GBT440, A NOVEL ANTI-POLYMERIZATION AGENT, FOR THE TREATMENT OF SICKLE CELL DISEASE

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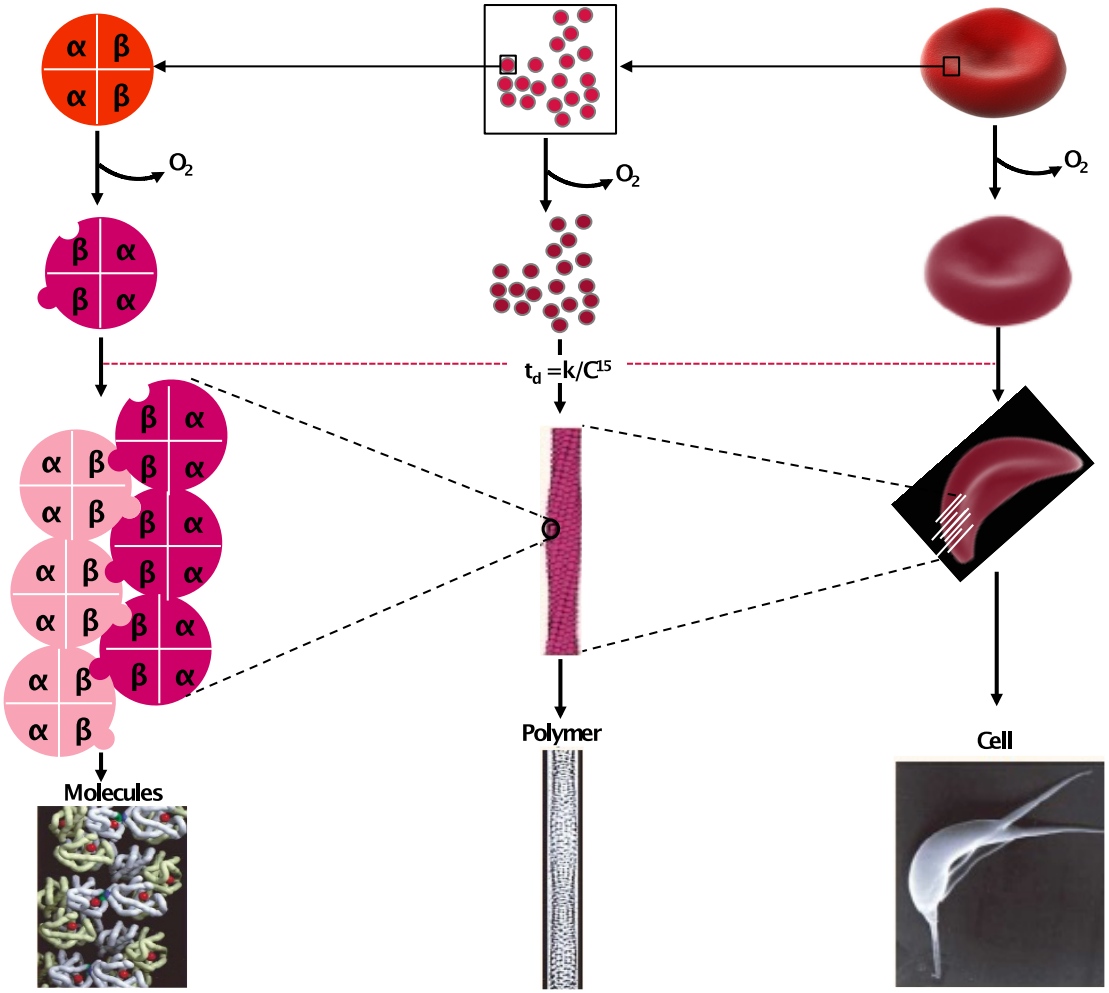
April 2016

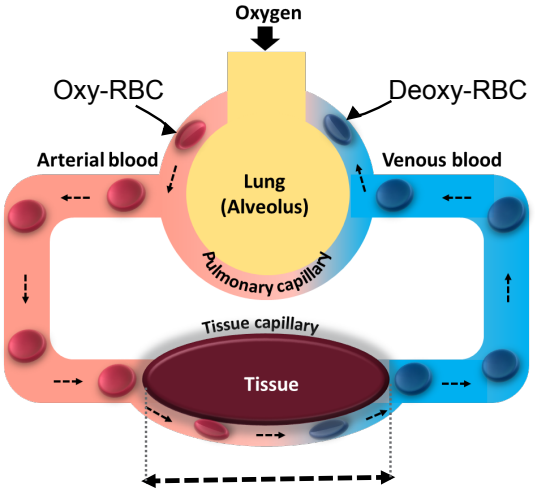
WHEN HEMOGLOBIN S (HBS) IS DEOXYGENATED, HBS POLYMERIZES LEADING TO RED BLOOD CELL SICKLING



Bunn HF. *N Engl J Med.* 1997.

HBS POLYMERIZATION OCCURS DURING TRANSIT TIME THROUGH DEOXYGENATED MICROCIRCULATION

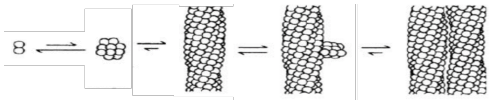
Transit Time through Microcirculation

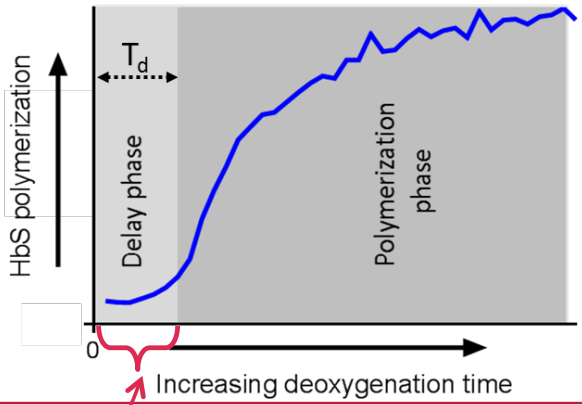


Transit Time
for RBC to travel through deoxygenated microcirculation

HbS Polymerization Delay Time (T_d)

HbS polymer formation within RBC





If Delay Time (Td) > Transit Time, then RBC remains deformable and does not sickle

Ferrone F. *Am Journal of Hematology*, 2015. Bunn HF. *N Engl J Med.* 1997.

ASYMPTOMATIC DISEASE WITH ~10-30% HEMOGLOBIN F (HBF), WHICH CANNOT PARTICIPATE IN POLYMERIZATION

Cases of individuals with Co-Inherited HbSS and Hereditary Persistence of Fetal Hemoglobin (H

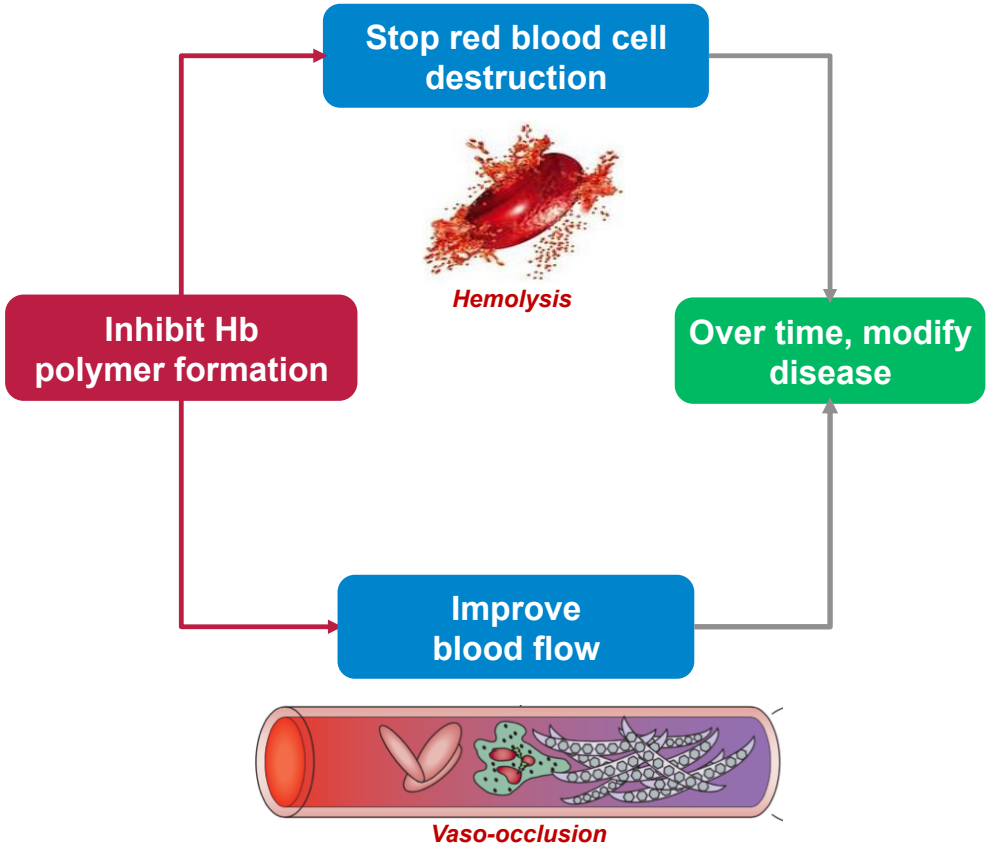
Cases	HbF (%)	Hb (g/dL)	Reticulocytes (%)	Irreversibly Sickled Cells (%)	Clinical Symptoms
Male, 52 yo [1]	24%	12.5	N/A	N/A	Asymptomatic
Female, 47 yo [1]	22%	N/A	N/A	N/A	Asymptomatic
Female, 16 yo [2]	35%	14.0	1%	0%	Asymptomatic
Female, 22 yo [2]	26%	11.6	3%	0%	Asymptomatic
Female, 24 yo [2]	28%	12.8	2%	0%	Mild retinopathy
Male, 46 yo [2]	30%	16.2	1%	0%	Mild retinopathy
Male, 39 yo [3]	25%	16.4	N/A	N/A	No SCD manifestations except possibly aseptic necrosis of right hip
Female, 10 yo [4]	20%	10.3	1%	N/A	Asymptomatic
28 cases [5]	31% (mean)	13.0 (mean)	N/A	N/A	Asymptomatic
Several cases (Hb Kenya-HbS) [5]	10% (mean)	N/A	N/A	N/A	Mild microcytic anemia

GOAL: MECHANISM-BASED, DISEASE-MODIFYING THERAPY FOR SICKLE CELL DISEASE

Goal: To develop an oral small molecule agent that inhibits HbS polymer formation

Approach:

- Design a long-lived, direct acting HbS modifier that binds selectively to HbS in a 1:1 molar ratio
- Inhibit HbS polymerization pan-cellularly by increasing the proportion of oxy-Hb within RBCs, as oxy-Hb cannot participate in polymerization
- Hypothesis: ~10-30% oxy-HbS across all RBCs will safely increase delay time and prevent polymer formation

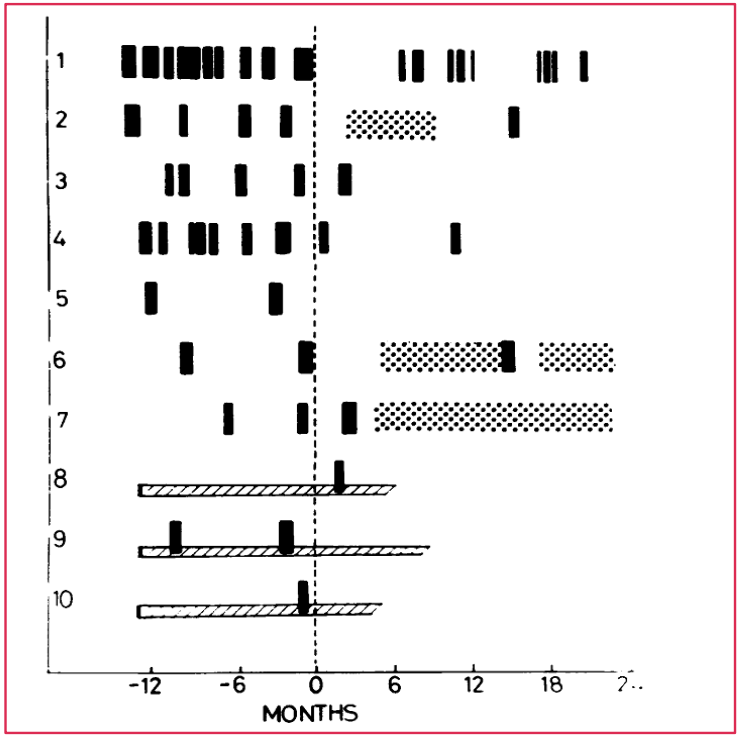


PRIOR HEMOGLOBIN-O_2 AFFINITY MODULATORS HAVE DEMONSTRATED BENEFIT, BUT LIMITED BY TOXICITY AND PK

Program	Sponsor	Summary
Oral sodium cyanate	P. Gillette, 1974	• Dose-dependent decrease in frequency of sickle cell crises • Limited by nerve damage and cataracts
Extracorporeal carbamylation	D. Dieterich, 1976	• 80% reduction in sickle cell crises over 24 months • Complete healing of chronic ulcerations (3/3) • P50 shift from 33 to 26 mmHg • Limited by difficult administration
BW12C / valeresol	Burroughs Wellcome, C Beddell, 1984	• Up to 23% HbS modified with single 20 mg/kg IV in SCD patients • Lower bilirubin, AST levels 4 hours post-infusion • Limited by short half life, IV administration
Tucaresol	Burroughs Wellcome, P. Rolan, 1993	• 10-24% HbS modified with 800-1200mg/day (3-5 days) + 300mg/d maintenance for 10 days in SCD patients • Reduced hemolysis (decreased bili/LDH, increased Hb), reduced ISCs • Discontinued due to immune toxicity characterized by painful lymphadenopathy, fever, rash occurring in 6/14 (38%) subjects within 7-11 days of dosing
5-HMF / AES-103 / BAX-555	AesRx / Baxter	• Terminated Phase 2 • Limited by short half life; Dose of 1 g four times/day (4g/day)

FREQUENCY OF PAINFUL CRISES DECREASED BY 80% WITH EXTRACORPOREAL CARBAMYLATION

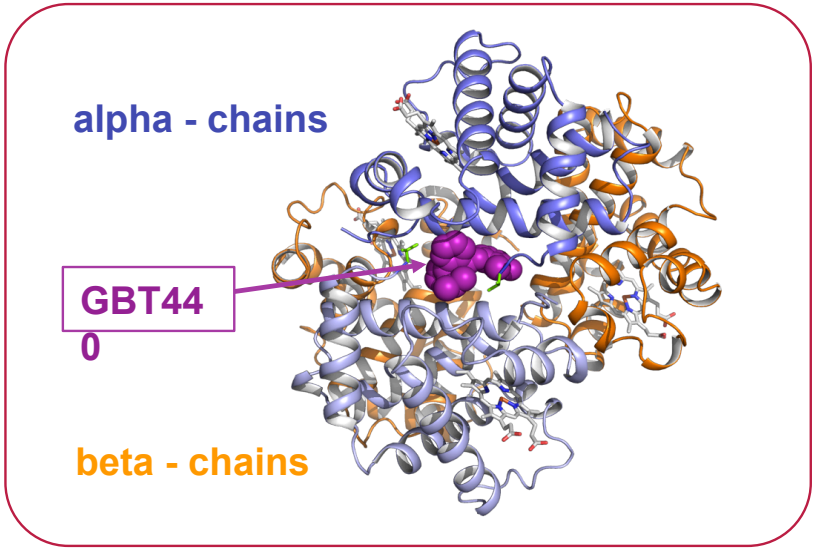
Frequency and Duration of Painful Crises (n=10)



- **Frequency of painful crises reduced by 80%** comparing 24 months prior vs. 24 months with carbamylation
  - Total hospital crisis days decreased by 85% from 461 to 71 days
  - # of spontaneous crises decreased from 35 to 1
- **Complete healing of chronic ulcerations in 3/3 patients**

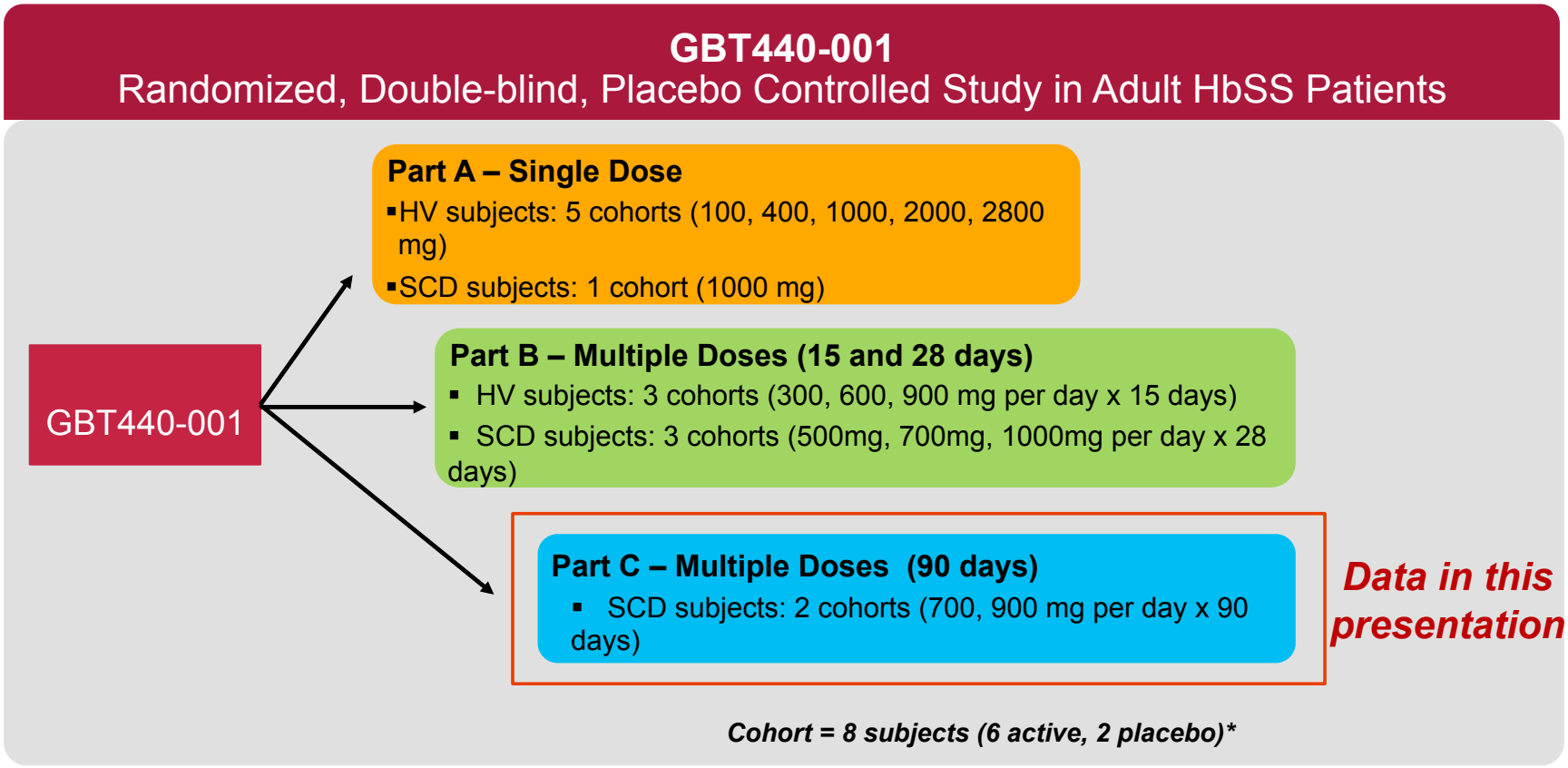
D Diederich, Journal of Clin Inv 1976. Frequency and duration of crises before and during extracorporeal carbamylation. Each crisis depicted by black bar with width of each bar proportionate to the duration of crises. Weekly carbamylation begun at week 0; subsequent carbamylation interruptions shown by the dotted areas in patients 2, 6, 7. Open active malleolar ulcerations in patients 8-10 is depicted by horizontal lines.

GBT440: DESIGNED TO BIND HEMOGLOBIN WITH HIGH SELECTIVITY



- Binding to hemoglobin α chain → stabilizes oxy-Hb conformation
- High selectivity for hemoglobin
  - 1:1 ratio of GBT440 to Hb tetramer binding
  - Preferential partitioning into RBCs (RBC: plasma ratio is 75:1 in humans; 150:1 *in vitro*)
  - Potent, dose-dependent increase in Hb-O_2 affinity

GBT440-001: ONGOING PHASE 1/2 STUDY OF ADULT SICKLE CELL DISEASE PATIENTS



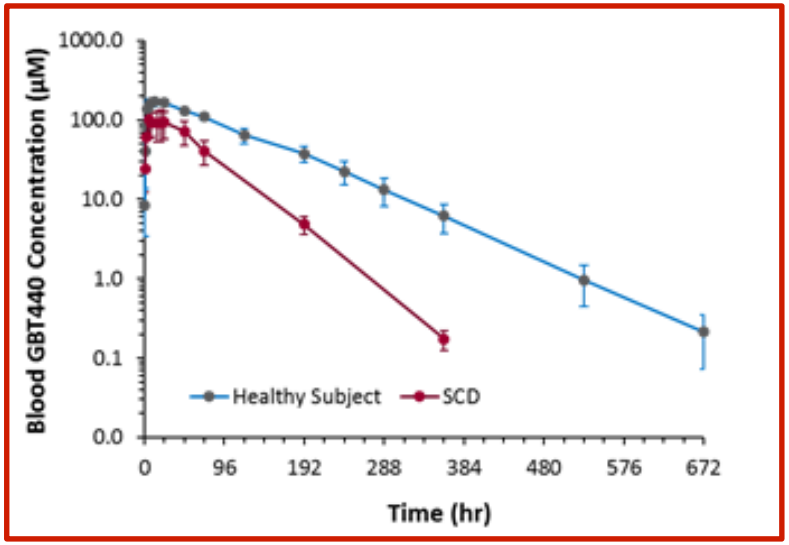
Objectives

- Safety
- Pharmacokinetics
- Pharmacodynamics
- SCD subjects: hematologic parameters

* Except SCD subjects in Part B: 500mg cohort (10:4); 700mg cohort (12:4)

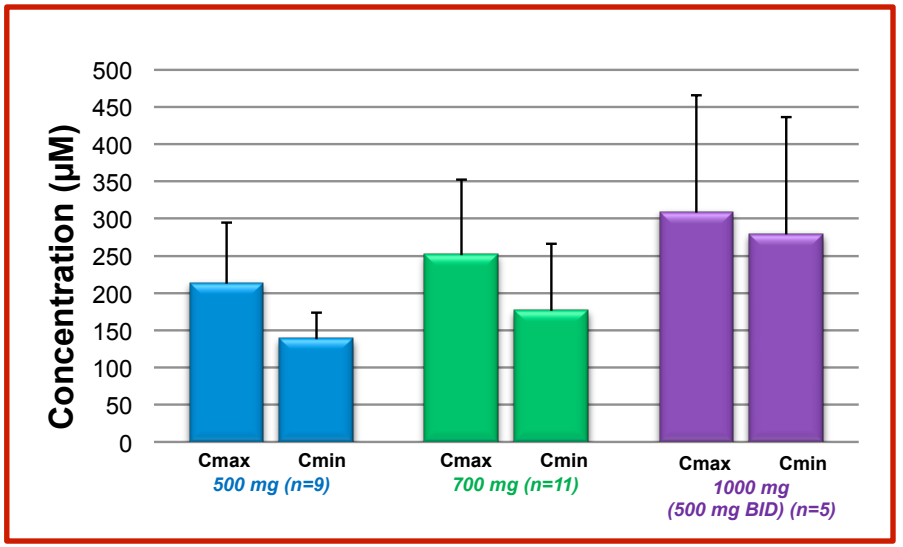
LINEAR, DOSE-PROPORTIONAL PHARMACOKINETICS AND LONG HALF LIFE SUPPORT ONCE DAILY DOSING

GBT440 Blood Concentrations after Single 1,000mg Oral Dose



	HV	SCD
$T_{1/2}$ (days)	2.8	1.6

GBT440 Blood Concentrations In SCD Subjects at Day 28 (mean ± SD)



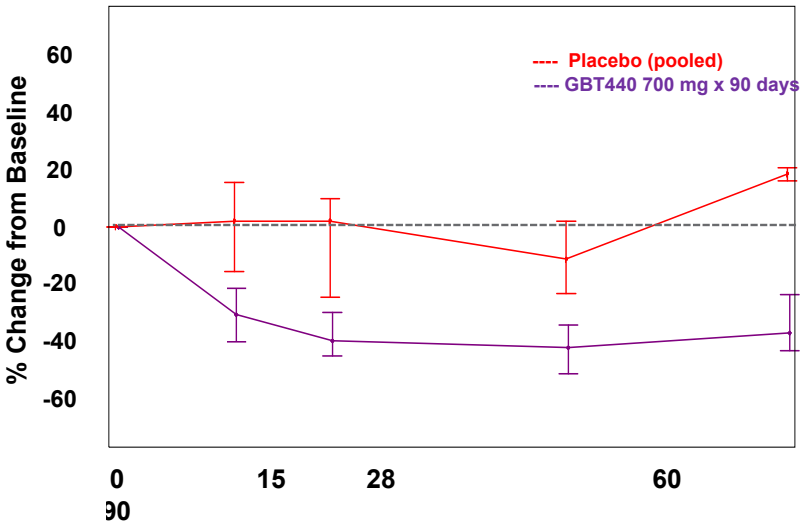
DOSE PROPORTIONAL LEFT-SHIFT IN P50 TO NORMAL RANGE

GBT440 Dose (x28 days)	Mean %HbMod	Mean p20	Mean p50
Placebo (n=10)	0%	18.0	33.6
500 mg per day (n=9)	12%	14.9	30.8
700 mg per day (n=10)	17%	13.1	29.0
500 mg BID (n=5)	27%	10.0	28.0

- *GBT440 results in left shift of the oxygen equilibrium curve*
  - *At baseline, SCD subjects are right shifted*
  - *GBT440 shifts p50 to normal range (26-29 mm Hg)*
- *Hemoglobin modification is proportional to dose*
- *Therapeutic target of 10-30% HbMod achieved at GBT440 doses ≥500 mg*

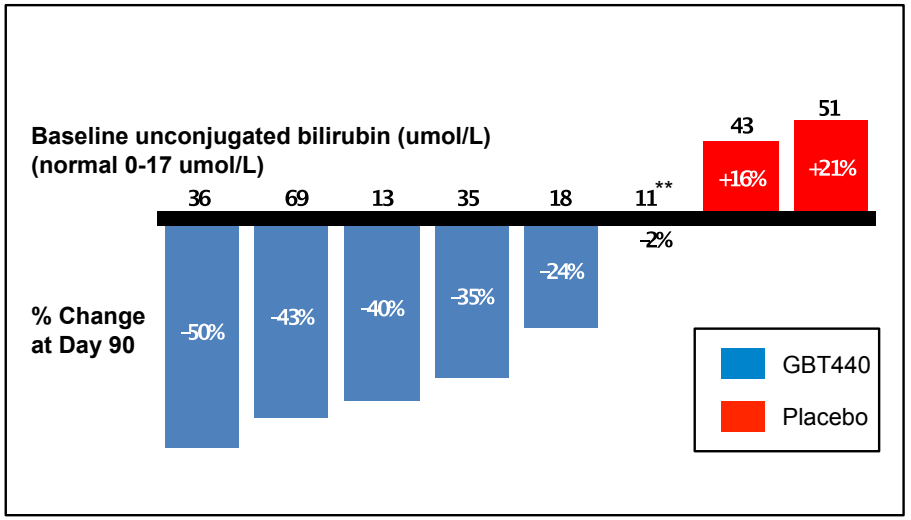
DURABLE REDUCTION IN HEMOLYSIS: >35% MEDIAN REDUCTION IN BILIRUBIN

Unconjugated Bilirubin (umol/L)*



* Relative change from baseline, median and 25th and 75th percentile

Jnconjugated Bilirubin (umol/L) Change at Day 90

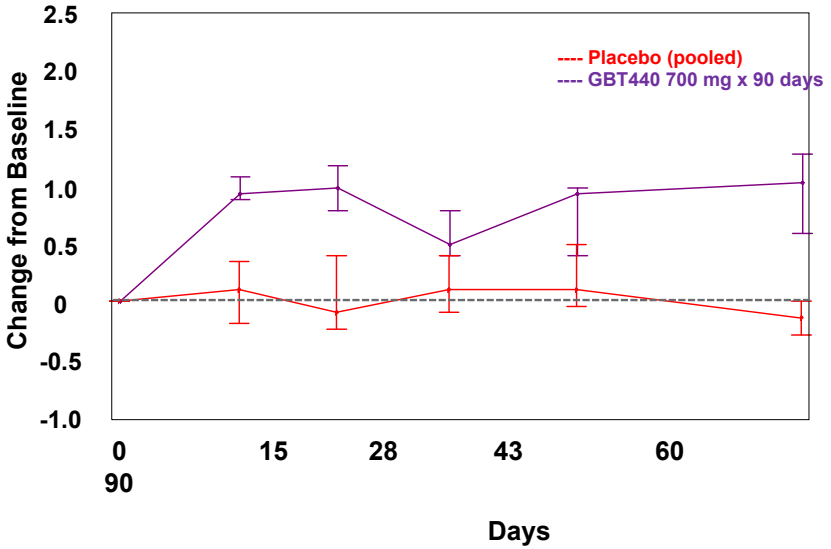


**Subject documented non adherence with study drug regimen

MEDIAN INCREASE IN HEMOGLOBIN OF ~1.1 G/DL

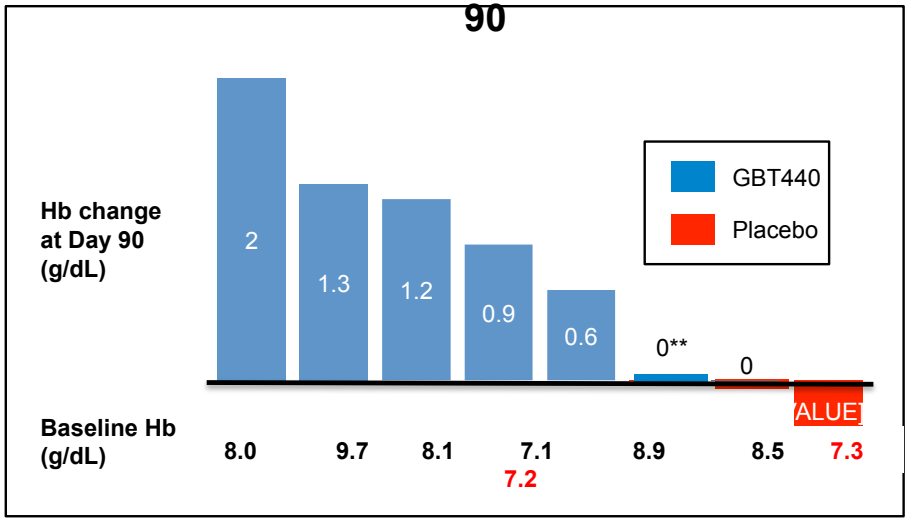
RED BLOOD CELL KINETICS APPEAR TO STABILIZE OVER 90 DAY PERIOD

Hemoglobin (g/dL)*



* Relative change from baseline, median and 25th and 75th percentile

Change in Hemoglobin at Day 90

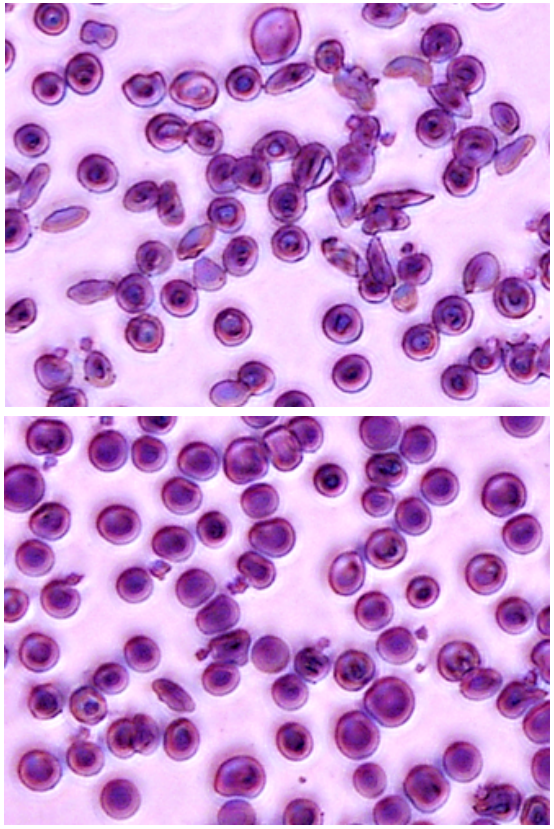


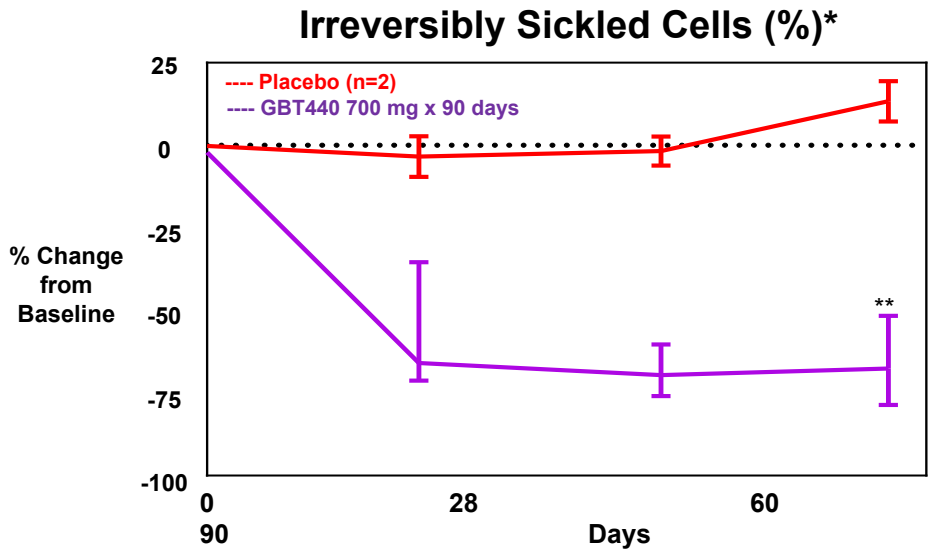
**Subject documented non adherence with study drug regimen

SUBSTANTIAL AND SUSTAINED REDUCTION IN IRREVERSIBLY SICKLED CELLS WITH GBT440

Baseline

Day 90





*Relative change from baseline, median and 25th and 75th percentile; baseline ISC counts ranged from 3.1 to 17.2%
** Represents 5 of 6 subjects at D90

EFFICACY SUMMARY

- 100% (34/34) of SCD patients dosed with GBT440 for 28 to 90 days have shown hematologic response
- 28 day treatment
  - Rapid and substantial reduction in bilirubin and reticulocytes consistent with mechanism of action
  - Hb response variable; bone marrow compartment is dynamic and has not reached equilibrium
- 90 day treatment
  - Profound and durable reduction in hemolysis and peripheral blood sickle cells
    - >35% reduction in bilirubin
    - Approximately 1.1 g/dL increase in hemoglobin
    - >20% reduction in % reticulocytes
    - Approximately 70% reduction in irreversibly sickled cells
- Dose dependent increase in oxygen affinity as measured by P50 (left shifting to normal range)

OVERALL GBT440 SAFETY SUMMARY

- GBT440 has been dosed in 177 adults, including 99 subjects in multiple dose cohorts up to 90 days
  - 137 healthy subjects, including 65 who received GBT440 from 4 to 15 days treatment duration
  - 40 SCD subjects, including 34 who received GBT440 from 28 to 90 days treatment duration
- Well tolerated to date, with no drug-related SAEs
  - Healthy subjects experienced mild (Grade 1) AEs
  - Patients with SCD experience mild to moderate AEs (Grade 1 or 2)
  - 4 cases of mild to moderate rash: quick resolution (2-5 days) upon discontinuation, continued dosing or re-introduction of drug; consistent with common drug eruption
- No evidence of tissue hypoxia
  - Approximately 40% Hb modification in healthy subjects
  - Approximately 30% Hb modification in SCD subjects
- No evidence of systemic immune reactions

GBT440 OVERALL CONCLUSIONS

- GBT440 treatment leads to a rapid, profound, and durable reduction in hemolysis and sickled cells in 100% of SCD patients dosed to date
  - Decrease in bilirubin
  - Reduction in reticulocytosis
  - Stabilization and increase in median hemoglobin > 1 g/dL
  - Approximately 70% median decline in irreversibly sickled cells
- Well tolerated in 177 subjects and up to 90 days duration
- Linear, dose-proportional PK with long half life supports once daily oral dosing

GBT440: novel, promising therapy with potential to improve the devastating clinical course of sickle cell disease

THANK YOU

Pfizer and Sickle Cell Disease

Emerging Treatments for SCD
June 14, 2016

Krupa Sivamurthy, MD
Global Medical Lead, SCD
Pfizer, Inc.

Pfizer Rare Disease

Pfizer's Development Portfolio in SCD*

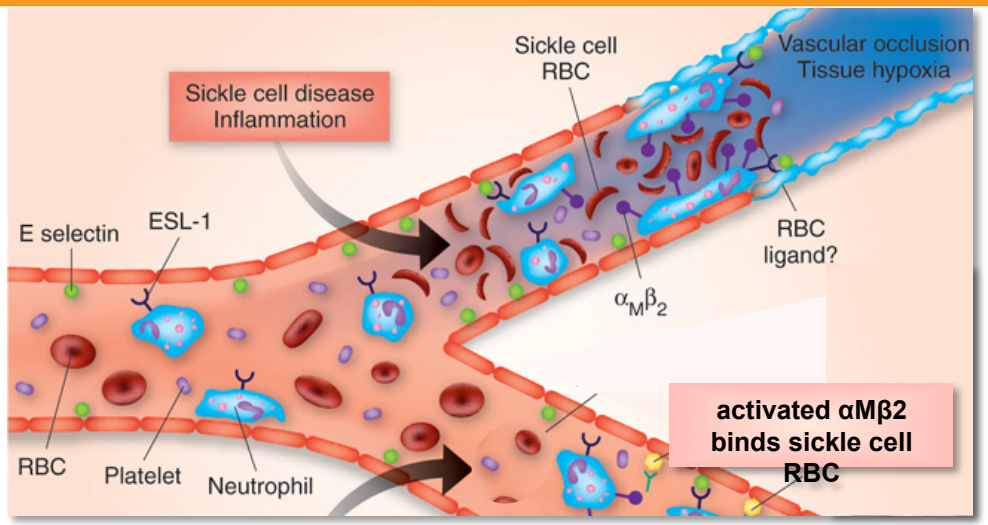
Phase 1***	Phase 3***
PDE9i Oral *VOC prevention*	**Rivipansel Intravenous** *VOC treatment*
Rivipansel Subcutaneous *VOC treatment*	

* Pipeline Status as of Dec 3, 2015
** The compounds identified in this column are investigational drugs in pre-clinical development and are not approved by the FDA
***The compounds identified in this column are investigational drugs in clinical development and are not approved by the FDA

*VOC=Vasco-occlusive crisis

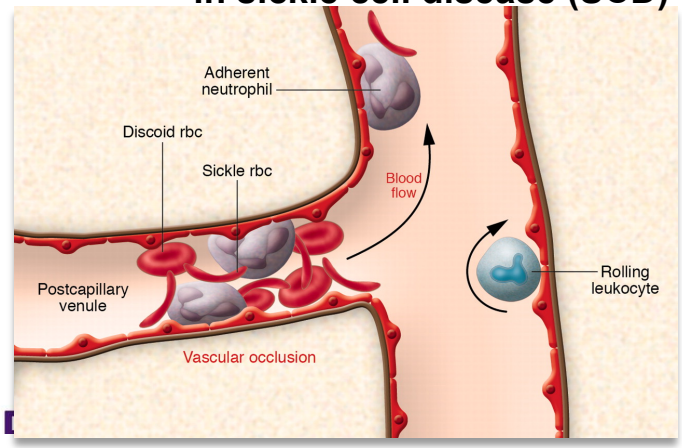
Rare Disease
A Pfizer Research Unit

Scientific Approach 1: Inhibit Occlusive Cell Adhesion for Acute Therapy



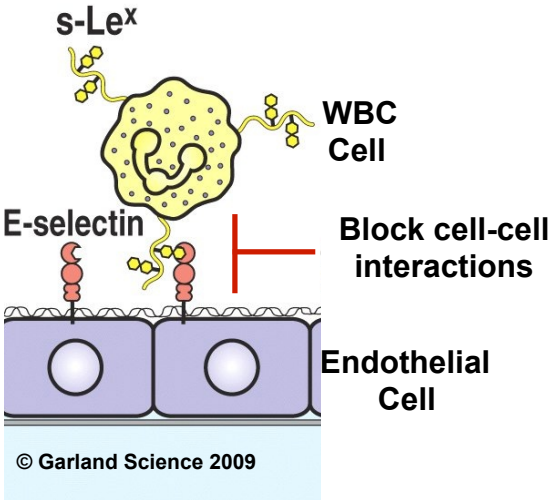
Adapted from Nature Medicine 15, 364 - 366 (2009)

Vaso-occlusion is the major cause of morbidity and mortality in sickle cell disease (SCD)



Blood 2010 116: 1779-1786
Nature Reviews Drug Discovery 2009 8: 661-677
J Clin Invest. 2007;117:850

Small Molecule Blocks Cell Membrane Adhesion Interactions

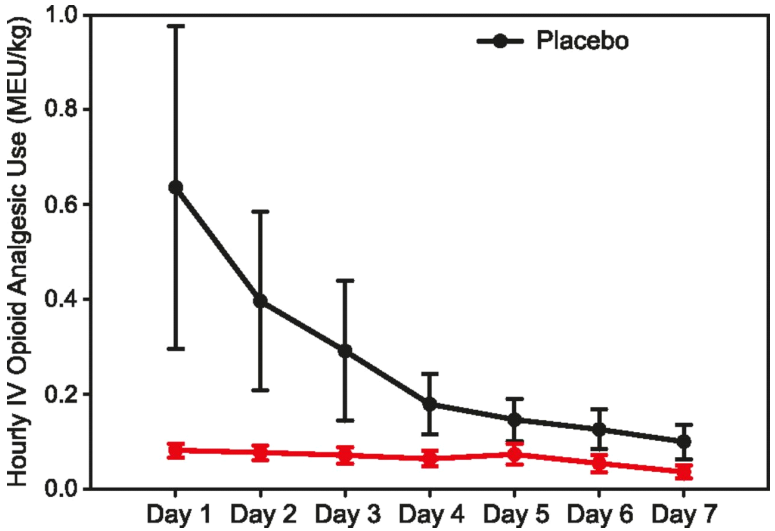


Rationally designed based on sLe^X conformation in carbohydrate-binding domain of E-selectin

What do we know?

Phase 2 Randomized, double-blind, placebo-controlled study

- Primary objective: efficacy
- Secondary objectives: safety, PK, clinical activity, biomarkers
- **Clinical endpoints**
  - Mean 55 hour (32%) reduction in Length of Hospital Stay
    - 5.2 days versus 7.3 days (placebo)
  - Opioid consumption endpoint
    - 89% decrease in IV opioid use in 1st 24 hr
    - Cumulative IV opioid use decreased by 83%
- Phase 2 results met both clinical and opioid use endpoints
- Results supported development program advancement: Pfizer's RESET: Phase 3 pivotal trial, Evaluating Safety, Efficacy and Time to Discharge study

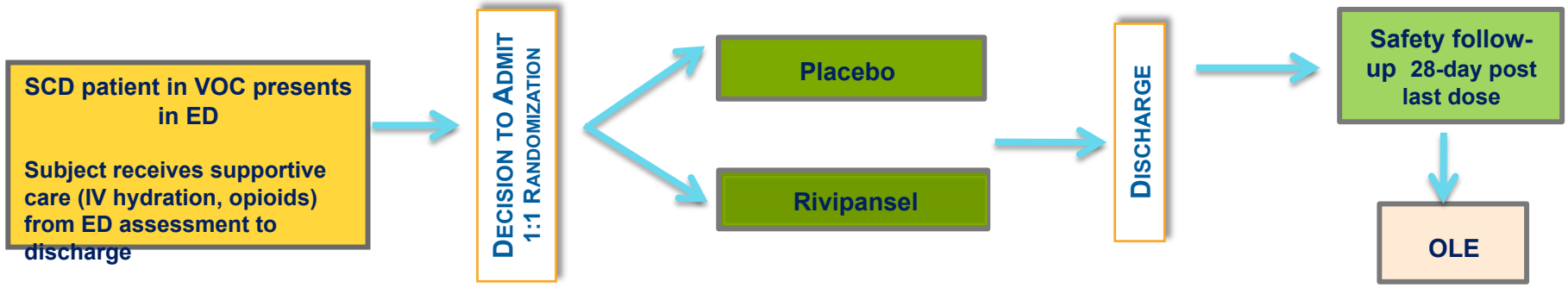


Randomized phase 2 study of GMI-1070 in SCD: reduction in time to resolution of vaso-occlusive events and decreased opioid use.
Marilyn J. Telen, Ted Wun, Timothy L. McCavit, Laura M. De Castro, Lakshmanan Krishnamurti, Sophie Lanzkron, Lewis L.Hsu, Wally R. Smith, Seungshin Rhee, John L. Magnani, HelenThackray
Blood Apr 2015, 125 (17) 2656-2664

Rare Disease
A Pfizer Research Unit

RESET: Rivipansel Phase 3 study

Phase III Design and Status



Pivotal Phase III study

N=350, double-blind, multicenter, placebo-controlled, efficacy and safety

- **Primary Endpoint: Readiness for discharge for VOC**
- **Secondary Endpoints**: Duration of hospitalization (LOHS), time to discontinuation of IV opioid; cumulative IV opioid consumption (over time and first 24 hours); time to confirmed VAS reduction from baseline

Rivipansel SC:

Phase 1 in **healthy volunteers; safety, tolerability, PK and pharmacodynamics**

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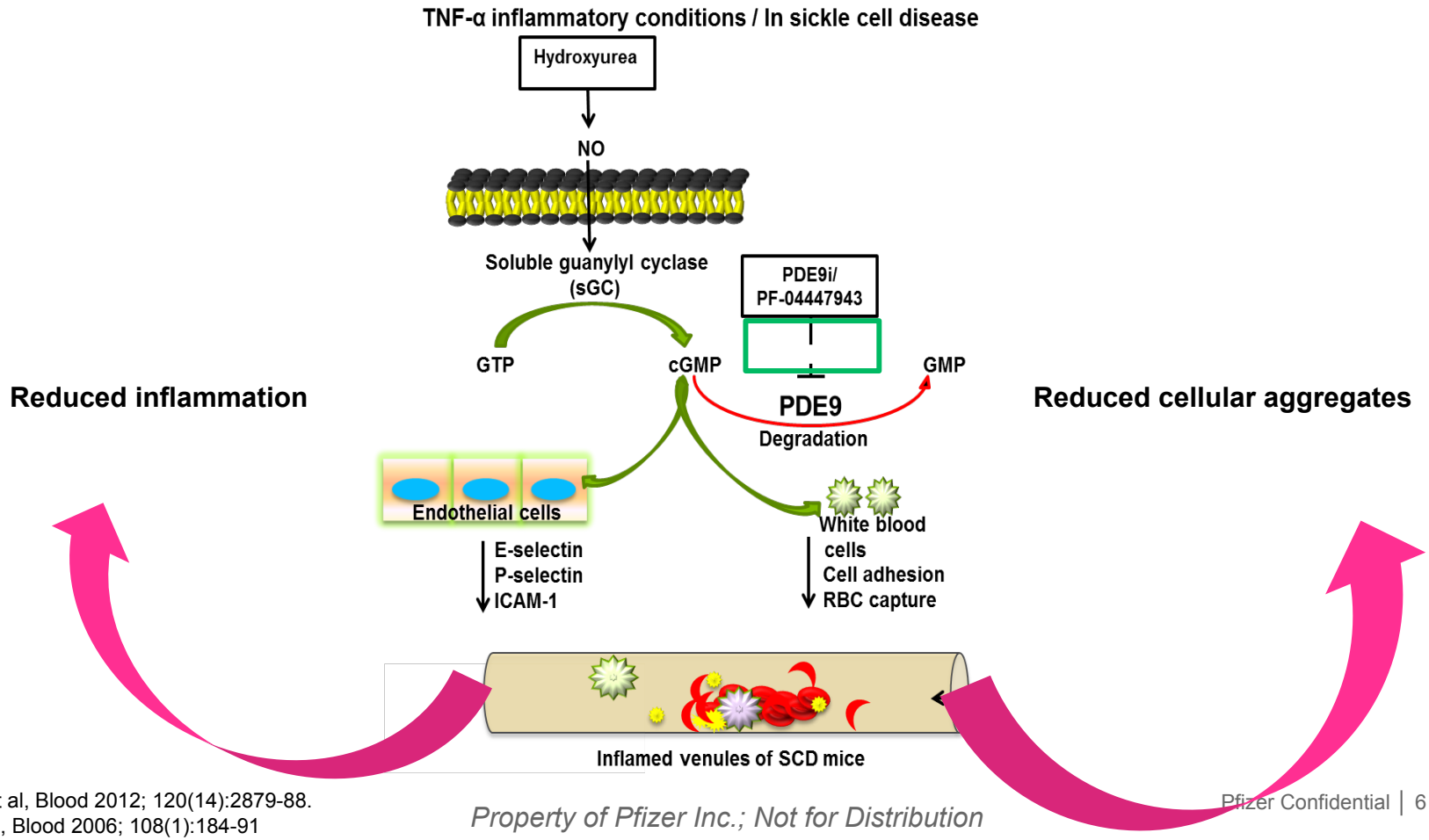
Scientific Approach 2: Vaso-occlusion Prevention in Sickle Cell Disease (PDE-9 Inhibitor)

Phase 1b: 28 day safety, tolerability, PK and pharmacodynamcis in SCD patients



Almeida et al, Blood 2012; 120(14):2879-88.
Cokic et al, Blood 2006; 108(1):184-91
Nemer et al, Blood 2012;120:2777-2778

Thank you

Pfizer Rare Disease

Bringing Hope to Patients with Sickle Cell Disease

Yutaka Niihara, MD, MPH
Chairman and CEO

June 2016

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Who We Are

Sickle Cell Disease is our Focus

- ☑ Phase 3 trial in sickle cell disease (SCD) completed
  - Cochran-Mantel Henszel (CMH) using "Modified Ridit" analysis, P-value of 0.005
- ☑ One of the largest trials conducted in sickle cell disease
  - 230 adult and pediatric patients
  - 48 week trial
  - Oral therapy
- ☑ Favorable regulatory environment
  - Orphan Drug Designation (U.S. & E.U.)
  - Fast Track Designation
- ☑ Founded December 2000

Corporate History

Approach Based on Academic Findings*

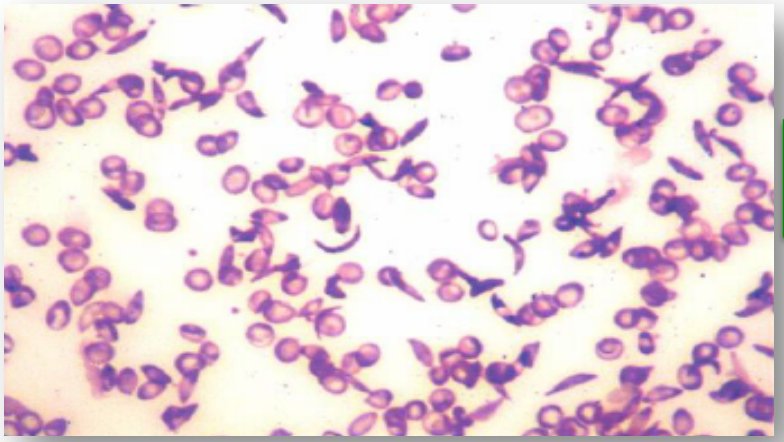
- Emmaus' research and development leverages L-glutamine research of Drs. Yutaka Niihara and Charles Zerez at Harbor UCLA / LA BioMed
- L-glutamine studies funded by National Institute of Health (1996)
  - Sought to understand link between glutamine availability in healthy and sickled red blood cell (RBC)
    - Heightened susceptibility to oxidation by sickle RBC
    - Identified nicotinamide adenine dinucleotide (NAD) and its reduced form (NADH) as the primary regulators of oxidation
    - Hypothesized that reduced levels of NADH to be an indicator of increased oxidation
    - Preliminary studies affirmed; Company entered into pilot trial
  - Pilot trial indicated statistically significant increases in NADH levels and redox potential
    - Follow-up dosing study was completed identifying the 20-30g daily dose
    - RBC endothelial adhesion was reduced with pharmaceutical grade L-glutamine therapy (PGLG) treatment
- Investigational New Drug application submitted May 1997

** From Dr. Niihara's early work at UCLA and LABioMed.*

Blood Smear Of Sickle Cell Patient

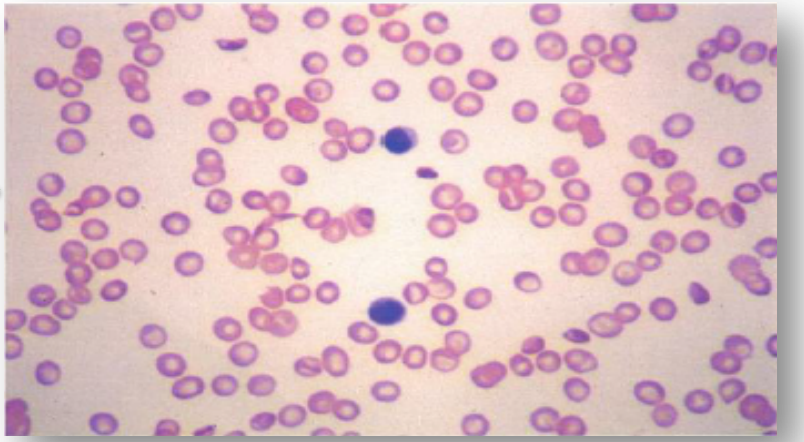
Transformational Impact

Before Treatment



PGLG

After Treatment



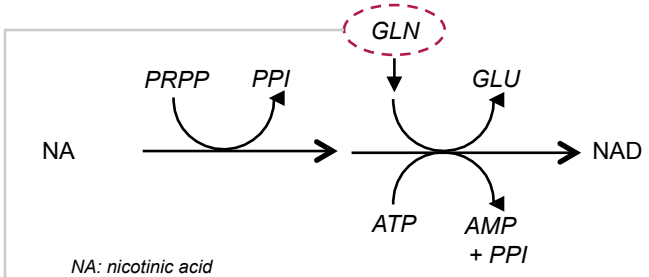
Result of 12-week treatment is improved red blood cell shape and reduced adhesion*

** Source: Emmaus Phase 1 clinical trials – same patient after 12 weeks of PGLG treatment*

NAD Metabolism and Glutamine

Glutamine Improves NAD Redox Potential

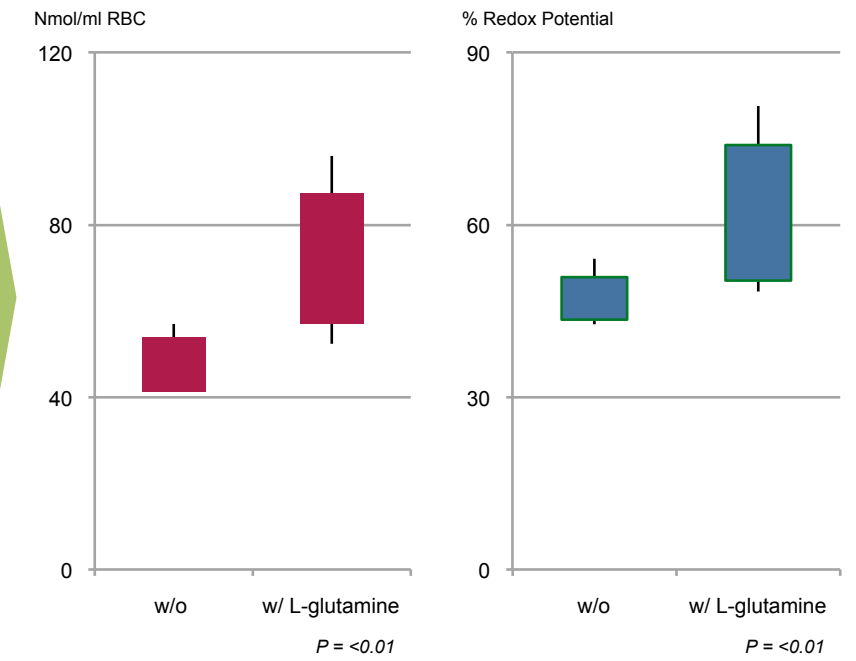
NAD Metabolism*



NA: nicotinic acid
PPI: pyrophosphate
PRPP: phosphoribosylpyrophosphate
GLN: glutamine
GLU: glutamate

- Oxidation plays an important part in pathophysiology of SCD
- NAD is an important physiological antioxidant in RBC
- In sickle RBC NAD, redox potential is significantly compromised
- Glutamine, a precursor for NAD, can improve NAD redox potential

NADH and Redox Potential**



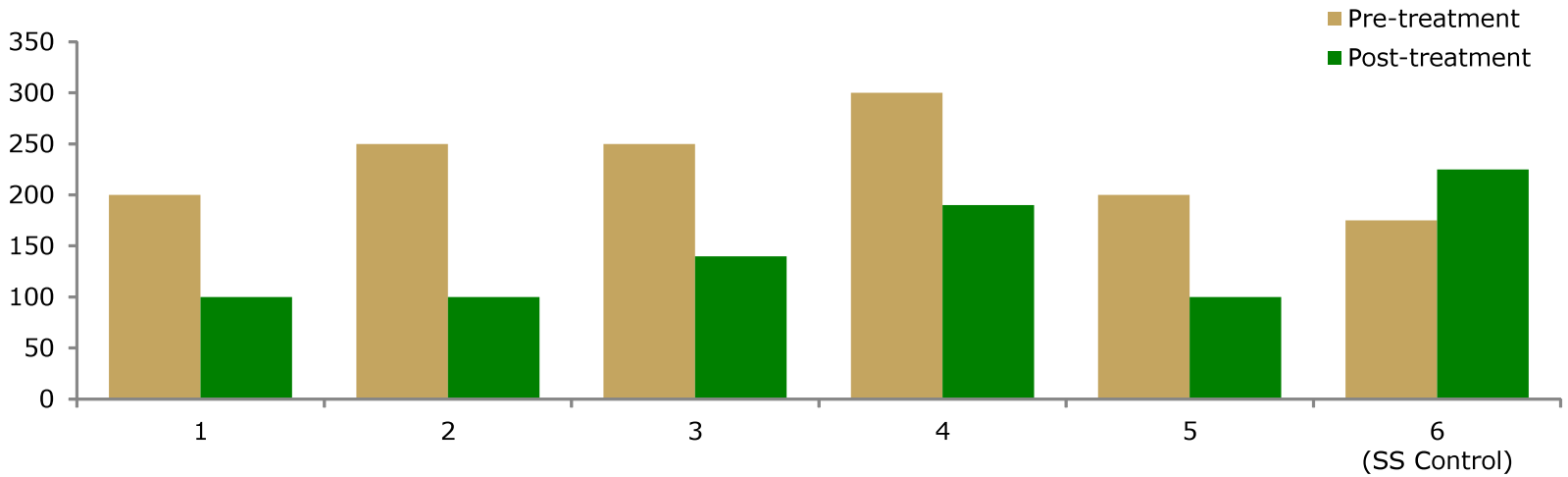
Pilot studies provided compelling clinical proof-of-concept highlighting PGLG's potential benefits

** Niihara Y, et al. Increased red cell glutamine availability in sickle cell anemia: demonstration of increased active transport, affinity, and increased glutamate level in intact red cells. J Lab Clin Med. 1997 Jul;130(1):83-90.*

*** Niihara Y, et al. Oral L-glutamine therapy for sickle cell anemia: I. Subjective clinical improvement and favorable change in red cell NAD redox potential. Am J Hematol. 1998 Jun;58(2):117-21.*

Study of RBC Adhesion Rates

L-glutamine Decreases Adhesion of Sickled RBCs*



6 sickle cell anemia patients: 5 treated with L-glutamine, 1 untreated control

Mean decrease among 5 patients treated with L-glutamine: 113% ($p<0.001$)

- Dose: 30 grams daily for at least 4 weeks
- Mean age: 39 years
- SS Control group: untreated with any anti-sickling therapy for at least 1 year
- Normal RBC set from healthy volunteers

** Y Niihara et al., L-glutamine Therapy Reduces Endothelial Adhesion of Sickle Red Blood Cells to Human Umbilical Vein Endothelial Cells, BMC Blood Disorders in 2005*

Phase 3 Results

Reductions in Frequency and Severity of Crises

	Primary Endpoint	Secondary Endpoint	Additional Analysis		
	Decrease in the frequency of sickle cell crises	Decrease in the frequency of hospitalization	Decrease in the cumulative days in hospital	Less incidence of acute chest syndrome	Delay in the onset of first sickle cell crises
Difference between treatment and placebo arms	**25%**	**33%**	**41%**	**58%**	**61%**

- Median reduction in frequency of crises from 4 to 3*
- Median reduction in frequency of hospitalization from 3 to 2**
- Reductions achieved despite 2/3 of patients being on Hydroxyurea therapy
- Decreases in the Severity of Sickle Cell Crises and length of stay in hospital

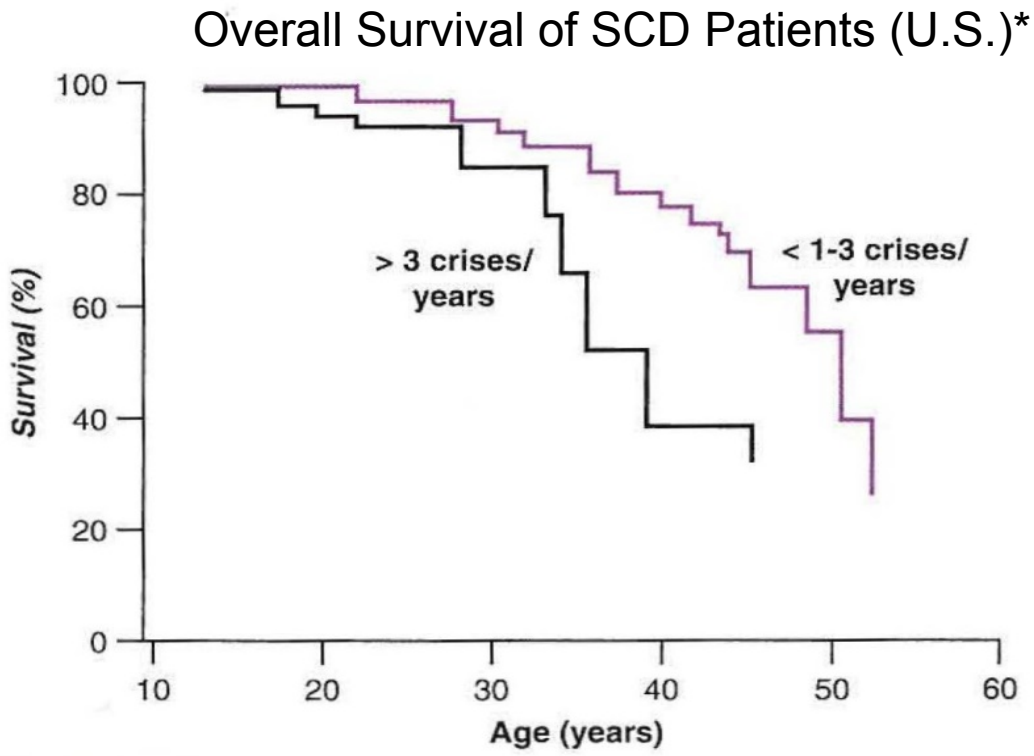
Strong safety and efficacy results represent a compelling risk/benefit profile

* Niihara Y., et al. A Phase 3 Study of L-Glutamine Therapy for Sickle Cell Anemia and Sickle ß0-Thalassemia. Blood 2014 124:86; Dec. 5, 2014

* * Niihara Y., et al. Decrease in the Severity of Painful Sickle Cell Crises with Oral Pglg. Blood 2015 126:2175; Dec. 4, 2015

Fewer Crises = Longer Lifespan

In our Trial, Median Number of Crises was Reduced from 4 to 3



Hillman Study from 2011 Demonstrates Potential Significance of Less SCD Crises

"The overall survival of patients in the U.S. with sickle cell anemia correlates with the severity of their disease state, especially the number of crises per year.

Patients with more than 3 crises per year will experience fatal complications during the fourth and fifth decades of life.

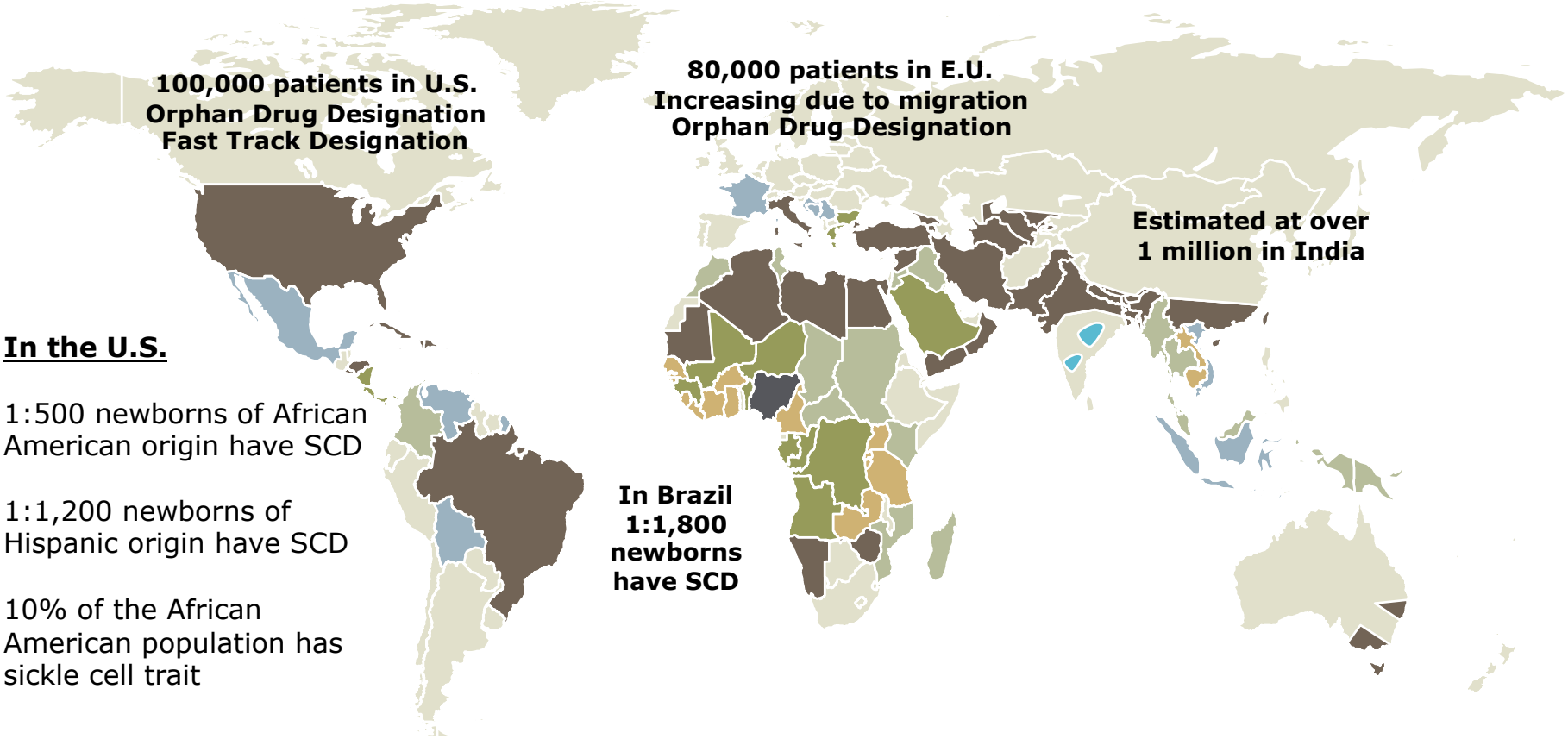
Whereas patients who experience between 1 and 3 crises per year have a median survival of nearly 50 years." *

Potential significance of reduction in sickle cell crises over time

* *Hematology in Clinical Practice/Robert S. Hillman et al., 5th Ed. McGraw-Hill 2011, page 86 – reference for both quoted text and chart.*

Global Perspective

SCD Represents a Substantial Unmet Medical Need*



In the U.S.

1:500 newborns of African American origin have SCD

1:1,200 newborns of Hispanic origin have SCD

10% of the African American population has sickle cell trait

20 to 25 million patients worldwide, primarily in Africa

* *http://www.iasp-pain.org/PublicationsNews/NewsDetail.aspx?ItemNumber=4896&navItemNumber=643*

Vepoloxamer (Investigational Agent)

CDC Webinar Series
Emerging Treatments for Sickle Cell Disease

June 14, 2016

Gregory D. Gorgas
Senior Vice President, Commercial

Safe Harbor Statement

This presentation includes forward-looking statements about our business prospects, financial position, and development of vepoloxamer for therapeutic use in humans. Any statement that is not a statement of historical fact should be considered a forward-looking statement. Because forward-looking statements relate to the future, they are subject to inherent risks, uncertainties and changes in circumstances that are difficult to predict. Actual events or performance may differ materially from our expectations indicated by these forward-looking statements due to a number of factors, including, but not limited to, results of our pending and future clinical studies, the timeline for clinical and manufacturing activities and regulatory approval; our dependency on third parties to conduct our clinical studies and manufacture our clinical trial material; our ability to raise additional capital, as needed; our ability to repay outstanding debt as payments come due; our ability to establish and protect proprietary rights related to our product candidates; and other risks and uncertainties more fully described in our press releases and our filings with the SEC, including our annual report on Form 10-K and quarterly report on Form 10-Q filed with the SEC on March 14, 2016 and May 6, 2016, respectively.

We caution you not to place undue reliance on any of these forward-looking statements, which speak only as of the date of this presentation. We do not intend to update any forward-looking statement included in this presentation to reflect events or circumstances arising after the date of the presentation, except as may be required by law.

Mast Therapeutics

- **Biopharmaceutical company developing novel, clinical-stage therapies for serious or life-threatening diseases with significant unmet needs**

- **Publically traded small company in San Diego, CA**

- **Developing vepoloxamer for treatment of vaso-occlusive crisis (VOC) in sickle cell disease; agent has potential in other serious vascular diseases, including heart failure and stroke**

- **A leading company focusing on sickle cell disease**
  - Enrollment complete in pivotal Phase 3 study in VOC
  - Potential first-in-class therapy
  - Extensive community and patient-focused initiatives

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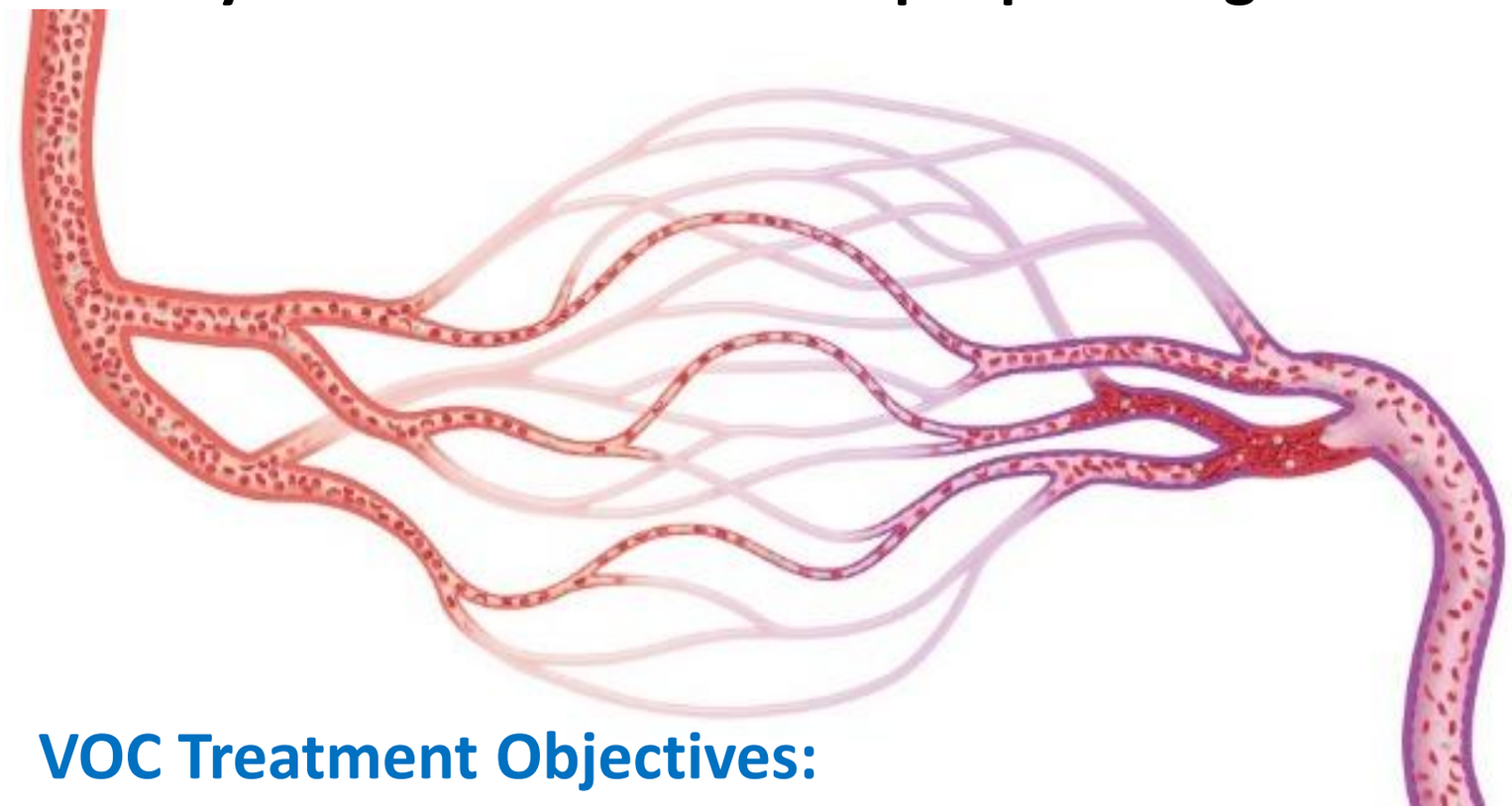
Vaso-Occlusive Crisis in Sickle Cell Disease

- **The underlying pathology in VOC results in diminished blood flow, which is associated with organ and tissue damage**

- **High unmet need to restore blood flow, especially during VOC**

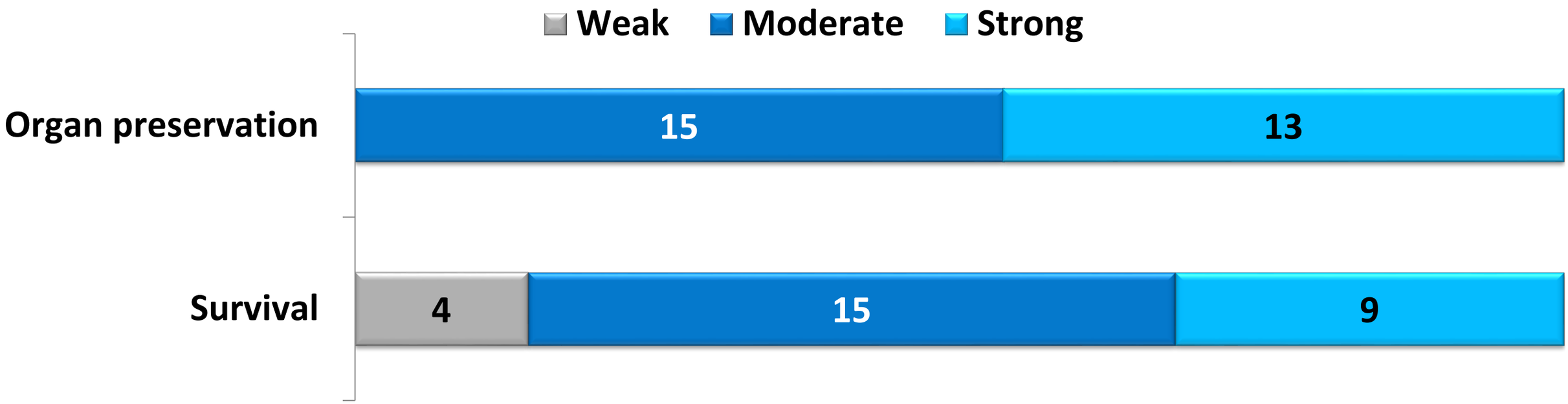
- **Optimal treatment may need to address multiple pathologies**
  - Adhesion
  - Hemolysis
  - Aggregation
  - Viscosity



VOC Treatment Objectives:
Improve blood flow to reduce ischemic injury and shorten the duration and severity of painful crises

Physicians Report a High Association of VOC with Organ Damage and Mortality

Frequency, Severity, and Duration of VOC Correlates with Morbidity and Mortality (# of mentions)



"My older patients have more organ issues than my younger patients" - IM

"It's like a heart attack- the longer you have pain, more damage is done and higher risk of dying" - Hem/Onc

"Each crisis chips away at the organs" - Hem/Onc

Source: RDS Consulting Group Research Report, 2015, n=30
Reference: Telen, M.J., Elmariah, H. et al., Factors Associated with Survival in a Contemporary Adult Sickle Cell Disease Cohort, *Am J Hematology* 2014 May; 89(5):530-535

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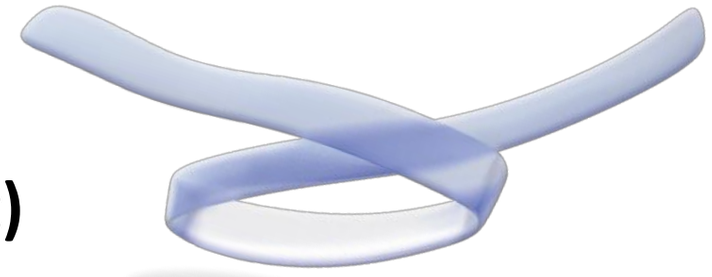
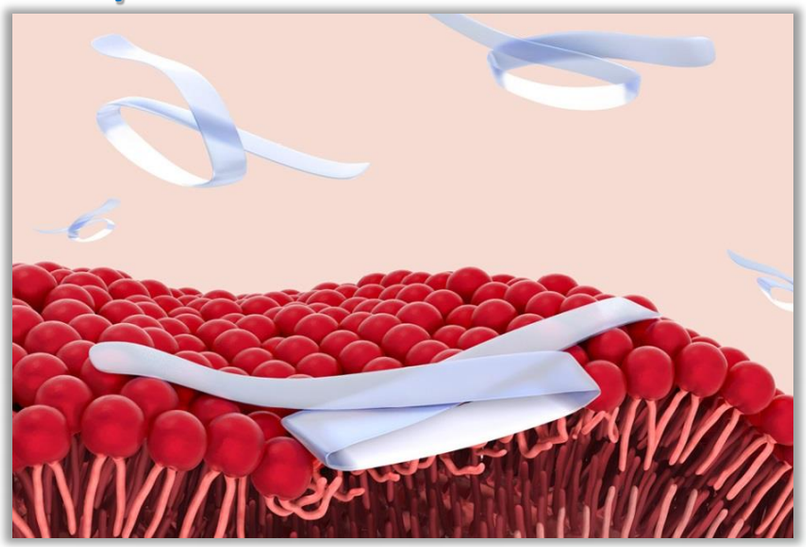
Vepoloxamer: A Novel Biophysical Agent

- **Damaged cell surfaces in the circulation can impair blood flow due to adhesion, hemolysis, and aggregation**

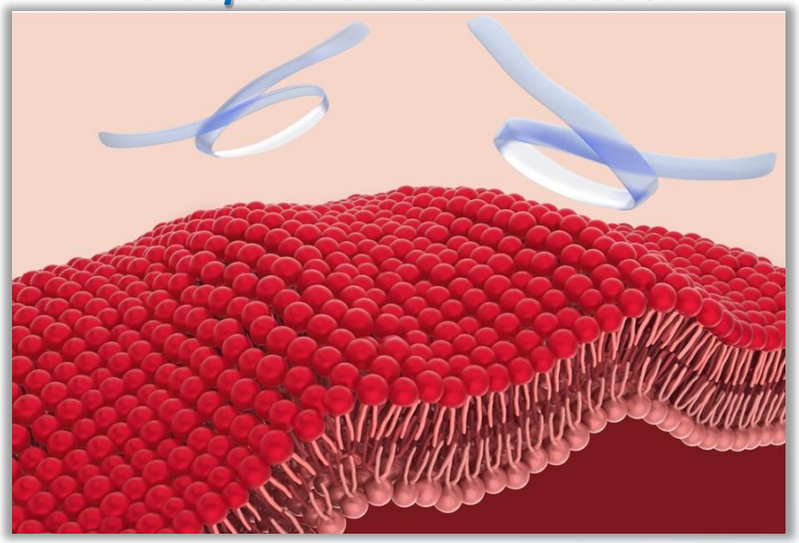


- **Vepoloxamer for injection (investigational agent)**
  - Normalizes cell surface features and actions
  - Targets damaged tissue; little or no activity in healthy tissue
  - Not metabolized; no active metabolites to track, no difference in fast vs slow metabolizers, less susceptible to drug-drug interactions
  - Less susceptible to genetic variation; independent of receptors, etc.

Damaged Cell Membrane
Vepoloxamer Adheres & Protects



Healthy Cell Membrane
No Vepoloxamer Interaction



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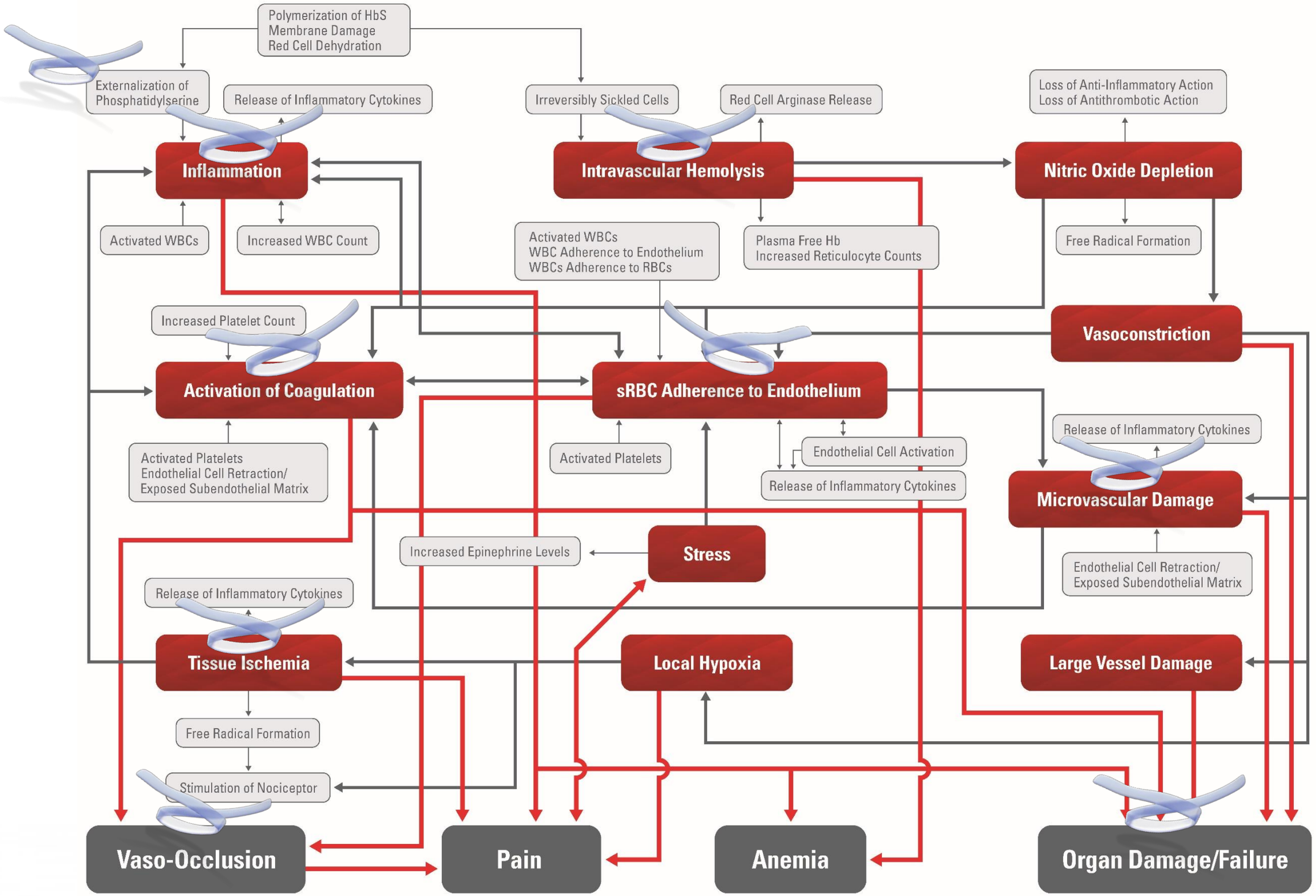
Vepoloxamer Addresses Multiple Pathophysiological Pathways Underlying Crisis



Adapted from: Rupa Redding-Lallinger and Christine Knoll, Curr Probl Pediatr Adolesc Health Care 2006; 36: 346-376 (1538-5442)

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Vepoloxamer: Development History

- **Over 100 nonclinical studies completed**
- **Phase 2 VOC – statistically significant shorter crisis and less opioid use**
- **Phase 3 VOC – demonstrated activity (p-value = 0.07), under enrolled**
  - Statistically significant shorter duration of crisis identified in two subgroups
    - Children (p=0.01)
    - Patients on hydroxyurea (p=0.02)
- **Lessons learned from clinical history and applied to "EPIC" Phase 3 study**
  1. Study design aligned with clinical practice is critical
  2. EPIC study design incorporated Medical Expert advice and FDA feedback
     - Utilize a clinically meaningful endpoint
     - Use as objective an endpoint as possible
     - Avoid use of pain scores due to variability
     - Provide a plan to minimize data loss

(VOC = Vaso-occlusive crisis)

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The EPIC Study

Evaluation of Purified Poloxamer 188 In Vaso-Occlusive Crisis

- **Double-Blind, Placebo-Controlled, International, VOC Intervention Study**
  - 388 patients, randomized 1:1 to standard of care +/- vepoloxamer
  - 1-hour loading dose followed by up to 48-hours continuous infusion
- **Primary Endpoint**
  - Duration of crisis (time of randomization to last dose of parenteral opioid)
- **Secondary Endpoints**
  - Re-hospitalization for VOC within 14 days
  - Occurrence of acute chest syndrome within 120 hours of randomization
- **Other Assessments**
  - Safety
  - Duration of hospitalization
  - Biomarkers
  - Opioid utilization
  - Sub-study outcomes

The EPIC Study – Enrollment Statistics

- **Complete enrollment achieved in February 2016**
- **>75 study sites in 14 countries, with >60% in U.S.**
- **Patient demographics**
  - Average patient age: 15 years (range 4-46)
  - Patients <18 years: 71%
  - Patients on hydroxyurea (HU): 61%
- **No unexpected safety signals**
  - Data Safety Monitoring Board oversight throughout study
  - Study performance consistent with statistical assumptions on which study was designed
- **Largest placebo-controlled sickle cell disease study for VOC intervention**

Clinical Study Enrollment Challenges and Strategies

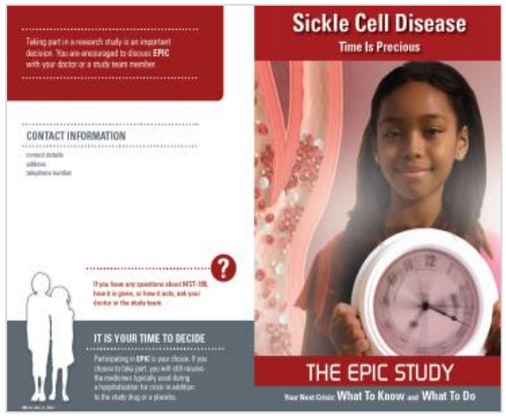
- **Provider Confidence and Enthusiasm**
  - Responsive to equipping and education opportunities
  - Investigator and clinical staff engagement

- **Patient Awareness and Acceptance**
  - Information materials / website
  - Sponsorships / partnerships

- **Timely Communication and Access**
  - Over 75 participating clinical sites
  - Transportation assistance
  - VOICE Crisis Alert™ mobile device app

Supporting Your Efforts to Improve the Lives of People Living with Sickle Cell Disease

Clinical Sites



the EPIC study

EPIC App

EPIC extension study

Advocacy

SCDAA
"Break The Sickle Cycle"

SICKLE CELL DISEASE
FOUNDATION OF CALIFORNIA

FOUNDATION FOR SICKLE CELL DISEASE RESEARCH
SUPPORTING AND PROMOTING HEMOGLOBINOPATHY RESEARCH

cscf
Children's Sickle Cell Foundation, Inc.

Lydia W Smith Foundation
Benefiting Sickle Cell Anemia

Community

SICKLE CELL WARRIORS

Inspiring DREAMS Camp Crescent Moon

HOPE for SCD

VOICE

Crisis Alert

MARTIN CENTER SICKLE CELL INITIATIVE

The William E. Proudford Sickle Cell Fund, Inc.®

Annual Sickle Cell Disease Therapeutics Conference

Partial listing of organizations engaged or supported by Mast Therapeutics above does not indicate their endorsement of vepoloxamer or the EPIC study

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Vepoloxamer in SCD: Next Steps

- **EPIC-Extension (EPIC-E) Study is ongoing**
  - Study to assess safety and tolerability of repeat administration of vepoloxamer, rate of re-hospitalization for VOC, and occurrence of ACS
  - Only potentially available to prior EPIC study participants

- **If approved by the FDA, vepoloxamer would be the first ever interventional therapy for VOC associated with sickle cell disease (SCD)**
  - Significant unmet need – No approved disease-modifying therapies available for VOC intervention
  - Strong support among medical / advocacy / patient communities
  - Orphan Drug Designation / Fast Track Designation
  - SCD is part of FDA “Patient-Focused Drug Development Initiative”
  - Addresses the hallmark of SCD: VOC

For additional information, please visit:

www.masttherapeutics.com

www.CrisisVOICE.com

www.theEPICstudy.com