A Phase 2a Proof-of-Mechanism, Open-Label Study to Determine the Effect of ACH 0144471 on C3 Levels in Patients with Low C3 Levels Due to Either C3 Glomerulopathy (C3G) or Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN)

Published: 09-01-2018
Last updated: 12-04-2024

The Primary objective is to determine whether the administration of ACH 0144471 can increase C3 levels in patients with low C3 levels due to either C3G or IC-MPGN.The secondary objectives are:* To evaluate the safety and tolerability of ACH 0144471…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Immune disorders NEC
Study type	Interventional

Summary

ID

NL-OMON46833

Source
ToetsingOnline

Brief title
N/A

Condition

- Immune disorders NEC
- Nephropathies

Synonym

C3 glomerulopathies, disease of the complement system, kidney disease

Research involving
Human

Sponsors and support

Primary sponsor: Achillion Pharmaceuticals
Source(s) of monetary or material Support: Achillion Pharmaceuticals;Inc

Intervention

Keyword: C3 Glomerulopathy, Immune Complex Membranoproliferative Glomerulonephritis

Outcome measures

Primary outcome

* Increase in C3 levels relative to baseline

Secondary outcome

* The incidence of AEs, SAEs, and discontinuations due to AEs

* Time (in days) to achieving peak C3 levels from the first day of dosing

* The pharmacokinetic (PK) profiles of ACH 0144471 following the administration

of multiple oral doses, and in the setting of dose taper

* Changes in biomarkers of alternative pathway activity (AP) relative to

baseline

* The relationship between ACH 0144471 pharmacokinetics and changes in C3

levels, and inhibition of alternative pathway activity (PK/PD)

Exploratory endpoints:

* Patients* experience of their disease (C3G or IC-MPGN), its impact, and its

management on everyday lives, from first symptoms to definitive diagnosis and

beyond

* Patients* expectations of ACH 0144471 in the treatment of their disease

Study description

Background summary

See protocol P21-22:

1.3.1 Complement Factor D:
Factor D is one of nine serine proteases in the complement system. It is a highly specific enzyme with only one known substrate, fB. Of all the complement proteins, it has the lowest abundance in serum with a concentration of approximately 2 µg/mL, and is the rate-limiting step of AP activation. It is a low molecular weight protein (24 kDa) that is primarily produced by adipocytes, but can also be produced and secreted by monocytes/macrophages and astrocytes in humans. Due to its small size, it is freely filtered at the glomerulus, and then taken up by the proximal tubule cell where it is catabolized with an estimated fractional catabolic rate of 60% per hour. It is this rapid catabolism that is responsible for maintaining low circulating fD levels. As a result, renal dysfunction is associated with elevated fD levels, which may lead to increased alternative pathway activity and inflammation. The biochemical, physiological, and functional features of fD make it an attractive target for pharmacological inhibition as this may prove useful in the treatment of a wide spectrum of complement-mediated diseases, including C3G.

1.3.2 C3 Glomerulopathy:
C3 glomerulopathy (C3G) is an ultra-rare disease with an incidence rate of approximately 2 per million people worldwide. It is widely accepted that C3G is attributable to excessive alternative pathway (AP) activity. The clinical course is characterized by variable amounts of proteinuria, hematuria, hypertension, and decreased renal function, with approximately 30%-50% of patients reaching end-stage renal disease (ESRD) within 10 years of diagnosis. The diagnosis is based on predominant deposition of C3 in the glomerulus on renal biopsy along with clinical evidence of hyper AP activity. C3G can be further subdivided into two separate entities, dense deposit disease (DDD) and C3 glomerulonephritis (C3GN), based on electron microscopic features of the renal pathology. Although the two disorders have similar clinical features, DDD tends to present earlier in life than C3GN. However, both diseases can present in either childhood or adulthood.
Unfortunately, no specific therapy has proven effective for the treatment of C3G. Therefore, care is largely non-specific and supportive. Given the lack of available therapeutic options, immunosuppressive and plasma infusion/exchange therapy are often attempted, as a subset of patients may

benefit. Treatment is otherwise focused on management of hypertension, proteinuria and the manifestations of chronic kidney disease. Dialysis and renal transplantation are options available for patients who reach ESRD; however, disease recurrence is frequent after transplantation, occurring in more than 50% of patients. Only about 50% of patients have a functioning graft 5 years after transplantation, which is significantly lower than renal graft survival in other settings.
Studies in animal models have indicated that the pathophysiology of C3G strongly relates to an excessive AP activity at the level of the C3 convertase. Specifically, mouse factor H-deficient animals have evidence of uncontrolled alternative pathway activation, with low plasma levels of intact C3, high levels of C3 breakdown product and evidence of C3G; yet, in mice deficient in both factor H (fH) and fD (knock-out mice), serum C3 levels were similar to wild-type and dense deposits were not present in the kidneys. These studies confirmed that removal of fD prevented the renal pathogenesis of C3G in the factor H-deficient mice.

1.3.3 Potential Advantages of ACH 0144471 in the Treatment of C3G:
Given that the pathophysiology of C3G derives from excessive C3 activation through the AP, treatment of the disease with an AP complement inhibitor is logical. Eculizumab, the only commercially available complement inhibitor, has been tested in patients with C3G, even though its mechanism of action (targeting the terminal complement pathway) would not be expected to affect C3 activation. Its use has been reported in more than 20 patients with C3G, of whom the majority were reported as individual cases, and only six were reported as part of an open-label proof-of-concept study. Of those presented as case reports, the majority had a successful response. However, this may represent a publication bias, as the results of the open-label trial were less impressive. Specifically, two of the six patients in the open-label trial seemed to have a good response, confirmed by worsening upon discontinuation of eculizumab. Of the remaining four patients, three had an increase in serum creatinine while on treatment. Based on the results of this open-label trial, the general consensus is that only a subset of patients appears to benefit from eculizumab therapy; however, identification of these patients prior to treatment remains a challenge. It has been suggested that response to eculizumab may be more likely in those patients with elevated soluble C5b-9 levels, indicative of excessive terminal pathway activity, although this hypothesis remains to be established.
A fD inhibitor like ACH 0144471, which inhibits directly at the level of the AP C3 convertase formation, is expected to provide superior efficacy than eculizumab or complement inhibitors that target the other complement pathways. This hypothesis is supported by animal data in which the renal disease observed with factor H deficiency, which is similar to human C3G, was completely prevented in the setting of simultaneous fD or fB deficiency. In contrast C5 deficiency only ameliorated, but did not prevent, renal disease. Furthermore, C6 deficiency had no effect on the renal disease in fH deficient mice. Taken

together, the data from the C5 and C6 deficient mice provide evidence that the membrane attack complex itself plays little role in renal pathogenesis of C3G in the setting of fH deficiency, but that C5a production may be a factor contributing to disease.

1.3.4 Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN):
Immune-complex membranoproliferative glomerulonephritis (IC-MPGN) is a renal disease which shares many clinical, pathologic, genetic and laboratory features with C3G, and therefore can be considered a sister disease of C3G. In the majority of patients with IC-MPGN, an underlying disease or disorder (most commonly infections, autoimmune diseases or monoclonal gammopathies) are identified to which the renal disease is secondary. Of note, the most common infections associated with IC-MPGN are hepatitis B and C. Up to 40% of patients with IC-MPGN have no identifiable underlying etiology, and are considered to have idiopathic IC-MPGN. Patients with idiopathic IC-MPGN can have low C3 and normal C4 levels, similar to those observed in C3G, as well as many of the same genetic or acquired factors that are associated with abnormal alternative pathway activity. Although there are current hypotheses suggesting that the majority of IC-MPGN is attributable to overactivity of the classical pathway, those patients with a low C3 and a normal C4 are likely to have significant overactivity of the alternative pathway. Therefore, IC-MPGN patients with a low C3 and a normal C4 may benefit from alternative pathway inhibition.

Study objective

The Primary objective is to determine whether the administration of ACH 0144471 can increase C3 levels in patients with low C3 levels due to either C3G or IC-MPGN.

The secondary objectives are:
* To evaluate the safety and tolerability of ACH 0144471 in patients with C3G or IC-MPGN
* To evaluate the pharmacokinetic (PK) profile of ACH 0144471 in patients with C3G or IC-MPGN
* To evaluate the effect of ACH 0144471 on biomarkers of alternative pathway activity (AP) in patients with C3G or IC-MPGN
* To explore the relationship between study drug exposure and changes in C3 levels and other biomarkers of alternative pathway activity

The exploratory objectives are:
* To explore patients* experience of their disease (C3G or IC-MGPN), its impact, and its management on everyday lives, from first symptoms to definitive diagnosis and beyond
* To explore patients* expectations of ACH 0144471 in the treatment of their

disease.

Study design

This open-label study will enroll up to 10 patients (between the ages of 16 and 65 years) with biopsy-confirmed C3G or idiopathic IC-MPGN and a low C3 level. The trial will evaluate the ability of ACH 0144471 to increase C3 levels via inhibition of factor D (fD) by enrolling patients in two groups. Group 1 will serve as a sentinel group consisting of two patients who will receive ACH 0144471 at a dose of 100 mg three times daily (TID) for 14 days followed by a taper over 7 days. Group 2 will be initiated upon confirmation that dosing was well-tolerated in Group 1 (based on Group 1 safety data through at least Day 28), and may include up to 8 patients. As discussed in Section 3.2.2, the dose for Group 2 will be selected based on the available safety, PK, and PD data from Group 1, but will not exceed 200 mg TID. The 100 mg TID dose level for Group 1 was selected based on safety, PK, and pharmacodynamics (PD) data from the Phase 1 single-ascending dose (SAD) and multiple-ascending dose (MAD) studies (ACH471-001 and ACH471-002), which demonstrated that similar dosing regimens in healthy volunteers were well-tolerated and able to inhibit the alternative pathway of complement. In addition, the relative bioavailability study (ACH471 006) supports transition from the liquid filled capsule (LFC) dosage form used in the SAD and MAD studies to the tablet dosage form to be used in this study. All patients will receive active drug.
Patients will receive study drug for 14 days (Treatment Period), followed by a taper over the next 7 days (Taper Period) to minimize the potential adverse effects of a rapid surge in complement activity following drug withdrawal. Patients will have daily clinic visits for the first 3 days of the taper, and then will continue to be followed for 28 days after the last dose of study drug (Follow-Up Period). Long-term follow up visits to allow collection of longitudinal observational data are included, but are not required. During the long-term follow up period, patients will be asked to return for an outpatient clinic visit approximately every 45 days for a maximum of 1 year.
If a patient has a C3 level that, at 2 consecutive evaluations, is greater than 125% the upper limit of normal (ULN), or is greater than 3× their baseline and greater than or equal to the lower limit of normal (LLN), then the taper period will be initiated before completion of the 14 days of dosing, as proof-of-mechanism will already be established for that patient. Furthermore, early tapering and possible prevention of supraphysiologic C3 levels may mitigate the theoretical risk for acute precipitation of C3 into the glomerulus upon drug discontinuation.
Safety, PK, and PD data will be obtained at multiple time points during the Treatment, Taper and Follow-Up periods. The primary endpoint for the study will be changes in C3 levels. Additional endpoints include the incidence of adverse events (AEs), serious adverse events (SAEs), and discontinuations due to AEs. Clinical measures of renal disease will be monitored (e.g., creatinine, proteinuria, and blood pressure), but are not expected to improve in this short-duration non-therapeutic trial. Additional secondary and

exploratory endpoints will include functional assays of complement activity and measurement of selected complement components in blood and urine, as described in Section 6.15. Finally, a PK/PD analysis will be conducted to explore the relationship between study drug exposure and changes in C3 levels and/or other secondary endpoints.
Concomitant medications will be considered on a case-by-case basis, and decisions made jointly between the PI and Sponsor, based on knowledge of ACH 0144471 and risks for drug-drug interactions, as well as potential to interfere with interpretation of the study.
Based on data from Groups 1 and 2, additional patients may be added to study additional dose levels or regimens (not to exceed 200 mg TID for two weeks, followed by a 7-day taper) or additional C3G or IC-MPGN patients.

Intervention

Group 1:
Treatment Period: 100 mg TID for 14 days (Days 1 * 14)
Taper Period:
100 mg twice daily (BID) for 3 days (Days 15, 16, and 17)
50 mg BID for 2 days (Days 18 and 19)
50 mg once daily (QD) for 2 days (Days 20 and 21)

Group 2:
The dose and taper schedule will be determined based on data from Group 1, with a maximum possible dose of 200 mg TID followed by a 7 day taper.

Study burden and risks

See protocol Page 22:

1.3.3 Potential Advantages of ACH 0144471 in the Treatment of C3G:
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consensus is that only a subset of patients appears to benefit from eculizumab therapy; however, identification of these patients prior to treatment remains a challenge. It has been suggested that response to eculizumab may be more likely in those patients with elevated soluble C5b-9 levels, indicative of excessive terminal pathway activity, although this hypothesis remains to be established.
A fD inhibitor like ACH 0144471, which inhibits directly at the level of the AP C3 convertase formation, is expected to provide superior efficacy than eculizumab or complement inhibitors that target the other complement pathways. This hypothesis is supported by animal data in which the renal disease observed with factor H deficiency, which is similar to human C3G, was completely prevented in the setting of simultaneous fD or fB deficiency. In contrast C5 deficiency only ameliorated, but did not prevent, renal disease. Furthermore, C6 deficiency had no effect on the renal disease in fH deficient mice. Taken together, the data from the C5 and C6 deficient mice provide evidence that the membrane attack complex itself plays little role in renal pathogenesis of C3G in the setting of fH deficiency, but that C5a production may be a factor contributing to disease.

See protocol Page 28-29:

3.2.4 Safety Considerations:
3.2.4.1 Risk of Infection:
One of the primary functions of the complement system is to fight infections as part of the innate immune system. As suggested by individual case reports with complement system deficiencies including complement factor D, inhibition of the complement system may result in a lifetime increased risk of infection, notably with Neisseria meningitidis (N. meningitidis), and other encapsulated organisms. Because of this potential risk, special safety precautions will be taken for patients participating in ACH471-201. Patients will be required to be previously vaccinated, or to receive vaccinations for N. meningitidis (serogroups A, C, Y and W135), Streptococcus pneumoniae (S. pneumoniae), and Haemophilus influenzae (H. influenzae) prior to receiving ACH 0144471. Throughout the study, including at clinic visits, patients will be monitored for the development of fever. A specific Fever Management Plan has been developed for this study.
Patients will also be counseled about behaviors to avoid during the study, and to recognize early and react appropriately to signs and symptoms of infection.
3.2.4.2 Hepatic Injury:
Hepatobiliary cholestasis has been observed in the dog toxicology studies at exposures higher than those intended for clinical use. In humans, elevations in ALT levels have been observed in some healthy volunteers with doses of 500 mg twice daily and 800 mg twice daily for 14 days. However, treatment-emergent ALT elevations have not been observed in healthy volunteer subjects receiving doses up to 200 mg twice daily for 14 days, or in PNH patients receiving up to 150 mg TID for 56 days. In this study, the selected doses are expected to result in similar or lower exposures to those following 200 mg twice daily.

Nonetheless, liver function tests, including ALT, AST, alkaline phosphatase, GGT, and total, direct, and indirect bilirubin, will be closely monitored.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Each patient must meet all of the following criteria to be enrolled in this study:
1. Must be between the ages of 16 and 65 years, inclusive
2. Must have a clinical diagnosis of C3G (C3 glomerulonephritis [C3GN] or dense deposit disease [DDD], the 2 types of C3G) or idiopathic immune-complex membranoproliferative glomerulonephritis (IC-MPGN) by renal biopsy for at least 3 months prior to dosing, with the pathologic diagnosis verified by review of the renal biopsy by the study central pathologist
3. C3 must be <50% of the lower limit of normal (LLN)
4. C4 must be >90% of the LLN

5. Female patients of childbearing potential must either agree to abstinence or to use two effective methods of contraception as defined in Section 5.5.5 from screening through 3 months after the last dose of ACH 0144471. Females who are of non-childbearing potential as defined in Section 5.5.5 need not employ a method of contraception.
6. Male patients must either agree to abstinence or to use two effective methods of contraception as defined in Section 5.5.5 throughout the dosing period and for at least 3 months after the last dose of ACH 0144471. Males who are surgically sterile need not employ additional contraception. Males must agree to not donate sperm throughout the dosing period and for at least 3 months following the last dose of ACH 0144471.
7. Must be capable of providing written informed consent, must be willing and able to comply with the requirements and restrictions listed in the consent form and with the visit schedule, treatment plan, laboratory tests, pharmacokinetic sampling schedule, and other study procedures, and must be willing and able to return for all study visits
8. Must be up-to-date on routine vaccinations, or be willing to be brought up-to-date, based on local guidelines
9. Must be willing to comply with study-specific vaccination requirements for Haemophilus influenzae, Streptococcus pneumoniae, and Neisseria meningitidis strains A, C, W, and Y
10. Must be willing, at all times for the duration of study participation, to have transportation and telephone access, and to be within one hour of an emergency medical center

Exclusion criteria

Patients who meet any of the following criteria will be excluded from the study:
1. History of a major organ transplant (e.g., heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant. Individuals receiving renal replacement therapy are also excluded
2. History or presence of any clinically relevant co-morbidities that would make the patient inappropriate for the study (for example, is likely to result in deterioration of the patient*s condition, affect the patient*s safety during the study, or confound the results of the study), in the opinion of the Principal Investigator
3. Evidence of monoclonal gammopathy of unclear significance (MGUS), infections, malignancy, autoimmune diseases, or other conditions to which C3 glomerulopathy or IC-MPGN may be secondary
4. Patients with other renal diseases that would interfere with interpretation of the study
5. Presence or evidence of hepatobiliary cholestasis
6. Known Gilbert*s syndrome and/or patients with a history suggestive of Gilbert*s syndrome
7. Females who are pregnant, nursing, or planning to become pregnant during the study or within 90 days of study drug administration, or patients with a female partner who is pregnant, nursing, or planning to become pregnant during the study or within 90 days of study drug administration
8. Estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m2 at the time of screening or at any time over the preceding four-weeks
9. History of febrile illness, a body temperature >38°C, or other evidence of a clinically significant active infection, within 14 days prior to study drug administration
10. Patients with evidence of human immunodeficiency virus, hepatitis B or hepatitis C infection (positive serology for HIV-1 antibody, positive hepatitis B surface antigen, or

positive anti-HCV antibody at Screening or historically)
11. History of meningococcal infection, or a first-degree relative or household contact with a history of meningococcal infection
12. Contraindication to one or more of the required vaccinations
13. History of hypersensitivity reactions to commonly used antibacterial agents, including beta-lactams, penicillin, aminopenicillins, fluoroquinolones, cephalosporins, and carbapenems, which, in the opinion of the investigator and/or an appropriately qualified immunology or infectious disease expert, would make it difficult to properly provide either empiric antibiotic therapy or treat an active infection
14. Participation in a clinical study in which an investigational drug was given within 30 days, or within 5 half-lives of the investigational drug, whichever is longer, prior to study drug administration
15. Receipt of eculizumab at any dose or interval within the past 75 days prior to dosing
16. Use of tacrolimus or cyclosporine within 2 weeks of the first dose of ACH 0144471
17. 12-lead electrocardiogram with a QTcF >500 msec or findings which, in the opinion of the PI, could put the patient at undue risk
18. Any of the following laboratory abnormalities at screening:
* Alanine transaminase > ULN
* Aspartate aminotransferase > ULN
* Alkaline phosphatase > ULN
* Absolute neutrophil counts <1,000/*L
* Total bilirubin >1.5× ULN
* Indirect bilirubin > ULN
* Any laboratory abnormality that, in the opinion of the PI, would make the patient inappropriate for the study, or put the patient at undue risk
19. Donation of blood or blood products in excess of 500 mL within a 60 day period prior to the first dose of the current study
20. Receipt of blood or blood products within 30 days of screening
21. Clinically significant history of drug allergy as determined by the Investigator
22. Unwilling or unable to comply with the study protocol for any reason

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-09-2018
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ACH-0144471
Generic name:	none

Ethics review

Approved WMO Date:	09-01-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-06-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-10-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-11-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-003525-42-NL
ClinicalTrials.gov	NCT03124368
CCMO	NL63197.091.17