



## Clinical trial results:

**A Phase II, open-label, randomised, dose-finding study to compare the efficacy (in terms of clearance of RhD-positive RBCs) and safety of LFB-R593, a monoclonal anti-RhD antibody, vs Rhophylac®, a polyclonal anti-RhD immunoglobulin in healthy RhD negative volunteers.**

### Summary

EudraCT number	2009-011017-24
Trial protocol	DE
Global end of trial date	11 July 2011

### Results information

Result version number	v1 (current)
This version publication date	05 April 2017
First version publication date	05 April 2017

### Trial information

#### Trial identification

Sponsor protocol code	ADNC-0726
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#### Additional study identifiers

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

Notes:

### Sponsors

Sponsor organisation name	LFB Biotechnologies
Sponsor organisation address	3 Avenue des Tropiques BP 40305, COURTABOEUF, France, 91958
Public contact	Global Clinical Development Leader, LFB Biotechnologies, 33 1 69 82 56 56,
Scientific contact	Global Clinical Development Leader, LFB Biotechnologies, 33 1 69 82 56 56,

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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	24 January 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 July 2011
Global end of trial reached?	Yes
Global end of trial date	11 July 2011
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

The primary objectives of the study are:

- To identify the IV effective dose (ED) of LFB-R593 required to effectively clear 15 ml of RhD positive RBCs pre-injected to healthy RhD-negative subjects when compared to Rhophylac® 300 µg IV.
- To determine the IM effective dose (ED) of LFB-R593 required to effectively clear 15 ml of RhD positive RBCs pre-injected to healthy RhD-negative subjects when compared to Rhophylac® 300 µg IM.

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Protection of trial subjects:

In order to prevent accidental immunisation of the volunteers in Part I (Groups 1 to 4), a "rescue" dose of 300 µg of Rhophylac® IV was planned to be administered at the latest 240 hours ±8 hours after RBC injection if the RBC clearance rate was under 90% at 165 hours after IMP injection (corresponding to 189 hours following RhD-positive RBCs administration). If the earlier clearance results (time points before 165 hours) strongly suggested that the subject did would not clear 90% of their RBCs at 165 hours (data to be received on an ongoing basis during the study), the Principal Investigator (PI) had to organise the administration of the rescue dose immediately after the sampling at 165 hours, without waiting for the clearance results of this time point.

No rescue medication was planned in Part II since each subject received an effective IM dose of Rhophylac® (Groups 6 and 8) or an effective IM dose of LFB-R593 (Groups 5 and 7). The only exception concerned the first 6 subjects in Group 5, who could receive a rescue medication, if the initial LFB-R593 IM dose administered was determined to be "not effective" (see Amendment 2).

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Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 August 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Germany: 78
Worldwide total number of subjects	78
EEA total number of subjects	78

Notes:

<b>Subjects enrolled per age group</b>	
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)	78
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

78 subjects were included in the study between 10/08/2009 and 16/12/2010 (last inclusion)

28 subjects in part I : dose finding IV

50 subjects in part II: dose finding IM

### Pre-assignment

Screening details:

See pre-assignment period.

### Pre-assignment period milestones

Number of subjects started	159 <sup>[1]</sup>
Number of subjects completed	78

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 15
Reason: Number of subjects	recruitment completed: 15
Reason: Number of subjects	Protocol deviation: 51

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 81 patients screening failure.

### Period 1

Period 1 title	Inclusion Visit
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	LFB-R593

Arm description: -

Arm type	Experimental
Investigational medicinal product name	LFB-R593
Investigational medicinal product code	ADNC
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use, Intramuscular use

Dosage and administration details:

No administration at inclusion visit.

<b>Arm title</b>	Rhophylac
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Rhophylac
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use, Intravenous use

Dosage and administration details:  
No administration at inclusion visit.

Number of subjects in period 1	LFB-R593	Rhophylac
Started	43	35
Part I Intra Venous	18 <sup>[2]</sup>	10 <sup>[3]</sup>
Part II Intra Muscular	25 <sup>[4]</sup>	25 <sup>[5]</sup>
Completed	43	35

Notes:

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 43 patients (18 IV and 25 IM)

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 35 patients (10 IV and 25 IM)

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 43 patients (18 IV and 25 IM)

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 35 patients (10 IV and 25 IM)

## Period 2

Period 2 title	Treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	LFB-R593 100µg IV - Part I
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	LFB-R593
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Injection of 100µg of LFB-R593 IV 24 hours after RhD-positive RBC injection.

<b>Arm title</b>	LFB-R593 200µg IV - Part I
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	LFB-R593
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details:	
Injection of 200µg of LFB-R593 IV 24 hours after RhD-positive RBC injection	
<b>Arm title</b>	LFB-R593 300µg IV - Part I
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	LFB-R593
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details:	
Injection of 300µg of LFB-R593 IV 24 hours after RhD-positive RBC injection.	
<b>Arm title</b>	Rhophylac 300µg IV - Part I
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Rhophylac
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intravenous use
Dosage and administration details:	
Injection of 300µg of Rhophylac IV 24 hours after RhD-positive RBC injection.	
<b>Arm title</b>	LFB-R393 300µg IM - Part II
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	LFB-R593
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
Injection of 300µg of LFB-R593 IM 24 hours after RhD-positive RBC injection.	
<b>Arm title</b>	Rhophylac 300µg IM - Part II
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Rhophylac
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use
Dosage and administration details:	
Injection of 300µg of Rhophylac IM 24 hours after RhD-positive RBC injection.	

<b>Number of subjects in period 2</b>	LFB-R593 100µg IV - Part I	LFB-R593 200µg IV - Part I	LFB-R593 300µg IV - Part I
Started	6	6	6
Completed	6	6	6

<b>Number of subjects in period 2</b>	Rhophylac 300µg IV - Part I	LFB-R393 300µg IM - Part II	Rhophylac 300µg IM - Part II
Started	10	25	25
Completed	10	25	25

## Baseline characteristics

### Reporting groups

Reporting group title	Inclusion Visit
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Reporting group description: -

Reporting group values	Inclusion Visit	Total	
Number of subjects	78	78	
Age categorical			
Units: Subjects			
Adults (18-64 years)	78	78	
Age continuous			
Units: years			
median	41		
full range (min-max)	22 to 60	-	
Gender categorical			
Units: Subjects			
Female	7	7	
Male	71	71	

### Subject analysis sets

Subject analysis set title	Part I TTS
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Subject analysis set type	Full analysis
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Subject analysis set description:

Total Treated Set part I

Subject analysis set title	Part II TTS
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Subject analysis set type	Full analysis
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Subject analysis set description:

Part II Total Treated Set

Reporting group values	Part I TTS	Part II TTS	
Number of subjects	28	50	
Age categorical			
Units: Subjects			
Adults (18-64 years)	28	50	
Age continuous			
Units: years			
median	42	41	
full range (min-max)	26 to 60	22 to 60	
Gender categorical			
Units: Subjects			
Female	1	6	
Male	27	44	



## End points

### End points reporting groups

Reporting group title	LFB-R593
Reporting group description:	-
Reporting group title	Rhophylac
Reporting group description:	-
Reporting group title	LFB-R593 100µg IV - Part I
Reporting group description:	-
Reporting group title	LFB-R593 200µg IV - Part I
Reporting group description:	-
Reporting group title	LFB-R593 300µg IV - Part I
Reporting group description:	-
Reporting group title	Rhophylac 300µg IV - Part I
Reporting group description:	-
Reporting group title	LFB-R393 300µg IM - Part II
Reporting group description:	-
Reporting group title	Rhophylac 300µg IM - Part II
Reporting group description:	-
Subject analysis set title	Part I TTS
Subject analysis set type	Full analysis
Subject analysis set description:	
Total Treated Set part I	
Subject analysis set title	Part II TTS
Subject analysis set type	Full analysis
Subject analysis set description:	
Part II Total Treated Set	

### Primary: Mean RhD-positive RBC clearance

End point title	Mean RhD-positive RBC clearance <sup>[1]</sup>
End point description:	

End point type	Primary
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End point timeframe:

Mean RBC clearance after injection in Part I and Part II with time to reach 50% and 90 %

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive analysis

End point values	LFB-R593 100µg IV - Part I	LFB-R593 200µg IV - Part I	LFB-R593 300µg IV - Part I	Rhophylac 300µg IV - Part I
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6 <sup>[2]</sup>	6 <sup>[3]</sup>	6 <sup>[4]</sup>	8 <sup>[5]</sup>
Units: percentage				
> 50 % results	69	74	61	71
> 90 % results	94	93	91	91

Notes:

[2] - time to RCB clearance : 4h > 50% and 10h >90%

[3] - time to RCB clearance : 4h > 50% and 10h >90%

[4] - time to RCB clearance : 2h > 50% and 4h >90%

[5] - time to RCB clearance : 4h > 50% and 8h >90%

End point values	LFB-R393 300µg IM - Part II	Rhophylac 300µg IM - Part II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25 <sup>[6]</sup>	25 <sup>[7]</sup>		
Units: percentage				
> 50 % results	54	56		
> 90 % results	93	93		

Notes:

[6] - Part II (IM) time to RCB clearance : 10h > 50% and 24h >90%

[7] - Part II (IM) time to RCB clearance : 24h > 50% and 69h >90%

## Statistical analyses

No statistical analyses for this end point

### Primary: RhD-positive RBC clearance at 165h

End point title	RhD-positive RBC clearance at 165h <sup>[8]</sup>
End point description:	

End point type	Primary
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End point timeframe:

RhD-positive RBC clearance at 165h after injection

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive analysis

End point values	LFB-R593 100µg IV - Part I	LFB-R593 200µg IV - Part I	LFB-R593 300µg IV - Part I	Rhophylac 300µg IV - Part I
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	8
Units: percentage	99	100	100	98

End point values	LFB-R393 300µg IM - Part II	Rhophylac 300µg IM - Part II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: percentage	99	99		

## Statistical analyses

No statistical analyses for this end point

### Primary: Elimination half-life of RhD-positive RBCs

End point title Elimination half-life of RhD-positive RBCs<sup>[9]</sup>

End point description:

End point type Primary

End point timeframe:

Geometric mean elimination half-life of RhD-positive RBCs after injection of LFB-R593 or Phophylac.

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive analysis

End point values	LFB-R593 100µg IV - Part I	LFB-R593 200µg IV - Part I	LFB-R593 300µg IV - Part I	Rhophylac 300µg IV - Part I
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	8
Units: hours				
geometric mean (standard deviation)	2.36 (± 1.8405)	2.504 (± 1.5724)	1.285 (± 2.7453)	4.354 (± 3.0327)

End point values	LFB-R393 300µg IM - Part II	Rhophylac 300µg IM - Part II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	25		
Units: hours				
geometric mean (standard deviation)	4.028 (± 1.8836)	7.366 (± 1.7453)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

overall the study in both parts, (6 months after IMP administration).

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.1
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### Reporting groups

Reporting group title	Drug-related AEs TTS part I
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Reporting group description: -

Reporting group title	Drug related AEs TTS Part II
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Reporting group description: -

Reporting group title	Adverse Event TTS TEAEs Part I
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Reporting group description: -

Reporting group title	Adverse Event TTS TEAEs Part II
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Reporting group description: -

Serious adverse events	Drug-related AEs TTS part I	Drug related AEs TTS Part II	Adverse Event TTS TEAEs Part I
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 28 (0.00%)	0 / 50 (0.00%)	1 / 28 (3.57%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Immune system disorders			
Alloimmunisation	Additional description: RhD Alloimmunisation (Rhophylac)		
subjects affected / exposed	0 / 28 (0.00%)	0 / 50 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Adverse Event TTS TEAEs Part II		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 50 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Immune system disorders			
Alloimmunisation	Additional description: RhD Alloimmunisation (Rhophylac)		
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4 %

<b>Non-serious adverse events</b>	Drug-related AEs TTS part I	Drug related AEs TTS Part II	Adverse Event TTS TEAEs Part I
Total subjects affected by non-serious adverse events subjects affected / exposed	11 / 28 (39.29%)	5 / 50 (10.00%)	16 / 28 (57.14%)
Nervous system disorders			
Headache	Additional description: 8 AEs Part I (IV): 7 AEs group LFB-R593 and 1 AE group Rhophylac 10 AEs Part II (IM): 7 AEs group LFB-R593 and 4 AEs group Rhophylac		
subjects affected / exposed	7 / 28 (25.00%)	2 / 50 (4.00%)	8 / 28 (28.57%)
occurrences (all)	7	2	8
General disorders and administration site conditions			
Chills	Additional description: 3 AEs group LFB-R593 and 1 AE group Rhophylac		
subjects affected / exposed	4 / 28 (14.29%)	0 / 50 (0.00%)	4 / 28 (14.29%)
occurrences (all)	4	0	4
Fatigue	Additional description: 5 AEs group LFB-R593		
subjects affected / exposed	5 / 28 (17.86%)	0 / 50 (0.00%)	5 / 28 (17.86%)
occurrences (all)	5	0	5
Influenza-like illness	Additional description: 3 AEs part II (IM), 2 AEs group LFB-R593 and 1 AE group Rhophylac		
subjects affected / exposed	0 / 28 (0.00%)	1 / 50 (2.00%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	Additional description: 1 AE part I (IV) group Rhophylac 3 AEs part II (IM) group LFB-R593		
subjects affected / exposed	0 / 28 (0.00%)	0 / 50 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis	Additional description: 3 AEs part I (IV) : 1 group LFB-R593 and 2 group Rhophylac 6 AEs part II (IM): 1 group LFB-R593 and 5 group Rhophylac		
subjects affected / exposed	0 / 28 (0.00%)	0 / 50 (0.00%)	3 / 28 (10.71%)
occurrences (all)	0	0	3

<b>Non-serious adverse events</b>	Adverse Event TTS TEAEs Part II		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	23 / 50 (46.00%)		
Nervous system disorders			
Headache	Additional description: 8 AEs Part I (IV): 7 AEs group LFB-R593 and 1 AE group Rhophylac 10 AEs Part II (IM): 7 AEs group LFB-R593 and 4 AEs group Rhophylac		
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	10		
General disorders and administration site conditions			
Chills	Additional description: 3 AEs group LFB-R593 and 1 AE group Rhophylac		
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Fatigue	Additional description: 5 AEs group LFB-R593		
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Influenza-like illness	Additional description: 3 AEs part II (IM), 2 AEs group LFB-R593 and 1 AE group Rhophylac		
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	Additional description: 1 AE part I (IV) group Rhophylac 3 AEs part II (IM) group LFB-R593		
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Infections and infestations			
Nasopharyngitis	Additional description: 3 AEs part I (IV) : 1 group LFB-R593 and 2 group Rhophylac 6 AEs part II (IM): 1 group LFB-R593 and 5 group Rhophylac		
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	6		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2009	Amendment included additional information requested by the Ethics Committee of the Land Berlin and the PEI. In addition, some inconsistencies in the protocol were corrected.
01 June 2010	Changes related to the choice of the 3rd IV dose level and IV effective dose of LFB-R593.
01 November 2010	Changes related to blood sampling Schedule for determination of RBC clearance. (additional blood samplings for the part II-2)
15 March 2011	Changes related to expedited notification of adverse events and related to study management.
20 June 2011	Changes related to the planned interim analyses.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 September 2009	<p>Due to the unexpected absence of RhD-positive RBC following 15 mL RBC administration in a healthy volunteer and before administration of the IMP (Rhophylac® 300 µg; reference), DSMB members recommended to halt temporarily the inclusions to investigate the reason of this lack of RhD-positive RBCs.</p> <p>Therefore, the inclusion of further subjects in the study was temporarily stopped on 08 September 2009. This decision was documented in a submission to the PEI on 21 September 2009. This was not related to either the safety or the efficacy of the IMP.</p> <p>A corrective action plan was set up in order to ensure the quality of subsequent RhD-positive preparations. The submission for study restart, dated 16 November 2009, was approved by the IEC on 01 December 2009 and by the PEI on 15 December 2009.</p>	16 November 2009

Notes:

### Limitations and caveats

None reported