

## **STATISTICAL REVIEW AND EVALUATION**

**Type/Application ID/Amendment #:** BLA 125287/0

**Proposed Use (Indication):** HAE attack

**Sponsor:** CSL Behring GmbH.

**Product name:** C1-Esterase Inhibitor Concentrate Pasteurized

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### **Executive Summary**

The is a multinational, randomized, parallel-group, placebo-controlled, dose-finding, three-arm, double-blind clinical trial to assess the safety and efficacy of Berinert in the treatment of acute abdominal or facial attacks in patients with hereditary angioedema. The study demonstrated the efficacy of a 20 U/kg dose of CE1145 compared to placebo in reducing the time to onset of relief from symptoms of an HAE attack (abdominal or facial) as determined by the subject's own assessment ( $p=0.004$  using Kaplan-Meier analysis for the ITT population). However, with consideration of separate Facial and GI attack, there is significant shorter time for the 20 U/kg dose of CE1145 than that for the placebo only for subjects with GI attack.

### **Background**

The study entitled "Human pasteurized C1 esterase inhibitor concentrate (CE1145) in subjects with congenital C1-INH deficiency and acute abdominal or facial HAE attack" is a multinational, randomized, parallel-group, placebo-controlled, dose-finding, three-arm, double-blind clinical trial to assess the safety and efficacy of Berinert in the treatment of acute abdominal or facial attacks in patients with hereditary angioedema. The study demonstrated the efficacy of a 20 U/kg dose of CE1145 compared to placebo in reducing the time to onset of relief from symptoms of an HAE attack (abdominal or facial) as determined by the subject's own assessment. Therefore, this final review for the efficacy is based on the results of high dose of CE1145 and placebo.

### **Statistical Review**

For filing this BLA, the sponsor was requested to provide a list of variables with definition for each dataset and analysis-ready dataset of efficacy analysis. CBER did not receive the requested

analysis-ready -b(4)- transport files with definition of variables until Mid September, 2008 (STN 125287/0.17).

During the review process, in the corresponding letter, CBER requested the sponsor to perform Kaplan-Meier analysis for the comparison between the high dose and placebo group on the primary efficacy endpoint through 4 hours with p-value.

For this BLA review, CBER also requested the sponsor to perform additional Kaplan-Meier analyses for the comparisons of high dose and placebo group on the primary endpoint with considerations of the subjects who received rescue medication or open label CTM or analgesics or anti-emetics after 4 hours and prior to initial relief of attack symptoms.

The analyses mentioned above are performed again by CBER, and are summarized below. The detailed results are included in the **Appendix**.

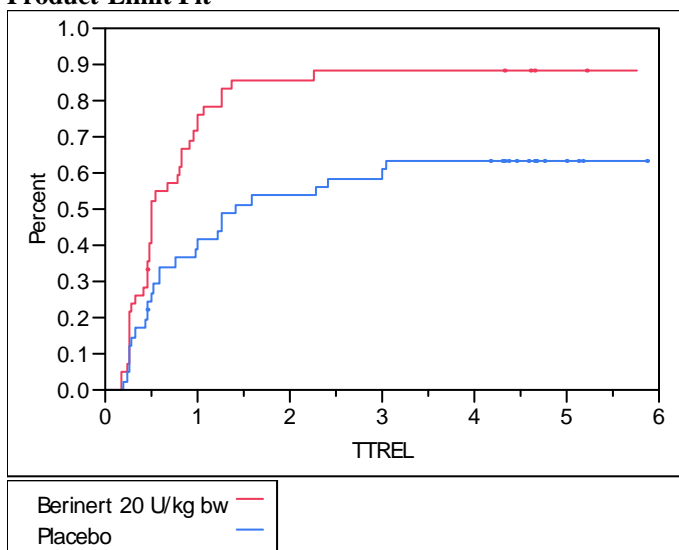
In order to understand the consistency between patients' self-reported scores and the primary endpoint of time to initial relief of symptoms, Dr. Pierce of OBRR generated datasets to include the comparisons of the primary endpoint for each subject with GI attack or Facial attack to the time when at least 1 symptom had fallen by at least 1 point for two consecutive time points. Based on Dr. Pierce datasets, the additional analyses using Kaplan-Meier approach for the comparison between high dose and placebo group on different types of attacks are performed in this BLA review. The results are shown in Table C, D, E, and in the Appendix as well.

## **Results**

I) The primary endpoint is time to initial relief (Intend to Treat, ITT)

In this analysis, the variable of time to event is TTREL. A censoring variable is assigned for time to initial relief greater than 4 hours. The Kaplan-Meier curves for two groups are indicated below with p-value of 0.004 for Wilcoxon Test.

### **Product-Limit Fit**



II) The results of additional analyses are summarized in the following tables.

**Table A. Comparison of Kaplan-Meier Curve for primary endpoint (ITT)**

Group	Number	censored	Median Time	P-value for the Product limit
1. <i>The primary endpoint with censored at 4 hours</i>				
Beriner 20 U/kg bw	37	5	0.5	0.0044 for Wilcoxon Test
Placebo	26	15	1.4167	
2. <i>The primary endpoint without censoring (using the actual record time)</i>				
Beriner 20 U/kg bw	42	0	0.5	0.0051 for Wilcoxon Test
Placebo	41	0	1.4167	
3. <i>The primary endpoint with imputation of 24 hours (if time to relief &gt; 4 hours)</i>				
Beriner 20 U/kg bw	42	0	0.533	0.0077 for Wilcoxon Test
Placebo	41	0	1.4167	

**Table B. Comparison of Kaplan-Meier Curve for Primary Endpoint with Consideration of Rescue Medication**

Group	Number	censored	Median Time	P-value for the Product limit
1. <i>The primary endpoint of patients without rescue medication before endpoint</i>				
Beriner 20 U/kg bw	37	0	0.5	0.278 for Wilcoxon Test
Placebo	25	0	0.5883	
2. <i>The primary endpoint for patients with rescue medication before endpoint</i>				
Beriner 20 U/kg bw	4	0	5.217	0.56 for Wilcoxon Test
Placebo	16	0	4.667	

**Table C. Comparison of Kaplan-Meier Curve for Time to Initial Relief (TTREL)**

Group	Number	censored	Median Time	P-value for the Product limit
1. <i>GI Attack</i>				
Berinert 20 U/kg bw	30	3	0.5	0.015for Wilcoxon Test
Placebo	22	10	1.25	
2. <i>Facial Attack</i>				
Berinert 20 U/kg bw	7	2	0.916	0.162 for Wilcoxon Test
Placebo	3	5	3	
3. <i>Combined</i>				
Berinert 20 U/kg bw	37	5	0.5	0.006 for Wilcoxon Test
Placebo	25	15	1.257	

**Table D. Comparison of Kaplan-Meier Curve for time to Time to -1 Change Any Symptom Score with No Increase.**

Group	Number	censored	Median Time	P-value for the Product limit
1. <i>GI Attack</i>				
Berinert 20 U/kg bw	34	0	0.5	0.024for Wilcoxon Test
Placebo	32	0	1.25	
2. <i>Facial Attack</i>				
Berinert 20 U/kg bw	8	0	1	0.68for Wilcoxon Test
Placebo	7	0	2	
3. <i>Combined</i>				
Berinert 20 U/kg bw	42	0	0.5	0.042 for Wilcoxon Test
Placebo	39	0	1.25	

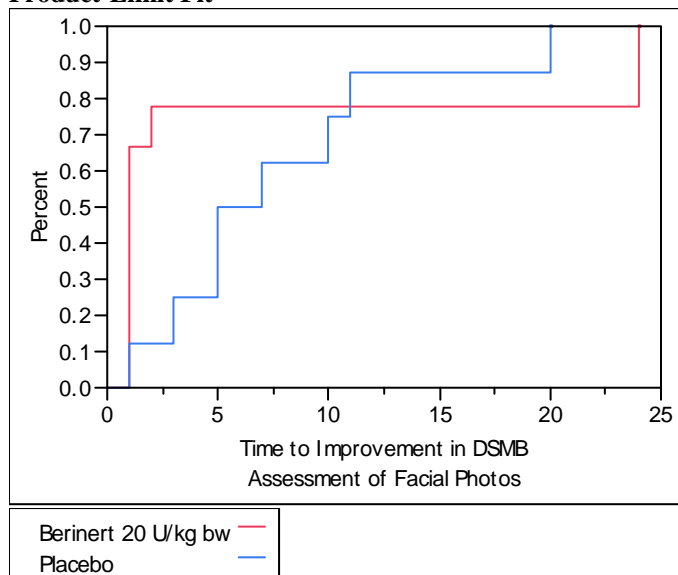
**Table E. Comparison of Kaplan-Meier Curve for Abstracted Time to Complete Resolution**

Group	Number	censored	Median Time	P-value for the Product limit
1. <i>GI Attack</i>				
Beriner 20 U/kg bw	26	0	3	0.11for Wilcoxon Test
Placebo	21	0	5	
2. <i>Facial Attack</i>				
Beriner 20 U/kg bw	6	0	24	0.64 for Wilcoxon Test
Placebo	5	0	24	
3. <i>Combined</i>				
Beriner 20 U/kg bw	32	0	4	0.18 for Wilcoxon Test
Placebo	26	0	5.75	

III) The results of analysis for the improvement in DSMB Assessment of Facial Photos

The Kaplan-Meier curves for two groups shows that there is no significant difference for the time to improvement ( p-value of 0.105 for Wilcoxon Test.).

**Product-Limit Fit**



## **Conclusions**

Using the primary efficacy endpoint of time to start of relief with censoring of subjects at 4 hours who received rescue study medication or open label CTM or analgesics or anti-emetics (before or after 4 hours) for ITT population, the analysis of Kaplan-Meier shows that there is significant shorter time for the high dose group of 20 U/kg dose of CE1145 than that for the placebo group with p-value of 0.004 (The Wilcoxon test is less sensitive to the censoring).

However, there is no significant difference between treatment and placebo groups if the Kaplan-Meier analysis is conducted only for subjects without rescue medication (37 of Berinert 20U/kg, and 25 of placebo). Similarly, there is no significant difference on the time to start of relief for the subjects with rescue medication (4 of Berinert 20U/kg, and 16 of placebo).

For different HAE attack, the analysis of Kaplan-Meier shows that there is significant shorter time for the high dose group of 20 U/kg dose of CE1145 than that for the placebo group with p-value of 0.015 for GI attack; but there is no significant difference on the time to start to relief for Facial attack (7 of Berinert 20U/kg, and 3 of placebo). The small size of subjects of Facial attack might be a factor for no significant difference on the efficacy.

With consideration of subjects experiencing the start of self-reported relief of symptoms, there is significant difference between Berinert 20 U/Kg and placebo groups for GI attack subjects for the time to-1 change of any symptom score with no increase (p-value = 0.024). Again, there is no significant difference on the same measure for subjects with Facial attack.

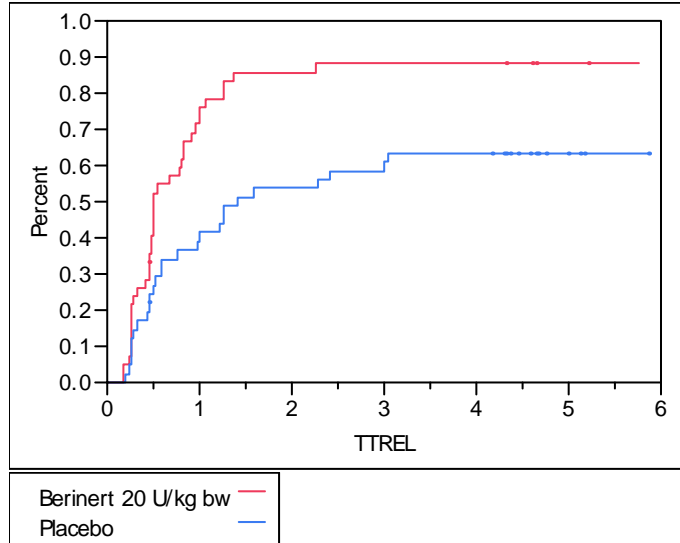
There is no significant difference between two treatment groups on the measure of abstracted time to complete resolution for subjects with GI attack as well as subjects with Facial attack. In addition, using time to Improvement in DSMB Assessment of Facial Photos, there is no significant difference between Berinert 20 U/Kg and placebo groups.

## **APPENDIX**

### **A. Kaplan-Meier Curves for the high dose and placebo groups of the primary endpoint (ITT).**

(1) Censored at 4 hours

#### **Product-Limit Fit**



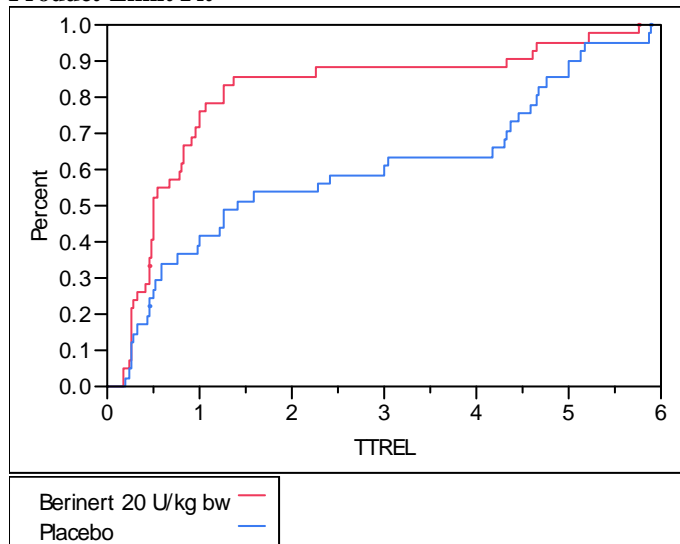
Group	Number	censored	Median Time	25% Time	75% Time
Berinert 20 U/kg bw	37	5	0.5	0.3333	1
Placebo	26	15	1.4167	0.5	.

#### **Tests Between Groups**

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	9.7618	1	0.0018
Wilcoxon	8.1072	1	0.0044

(2) No censored at 4 hours.

#### **Product-Limit Fit**



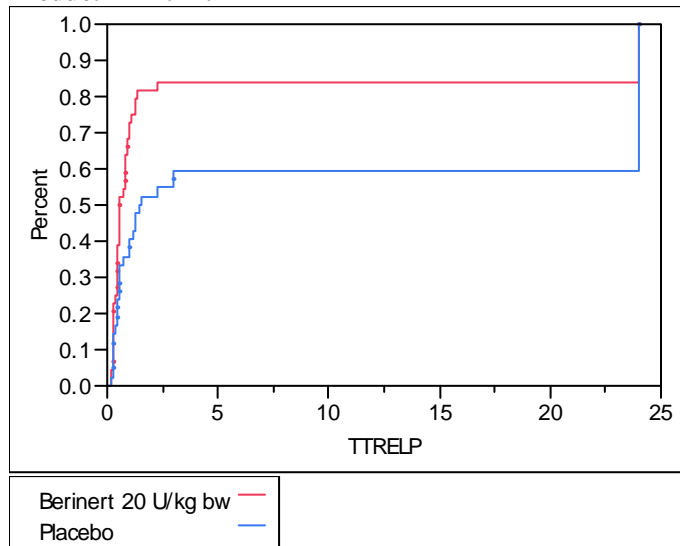
Group	Number	censored	Median Time	25% Time	75% Time
Beriner 20 U/kg bw	42	0	0.5	0.3333	1
Placebo	41	0	1.4167	0.5	4.45

### Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	7.5912	1	0.0059
Wilcoxon	7.8300	1	0.0051

(3) Use TTRELP (impute 24 hours for TTREL > 4 hours)

### Product-Limit Fit



Group	Number	censored	Median Time	25% Time	75% Time
Beriner 20 U/kg bw	44	0	0.5333	0.4167	1.25
Placebo	42	0	1.4167	0.5	24

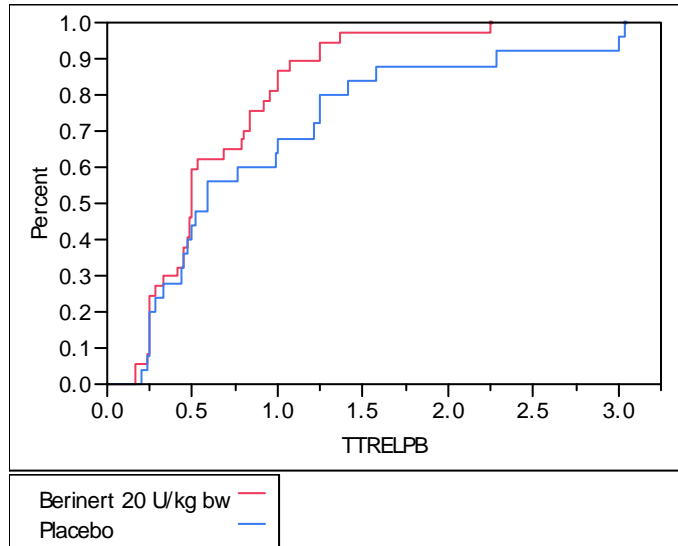
### Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	8.2606	1	0.0041
Wilcoxon	7.1122	1	0.0077

**B. Kaplan-Meier Curves for the high dose and placebo groups of the primary endpoint, with consideration of rescue medication or open label CTM or analgesics or anti-emetic prior to initial relief of system.**

(1) Using variable TTRELPB (eliminate the subjects with rescue medication)

**Product-Limit Fit**



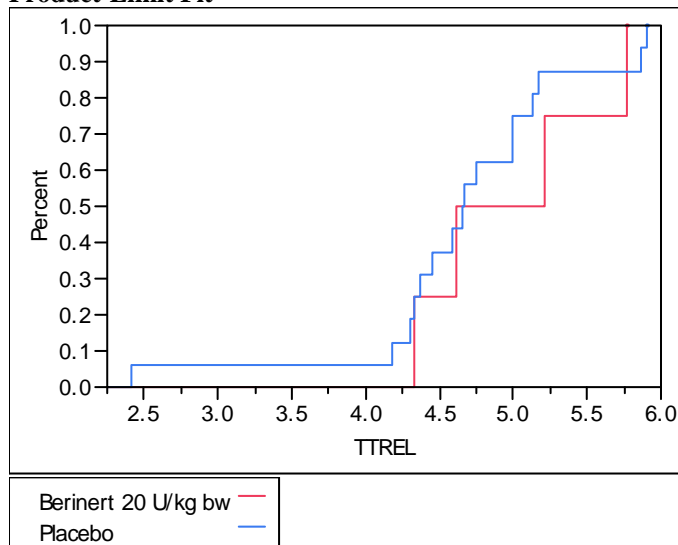
Group	Number	censored	Median Time	25% Time	75% Time
Berinert 20 U/kg bw	37	0	0.5	0.2833	0.8333
Placebo	25	0	0.5883	0.3333	1.25

**Tests Between Groups**

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	3.2603	1	0.0710
Wilcoxon	1.1794	1	0.2775

(2) For patients with rescue medication

**Product-Limit Fit**





Group	Number	Median Time	25% Time	75% Time
Beriner 20 U/kg bw	4	5.2167	4.6167	5.7667
Placebo	16	4.6667	4.3667	5.1333

### Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.1370	1	0.7113
Wilcoxon	0.3434	1	0.5578

### Beriner 20 U/kg bw

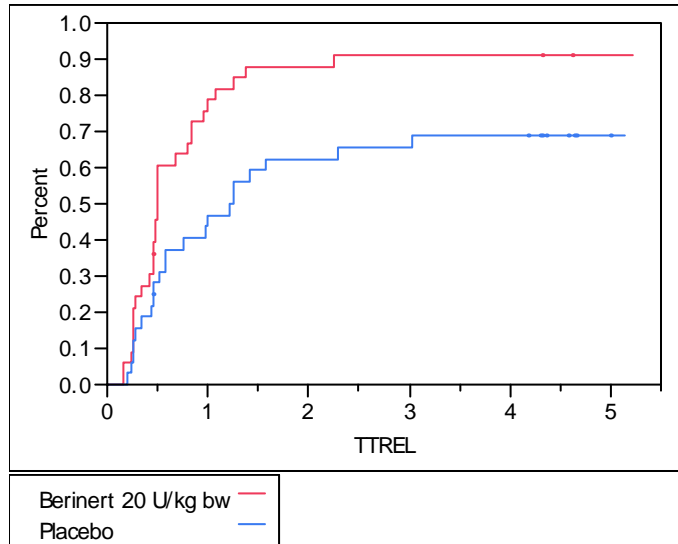
### Placebo

TTREL	Failure	At Risk	TTREL	Failure	At Risk
0.00000	0.0000	4	0.00000	0.0000	16
4.33333	0.2500	4	2.41667	0.0625	16
4.61667	0.5000	3	4.18333	0.1250	15
5.21667	0.7500	2	4.30000	0.1875	14
5.76667	1.0000	1	4.33333	0.2500	13
			4.36667	0.3125	12
			4.45000	0.3750	11
			4.58333	0.4375	10
			4.65000	0.5000	9
			4.66667	0.5625	8
			4.75000	0.6250	7
			5.00000	0.7500	6
			5.13333	0.8125	4
			5.16667	0.8750	3
			5.86667	0.9375	2
			5.90000	1.0000	1

### C. Kaplan-Meier Curves for the high dose and placebo groups of TTREL for Patients with GI & Facial Attack

#### (1) GI attack

##### Product-Limit Fit



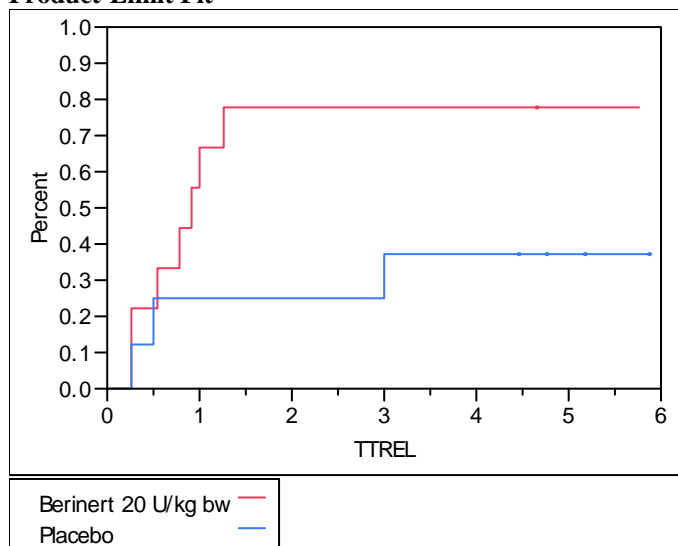
Group	Number	censored	Median Time	25% Time	75% Time
Berinert 20 U/kg bw	30	3	0.5	0.3333	0.95
Placebo	22	10	1.25	0.4667	.

##### Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	7.2267	1	0.0072
Wilcoxon	5.8851	1	0.0153

#### (2) Facial attack

##### Product-Limit Fit



Group	Number	censored	Median Time	25% Time	75% Time
Beriner 20 U/kg bw	7	2	0.916	0.5333	1.25
Placebo	3	5	3*	3*	3*

\* One obs. of non-censored.

#### Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	2.5786	1	0.1083
Wilcoxon	1.9600	1	0.1615

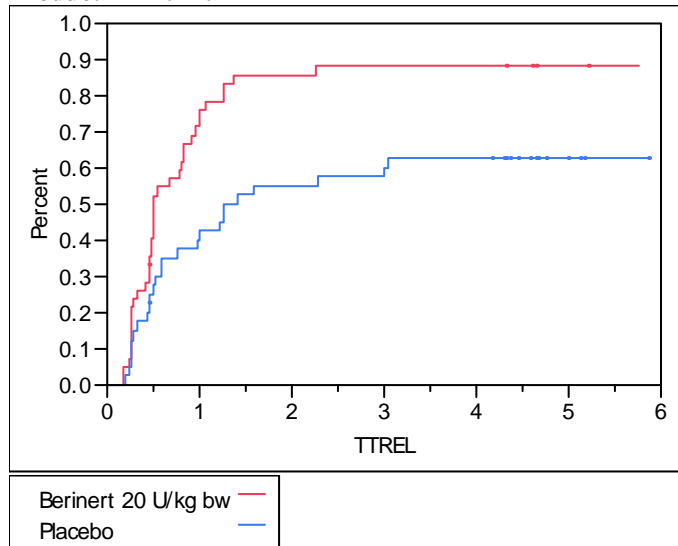
#### Beriner 20 U/kg bw

#### Placebo

TTREL	Failure	At Risk	TTREL	Failure	At Risk
0.00000	0.0000	9	0.00000	0.0000	8
0.25000	0.2222	9	0.25000	0.1250	8
0.53333	0.3333	7	0.50000	0.2500	7
0.78333	0.4444	6	3.00000	0.3750	6
0.91667	0.5556	5	4.45000	0.3750	5
1.00000	0.6667	4	4.75000	0.3750	4
1.25000	0.7778	3	5.16667	0.3750	3
4.65000	0.7778	2	5.86667	0.3750	2
5.76667	0.7778	1	5.90000	0.3750	1

#### (3) Combined

#### Product-Limit Fit



Group	Number	censored	Median Time	25% Time	75% Time
Beriner 20 U/kg bw	37	5	0.5	0.3333	1
Placebo	25	15	1.25	0.4667	.

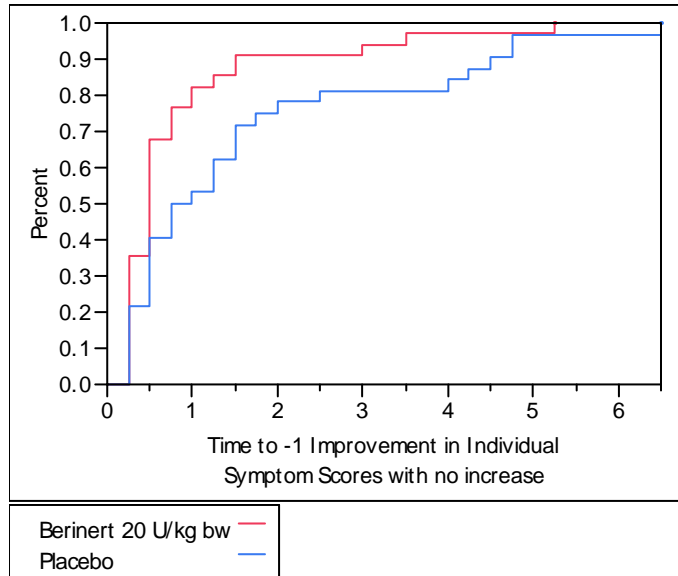
#### Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	9.3911	1	0.0022
Wilcoxon	7.5265	1	0.0061

**D. Kaplan-Meier Curves for the high dose and placebo groups for Time to -1 Change any symptom score with no increase.**

**(1) GI Attack**

**Product-Limit Fit**



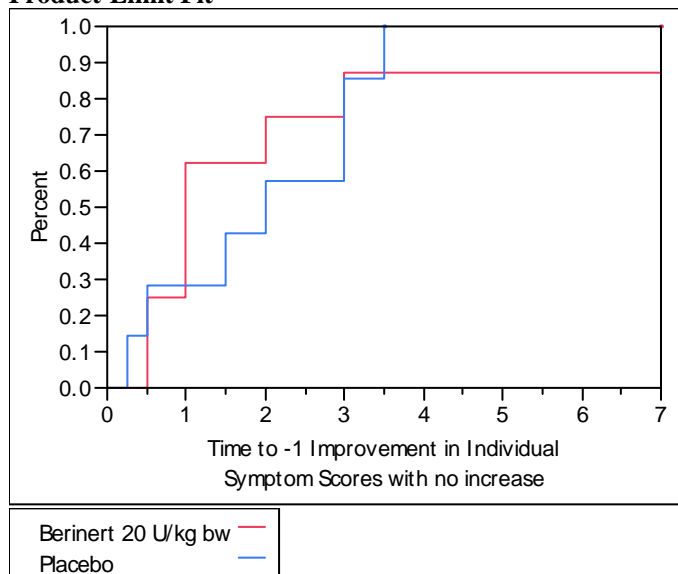
Group	Number	censored	Median Time	25% Time	75% Time
Berinert 20 U/kg bw	34	0	0.5	0.25	0.75
Placebo	32	0	1	0.5	2

**Tests Between Groups**

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	4.9886	1	0.0255
Wilcoxon	5.0663	1	0.0244

**(2) Facial**

**Product-Limit Fit**



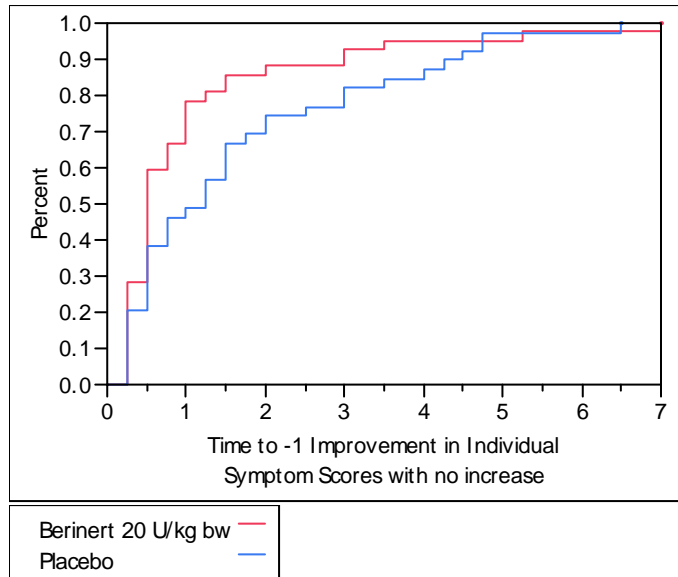
Group	Number	censored	Median Time	25% Time	75% Time
Berinert 20 U/kg bw	8	0	1	1	3
Placebo	7	0	2	0.5	3

### Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.0124	1	0.9112
Wilcoxon	0.1662	1	0.6835

### (3) Combined

### Product-Limit Fit



Group	Number	censored	Median Time	25% Time	75% Time
Berinert 20 U/kg bw	42	0	0.5	0.25	1
Placebo	39	0	1.25	0.5	2.5

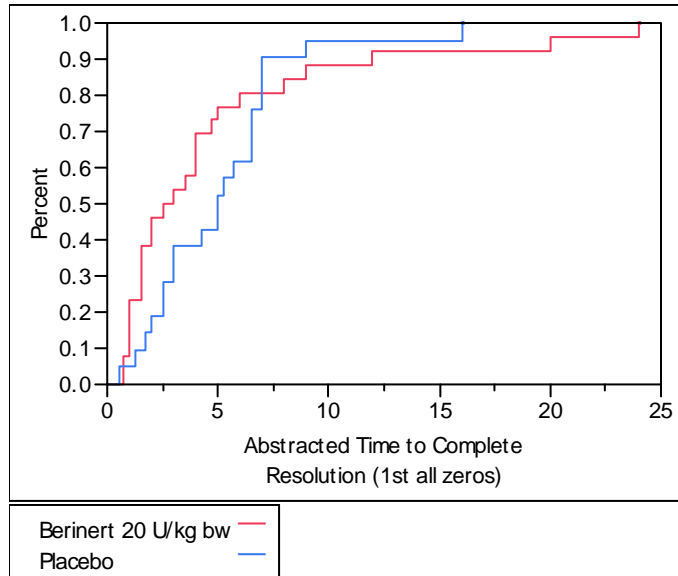
### Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	2.5753	1	0.1085
Wilcoxon	4.1456	1	0.0417

## E. Kaplan-Meier Curves for the high dose and placebo groups of Abstracted Time to complete resolution

### (1) GI Attack

#### Product-Limit Fit



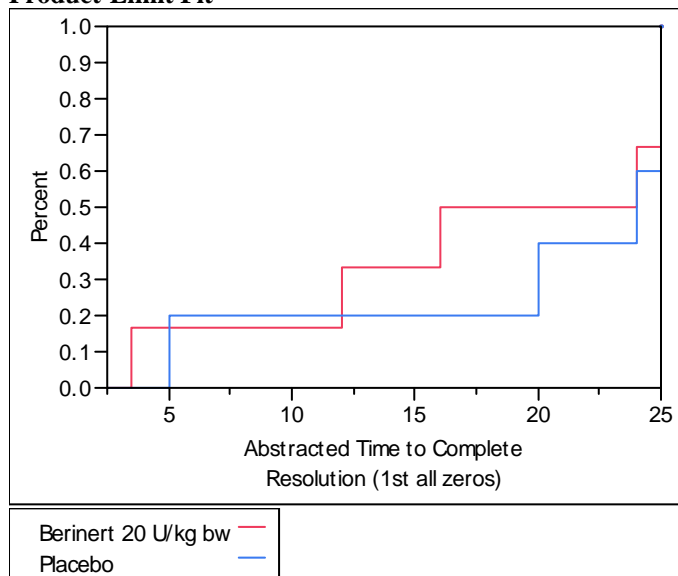
Group	Number	censored	Median Time	25% Time	75% Time
Berinert 20 U/kg bw	26	0	3	1.5	5
Placebo	21	0	5	2.5	6.5

#### Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.3608	1	0.5481
Wilcoxon	2.5932	1	0.1073

### (2) Facial Attack

#### Product-Limit Fit



Group	Number	censored	Median Time	25% Time	75% Time
Beriner 20 U/kg bw	6	0	24	12	25
Placebo	5	0	24	20	25

### Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.1350	1	0.7133
Wilcoxon	0.2129	1	0.6445

### Beriner 20 U/kg bw

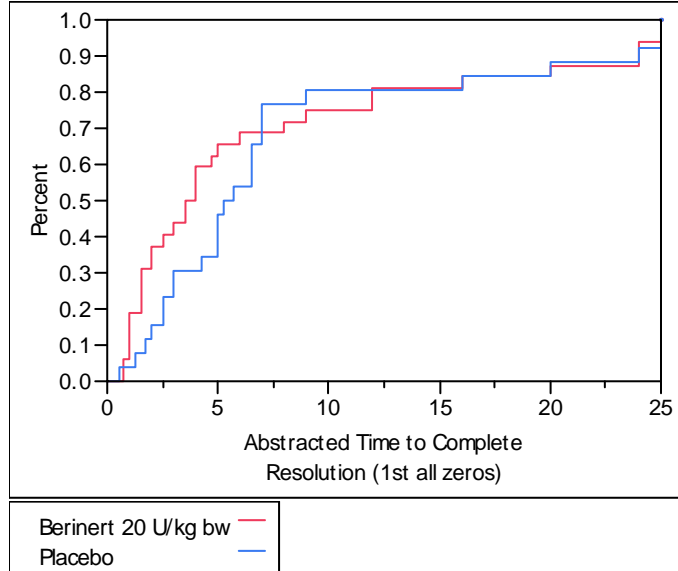
Abstracted Time to Complete Resolution (1st all zeros)	Failure	At Risk
0.0000	0.0000	6
3.5000	0.1667	6
12.0000	0.3333	5
16.0000	0.5000	4
24.0000	0.6667	3
25.0000	1.0000	2

### Placebo

Abstracted Time to Complete Resolution (1st all zeros)	Failure	At Risk
0.0000	0.0000	5
5.0000	0.2000	5
20.0000	0.4000	4
24.0000	0.6000	3
25.0000	1.0000	2

### (3) Combined Attack

### Product-Limit Fit



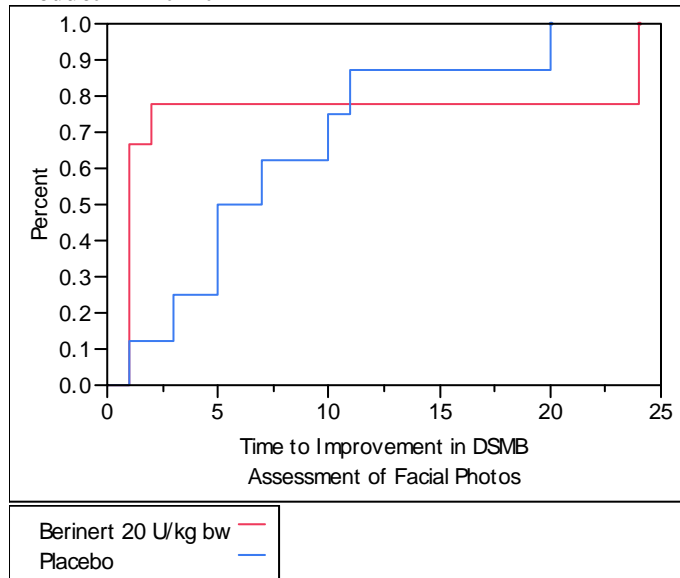
Group	Number	censored	Median Time	25% Time	75% Time
Beriner 20 U/kg bw	32	0	4	1.5	12
Placebo	26	0	5.75	3	7

### Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.5093	1	0.4754
Wilcoxon	1.7920	1	0.1807

## F. Kaplan-Meier Curves for the high dose and placebo groups of Time to Improvement in DSMB Assessment of Facial Photos

### Product-Limit Fit



Group	Number	censored	Median Time	25% Time	75% Time
Berinert 20 U/kg bw	9	0	1	1	2
Placebo	8	0	7	5	11

### Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.0507	1	0.8219
Wilcoxon	2.6218	1	0.1054

### Berinert 20 U/kg bw

Time to Improvement in DSMB Assessment of Facial Photos	Failure	At Risk
0.0000	0.0000	9
1.0000	0.6667	9
2.0000	0.7778	3
24.0000	1.0000	2

### Placebo

Time to Improvement in DSMB Assessment of Facial Photos	Failure	At Risk
0.0000	0.0000	8
1.0000	0.1250	8
3.0000	0.2500	7
5.0000	0.5000	6
7.0000	0.6250	4
10.0000	0.7500	3
11.0000	0.8750	2
20.0000	1.0000	1