Plain Language Summary of Publication

Journal of Comparative Effectiveness Research

Ravulizumab in adults and children with atypical hemolytic uremic syndrome: a plain language summary of three studies

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Summary

What is this summary about?

This summary gives an overview of three published articles that report the results of research studies of ravulizumab, an approved treatment for people with atypical hemolytic uremic syndrome (often shortened to aHUS). This is a rare and serious condition where blood clots form in small blood vessels. Blood vessels are structures that transport blood around the body. Blood clots are the body's way of stopping someone from bleeding too much. However, if they form when they are not needed, they can cause harm. In atypical hemolytic uremic syndrome, the blood clots can cause injury to organs like the kidney. In the three studies, the researchers wanted to know if ravulizumab could decrease the formation of these clots and improve kidney function.

How to say (double click on the sound icon to play the sound)

Atypical hemolytic uremic syndrome: ay-TI-puh-kl hee-mow-LI-tuhk yoo-REE-mik SIN-drowm
Ravulizumab: RAV-yoo-LIH-zoo-mab
Complement system: KOM-pluh-muhnt SIST-uhm
Dialysis: dai-A-luh-suhs

- Children who had never received ravulizumab or a similar treatment took part in the first study.
- Adults who had never received ravulizumab or a similar treatment took part in the second study.
- In the third study, children whose disease was already controlled by a medication called eculizumab switched to ravulizumab. Ravulizumab is dosed less frequently than eculizumab.

The researchers looked at kidney function and the levels of different blood components to see how well the treatment was working. They also monitored the adverse effects that participants experienced.

What were the results?

Across the three studies, ravulizumab improved indicators of blood clotting in small vessels and improved kidney function in both children and adults. In addition, ravulizumab was similarly effective to eculizumab for children who were already receiving eculizumab and switched to ravulizumab. Overall, the adverse effects that people experienced with ravulizumab were manageable.

What do the results mean?

These studies showed that ravulizumab is a treatment option for children and adults with aHUS. In addition, a switch to ravulizumab can be considered for children who are already responding well to eculizumab and would benefit from less frequent dosing.

Becaris PUBLISHING

Where can I find the original articles on which this summary is based?

You can read the original articles for free in the following sources:

- First study discussed about ravulizumab in children in the journal *Kidney International*, "The long-acting C5 inhibitor, ravulizumab, is effective and safe in pediatric patients with atypical hemolytic uremic syndrome naïve to complement inhibitor treatment." – https://www.kidney-international.org/article/S0085-2538(20)31418-6/fulltext

- Second study discussed about ravulizumab in adults in the journal *Kidney International Reports*, "Kidney International Reports Long-Term Efficacy and Safety of the Long-Acting Complement C5 Inhibitor Ravulizumab for the Treatment of Atypical Hemolytic Uremic Syndrome in Adults." – https://www.kireports.org/article/S2468-0249(21)01032-9/fulltext

- Third study discussed about children switching from eculizumab to ravulizumab in the journal *Pediatric Nephrology*, "The long-acting C5 inhibitor, ravulizumab, is efficacious and safe in pediatric patients with atypical hemolytic uremic syndrome previously treated with eculizumab." – https://link.springer.com/article/10.1007/s00467-020-04774-2

Who is this article for?

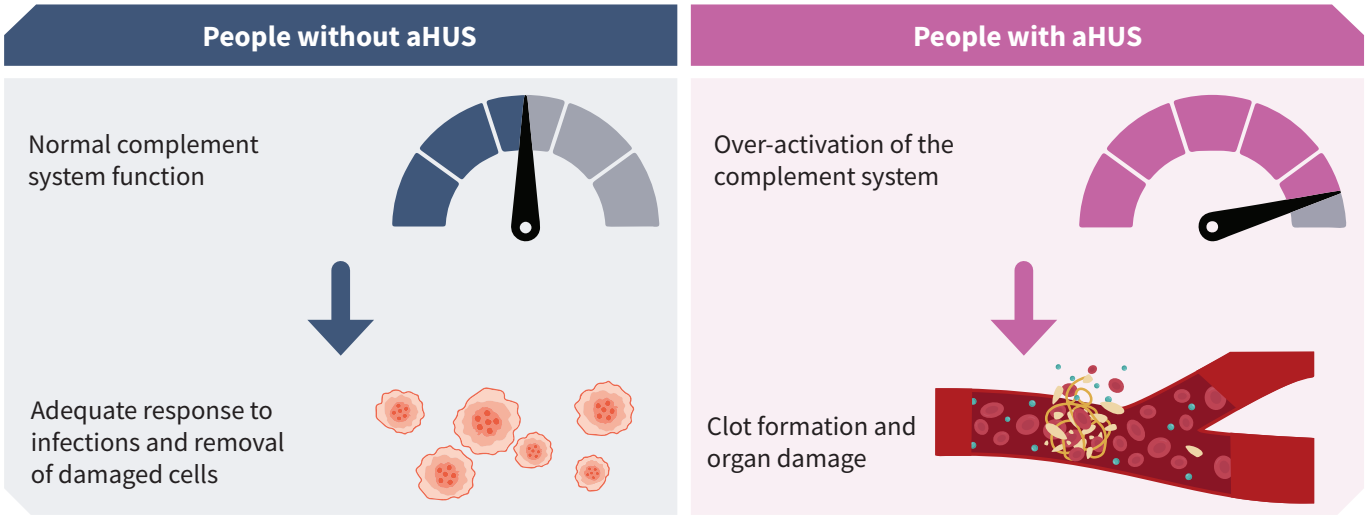
This article may be helpful for:

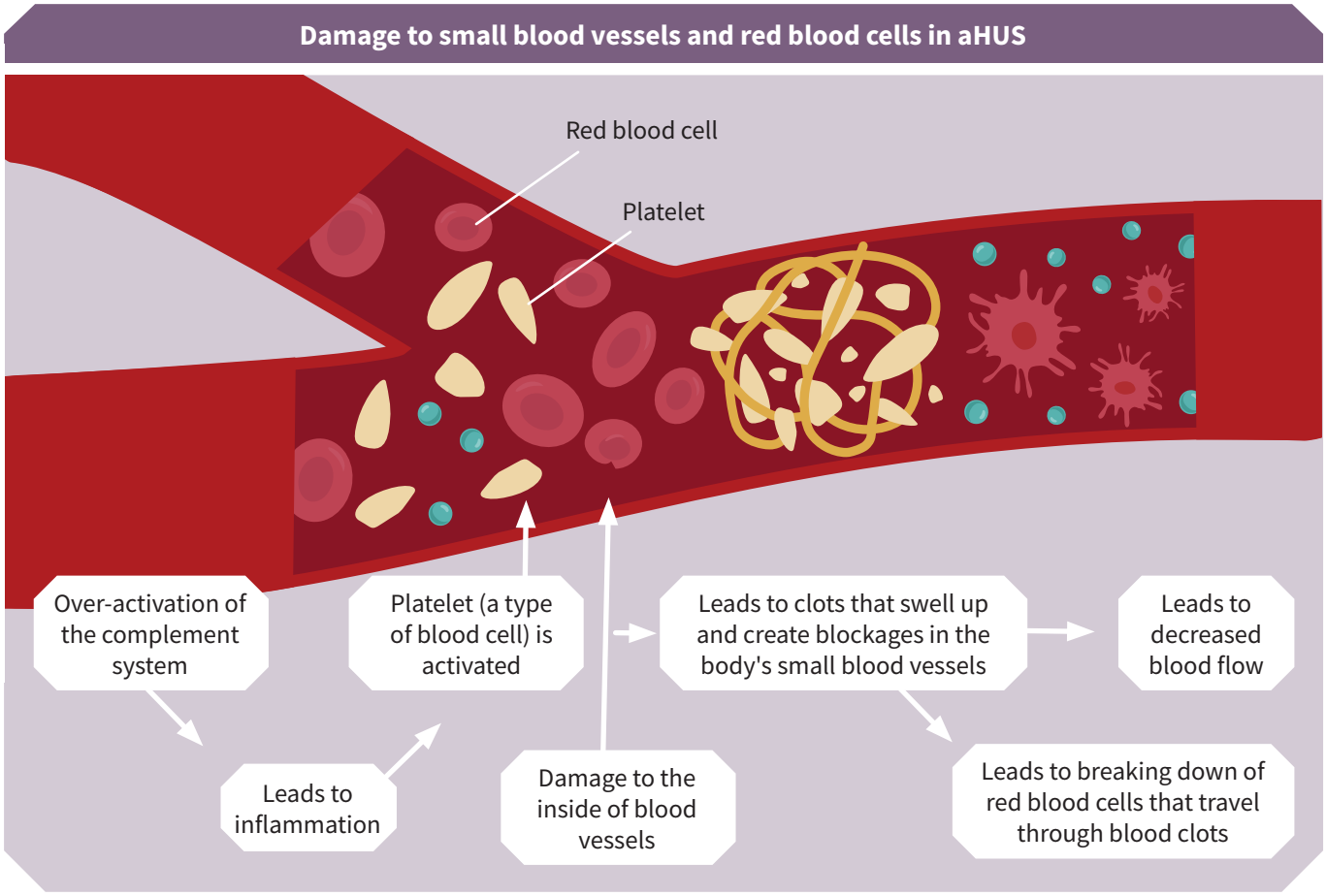
- People who have atypical hemolytic uremic syndrome (aHUS) as active participants in their care, and their relatives or non-professional caregivers who care for someone with this condition.
- Patient associations or other groups which support people with aHUS.
- Healthcare providers (including physicians and nurses) who provide care for people with aHUS.
- Healthcare providers or policymakers who draft aHUS management recommendations.

What is atypical hemolytic uremic syndrome?

- aHUS is a rare condition, with a global prevalence estimated at approximately 1 to 2 cases per million people. In the United States, the prevalence is estimated to be around 0.23 to 0.40 per million inhabitants.
- aHUS is a serious health condition that causes blood clots and damage to the walls of the smallest blood vessels in the body (capillaries and small arteries).
  - Blood vessels are structures that transport blood around the body.
  - Blood clots are the body's way of stopping someone from bleeding too much. However, if they form when they are not needed, they can cause harm.
- Blood clots can cause serious damage to organs, especially the kidneys.
  - Impaired kidney function means that people with aHUS may need dialysis (a treatment to remove metabolic wastes and extra fluid from the blood) or a kidney transplant.
- aHUS is caused by a combination of genetic factors (such as mutations in specific genes) and/or environmental triggers (like infections or certain medications) which unbalances a group of proteins called the complement system.
  - Genetic factors are traits we inherit from our parents through DNA, which is like an instruction manual for our bodies. When genes change, it can make some people more likely to get diseases like aHUS.
  - The complement system is a part of the immune system (the body's natural defense system) and is essential to the body's defense against infection.

- When the complement system becomes overactive or their regulation is disrupted, it can damage healthy cells and tissues.
- In aHUS, an overactive complement system damages the cells lining small blood vessels. This leads to the vessels becoming swollen and blocked by blood clots.
  - Small blood cell fragments (called platelets) are involved in clot formation.
  - Red blood cells that pass through the blood clots are shredded (a process called hemolysis).





- Although there is no known cure for aHUS, successful management is possible with treatment.

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How does atypical hemolytic uremic syndrome affect the body?

The three most common signs of aHUS are:

- Kidney damage or kidney failure – due to a reduced blood flow in the kidneys because of clots in their small blood vessels.
- Low counts of red blood cells (known as anemia) – due to the destruction of red blood cells as they pass through clots in the blood vessels.
- Low counts of platelets in the blood – due to platelets being destroyed and accumulating in clots.

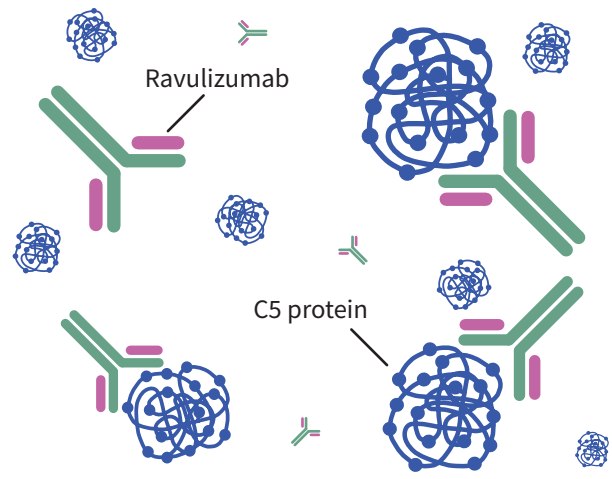
Other symptoms of aHUS can include stomach pain, swelling, seizures, fatigue (extreme tiredness), bruises and loss of consciousness. The condition may be life-threatening.

What is ravulizumab, and how does it work?

Ravulizumab is a type of treatment called a monoclonal antibody. This is a type of protein that can bind to specific targets in the body that cause health conditions.

The target of ravulizumab is the C5 protein, a key protein in the complement system. Ravulizumab binds to C5 and inhibits it.

When the C5 protein is inhibited, the complement system cannot damage small vessels.



- People receive ravulizumab by infusion into a vein (known as intravenous infusion). They receive an initial high dose (known as a loading dose). After this they receive a series of lower maintenance doses every 4-8 weeks for children (depending on their body weight) and every 8 weeks for adults. Loading doses are larger than maintenance doses and are given to quickly achieve a good amount of the drug in the blood.
- Treatment with ravulizumab for aHUS is typically indefinite to prevent disease relapse, as discontinuation poses a significant risk of recurrence.

Why were these studies done?

The researchers wanted to know whether ravulizumab is effective and safe for children and adults with aHUS. They also wanted to compare ravulizumab with eculizumab. Both ravulizumab and eculizumab work by preventing damage caused by an overactive complement system. Eculizumab is an older treatment that is dosed more frequently than ravulizumab.

Ravulizumab was approved in the USA in October 2019 to treat aHUS, in the European Union in June 2020 and in Japan in September 2020.

What did researchers find out in the first study in children?

What did the first study look at?

The first study looked at whether ravulizumab was effective for children with aHUS who have not previously received treatments that target the complement system.

The researchers reported how well the treatment worked after 26 weeks of treatment (6.5 months) and again after 50 weeks (almost one year) of treatment.

Who took part in the study?

Who can join (inclusion criteria)

- Children under 18 who weigh at least 5 kg.
- Children showing signs of active disease based on lab tests.

Who can't join (exclusion criteria)

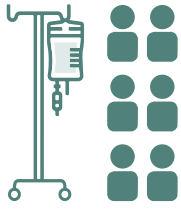
- Children with certain deficiencies, genetic abnormalities or infections.
- Those undergoing dialysis for very advanced kidney disease.
- Children treated with immunosuppressants or procedures to suppress the immune system.
- Those with prior use of complement inhibitors similar to ravulizumab.

Three of the 21 initial study participants withdrew from the study due to uncertainty about aHUS diagnosis.

Eighteen children continued in the study. **Eight** of these children were boys, and **ten** were girls.

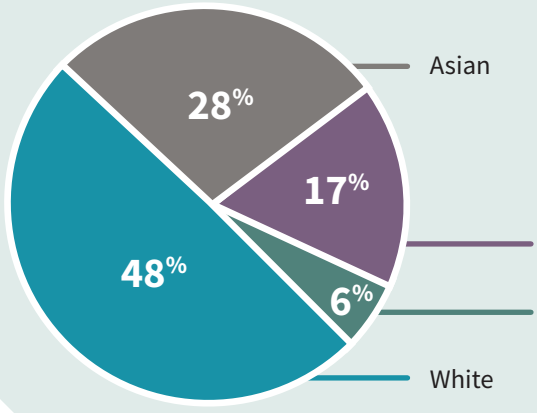
The average age of the children was five years old.

Six children were on dialysis.

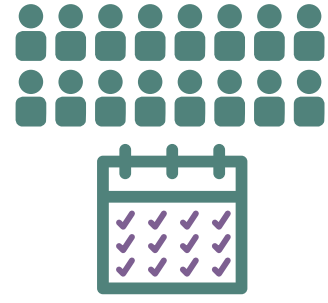


Six children received plasma exchange or plasma infusion (plasma exchange removes the liquid part of the blood and replaces it with a substitute to eliminate harmful substances. Plasma infusion involves injecting plasma from a donor into the bloodstream to replace missing or abnormal components).

Seven children needed intensive care (ICU) before they joined the study.



One child had a kidney transplant before the study.



Sixteen children completed 50 weeks of the study.

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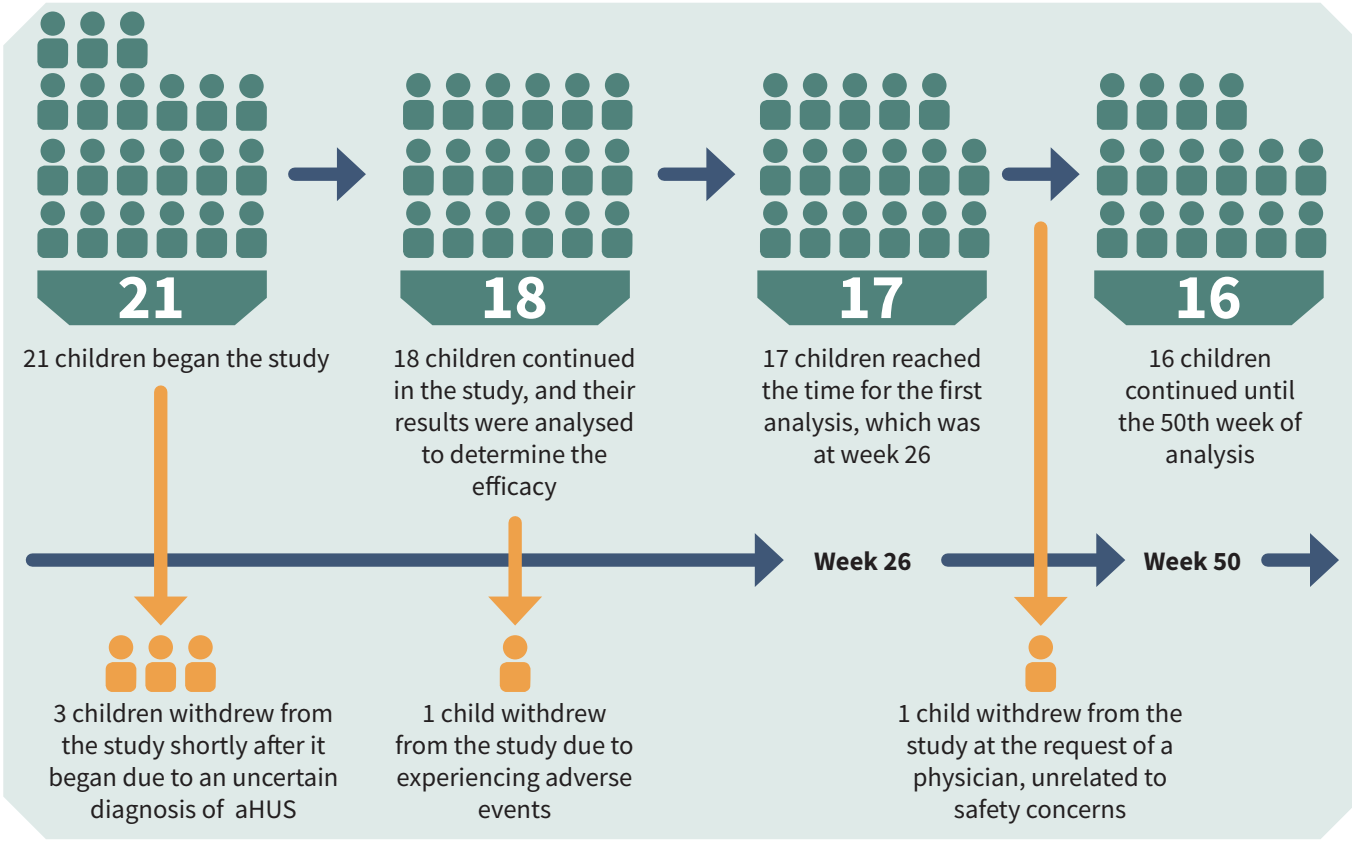

How effective was treatment with ravulizumab?

By week 26, around three quarters (78%) of children achieved a complete response to ravulizumab. On average, this response took 30 days

Week 26
78% complete response

By week 50, almost all (94%) of the children had achieved a complete response.

Week 50
94% complete response

In addition, by week 50:

- All of the children (100%) who were on dialysis due to poor kidney function at the beginning of the study were able to come off dialysis.
- All of the children (100%) had improved kidney function.
- Nine children completed a quality-of-life evaluation using a questionnaire at weeks 26 and 50. All nine children (100%) showed significant improvements.
  - The study used a questionnaire called FACIT-Fatigue to measure how much fatigue children with aHUS experienced. It asked about their energy levels and how tiredness affected their daily activities. This helped the researchers understand whether the treatment, ravulizumab, made the children feel less tired and improved their quality of life.

What were the main adverse events that occurred?

- An adverse event is any negative medical problem that occurs after taking a medication. Adverse events may or may not be directly related to the medication.
- In this study, all the children experienced at least one adverse event. Around half of these (47%) of these were related to ravulizumab.
- The most common adverse events that happened during treatment were as follows:

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- One child had to leave the study due to experiencing a serious adverse event: a sudden and severe increase in blood pressure and worsening anemia.
- By blocking the complement system, ravulizumab may increase the risk of meningococcal infections. This is a rare and serious bacterial infection of the brain, spinal cord and bloodstream. Everyone in the study was vaccinated against this condition before starting ravulizumab, and none of the children developed it during the study.
- No deaths were reported in this study.

What do the results of this study mean?

- In this study, treatment with ravulizumab resulted in the rapid improvement of symptoms in children with aHUS.
- Researchers found that the response to ravulizumab increased the longer participants were treated, and there were no unexpected safety concerns.
- Taken together, this study's results show that ravulizumab is a treatment option for children with aHUS, who have not previously received treatment that target the complement system.

What did researchers find out in the second study in adults?

What did the second study look at?

The second study looked at whether ravulizumab was effective for adults with aHUS who have not previously received treatments that target the complement system.

The researchers reported how well the treatment worked after 26 weeks of treatment and again after 50 weeks of treatment.

Who took part in the study?

Who can join (inclusion criteria)

- Adults 18 years or older who weigh at least 40 kg
- Those showing signs of active disease based on lab tests.

Who can't join (exclusion criteria)

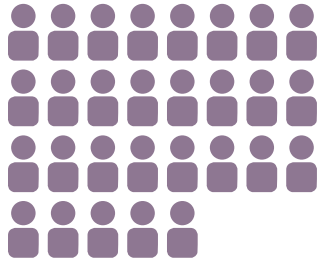
- People with certain deficiencies, genetic abnormalities or infections.
- Those undergoing dialysis for very advanced kidney disease.
- People treated with immunosuppressants or procedures to suppress the immune system.
- Those with prior use of complement inhibitors similar to ravulizumab.

A total of 56 people participated in the study. Of these, **37** were women, and **19** were men.

41 years The average age of the participants was around 41 years.

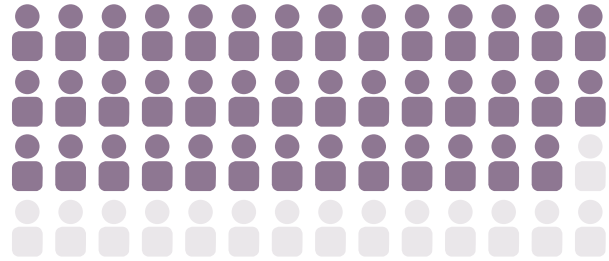
Two people withdrew from the study since the diagnosis of aHUS was not confirmed.

Who took part in the study?

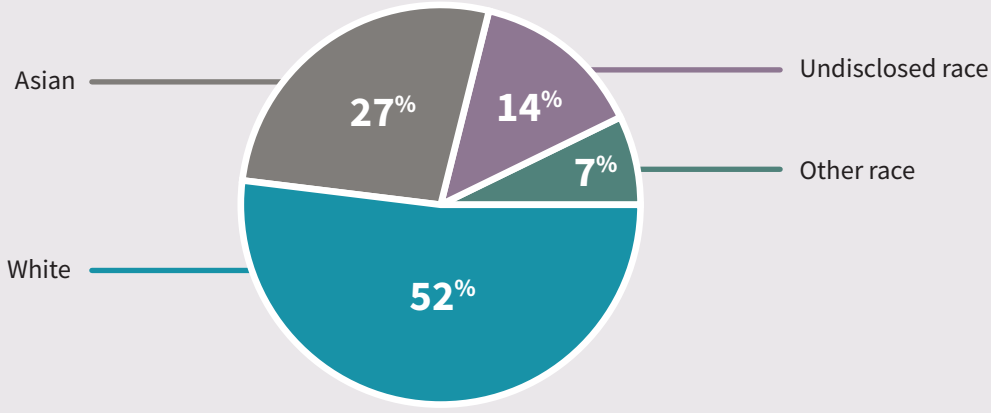


Of the participants, 29 were on dialysis.

Eight of the participants had a previous kidney transplant.



41 out of the 56 participants completed the 52-week treatment



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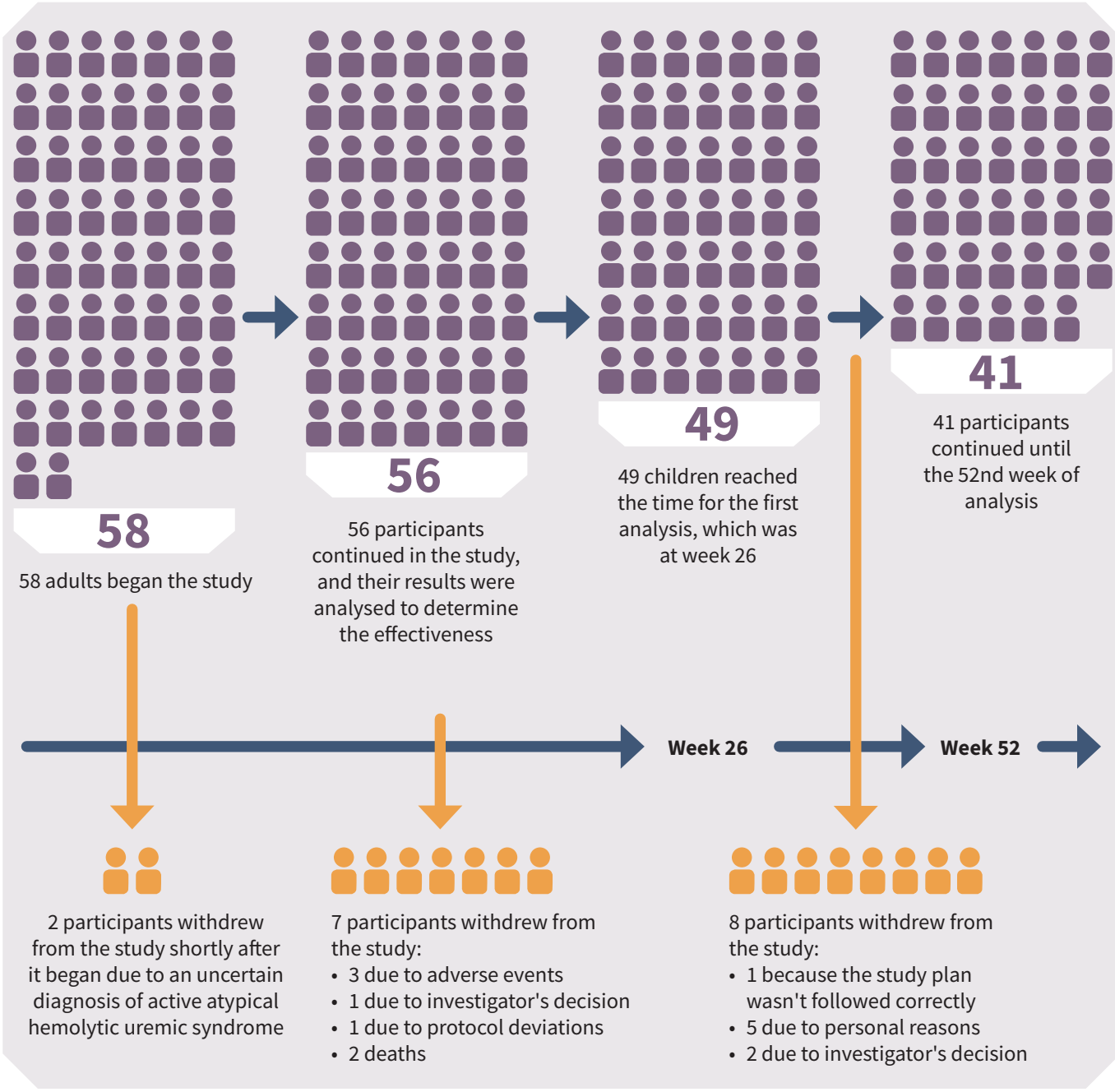


How effective was the ravulizumab treatment?

By week 26, around half of the people (54%) achieved a complete response.

Week 26
54% **complete response**

By week 52, around 6 in 10 people (61%) had achieved a complete response.

Week 52
61% complete response

In addition, by week 52:

- Platelet levels had returned to normal in 86% of participants, compared to 84% in the first 26 weeks of treatment.

Platelet level returned to normal by week 52:
86% of participants

- LDH levels had returned to normal in 84% of participants, compared to 77% in the first 26 weeks of treatment.

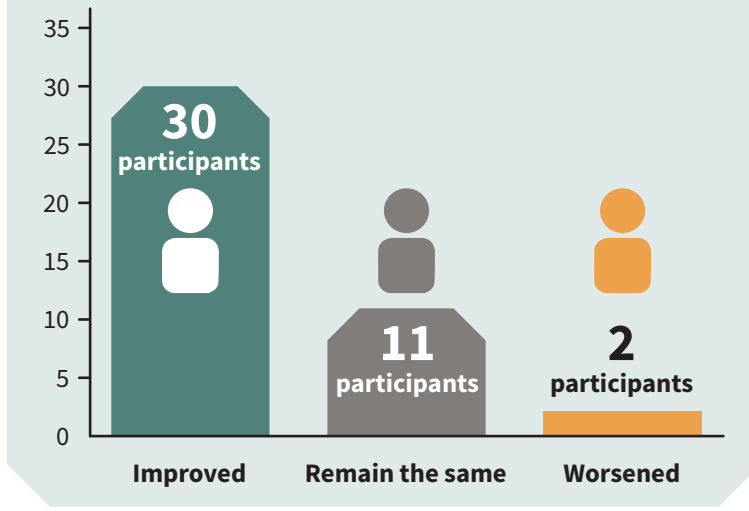
LDH returned to normal by week 52:
84% of participants

- Kidney function improved for 30 people, remained the same for 11, and worsened for two.

Quality of life improved from the beginning of the study to week 26 and was maintained until week 52:

- To assess the quality of life, the study utilized the FACIT-Fatigue questionnaire, which enables researchers to quantify participants' fatigue levels and its impact on their everyday activities.

Changes in kidney function from week 26 to 52



What were the main adverse events that occurred?

- During the study, ravulizumab did not cause any adverse events that the researchers did not expect to see.
- Everyone in the study had at least one adverse event. Around a third of these (35%) of these were related to the treatment.
- The most frequent treatment-related adverse events were:
  - Headache: 38%
  - Diarrhea: 33%
  - Vomiting (being sick): 31%

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- Three people had to leave the study due to experiencing serious adverse events. Serious adverse events are ones that may lead to hospitalization, disability or death.
- Everyone was vaccinated against meningococcal infection before starting the study. No-one developed meningococcal infection during the study.
- During the first 26 weeks of the study, four people died. However, none of the deaths were related to the treatment. No further deaths were reported in the final 26 weeks of the study.

What do the results of this study mean?

- This study shows that giving ravulizumab every 8 weeks is an effective treatment for adults with aHUS and provides additional clinical benefits beyond 26 weeks of treatment.
- Overall, the adverse events that people experienced with ravulizumab were manageable.

What did researchers find out in the third study in children who switched from eculizumab to ravulizumab?

What did the third study look at?

In the third study, researchers focused on children who were already responding well to eculizumab, another complement inhibitor treatment.

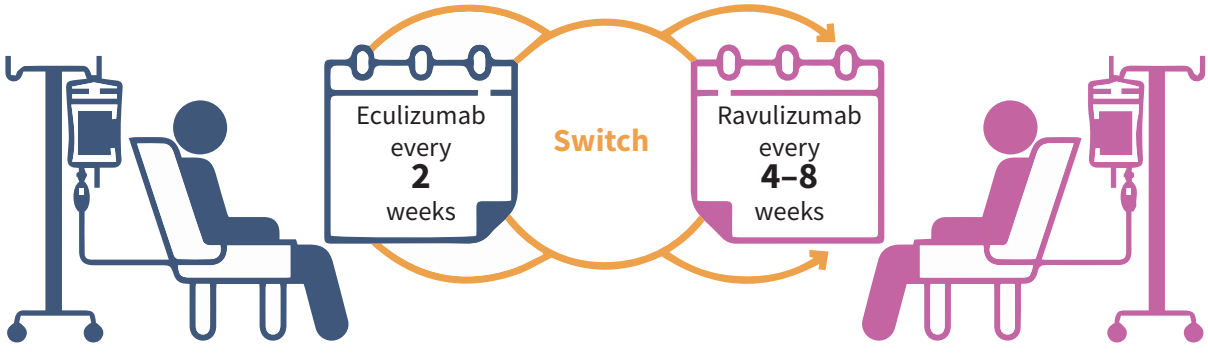
Despite its proven effectiveness, eculizumab infusions are given once every 2 weeks, which may be burdensome.

The study looked at whether switching to ravulizumab, which igiven every 4-8 weeks, could maintain the same level of effectiveness and safety.

Who took part in the study?

- Ten children took part in the study

- The children received a loading dose of ravulizumab on the first day (14 days after the last dose of eculizumab) and maintenance doses starting on day 15. After that, they received maintenance doses every 4-8 weeks. The dose depended on their body weight.



- The trial had three parts: a screening phase of up to 28 days, a main evaluation period of 26 weeks, and a follow-up that could last up to 4.5 years.

Screening phase	Main evaluation	Follow-up
28 days	25 weeks	4.5 years

- In this article, the investigators checked how well the treatment worked and reported the results at 26 and 52 weeks.

Who can join (inclusion criteria)

- Children under 18 who weigh at least 5 kg.
- Those who have shown a positive response to eculizumab, meaning their condition is stable.

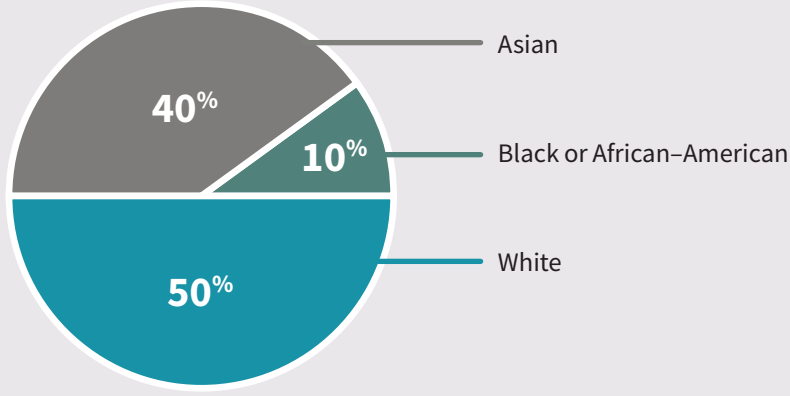
Who can't join (exclusion criteria)

- Children with certain deficiencies, genetic abnormalities or infections.
- Those undergoing dialysis for very advanced kidney disease.
- Children treated with immunosuppressants or procedures to suppress the immune system.

The characteristics of the 10 children who took part in the study were as follows:

- There were 9 boys and 1 girl

- Their average age was around 12.5 years



- One child had previously had a kidney transplant.

- None of the children were on dialysis at the time of starting the trial.
- None of the children had received plasma infusion/plasma exchange before receiving ravulizumab.
- All the children were responding well to eculizumab, with normal LDH levels and adequate platelet count and kidney function.
- Children had received eculizumab for between 98 days (3.5 months) and 1701 days (4.5 years).

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How effective was the ravulizumab treatment?

- No children required dialysis at any point throughout the study.
- Their kidney function remained within normal limits and stable at 26 and 52 weeks.
- Their platelet and LDH levels remained normal throughout the study, and no children developed anemia.
- These results indicate that treatment with ravulizumab maintained the response already achieved with eculizumab.

What were the main adverse events that occurred?

- All the children had adverse events.
- The most common adverse events that happened during the study were upper airways infections (40%) and sore throat (30%). These may or may not have been related to the treatment.
- Two children (20.0%) reported adverse events related to the treatment. One of the children experienced dyspepsia (discomfort in the upper abdomen) and the other child reported musculoskeletal pain (pain in muscles, bones, or joints)
- There were no serious adverse events related to the treatment.

There were no reported cases of meningococcal infections or deaths. All the children continued treatment for the full duration of the study.

What do the results of this study mean?

- Children with aHUS can safely switch from eculizumab to ravulizumab without reducing the effectiveness or safety of their treatment.
- They may benefit from receiving ravulizumab every 4-8 weeks instead of every two weeks with eculizumab, which results in fewer treatment sessions.

Where can readers find more information on these studies?

This summary is based on three published articles and readers can find more information about these publications below.

First study about ravulizumab in children

- The original article is called: The long-acting C5 inhibitor, ravulizumab, is effective and safe in pediatric patients with atypical hemolytic uremic syndrome naïve to complement inhibitor treatment.
- The full citation of this article is: Ariceta G, Dixon BP, Kim SH, *et al.* The long-acting C5 inhibitor, ravulizumab, is effective and safe in pediatric patients with atypical hemolytic uremic syndrome naïve to complement inhibitor treatment. *Kidney Int.* 100(1):225–37 (2021).
- You can read the article for free at: https://www.kidney-international.org/article/S0085-2538(20)31418-6/fulltext

Second study about ravulizumab in adults

- The original article is called: Long-term efficacy and safety of the long-acting complement C5 inhibitor ravulizumab for the treatment of atypical hemolytic uremic syndrome in adults.
- The full citation of this article is: Barbour T, Scully M, Ariceta G, *et al.* Long-term efficacy and safety of the long-acting complement C5 inhibitor ravulizumab for the treatment of atypical hemolytic uremic syndrome in adults. *Kidney Int Rep.* 6(6):1603–13 (2021).
- You can read the article for free at: https://www.kireports.org/article/S2468-0249(21)01032-9/fulltext

Third study in children switching from eculizumab to ravulizumab

- The original article is called: The long-acting C5 inhibitor, ravulizumab, is efficacious and safe in pediatric patients with atypical hemolytic uremic syndrome previously treated with eculizumab.
- The original citation is: Tanaka K, Adams B, Aris AM, *et al.* The long-acting C5 inhibitor, ravulizumab, is efficacious and safe in pediatric patients with atypical hemolytic uremic syndrome previously treated with eculizumab. *Pediatr Nephrol.* 36(4):889–98 (2021).
- You can read the article for free at: https://link.springer.com/article/10.1007/s00467-020-04774-2

Where can readers find more information about aHUS?

For more information about aHUS, readers can check the following websites:

- https://rarediseases.org/rare-diseases/atypical-hemolytic-uremic-syndrome/
- https://www.ahusallianceaction.org/
- https://ahus.org/
- https://www.kidneyresearchuk.org/health-information/a-to-z-health-information/atypical-haemolytic-uraemic-syndrome/
- https://rarediseases.info.nih.gov/diseases/8702/atypical-hemolytic-uremic-syndrome

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Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing disclosure

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