Thallion PHARMACEUTICALS

(FORMERLY CAPRION PHARMACEUTICALS INC)

Trial Design for Shiga Toxin-Producing Bacterial Infection

Disease Process

Intestinal colonization with STEC

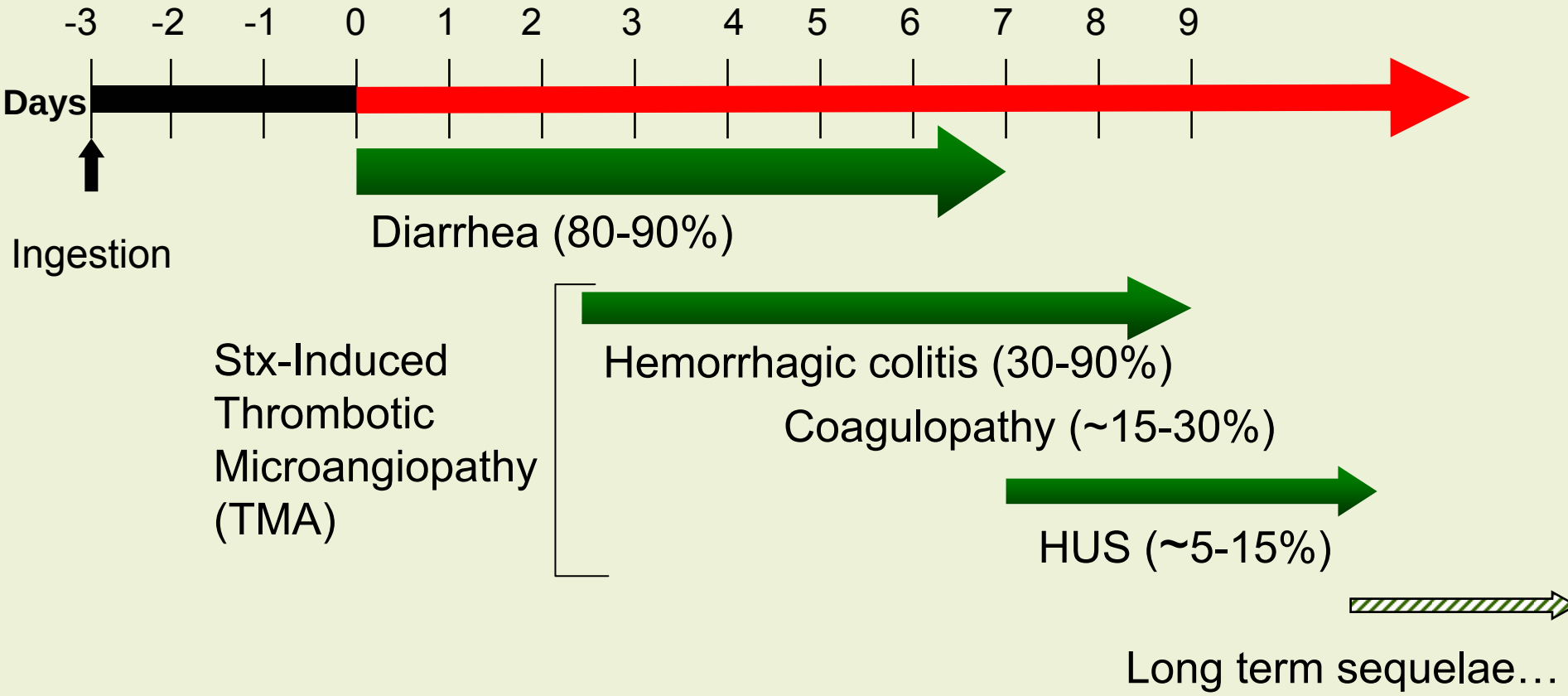
Production / uptake of Stx1/2

Upregulation of endothelial Stx receptors by cytokines

Stx binding to endothelial cell Gb3 and internalization

Stx induced vascular endothelial injury

Pathophysiology of STEC Infections



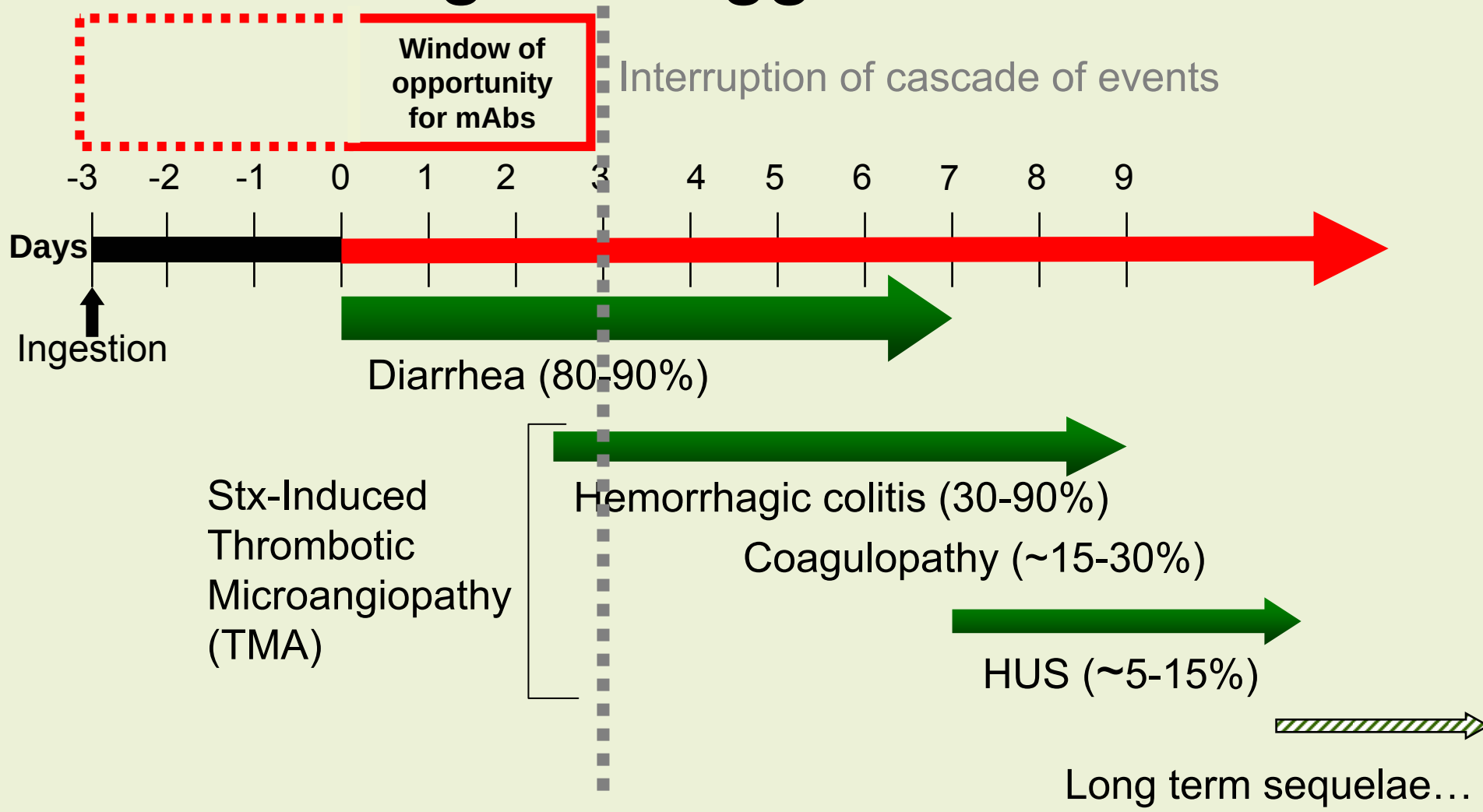
Challenges of Therapeutic Intervention

- No method to detect circulating levels of either toxin in human
- Predicting who will develop HUS during STEC infection is impossible
- Number of HUS cases is very low so that therapeutic benefit will be difficult to prove if development of HUS is the only indicator of efficacy
- Timing of intervention is critical; very rapid diagnosis is essential

Interruption of Shiga Toxin Mediated Events (STMEs) Is the GOAL

- Subjects with STEC diarrhea are likely to benefit from Stx neutralizing mAbs if given before the cascade results in irreversible changes
- Early interruption of STMEs is expected to alleviate rate and severity of illness as measured by the STEC Disease Severity Scale

Blocking Stx-triggered Cascade



Monoclonal Antibodies Against Shiga Toxins 1 and 2

- Chimeric IgG1 mAbs (cαStx1 and cαStx2) binding exclusively to Shiga toxin 1 (Stx1) and Shiga toxin 2 (Stx2) respectively (simultaneous protection)
- The majority of North American STEC strains encode for both Shiga toxins 1 and 2

cαStx1

- Targets Stx1 B subunit (13C4, IgG_1) (Strockbine 1985)
- Immunoprecipitates Stx1
- Blocks Stx1 binding to Gb3
- Epitope: 3 noncontiguous segments on the B subunit of Stx1
- Neutralizes Stx1 toxicity for Vero cells and protects animals in a murine toxemia model

cαStx2

- Targets Stx2 A subunit (11E10, IgG_1) (Perera 1988)
- Immunoprecipitates Stx2
- Epitope: N-terminal region of A subunit of Stx2
- Neutralizes the cytotoxicity of Stx2, Stx2c, and Stx2dact for Vero cells
- Rescues animals when administered up to 48-72 hours post-infection in a murine model

Preclinical Toxicology Summary

- cαStx1 and cαStx2 (alone or in combination) are not associated with significant/serious toxicity in healthy (mice and marmosets) or infected (mice) animals
- cαStx1 and cαStx2 do not exacerbate disease
- cαStx1 and cαStx2 do not activate complement in a kidney cell culture model

Clinical Summary - Phase I

- cαStx1 and cαStx2 (alone or in combination) are safe and well-tolerated in 4 Phase I studies with healthy adult volunteers (N=50)
- PK parameters are consistent with monoclonal antibodies with a half-life of ~ 9 days (for 3 mg/kg)
- Human Anti-Chimeric Antibody response is in anticipated range

Most Frequent Adverse Events from 4 Phase I Studies - cαStx1 and/or cαStx2 (1 to 10 mg/kg each)

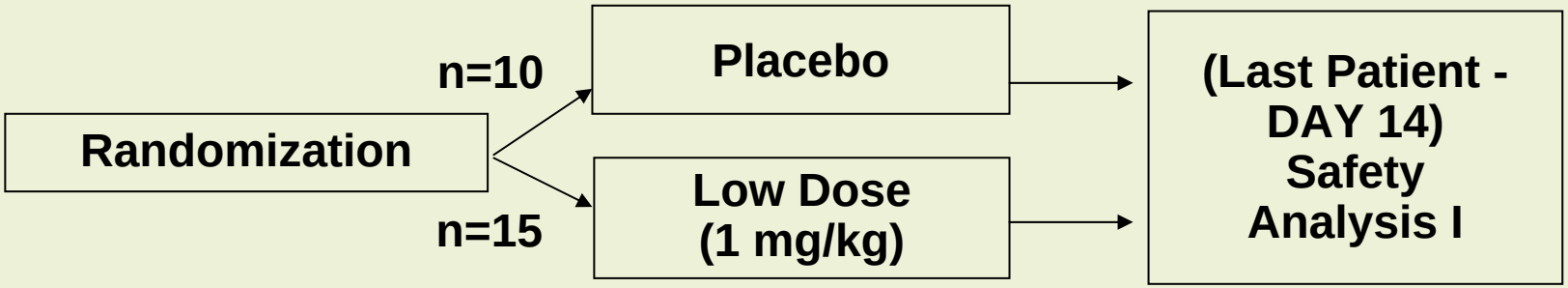
N=50	n	%
Headache	17	34
Fatigue	5	10
Somnolence	5	10
Back Pain	4	8
Elevated AST and/or ALT	4	8
Abdominal Distension	3	6
Abdominal Pain	3	6
Cough	3	6
Diarrhea	3	6
Dizziness	3	6
Nausea	3	6

Rationale for the Proposed Randomized Controlled Double-Blind Phase II/III Study

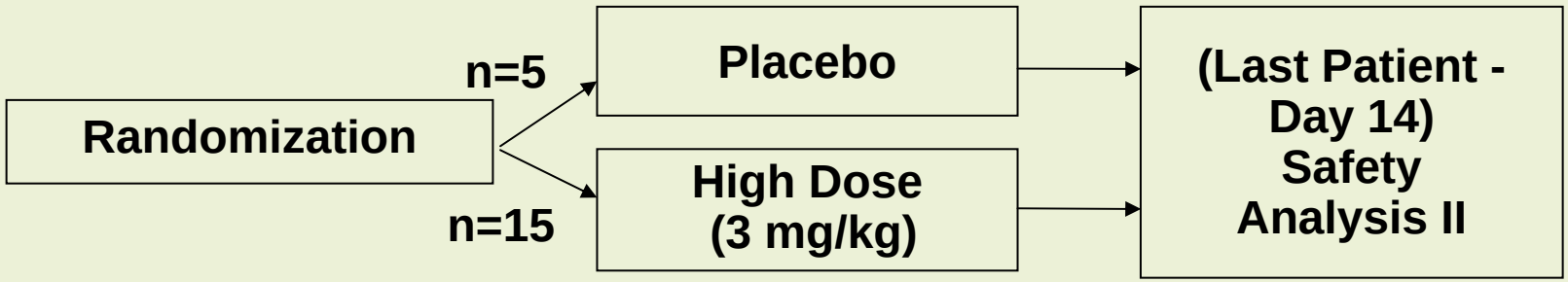
- Urgency to develop an effective intervention
- With a rare disease (orphan indication) it is critical to optimize data collection
  - Unpredictable occurrence
  - Recruitment issues
  - International site participation (>50 sites needed-estimate 1pt/site/month)

Phase II/III Trial - Part A

Safety of cαStx1/cαStx2 in STEC infected children-dose range tested based on Phase I and animal model data

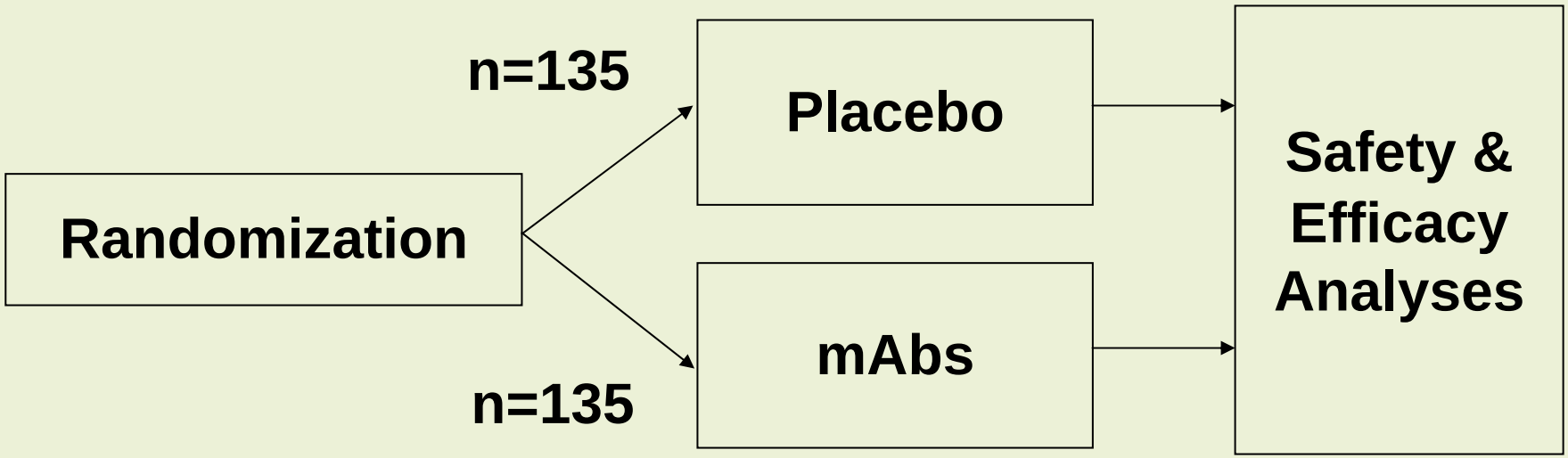


If no safety concerns proceed to higher dose



Phase II/III Trial - Part B

Primary focus on efficacy



Total number of patients available for efficacy: 150/group (including 20% drop-outs)

Study Population

- Children (6 months - 18 years of age)
- Diarrhea for no more than 3 consecutive days
- Stools positive for Shiga toxins
  - Direct stool Biostar OIA® SHIGATOX (15 minute assay)
  - Recently approved in the US

Endpoint Considerations

- Although it is anticipated that a decrease in HUS will be observed, it is not expected to reach statistical significance - The primary efficacy endpoint is not HUS
- However, the severity of the disease spectrum will be shifted to less severe HUS, and milder coagulopathy and enteropathy

Primary Endpoint

- The primary efficacy endpoint will be:
  - Proportion of patients with STME progression (new or increased by 2 points on Bitzan scale)

    OR

  - Total disease burden as indicated by daily cumulative STME scores (over 14 days post-dose)

- For sample size calculation, a 50% difference between groups was assumed

STME Progression

Enteropathy (Hemorrhagic Colitis)					
	0	1	2	3	4
Diarrhea (stool frequency)	No diarrhea	<5	5 - <10	10 - <15	≥ 15
Abdominal Pain/Cramps	None	Mild	Moderate	Severe or requiring pain medication	Unbearable
Bloody Diarrhea	No visible blood	Occasional / small amount of blood	Blood mixed with stool, streaks of fresh blood	Frank blood (hemorrhage)	Hemorrhage requiring colonoscopy or surgery
Thrombotic Microangiopathy and Nephropathy					
Hemoglobin (g/L)	≥115	< 115 - 105	<105 - 90	<90 - 65	<65 or PRBC transfusion
Platelets (N/nL)	≥150	<150 - 125	<125 - 75	<75 - 25	<25 or platelet transfusion / bleeding
Hematuria (Dipstick analysis)	None or trace	Small	Moderate	Large	Anuria
Serum Creatinine (µmol/L for age)	Normal	>1 – 2x upper normal	>2 – 4x upper normal	>4x upper normal	Dialysis

STME worsening

new STME

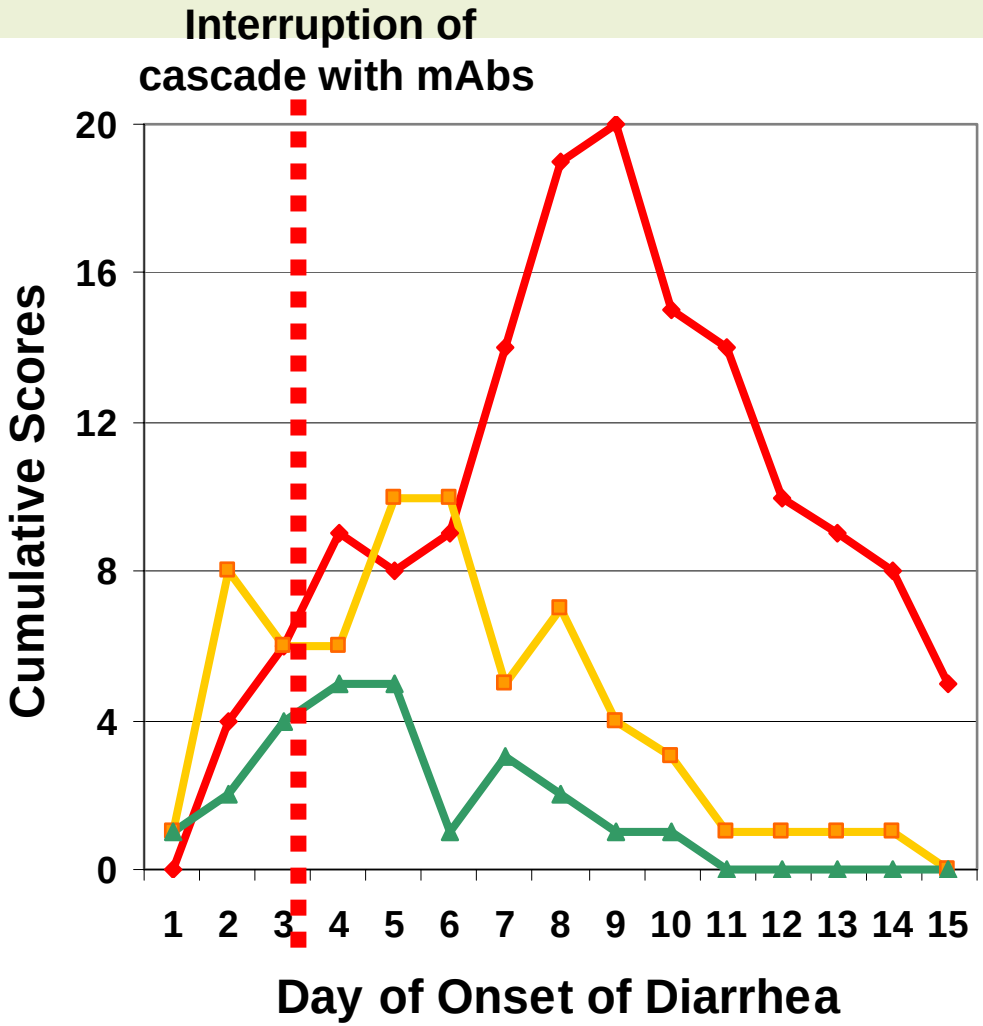
Total Disease Burden – Severe HUS (Score 19)

Enteropathy (Hemorrhagic Colitis)					
	0	1	2	3	4
Diarrhea (stool frequency)	No diarrhea	<5	5 - <10	10 - <15	≥ 15
Abdominal Pain/Cramps	None	Mild	Moderate	Severe or requiring pain medication	Unbearable
Bloody Diarrhea	No visible blood	Occasional / small amount of blood	Blood mixed with stool, streaks of fresh blood	Frank blood (hemorrhage)	Hemorrhage requiring colonoscopy or surgery
Thrombotic Microangiopathy and Nephropathy					
Hemoglobin (g/L)	≥115	< 115 - 105	<105 - 90	<90 - 65	<65 or PRBC transfusion
Platelets (N/nL)	≥150	<150 - 125	<125 - 75	<75 - 25	<25 or platelet transfusion / bleeding
Hematuria (Dipstick analysis)	None or trace	Small	Moderate	Large	Anuria
Serum Creatinine (µmol/L for age)	Normal	>1 – 2x upper normal	>2 – 4x upper normal	>4x upper normal	Dialysis

Total Disease Burden – Mild HUS (Score 8)

Enteropathy (Hemorrhagic Colitis)					
	0	1	2	3	4
Diarrhea (stool frequency)	No diarrhea	<5	5 - <10	10 - <15	≥ 15
Abdominal Pain/Cramps	None	Mild	Moderate	Severe or requiring pain medication	Unbearable
Bloody Diarrhea	No visible blood	Occasional / small amount of blood	Blood mixed with stool, streaks of fresh blood	Frank blood (hemorrhage)	Hemorrhage requiring colonoscopy or surgery
Thrombotic Microangiopathy and Nephropathy					
Hemoglobin (g/L)	≥115	< 115 - 105	<105 - 90	<90 - 65	<65 or PRBC transfusion
Platelets (N/nL)	≥150	<150 - 125	<125 - 75	<75 - 25	<25 or platelet transfusion / bleeding
Hematuria (Dipstick analysis)	None or trace	Small	Moderate	Large	Anuria
Serum Creatinine (µmol/L for age)	Normal	>1 – 2x upper normal	>2 – 4x upper normal	>4x upper normal	Dialysis

Total Disease Burden – Cumulative Score



	Cumulative Score (Day 1-14)
HUS (w/o dialysis)	145
"incomplete" HUS	64
Uncomplicated HC	25

Summary

- Evaluations in animals and in human volunteers suggest that the product is likely to be safe in children
- The proposed Phase II/III design for this orphan indication in its early phase is feasible
- Using the STME scale, we propose to demonstrate a clinically relevant decrease in severity of disease
- A major advantage to the proposed approach is that the combination of cαStx1 and cαStx2 early in disease is likely to block both toxin 1 and 2 mediated disease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