



Clinical trial results:

A phase IV, interventional, non-blinded, randomized, controlled, multicenter study of Posaconazole prophylaxis for the prevention of influenza-associated aspergillosis (IAA) in critically ill patients

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2017-003270-14 |
| Trial protocol | BE NL FR |
| Global end of trial date | 14 June 2020 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v1 (current) |
| This version publication date | 15 July 2022 |
| First version publication date | 15 July 2022 |
| Summary attachment (see zip file) | Posaconazole for prevention of invasive pulmonary aspergillosis in critically ill influenza patients (POSAFLU): a randomised, openlabel, proofofconcept trial (Vanderbeke2021_Article_PosaconazoleForPreventionOfInv.pdf) |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | POSA-FLU |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03378479 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | UZ Leuven |
| Sponsor organisation address | Herestraat 49, Leuven, Belgium, 3000 |
| Public contact | Prof. Dr. Joost Wauters, UZ Leuven, joost.wauters@uzleuven.be |
| Scientific contact | Prof. Dr. Joost Wauters, UZ Leuven, joost.wauters@uzleuven.be |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 14 June 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 14 June 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 June 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Influenza-associated pulmonary aspergillosis (IAPA) is a frequent complication in critically ill influenza patients, associated with significant mortality. We investigated whether antifungal prophylaxis reduces the incidence of IAPA.

Protection of trial subjects:

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial and are out-with standard routine care at the participating site (including the collection of identifiable participant).

The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment and must be provided with a contact point where he/she may obtain further information about the trial. Where a participant is required to re-consent or new information is required to be provided to a participant, it is the responsibility of the PI to ensure this is done in a timely manner.

The PI takes responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence. Where the participant population is likely to include a significant proportion of participants who cannot read or write, require translators or have cognitive impairment, appropriate alternative methods for supporting the informed consent process should be employed. This may include allowing a witness to sign on a participant's behalf (in the case of problems with reading or writing), designate a legal representative, or providing Participant Information Sheets in other languages or in a format easily understood by the participant population (in the case of minors or cognitive impairment) providing they are approved by the EC.

Background therapy:

Oseltamivir (non-IMP) will be started at the discretion of the treating physician from the first day of ICU admission as 2x150mg for a duration of 10 days.

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 01 December 2017 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 3 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Netherlands: 11 |
| Country: Number of subjects enrolled | Belgium: 69 |
| Country: Number of subjects enrolled | France: 8 |

| | |
|------------------------------------|----|
| Worldwide total number of subjects | 88 |
| EEA total number of subjects | 88 |

Notes:

| Subjects enrolled per age group | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 56 |
| From 65 to 84 years | 26 |
| 85 years and over | 6 |

Subject disposition

Recruitment

Recruitment details:

Patients admitted to intensive care unit (ICU) with a severe influenza pneumonia will be screened. When all eligibility criteria are met, the principle investigator (PI) or the treating physician will approach the patient or his/her relatives in order to give study information and request informed consent.

Pre-assignment

Screening details:

After eligibility screening, the following screening assessments will be done:

- Patient demographics and baseline parameters
- Medical History

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Posaconazole prophylaxis group + standard-of-care |

Arm description:

Posaconazole (Noxafil) will be started intravenously from day 1 of randomisation (2x300mg on day 1, followed by 1x300mg from day 2 for 7 days). Noxafil concentrate injections (vials made of type I glass containing 18mg posaconazole/mL, 300mg posaconazole/vial in total) for intravenous use will be provided by MSD.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Posaconazole, noxafil |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solution for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

2x300mg on day 1
1x300mg on day 2 for 7 days
Intravenously

| | |
|------------------|------------------|
| Arm title | Standard-of-care |
|------------------|------------------|

Arm description:

The treating physician can decide to perform an additional bronchoscopy with BAL between day 2 after randomisation and ICU discharge in case of respiratory deterioration and clinical suspicion of an IAA-infection. Any bronchoscopy will only be performed if the safety of the patient will not be compromised. In case of positive mycological evidence of an IAA-infection, a CT thorax without IV contrast is performed if possible. If an IAA-infection is documented, antifungal treatment will be started and - in case the IAA-infection is diagnosed before the ending of the study drug - the patient will be withdrawn from the study. Again, type and duration of antifungal therapy will be at the discretion of the treating physician.

Oseltamivir will be started at the discretion of the treating physician from the first day of ICU admission as 2x150 mg/day for a duration of 10 days. If oseltamivir had already been started up before ICU admission, oseltamivir treatment will be continued up to 10 days

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 | Posaconazole prophylaxis group + standard-of-care | Standard-of-care |
|--------------------------------|---|------------------|
| | | |
| Started | 43 | 45 |
| Completed | 37 | 36 |
| Not completed | 6 | 9 |
| IAPA at ICU admission | 6 | 9 |

Baseline characteristics

Reporting groups

| | |
|------------------------------|---------------|
| Reporting group title | Overall trial |
| Reporting group description: | |
| Overall | |

| Reporting group values | Overall trial | Total | |
|--|---------------|-------|--|
| Number of subjects | 88 | 88 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 56 | 56 | |
| From 65-84 years | 26 | 26 | |
| 85 years and over | 6 | 6 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 61 | | |
| standard deviation | ± 15 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 38 | 38 | |
| Male | 50 | 50 | |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Posaconazole prophylaxis group + standard-of-care |
| Reporting group description: Posaconazole (Noxafil) will be started intravenously from day 1 of randomisation (2x300mg on day 1, followed by 1x300mg from day 2 for 7 days). Noxafil concentrate injections (vials made of type I glass containing 18mg posaconazole/mL, 300mg posaconazole/vial in total) for intravenous use will be provided by MSD. | |
| Reporting group title | Standard-of-care |
| Reporting group description: The treating physician can decide to perform an additional bronchoscopy with BAL between day 2 after randomisation and ICU discharge in case of respiratory deterioration and clinical suspicion of an IAA-infection. Any bronchoscopy will only be performed if the safety of the patient will not be compromised. In case of positive mycological evidence of an IAA-infection, a CT thorax without IV contrast is performed if possible. If an IAA-infection is documented, antifungal treatment will be started and - in case the IAA-infection is diagnosed before the ending of the study drug - the patient will be withdrawn from the study. Again, type and duration of antifungal therapy will be at the discretion of the treating physician. Oseltamivir will be started at the discretion of the treating physician from the first day of ICU admission as 2x150 mg/day for a duration of 10 days. If oseltamivir had already been started up before ICU admission, oseltamivir treatment will be continued up to 10 days | |

Primary: IAPA incidence

| | |
|---|----------------|
| End point title | IAPA incidence |
| End point description: | |
| End point type | Primary |
| End point timeframe: During ICU stay | |

| End point values | Posaconazole prophylaxis group + standard-of-care | Standard-of-care | | |
|-----------------------------|---|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 37 | 36 | | |
| Units: number of patients | | | | |
| number (not applicable) | 2 | 4 | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | One-sided Fisher's Exact test |
| Comparison groups | Posaconazole prophylaxis group + standard-of-care v Standard-of-care |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 73 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 ^[1] |
| Method | Fisher exact |

Notes:

[1] - Significance was defined as p values <0.05

Secondary: Time to IAPA diagnosis

| | |
|------------------------|------------------------|
| End point title | Time to IAPA diagnosis |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Time to IAPA diagnosis | |

| End point values | Posaconazole prophylaxis group + standard-of-care | Standard-of-care | | |
|---------------------------------------|---|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 37 | 36 | | |
| Units: days | | | | |
| median (inter-quartile range (Q1-Q3)) | 10 (8 to 12) | 5 (3 to 8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Length of ICU stay

| | |
|------------------------|--------------------|
| End point title | Length of ICU stay |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Length of ICU stay | |

| End point values | Posaconazole prophylaxis group + standard-of-care | Standard-of-care | | |
|---------------------------------------|---|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 27 | | |
| Units: days | | | | |
| median (inter-quartile range (Q1-Q3)) | 16 (8 to 29) | 6 (3 to 12) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Length of hospital stay

| | |
|-------------------------|-------------------------|
| End point title | Length of hospital stay |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Length of hospital stay | |

| End point values | Posaconazole prophylaxis group + standard-of-care | Standard-of-care | | |
|---------------------------------------|---|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 25 | | |
| Units: days | | | | |
| median (inter-quartile range (Q1-Q3)) | 25 (18 to 45) | 12 (9 to 35) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: ICU mortality

| | |
|------------------------|---------------|
| End point title | ICU mortality |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| ICU mortality | |

| End point values | Posaconazole prophylaxis group + standard-of-care | Standard-of-care | | |
|-----------------------------|---|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 37 | 36 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 7 | 9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Hospital mortality

| | |
|------------------------|--------------------|
| End point title | Hospital mortality |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Hospital mortality | |

| End point values | Posaconazole prophylaxis group + standard-of-care | Standard-of-care | | |
|-----------------------------|---|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 37 | 36 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 8 | 10 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 90-day mortality

| | |
|------------------------|------------------|
| End point title | 90-day mortality |
| End point description: | |
| End point type | Secondary |

End point timeframe:

90-day mortality

| End point values | Posaconazole prophylaxis group + standard-of- care | Standard-of- care | | |
|-----------------------------|--|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 37 | 36 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 9 | 11 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Adverse events should be reported in the eCRF.

SAE should be reported to the sponsor immediately (within 24h of becoming aware of the event)

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

| | |
|--------------------|-----|
| Dictionary version | 5.0 |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall trial |
|-----------------------|---------------|

Reporting group description:

Adverse event at the ICU department are very hard to define.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Adverse events are very hard to define at the intensive care unit.

Therefore, we only reported SAE's.

| Serious adverse events | Overall trial | | |
|---|---|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 29 / 88 (32.95%) | | |
| number of deaths (all causes) | 29 | | |
| number of deaths resulting from adverse events | 0 | | |
| Infections and infestations | | | |
| Death | Additional description: 29 patients died during the study (until 90 days) | | |
| subjects affected / exposed | 29 / 88 (32.95%) | | |
| occurrences causally related to treatment / all | 0 / 29 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Overall trial | | |
|---|----------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|-------------|
| 03 January 2018 | PK substudy |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34050768>