Overall Summary

• Crohn's disease (CD) is a long-lasting disease of the bowel that causes inflammation of any part of the gastrointestinal tract.

• Symptoms vary from person to person and can have changes in severity over time. Increases in severity are called flares.

• The reason people have Crohn's disease is unknown, but researchers think it is caused by a combination of reasons that include genetics and the body's immune system.

• In this study, study doctors (investigators) tested a medicine called adalimumab to treat symptoms of Crohn's disease.

• The study was done in two parts. In Part one, 514 adults participated. In Part two, 218 adults who finished the first part continued in part two.

• The main aim of the study was to see if a higher dose of adalimumab in Part 1 improved patient symptoms better than the standard dose for 12 weeks.

• Patients' symptoms were scored after 4 weeks of treatment using the Crohn's disease activity index (CDAI) which measures symptoms such as abdominal pain, wellbeing, complications, and weight change.

• The study doctors used a camera (endoscopy) to look at the patients' bowels after 12 weeks of treatment. Patients who took the higher dose of adalimumab in Part 1 did not have improved CDAI or endoscopy scores compared to patients who took the standard dose.

• Around 25.1% of patients (129 patients) in Part 1 and 28.4% of patients (62 patients) in Part 2 had side effects. The most common side effects were injection site redness, injection site itchiness, and arthralgia (joint pain) in Part 1 and dermatitis (itchy, dry skin or rash), nasopharyngitis (common cold), nausea, and rash in Part 2.

• 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.
Researchers are looking for a better way to treat Crohn’s disease. Crohn’s disease is an inflammatory bowel disease which can cause many different symptoms including stomach pain, diarrhea, tiredness, and weight loss. Symptoms are different for every patient.

The medicines used to treat Crohn’s disease 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 medicines 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, and adalimumab is currently approved to treat moderate to severe Crohn’s disease. Adalimumab works to control the activity of the immune system to help patients with inflammatory disease. 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. The study was also “double-blinded”, which means that neither the patients nor the study doctors knew who was given which dose of adalimumab.

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 treatments. The study also looked for any side effects after starting treatment with adalimumab.

1. General information about the study

1.1. What was the main objective of this study?
1.2. When and where was the study done?

This study took place from May 2014 to January 2020 in the following countries: Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, 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 was 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 to avoid the symptoms getting worse.

A total of 514 adult patients with Crohn’s disease took part in the study. Of the 514 patients, 479 completed Part 1. Of those patients who completed Part 1, 218 adult patients enrolled in Part 2. When this study started, after finishing induction treatment, patients could join a separate study for maintenance treatment. This study was then changed (amended) to allow patients to receive maintenance treatment within this study which explains why patient enrollment in Part 2 was lower.

To participate in the study, patients had to have a confirmed diagnosis of moderate to severe Crohn’s disease based on Crohn’s disease activity index (CDAI) score for 3 or more months even after treatment with steroids or other treatments.

More women (52%) than men (48%) joined the study and patient ages ranged from 18 to 73 years of age.
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 Crohn's disease and a higher dose. In Part 2 (Maintenance), the study tested a clinically adjusted dose group compared to an adjusted dose strategy group. In the clinically adjusted dose group, the dose schedule could be increased from every other week to every week based on evaluation of symptoms and blood tests. In the adjusted dose strategy group, the dose schedule could be changed from every other week to every week based on the same symptoms and blood tests in the clinically adjusted dose group plus blood tests for adalimumab levels.

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 the study doctors knew which dose of the study drug was given.

Patients were given different doses of the adalimumab depending on which group they were in. The study drug was given to patients to inject under their skin using a syringe.

After 12 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 study 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 were considered by the study doctor to be at least possibly related to the study drug.

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.

0.6% of patients (3 patients) in Part 1 and 1.4% of patients (3 patients) in Part 2 had serious side effects during the study.

1.0% of patients (5 patients) in Part 1 and 2.8% of patients (6 patients) in Part 2 stopped taking the study drug because of side effects during the study.

No patient died during the study.

The table below shows information about the serious side effects patients had in the study, as well as side effects patients had that led to the patient stopping study drug.

<table>
<thead>
<tr>
<th></th>
<th>Part 1: Induction</th>
<th>Part 2: Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adalimumab Standard Dose (206 Patients)</td>
<td>Adalimumab Higher Dose (308 Patients)</td>
</tr>
<tr>
<td>Number of patients with serious side effects</td>
<td>3 (1.5% of patients)</td>
<td>0 (0.0% of patients)</td>
</tr>
<tr>
<td>• Amnesia (partial or total loss of memory)</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>• Cellulitis (skin infection) and limb abscess (swollen area in tissue containing pus)</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>• Chickenpox</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>• Drug eruption (drug reaction skin rash)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>• Intestinal tuberculosis (infection of the abdominal organs)</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>• Mononucleosis (virus causing sore throat and fever) and sepsis (the body’s extreme reaction to an infection)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Number of patients who stopped taking study drug because of side effects</td>
<td>1 (0.5%)</td>
<td>4 (1.3%)</td>
</tr>
<tr>
<td>• Reasons for stopping</td>
<td>Intestinal tuberculosis (infection of the abdominal organs)</td>
<td>Dental caries (tooth decay), erythema (redness), injection site reaction, herpes, trichorrhexis (hair breakage)</td>
</tr>
<tr>
<td>Number of side effects leading to death</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>
About 25.1% of patients (129 patients) in Part 1 and 28.4% of patients (62 patients) in Part 2 had side effects during the study. The table below shows information about the common side effects (in at least 3 or more patients) in this study. The most common side effects were injection site redness, injection site itchiness, and arthralgia (joint pain) in Part 1 and dermatitis (itchy, dry skin or rash), nasopharyngitis (common cold), nausea, and rash in Part 2.

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<th>Part 1: Induction</th>
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<tbody>
<tr>
<td>Adalimumab Standard Dose (206 Patients)</td>
<td>Adalimumab Higher Dose (308 Patients)</td>
</tr>
<tr>
<td>Number of patients with at least one side effect</td>
<td>54 (26.2% of patients)</td>
</tr>
<tr>
<td>Adalimumab Clinically Adjusted Dose (109 Patients)</td>
<td>Adalimumab Adjusted Dose Strategy (109 Patients)</td>
</tr>
<tr>
<td>Number of patients with at least one side effect</td>
<td>29 (26.6% of patients)</td>
</tr>
</tbody>
</table>

Common Side Effects
Related side effects occurring in at least 3 patients in any group

Part 1: Arthralgia (joint pain), dizziness, erythema (redness), fatigue (tiredness), headache, injection site pain, injection site reaction, injection site redness, injection site swelling, nausea, neurodermatitis (itching or scaling of skin), oropharyngeal pain (pain in back of throat), pain in extremity

Part 2: Arthralgia (joint pain), asthenia (abnormal lack of energy), erythema (redness), fever, headache, injection site bruising, injection site itchiness, injection site reaction, injection site redness, injection site swelling, itchiness, nasopharyngitis (common cold), nausea, oral herpes, oropharyngeal pain (pain in back of throat), rash, upper respiratory tract infection, urticaria (hives), white blood cell count decreased

Nasopharyngitis (common cold), nausea, rash
Dermatitis (itchy, dry skin or rash)

Across the whole study, patients who took higher doses did not necessarily suffer from more side effects. This showed that there was no link between the dose and the number of side effects patients had in this study.
5. What were the overall results of the study?

The study was completed as planned. The main aim of the study was to see if patients given the higher dose of adalimumab in Part 1 responded better to treatment than patients given the standard dose.

After 4 weeks of treatment, patient response to treatment was scored using the Crohn’s disease activity index (CDAI) which measures patient symptoms such as abdominal pain, wellbeing, complications, and weight change. 43.5% of patients who took the higher dose had an improvement in their CDAI score after 4 weeks of treatment compared to 43.7% of patients who took the standard dose.

After 12 weeks of treatment (at the end of Part 1), patient response to treatment was scored by endoscopy where a small camera was used to look at the patient’s bowels and measure number and size of ulcers and percentage of surface affected by Crohn’s disease. 42.9% of patients who took the higher dose had improvement in their endoscopic score after 12 weeks of treatment compared to 39.3% of patients who took the standard dose.

The study doctors found that the patients in the group who had taken the higher dose of adalimumab did not have better response to treatment at Week 4 or Week 12 when compared to patients in the group who had taken the standard dose.

The number and frequency of side effects were similar to those expected in patients with moderate to severe Crohn’s disease. Higher doses did not give patients more side effects than lower doses.

6. How has the study helped patients and researchers?

This study showed that adalimumab remains safe and effective for patients with Crohn’s disease. It showed that response to treatment is about equal in patients given higher and standard doses during the induction part of treatment.

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?

<table>
<thead>
<tr>
<th>Title of Study</th>
<th>A Multicenter, Randomized, Double-Blind Study to Evaluate Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Subjects With Moderately to Severely Active Crohn’s Disease and Evidence of Mucosal Ulceration</th>
</tr>
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<tr>
<td>Protocol Number</td>
<td>M14-115</td>
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| Clinicaltrials.gov | NCT02065570  
https://clinicaltrials.gov/ct2/show/NCT02065570?term=NCT02065570&draw=2&rank=1 |
| EudraCT         | 2013-001746-33  
| Study Sponsor   | AbbVie, Inc.  
Phone: +1 800-633-9110  
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!