



## Clinical trial results:

### Characterization of humoral and cellular immunity for tick-borne encephalitis (TBE) vaccination in allogeneic blood and marrow graft recipients: a pilot study

#### Summary

EudraCT number	2011-002928-41
Trial protocol	AT
Global end of trial date	28 October 2018

#### Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022
Summary attachment (see zip file)	Publication npj vaccines 2020 (Humoral response to tick-borne encephalitis vaccination in allogeneic blood and marrow graft recipients_Harrison et al_2020.pdf) Publication Vaccines 2021 (Tick-Borne Encephalitis Specific Lymphocyte Response after allogeneic HSCT predicts humoral immunity after vaccination_Harrison et al_2021.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	Immunity_TBE
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01991067
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Währinger Gürtel 18-20, Vienna, Austria, 1090
Public contact	Christina Forstner, Med. Uni Wien, +43 1404004440, nicole.harrison@meduniwien.ac.at
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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	28 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 October 2018
Global end of trial reached?	Yes
Global end of trial date	28 October 2018
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To assess the humoral immunogenicity to a TBE vaccination in allogeneic blood and marrow graft (HSCT) recipients compared to healthy volunteers without previous TBE vaccination, by measuring the quantitative antibody levels using neutralization test (NT) and enzyme-linked immunosorbent assay test (ELISA)

Protection of trial subjects:

Patients were vaccinated and blood draws were taken by professional staff. All patients were covered by insurance during the trial.

Background therapy:

not applicable

Evidence for comparator:

not applicable

Actual start date of recruitment	01 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 34
Worldwide total number of subjects	34
EEA total number of subjects	34

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)	34
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

In this prospective single-center open-label study, adult patients  $\geq 18$  years of age were screened 11 to 13 months after allogeneic HSCT at the Outpatient Clinic of the Bone Marrow Transplant Unit of the University Hospital of Vienna, Austria.

### Pre-assignment

Screening details:

Between July 2014 and January 2018, 136 patients were assessed for eligibility and 117 were excluded for following reason: not meeting the inclusion criteria (n=39), declined to participate (n=56), other reasons (n=22). 19 Patients were included in the study and 15 age-matched healthy controls.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Patients

Arm description:

Patients after allogeneic hematopoietic stem cell transplantation

Arm type	Active comparator
Investigational medicinal product name	FSME Immun
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Injection

Dosage and administration details:

FSME Immun® (each dose contains 2.4 µg of inactivated TBE virus strain Neudörfl) is applied intramuscularly (M. deltoideus)

<b>Arm title</b>	Healthy controls
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Arm description:

Healthy controls

Arm type	Active comparator
Investigational medicinal product name	FSME Immun
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Injection

Dosage and administration details:

FSME Immun® (each dose contains 2.4 µg of inactivated TBE virus strain Neudörfl) is applied intramuscularly (M. deltoideus)

<b>Number of subjects in period 1</b>	Patients	Healthy controls
Started	19	15
Completed	17	15
Not completed	2	0
Lost to follow-up	2	-

## Baseline characteristics

### Reporting groups

Reporting group title	Patients
Reporting group description:	
Patients after allogeneic hematopoietic stem cell transplantation	
Reporting group title	Healthy controls
Reporting group description:	
Healthy controls	

Reporting group values	Patients	Healthy controls	Total
Number of subjects	19	15	34
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	19	15	34
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
median	31	30	-
full range (min-max)	22 to 61	21 to 60	-
Gender categorical			
Units: Subjects			
Female	8	6	14
Male	11	9	20
Underlying disease			
Underlying disease of patients			
Units: Subjects			
acute myeloid leukemia	13	0	13
acute lymphoblastic leukemia	3	0	3
lymphoma	2	0	2
aplastic anemia	1	0	1
not applicable	0	15	15
Conditioning regimen			
Conditioning regimen used before hematopoietic stem cell transplantation			
Units: Subjects			
myeloablative regimen	9	0	9
non-myeloablative regimen	10	0	10
not applicable	0	15	15

## End points

### End points reporting groups

Reporting group title	Patients
Reporting group description:	
Patients after allogeneic hematopoietic stem cell transplantation	
Reporting group title	Healthy controls
Reporting group description:	
Healthy controls	

### Primary: antibody response by neutralization assay

End point title	antibody response by neutralization assay
End point description:	
The primary endpoint of this study was the antibody response after TBE-vaccination as measured by neutralization assay (NT) four weeks after the second vaccination. Antibody response was defined as a composite endpoint by a NT-titer of $\geq 10$ , which is considered as a surrogate marker for protection and at least a two-fold increase of titer from baseline (or titer above highest level of measurement).	
End point type	Primary
End point timeframe:	
four weeks after second vaccination	

End point values	Patients	Healthy controls		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	15		
Units: count	6	14		

### Statistical analyses

Statistical analysis title	antibody response by neutralization assay
Statistical analysis description:	
Antibody response measured by neutralization assay was compared between patients and controls using Fishers Exact test.	
Comparison groups	Patients v Healthy controls
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Fisher exact

### Secondary: Geometric mean titer

End point title	Geometric mean titer
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End point description:

Geometric mean titers measured by neutralization assay were compared between patients and healthy controls after second vaccination.

End point type	Secondary
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End point timeframe:

after second vaccination

End point values	Patients	Healthy controls		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	15		
Units: titer				
geometric mean (confidence interval 95%)	64.7 (28.1 to 149.4)	58.5 (32.2 to 106.1)		

## Statistical analyses

Statistical analysis title	Geometric mean titer
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Statistical analysis description:

The geometric mean titer after second vaccination was compared between patients and controls using Wilcoxon test.

Comparison groups	Patients v Healthy controls
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Number of subjects included in analysis	32
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Analysis specification	Pre-specified
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Analysis type	non-inferiority
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P-value	> 0.05
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Method	Wilcoxon (Mann-Whitney)
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## Secondary: antibody response by ELISA

End point title	antibody response by ELISA
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End point description:

The antibody response was measured by ELISA four weeks after second vaccination and defined by ELISA titer of  $\geq 220$  Vienna Units and at least a two-fold increase of titer from baseline.

End point type	Secondary
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End point timeframe:

four weeks after second vaccination



End point values	Patients	Healthy controls		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	15		
Units: total	9	14		

## Statistical analyses

<b>Statistical analysis title</b>	antibody response by ELISA
Statistical analysis description: Antibody response measured by ELISA four weeks after second vaccination was compared between patients and controls by Fishers Exact test.	
Comparison groups	Patients v Healthy controls
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.02
Method	Fisher exact

## Secondary: Geometric mean fold change of titer

End point title	Geometric mean fold change of titer
End point description: Geometric mean fold change of NT titer between baseline and four weeks after third vaccination was compared between HSCT patients and controls.	
End point type	Secondary
End point timeframe: between baseline and four weeks after third vaccination	

End point values	Patients	Healthy controls		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: fold change				
geometric mean (confidence interval 95%)	3.9 (1.3 to 11.9)	45.2 (17.5 to 117.0)		

## Statistical analyses

<b>Statistical analysis title</b>	Geometric mean fold change
Statistical analysis description: Geometric mean fold change of titers between baseline and after third vaccination comparing patients and controls.	
Comparison groups	Patients v Healthy controls

Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.01
Method	Wilcoxon (Mann-Whitney)

### Secondary: Lymphocyte proliferation second vaccination

End point title	Lymphocyte proliferation second vaccination
End point description:	Lymphocyte proliferation detected by thymidine incorporation assay measured one week after second vaccination comparing patients and controls.
End point type	Secondary
End point timeframe:	one week after second vaccination

End point values	Patients	Healthy controls		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	8		
Units: SI				
median (full range (min-max))	8.43 (0.67 to 76.56)	8.3 (1.75 to 23.93)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Lymphocyte proliferation Baseline

End point title	Lymphocyte proliferation Baseline
End point description:	Lymphocyte proliferation detected by thymidine incorporation assay measured at baseline comparing patients and controls.
End point type	Secondary
End point timeframe:	at baseline before vaccination

End point values	Patients	Healthy controls		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	8		
Units: SI				
median (full range (min-max))	4.15 (1.02 to 69.7)	0.98 (0.61 to 2.37)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Lymphocyte proliferation third vaccination

End point title	Lymphocyte proliferation third vaccination
End point description: Lymphocyte proliferation detected by thymidine incorporation assay measured one week after third vaccination comparing patients and controls	
End point type	Secondary
End point timeframe: one week after third vaccination	

End point values	Patients	Healthy controls		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	5		
Units: SI				
median (full range (min-max))	21.02 (0.84 to 109.3)	12.99 (1.79 to 27.79)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: IL-13 at baseline

End point title	IL-13 at baseline
End point description: Interleukin 13 was measured by Luminex at baseline and compared between patients and controls.	
End point type	Secondary
End point timeframe: at baseline before vaccination	

End point values	Patients	Healthy controls		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	8		
Units: fold induction				
median (full range (min-max))	1 (0.96 to 98.93)	0.61 (0.57 to 0.84)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: IL-13 after second vaccination

End point title	IL-13 after second vaccination
End point description: Interleukin 13 was measured by Luminex one week after second vaccination and compared between patients and controls.	
End point type	Secondary
End point timeframe: one week after second vaccination	

End point values	Patients	Healthy controls		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	8		
Units: fold induction				
median (full range (min-max))	5.61 (0.96 to 184.1)	2.07 (0.6 to 5.89)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: IL-13 after third vaccination

End point title	IL-13 after third vaccination
End point description: Interleukin 13 was measured by Luminex one week after third vaccination and compared between patients and controls.	
End point type	Secondary
End point timeframe: one week after third vaccination	

<b>End point values</b>	Patients	Healthy controls		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	5		
Units: SI				
median (full range (min-max))	32.26 (0.53 to 153.83)	3.41 (0.61 to 7.21)		

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

During the whole study period from 1st of July 2014 to 28th of October 2018

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18
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### Reporting groups

Reporting group title	Patients
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Reporting group description:

Patients after allogeneic hematopoietic stem cell transplantation

Reporting group title	Healthy controls
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Reporting group description:

Healthy controls

Serious adverse events	Patients	Healthy controls	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 19 (21.05%)	0 / 15 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Relapse of acute myeloid leukemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Haematometra			
subjects affected / exposed	1 / 19 (5.26%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholezystolithiasis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Influenza			
subjects affected / exposed	1 / 19 (5.26%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

<b>Non-serious adverse events</b>	Patients	Healthy controls	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 19 (78.95%)	6 / 15 (40.00%)	
Cardiac disorders			
subjective tachycardia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
headache			
subjects affected / exposed	3 / 19 (15.79%)	0 / 15 (0.00%)	
occurrences (all)	4	0	
General disorders and administration site conditions			
shivering			
subjects affected / exposed	2 / 19 (10.53%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
fatigue			
subjects affected / exposed	2 / 19 (10.53%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
sweating			
subjects affected / exposed	1 / 19 (5.26%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
fever			
subjects affected / exposed	1 / 19 (5.26%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
cold-like symptoms			
subjects affected / exposed	2 / 19 (10.53%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Immune system disorders			

increase of Graft-versus-host-disease (skin exanthema) subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 15 (0.00%) 0	
Increase of Graft-versus-host-disease (mucosal lesions) subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 15 (0.00%) 0	
Gastrointestinal disorders nausea subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 2	0 / 15 (0.00%) 0	
weight loss subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 15 (0.00%) 0	
Skin and subcutaneous tissue disorders local pressure pain subjects affected / exposed occurrences (all)	9 / 19 (47.37%) 13	5 / 15 (33.33%) 7	
local swelling subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 2	0 / 15 (0.00%) 0	
local redness subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 15 (0.00%) 0	
local induration subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 15 (0.00%) 0	
fever blister subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 2	0 / 15 (0.00%) 0	
skin exanthema subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 15 (0.00%) 0	
Endocrine disorders swelling of parotid gland subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 15 (6.67%) 1	





## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32728481>

<http://www.ncbi.nlm.nih.gov/pubmed/34452033>