Therapeutic Benefits of Stannsoporfin in the Treatment of Severe Hyperbilirubinemia

Mallinckrodt Pharmaceuticals

Disease Overview

- Infant jaundice, a yellow discoloration of a baby's skin and eyes, is common and usually self-limiting, but it can be severe[1]

- Jaundice is caused by hyperbilirubinemia, a condition in which excess bilirubin is produced in the blood; this yellow pigment of red blood cells is formed during hemolysis, the normal breakdown of hemoglobin[2]

- In some infants, hemolysis occurs at a greater rate and may lead to high bilirubin levels[2]; considering the number of infant term births with jaundice due to elevated bilirubin levels,[3] it is estimated that each year about 70,000 to 125,000 infants born in the United States are at risk of developing severe hyperbilirubinemia[4,5]

- If left untreated, severe hyperbilirubinemia can cause acute bilirubin encephalopathy, which can lead to hearing loss and brain damage[1,2]

Unmet Need

- Phototherapy is a standard treatment to reduce bilirubin levels,[1] but it may not address severe cases
- In some severe cases, HCPs resort to invasive options including blood exchange transfusion or IVIG[1]
- There are currently no treatments indicated for severe hyperbilirubinemia

Background and Benefits[6]

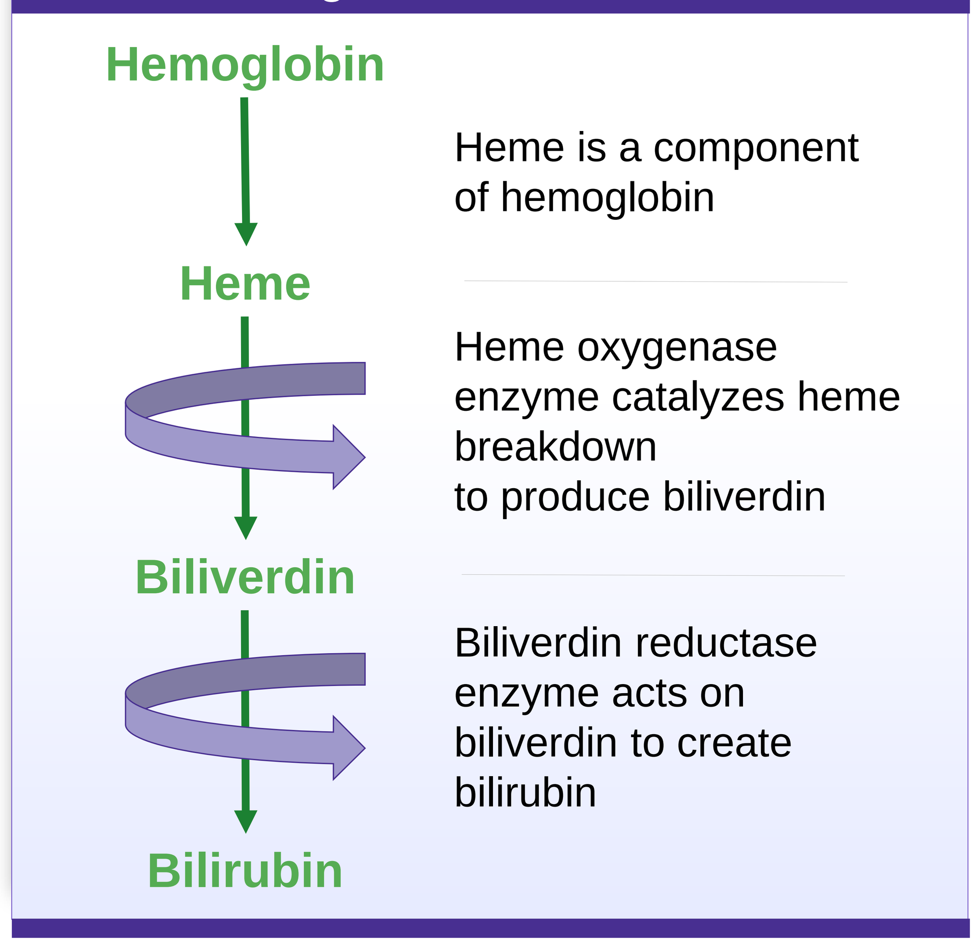
- Stannsoporfin is a competitive heme oxygenase inhibitor (HO) that is expected to be the first FDA-approved treatment for infants at risk of severe neonatal jaundice
- Administered by a single intramuscular injection
- Effects last for ~7-8 days following administration
- Reduces potential of bilirubin increasing to levels that require more intrusive therapies
- May lower risks (ie, bilirubin rebound) associated with
 - Other treatments
 - Prolonged/severe bilirubin elevation (which can impact CNS development)
- Exhibits favorable safety/tolerability profile
- May eliminate the need for more invasive, complex, and lengthy treatments beyond phototherapy



Stannsoporfin is a single intramuscular injection administered to reduce bilirubin production in infants with severe hyperbilirubinemia.

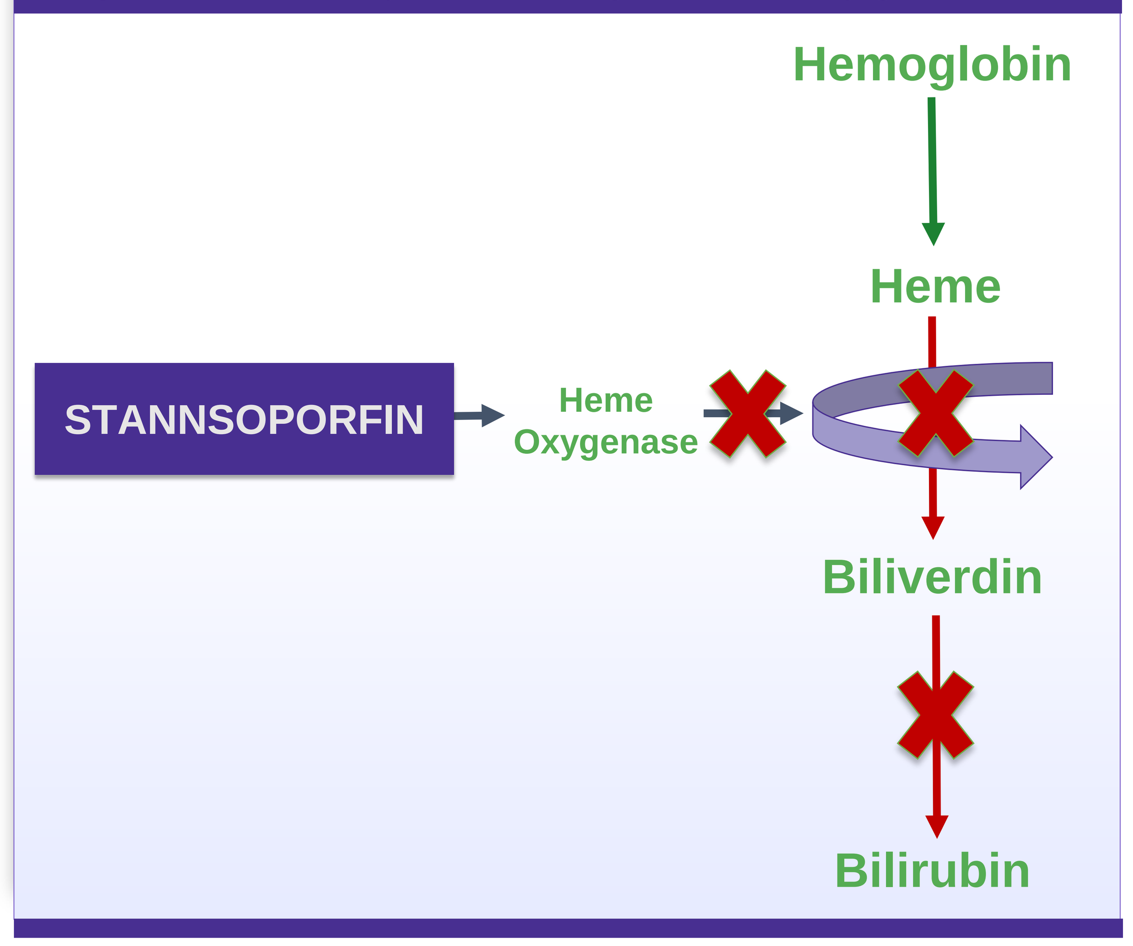
Mechanism of Action

Bilirubin forms from breakdown of hemoglobin in red blood cells



Hemoglobin
Heme
Biliverdin
Bilirubin
Heme is a component of hemoglobin
Heme oxygenase enzyme catalyzes heme breakdown to produce biliverdin
Biliverdin reductase enzyme acts on biliverdin to create bilirubin

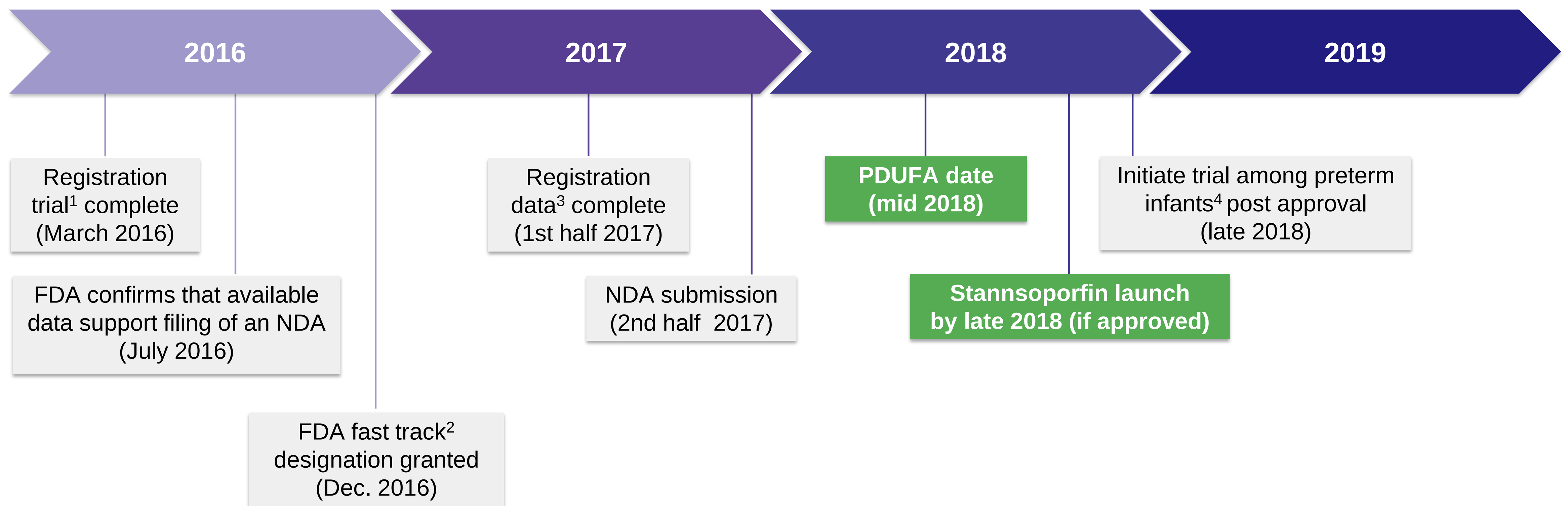
Stannsoporfin reduces bilirubin production by inhibiting heme oxygenase



Hemoglobin
Heme
STANNSOPORFIN
Heme Oxygenase
Biliverdin
Bilirubin

Timeline

- US launch of stannsoporfin anticipated by late 2018
- FDA fast track status supports a rolling NDA data submission
- NDA filing in progress with FDA agreement to accept totality of data, including 2 Phase 2(b) trials (one pivotal)
 - No additional trials necessary to reflect medical need



2016
2017
2018
2019
Registration trial1 complete (March 2016)
FDA confirms that available data support filing of an NDA (July 2016)
FDA fast track2 designation granted (Dec. 2016)
Registration data3 complete (1st half 2017)
NDA submission (2nd half 2017)
PDUFA date (mid 2018)
Stannsoporfin launch by late 2018 (if approved)
Initiate trial among preterm infants4 post approval (late 2018)

1. Registration trial is a Phase 2(b) study (JASMINE 204); completed treatment phase by March 2016. 2. https://www.fda.gov/forpatients/approvals/fast/ucm405399.htm. 3. Completed gathering follow-up safety data for registration trial required for NDA submission. 4. Conducting trials among preterm infants at less than 35 weeks' gestational age is part of FDA's pediatric requirement.
Additional Sources: Mallinckrodt's assessment of regulatory timelines and clinical trials; minutes of InfaCare meeting with FDA; management projections.

References

1. Mayo Clinic. Diseases and Conditions: Infant Jaundice. http://www.mayoclinic.org/diseases-conditions/infant-jaundice/basics/definition/con-20019637. Accessed September 14, 2017.
2. MedlinePlus. Bilirubin Encephalopathy. https://medlineplus.gov/ency/article/007309.htm. Accessed September 14, 2017.
3. Healthcare Cost and Utilization Project KID data. https://www.hcup-us.ahrq.gov/kidoverview.jsp.
4. Mallinckrodt market research/management projections.
5. Young PC, Korgenski K, Buchi KF. Early readmission of newborns in a large health care system. *Pediatrics*. 2013;131(5):e1538-e1544.
6. Data on file.

INVESTOR DAY ◆ OCTOBER 4, 2017 ◆ NEW YORK, NY

Abbreviations: CNS, central nervous system; FDA, Food and Drug Administration; HCP, healthcare professional; IVIG, intravenous immunoglobulin; NDA, New Drug Application; PDUFA, Prescription Drug User Fee Act.

Therapeutic Benefits of Inhaled Xenon Gas in Reducing Brain Damage Caused by Cardiac Arrest

Mallinckrodt Pharmaceuticals

Disease Overview

- Cardiac arrest results in abrupt loss of function; each year more than 350,000 out-of-hospital and more than 209,000 in-hospital cardiac arrests occur in the United States[1]
- Of the patients who are revived following a cardiac arrest, only 12% to 25% survive to hospital discharge,[1] and many survivors may experience significant brain damage and/or coma
- The average cost of care per each cardiac arrest survivor is estimated to be ~$100,000 within the first year[2]

Unmet Need

- TTM (or hypothermia) therapy is the current standard of care in treating comatose ROSC patients[2] and is recommended by AHA guidelines for post–cardiac arrest care[3]
- There are currently no approved pharmacological treatments to prevent neuronal damage in ROSC patients

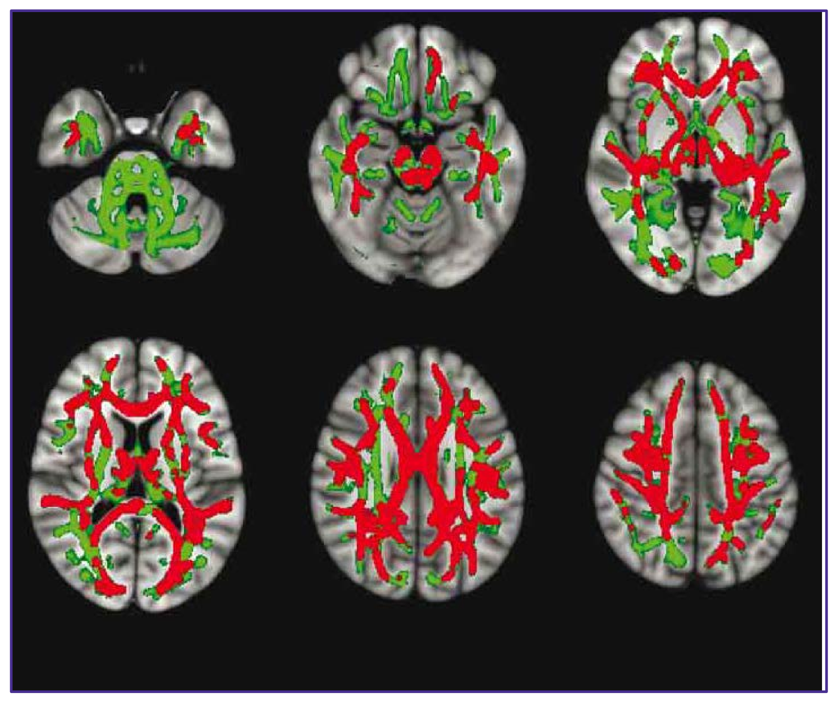
Background and Benefits

- Xenon, a noble gas with low chemical reactivity, has been used safely as an inhaled therapy in several studies to date[4]
- Xenon is delivered into the breathing circuit via a proprietary delivery device



Xenon gas proprietary delivery device

- Planned use will be in conjunction with TTM in the hospital ED and ICU settings
- Preliminary studies show less brain damage on a primary neuroimaging endpoint measured through MRI[5]
- A post hoc analysis of patients resuscitated in ≤30 minutes who received xenon gas demonstrated improved 60-day mortality as well as improved cognitive and motor functions as shown on modified Rankin scores[7]



Red: Significantly more damage in TTM-alone group vs xenon+TTM group

Green: No difference between groups

- Reduced neuronal cell death will lessen time in coma, lower mortality rates, and improve cognitive and motor functions
- Functional improvements may lower cost of patient care

Proposed Mechanism of Action

Cardiac arrest interrupts blood flow to the brain

↓

Negative cascade opens calcium channels

↓

⇧ Ca^{2+} flow into cells causes neuronal cell death[4]

- Overactivation of calcium channels is known to cause neuronal damage and cell death[6]
- Xenon binds to NMDA receptors through **a unique glycine-binding mechanism** to regulate Ca^{2+} flow through the channel

Timeline

- 7 years of US commercial exclusivity from orphan status*
- Exploring device patents and manufacturing exclusivity to expand protections

2016 → 2017 → 2018 → 2019 → 2020

- 2016: Phase 2b complete
- 2018: Phase 3 trial starts (Q1 2018)
 - **Single registration trial with 1436 patients conducted under SPA from FDA**
- 2019: Interim analysis (2019)
 - **Interim analysis at n=50% (completion of primary endpoint follow-up):**
 - **If primary <u>and</u> secondary endpoints are positive → stop for success**
 - **If primary <u>or</u> secondary endpoint is futile → stop for futility**
- 2019: Trial complete (2019)
- 2020: NDA submission (2020)
- 2020: Expected product approval / launch (2020)

* Orphan drug status granted by FDA in May 2015.

References

1. American Heart Association. CPR & First Aid Emergency Cardiovascular Care. http://cpr.heart.org/AHAECC/CPRAndECC/General/UCM_477263_Cardiac-Arrest-Statistics.jsp. Accessed September 19, 2017.
2. Merchant RM, Becker LB, Abella BS, Asch DA, Groeneveld PW. Cost-effectiveness of therapeutic hypothermia after cardiac arrest. *Circ Cardiovasc Qual Outcomes.* 2009;2(5):421-428.
3. American Heart Association. Post-Cardiac Arrest Care. https://eccguidelines.heart.org/index.php/circulation/cpr-ecc-guidelines-2/part-8-post-cardiac-arrest-care/. Accessed September 19, 2017.
4. Dickinson R, Franks NP. Bench-to-bedside review: molecular pharmacology and clinical use of inert gases in anesthesia and neuroprotection. *Crit Care.* 2010;14(4):229.
5. Laitio R, Hynninen M, Arola O, et al. Effect of inhaled xenon on cerebral white matter damage in comatose survivors of out-of-hospital cardiac arrest: a randomized clinical trial. *JAMA.* 2016;315(11):1120-1128.
6. Luo T, Wu WH, Chen BS. NMDA receptor signaling: death or survival? *Front Biol (Beijing).* 2011;6(6):468-476.
7. Data on file at NeuroproteXeon.

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Abbreviations: AHA, American Heart Association; ED, emergency department; FDA, Food and Drug Administration; ICU, intensive care unit; MRI, magnetic resonance imaging; NDA, New Drug Application; NMDA, *N*-methyl-D-aspartate; PMA, premarket approval (for device registration); ROSC, return of spontaneous circulation; SPA, special protocol assessment; TTM, targeted temperature management.

StrataGraft Skin Tissue Treatment Heals Severe Burns and Supports Advancement to Phase III Study

B. Lynn Allen-Hoffmann[1,4], Allen R. Comer[1], Mary A. Lokuta[1], Kelly Barbeau[1], Stuart Mohoney[1], Michael J. Schurr[2], Kevin N. Foster[3], Angela L. F. Gibson[4], Lee D. Faucher[4], Steven E. Wolf[5], Booker T. King[6], James H. Holmes IV[7]

[1]Stratatech – A Mallinckrodt Company, [2]University of Colorado at Denver and Mission Health Hospital Trauma Center, [3]The Arizona Burn Center, [4]University of Wisconsin-Madison, [5]University of Texas Southwestern, [6]US Army Institute for Surgical Research, [7]Wake Forest University

Abstract

Introduction

▸ StrataGraft skin tissue is a living human skin substitute that reproduces many structural and biological features of human skin and was designed to provide immediate wound coverage, barrier function, and sustained expression of wound healing factors to promote the healing of severe burns without autografting. By obviating the surgical harvest of donor sites, StrataGraft skin tissue treatment is anticipated to reduce the pain, scarring, and other donor site wound complications associated with autografting. We present the results of a recently completed clinical trial of StrataGraft skin tissue treatment of deep partial-thickness (DPT) thermal burns.

Methods

▸ An open-label, dose-escalation, multicenter trial examined the safety of StrataGraft skin tissue treatment and its efficacy in promoting the healing of DPT burns. Subjects with 3-49% total body surface area thermal burns were enrolled in three cohorts of 10 subjects each. An intrapatient comparator design was used to account for subject-specific comorbidities and healing trajectories. Two comparable excised areas of DPT burn per subject were identified and randomized to receive treatment with either a single application of StrataGraft skin tissue or an autograft comparator. Subjects received up to 220 cm² (cohort 1) or 440 cm² (cohort 2) of refrigerated StrataGraft tissue, while subjects in cohort 3 received up to 440 cm² of cryopreserved StrataGraft tissue. Prospective donor sites were identified for StrataGraft treatment sites in the event autografting was required. Subjects were monitored for up to one year. Primary clinical endpoints were the percent of the treatment areas autografted by day 28 and wound closure at three months. Other assessments included cosmesis, donor site pain, antibody responses, adverse event monitoring, and presence of allogeneic DNA from StrataGraft skin tissue at three months.

Results

▸ Study outcomes exceeded expectations. No DPT burns treated with StrataGraft skin tissue required autografting by day 28. At three months, StrataGraft skin tissue treatment sites were completely closed in 27 of 28 per-protocol subjects (96%). In addition, all StrataGraft-treated areas evaluated at six and/or 12 months remained closed. No safety signal related to StrataGraft skin tissue treatment was seen. StrataGraft skin tissue DNA was not detected in any subjects at three months. Results from cryopreserved StrataGraft skin tissue were comparable to those of the refrigerated tissue. Trial results were extremely positive and support progression to a phase III registration study.

Conclusions

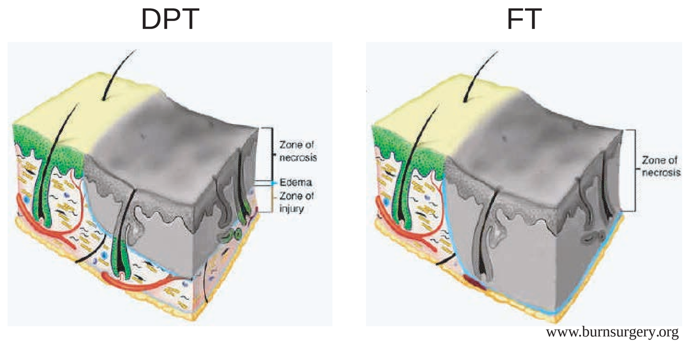
▸ Trial results demonstrated that a single application of StrataGraft skin tissue to DPT thermal burns promoted wound closure and eliminated the need for donor site harvest. Closure occurred by autologous tissue regeneration rather than implantation. Comparable clinical performance of refrigerated and cryopreserved StrataGraft skin tissue will allow an increased shelf life for the tissue. Together, these safety and efficacy data suggest that StrataGraft skin tissue will provide an efficacious and readily available alternative to autograft harvest and transplantation while providing substantial improvement in the medical management of patients with DPT burns. Results have been reviewed by the FDA, and a phase III registration study is being developed, with initiation of patient enrollment projected for the first half of 2017.

Objectives

Clinical Need

▸ DPT burns generally take more than 3 weeks to heal, and the preferred medical management is the same as that for full-thickness (FT) burns in that they are excised to viable tissue and closed with split-thickness autologous skin grafts. However, surgical excision of autologous skin grafts generates painful donor site wounds that are susceptible to infection and scarring. In cases of large TBSA burns, there is often insufficient uninjured skin remaining to cover both the FT and DPT components, requiring sequential harvesting of limited donor sites. The ability to achieve closure of DPT burns without the need for autografting would significantly improve the treatment and recovery of individuals with severe burns.

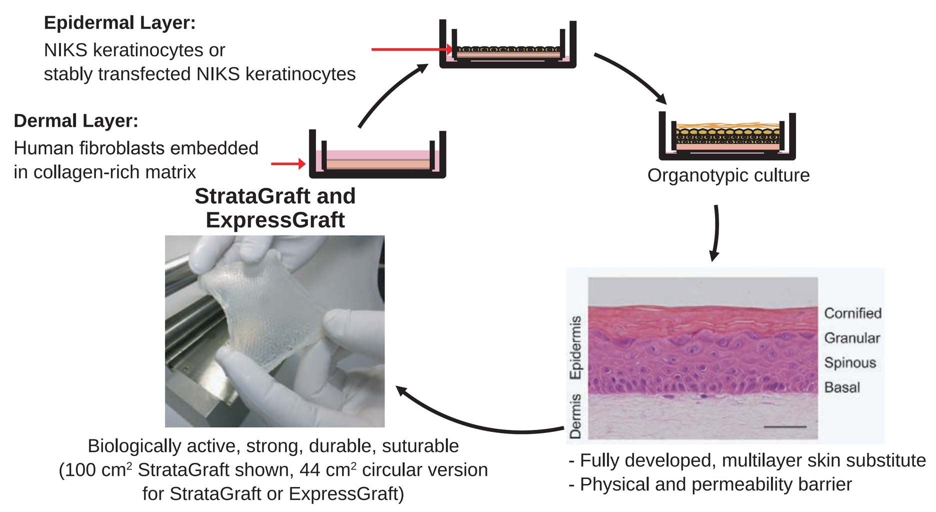
DPT FT


Zone of necrosis
Edema
Zone of injury
Zone of necrosis
www.burnsurgery.org

Study Objectives

▸ Evaluate the safety and efficacy of StrataGraft tissue as an alternative to autografting of deep partial-thickness burns

Methods and Trial Design


Epidermal Layer:
NIKS keratinocytes or stably transfected NIKS keratinocytes
Dermal Layer:
Human fibroblasts embedded in collagen-rich matrix
StrataGraft and ExpressGraft
Organotypic culture
Epidermis
Dermis
Cornified
Granular
Spinous
Basal
Biologically active, strong, durable, suturable (100 cm² StrataGraft shown, 44 cm² circular version for StrataGraft or ExpressGraft)
- Fully developed, multilayer skin substitute
- Physical and permeability barrier

StrataGraft skin tissue is prepared by seeding NIKS human keratinocytes on a dermal equivalent containing human dermal fibroblasts embedded in a collagen-rich matrix. Epidermal stratification and differentiation is achieved by air-exposed organotypic culture. The resulting StrataGraft tissue is a strong, suturable, meshable skin substitute that can be handled and applied to excised wounds using standard procedures as for split-thickness skin grafts.

STRATA2011

- Study Design
 - Cohort 1: 10 subjects treated with up to 220 cm² of refrigerated StrataGraft tissue and a matched autograft control site
 - Cohort 2: 5-10 subjects treated with up to 440 cm² of refrigerated StrataGraft tissue and a matched autograft control site
 - Cohort 3: 5-10 subjects treated with up to 440 cm² of cryopreserved StrataGraft tissue and a matched autograft control site
 - Interim safety assessments by DSMB prior to progression to enrollment in a new cohort
- Primary Clinical Endpoints
 1. Percent area of the StrataGraft treatment site requiring autografting by day 28
 2. Wound closure at 3 months
- Secondary Efficacy Assessments
 - Wound closure, percentage of subjects who require autografting of the StrataGraft treatment site, pain of donor sites, cosmesis of treatment sites and donor sites to 12 months
- Secondary Safety Assessments
 - Adverse events, vital signs, hematologic parameters, incidence of wound infection, immunologic responses, and persistence of allogeneic DNA

Inclusion Criteria

Patient-Specific Criteria	Wound-Specific Criteria
Men and women aged 18-65 years, inclusive	Complex skin defects of 3-49% TBSA requiring excision and autografting
Written informed consent	Total burn may consist of more than one wound area
Sufficient healthy skin identified and designated as a donor site in the event that the StrataGraft treatment site requires autografting	Deep partial-thickness thermal burn(s) with total area of 88 to 880 cm² requiring excision and autografting
	First excision and grafting of treatment sites

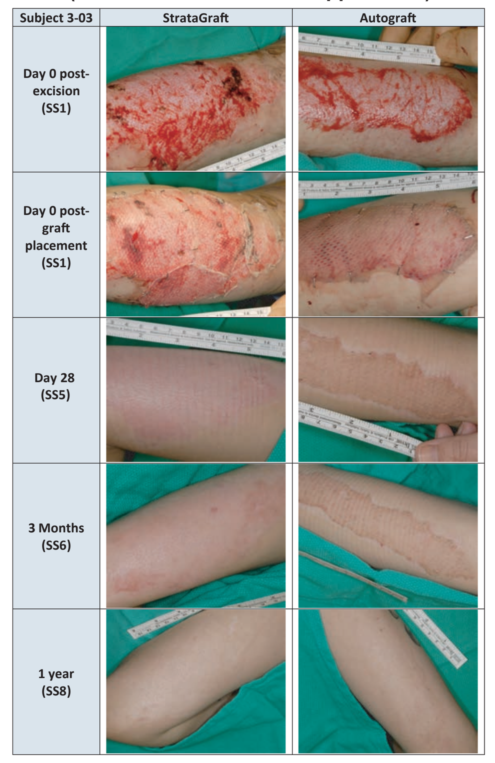
Exclusion Criteria

Patient-Specific Criteria	Wound-Specific Criteria
Pregnant women and prisoners	Full-thickness burns will be excluded as treatment sites
Patients receiving systemic immunosuppressive therapy	Chronic wounds will be excluded as treatment sites
Patients with a known history of malignancy	The face, head, neck, hands, feet, buttocks, and areas over joints will be excluded as treatment sites
Preadmission insulin-dependent diabetic patients	Treatment sites adjacent to unexcised eschar (Target no less than 5 cm from treatment site to unexcised eschar)
Patients with concurrent conditions that in the opinion of the investigator may compromise patient safety or study objectives	Clinical suspicion of burn wound infection at the anticipated treatment site
Expected survival of less than three months	
Participation in the treatment group of an interventional study within preceding 90 days prior to enrollment	

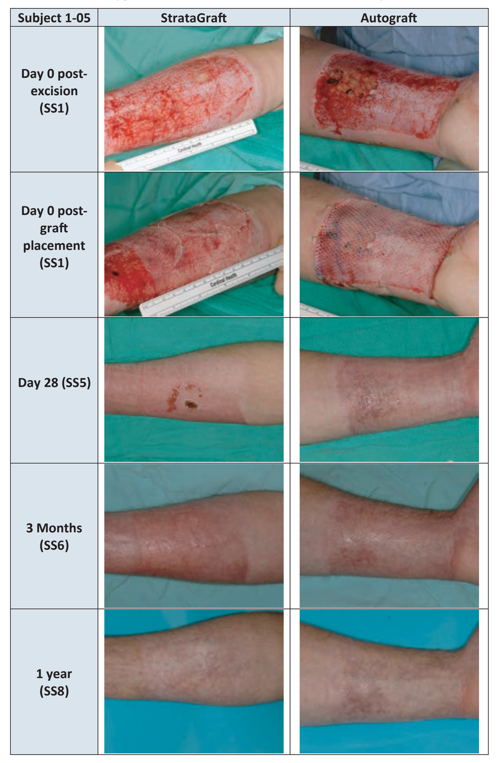
Results

▸ Images below are from study subjects enrolled in the STRATA2011 clinical trial. Two DPT burns of comparable depth on each subject were randomized and received autograft or StrataGraft skin tissue. Subjects in the first two cohorts were treated with StrataGraft skin tissue that had been stored at refrigerated temperatures, while subjects in the third cohort were treated with cryopreserved StrataGraft that was thawed in the operating room just prior to placement. Cryopreservation allows for a significantly longer shelf life than refrigerated tissue. Shown below are two subjects that received refrigerated StrataGraft and two subjects that received cryopreserved StrataGraft skin tissue. Photo compilations include StrataGraft skin tissue–treated sites and autografted sites from the same subject after surgical excision and after graft placement on day 0 followed by the indicated post-treatment times.

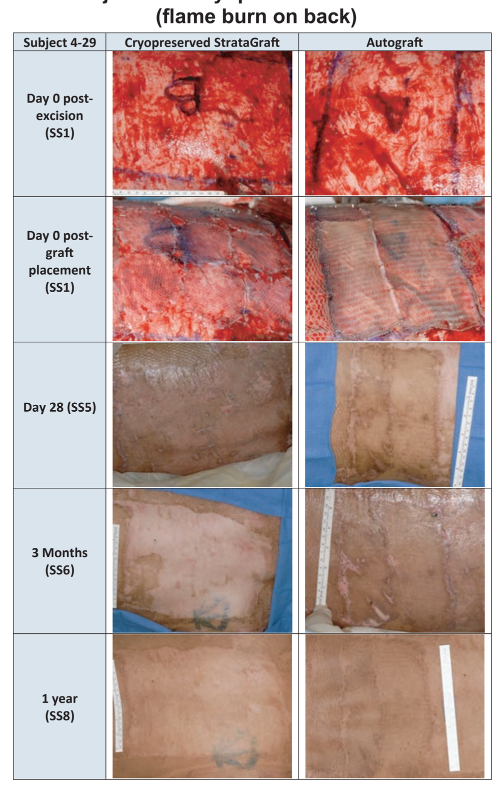
Subject 3-03 Refrigerated StrataGraft (flame burn back of both upper arms)


Subject 3-03
StrataGraft
Autograft
Day 0 post-excision (SS1)
Day 0 post-graft placement (SS1)
Day 28 (SS5)
3 Months (SS6)
1 year (SS8)

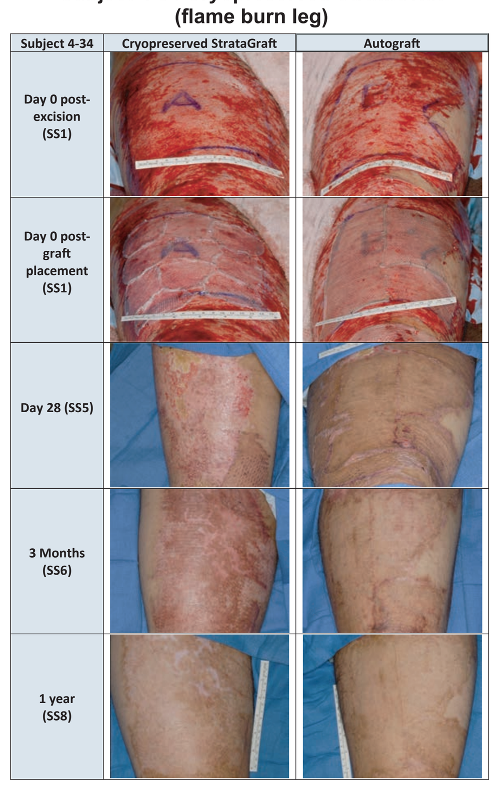
Subject 1-05 Refrigerated StrataGraft (grease burn both forearms)


Subject 1-05
StrataGraft
Autograft
Day 0 post-excision (SS1)
Day 0 post-graft placement (SS1)
Day 28 (SS5)
3 Months (SS6)
1 year (SS8)

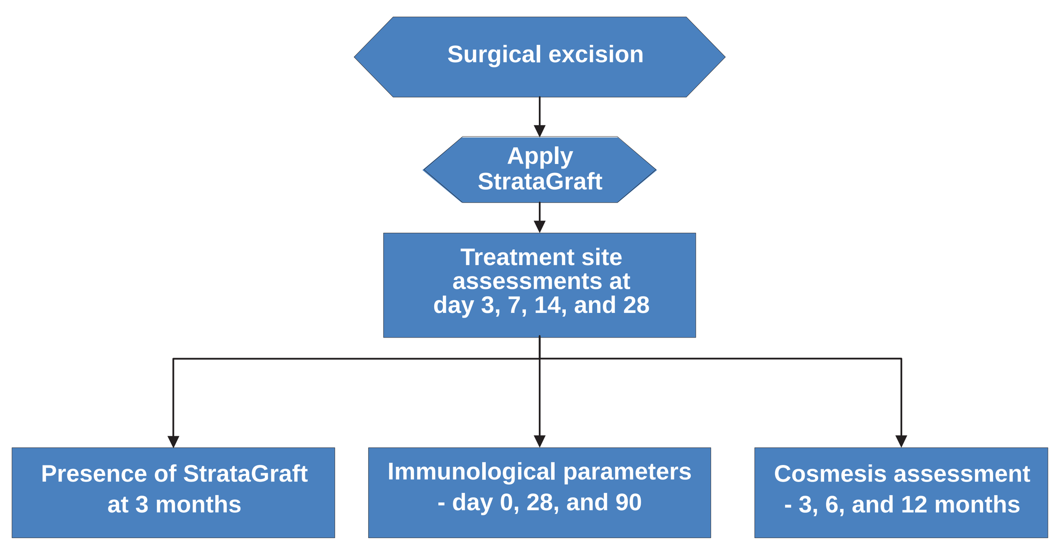
Subject 4-29 Cryopreserved StrataGraft (flame burn on back)


Subject 4-29
Cryopreserved StrataGraft
Autograft
Day 0 post-excision (SS1)
Day 0 post-graft placement (SS1)
Day 28 (SS5)
3 Months (SS6)
1 year (SS8)

Subject 4-34 Cryopreserved StrataGraft (flame burn leg)

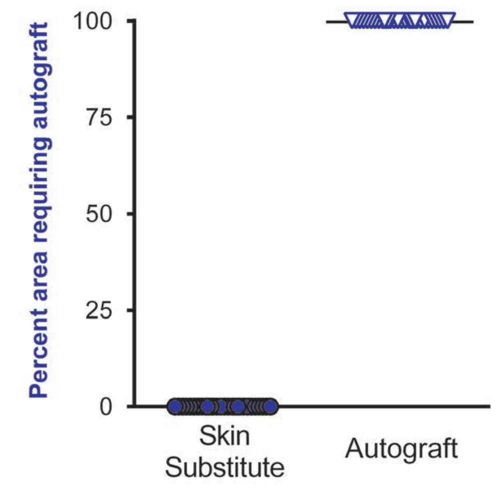

Subject 4-34
Cryopreserved StrataGraft
Autograft
Day 0 post-excision (SS1)
Day 0 post-graft placement (SS1)
Day 28 (SS5)
3 Months (SS6)
1 year (SS8)

Trial Design Flow Chart

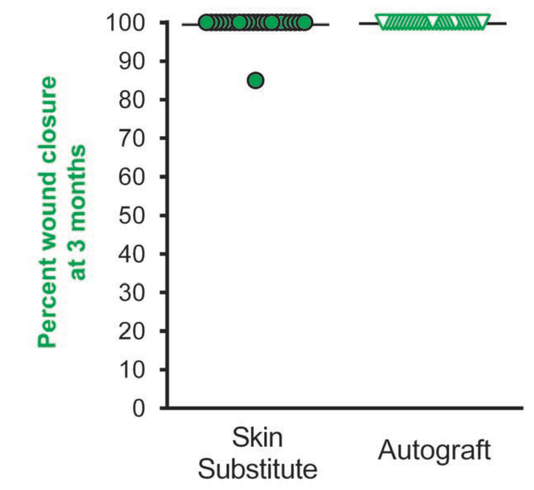

Surgical excision
Apply StrataGraft
Treatment site assessments at day 3, 7, 14, and 28
Presence of StrataGraft at 3 months
Immunological parameters - day 0, 28, and 90
Cosmesis assessment - 3, 6, and 12 months

Primary Clinical Endpoints

Primary Efficacy Endpoint
Percent of the skin substitute treatment site requiring autograft by day 28
Per-protocol subjects, n=29


Percent area requiring autograft
100
75
50
25
0
Skin Substitute
Autograft

Primary Safety Endpoint
Percent wound closure at 3 months
Per-protocol subjects, n=28


Percent wound closure at 3 months
100
90
80
70
60
50
40
30
20
10
0
Skin Substitute
Autograft

Secondary Efficacy Assessments

Secondary Efficacy Endpoint
Donor site pain

FACES Pain Rating Scale Data	Day 3 (N=28)	Day 7 (N=28)	Day 14 (N=28)	Day 28 (N=28)
Skin subsitute donor site Mean (SD)	1.0 (1.6)*	1.1 (1.7)*	0.5 (1.2)*	0.3 (1.1)*
Autograft donor site Mean (SD)	2.7 (1.6)	2.9 (1.6)	1.9 (1.4)	0.8 (1.3)

Indicates statistical significance between skin substitute and autograft donor sites based on Student *t* test (p<0.05).
Data not available for all subjects due to intubation/sedation, inclement weather, etc., on pain assessment days.

Conclusions

- No safety signal has been seen
- No wounds treated with StrataGraft tissue have required autografting by day 28
- No evidence of residual DNA from StrataGraft skin tissue has been detected at 3 months
- All but one of the per-protocol subjects were healed by 3 months
- Subjects had less pain at the StrataGraft donor site

Potential Benefits of StrataGraft Skin Tissue

- Promotes DPT wound healing without autografting
- Minimizes or eliminates donor sites
- Reduces pain
- Reduces scarring

Acknowledgments

Development and clinical evaluation of StrataGraft skin tissue funded in part by grants from the National Institute of Arthritis and Musculoskeletal and Skin Disease (NIAMS) and the Armed Forces Institute for Regenerative Medicine (AFIRM)

References

1. Allen-Hoffmann et al., *J of Inv Derm*, 2000;114(3):444-455
2. Schurr et al., *J of Trauma*, 2009;66(3):866-874
3. Centanni et al., *Ann Surg*, 2011;153:1-12

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A Phase III Open-label, Controlled, Randomized, Multicenter Study Evaluating the Efficacy and Safety of StrataGraft Skin Tissue in Promoting Autologous Skin Tissue Regeneration of Complex Skin Defects Due to Thermal Burns that Contain Intact Dermal Elements and for which Excision and Autografts are Clinically Indicated

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Background

- Every year in the United States, 45,000 patients experience burns that require hospitalization, and ~10-20% require surgical intervention
- Autografting, the standard of care for serious burns, is the surgical harvest of a sheet of healthy skin from an uninjured site on the patient and transplant to the wound after excision. It results in an iatrogenic donor site wound that requires medical management of pain, possibility of infection, scarring etc.
- In the STRATA2011 clinical study, 27 of 28 per-protocol subjects had complete wound closure of treatment sites at 3 months, and no subjects required autografting by day 28
- No evidence of DNA from cells of StrataGraft skin tissue was seen after 3 months in all tested patients
- No safety signal associated with StrataGraft skin tissue has been seen

Purpose

- The purpose of this study is to provide clinical evidence to support a BLA for the use of StrataGraft skin tissue in complex skin defects due to thermal burns that contain intact dermal elements.

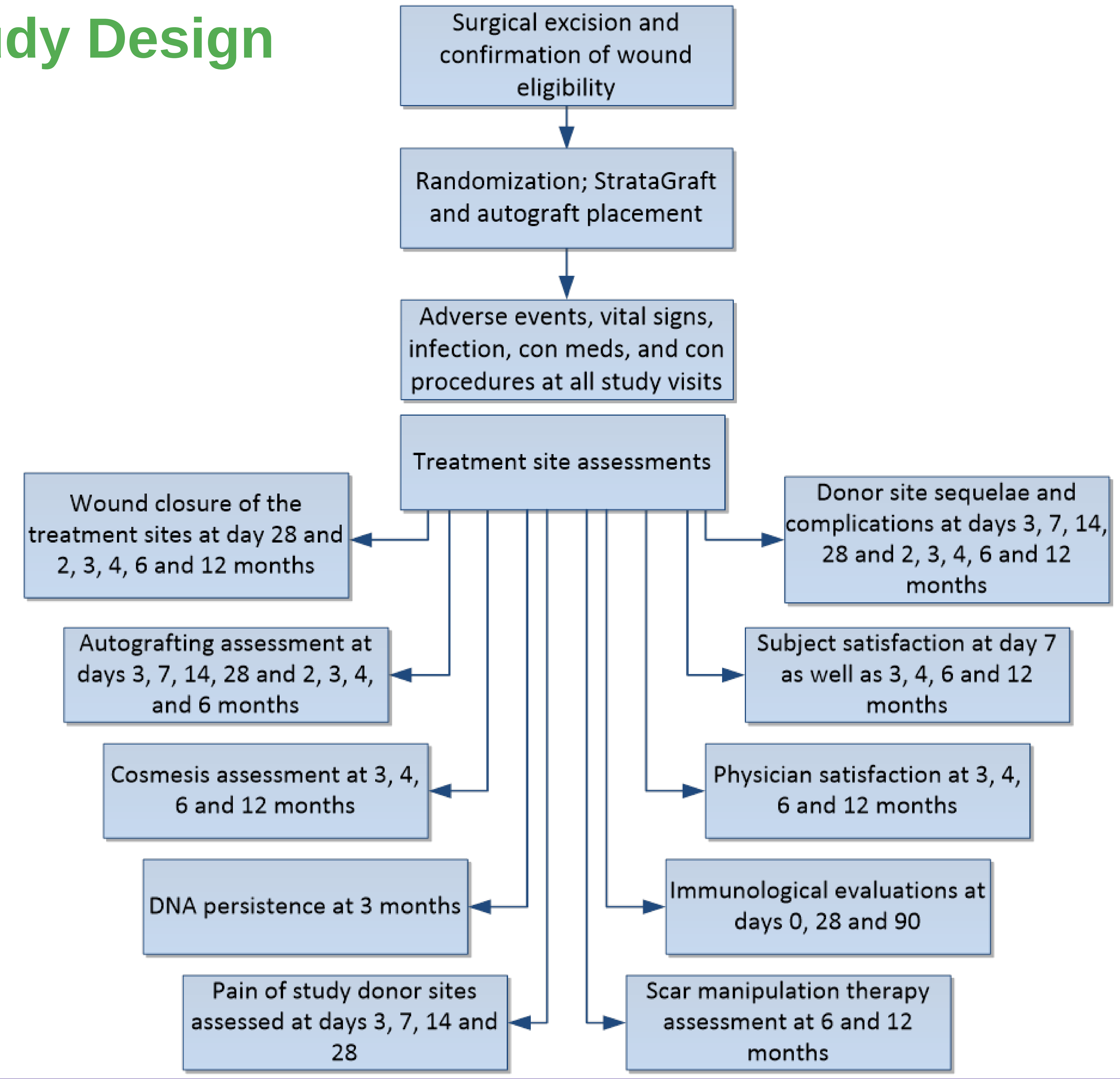
Objective

- The primary objective of this study is to assess the efficacy and safety of a single application of StrataGraft skin tissue in the treatment of complex skin defects due to thermal burns containing intact dermal elements and for which surgical excision and autografting are clinically indicated.
- Targeted enrollment is 70 subjects

Study Population

- ***Key Inclusion Criteria***
 - Men and women aged ≥18 years
 - Complex skin defects 3-49% TBSA requiring excision and autografting
 - Total skin defect may consist of more than one wound area
 - Thermal burns on torso, arms, legs
- ***Key Exclusion Criteria***
 - Pregnant women
 - Prisoners
 - Subjects receiving systemic immunosuppressive therapy
 - Known history of malignancy
 - Concurrent conditions that may compromise safety or study objectives
 - Preadmission insulin-dependent diabetic subjects
 - Full-thickness burns, chronic wounds

Study Design



Surgical excision and confirmation of wound eligibility
Randomization; StrataGraft and autograft placement
Adverse events, vital signs, infection, con meds, and con procedures at all study visits
Treatment site assessments
Wound closure of the treatment sites at day 28 and 2, 3, 4, 6 and 12 months
Autografting assessment at days 3, 7, 14, 28 and 2, 3, 4, and 6 months
Cosmesis assessment at 3, 4, 6 and 12 months
DNA persistence at 3 months
Pain of study donor sites assessed at days 3, 7, 14 and 28
Donor site sequelae and complications at days 3, 7, 14, 28 and 2, 3, 4, 6 and 12 months
Subject satisfaction at day 7 as well as 3, 4, 6 and 12 months
Physician satisfaction at 3, 4, 6 and 12 months
Immunological evaluations at days 0, 28 and 90
Scar manipulation therapy assessment at 6 and 12 months

Study Endpoints

Co-Primary Endpoint

- The difference in the percent area of the StrataGraft treatment site and control autograft treatment site that is autografted by 3 months
- The proportion of subjects achieving durable wound closure of the StrataGraft treatment site at 3 months without autograft placement

Ranked Secondary Endpoints

- Difference between the StrataGraft and autograft donor sites in the average pain intensity through day 14 based on the FPRS
- Difference between the StrataGraft and autograft donor site cosmesis at 3 months based on observer Patient and Observer Scar Assessment (POSAS) total score
- Difference between the StrataGraft and autograft treatment site cosmesis at 12 months based on observer POSAS total score

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An Open-Label, Controlled, Randomized, Multicenter, Dose Escalation Study Evaluating The Safety, Tolerability, And Efficacy Of Single or Multiple Applications of StrataGraft® Skin Tissue as an Alternative To Autografting Full-Thickness Complex Skin Defects

Mallinckrodt Pharmaceuticals

Background

- Every year, 45,000 patients in the United States experience burns that require hospitalization, and ~10-20% require surgical intervention
- The current standard of care for severe burns and other complex skin defects is autografting
- Autografting is the surgical harvest of a sheet of healthy skin from an uninjured site on the patient and transplant to the wound after excision. It results in an iatrogenic donor site wound that requires medical management of pain, possibility of infection, scarring etc.
- The STRATA2001 study in full-thickness complex skin defects showed that StrataGraft skin tissue remained intact and viable throughout the 7 day placement period
- The STRATA2011 study in deep partial-thickness burns showed that StrataGraft skin tissue closed wounds and reduced autografting
- No safety signal associated with StrataGraft skin tissue has been detected in previous clinical experience

Purpose

- The purpose of this study is to collect clinical evidence regarding the use of single of multiple applications of StrataGraft skin tissue in full-thickness complex skin defects as an alternative to autografting.

Objective

- The primary objective of this study is to assess the safety, tolerability, and efficacy of increasing dosages of a single or multiple (up to a total of 3) applications of StrataGraft skin tissue in comparison to autograft in the treatment of full-thickness complex skin defects resulting from acute traumatic skin loss (*e.g.*, thermal burns or degloving injuries) requiring surgical excision and autografting

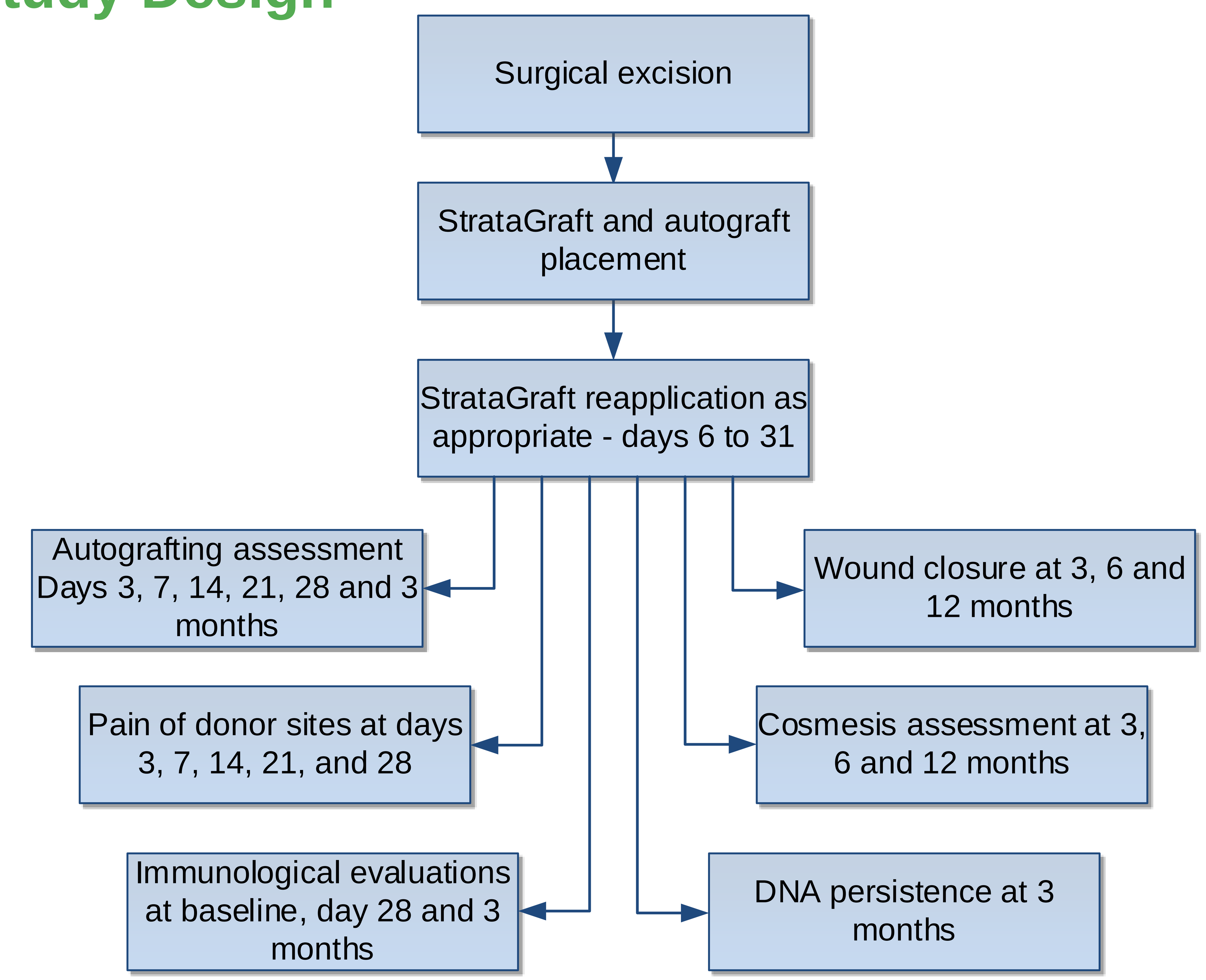
Cohort 1: 10 subjects, initial dosage up to 200 cm^2 of StrataGraft skin tissue and autograft
Cohort 2: 10 subjects, initial dosage up to 400 cm^2 each of StrataGraft skin tissue and autograft

Study Population

Key Inclusion Criteria
- Men and women aged 18-65 years
- Complex skin defects of up to 49% TBSA requiring excision and autografting
- Study treatment sites are on the torso and limbs, may be up to 200 cm^2 in Cohort 1 and 400 cm^2 in Cohort 2

Key Exclusion Criteria
- Pregnant women and prisoners
- Subjects receiving systemic immunosuppressive therapy
- Known history of malignancy
- Concurrent conditions that may compromise safety or study objectives
- Chronic wounds
- Chemical and electrical burns

Study Design



Surgical excision
StrataGraft and autograft placement
StrataGraft reapplication as appropriate - days 6 to 31
Autografting assessment Days 3, 7, 14, 21, 28 and 3 months
Pain of donor sites at days 3, 7, 14, 21, and 28
Immunological evaluations at baseline, day 28 and 3 months
Wound closure at 3, 6 and 12 months
Cosmesis assessment at 3, 6 and 12 months
DNA persistence at 3 months

Study Endpoints

Primary Endpoint

- Percent area of StrataGraft treatment site requiring autografting by three months
- Wound closure of the StrataGraft treatment site at three months

Key Secondary Endpoints

- Percent of subjects requiring autografting of StrataGraft treatment site by 3 months
- Incidence of complete wound closure of the treatment sites at 3, 6, and 12 months
- Percent wound closure at 3, 6, and 12 months
- Cosmesis of treatment and donor sites at 3, 6, and 12 months
- Pain at donor sites through day 28
- Immunology assessments at baseline, day 28, and 3 months
- Persistence of allogeneic DNA at 3 months

INVESTOR DAY 2017 OCTOBER 4 NEW YORK, NY

Preclinical Development and Evaluation of a Human Skin Substitute Expressing Elevated Levels of Cathelicidin

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Abstract

Introduction

▸ The increasing prevalence of chronic non-healing ulcers poses significant clinical challenges to wound care, often requiring the use of potent antibiotics with undesirable side effects on wound healing. However, no current product addresses both infection and closure of chronic non-healing ulcers. We describe development of a skin substitute capitalizing on one of the skin's native antimicrobial defense mechanisms. Microbial infection triggers keratinocytes to increase production of potent host defense peptides (HDPs) such as cathelicidin, a multifunctional HDP that possesses antimicrobial activity and stimulates vascularization and reepithelialization. Though abundant in acute injuries, expression of cathelicidin is reduced in chronic cutaneous wounds. ExpressGraft-C9T1 skin tissue was engineered as a living skin substitute tissue with enhanced expression of human cathelicidin to promote the healing of chronic wounds. We present preclinical evaluation of the tissue and the strategy for clinical assessment of its safety in the treatment of diabetic foot ulcers (DFUs).

Methods

▸ A non-viral plasmid DNA fragment encoding human cathelicidin was stably introduced into a well-characterized, pathogen-free, human keratinocyte progenitor cell line previously used in the development of a skin substitute showing positive clinical results in wound healing. The resulting clonal, stably modified keratinocyte line was used to produce the epidermal compartment of a living, bilayered, full-thickness human skin substitute. The impact of cryopreserved ExpressGraft-C9T1 skin tissue on growth of wound-associated biofilms was evaluated using a rodent full-thickness excisional wound model. Wounds were inoculated with disaggregated biofilm from an antibiotic-resistant, clinical isolate of *Acinetobacter baumannii* and grafted with ExpressGraft-C9T1 skin tissue or unmodified skin tissue. Grafted tissues and wound beds were harvested for bacterial quantification 5 days after inoculation.

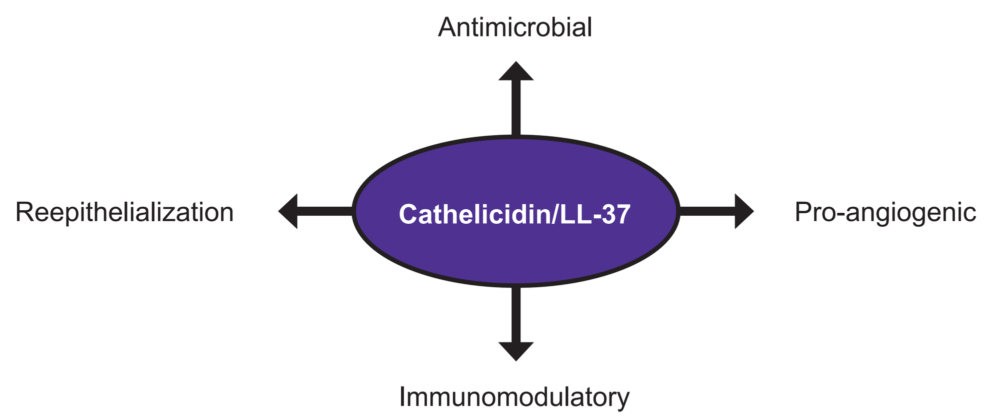
Results

▸ ExpressGraft-C9T1 skin tissue demonstrated elevated cathelicidin expression, shared structural and functional elements with human skin, and was amenable to cryopreservation. Application of ExpressGraft-C9T1 skin tissue reduced the number of viable *A. baumannii* by greater than two logs compared to control ($p<0.05$), resulting in a microbial burden below the threshold of clinical infection. Based on these promising results, master and working cell banks of the cathelicidin-expressing keratinocytes were prepared and thoroughly characterized, and an investigational new drug (IND) application was submitted to the FDA to enable a phase I clinical study evaluating cryopreserved ExpressGraft-C9T1 skin tissue in the treatment of DFUs. In this multicenter study, each subject will receive one application of ExpressGraft-C9T1 skin tissue on a DFU of 1-10 cm^2. Subjects will be followed for one year. The safety and tolerability of ExpressGraft-C9T1 skin tissue treatment is the primary study endpoint. Assessments include vital signs, safety laboratory values, monitoring for treatment-emergent adverse events and autoantibody development, rate of ulcer recurrence, condition of study ulcer, wound closure, percentage change in wound size, and subject satisfaction.

Conclusions

▸ A cryopreserved human skin substitute expressing elevated levels of human cathelicidin suppressed the growth of an antibiotic-resistant clinical isolate of *A. baumannii*. ExpressGraft-C9T1 skin tissue is anticipated to provide immediate wound coverage and sustained release of cathelicidin and other wound healing factors, serving as a readily available skin substitute tissue for the treatment of DFUs.

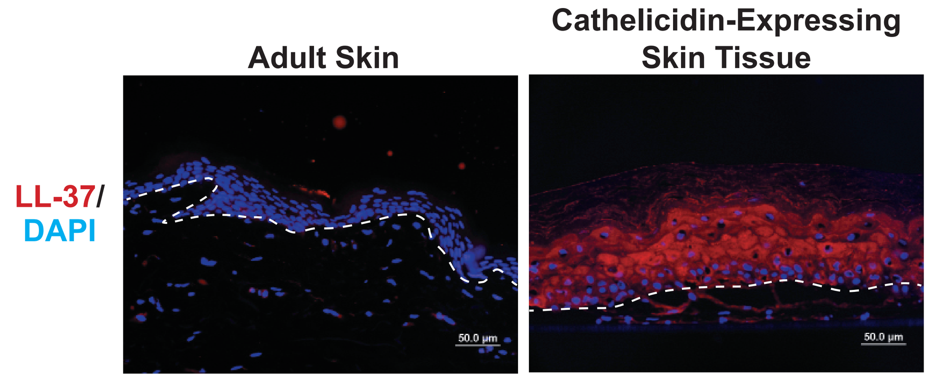
Cathelicidin Function


Antimicrobial
Reepithelialization
Cathelicidin/LL-37
Pro-angiogenic
Immunomodulatory

▸ Cathelicidin is a multifunctional host defense peptide exhibiting broad-spectrum antimicrobial activity against gram-positive and gram-negative bacteria, yeast, fungi, and some viruses. In addition to its antimicrobial activities, cathelicidin is a strong mediator of wound healing, promoting both vascularization and reepithelialization while acting as a link between the innate and adaptive immune systems through diverse biological activities such as chemotaxis, histamine release, and cytokine production. The pleiotropic activities of cathelicidin, which directly address many of the issues associated with burn wounds, make it an attractive choice for clinical program development.

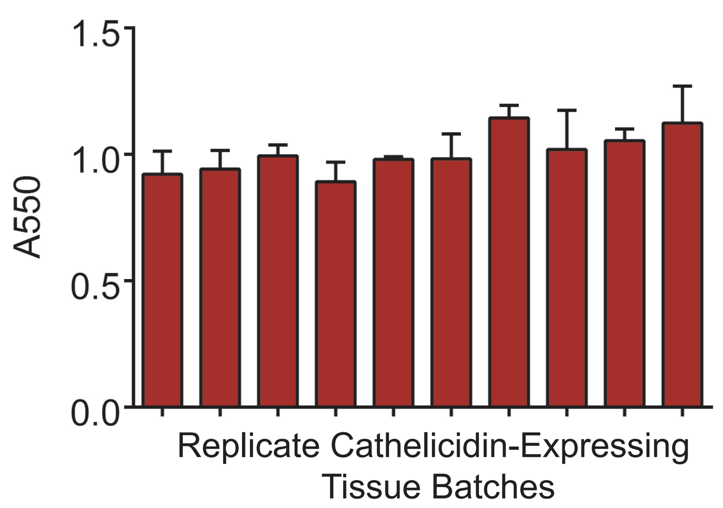
Results

1. Cathelicidin-Expressing Tissue Possesses High Levels of hCAP-18/LL-37 Protein


Adult Skin
Cathelicidin-Expressing Skin Tissue
LL-37/
DAPI
50.0 µm
50.0 µm

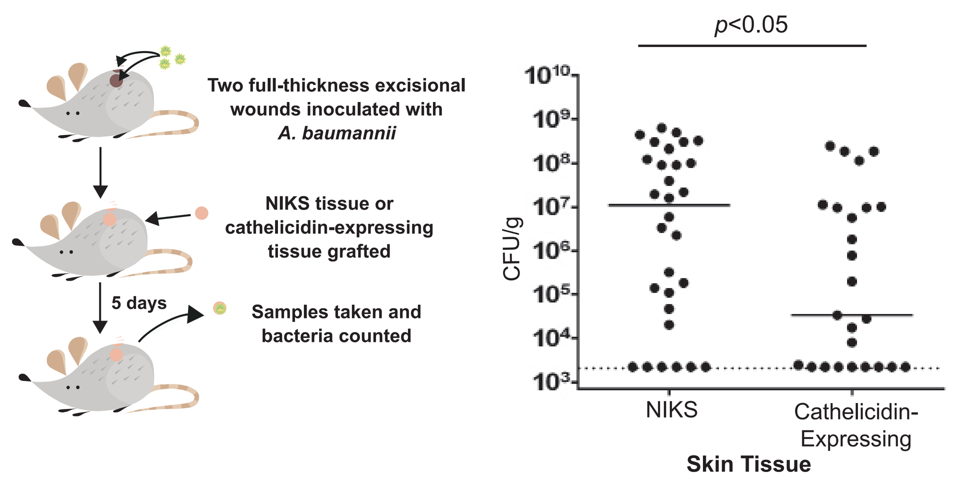
Indirect immunofluorescence was employed to assess the distribution of cathelicidin within the skin tissue. An antibody detecting the mature form of cathelicidin, LL-37, was used on tissue sections of both normal adult skin and cathelicidin-expressing skin. The cryopreserved cathelicidin-expressing tissue sample was harvested one day after thaw. Sections were exposed to DAPI to facilitate nuclei localization (blue). The dashed white line denotes the dermal-epidermal junction of the skin tissue. Robust expression of cathelicidin/LL-37 is evident in the epidermal compartment of the cathelicidin-expressing tissue. Cathelicidin/LL-37 reactivity is also present in the dermal compartment, indicating the cathelicidin/LL-37 can diffuse throughout the tissue. Exposure for the adult tissue was 100 msec. Exposure for the cathelicidin-expressing skin tissue was 10 msec. Bar = 50 mm.

2. Cathelicidin-Expressing Tissue Exhibits Consistent Viability


1.5
1.0
0.5
0.0
A550
Replicate Cathelicidin-Expressing Tissue Batches

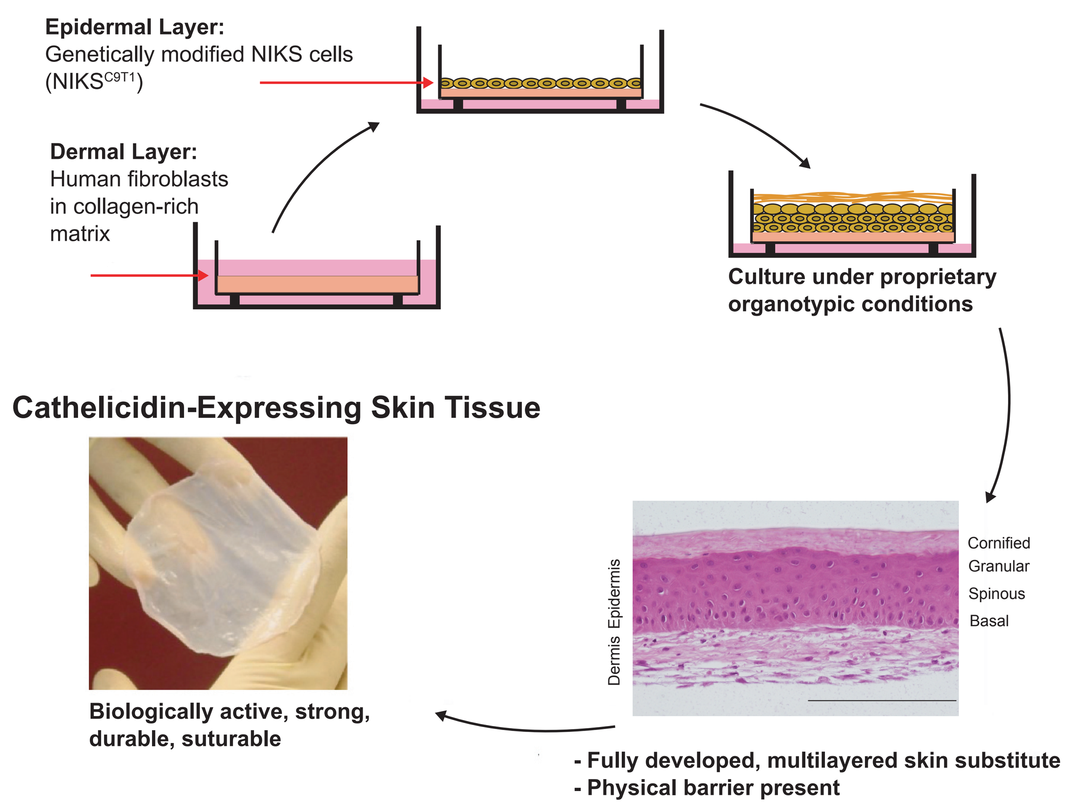
Viability of cryopreserved cathelicidin-expressing tissue was evaluated one day after thawing using an MTT assay. Multiple biopsy samples taken from representative tissues in each batch were incubated with MTT reagent (Sigma, St. Louis, MO), and the extent of MTT reduction was subsequently quantified by measuring absorbance of the samples at 550 nm. Data represent mean +/- SD.

3. Cathelicidin-Expressing Tissue Decreases *A. baumannii* in an *In Vivo* Infected Full-Thickness Excisional Wound Model


Two full-thickness excisional wounds inoculated with A. baumannii
NIKS tissue or cathelicidin-expressing tissue grafted
5 days
Samples taken and bacteria counted
p<0.05
CFU/g
10^10
10^9
10^8
10^7
10^6
10^5
10^4
10^3
NIKS
Cathelicidin-Expressing
Skin Tissue

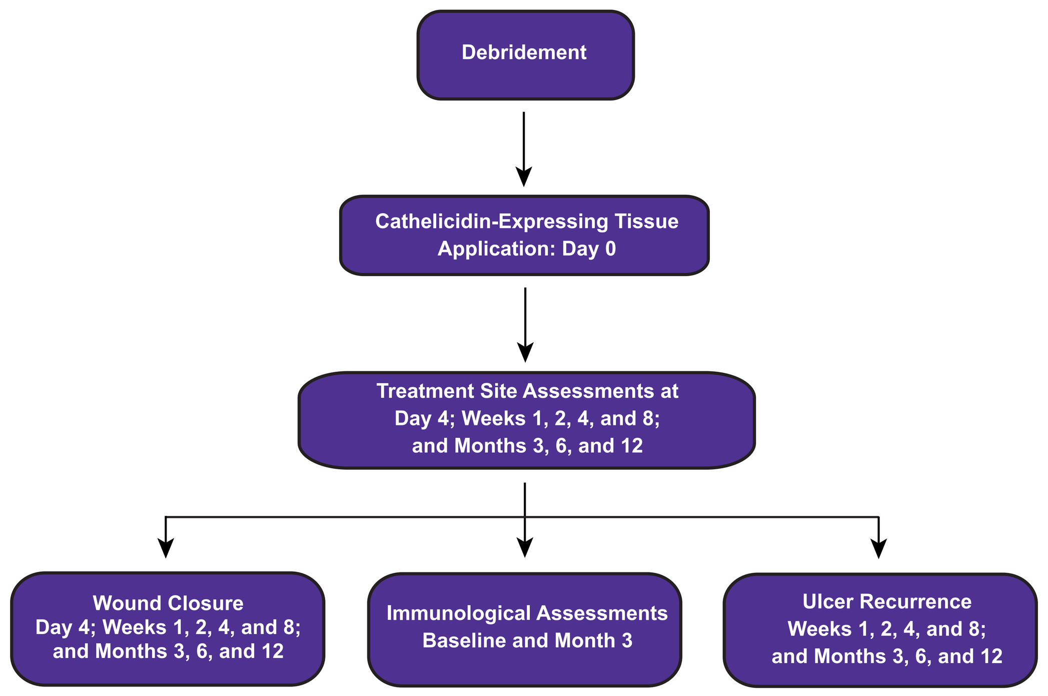
Duplicate experiments (shown combined) were performed in 9-week-old C57BL/6 mice. Two 10-mm full-thickness wounds were created on the backs of mice and splinted using silicone O-rings. The wounds were inoculated with 165 colony-forming units (CFUs) (Experiment 1) and 153 CFUs (Experiment 2) of a disaggregated biofilm of an antibiotic-resistant clinical isolate of *A. baumannii*. Both wounds were then grafted with either NIKS tissue or cathelicidin-expressing tissue. Animals were sacrificed 5 days after inoculation. Data are expressed as the number of CFUs per gram of tissue harvested, each point representing the CFU/g from a single graft / wound bed. Data points at the dotted line represent wounds in which no CFUs were observed. These data points were placed at the level of detection (LOD) for the experiment (2235 CFU/g). NIKS tissue, n=30; cathelicidin-expressing tissue, n=25. $p<0.05$ by Mann Whitney test. Horizontal bars indicate the median.

Tissue Production Schematic


Epidermal Layer:
Genetically modified NIKS cells (NIKS^C9T1)
Dermal Layer:
Human fibroblasts in collagen-rich matrix
Culture under proprietary organotypic conditions
Cathelicidin-Expressing Skin Tissue
Cornified
Granular
Spinous
Basal
Dermis Epidermis
Biologically active, strong, durable, suturable
- Fully developed, multilayered skin substitute
- Physical barrier present

NIKS keratinocytes genetically modified to produce cathelicidin ($NIKS^{C9T1}$) terminally differentiate to generate a fully stratified, multilayered human skin tissue. Analysis of tissue morphology (hematoxylin and eosin staining) performed on cryopreserved cathelicidin-expressing tissue indicates skin tissue architecture possessing distinct basal, spinous, granular, and cornified layers characteristic of stratified squamous epithelia. Cryopreservation will enable long-term storage and availability of the tissue for commercial use.

Clinical Trial Design


Debridement
Cathelicidin-Expressing Tissue Application: Day 0
Treatment Site Assessments at Day 4; Weeks 1, 2, 4, and 8; and Months 3, 6, and 12
Wound Closure Day 4; Weeks 1, 2, 4, and 8; and Months 3, 6, and 12
Immunological Assessments Baseline and Month 3
Ulcer Recurrence Weeks 1, 2, 4, and 8; and Months 3, 6, and 12

Conclusions

- ▸ ExpressGraft-C9T1 tissue has been genetically engineered to produce high levels of cathelicidin (hCAP-18/LL-37)
- ▸ ExpressGraft-C9T1 tissue is a fully stratified human skin tissue that retains viability and barrier function after cryopreservation and thawing
- ▸ ExpressGraft-C9T1 tissue displays *in vivo* efficacy against an antibiotic-resistant clinical isolate of the pathogen *A. baumannii*
- ▸ An IND for this product was submitted in early 2015
- ▸ A first-in-human safety study of ExpressGraft-C9T1 tissue is scheduled to start in the next 6 months

Acknowledgments

Development and future clinical evaluation of cathelicidin-expressing tissue funded in part by grants from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Allergy and Infectious Diseases (NIAID), and the Defense Medical Research and Development Program (DMRDP)

References

1. Allen-Hoffmann et al., *J of Inv Derm*, 2000;114(3):444-455.
2. Schurr et al., *J of Trauma*, 2009;66(3):866-874.
3. Centanni et al., *Ann Surg*, 2011;253(4):672-683.
4. Thomas-Virnig et al., *Mol Ther*, 2009;17(3):562-569.

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NIH NIAID

NIDDK
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

DEFENSE MEDICAL RESEARCH AND DEVELOPMENT

Investor Day • October 4, 2017 • New York, NY

A Multicenter, Randomized, Placebo-Controlled, Double-Blind Study to Confirm Efficacy and Safety of Terlipressin in Subjects With Hepatorenal Syndrome Type 1 (CONFIRM Study)

Mallinckrodt Pharmaceuticals

Background

- HRS-1 is a serious, rapidly progressing yet potentially reversible renal failure in patients with chronic liver disease
- HRS Type 1 is a devastating disease impacting ~20,000 patients annually in US
- Mortality in HRS Type 1 is high, with only half of patients surviving past first 2 weeks
- There is no US approved pharmacological therapy for treatment of HRS Type 1
- Terlipressin is the most widely studied and clinically accepted pharmacological therapy for patients with HRS-1
- Terlipressin has been approved since 1980s and is currently available in > 60 countries for treatments of number of critical care indications

Purpose

- To confirm the efficacy and safety of intravenous Terlipressin versus placebo in the treatment of adult subjects with Hepatorenal syndrome (HRS) Type 1 receiving standard of care albumin therapy

Objective

- The primary objective of this study is to assess the difference in HRS Reversal for subjects with Terlipressin versus placebo

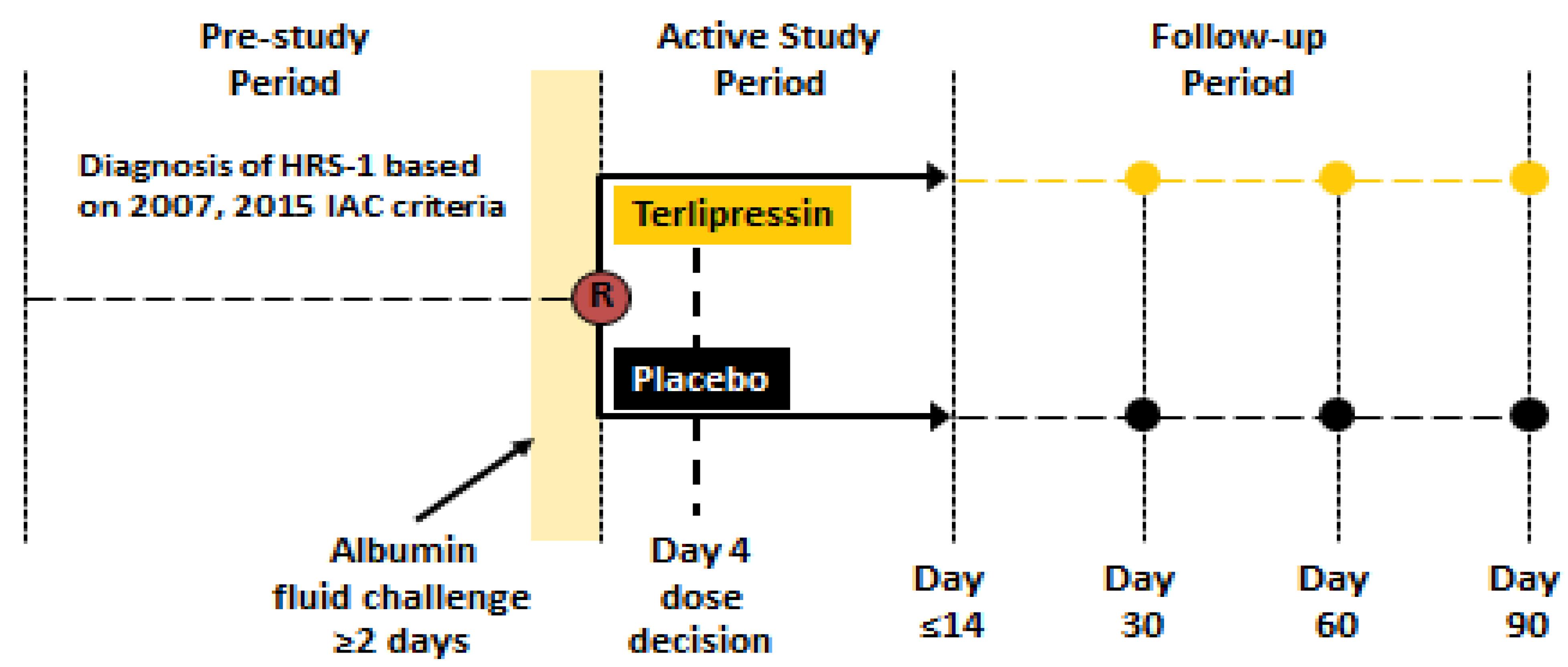
Sample Size

- Total subject Planned: 300
- Interim analysis: 150
- US and Canada only

Study Population

- Adult patients with cirrhosis, ascites & HRS type 1 diagnosis
- Rapidly progressive worsening in renal function to SCr ≥ 2.25 mg/dL
- No sustained improvement in renal function at least 48 hours after diuretic withdrawal and beginning of plasma volume expansion with albumin

Study Design



Pre-study Period
Active Study Period
Follow-up Period
Diagnosis of HRS-1 based on 2007, 2015 IAC criteria
Terlipressin
R
Placebo
Albumin fluid challenge ≥2 days
Day 4 dose decision
Day ≤14
Day 30
Day 60
Day 90

2:1 Randomization for Terlipressin vs. placebo
Initial Treatment up to 14 days.

Study Endpoints

Primary Endpoint

- Verified HRS Reversal, percentage of subjects with 2 consecutive SCr values ≤1.5 mg/dL at least 2 hours apart

Key Secondary Endpoints

- Incidence of subjects with HRS reversal, defined as the percentage of subjects with a SCr value ≤1.5 mg/dL by Day 14 or discharge.
- Durability of HRS Reversal, defined as percentage of subjects with HRS Reversal without RRT to Day 14
- Incidence of HRS Reversal in systemic inflammatory response syndrome (SIRS) subgroup

INVESTOR DAY 2017 OCTOBER 4 NEW YORK, NY

Time for a New, More Inclusive Endpoint for Treatment of Type 1 Hepatorenal Syndrome (HRS-1)? Small Changes in Serum Creatinine (SCr) of >20% Are Equivalent to HRS Reversal (HRSR) in Predicting Survival and Need for Renal Replacement Therapy (RRT) During Treatment of HRS-1 With Terlipressin and Albumin

Thomas D. Boyer,[1] Florence Wong,[2] Arun J. Sanyal,[3] Stephen Chris Pappas,[4] Khurram Jamil[5]

[1]University of Arizona, Tucson, AZ; [2]University of Toronto, Toronto, ON, Canada; [3]Virginia Commonwealth University, Richmond, VA; [4]Orphan Therapeutics, Lebanon, NJ; [5]Ikaria Therapeutics, a Mallinckrodt Company, Hampton, NJ

Background and Aims

- The generally accepted and clinically applied endpoint for successful treatment of type 1 hepatorenal syndrome (HRS-1) is a fall in serum creatinine (SCr) from ≥2.5 mg/dL to ≤1.5 mg/dL, so called HRS reversal (HRSR)[1]
- Recently, a new classification for acute kidney injury in patients with cirrhosis has been proposed, using the Acute Kidney Injury Network (AKIN) criteria[2]
- The AKIN classification is based on observations that an acute increase in SCr in cirrhotics is associated with a worse prognosis[2]
 - Assesses response to treatment based on regression of AKIN stage
- Based on our previous observation of a correlation of changes in SCr during treatment with survival,[3] we questioned whether small decreases in SCr following treatment would be associated with improved survival and reduced use of renal replacement therapy (RRT) with similar or better predictive values compared with HRSR

Material & Methods

- We analyzed the large, combined data set from our 2 published studies (OT-0401 and REVERSE) evaluating terlipressin in HRS-1[3,4]
- Data were available for 308 patients with well-characterized HRS-1 from the 2 studies
- Data were analyzed for the predictive value of HRSR (20% or 30% improvement in SCr) for survival and the use of RRT. Positive predictive value (PPV), negative predictive value (NPV), accuracy, sensitivity, and specificity were determined using standard definitions
- Receiver operator curves (ROCs) were generated for overall survival by improvement in SCr from baseline to the end of treatment (EOT) and HRSR by improvement in SCr from baseline to EOT
- Youden's index as an estimate of optimal cutoff for the ROCs was derived using the standard formula (Youden index = sensitivity + specificity – 1)

Results

- 64 patients (21%) achieved HRSR and 118 patients (38%) had at least a 20% fall in SCr
- A 20% reduction in SCr gave predictive, sensitivity, and specificity values that were similar to HRSR for survival (**Table 1**); 30% improvement in SCr did not increase accuracy
- For RRT, results were similar (**Table 2**); HRSR was somewhat more accurate in predicting the use of RRT
- HRSR or improvement in SCr reduced the use of RRT from 50–56% to 9–12%
- The number of patients achieving ≥20% improvement in SCr was twice that of those achieving HRSR in these 2 large studies
- The highest values for the Youden index* for overall survival was 0.353, suggesting an optimal cutoff of 15% improvement in SCr from baseline to EOT (**Figure 1**). The highest value of the Youden index for HRSR was 0.896, suggesting an optimal cutoff of 40% improvement in SCr from baseline to EOT (**Figure 2**)

*The Youden index is the vertical distance between the 45-degree line and a point on the ROC. A recommended approach to determine the optimal cutoff is to identify the cutoff with the highest Youden index.

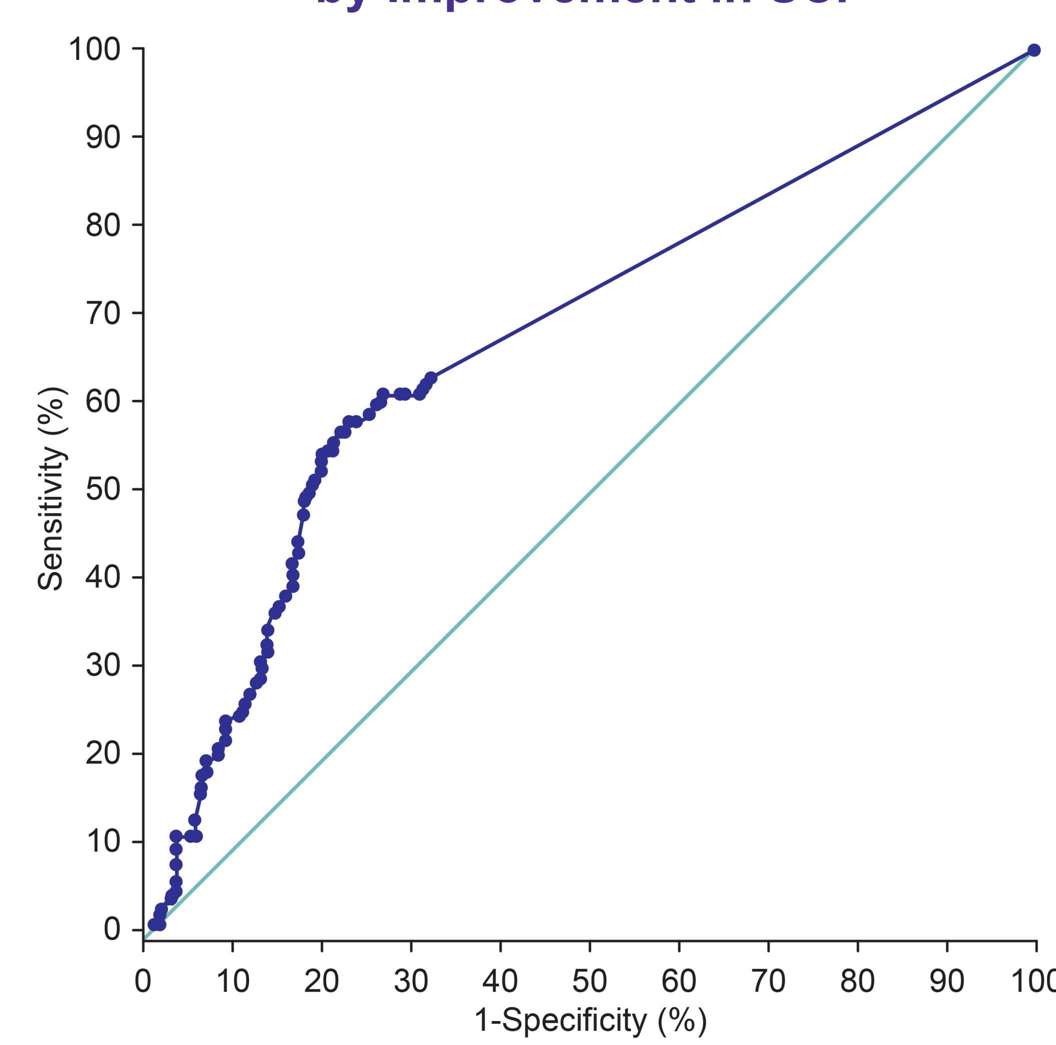
Table 1. Predictive Value of HRSR and SCr Improvement for Survival

	HRSR	≤20% Reduction in SCr	≤30% Reduction in SCr
PPV	76.6	74.6	74.0
NPV	54.1	61.6	57.6
Sensitivity	30.4	54.7	44.1
Specificity	89.9	79.6	83.0
Accuracy	58.8	66.6	62.7

Table 2. Predictive Value of HRSR and SCr Improvement for Use of RRT

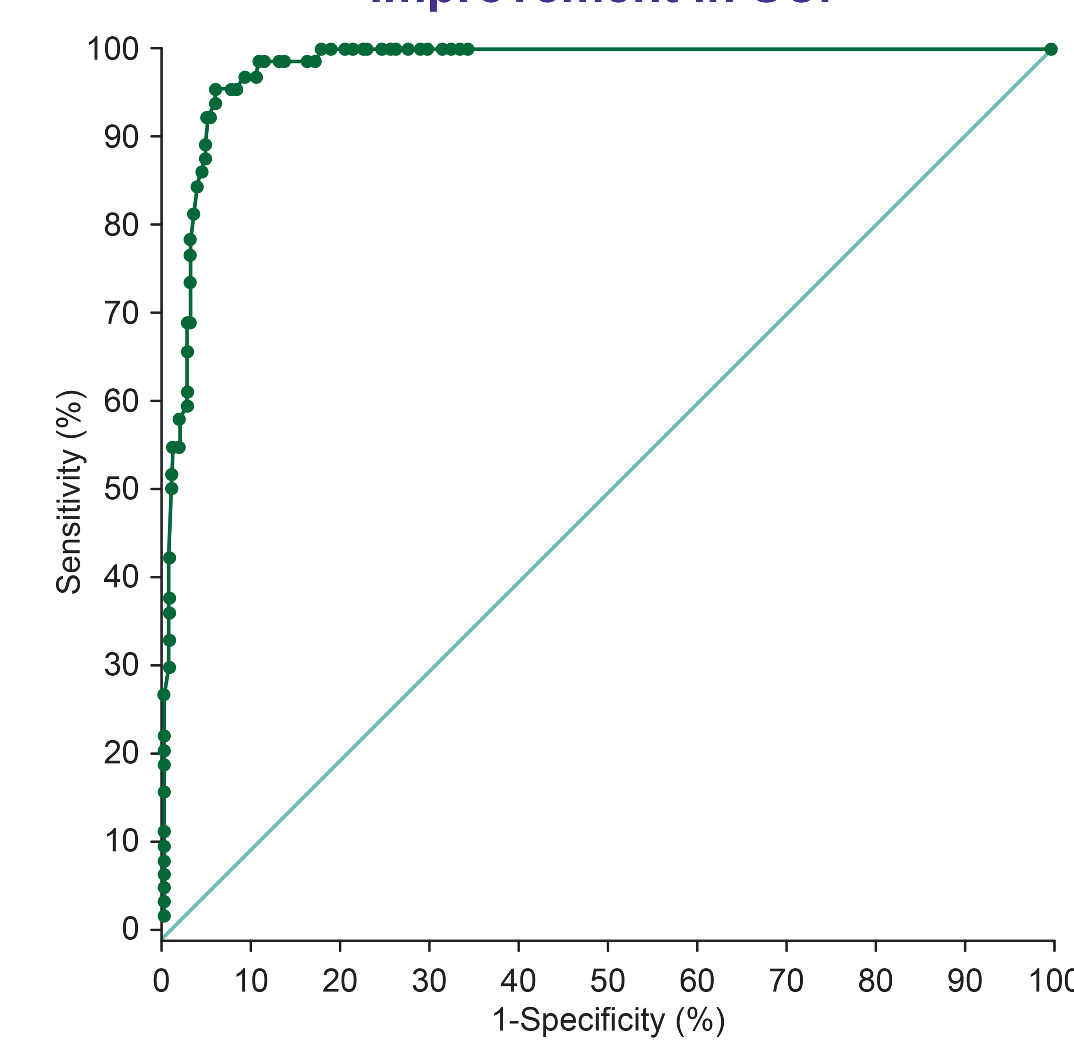
	HRSR	≤20% Reduction in SCr	≤30% Reduction in SCr
PPV	7.8	13.6	12.5
NPV	56.6	50.0	53.3
Sensitivity	4.5	14.4	10.8
Specificity	70.1	48.2	57.4
Accuracy	46.4	36.0	40.6

Figure 1. ROC for Overall Survival by Improvement in SCr


Sensitivity (%)
1-Specificity (%)
0
10
20
30
40
50
60
70
80
90
100

Area under the curve=0.673.

Figure 2. ROC for HRSR by Improvement in SCr


Sensitivity (%)
1-Specificity (%)
0
10
20
30
40
50
60
70
80
90
100

Area under the curve=0.979.

Summary

- Improvement in SCr had similar PPV, NPV, sensitivity, and specificity as HRSR in predicting survival; HRSR and improvement in SCr were similarly accurate in predicting the use of RRT
- The number of patients achieving at least a 20% improvement in SCr was twice that of those achieving HRSR in these 2 large studies
- Small improvements in SCr of 15% are associated with increased survival; an improvement in SCr of 40% was the optimal cutoff for achieving HRSR

CONCLUSIONS

- An improvement in SCr of at least 15–20% is a more inclusive endpoint compared with HRSR, with similar sensitivity and specificity, and thus may be a better assessment of the response to treatment for patients with HRS-1

REFERENCES

1. Salerno F, Gerbes A, Gines P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut*. 2007;56:1310-1318.
2. Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *J Hepatol*. 2015;62:968-974.
3. Boyer TD, Sanyal AJ, Wong F, et al. Terlipressin plus albumin is more effective than albumin alone in improving renal function in patients with cirrhosis and hepatorenal syndrome type 1. *Gastroenterology*. 2016;150:1579-1589.
4. Sanyal AJ, Boyer T, Garcia-Tsao G, et al. A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. *Gastroenterology*. 2008;134:1360-1368.

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The Burden of Hepatorenal Syndrome (HRS)

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BACKGROUND/AIMS

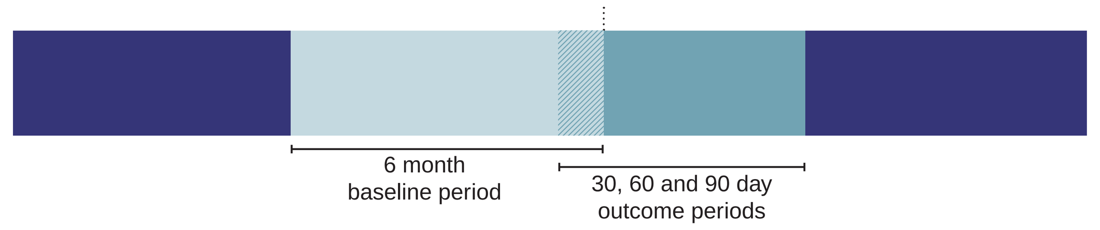
- Hepatorenal syndrome (HRS) is the development of renal failure in patients with chronic or acute liver disease[1]
- Despite the occurrence of renal failure, some studies have shown that dialysis is not effective for managing HRS, while others have shown that dialysis does benefit select HRS patients[2–5]
- HRS is associated with poor prognosis; one study estimated the median survival for patients with HRS was only 8–10 weeks[6]
- A study conducted by Do and Ezaz using the Nationwide Inpatient Sample data found that the annual expenditure of HRS patients in the US increased from $1.4 billion to $3.5 billion between 2005 and 2011[7]
- Little is known, however, about the characteristics of HRS patients and the overall economic burden of HRS, both in terms of healthcare resource utilization (HCRU) and drivers of cost and in terms of the overall costs borne by payers
- This study evaluated the characteristics, medical visits, rates and days on dialysis, rates of liver and kidney transplants, and costs from the payer perspective of HRS patients covered by commercial and Medicare insurance in the United States

METHODS

Data Sources

- This study used OptumHealth Care Solutions, Inc., a de-identified privately-insured administrative claims database with claims spanning from January 1, 1998 to December 31, 2014 and a Medicare 5% Analytic Sample with claims spanning January 1, 2009 to December 31, 2013
- OptumHealth Care Solutions, Inc. includes claims for over 18.5 million beneficiaries with commercial insurance from over 80 large self-insured Fortune 500 companies with locations across the US. The database also contains information regarding patient age, gender, enrollment history, medical diagnoses, procedures performed, date and place of service, and payment amounts as well as prescription drug fills for all beneficiaries
- The Medicare 5% Analytic Sample contains similar medical and demographic information, with no information on prescription drug use

Study Period


Index date
6 month
baseline period
30, 60 and 90 day
outcome periods

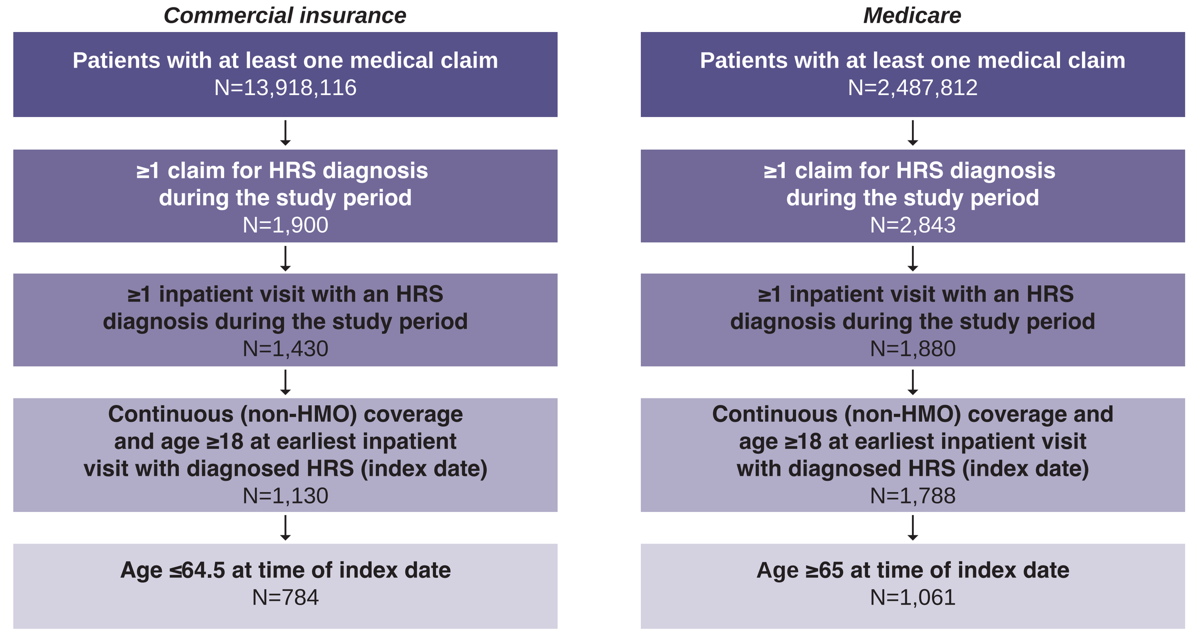
Diagnosis period
Patients with an HRS diagnosis during the study period (Commercial: January 1, 1998 – December 31, 2014; Medicare: January 1, 2009 – December 31, 2013), with the date of each patient's first inpatient admission with an HRS diagnosis (ICD-9 code 572.4) defined as the index date

Baseline period
Patient characteristics were assessed on the index and during the 6 months prior to the index date ("baseline period")

Outcome period
Medical resource utilization and costs of care during the 30 days prior to and the 30, 60 and 90 days following the index date ("outcome period") were reported to determine burden of illness (periods of 60, 90, and 120 days, respectively)

Sample Selection

Figure 1. Selection of HRS patients


Commercial insurance
Patients with at least one medical claim
N=13,918,116
≥1 claim for HRS diagnosis during the study period
N=1,900
≥1 inpatient visit with an HRS diagnosis during the study period
N=1,430
Continuous (non-HMO) coverage and age ≥18 at earliest inpatient visit with diagnosed HRS (index date)
N=1,130
Age ≤64.5 at time of index date
N=784
Medicare
Patients with at least one medical claim
N=2,487,812
≥1 claim for HRS diagnosis during the study period
N=2,843
≥1 inpatient visit with an HRS diagnosis during the study period
N=1,880
Continuous (non-HMO) coverage and age ≥18 at earliest inpatient visit with diagnosed HRS (index date)
N=1,788
Age ≥65 at time of index date
N=1,061

METHODS (CONT.)

Study Measures

- Baseline period evaluation
 - Demographic and clinical characteristics were summarized for commercially-insured and Medicare patients during the 6-month baseline period
- Mortality
- Outcome period evaluation
 - *All-cause healthcare resource use and costs (inflated to 2015 USD)*
 - Number and costs of medical visits, overall as well as categorized by place of service: inpatient, outpatient/physician office, emergency department (ED), other (e.g., home health, extended care, hospice)
 - Inpatient length of stay
 - Hospital readmissions
 - HRS-related services, including dialysis, renal transplants, liver transplants, and simultaneous liver and renal transplants (defined as a liver transplant and a renal transplant performed on the same day or during the same hospital stay)
 - *Overall economic burden*

Data Analysis

- Survival and readmission rates were determined using Kaplan-Meier analysis with censoring at the end of insurance coverage or data availability, whichever came first. In the commercial insurance data, the end of insurance coverage was used as a proxy for date of death (not available) when assessing mortality
- Average healthcare costs were summarized and stratified by medical setting and dialysis status
- The total direct economic burden of HRS was estimated using incidence rates estimated by Pant et al. 2016[8], US population statistics from the Census Bureau and per patient healthcare costs during the 30 days prior to and the 90 days following the first inpatient admission. Medicare per patient costs were applied to adults ages 65 and older with Medicare insurance while commercial per patient costs were applied to adults ages 18-64 with commercial insurance

RESULTS

Baseline Characteristics

- A total of 784 commercially-insured HRS patients and 1,061 Medicare HRS patients met the inclusion criteria (**Figure 1**)
- Average age was 54.1 among commercially-insured and 74.1 among Medicare patients (**Table 1**)
- A majority of commercially-insured (63%) and Medicare patients (58%) were male
- Both cohorts had substantial rates of underlying chronic comorbidities as measured by the Charlson Comorbidity Index (6.2 commercial; 7.9 Medicare)
- Many patients had alcoholic and non-alcoholic cirrhosis (45.3% and 71.9% in commercial, respectively; 28.7% and 59.8% in Medicare, respectively)
- The two most common etiologies of non-alcoholic cirrhosis were hepatitis C and non-alcoholic fatty liver disease

Table 1. Patient characteristics and comorbidities during the baseline period

	Commercial Insurance (N=784)	Medicare (N=1,061)
Age, mean	54.1	74.1
Male, %	63.0%	57.9%
Charlson Comorbidity Index, mean	6.2	7.9
Selected comorbidities, %		
Ascites	57.1%	64.8%
Chronic liver disease / cirrhosis	93.1%	83.9%
Chronic liver disease without mention of cirrhosis	14.8%	17.3%
Chronic liver disease and cirrhosis	78.3%	66.5%
Alcoholic cirrhosis	45.3%	28.7%
Non-alcoholic cirrhosis	71.9%	59.8%
Biliary cirrhosis	5.9%	4.3%
Esophageal varices	22.4%	24.2%
Hepatitis C	25.8%	15.0%
Hepatic encephalopathy	47.7%	42.4%
Portal hypertension	24.2%	34.6%
Other sequelae of chronic liver disease	48.5%	29.6%
Non-alcoholic fatty liver disease	20.3%	13.0%

RESULTS (CONT.)

HCRU During the Outcome Period

Commercially-insured and Medicare patients had high rates of healthcare resource use. During follow-up, 1.4% of commercially-insured and 0.2% of Medicare patients received renal transplants.

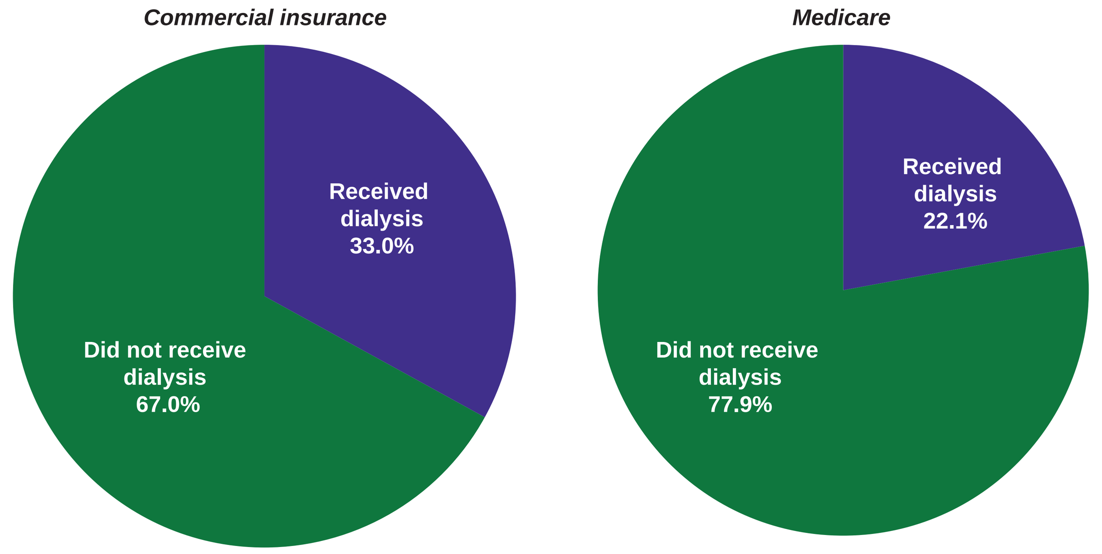
Table 2. Healthcare resource utilization during the outcome period

	Commercial Insurance (N=784)			Medicare (N=1,061)		
	Within 30 days	Within 60 days	Within 90 days	Within 30 days	Within 60 days	Within 90 days
Medical visits, mean	11.0	14.5	17.7	10.3	12.4	13.9
Emergency department visits	1.5	1.8	2.0	1.4	1.7	1.8
Inpatient admissions	1.9	2.2	2.4	1.5	1.6	1.7
Average length of inpatient admission, days	12.3	14.2	14.6	10.8	11.5	11.6
Readmissions following the index date	0.3	0.5	0.8	0.1	0.2	0.3
Outpatient/physician office visits	5.2	7.1	9.0	4.4	5.4	6.1
Other visits	2.4	3.4	4.3	3.0	3.7	4.3
Selected medical procedures						
Liver transplant	9.3%	10.5%	10.7%	1.2%	1.5%	1.6%
Renal transplant	1.0%	1.4%	1.4%	0.2%	0.2%	0.2%
Simultaneous liver and renal transplant	1.0%	1.4%	1.4%	0.2%	0.2%	0.2%

Note: Healthcare resource use evaluated during the 30 days prior to and the 30 days, 60 days, and 90 days following the earliest inpatient visit with diagnosed HRS (ICD-9-CM Diagnosis Code 572.4).

During the 90 day outcome period, 33% of commercially-insured and 22% of Medicare patients were on dialysis. Commercially-insured patients spent an average of 8.2 days on dialysis.

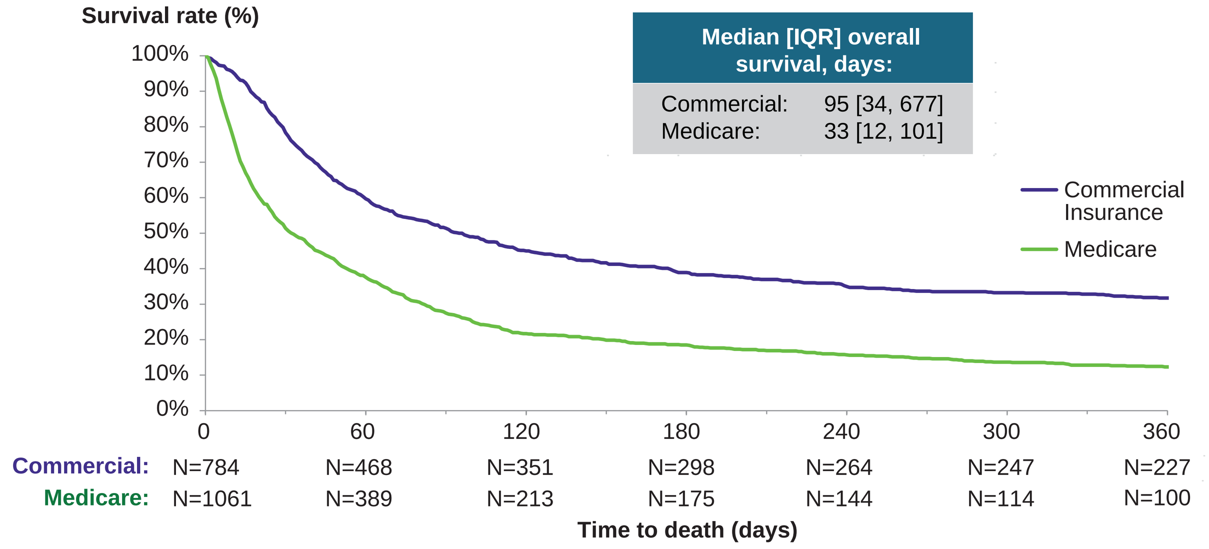
Figure 2. Dialysis rates of HRS patients during the 90 day outcome period


Commercial insurance
Received dialysis 33.0%
Did not receive dialysis 67.0%
Medicare
Received dialysis 22.1%
Did not receive dialysis 77.9%

Mortality

After admission, median survival was short, particularly among Medicare patients (commercial: 95 days; Medicare: 33 days)

Figure 3. Survival rates of HRS patients

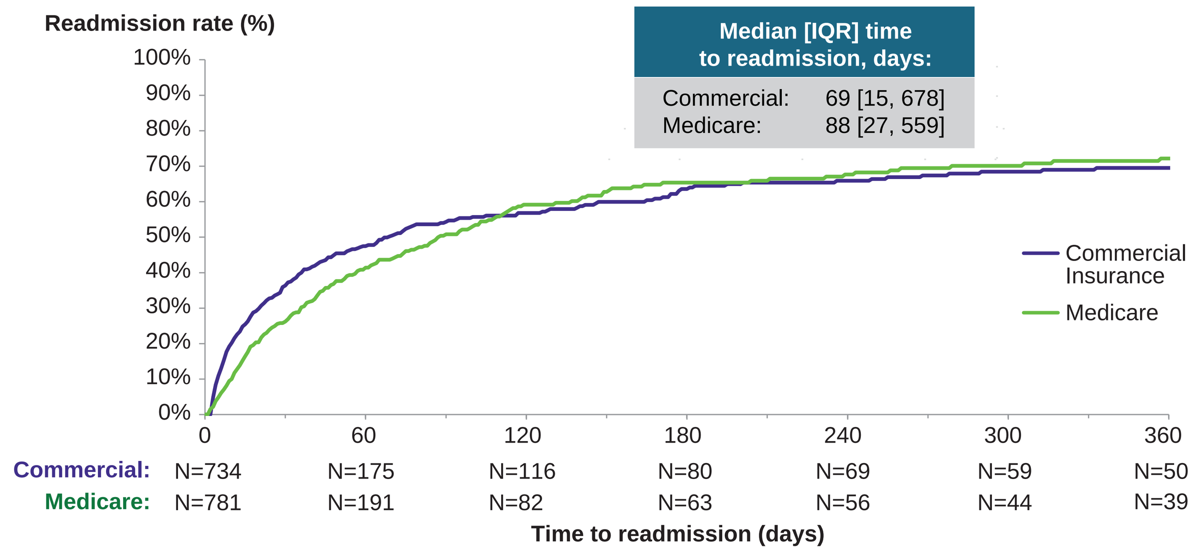

Survival rate (%)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Median [IQR] overall survival, days:
Commercial: 95 [34, 677]
Medicare: 33 [12, 101]
Commercial Insurance
Medicare
0
60
120
180
240
300
360
Commercial: N=784 N=468 N=351 N=298 N=264 N=247 N=227
Medicare: N=1061 N=389 N=213 N=175 N=144 N=114 N=100
Time to death (days)

RESULTS (CONT.)

Readmission Rates

Readmission rates were similar for both cohorts. 36% of commercially-insured and 26% of Medicare patients were readmitted within the next 30 days; median time-to-readmission was 69 days and 88 days, respectively

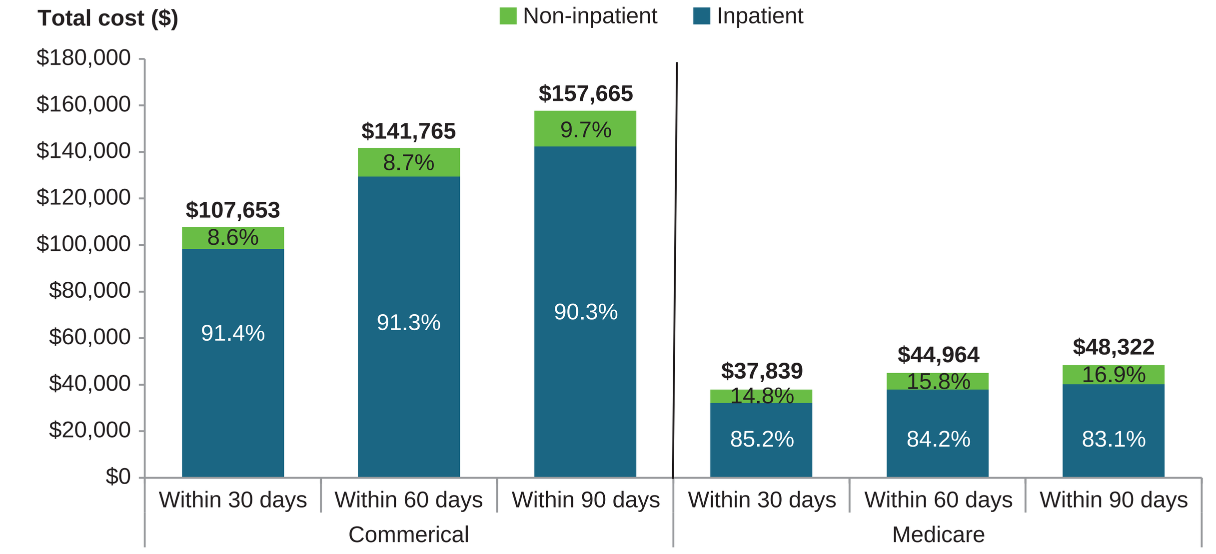
Figure 4. Readmission rates of HRS patients


Readmission rate (%)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Median [IQR] time to readmission, days:
Commercial: 69 [15, 678]
Medicare: 88 [27, 559]
Commercial Insurance
Medicare
0
60
120
180
240
300
360
Commercial: N=734 N=175 N=116 N=80 N=69 N=59 N=50
Medicare: N=781 N=191 N=82 N=63 N=56 N=44 N=39
Time to readmission (days)

Costs During the Outcome Period

The primary cost driver was inpatient visits, accounting for 90% of commercial and 83% of Medicare costs during the 90 day follow-up period

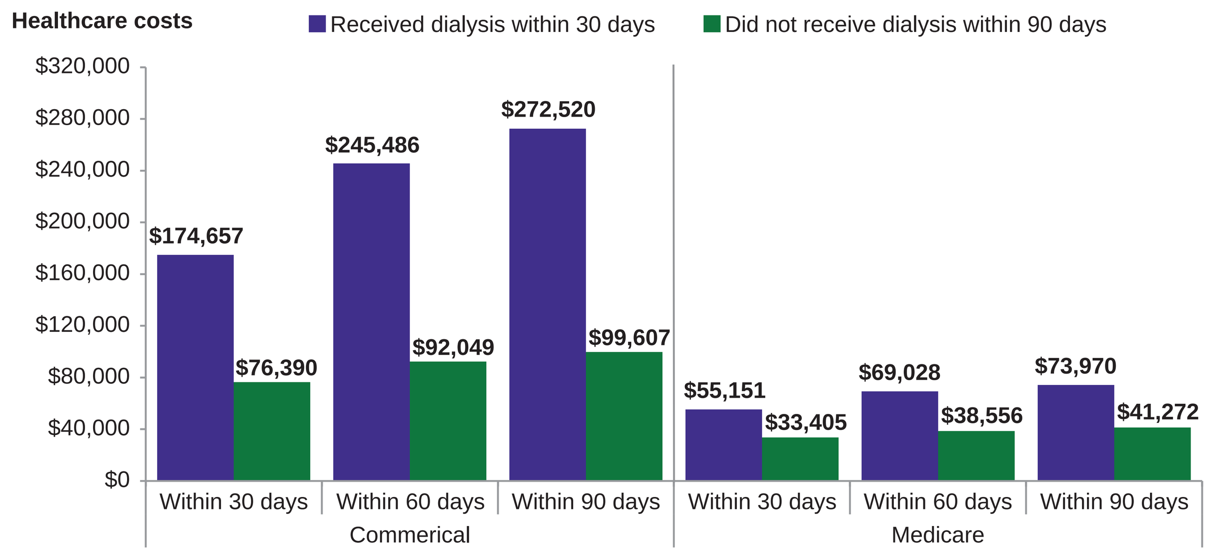
Figure 5. Total healthcare costs during the outcome period


Total cost ($)
Non-inpatient
Inpatient
$180,000
$160,000
$140,000
$120,000
$100,000
$80,000
$60,000
$40,000
$20,000
$0
$107,653
8.6%
91.4%
$141,765
8.7%
91.3%
$157,665
9.7%
90.3%
$37,839
14.8%
85.2%
$44,964
15.8%
84.2%
$48,322
16.9%
83.1%
Within 30 days
Within 60 days
Within 90 days
Commerical
Within 30 days
Within 60 days
Within 90 days
Medicare

Note: Healthcare costs evaluated during the 30 days prior to and the 30 days, 60 days, and 90 days following the earliest inpatient visit with diagnosed HRS (ICD-9-CM Diagnosis Code 572.4).

Within the first 30 days, a substantial number of patients received dialysis (commercial: 30.5%; Medicare: 20.6%). Average costs were higher among patients who received dialysis than among those who did not receive dialysis

Figure 6. Total healthcare costs stratified by dialysis status


Healthcare costs
Received dialysis within 30 days
Did not receive dialysis within 90 days
$320,000
$280,000
$240,000
$200,000
$160,000
$120,000
$80,000
$40,000
$0
$174,657
$76,390
$245,486
$92,049
$272,520
$99,607
$55,151
$33,405
$69,028
$38,556
$73,970
$41,272
Within 30 days
Within 60 days
Within 90 days
Commerical
Within 30 days
Within 60 days
Within 90 days
Medicare

Note: Healthcare costs evaluated during the 30 days prior to and the 30 days, 60 days, and 90 days following the earliest inpatient visit with diagnosed HRS (ICD-9-CM Diagnosis Code 572.4).

RESULTS (CONT.)

HCRU and Costs During the Outcome Period

- Medical visits and HRS-related services
 - Within the first 30 days after admission, the average inpatient length of stay was 11–12 days in both groups
 - In the 30 days prior to and 90 days following the first inpatient admission, on average, commercially-insured patients had 17.7 medical visits and Medicare patients had 13.9 visits
 - During the 90-day outcome period, 10.7% of commercially-insured and 1.6% of Medicare patients received liver transplants while 1.4% and 0.2% received renal transplants, respectively (**Table 2**)
- Average costs within the 90 day follow-up period were $157,665 for commercially-insured and $48,322 for Medicare patients, with most costs occurring within the first 30 days (**Figure 5**)
- Costs by setting and dialysis status
 - Costs were driven by inpatient visits (commercial: 90.3% of costs; Medicare: 83.1% of costs) (**Figure 5**)
 - In both the commercially-insured and Medicare populations, patients who received dialysis incurred higher costs compared to patients who did not receive dialysis (**Figure 6**)
- Total direct economic burden
 - Using US population and prevalence statistics, these results suggest that HRS imposes a total direct medical cost burden of approximately $3.0–$3.8 billion to payers

CONCLUSION

- This study used recent, nationally representative administrative claims data to assess the economic burden of HRS in the United States from the payer perspective
- HRS is associated with high mortality and rates of nephrology-related healthcare resource utilization and imposes a significant economic burden
- Together with US population and prevalence statistics, these findings suggest that HRS imposes a total direct medical cost burden of approximately $3.0–$3.8 billion to public and private payers

REFERENCES

1. Arroyo V, Gines P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. *Hepatology.* 1996; 23: 164–76.
2. Wong LP, Blackley MP, Andreoni KA, et al. Survival of liver transplant candidates with acute renal failure receiving renal replacement therapy. *Kidney Int.* 2005; 68: 362.
3. Perez GO, Oster JR. A critical review of the role of dialysis in the treatment of liver disease. In: Epstein M, Ed. *The Kidney in Liver Disease. 1st Ed.* New York: Elsevier; 1978: 325–336.
4. Wilkinson SP, Weston MJ, Parsons V, Wilhams R. Dialysis in the treatment of renal failure in patients with liver disease. *Clin Nephrol.* 1977; 8: 287–292.
5. Perez GO, Epstein M, Oster JR. Role of dialysis and ultrafiltration in the treatment of the renal complications of liver disease. In: Epstein M, Ed. *The Kidney in Liver Disease. 3rd Ed.* Baltimore: Williams & Wilkins; 1988: 613–62.
6. Ng CK, Chan MH, Tai MH and Lam CW. Hepatorenal syndrome. *Clin Biochem Rev.* 2007; 28: 11–7.
7. Do A and Ezaz G. Increasing incidence and cost, but decreasing mortality in patients with hepatorenal syndrome: a study of the National Inpatient Sample 2005–2011. American Association for the Study of Liver Diseases. San Francisco: *Hepatology.* 2015.
8. C Pant, Jani BS, Desai M, et al. Hepatorenal syndrome in hospitalized patients with chronic liver disease: results from the Nationwide Inpatient Sample 2002–2012. *J Investig Med.* 2016; 64: 33–38.

DISCLOSURES

- This study was sponsored by Mallinckrodt Pharmaceuticals
- Dr Kevin M. Korenblat, MD, is an Associate Professor of Medicine at the Washington University School of Medicine in St. Louis and has received research funding from Mallinckrodt Pharmaceuticals for the conduct of clinical trials, but acted as an uncompensated consultant on this project
- Belinda Lovelace, PharmD, George J. Wan, PhD, MPH, and Khurram Jamil, MD are employees of Mallinckrodt Pharmaceuticals
- J. Bradford Rice, PhD, Alan White, PhD, Philip Galebach, BA, and Aneesha Wagh, BA are employees of Analysis Group, Inc., which has received consultancy fees from Mallinckrodt Pharmaceuticals

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Reversal of Hepatorenal Syndrome Type 1 (HRS-1) with Terlipressin plus Albumin versus Placebo plus Albumin - Not All Responses Are Created Equal - An Analysis of the REVERSE and OT-0401 Trials

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1. BACKGROUND

- Renal function affects outcomes in patients with decompensated liver disease and acute kidney injury, including HRS-1 (du Cheyron 2005)
- Terlipressin plus albumin has been shown to improve renal function in HRS-1 to a greater degree than placebo plus albumin (Boyer 2014, Gluud 2010, Sanyal 2008)
- Improvement in renal function correlates with survival (Boyer 2014)
- However, it is unclear whether outcomes following reversal of HRS-1 are the same when reversal is achieved

2. OBJECTIVES

- The aim of this study was to review pooled data from two pivotal, Phase 3 trials in HRS-1 and evaluate outcomes of those patients who achieved reversal of HRS-1.
 - Survival and survival without renal replacement therapy (RRT) were evaluated

3. MATERIALS & METHODS

Serum creatinine (SCr), renal replacement therapy (RRT), and survival data from the REVERSE and OT-0401 trials, both randomized, placebo-controlled trials of terlipressin and albumin versus placebo plus albumin with similar designs and patients enrolled (Table), were pooled to analyze: incidence of confirmed HRS reversal (CHRSR), use of RRT, overall survival, and survival at Day 90 without RRT. CHRSR was defined as 2 SCr values ≤1.5 mg/dL, at least 48 hours apart, on treatment, without RRT or liver transplant.

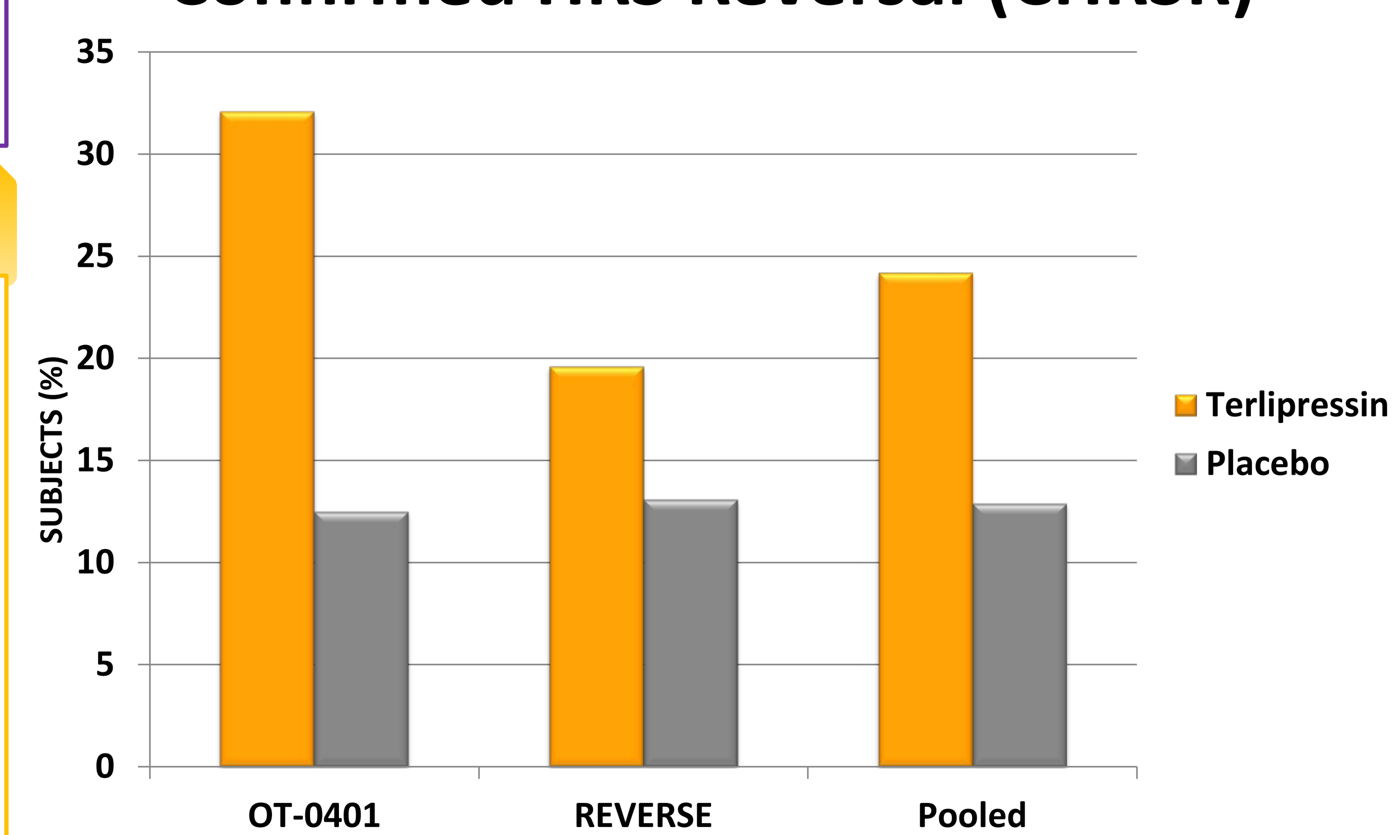
Study	Design	Treatment	HRS Subjects / Number Exposed to Terlipressin	Key Endpoints
OT-0401	Multicenter, double-blind, randomized, placebo-controlled patients with HRS-1 based on modified IAC criteria , 1996	Terlipressin: 4-8 mg/d (IV q6h) Placebo Albumin (100 g on Day 1 then 25 g/d): recommended for both groups Up to 14 d	112/56	Treatment Success at Day 14; HRS Reversal; Change in SCr Survival
REVERSE	Multicenter, double-blind, randomized, placebo-controlled patients with HRS-1 based on modified IAC criteria , 2007	Terlipressin: 4-8 mg/d (IV q6h) Placebo Albumin (up to 100 g on Day 1 then 20-40 g/d): recommended for both groups Up to 14 d (15-16 d if initial response on Day 13 or 14)	196/97	Confirmed HRS Reversal; HRS Reversal; Change in SCr Survival

4. RESULTS

- Data from 308 patients were analyzed; 153 were randomized to terlipressin, 155 to placebo
- Baseline characteristics were similar across the two studies and between treatment groups (Table)

	OT0401		REVERSE	
	Terlipressin N = 56	Placebo N = 56	Terlipressin N = 97	Placebo N = 99
Age, mean (SD)	50.6 (10.5)	52.9 (11.4)	55.8 (8.38)	54.8 (8.50)
Gender (n, %)				
Male	41 (73.2)	39 (69.6)	52 (53.6)	67 (67.7)
Female	15 (26.8)	17 (30.4)	45 (46.4)	32 (32.3)
MELD Score				
Mean (SD)	33.4 (6.0)	33.4 (6.3)	33.5 (6.18)	32.6 (5.45)
Alcoholic Hepatitis (n, %)				
Present	20 (35.7)	20 (35.7)	20 (20.6)	25 (25.3)
Not Present	36 (64.3)	36 (64.3)	77 (79.4)	74 (74.7)
Serum Creatinine at Baseline(mg/dL)				
Mean concentration (SD)	3.96 (2.19)	3.85 (1.17)	3.6 (1.05)	3.7 (1.11)
Min, Max	2, 11.9	1.6, 6.9	1.7, 6.4	1.9, 6.8

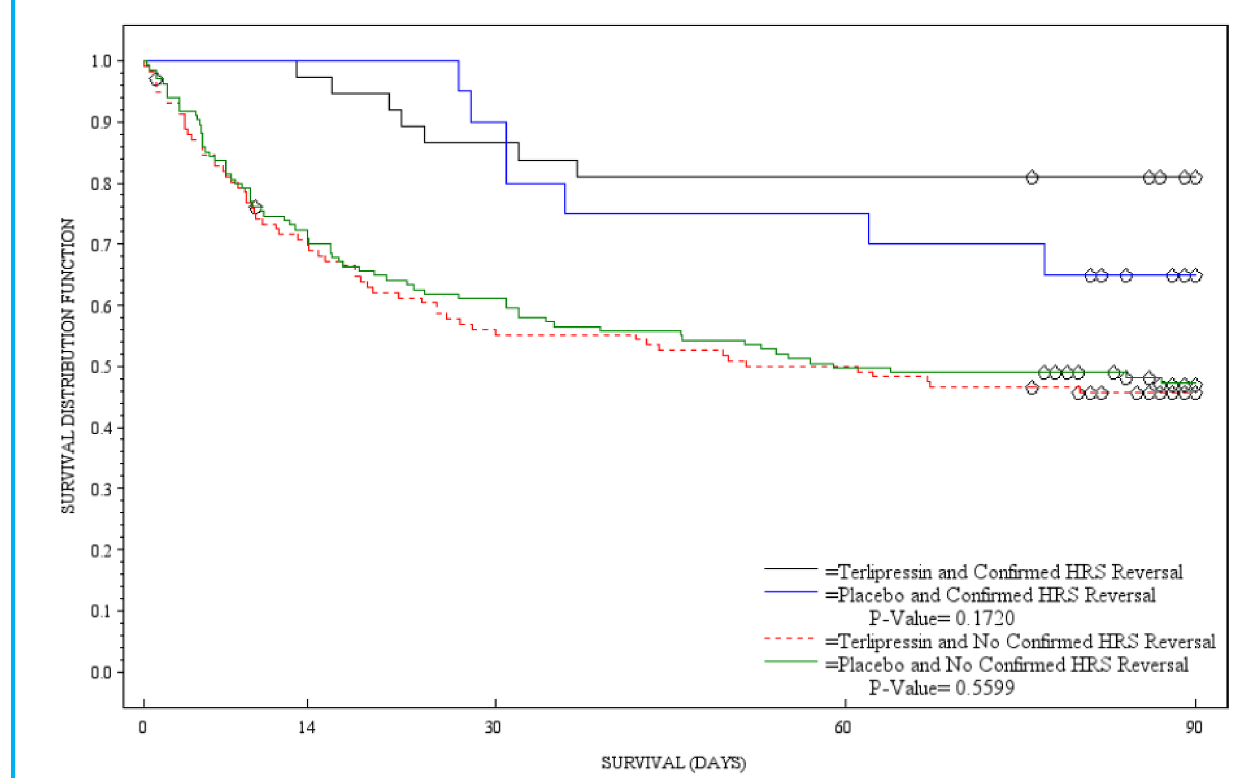
Confirmed HRS Reversal (CHRSR)


35
30
25
20
15
10
5
0
SUBJECTS (%)
OT-0401
REVERSE
Pooled
Terlipressin
Placebo

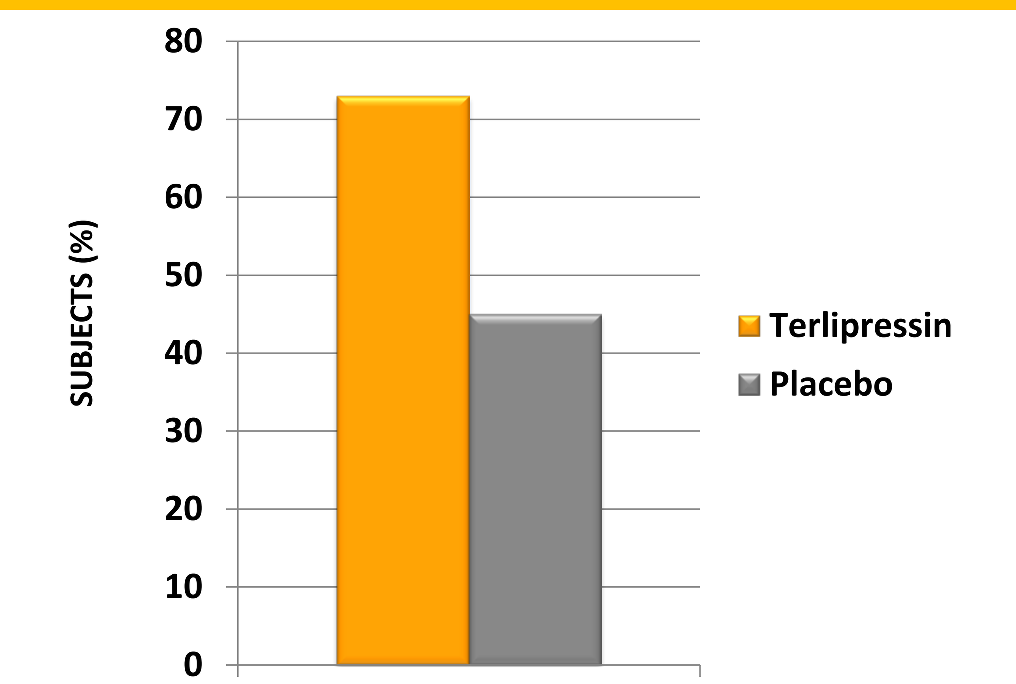
RRT at Day 90, Subjects with and without CHRSR

STUDY	CHRSR-YES (n)	CHRSR-RRT (%)	CHRSR–NO (n)	No CHRSR–RRT (%)
OT-0401	25	**1(4.0)**	87	**34(39.1)**
REVERSE	32	**3(9.4)**	164	**75(45.7)**
POOLED	57	**4(7.0)**	251	**109(43.4)**

SURVIVAL BY CHRSR STATUS AND TREATMENT ARM


SURVIVAL DISTRIBUTION FUNCTION
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
14
30
60
90
SURVIVAL (DAYS)
=Terlipressin and Confirmed HRS Reversal
=Placebo and Confirmed HRS Reversal
P-Value= 0.1720
=Terlipressin and No Confirmed HRS Reversal
=Placebo and No Confirmed HRS Reversal
P-Value= 0.5599

SUBJECTS ALIVE, WITHOUT RRT, DAY 90


80
70
60
50
40
30
20
10
0
SUBJECTS (%)
Terlipressin
Placebo

No patient with CHRSR in the terlipressin group received RRT; 4/16 (25%) of patients with CHRSR in the placebo group received RRT.

5. SUMMARY

- Pooled data from two large trials show that terlipressin plus albumin treatment was associated with an increased frequency of CHRSR compared to placebo and albumin.
- Survival in patients with CHRSR was significantly higher, and use of RRT significantly lower, than in patients without CHRSR.
- There were significantly more patients in the terlipressin group with CHRSR alive at Day 90 without RRT compared to placebo.

6. CONCLUSIONS

- Reversal of HRS Type 1 following treatment with terlipressin plus albumin occurs significantly more frequently than with placebo plus albumin.
- Achieving confirmed HRS reversal reduces the need for RRT and improves survival.
- Patients treated with terlipressin and albumin who achieve CHRSR appear to have a better outcome at Day 90 (survival and less need for RRT) compared to patients achieving CHRSR with albumin alone

7. REFERENCES

1. du Cheyron D, Bouchet B, Parienti JJ, Ramakers M, Charbonneau P. The attributable mortality of acute renal failure in critically ill patients with liver cirrhosis. Intensive Care Med 2005;31:1693-1699.
2. Boyer TD Sanyal AJ, Wong F, et al. Initial report of a large, randomized, double blind, placebo-controlled, phase 3 trial of terlipressin plus albumin for the treatment of Type 1 hepatorenal syndrome (HRS-1): The REVERSE study. Hepatology 2014;60:255A.
3. Gluud LL, Christensen K, Christensen E, Krag A. Systematic review of randomized trials on vasoconstrictor drugs for hepatorenal syndrome. Hepatology 2010;51:576-584.
4. Sanyal AJ, Boyer T, Garcia-Tsao G, Regenstein F, Rossaro L, Appenrodt B, Blei A, et al. A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. Gastroenterology 2008;134:1360-1368.

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All Authors' Disclosures on file with the AASLD

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