Clinical trial results:
A randomized placebo-controlled double blind study to prevent BOS

Summary

EudraCT number	2010-022027-30
Trial protocol	BE
Global end of trial date	11 November 2015

Results information

Result version number	v1 (current)
This version publication date	29 November 2024
First version publication date	29 November 2024
Summary attachment (see zip file)	Study Results (Vit D study Results.pdf)

Trial information

Trial identification

Sponsor protocol code	VIT001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01212406
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	KU Leuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Anja Gilissen Clinical Trial Center (CTC) anja.gilissen@uzleuven.be +32 16 342101 , University Hospitals Leuven and KU Leuven, 0032 342101, anja.gilissen@uzleuven.be
Scientific contact	Anja Gilissen Clinical Trial Center (CTC) anja.gilissen@uzleuven.be +32 16 342101 , University Hospitals Leuven and KU Leuven, 0032 342101, anja.gilissen@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	08 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Prevalence of BOS (grade 1) at 2 and 3 year post-transplant in patietns treated with Vitamin D vs. Placebo

Protection of trial subjects:

Standard Operating Procedures as per Institution's post-transplant protcol

Background therapy:

Standard immunosuppressive regimen and infectious prophylaxis according to Standard Operating Procedures.

Evidence for comparator:

1,25(OH)2D demonstrates anti-inflammatory effects in the lungs due to local inhibition of NF-κB and mitogen-activated protein kinase (MAPK) activity, thus attenuating secretion of inflammatory cytokines and chemokines, such as interleukin (IL)-1β, IL-6 and IL-8; and influx of inflammatory cells. Next to this, 1,25(OH)2D reduces oxidative stress by inhibiting anti-protease activity and acting on nuclear factor erythroid 2-related factor 2 (Nrf2), a transcriptional regulator of most antioxidant genes (4). 1,25(OH)2D also has anti-infectious properties, by increasing maturation and proliferation of monocytes into macrophages; and transcriptional up-regulation of cathelicidin and defensin-β2 by airway epithelial cells, pulmonary macrophages and neutrophils, which suppress inflammation and are effective in microbial killing, including fungi and Pseudomonas species. 1,25(OH)2D is involved in tissue remodeling, as it demonstrates inhibitory effects on expression of matrix metalloproteinases in airway smooth muscle cells, monocytes and alveolar macrophages, on proliferation and activation of bronchial airway muscle cells and fibroblasts, on extra-cellular matrix deposition by fibroblasts; and on epithelial-mesenchymal transition. Finally, 1,25(OH)2D inhibits proliferation and differentiation of B-cells, suppresses secretion of pro-inflammatory cytokines by CD4+ T-cells, inhibits T-helper (Th)-cells, such as Th1, Th9, Th17 and possibly also Th2, increases development of regulatory T-cells (Treg) and promotes a tolerogenic phenotype of dendritic cells.
We therefore investigated the possible immunomodulatory effects of vitamin D in lung transplatation.

Actual start date of recruitment	29 October 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 87
Worldwide total number of subjects	87
EEA total number of subjects	87

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)	83
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Following written informed consent, patients were randomly assigned to receive either oral vitamin D or placebo using a 1:1 ratio by the University's Hospital Experimental Pharmacy (http://www.randomization.com). Adult lung transplant recipients able to take oral drugs at hospital discharge following LTx were eligible for inclusion.

Pre-assignment

Screening details:

See added summary of the published study results

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Blinding implementation details:

Study groups were generated through permuted-block randomization using a 1:1 ratio by the University's Hospital Experimental Pharmacy (http://www.randomization.com). . Both vitamin D and placebo were stored and subsequently delivered by the University's Hospital Experimental Pharmacy in blinded, sequentially numbered syringes (Exactamed 10 ml 1610 Amber) for oral intake. All participants, nurses and treating physicians were blinded to group assignment during study treatment and later

Arms

Are arms mutually exclusive?	Yes
Arm title	Vitamin D

Arm description:

Vitamin D (D-Cure™, cholecalciferol, 100,000 IU, 4 mL, orally, once monthly)

Arm type	Active comparator
Investigational medicinal product name	D-Cure
Investigational medicinal product code	Vitamin D
Other name	cholecalciferol
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

100,000 IU, 4 mL, orally, once monthly

Arm title	Placebo

Arm description:

arachide oil (4 mL, orally, once monthly)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	arachide oil
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

4 mL, orally, once monthly

Number of subjects in period 1	Vitamin D	Placebo
Started	44	43
Completed	36	34
Not completed	8	9
Consent withdrawn by subject	5	6
Adverse event, non-fatal	1	-
Lost to follow-up	2	3

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	87	87	
Age categorical			
Age of included patients			
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)	83	83	
From 65-84 years	4	4	
85 years and over	0	0	
Gender categorical			
Overall trial			
Units: Subjects			
Female	39	39	
Male	48	48	

Subject analysis sets

Subject analysis set title	Overall trial
Subject analysis set type	Full analysis

Subject analysis set description:

See added summary of the published study results

Reporting group values	Overall trial		
Number of subjects	87		
Age categorical			
Age of included patients			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	83		
From 65-84 years	4		

85 years and over	0		

Gender categorical			
Overall trial			
Units: Subjects			
Female	39		
Male	48		

End points

End points reporting groups

Reporting group title	Vitamin D
Reporting group description: Vitamin D (D-Cure™, cholecalciferol, 100,000 IU, 4 mL, orally, once monthly)	
Reporting group title	Placebo
Reporting group description: arachide oil (4 mL, orally, once monthly)	
Subject analysis set title	Overall trial
Subject analysis set type	Full analysis
Subject analysis set description: See added summary of the published study results	

Primary: CLAD

End point title	CLAD
End point description: See added summary of the published study results	
End point type	Primary
End point timeframe: at 3 years post transplant	

End point values	Vitamin D	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: events				
CLAD event	6	5		

Statistical analyses

Statistical analysis title	Primary Endpoint Analysis
Comparison groups	Vitamin D v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05 [2]
Method	Logrank
Parameter estimate	logrank p-value

Notes:

[1] - log-rank analysis showed no statistical difference between both arms

[2] - log-rank analysis showed no statistical difference between both arms

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During the study	
Adverse event reporting additional description:	
Nausea leading to IMP discontinuation	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	clincial symptoms
Dictionary version	N/A

Reporting groups	
Reporting group title	Overall study
Reporting group description:	
nausea leading to discontinuation of IMP	

Serious adverse events	Overall study		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 87 (0.00%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Overall study		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 87 (1.15%)		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

See added summary of the published study results

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28365177