A Phase I, Randomized, Placebo-controlled, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Activity of Repeated Intranasal Administration of Ampligen® (Poly I:Poly C12U) in Healthy Subjects

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* To assess the safety and tolerability of Ampligen administered intranasally in a dosing schedule for 13 days (7 doses) in healthy subjects.* To characterize the mucosal immune response following Ampligen administration over time.

Ethical review	Approved WMO
Status	Completed
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON50834

Source
ToetsingOnline

Brief title
Intranasal Ampligen in healthy volunteers.

Condition

- Viral infectious disorders

Synonym
Corona, COVID-19, SARS-CoV-2

Research involving

Human

Sponsors and support

Primary sponsor: AIM ImmunoTech Inc.
Source(s) of monetary or material Support: AIM ImmunoTech Inc.

Intervention

Keyword: Ampligen, COVID-19, Intranasal, mucosal immune response

Outcome measures

Primary outcome

* Frequency of local Treatment-Emergent Adverse Events (TEAEs)

* Frequency of systemic Treatment-Emergent Adverse Events (TEAEs)

* Frequency of any serious adverse events (SAEs)

* Frequency of any withdrawals due to Adverse Events (AEs)

* Frequency of any Dose Limiting Toxicities (DLTs)

* Change in laboratory values, vital signs, physical examination findings

(including nasal and oral examination)

* Nasal pain assessed by visual analogue scale (VAS)

* Integrity of the nasal mucosa by anterior rhinoscopy

* Levels of mucosal cytokines

* Characterization of mucosal immune cells

Secondary outcome

N.A.

Study description

Background summary

Ampligen®, a synthetic double-stranded RNA (Poly I: Poly C12U), is a well-defined selective Toll-like receptor 3 (TLR3) agonist inducing innate immune antiviral responses. TLR3 is expressed at high level in human airway epithelial cells, including the nose and nasal pharynx. TLR3 serves as a pathogen recognition receptor to stimulate the innate immune response against many respiratory pathogens including coronaviruses (2). As a highly specific TLR3 agonist, Ampligen stimulates the production of type I interferons, which exert both antiviral and immunomodulatory activity. Besides activating TLR3, Ampligen modulates the 2', 5' oligoadenylate synthetase/RNase L system and p68 protein kinase, which are both important natural antiviral pathways.

Ampligen has been administered intravenously in approximately 100,000 doses in clinical trials (predominantly in the field of oncology) and compassionate use programs (myalgic encephalomyelitis/chronic fatigue syndrome). Intranasal administration of Ampligen as an universal flu adjuvant in combination with an intranasal flu vaccine (Flumist®) was found to be well tolerated up to doses of 1250 *g (maximum proposed dose in this trial) administered thrice with an interval of four weeks.

The route of human infection of SARS-CoV-2 is believed to be primarily by entry into the nasal epithelium. Ampligen has been shown to inhibit the replication of a wide variety of viruses in vitro and in vivo. Studies with the genetically similar SARS-CoV in mice showed a significant protective effect of Ampligen, coinciding with a significant decrease in pulmonary IL-6 levels. More recently, in vitro antiviral activity against SARS-CoV-2 has been confirmed (unpublished preclinical data). By dosing Ampligen every other day intranasally, it is believed that SARS-CoV-2 can be inhibited at the point of entry, and thus will be much less likely to progress to a pulmonary infection, or moderate COVID-19 disease. These characteristics make Ampligen a potent candidate to be developed for an early treatment strategy and (post-exposure) prophylaxis against COVID-19. Because Ampligen does not act by binding to proteins or specific nucleic acid sequences of viruses it can also be developed for potential future outbreaks with pathogenic coronavisurses (CoVs), or even other respiratory viruses.

This phase I trial will assess the safety, tolerability and biological activity of repeated administration of Ampligen intranasally every other day for 13 days (7 doses) in healthy volunteers. This study is necessary for the further development of Ampligen as a potential treatment modality for COVID-19 and other pulmonary viral diseases.

Study objective

* To assess the safety and tolerability of Ampligen administered intranasally in a dosing schedule for 13 days (7 doses) in healthy subjects.
* To characterize the mucosal immune response following Ampligen administration

over time.

Study design

This is a, randomized, double-blind, placebo-controlled, repeated dose study performed in healthy adults.

Intervention

Ampligen will be administered intranasally via a nasal sprayer. An amount of 250 *L will be administered in each nostril (total volume of 500 *L per dose). Each individual will receive the same dose throughout the treatment period. Subjects will receive a total of 7 doses of Ampligen or placebo. Dosing will be started on day 1 and will be administered every other day until day 13. A starting dose of 75 *g will be used in the first cohort. Doses will be escalated to 200 *g, 500 *g and a maximum dose of 1250 *g in the respective following cohorts using a dose escalation design.
A placebo (normal saline) will be used as comparator in this study. The placebo will be indistinguishable from the active compound.

Study burden and risks

Study participants will not have health benefit from study participation. Study participants will not be protected from the coronavirus, COVID-19 or any other respiratory infection. This clinical study will be important to support further clinical evaluation of Ampligen as prophylactic or therapeutic modality to fight COVID-19. The study will not only generate data on the safety/tolerability of intranasal Ampligen administration, but also provide insight into the proximal pharmacological activities of the compound, and potential dose- and time-dependent effects. This information is critical for rational dose selection for future clinical trials in COVID-19, or other pulmonary viral diseases.

Participating in this study will take aproximatly 2 months, and a total of 13 visits. Subjects will have a medical screening (1 hour), a basline visit (1 hour), 2 long visits (8 hours), 8 short visits (1.5 hours) and a follow up visit (1 hour). During the study, subjects will receive 7 doses of the investigational compound or placebo spread over 14 days.

The following actions will be performed during these visits:
- Physical examination
- Questions about adverse events
- ECG
- Blood examination. The total blood that will be drawn during this study is 50 mL.
- Questionaire about nasal complaints after dosing

- Nose and throat swab to test for the presence of a SARS-CoV-2 infection or any other respiratory infection.
- Nasal scrape to study the immune cells in the nose
- Nasal fluid will be taken by holding a small cotton swab in the nose for 1 minute

The possible side effects of the Ampligen are:
- Runny nose
- Headache
- Stuffy nose
- Sore throat
- Cough
- Fatigue
- Muscle strain
- Sinus pain

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

1. Signed informed consent prior to any study-mandated procedure;
2. Male or female subjects, 18 to 70 years of age, inclusive at screening;
3. Body mass index (BMI) between 18 and 32 kg/m2, inclusive at screening, and with a minimum weight of 50 kg.
4. Participant must be healthy, in the investigator*s clinical judgment, as confirmed by medical history, physical examination, vital signs, ECG and laboratory assessments performed at screening. Repeated laboratory testing may be performed at the discretion of the clinical investigators for spurious results on a case by case basis;
5. Willing to comply with effective contraception during the study if subject is male or women of child bearing potential, up to 90 days after the last dose of study treatment.
6. Has the ability to communicate well with the investigator in the Dutch language and willing to comply with the study restrictions

Exclusion criteria

1. Evidence of any active or chronic disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the investigator (following a detailed medical history, physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, body temperature) and 12-lead electrocardiogram (ECG). Minor deviations from the normal range may be accepted, if judged by the Investigator to have no clinical relevance;
2. Clinically significant abnormalities, as judged by the investigator, in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis. In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects;
3. Positive hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV ab), or human immunodeficiency virus antibody (HIV ab) at screening;
4. Respiratory tract infection (including flu and common cold symptoms) or any febrile illness (>38°celsius) in the period of 3 days before first treatment administration;
5. Presence of respiratory viral infection as determined by respiratory panel on nasal swab at baseline (including positive SARS-CoV-2 PCR test);
6. History of chronic respiratory diseases (e.g. chronic obstructive pulmonary disease, emphysema, chronic rhinitis or sinusitis, asthma or other reactive

airway diseases) in adulthood. Childhood asthma and non-active allergic rhinitis (including hay fever) will be permitted at the discretion of the investigator;
7. History of frequent nose bleeds;
8. Significant anatomical nasal abnormalities or other nasal abnormalities that might impact the study executions (including, but not limited to, nasal septal defects, cleft palate, nasal polyps, previous nasal cautery or surgery that impacts study assessments);
9. Immunocompromised (known or expected immune deficiency, disease, or use of medication that may affect the immune system) or evidence of autoimmune disorder (deemed clinically relevant by the investigator);
10. Participation in an investigational drug or device study (last dosing of previous study was within 90 days or 5 half-lives prior to first dosing of this study);
11. History of abuse of addictive substances (alcohol, illegal substances) or current use of more than 21 units of alcohol per week, drug abuse, or regular user of sedatives, hypnotics, tranquillisers, or any other addictive agent;
12. Positive test for drugs of abuse at screening or pre-dose. Drugs test may be repeated;
13. A routine smoker of tobacco products, currently or in the past year. No (incidental) smoking will be allowed in the two weeks prior to first dosing;
14. Use of immunomodulatory drug; including systemic corticosteroids as well as nasal preparations within 30 days before first dosing. Low dose topical use of corticosteroids will be permitted. Other exceptions will only be made if the rationale is clearly documented by the investigator;
15. Receipt of any vaccine within 1 week prior to IMP administration, or planning to get vaccinated during the study;
16. Therapy with interferons, interleukins, or other cytokines within 6 weeks of first dosing;
17. Known hypersensitivity to Ampligen or its excipients;
18. If a woman, pregnant, or breast feeding, or planning to become pregnant during the study;
19. Any known factor, condition, or disease that might interfere with treatment compliance, study conduct or interpretation of the results such as drug or alcohol dependence or psychiatric disease.
20. History of Bell*s Palsy or other forms of facial paralysis.
21. Loss or donation of blood over 500 mL within three months (males) or four months (females) prior to screening, or donation of plasma within 14 days of screening or intention to donate blood or blood products during the study

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	17-02-2021
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AMPLIGEN®
Generic name:	RINTATOLIMOD

Ethics review

Approved WMO

Date:	19-01-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	10-02-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 21868
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2020-005898-26-NL
CCMO	NL76226.058.21

Study results

Date completed: 16-06-2021

Results posted: 09-06-2022

First publication
21-04-2022