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