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Summary of Clinical Trial Results

For Laypersons

A study to learn how effective and safe higher doses of the study drug adalimumab is for patients with ulcerative colitis

Overall Summary

- Ulcerative colitis (UC) is a long-lasting disease of the bowel that causes inflammation of the large intestine.
- Symptoms vary from person to person and can have changes in severity over time. Increases in severity are called flares.
- The reason people have UC is unknown, but researchers think it is caused by a mixture of reasons that include genetics and the body's immune system.
- In this study, study doctors (investigators) tested a medicine called adalimumab in patients who had been treated for UC.
- The study had two parts. 952 patients participated in Part 1. 846 patients participated in Part 2.
- The main aim of the study was to see how patient's responded to different doses of study drug adalimumab after 8 weeks (Part 1) and 44 weeks (Part 2) of treatment.
- Response to treatment was based on four categories (called a Full Mayo score): stool frequency, rectal bleeding, endoscopic evaluation (a long flexible tube is inserted into the rectum with a tiny video camera that allows the doctor to see the inside of the body) and evaluation by the study doctor.
- The most common side effects in Part 1 were nasopharyngitis (common cold), injection site redness, and fever.
- The most common side effects in Part 2 were gastrointestinal disorder, infections and infestations.
- The results of this study may be used by researchers to further develop this medicine.
- If you participated in this study and have questions about your individual care, contact the doctor or staff at your study site.

1. General information about the study

1.1 Why was this study done?

Researchers are looking for a better way to treat ulcerative colitis. Ulcerative colitis is an inflammatory bowel disease which can cause many different symptoms including urgent or frequent bowel movements, abdominal pain and cramping, and diarrhea. Symptoms may be different for every patient.

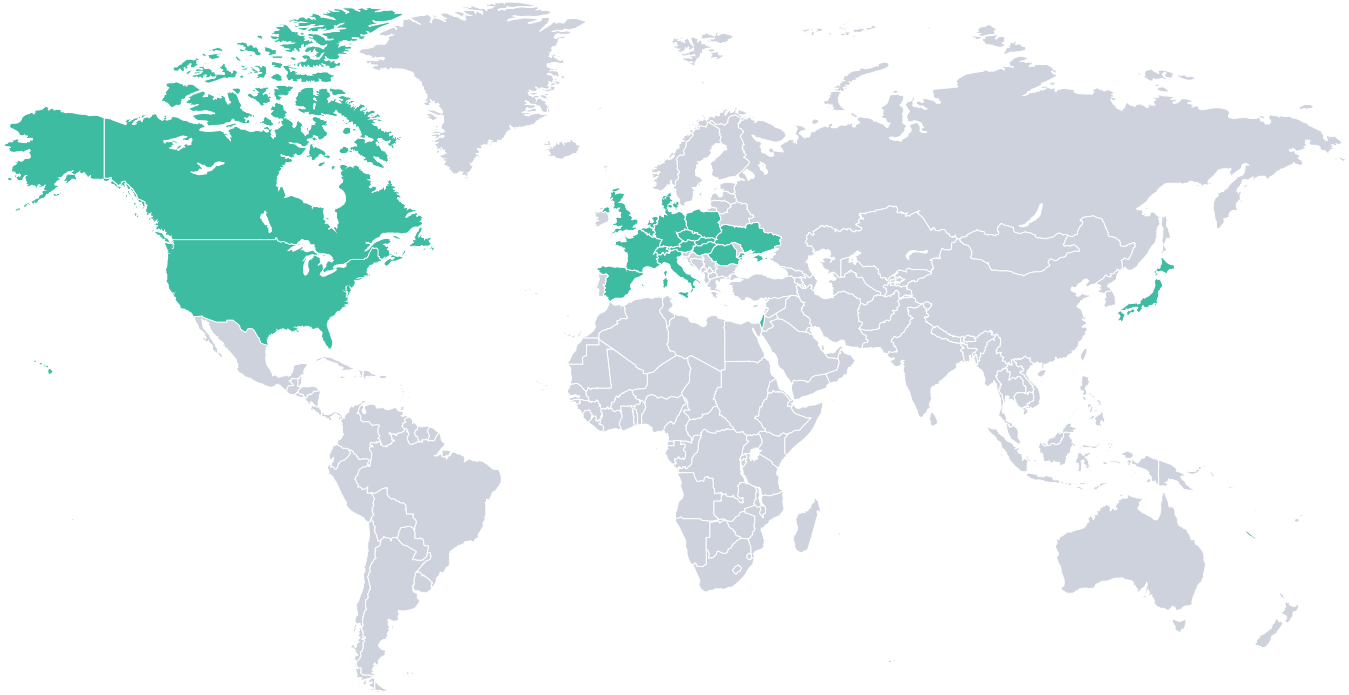
The medicines used to treat ulcerative colitis do not work the same for all patients. Symptoms do not improve for some patients receiving treatment. Because of this, researchers are looking for different ways to treat the disease.

The study doctors in this study used a medicine called adalimumab. Researchers have tested this medicine in many studies of people with different inflammatory diseases. Adalimumab works to control the activity of the immune system to help patients with inflammatory diseases and is currently approved to treat moderate to severe ulcerative colitis at the standard dose used in this study. The main aim of the study was to find out if adalimumab was safe and effective for patients to take at a higher dose than currently approved and if there were any unwanted side effects.

This study was a Phase 3 study. Phase 3 studies test potential new treatments in a large number of patients with a disease. This study was “double-blinded”, which means that neither the patients nor the study doctors knew who was given which dose of adalimumab. This ensured that no study results were influenced. The study looked at the benefits of the study drug given at the standard approved dose compared to a higher dose in patients who did not improve on other treatment. The study also looked for any side effects after starting treatment with adalimumab.

1.2. When and where was the study done?

This study took place from March 2014 to November 2019 in the following countries: Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Japan, Netherlands, Poland, Romania, Slovakia, Spain, Switzerland, Ukraine, United Kingdom, and United States.

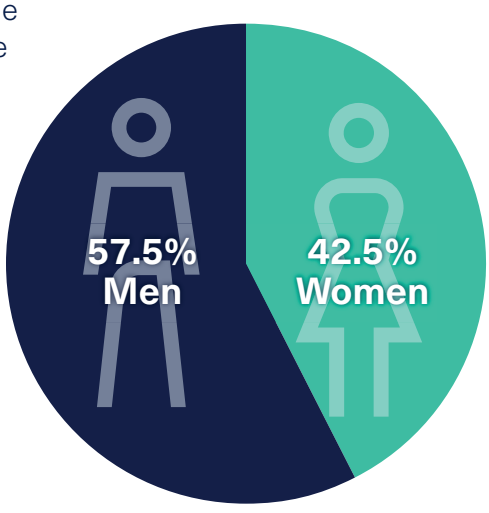


2. What patients were included in this study?

This study included two parts, Part 1 (Induction) and Part 2 (Maintenance). Induction is the first round of treatment which aimed to improve symptoms and make patients feel better. After induction treatment, patients continued in the study on maintenance treatment to keep symptoms under control and tried to avoid the symptoms getting worse.

A total of 952 adult patients with UC took part in the study. Among the 952 patients, 846 completed Part 1 and continued in Part 2. 572 patients then completed Part 2.

A total of 380 patients did not complete the study: 193 patients left the study because of lack of improvement in UC, 90 patients left because of side effects, 31 patients chose to withdraw from the study, 23 left to undergo other therapy for UC, 8 patients left because they were not following study requirements, 7 patients were lost to follow up (patient did not return to continue treatment or testing), and 28 patients left for other reasons.



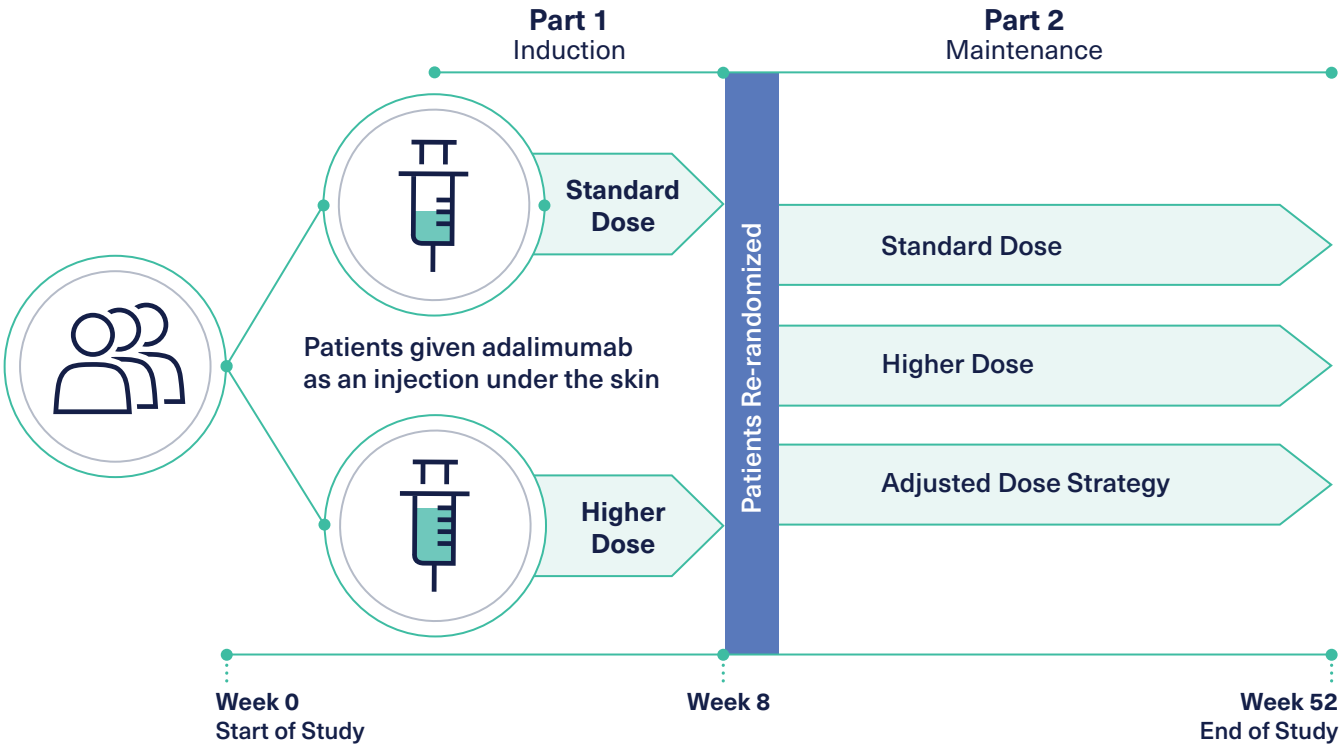
Adult participants with moderately to severely active ulcerative colitis for at least 3 months prior to joining the study and current diagnosis of active UC even while on, or having recently finished, treatment for UC were included in the study.

There were more men (57.5%) than women (42.5%) in the study and ages ranged from 18 to 75 years.

3. Which medicines were studied?

The medicine in this study was called adalimumab. The study was split into 2 parts. In Part 1 (Induction), the study tested two different doses of the medicine, the standard approved dose for UC and a higher dose. In Part 2 (Maintenance), the study tested the standard approved dose for UC, a higher dose, and an adjusted dose strategy group that starts at the standard approved dose and could increase to the higher dose if the patient met specific study criteria.

The diagram below shows how the study was organized.



At the beginning of the study, a computer program was used to randomly (by chance) put the patients into 1 of 2 groups. This process is called "randomization", which helps make the groups equal and reduces the differences between the groups. Randomization allows the results of each treatment to be compared as accurately as possible. Neither the patients nor study doctors knew which dose of the study drug was given.

Study doctors gave the patients different doses of the medicine depending on which group they were in. The drugs were given to patients to inject under their skin using a syringe.

After 8 weeks of treatment, patients who completed Part 1 (Induction) were re-randomized by a computer program into new groups to continue treatment for another 44 weeks in Part 2 (Maintenance).

The patients and doctors still did not know which dose of the study drug was given.

4. What were the side effects?

Side effects are unwanted medical events that happen during a study. They may or may not be caused by the treatment in the study.

A side effect is serious if it leads to death, is life-threatening, puts a patient in the hospital, keeps a patient in the hospital for a long time, or causes a disability that lasts a long time.

Related side effects are side effects that were considered by the study doctor to be at least possibly related to the study drug.

About 4.3% of patients (41 patients) in Part 1 and 12.2% of patients (103 patients) in Part 2 had serious side effects during the study. Of those patients, the total number of patients that had serious side effects considered by the study doctor to be at least possibly related to the study drug was 0.4% (4 patients) in Part 1 and 2.6% (22 patients) in Part 2.

5 patients died during the study; 1 patient died in Part 1 from a heart attack and 4 patients died in Part 2. 1 patient died from pulmonary embolism (blockage of an artery in the lung), 1 patient died from esophageal cancer, 1 patient died from lung cancer, and 1 patient died from severe pneumonia with blockage of an artery in the lung. None of the deaths were assessed by study doctor as possibly related to study drug.

Across the whole study, patients who took higher doses did not suffer from more side effects. This meant that this study showed no link between the dose of study drug and the number of side effects patients had.

The table on the following page shows information about the related serious side effects patients had in the study.

	Part 1: Induction		Part 2: Maintenance		
	Adalimumab Standard Dose (379 patients)	Adalimumab Higher Dose (573 patients)	Adalimumab Standard Dose (345 patients)	Adalimumab Higher Dose (350 patients)	Adalimumab Adjusted Dose Strategy (151 patients)
Number of patients with related serious side effects	3 (0.8% of patients)	1 (0.2% of patients)	9 (2.6% of patients)	9 (2.6% of patients)	4 (2.6% of patients)
• Blood and lymph node system disorders	0 (0.0% of patients)	0 (0.0% of patients)	0 (0.0% of patients)	2 (0.6% of patients)	0 (0.0% of patients)
• Eye disorders	0 (0.0% of patients)	0 (0.0% of patients)	1 (0.3% of patients)	1 (0.3% of patients)	0 (0.0% of patients)
• Gastrointestinal disorders	0 (0.0% of patients)	0 (0.0% of patients)	2 (0.6% of patients)	1 (0.3% of patients)	1 (0.7% of patients)
• Infections	2 (0.5% of patients)	1 (0.2% of patients)	3 (0.9% of patients)	2 (0.6% of patients)	1 (0.7% of patients)
• Investigations (abnormal blood tests)	0 (0.0% of patients)	0 (0.0% of patients)	0 (0.0% of patients)	1 (0.3% of patients)	0 (0.0% of patients)
• Kidney and urinary disorders	0 (0.0% of patients)	0 (0.0% of patients)	1 (0.3% of patients)	0 (0.0% of patients)	1 (0.7% of patients)
• Muscle, skeletal, or tissue disorders	0 (0.0% of patients)	0 (0.0% of patients)	0 (0.0% of patients)	1 (0.3% of patients)	0 (0.0% of patients)
• Nervous system disorders	0 (0.0% of patients)	0 (0.0% of patients)	1 (0.3% of patients)	1 (0.3% of patients)	1 (0.7% of patients)
• Respiratory (breathing)/ chest disorders	0 (0.0% of patients)	0 (0.0% of patients)	0 (0.0% of patients)	1 (0.3% of patients)	0 (0.0% of patients)
• Skin and tissue disorders	0 (0.0% of patients)	0 (0.0% of patients)	1 (0.3% of patients)	1 (0.3% of patients)	1 (0.7% of patients)
• Tumors (noncancerous, cancer, including cysts and polyps)	1 (0.3% of patients)	0 (0.0% of patients)	0 (0.0% of patients)	1 (0.3% of patients)	0 (0.0% of patients)

The table below shows patients that stopped treatment because of related serious side effects and any related serious side effects that led to death.

	Part 1: Induction		Part 2: Maintenance		
	Adalimumab Standard Dose (379 patients)	Adalimumab Higher Dose (573 patients)	Adalimumab Standard Dose (345 patients)	Adalimumab Higher Dose (350 patients)	Adalimumab Adjusted Dose Strategy (151 patients)
Number of patients who stopped taking study drug because of related side effects	4 (1.1% of patients)	11 (1.9 % of patients)	12 (3.5% of patients)	16 (4.6% of patients)	7 (4.6% of patients)
Reasons for stopping	Cancer of the skin, herpes, injection site redness, psoriasiform dermatitis (skin disorder that is similar to psoriasis)	Angioedema (swelling of the skin), chills, clostridium difficile (bacteria that can cause diarrhea and colitis), diarrhea, eczema, hypersensitivity, injection site hypersensitivity, injection site pain, injection site reaction, injection site swelling, itching, pneumonia, tuberculosis, worsening of UC	Blood creatinine increased (waste product of muscles in the blood), clostridium difficile, decreased neutrophil (white blood cell) count, disease of the liver and biliary system, erythema (redness of the skin), increased liver enzymes (indicating inflammation or damage in the liver), leukopenia (low white blood cells), linear IgA disease (blistering of the skin), myositis (inflammation of the muscles), nephrotic syndrome (kidney disorder causing too much protein in the urine), optic atrophy (nerve damage in the eye), swelling near injection site, thrombocytosis (low blood platelets), worsening of UC	Arthralgia (joint pain), dizziness, eyelid ptosis (droopy eyelid), fibromatosis (soft tissue tumors), head discomfort, hypoaesthesia (numbness of the skin), leukopenia, lupus-like syndrome, mononeuropathy (damage to a single nerve causing pain, loss of movement or numbness), pain in extremities, paraesthesia (pins and needles feeling), pyelonephritis acute (bacterial infection causing inflammation of the kidneys), rash, subcorneal pustular dermatosis (skin disease where pus-filled pimples or blisters form under the top layer of skin), tonsillitis (inflammation of the tonsils causing sore throat), tuberculosis, worsening of UC	Chronic inflammatory demyelinating pemphigoid (rare autoimmune condition that causes blistering and rashes), low white blood cell count, pneumonia, polyradiculone-uropathy (a slow developing immune system disorder that causes symptoms such as gradual weakness or changes in sensations in the arms or legs), rash, sepsis (the body's extreme response to an infection), worsening of UC
Number of related side effects leading to death	0 (0.0% of patients)	0 (0.0% of patients)	0 (0.0% of patients)	0 (0.0% of patients)	0 (0.0% of patients)

About 53% of patients (505 patients) in Part 1 and 72.8% of patients (616 patients) in Part 2 had side effects during the study. The total number of patients that had side effects considered by the study doctor to be at least possibly related to the study drug was 24.4% (232 patients) in Part 1 and 30.1% (255 patients) in Part 2.

The table below shows information about the common related side effects (in at least 4 or more patients) in this study.

	Part 1: Induction		Part 2: Maintenance		
	Adalimumab Standard Dose (379 patients)	Adalimumab Higher Dose (573 patients)	Adalimumab Standard Dose (345 patients)	Adalimumab Higher Dose (350 patients)	Adalimumab Adjusted Dose Strategy (151 patients)
Number of patients with at least one related side effect	83 (21.9% of patients)	149 (26.0% of patients)	89 (25.8% of patients)	117 (33.4% of patients)	49 (32.5% of patients)
Common Related Side Effects Related side effects occurring in at least 4 patients	Cough, feeling cold, hair loss, headache, joint pain, nausea, rash	Common cold, cough, dizziness, feeling cold, hair loss, headache, injection site itchiness, injection site pain, injection site reaction, injection site redness, injection site swelling, joint pain, nausea, oropharyngeal pain (pain in throat right behind the tongue), rash, skin redness, vomiting	Common cold, joint pain, rash, upper respiratory tract infection	Asthenia (physical weakness or lack of energy), common cold, cough, eczema, flu, hair loss, headache, increased aspartate aminotransferase (AST) test (can show liver disease or injury), itchiness, joint pain, rash, upper respiratory tract infection, worsening of UC	Common cold, hyper-transaminasemia (high level of certain liver enzymes in the blood), rash

5. What were the overall results of the study?

The study was completed as planned. The main aim of this study was to see how patients respond to different doses of adalimumab after 8 weeks (Part 1) and 44 weeks (Part 2) of treatment. Response to treatment (clinical remission) was based on a scoring system called Full Mayo score that looks at four categories: stool frequency, rectal bleeding, endoscopic evaluation (a long flexible tube is inserted into the rectum and a tiny video camera allows videos and images to be taken for review), and evaluation by the study doctor.

In Part 1, the study results showed that the standard and higher doses were about equal in number of patients achieving clinical remission after 8 weeks of treatment. 11.6% of patients receiving the standard dose (44 patients) and 13.8% of patients receiving the higher dose (79 patients) achieved clinical remission at Week 8.

In Part 2, the study looked at the patients who achieved clinical remission at the end of Part 1 to see how many of these patients had clinical remission at the end of Part 2. They found that more patients taking the higher dose had clinical remission at Week 52 than patients taking the standard dose or patients in the adjusted dose strategy group. 52% of patients receiving the higher dose (91 patients) compared to 41.7% of patients receiving the standard dose (91 patients) and 36.5% of patients in the adjusted dose strategy group (27 patients) still had clinical remission at Week 52.

The number and frequency of side effects in the dosing groups were like those expected in patients with moderate to severe ulcerative colitis treated with adalimumab. Higher doses of adalimumab did not give patients more side effects than standard doses or the adjusted dosing group.

6. How has the study helped patients and researchers?

This study showed that adalimumab remains safe and effective for patients with UC. It showed that clinical remission is about equal in patients given higher and standard doses during the induction part of treatment but that higher doses are more effective in achieving clinical remission during the maintenance part of treatment when compared to the standard dose and the adjusted dose strategy group.

This summary only shows the results from this study, which may be different from the results of other studies.

7. Are there any plans for future studies?

Multiple adalimumab studies are ongoing for a wide range of conditions.

8. Who sponsored this study?

This study was sponsored by AbbVie. This summary was reviewed for readability by a patient advocacy group.

9. Where can I find out more information about this study?

Title of Study	A Double-Blind, Randomized, Multicenter Study of Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Subjects With Moderately to Severely Active Ulcerative Colitis
Protocol Number	M14-033
Clinicaltrials.gov	NCT02065622 https://clinicaltrials.gov/ct2/show/NCT02065622?term=M14-033&draw=2&rank=1
EudraCT	2013-001682-16 https://www.clinicaltrialsregister.eu/ctr-search/search?query=2013-001682-16
Study Sponsor	AbbVie Phone: (800) 633-9110 Email: abbvieclinicaltrials@abbvie.com

Thank You

AbbVie wants to thank all the participants for their time and effort that went into making this study possible.

Clinical study participants help advance science!