab-Treated Patients with Paediatric Ulcerative Colitis (Claims-Based Real-World Cohorts)

	Clinformatics Database (N = 176)			MarketScan Database (N = 439)		
Adverse Event	n (%)[a]	E/100 PYs (95% CI)[b]	Mean Time to Occurrence, Days (CI)[c]	n (%)[a]	E/100 PYs (95% CI)[b]	Mean Time to Occurrence, Days (CI)[c]
UC-related hospitalizations	27 (15.34)	26.45 (16.48 - 36.43)	1,219.60 (1,037.95, 1,401.24)	54 (12.30)	19.30 (14.15 - 24.45)	1,545.83 (1,421.63, 1,670.04)
Intestinal resection procedure	11 (6.25)	10.16 (4.15 - 16.16)	1,506.72 (1,410.50, 1,602.94)	14 (3.19)	4.78 (2.28 - 7.29)	1,852.08 (1,792.12, 1,912.03)
Hospitalized infection, excluding TB and herpes infections	2 (1.14)[d]	1.83 (0.22 - 6.62)	1,628.39 (1,573.30, 1,683.48)	2 (0.46)[e]	0.67 (0.08 - 2.42)	1,943.83 (1,926.46, 1,961.21)
TB	0 (0.00)	0.00 (0.00 - 3.31)	N/A	0 (0.00)	0.00 (0.00 - 1.23)	N/A
Herpes infections	0 (0.00)	0.00 (0.00 - 3.31)	N/A	0 (0.00)	0.00 (0.00 - 1.23)	N/A
Malignancy excluding NMSC	0 (0.00)	0.00 (0.00 - 3.31)	N/A	1 (0.23)[f]	0.34 (0.01 - 1.87)	1,950.38 (1,939.38, 1,961.38)
NMSC	0 (0.00)	0.00 (0.00 - 3.31)	N/A	0 (0.00)	0.00 (0.00 - 1.23)	N/A

ADA = adalimumab; CI = confidence interval; E = events; N/A = not applicable; NMSC = non-melanoma skin cancer; PYs = patient-years; TB = tuberculosis; UC = ulcerative colitis

a. Number of patients with an event on treatment with ADA (% of total in cohort).

b. Rate calculated as number of patients with an event on treatment, divided by total person-years on treatment with ADA.

c. CI was estimated as area under the survival curve.

d. Two events of infection occurred in the follow-up period (in separate patients): Methicillin susceptible Staphylococcus aureus septicemia; Sepsis, unspecified.

e. Two events of infection occurred in the follow-up period (in separate patients): cellulitis of trunk, unspecified; Sepsis, unspecified.

f. One patient had the following malignancy during the follow-up period: malignant neoplasm of brain, unspecified.

2.5.1. Discussion on clinical safety

Adalimumab is approved for several paediatric indications: Juvenile idiopathic arthritis (from 2 years), Paediatric plaque psoriasis (from 4 years), Paediatric Crohn's disease (from 6 years) and Paediatric Uveitis (from 2 years). It is also approved for adolescent hidradenitis suppurativa from 12 years. With this variation, the MAH seeks to add a new indication for the treatment of paediatric patients 5 to 17 years of age with moderately to severely active ulcerative colitis. This application is supported by data from 2 Phase 3 clinical studies: a randomized, controlled study (Study M11-290) and its open-label (OL) long-term study (Study M10-870).

The recommended standard maintenance dose for the JIA, paediatric plaque psoriasis and paediatric uveitis indications are lower than what is now proposed for UC:

- *JIA and paediatric plaque psoriasis*:
  <30 kg: 20 mg every other week (eow) and ≥30 kg: 40 mg eow
- *Adolescent hidradenitis suppurativa (from 12 years):*
  ≥30 kg: 40 mg eow
- *Paediatric Crohn's disease:*
  <40 kg: 20 mg eow and ≥40 kg: 40 mg eow
  Patients with insufficient response may increase the dose as follows:
  < 40 kg: 20 mg every week; and ≥ 40 kg: 40 mg every week or 80 mg every other week

The proposed maintenance dose for the paediatric UC population is <40 kg: 40 mg eow and ≥40 kg: 80 mg eow

Thus, the recommended maintenance dose is doubled compared to the standard maintenance dose in the paediatric Crohn's disease population.

For the adult population, the same dose is recommended for both the Crohn's and UC population: 40 mg eow with possibility to dose increase to 40 mg ew or 80 mg eow in patients who experience decrease in their response.

The mean duration of adalimumab exposure for the 93 subjects included in study M11-290 was 569.6 days, giving a total of 145.0 PYs of exposure. Among the 93 patients, 57 patients (61.3%) were exposed to Humira for more than 1 year. This can be compared to the approval of the paediatric CD indication, where a total of 192 patients were exposed to at least 1 dose of Humira whereof 115 patients were exposed for more than 1 year (Humira II-88 EPAR, variation approved in 2013). Although the exposure is markedly smaller in the current application, this can be acceptable given the overall exposure to date of Humira in paediatric patients, and especially given that UC and CD share many common features and the same safety profiles can be expected in both populations.

As stated in the EMA Guideline on Development of new medicinal products for the treatment of ulcerative colitis, the following factors should be considered to justify extrapolation of data from use in adults:

- *Whether the substance belongs to a well-studied pharmacological class for which several substances have already been granted a paediatric indication* – this requirement is considered fulfilled by CHMP, since infliximab is approved for the treatment of paediatric UC.
- *Whether a comprehensive amount of data has already been collected in adults with UC* - this requirement is considered fulfilled by CHMP since adalimumab is approved for the treatment of adults with UC
- *Whether a safe dose in children has been identified for the same medicinal product for other diseases* - this requirement is fulfilled based on the other approved paediatric indications

The mean age of the studied patients was 14.1 years (range 5-17). The majority (~80%) was older than 12 years, and only 19 of the patients were below 12 years of age (5, 6, 7 (n=2), 8 (n=2), 9 (n=3), 10 (n=3), 11 (n=7)).

Study M11-290 had an 8-week double-blind (DB) induction period and a 44-week DB maintenance period. Study M10-870 (extension study of Study M11-290) has a 288-week maintenance period, with subjects receiving OL adalimumab beginning at the baseline visit (Week 52 visit from Study M11-290).

Induction phase

Two different induction regimens were studied (differences between the two regimens are highlighted in bold):

- High dose: adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.
- Standard dose: adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and matching placebo at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.

During the induction phase, a total of 55.9% of the patients reported any AEs. The frequency of AEs was slightly higher among subjects receiving the "standard" dose induction (56.7%) than those receiving "high" dose induction (48.9%). Most TEAEs reported were mild to moderate in severity. The SOCs with the most frequently reported TEAEs were infections and infestations (21.5%) and gastrointestinal disorders (21.5%). Headache, anaemia and ulcerative colitis were most commonly observed adverse events. Headache is a known side effect, reported as "very common" in the SmPC. Regarding anaemia, the frequency was higher in the standard dose group, probably reflecting disease activity rather than a consequence of the treatment.

The proportion of subjects with serious AEs was higher in the I- SD group (16.7%) than the I- HD group (8.5%). Only 3 patients (3.2%) experienced adverse events leading to discontinuation of the study drug. In summary, the observed adverse events are expected given the known safety profile of Humira, and there seemed to be no dose-relation in the frequency or severity of adverse events.

Maintenance phase

Two different maintenance regimens were studied (from week 8 and onwards):

- Standard dose: Adalimumab 0.6 mg/kg (maximum dose of 40 mg) eow
- High dose: Adalimumab 0.6 mg/kg (maximum dose of 40 mg) ew

During the maintenance phase, a total of 66.7% of the adalimumab-treated patients reported adverse events (64.5% in the standard dose group and 68.8% in the high dose group). The proportion of patients experiencing any treatment-emergent adverse events was higher among placebo-treated patients than among patients treated with adalimumab (both standard dose and high dose), whereas severe adverse events were more frequent among adalimumab-treated patients. It is noted that most of these were not considered related to the study drug. Adverse events and serious adverse events were slightly more frequent for the high dose regimen, than for the standard dose regimen. There were no deaths in any of the study groups. It should be noted that also placebo-treated patients achieved induction treatment with adalimumab.

The SOCs with the most frequently reported TEAEs were infections and infestations (37.3%) and gastrointestinal disorders (29.3%). Headache and ulcerative colitis were most commonly observed adverse events.

The proportion of adalimumab-treated subjects who experienced TEAEs related to study drug was slightly higher in the HD group than in the SD group (31.3% vs. 25.8%). The most frequently reported TEAEs having a reasonable possibility of being related to study drug were colitis ulcerative (4.8%), fatigue, headache, and rash (all 3.2%). It is noted that serious infections were slightly more frequent for the high dose regimen (3/32 subjects, 9.4%) than for the SD regimen (2/31 subjects, 6.5%), but the absolute number of cases was very low in both groups.

Long-term extension study M10-870

In the long-term extension study M10-870, all patients received open-label Humira as follows:

- Subjects who enrolled into the study from blinded treatment in Study M11-290 received OL adalimumab 0.6 mg/kg (maximum of 40 mg) every other week (eow).
- Subjects who received OL adalimumab (ew at 0.6 mg/kg [maximum of 40 mg]) in Study M11-290 maintained the same dose in Study M10-870

Subjects with a disease flare who were on adalimumab 0.6 mg/kg (maximum dose of 40 mg, weight based) eow could receive adalimumab 0.6 mg/kg (maximum of 40 mg, weight based) every week (ew). Subjects with a disease flare who were on adalimumab 0.6mg/kg ew could receive adalimumab 40 mg ew (maximum dose of 40 mg).

Thus, only patients who flared in this study received the higher dose regimen.

Combined dataset (“Any Adalimumab dataset”)

A total of 80/93 patients (86%) experienced adverse events. The most commonly occurring side effects were headache and infections. Many of the described adverse events are more likely to be associated with the disease per se (i.e. ulcerative colitis, abdominal pain and increased CRP) while for example anaemia can be associated with both the disease and adalimumab treatment.

A total of 26/93 patients (28%) experienced serious adverse events. Most common were gastrointestinal disorder which is not likely associated with the treatment but rather with the disease. Anaemia occurred in 5% of the patients, but causality with Humira is difficult to assess because it is a common symptom of UC. Serious infections occurred in 6/93 patients (6.5%); bronchitis, gastroenteritis (2 cases), aseptic meningitis, pharyngitis and urinary tract infection. This is consistent with the known safety profile of Humira.

Upon request from CHMP, the MAH presented the frequency of adverse events, serious adverse events and infections in pooled data from studies M11-290 and M10-870 for the two different maintenance dosing regimens (SD/HD) separately. For infections and serious infections the exposure-adjusted incidence rates were lower for the SD regimen than for the HD regimen (infections: 53.2 E/100PYs vs 79.4 E/100PYs, serious infections: 3.7 E/100PYs vs 6.3 E/100PYs). It is agreed with the MAH that overall, the safety profile of subjects who received the M-SD and the M-HD regimens were similar during Studies M11-290 and M10-870.

There were no malignancies or deaths in the studies. The rate of ADAs was low.

Among the AESIs, infections were the most common adverse event. Most infections were mild, and serious infections were uncommon and did not lead to treatment discontinuation in any case. There were 6 cases of allergic reactions, but none of these patients had to discontinue treatment. Regarding anaemia, this is a common symptom of UC and causality with Humira is difficult to assess. The fact that 3/5 patients had a history of anaemia makes confounding by disease more likely.

To conclude, the AESIs reported are consistent with the expected safety profile of Humira.

Serious adverse events were slightly more frequent in patients aged ≥13 years than in the younger age group, while infections were more common among the younger children. Serious infections were however less frequent among the younger children, which is reassuring.

The rate of anti-adalimumab antibody in patients with moderately to severely active paediatric UC receiving adalimumab was 3%. Section 5.1 of the SmPC is updated with the immunogenicity in this patient population.

One patient (1/93) had an ALT value > 3 × upper limit of normal. Section 4.8 of the SmPC is updated to include this information.

There was no specific pattern observed with regards to adverse events by weight group. Safety data in the youngest patients is very limited, since only 19 of the patients were below 12 years of age (5, 6, 7 (n=2), 8 (n=2), 9 (n=3), 10 (n=3), 11 (n=7)). PK data indicates high exposures in subjects of low weight. The initially proposed indication for patients 5 years older was therefore not supported from a safety perspective. The MAH was in the first round asked to discuss to include a lower weight cut-off in the indication statement. Based on the presented data, the MAH was asked to revise the indication to include only children aged 6 years and older. The MAH revised the indication as requested and the issue was solved.

The MAH has summarised post-marketing data from several sources to support the recently proposed indication. These include the ICN registry and literature reports, including a total of 184 paediatric UC patients. There were no deaths, malignancies or TB cases reported from these sources.

There is also data on paediatric use of adalimumab from other indications. In a publication by Horneff, a total of 577 patients were included. The authors conclude that the safety profile of adalimumab across paediatric indications was similar to the respective adult indications taking differences between study populations into account; no new safety signals were identified with adalimumab treatment.

The MAH has also summarised pharmacovigilance data from other paediatric indications. These include polyarticular JIA (2204 patient-years) and CD (192 patients, 522 patient-years in clinical studies and 887 patients (1641.5 patient-years) in a non-interventional registry).

Finally, data is presented from two US-based claims databases (Optum and IBM MarketScan). These include a total of 615 Humira-treated UC patients aged <18 years. There were no deaths and no cases of TB observed in these data. There was one case of malignancy; a malignant brain tumour.

Although the limitations with these data must be acknowledged, it is agreed with the MAH that the exposure of Humira in paediatric patients is large and that these data can be considered supportive for the safety of Humira in paediatric UC.

In the SmPC, there was an option to repeat the induction dose of 80 mg (<40 kg) or 160 mg (≥40 kg) in patients who experience a disease flare after beginning maintenance therapy. A higher proportion of subjects who received a re-induction dose (33.3%) demonstrated clinical response at Week 52 compared to subjects without re-induction (22.2%). Nonetheless, the benefit of this re-induction dose is not considered to overweigh the potential risks since it will lead to exposures outside the previously studied exposure range for Humira which is not accepted. The MAH removed this re-induction regimen from the SmPC as requested.

Patients with UC are at increased risk for colorectal cancer and cholangiocarcinoma. The presented data are too limited to assess the long-term risks associated with Humira treatment in children with UC. As stated in the EMA Guideline on Development of new medicinal products for the treatment of ulcerative colitis, *"Collection of safety data will always be required to identify any unexpected age-specific safety events. For the confirmation of efficacy and to evaluate safety in larger populations long-term post-marketing observational studies (i.e. registries) may be used"*. Therefore, long-term data in paediatric UC patients will be important. The MAH has provided a discussion on the feasibility to collect observational data within a relevant study setting with special focus on dysplasia of the colon and colorectal cancer. Assuming an annual background risk to develop CRC of 0.011% for paediatric patients with UC, a study with a follow-up time of up to 10 years would lead to a sample size of N = 8,838. It is agreed with the MAH that this is not considered feasible. Therefore, the MAH's proposal to perform standard postmarketing safety surveillance is acceptable. Long-term safety information in peadiatric UC patients is included as missing information in the RMP and will be reviewed in future PSURs. Furthermore, the final report from the extension phase of the paediatric UC study, which is a Category 3 in the RMP, will be submitted in 2025.

2.5.2. Conclusions on clinical safety

Although the exposure of adalimumab to paediatric patients with UC is limited, there is no new safety signal identified in the paediatric clinical development program submitted. Adalimumab has a well characterised safety profile in several authorised indications, including adult UC and juvenile idiopathic arthritis (from 2 years), paediatric plaque psoriasis (from 4 years), paediatric Crohn's disease (from 6 years) and paediatric uveitis (from 2 years).

The MAH proposes a higher maintenance dose for the paediatric UC indication than what is approved as standard dose for the other paediatric indications (although a dose increase to the currently proposed dose is possible in the paediatric Crohn's population). Although a slightly higher frequency of infections was observed for the high-dose regimen than compared to the standard dose regimen, the overall safety profile is similar for the two regimens.

The MAH was in the first round asked to discuss to include a lower weight cut-off in the indication statement. Based on the presented data indicating exposures exceeding previously approved ones and

largest deviations between the body-weight dosing of the clinical study and the proposed flat dosing observed in lowest group, the MAH was asked to revise the indication to include only children aged 6 years and older. The MAH revised the indication as requested and the issue was solved.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The PRAC considered that the risk management plan version 15.1 is acceptable. The CHMP endorsed the Risk Management Plan version 15.1 with the following content:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risk		
Serious infections	Routine risk minimization measures: Text in SmPC sections 4.3, 4.4, 4.8 and corresponding sections of the PL Additional risk minimization measures: To remind patients about the risk of serious infections associated with the use of Humira: • Patient Reminder Card	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: Additional pharmacovigilance activity: monitoring as an event of special interest in registry studies.
Tuberculosis (TB)	Routine risk minimization measures: Text in SmPC sections 4.3 and 4.4 and corresponding sections of the PL Additional risk minimization measures: To remind patients about the risk of TB associated with the use of Humira: • Patient Reminder Card.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: Additional pharmacovigilance activity: monitoring as an event of special interest in registry studies.
Malignancies	Routine risk minimization measures: Text in SmPC sections 4.4 and 4.8 and corresponding sections of the PL Additional risk minimization measures: To remind patients about the risk of malignancies associated with the use of Humira: • Patient Reminder Card.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: monitoring as an event of special interest in registry studies.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Demyelinating disorders (including MS, GBS, and ON)	Routine risk minimization measures: Text in SmPC sections 4.4 and 4.8 and corresponding sections of the PL Additional risk minimization measures: To remind patients about the risk of demyelinating disorders associated with the use of Humira. • Patient Reminder Card.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: None.
BCG disease following live BCG vaccination in infants with in utero exposure to Humira	Routine risk minimization measures: Text in SmPC section 4.4. and corresponding sections of the PL Additional risk minimization measures: To remind patients about the risk of BCG disease following live BCG vaccination in infants with in utero exposure to Humira. • Patient Reminder Card.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: None.
Important Potential Risks		
Progressive multifocal leukoencephalopathy (PML)	Routine risk minimization measures: The SmPC currently contains no text regarding PML. Additional risk minimization measures: None.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: None.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Reversible posterior leukoencephalopathy syndrome (RPLS)	Routine risk minimization measures: The SmPC currently contains no text regarding reversible posterior leukoencephalopathy syndrome. Additional risk minimization measures: None.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: None.
Adenocarcinoma of colon in UC patients	Routine risk minimization measures: Text in SmPC section 4.4. Additional risk minimization measures: None.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: Monitoring as an event of special interest in registry for UC patients (Study P11-282).
Missing Information		
Patients with Immune Compromised conditions	Routine risk minimization measures: Text in SmPC section 4.4. and corresponding sections of the PL Additional risk minimization measures: None.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: None.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD	Routine risk minimization measures: None. Additional risk minimization measures: None.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: Registry for pedCD patients (Study P11-292).
Episodic treatment in Ps, UC, and JIA	Routine risk minimization measures: The SmPC currently contains no text regarding Episodic treatment in Ps, UC, and JIA. Additional risk minimization measures: None.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: Treatment interruptions in registry studies will be evaluated.
Long-term safety information in the treatment of children with uveitis	Routine risk minimization measures: Text in SmPC section 4.2 and corresponding sections of the PL Additional risk minimization measures: None.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: Long-term uveitis data from the ongoing JIA registry (Study P10-262).

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis	Routine risk minimization measures: None. Additional risk minimization measures: None.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: Extension study data from ongoing study (Study M10-870)

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC for 40mg/0.8mL, 40mg/0.4mL and 80mg/0.8mL presentations have been updated to include treatment of moderately to severely active ulcerative colitis in paediatric patients for Humira. The Package Leaflet has been updated accordingly.

The MAH took the opportunity to introduce minor editorial changes to sections 5.1, 5.2 and 5.3 of the SmPC for all the presentations.

Furthermore, the PI is being brought in line with the latest QRD template (version 10.1).

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reason: the proposed changes are limited and not considered to significantly affect the readability of the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Ulcerative colitis (UC) is one of the two primary forms of idiopathic inflammatory bowel disease (IBD). It is a chronic, relapsing inflammatory disease of the rectum and/or large intestine characterized by inflammation and ulceration of the mucosal and submucosal intestinal layers. The hallmark clinical symptoms include bloody diarrhoea associated with rectal urgency and tenesmus.

The clinical course of UC is marked by exacerbation and remission of symptoms and may eventually require a restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) in up to 30% of patients. The most severe intestinal manifestations of UC are toxic megacolon, perforation, and massive

haemorrhage. Furthermore, UC may be accompanied by extra-intestinal manifestations such as arthritis, dermatological conditions, uveitis, and primary sclerosing cholangitis (which can progress to liver failure requiring transplantation, and is associated with an increased risk of colorectal, bile duct, and gallbladder cancers).

The general clinical and histopathological features of UC as well as the drug effects are similar in adults and children. Both patient populations share the same clinical hallmark symptoms: inflammation being limited to large intestine and rectum, the occurrence of extra-intestinal manifestations, and the clinical course which usually alternates between exacerbation and remission and may lead to colectomy. There is also substantial overlap of gene expression profiles from disease tissues in both paediatric and adult UC patients suggesting strong similarity of molecular pathways. In addition, treatment paradigms are essentially similar for both populations, and pharmacological therapies such as aminosalicylates, corticosteroids, immunosuppressants (IMMs), and anti-tumour necrosis factors (TNFs) (e.g., infliximab) have shown efficacy in adult and paediatric patients with UC. However, there are differences in the phenotypic presentation and progression of the disease. While the vast majority of adults with UC have limited or left-sided colitis, pancolitis is more common in children. Ulcerative colitis often presents as a more severe disease in children. Severity of disease correlates with the likelihood of colectomy; 10-year colectomy rates in adults are 15% to 25% compared to 30% to 40% in paediatric patients.

The burden of colectomy is high in paediatric UC; among children presenting with moderate or severe disease, 9% had surgery within 1 year and 26% within 5 years. The cumulative likelihood of colectomy is generally similar between adults and children (in children 6% after 1year, 29% after 20years).

Age of Onset, Incidence, and Prevalence

Ulcerative colitis onset can occur at any age, but it is rare in infants and relatively infrequent in early childhood. The overall (adult and paediatric) incidence of UC has been reported as 1.2 to 20.3 cases per 100,000 persons/year. Incidence of paediatric IBD (CD and UC) has been increasing worldwide, including in the US. Evidence suggests that the incidence of early-onset IBD, including UC, is increasing in younger age groups. Recent studies provide incidence estimates for children under 5 years old in European countries, including up to 1.0 per 100,000 for females in the UK, 0.7 per 100,000 in Hungary, and 2.22 per 100,000 in Germany. Among older children, estimated incidence rates are higher. In France, the estimated incidence of UC is 0.6 per 100,000 person-years among children aged 0 to 9 years old and 4.1 per 100,000person-years among children aged 10 to 16. Corresponding estimates in Finland are 3.1 per 100,000 person-years for children 0 to 9 years, 15.4 per 100,000 person-years for 10to 15 years, and finally 40.4 per 100,000 person years for 15 to 19years old. Similar increases in incidence with increases in age was also seen in Germany, Italy, the UK, and Hungary.

There are some published prevalence estimates of UC for a few European countries, although the bulk of the recently published literature reports estimated incidence rates as opposed to prevalence estimates. Unsurprisingly, prevalence increases with increasing age. The highest published prevalence estimate was from Denmark, with an estimated 83.4 cases per 100,000 people under 16 years old. The lowest prevalence estimate is from Germany, which was 23.74 cases per 100,000 children 18 years old or younger.

In a commercially insured US population of over 12.5million people for the period 2008– 2009, the prevalence of paediatric UC (<20 years of age) was estimated as 34 (95% confidence interval [CI] 32 – 36) per 100,000 persons. The prevalence of paediatric UC increased with age.

More recently, in an observational retrospective cross-sectional study conducted in 2 claims databases in the US, the pooled prevalence in 2016 per 100,000 was 21.6 for UC (95% CI, 20.3– 22.8) for paediatric patients (2 to 17 years of age). This real-world data study reported a 152% increase in prevalence for UC

from 2007 to 2016 (8.6 to 21.6), which was attributed mainly to increases in the 10 to 17-year-old subgroup.

3.1.2. Available therapies and unmet medical need

The pharmacological treatment of UC in childhood is largely the same as in adulthood. Conventional pharmaceutical therapies do not completely abate the inflammatory process and have significant side effects. Conventional therapies for the induction of remission have included anti-inflammatory agents (5-aminosalicylic acid [5-ASA] derivatives and corticosteroids) and the immunomodulatory agent cyclosporine. 5-aminosalicylic acid derivatives as well as immunomodulatory agents (azathioprine [AZA]or 6-mercaptopurine [6-MP]) have been used for the maintenance of remission. Safety issues associated with the use of thiopurines include bone marrow suppression, malignancies including lymphoma, and serious infections including progressive multifocal leukoencephalopathy. Corticosteroids are not effective for the maintenance of remission. In addition to the induction and maintenance of clinical remission, absence of adverse effects on linear growth and maturation is demanded from therapy of paediatric UC. Similar to adults, corticosteroid dependence is frequent, but long-term corticosteroids are absolutely contraindicated because they do not maintain remission and have a negative effect on linear growth and bone mineralization. Infliximab (a chimeric monoclonal anti-TNF-α antibody) was approved in Europe for the treatment of paediatric patients with severe UC and in the US for the treatment of paediatric patients with moderate to severe UC based on the results of an open-label (OL) study in 60 subjects. However, infliximab is an intravenous (IV) therapy, may pose a burden to paediatric patients. For adult UC, vedolizumab and tofacitinib were approved globally and in the US and European Union (EU) respectively, and ustekinumab was approved in the US and EU recently, but none have been approved for paediatric UC patients. Hence, additional treatment options that offer induction and maintenance of remission to a clinically meaningful number of patients, an acceptable safety profile, and more convenient dosing regimens than currently approved therapies are needed for paediatric UC patients.

3.1.3. Main clinical studies

The main studies to support the new indication is study M11-290, and its open-label extension study M10-870.

Study M11-290 was a Phase 3, multicenter, randomized, DB trial designed to evaluate the efficacy and safety of adalimumab in paediatric subjects with moderate to severe UC who have failed therapy with corticosteroids and/or immunosuppressant (IMM). Study M11-290 had an 8-week DB induction period and a 44-week DB maintenance period.

Prior to an important amendment (4) due to recruitment issues, enrolled subjects were randomized 3:2 at Baseline to 1 of 2 DB adalimumab induction doses, induction high dose (I-HD) or induction standard dose (I-SD). At Week 8, subjects demonstrating a clinical response were randomized to the following groups: adalimumab maintenance standard dose (M-SD), adalimumab maintenance high dose (M-HD), or placebo. Subjects will continue their blinded treatment during the maintenance period until Week 52.

After this amendment, enrolled subjects received adalimumab induction high dose open-label (I-HD-OL). At Week 8, subjects demonstrating a clinical response were randomized to 1 of 2 adalimumab maintenance treatment groups, M-SD or M-HD. Subjects continued on their blinded treatment during the maintenance period until Week 52

Study M10-870 (extension of Study M11-290) had a 288-week maintenance period, with subjects receiving OL adalimumab beginning at the baseline visit (Week 52 visit from Study M11-290).

3.2. Favourable effects

At week 8 after the induction phase, clinical remission per Partial Mayo Score (PMS, evaluates clinical symptoms such as stool frequency and rectal bleeding and includes a physician's global score) was received in 59.6% of the patients receiving the higher induction dose (I-HD) and in 43.3% of the patients receiving the standard induction dose (I-SD). In the group receiving I-HD OL, 68.8% of the patients reached clinical remission. Although an exploratory statistical comparison was made between the doses, it is noted that a numerically higher proportion of patients receiving the higher induction dose reached clinical remission. Compared to an external placebo rate (19.83%) derived from a meta-analysis of placebo-controlled studies from an adult population with UC, I-HD was statistically significantly better.

At week 52, clinical remission per Full Mayo Score (FMS includes in addition to PMS also an endoscopic evaluation) were reached by 14 patients (45.2%) in the maintenance high dose group (M-HD) and 9 patients (29.0%) in the maintenance standard dose group (M-SD). Although no statistical comparison was made regarding the internal placebo it is noted that 4 patients (33.3%) in the placebo group also received clinical remission per FMS. Compared to the external placebo rate (18.37%), derived from an adult population, statistically significant better effect was seen only in the higher dose. The same result was seen when analysing the second ranked secondary endpoint where mucosal healing at Week 52 as measured by Mayo endoscopy subscore (defined as ≤ 1) in Week 8 PMS responders was achieved by 51.6% of subjects who were randomized to the adalimumab M-HD group and 38.7% of subjects in the M-SD group.

Among the 22 patients who experienced a disease flare during the maintenance treatment, a numerically greater proportion of subjects who received a re-induction dose (33.3%) demonstrated clinical response at Week 52 compared to subjects without re-induction (22.2%), although the number in each subgroup were too small to be conclusive.

3.3. Uncertainties and limitations about favourable effects

Since recruitment to the internal placebo group was ceased after amendment 4, the presented efficacy endpoints rely on data derived from an adult population. A central assumption in these comparisons is that placebo remission rates are at the same level for adults and children. Also, they require that the studies are conducted in a comparable manner. The submitted application did not provide support of these assumptions. It is therefore hard to make any conclusions about the effect in children from these comparisons, and the corresponding p-values should not be used to make claims about the efficacy. The study was not designed to compare the two different doses used, neither for induction therapy nor for maintenance therapy. Results from the external placebo control group are therefore not included in the approved SmPC.

The MAH proposes a higher maintenance dose for the paediatric UC indication than what is approved as standard dose for the adult UC population and for the other paediatric indications. A dose increase to the currently proposed dose is possible in both adult UC and the paediatric Crohn's population as of 6 years of age. A flat dosing is proposed while a body weight dosing was used in the clinical study. Simulated exposures in children down to 15kg indicated exposures exceeding previously approved exposures, the largest deviations between the body-weight dosing of the clinical study and the proposed flat dosing were observed in the lowest age group. The available data, from other authorised indications, were thus considered sufficient to support a use in children as of 6 years age. At the CHMP's request, the MAH restricted therefore the indication to patients 6 years and older.

Upon request from CHMP, the MAH has deleted the previous suggested "flare-treatment", since none of the patients who flared achieved FMS remission at week 52, regardless of re-induction therapy or not and

the maintenance adalimumab concentrations subsequent a re-induction dose are higher than has been previously accepted for adalimumab in the paediatric and adult populations.

3.4. Unfavourable effects

During the induction phase, a total of 55.9% of the patients reported any AEs; 56.7% among subjects receiving the "standard" dose induction and 48.9% among those receiving "high" dose induction. The SOCs with the most frequently reported TEAEs were infections and infestations (21.5%) and gastrointestinal disorders (21.5%). Headache, anaemia and ulcerative colitis were most commonly observed adverse events. Serious AEs were reported in 16.7% of the patients in the standard dose group and 8.5% of the patients in the high dose group.

During the maintenance phase, a total of 66.7% of the patients reported adverse events (64.5% in the standard dose group and 68.8% in the high dose group). The SOCs with the most frequently reported TEAEs were infections and infestations (37.3%) and gastrointestinal disorders (29.3%). Headache and ulcerative colitis were most commonly observed adverse events.

In the combined dataset ("any adalimumab dataset"), a total of 80/93 patients (86%) experienced adverse events. The most commonly occurring side effects were headache and infections. A total of 26/93 patients (28%) experienced serious adverse events, with gastrointestinal disorder being most frequent.

There were no malignancies or deaths in the studies.

3.5. Uncertainties and limitations about unfavourable effects

The MAH proposes a higher maintenance dose for the paediatric UC indication than what is approved as standard dose for the other paediatric indications (although a dose increase to the currently proposed dose is possible in the paediatric Crohn's population). Although short-term safety data is considered acceptable, long-term data in paediatric UC patients will be important. Additional safety data will be collected from the extension study M10-870 (Category 3 in the RMP).

Other important uncertainties pertain to adverse events occurring with a low frequency and long latency, because of the small study size and relatively short follow-up time. Patients with ulcerative colitis are at increased risk for colorectal cancer and cholangiocarcinoma. Paediatric UC can be more complicated and more inflammatory active than adult UC (as stated in the EMA GL), leading to an even higher risk for malignancies in children than in adults. Long-term safety data is included as missing information in the RMP and will be reviewed in future PSURs. Furthermore, the final report from the extension phase of the paediatric UC study M10-870 will be submitted in 2025.

3.6. Effects Table

Table 50 Effects Table for Humira in paediatric ulcerative colitis (data cut-off: 28 August 2019)

Effect	Short description	Unit	Treatment	External placebo rate#	Uncertainties/ Strength of evidence	References
Favourable Effects						
PMS remission at week 8*	% patients achieving clinical remission per PMS at week 8	n/N (%)	I-HD 28/47 (59.6%) I-SD 13/30 (43.3%)	19.83%	No internal placebo control	M11-290

Effect	Short description	Unit	Treatment	External placebo rate#	Uncertainties/ Strength of evidence	References
FMS remission at week 52 in PMS responders at week 8*	% patients achieving clinical remission per FMS at week 52 in patients who achieved clinical response per PMS at week 8	n/N (%)	M-HD 14/31 (45.25%) M-SD 9/31 (29.0%)	18.37%	No internal placebo control	M11-290
Mayo clinical response at week 52 in week 8 responders per PMS	% patients achieving clinical response per FMS at week 52 in patients who achieved clinical response per PMS at week 8.	n/N (%)	M-HD 21/31 (67.7%) M-SD 19/31 (61.3%)	26.1%	No internal placebo control	M11-290
Mucosal healing at Week 52 in Week 8 responders per PMS	% patients achieving mucosal healing at week 52 in patients who achieved clinical response per PMS at week 8.	n/N (%)	M-HD 16/31 (51.6%) M-SD 12/31 (38.1%)	22.0%	No internal placebo control	M11-290
Mayo clinical remission at week 52 in week 8 remitters per PMS	% patients achieving Mayo clinical remission at week 52 in patients who achieved remission per PMS at week 8	n/N (%)	M-HD 10/22 (45.5%) M-SD 9/21 (42.9%)	14.8%	No internal placebo control	M11-290
CS-free Mayo clinical remission at week 52 in week 8 responders per PMS.	% patients achieving cs-free mayo clinical remission at week 52 in patients who received response per PMS at week 8	n/N (%)	M-HD 5/16 (31.3%) M-SD 4/13 (30.8%)	24.1%	No internal placebo control	M11-290
Unfavourable Effects						
AE	Adverse	n/N	80/93 (86%)		No active	M11-290/

Effect	Short description	Unit	Treatment	External placebo rate#	Uncertainties/ Strength of evidence	References
	event	(%)			control	M10-870, any ADA dataset
SAE	Serious adverse event	n/N (%)	26/93 (28%)		No active control	M11-290/ M10-870, any ADA dataset
Infections		n/N (%)	50/93 (53.8%)		No active control	M11-290/ M10-870, any ADA dataset
Serious infections		n/N (%)	6/93 (6.5%)		No active control	M11-290/ M10-870, any ADA dataset
Malignancies		N	0			M11-290/ M10-870, any ADA dataset
Deaths		N	0			M11-290/ M10-870, any ADA dataset

Abbreviations: ADA=adalimumab, CS= corticosteroids, I-HD=induction high dose, I-SD=induction standard dose, FMS= Full Mayo Score, PMS=Partial Mayo Score
Notes:* co-primary endpoints. # external placebo rate for statistical comparison achieved from an adult population. Clinical remission per PMS: PMS≤2 and no individual subscore >1). Clinical remission per FMS: Mayo score≤2 and no subscore >1. Clinical response per PMS: Decrease in PMS ≥2 points and ≥ 30% from baseline. Clinical response per FMS: Decrease in mayo score ≥3 points and ≥ 30% from baseline.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The pivotal study in children and adolescents had no internal control arm. Control arm was initially included in the study design, study protocol was updated to remove it due to recruitment issues. Instead, the MAH proposes a comparison to an external placebo group, achieved from an adult population. This comparison has several limitations and is not considered valid. However, the results clearly indicate that treatment with Humira results in clinically significant effects both in reducing symptoms and mucosal healing.

The study was not designed to compare the two different doses used, neither for induction therapy nor for maintenance therapy, but the results indicate a better response in the patients receiving the higher induction dose and also with the higher maintenance dose. Such results would not be expected without active treatment in a population who is non responders to standard of care, and thus, a drug effect is undoubtedly shown.

The MAH proposes a higher maintenance dose for the paediatric UC indication than what is approved as standard dose for the other paediatric indications, although a dose increase to the currently proposed dose is possible in the paediatric Crohn's population. For infections and serious infections, the exposure-adjusted incidence rates were lower for the SD regimen than for the HD regimen (infections: 53.2 E/100PYs vs 79.4 E/100PYs, serious infections: 3.7 E/100PYs vs 6.3 E/100PYs). It is agreed with the MAH that overall, the safety profile of subjects who received the M-SD and the M-HD regimens were similar during Studies M11-290 and M10-870.

Safety data in the youngest patients is very limited, since only 19 of the patients were below 12 years of age (5, 6, 7 (n=2), 8 (n=2), 9 (n=3), 10 (n=3), 11 (n=7)). The MAH was first asked to discuss to include a lower weight cut-off in the indication statement. Based on the presented data indicating exposures

exceeding previously approved ones and largest deviations between the body-weight dosing of the clinical study and the proposed flat dosing observed in lowest group, the MAH was asked to revise the indication to include only children aged 6 years and older. The MAH revised the indication as requested and the issue was solved.

There were no new safety signals observed during the study period. The most commonly reported adverse events were infections and gastrointestinal disorders, the latter rather representing a disease manifestation. The observed safety profile is consistent with the known safety profile of adalimumab and other TNF inhibitors. Although the exposure of paediatric UC patients is limited, the use of Humira in other paediatric indications is large and knowledge on the safety profile from these indications could be considered supportive for this new indication, provided that the MAH can present supportive data for the currently proposed dose. There is however need for long-term data that will be collected post-approval from the extension study M10-870 (Category 3 in the RMP), especially because of the concern on an increased risk for malignancies in paediatric patients with UC.

3.7.2. Balance of benefits and risks

The results of the pivotal study show a clinically significant effect both in reducing symptoms and mucosal healing. The results indicate a better response in the patients receiving the higher induction dose and also with the higher maintenance dose.

The safety profile observed in the studies is consistent with the known safety profile of Humira, and no new safety signals were observed.

There is need for further long-term follow up post marketing considering that the dose is higher compared to standard maintenance dose in other indications. Long term data in paediatric patients with UC will be collected in the extension study M10-870 (Category 3 in the RMP).

The benefit/risk balance of Humira in paediatric patients from 6 years with moderately to severely active ulcerative colitis is positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Humira is positive in the following indication:

Paediatric ulcerative colitis
Humira is indicated for the treatment of moderately to severely active ulcerative colitis in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including corticosteroids and/or 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and

therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include treatment of moderately to severely active ulcerative colitis in paediatric patients from 6 years of age for Humira; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC for 40mg/0.8mL, 40mg/0.4mL and 80mg/0.8mL presentations are updated. The MAH took the opportunity to introduce minor editorial changes to sections 5.1, 5.2 and 5.3 of the SmPC for all the presentations. The Package Leaflet is updated in accordance. Furthermore, the PI is being brought in line with the latest QRD template (version 10.1). Version 15.1 of the RMP is also agreed.

The variation leads to amendments to the Summary of Product Characteristics, Annnex II and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Humira-H-C-000481-II-0198’