An open label, single arm study to evaluate single and multiple dose pharmacokinetics, safety and tolerability, and to explore clinical outcomes of treatment with intravenous |(IV) zanamivir in neonates and infants under 6 months of age with confirmed complicated influenza infection

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PrimaryTo characterise the single and multiple dose to steady state pharmacokinetics of IV zanamivirin hospitalised neonates and infants under 6 months of age with influenza infection.SecondaryTo evaluate the safety and tolerability of IV zanamivir...

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

Summary

ID

NL-OMON50842

Source
ToetsingOnline

Brief title
200925 - Influenza

Condition

- Viral infectious disorders

Synonym
Influenza; Flu

Research involving
Human

Sponsors and support

Primary sponsor: GlaxoSmithKline
Source(s) of monetary or material Support: GlaxoSmithKline B.V.

Intervention

Keyword: Influenza, Intravenous, Neonates and infants <6 months, Zanamivir

Outcome measures

Primary outcome

Area under the serum concentration-time curve (AUC)

Maximum serum concentration (Cmax)

Clearance (CL)

Terminal half-life (t1/2)

Secondary outcome

Adverse events

Vital signs including heart rate, oxygen saturation, respiration rate and

temperature

Quantitative viral load over time and change from baseline

Viral susceptibility to zanamivir at baseline, and if virus can be cultured, at

subsequent

timepoints during the study

Nucleotide sequence analysis to determine emergence of resistance to zanamivir

Study description

Background summary

Influenza infection continues to be an important public health priority, with seasonal outbreaks and pandemics causing considerable global morbidity and mortality. It is estimated that, each year around the world seasonal influenza accounts for 3-5 million cases of severe illness and 290,000 to 650,000 respiratory deaths.
Between 3% and 11% of children aged < 2 years in developed countries acquire influenza-associated illness every year, creating a major burden on both primary and secondary care services.
Most of the clinical experience with IV zanamivir administration in paediatric population comes from the paediatric cohort of the phase II study (NAI113678, Bradley, 2017), in which 71 subjects 6 months - <18 years were included. Paediatric and adolescent subjects (6 months - 18 years of age) received an age-adjusted, weight-based dose intended to provide systemic exposure comparable to 600 mg in adults. The dosage adjustments in paediatric subjects based on age, weight and renal function resulted in areas under the curves (AUCs) similar to adults. In the paediatric cohort, the safety profile of IV zanamivir was consistent with that expected in children with severe influenza. There were no new safety signals found in the paediatric population compared to the adult population.

Clinical laboratory tests, electrocardiograms (ECGs), and vital signs data did not reveal any pattern of adverse findings associated with IV zanamivir treatment in paediatric/adolescent patients compared with adult patients. In this study, children with more severe influenza at the time of enrolment, were found to have less favourable clinical improvement. The majority of treated children in this study experienced clinical improvement during the treatment course. IV zanamivir treatment was associated with an antiviral effect in paediatric population.

While participants <6 months were not eligible for enrolment in completed GSK clinical studies of IV zanamivir, patients <6 months of age have been treated with zanamivir aqueous solution in the compassionate use program (CUP). The CUP was initiated in 2009 to provide zanamivir aqueous solution (IV or nebulised administration) on a named patient basis. As of 6 May 2019, the termination date of the CUP, >4000 requests for zanamivir aqueous solution have been received, including 406 patients <18 years. Over
96% of patients received zanamivir intravenously. At least 20 patients in the CUP were 0-6 months (12 born prematurely with a gestation age of 23 -35 weeks).

Study objective

Primary
To characterise the single and multiple dose to steady state pharmacokinetics of IV zanamivir
in hospitalised neonates and infants under 6 months of age with influenza infection.

Secondary
To evaluate the safety and tolerability of IV zanamivir in hospitalised neonates and
infants under 6 months of age with influenza infection
To investigate clinical virology before, during and after the treatment of IV zanamivir

Exploratory
To evaluate clinical outcomes following treatment with IV zanamivir

Study design

This will be an open-label, multi-centre and single arm study in neonates and infants under 6 months of age with complicated influenza infection. Preterm neonates and infants will be eligible for inclusion but must have reached Post-Menstrual Age (PMA) of at least 28 weeks.

The total duration of study participation for each participant is up to 24 days, which consists of a study treatment period up to 10 days and 14 days post-treatment follow up period.
The initial treatment duration is 5 days. However, for a given subject, the initial 5-day treatment course may be extended for up to 5 additional days if clinical symptoms, patient characteristics or virological tests as assessed by the investigator warrant further treatment.

Intervention

The initial dose of IV zanamivir will be determined by PMA/corrected age and bodyweight. The maintenance dose and interval between the initial dose and subsequent twice-daily maintenance dose will be further determined by renal function. Renal function will be monitored if treatment continues beyond 5 days during the treatment period for dose adjustment if needed.
When the first dose is administered in the morning of Day1, the treatment day for the twice daily maintenance dosing schedule will correspond to that calendar day. However if the first dose of IV zanamivir is administered in the afternoon or evening of Day 1, the twice daily maintenance dosing schedule will result in one treatment day encompassing two calendar days.

Study burden and risks

The details are based on information from patients ranging from babies above 6 months of age to adult. Some effects cannot be seen in babies but need to be mentioned to provide as complete a list as is possible.

Serious skin and allergic reactions may occur with zanamivir, but there isn*t enough information to estimate how likely they are. The doctor will look out for:
• very severe skin reactions such as a skin rash, which may cause blisters that may be widespread and include skin peeling.
• severe allergic reactions, including features such as itchy rash, swelling of the face, throat or tongue, breathing difficulty, light headedness and vomiting.

Common side effects
These may affect up to 1 in 10 people
• diarrhoea
• damage to liver cells (hepatocellular injury). This may show up in blood tests for your baby as an increase in the level of liver enzymes (raised aminotransferase).
• rash

Uncommon side effects
These may affect up to 1 in 100 people
• itchy, bumpy rash (hives).

Uncommon side effects that may show up in the blood tests for the baby:
• increase in the level of liver or bone enzymes (raised alkaline phosphatase).

Side effects where it is not known how likely they are to happen
• acting strangely
• seeing, hearing or feeling things which are not there
• confused thinking
• fits (seizures)
• being less alert or not responding to loud sounds or being shaken
Severe flu can cause these symptoms. It is unknown if zanamivir also causes them. They tend to happen early in the illness and get better quickly. They have been seen in children with flu who were taking zanamivir and in children with flu who were not taking zanamivir.

Study procedure:
When taking a blood sample from the baby: they may feel faint, or experience mild pain, bruising, irritation or redness at the site. In rare cases, they may get an infection.

Contacts

Public
GlaxoSmithKline

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Babies and toddlers (28 days-23 months)
Newborns
Premature newborns (<37 weeks pregnancy)

Inclusion criteria

1. Neonates and infants who are aged less than 6 months (corrected age). Preterm neonates and infants will be eligible for inclusion but must have reached Post-Menstrual Age (PMA) of at least 28 weeks
2. Participants who are hospitalised with influenza infection.
3.Participants with a high risk of altered oral drug absorption, represented by multi-organ dysfunction (dysfunction of at least 2 organs, as defined by the treating physician).
4. Body weight >=1kg

Exclusion criteria

1. Participants who are known or suspected to be hypersensitive to any component of the study medication.
2. Participants with a disease process which is likely to be irreversible.
3. Liver function:
Subjects who meet the following criteria at Baseline:
ALT >=3xULN with Bilirubin >=2xULN, or Isolated bilirubin >= 2xULN and >50% direct bilirubin, or ALT >=5xULN
Current or chronic history of liver disease or known hepatic or biliary abnormalities.
4. Participants who require concurrent therapy with another influenza antiviral drug.
5. Participants who have participated in a study using an investigational drug within 30 days prior to Baseline.
6. Child in care (CiC), as defined below:
• A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation.
• The definition of a CiC can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a CiC does not include a child who is adopted or has an appointed legal guardian.
7. Patients undergoing treatment by Extracorporeal membrane oxygenation (ECMO) or hemofiltration.
8. Participants who are positive for SARS-CoV-2, as determined by a diagnostic test, at screening

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	21-01-2021
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	DECTOVA
Generic name:	zanamivir IV
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-10-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-04-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-12-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-12-2021
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	EUCTR2019-001588-63-NL
CCMO	NL75414.091.20
Other	www.gsk-clinicalstudyegister.com; 200925