ClinicoEconomics and Outcomes Research

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

# Impact on Inpatient Length of Stay in Adults with Deep Partial-Thickness Burns: Comparing the Bioengineered Allogeneic Cellularized Construct Expanded-Access Trial with National Burn Repository Data

Tzy-Chyi Yu[1], Helen Hahn[2], Randi Rutan[2], Feng-Sheng Hu[3], Zhishui Zheng[3]

[1]Health Economics and Outcomes Research, Mallinckrodt Pharmaceuticals, Bridgewater, NJ, USA; [2]Clinical Development and Medical Affairs, Mallinckrodt Pharmaceuticals, Bridgewater, NJ, USA; [3]Health Economics and Outcomes Research, KMK Consulting, Inc, Morristown, NJ, USA

Correspondence: Tzy-Chyi Yu, HEOR, Regenerative Medicine, Mallinckrodt Pharmaceuticals, 440 Route 22 East, Suite 302, Bridgewater, NJ, 08807, USA, Email tzychyiyu@hotmail.com



**Purpose:** To investigate the effect of StrataGraft (bioengineered allogeneic cellularized construct [BACC]) treatment on inpatient length of stay (LOS) as an indicator of hospital resource utilization.

**Patients and Methods:** Data from the single-arm StrataCAT trial for adult patients with deep partial-thickness (DPT) burns who received BACC were compared with data from a matched external control arm comprising patients who received autografting for burn treatment from the National Burn Repository (NBR) during the same time period as StrataCAT. A matching, quasi-experimental approach was used to investigate the cause-and-effect relationship between BACC treatment and LOS (days). Matching factors included sex, age, ethnicity, race, burn causes, %TBSA burned (third-degree), %TBSA burned (second- and third-degrees), inhalation injury, diabetes mellitus, and hypertension. Balance was assessed between the cohorts for each confounder by standardized mean differences (SMD). Outcome was reported as average treatment effect on the treated.

**Results:** The BACC and NBR Autograft cohorts included 47 and 2641 patients, respectively. Following matching, the Autograft cohort had 137 patients and was weighted to 47 patients. Patients in the BACC and final (matched) Autograft cohorts were similar in all demographic and clinical covariate categories after matching (ie, the absolute SMD were < 0.1). Treatment with BACC reduced the inpatient LOS by an average of 4.84 days ($P$ = 0.0127) relative to the comparable (matched) Autograft cohort. An ad hoc analysis revealed that mean [SD] LOS for BACC and the weighted Autograft cohorts were 17.68 [12.75] and 22.51 [19.75] days, respectively, and were 1.39 [0.94] and 1.88 [1.31] days per %TBSA burned, respectively.

**Conclusion:** The significantly reduced inpatient LOS observed with BACC compared to Autograft in adults with DPT burns may translate into reduced burden on the healthcare system, reduced costs for inpatient burn treatment, and clinical benefits for patients.

**Keywords:** deep partial-thickness burns, severe burns, length of stay, National Burn Repository, bioengineered allogeneic cellularized construct

## Introduction

Burn injuries can be classified as superficial, superficial partial-thickness (SPT), deep partial-thickness (DPT), full-thickness (FT), or fourth-degree, depending on the depth of the burn wound.[1] SPT and DPT burn wounds are classified as second-degree wounds, while FT burn wounds are classified as third-degree wounds.[1]

Burn wound depth impacts the patient's long-term functional and cosmetic outcomes and thus influences the choice of burn treatment during the acute post-injury phase.[2] Patients with DPT and FT burns typically require expensive specialized care, including prolonged hospitalization for surgery and treatment.[1,3] Specifically, autografting following

Received: 25 June 2024
Accepted: 21 August 2024
Published: 6 September 2024

burn excision is a current standard of care for DPT and FT burns; however, autografting requires the creation of a donor-site wound, which can be associated with morbidity including pain, scarring, and impaired function.[4,5]

In addition to this patient burden, the burden related to healthcare resources and costs associated with autografting is substantial. There are nearly 40,000 patients hospitalized every year in the United States for burn treatment.[6] Researchers have found that the reported percentage needing autografting ranges from 21% to 25% among hospitalizations for burn.[7] A recent analysis of administrative claims and electronic medical records of patients undergoing inpatient autografting in the United States between 2010 and 2019 indicated the mean length of hospital stay (LOS) for these patients was between 10.6 days (for patients with burns <10% total body surface area [TBSA]) and 46.5 days (for patients with burns ≥25% TBSA) and that LOS positively correlated with %TBSA.[8] This corresponded to approximately $75,000 to $560,000 in average inpatient costs for burn-related treatment.[8] LOS is also a major quality indicator for inpatient care.[9] A shorter LOS can reduce the risk of hospital-acquired infections and improve patient quality of life.[9] In addition, given the positive correlation between LOS and costs in burn treatment,[3] a reduced LOS may reduce healthcare resource use and costs and help to alleviate the burden on the healthcare system (eg, through decreased staffing needs and associated cost savings).[10]

Given the burden autografting imposes on both patients and healthcare systems, there is a need for alternative therapeutic options for burn wound coverage and promotion of wound closure that can improve quality of care and patients' quality of life and reduce the length of inpatient stay over the current standard of care.[4] StrataGraft, a bioengineered allogeneic cellularized construct (BACC), is a US Food and Drug Administration (FDA)-approved alternative treatment option to autografting for DPT thermal burns in adults.[4] The clinical benefit of BACC has been demonstrated in several clinical trials,[4,11,12] including the pivotal phase 3, randomized controlled trial STRATA2016 (NCT03005106),[4] and a recent phase 3b, open-label, single-arm, multicenter, expanded-access study (StrataCAT, NCT04123548), which found that 90.6% of BACC-treated DPT thermal burn wounds in adults did not require autografting, and 55.8% of patients achieved durable wound closure without autografting by Week 24 of BACC treatment.[11] Additionally, hypertrophic scars in burns treated with BACC were similar to those of autografting in metrics related to clinical POSAS scores, extracellular matrix, and collagen structure, without the burden of a donor site.[13] The impact of BACC on healthcare resource utilization among adults with DPT burns remains a subject of continuing investigation. The aim of this study was to investigate the effect of BACC treatment on inpatient LOS as hospital resource utilization.

## Materials and Methods

Data from the single-arm StrataCAT trial for patients who received BACC were compared with data from a rigorously matched external control arm comprising patients who received autografting for burn treatment from the National Burn Repository (NBR) during the same time period as StrataCAT.[11,14,15] The ABA Full Burn Dataset is a comprehensive dataset representing fully harmonized variables collected about burn admissions in the United States from 2008 to 2021. The data are sourced from over 100 unique treating facilities and include initial inpatient burn encounters with admission dates from January 2008-December 2021.[14] Patients enrolled in the expanded-access StrataCAT trial served as the experimental (BACC) arm of this study. Following the StrataCAT inclusion criteria, patients in the BACC arm were aged 18 years or older, had 3% to <50% TBSA of thermal burns, and received up to 2000 $cm^2$ of treatment with BACC. Patients were excluded if they were pregnant, prisoners, or had less than 3 months expected survival. Treatment sites were excluded if they were FT burns, chronic wounds, or burns covering the face, head, neck, hands, feet, digits, buttocks, perineum/genitals, and areas over joints.

To align with the experimental arm from the StrataCAT trial, inclusion/exclusion criteria were applied to data from the NBR to create a comparable external control (Autograft) arm. Patients in this arm were aged 19–87 years with 3%–<50% TBSA (including second- and third-degree burns), were hospitalized for burn treatment in the years 2020 and 2021 (during the same period as StrataCAT), and underwent at least one autografting procedure. Patients were excluded if they were pregnant, died during hospitalization, or discontinued hospital treatment against medical advice. Only patients with at least one burn location in the anterior or posterior trunk, upper arm, leg, or thigh were included in the Autograft arm. A few StrataCAT exclusion criteria (eg, patients undergoing systemic immunosuppressive therapy at the time of injury, patients with a known history of malignancy or preadmission insulin-dependent diabetes) were not applied to the Autograft external control arm, as such information was not available from the NBR. However, to ensure completeness of the NBR data and, to the extent possible, alignment with StrataCAT criteria for the purposes of this analysis, the Autograft cohort excluded

patients missing information on gender, ethnicity, LOS; patients who transferred to a different treatment facility (ie, had incomplete LOS information), and patients who were not White, Black/African American, or Asian. The complete list of criteria used for the Autograft cohort to be comparable with the StrataCAT criteria is shown in Supplemental Table 1.

Once the study cohorts had been assembled, a matching, quasi-experimental approach was used to investigate the cause-and-effect relationship between BACC treatment and LOS.[16] Matching is often used in observational studies to investigate a cause-and-effect relationship when randomization (as in a clinical trial) is not appropriate.[17] Matching is intended to find similar or comparable groups, and, if appropriately done, the patients in different groups are similar across the matching variables/confounders.[18] A bias-corrected matching estimator developed by Abadie and Imbens was implemented in this study following the counterfactual framework.[16,17] This was done to find a potential outcome (ie, counterfactual) for a BACC patient by averaging the outcome of matched Autograft patients. Nearest-neighbor matching on Mahalanobis distance was conducted with replacement, ties allowed, and at least 2 controls; weights were incorporated into the analysis.[16,19] The matching factors included the critical baseline demographic and clinical confounders: gender, age, ethnicity, race, burn causes, %TBSA burned (third-degree), %TBSA burned (second- and third-degrees), inhalation injury, diabetes mellitus, and hypertension.

Balance was assessed between the BACC and Autograft cohorts for each of the aforementioned confounders by standardized mean differences (SMD) before and after matching. Between the 2 cohorts, a covariate category that differed by at least 0.1 absolute SMD was considered imbalanced (ie, an absolute SMD of <0.1 was used to indicate a negligible difference between the 2 cohorts).[20,21] Once balanced after matching, the outcome of interest, LOS, was reported as the average treatment effect on the treated (ATT); bias adjustment and robust variances were calculated. An ad hoc analysis was performed to compare LOS between the BACC and the matched cohorts. Finally, a Rosenbaum sensitivity analysis was conducted to assess potential hidden biases.[22] Analyses were carried out using the R packages *Matching* and *Sensitivitymult*.[23]

## Results

The BACC cohort included 47 patients after data clean-up. Not all 52 patients in the StrataCAT study were included in the present analysis. In the StrataCAT study, there were 49 inpatients and 3 outpatients. The 3 outpatients were excluded in this study because outpatients did not have LOS (the primary endpoint). Moreover, 2 patients were removed from this analysis because they died 1 day after the surgery (unrelated to BACC). Those 2 patients might not have been appropriate trial candidates for BACC.

Following the application of StrataCAT inclusion/exclusion criteria to NBR data from the years 2020to 2021 and data clean-up, the final NBR Autograft cohort had 2641 patients (Figure 1). This cohort was a potentially eligible population from a real-world repository that could have participated in the StrataCAT clinical trial.

The study cohorts differed in demographics and key clinical characteristics before matching (Table 1). Compared with the Autograft cohort, the BACC cohort initially had older patients, more male patients, fewer Hispanic patients and more White patients. Before matching, the BACC cohort also had more patients with diabetes mellitus and hypertension, fewer patients with <10% TBSA burn, and more patients in the categories 20% to <30% and 40% to <50% TBSA burn (second- and third-degrees).

Confounder imbalances (with ≥0.1 absolute SMD) were observed in 12 out of 19 cohort characteristics at baseline (Figure 2). These covariates included age, ethnicity, race, 2 out of 3 types of burn causes, some categories of %TBSA burned (second- and third-degrees), diabetes mellitus, and hypertension.

Matching was then carried out to ensure that the patients in the 2 study cohorts were similar on the aforementioned covariates. Each patient in the BACC cohort was matched to at least 2 patients in the Autograft cohort and then weighted to 1. Following matching, the final Autograft cohort had 137 patients and was weighted to 47 patients, the same as in the BACC cohort. Patients in the BACC and final (matched) Autograft cohorts were similar in all demographic and clinical covariate categories after matching (ie, the absolute SMD were <0.1) (Table 1).

The analysis for ATT indicated that treatment with BACC reduced the inpatient LOS by an average of 4.84 days ($P$=0.0127) relative to the comparable (matched) Autograft cohort (Table 2 and Supplemental Table 2). An ad hoc

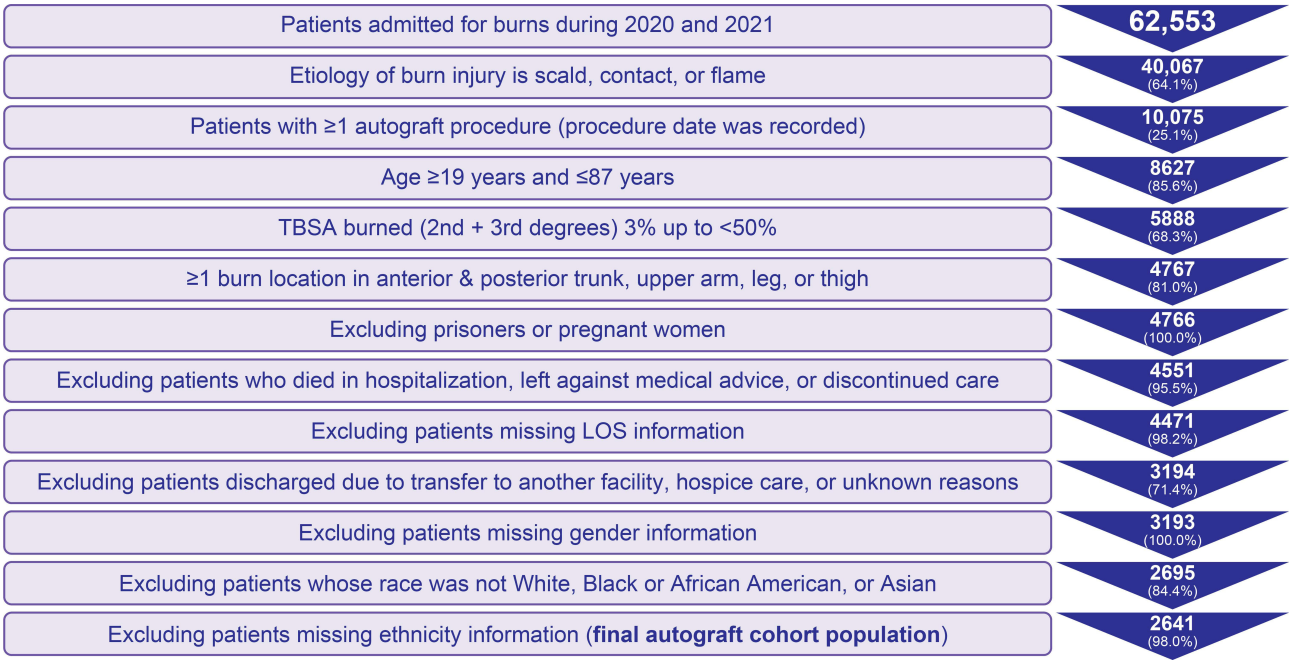


**Figure 1** Attrition diagram for patients from the National Burn Repository.
**Notes**: The number in parentheses at each step indicates the percentage of patients in the previous step.
**Abbreviations**: LOS, length of stay; TBSA, total body surface area.

analysis revealed that mean [SD] LOS for the BACC and the weighted Autograft cohorts were 17.68 [12.75] and 22.51 [19.75] days, respectively, and were 1.39 [0.94] and 1.88 [1.31] days per %TBSA burned, respectively (Table 3). The Rosenbaum sensitivity analysis revealed a gamma of 1.29 (Supplemental Table 3).

**Table 1** Confounder Balance Assessment Between BACC and Autograft Cohorts Before and After Matching

| | Raw | | | Matched | | |
|---|---|---|---|---|---|---|
| | **BACC (n = 47)** | **Autograft (n = 2641)** | **SMD** | **BACC (n = 47)** | **Autograft (n = 137, weighted = 47)** | **SMD** |
| **Demographic characteristics** | | | | | | |
| **Age (mean, years)** | 48.83 | 46.54 | 0.14 | 48.83 | 48.24 | 0.04 |
| **Gender, %** | | | | | | |
| Male | 72.34 | 67.85 | 0.0992 | 72.34 | 74.47 | −0.05 |
| **Ethnicity, %** | | | | | | |
| Hispanic or Latino | 4.26 | 8.71 | −0.22 | 4.26 | 4.26 | 0.00 |
| **Race, %** | | | | | | |
| Asian | 6.38 | 3.52 | 0.12 | 6.38 | 6.38 | 0.00 |
| Black or African American | 12.77 | 22.83 | −0.30 | 12.77 | 12.77 | 0.00 |
| White | 80.85 | 73.65 | 0.18 | 80.85 | 80.85 | 0.00 |

(*Continued*)

**Table 1** (Continued).

| | Raw | | | Matched | | |
|---|---|---|---|---|---|---|
| | **BACC (n = 47)** | **Autograft (n = 2641)** | **SMD** | **BACC (n = 47)** | **Autograft (n = 137, weighted = 47)** | **SMD** |
| **Clinical characteristics** | | | | | | |
| **Causes of burns-injury, %** | | | | | | |
| Contact | 12.77 | 7.99 | 0.14 | 12.77 | 12.77 | 0.00 |
| Flame | 70.21 | 66.22 | 0.09 | 70.21 | 72.34 | −0.05 |
| Scald | 17.02 | 25.79 | −0.23 | 17.02 | 14.89 | 0.06 |
| **%TBSA burned (third-degree), %** | | | | | | |
| 0% to < 10% | 89.36 | 91.71 | −0.08 | 89.36 | 89.36 | 0.00 |
| 10% to < 30% | 10.64 | 7.54 | 0.0996 | 10.64 | 10.64 | 0.00 |
| **%TBSA burned (second- and third-degrees), %** | | | | | | |
| 0.1% to <10% | 40.43 | 51.57 | −0.22 | 40.43 | 41.49 | −0.02 |
| 10% to <20% | 29.79 | 32.26 | −0.05 | 29.79 | 30.85 | −0.02 |
| 20% to <30% | 19.15 | 10.26 | 0.22 | 19.15 | 17.02 | 0.05 |
| 30% to <40% | 4.26 | 4.32 | 0.00 | 4.26 | 4.26 | 0.00 |
| 40% to <50% | 6.38 | 1.59 | 0.19 | 6.38 | 6.38 | 0.00 |
| **Concomitant conditions affecting outcomes, %** | | | | | | |
| Inhalation injury | 4.26 | 5.68 | −0.07 | 4.26 | 4.26 | 0.00 |
| **Targeted comorbidities of interest, %** | | | | | | |
| Diabetes mellitus | 25.53 | 11.47 | 0.32 | 25.53 | 22.34 | 0.07 |
| Hypertension | 44.68 | 26.54 | 0.36 | 44.68 | 42.55 | 0.04 |

**Abbreviations**: %TBSA, percentage of total body surface area; BACC, bioengineered allogeneic cellularized construct; SMD, standardized mean difference.

## Discussion

The aim of this study was to evaluate whether treatment with BACC (ie, the cause) impacts LOS (ie, the effect) in treatment of adult patients with DPT burns. To achieve this goal, the present study compared data from a single-arm clinical trial to a rigorously matched external control arm from the NBR real-world data.[11,14] NBR represents the largest resource in epidemiology of thermal injury for patients admitted to burn centers in North America;[14] therefore, these results are expected to be broadly generalizable across patients with DPT burn injuries.

Our analysis indicated that treatment of adult patients with DPT burns with BACC significantly reduced inpatient LOS by 4.84 days relative to autografting, the current standard of care. Additional research would be needed to clarify the reasons for this difference, but it could be related to the use of BACC reducing or eliminating the harvest of donor sites, and thus, the associated wound-related care and potential complications.[11] LOS reduction may translate to substantial clinical and economic benefits for patients and healthcare systems.[9,10] A shorter LOS enhances bed turnover rates, allowing hospitals to more efficiently allocate resources and manage patient capacity, crucial in periods of high demand or limited resources.[9] This capability is especially important in light of the current nursing shortage and the associated risk of increased medical errors and higher patient morbidity and mortality.[24] In addition to resource savings, treatment of adult patients with DPT burns with BACC, by eliminating donor-site harvest, may result in improved quality

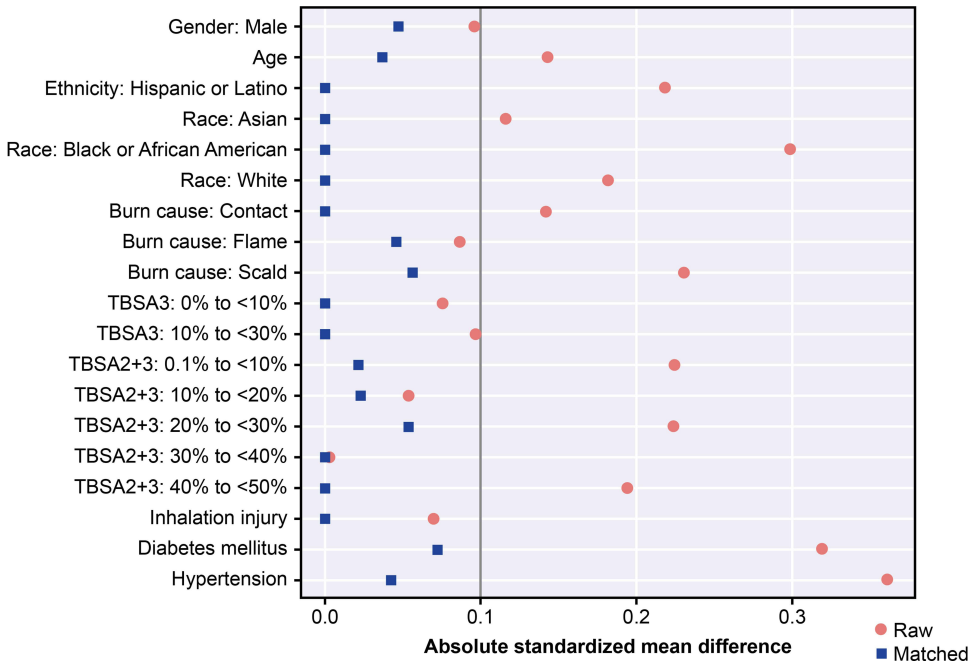


**Figure 2** Confounder balance assessment between BACC and Autograft cohorts before and after matching.
**Abbreviations**: BACC, bioengineered allogeneic cellularized construct; TBSA2+3, total body surface area, 2nd and 3rd degrees burned; TBSA3, total body surface area, 3rd degree burned.

of care and quality of life.[11] For example, patients may be at a lower risk of contracting hospital-acquired complications like infections (as well as costs associated with these infections) when recovering at home rather than in the hospital.[9,10]

The present study compared data from the single-arm StrataCAT trial for patients who received BACC to data from a rigorously matched external control arm comprising patients who received autografting for burn treatment during the

**Table 2** LOS in BACC Cohort versus Autograft Cohort

| ATT | Difference in LOS (days) | Robust Standard Error | *P* value | 95% Confidence Interval |
|---|---|---|---|---|
| BACC vs Autograft | −4.84 | 1.94 | 0127 | (−8.6389, −1.0333) |

**Abbreviations**: ATT, average treatment effect on treated; BACC, bioengineered allogeneic cellularized construct; LOS, length of stay.

**Table 3** Ad Hoc Analysis

| | Raw | | | | Matched | | | |
|---|---|---|---|---|---|---|---|---|
| | BACC (n = 47) | | Autograft (n = 2641) | | BACC (n = 47) | | Autograft (weighted: n = 47) | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| **LOS (day)** | 17.68 | 12.75 | 18.39 | 15.74 | 17.68 | 12.75 | 22.51 | 19.75 |
| **TBSA2+3 burned (%)** | 14.93 | 10.87 | 12.04 | 8.83 | 14.93 | 10.87 | 14.31 | 10.47 |
| **LOS/TBSA2+3 burned (day/%)** | 1.39 | 0.94 | 1.90 | 1.46 | 1.39 | 0.94 | 1.88 | 1.31 |
| **BACC total treatment area ($cm^2$)** | 709.36 | 576.23 | | | 709.36 | 576.23 | | |

**Abbreviations**: BACC, bioengineered allogeneic cellularized construct; LOS, length of stay; SD, standard deviation; TBSA2+3, total body surface area, 2nd and 3rd degrees burned.

same time period. Well-designed external control arms provide a viable alternative for interventional clinical studies in scenarios where using a control arm is impractical or ethically untenable.[25] The FDA has long recognized and supported the use of appropriate external controls from real-world data when necessary to support pivotal studies evaluating the clinical effectiveness of various interventions.[15,25] As a recent example, the FDA approved the first drug treatment for Friedreich's ataxia based in part on evidence from an open-label extension of a clinical trial and comparable untreated patients from a natural history study as an external control arm.[26]

Externally controlled studies do not involve randomization of the study patients to the interventions being compared.[15] Therefore, when designing a study, it is important to ensure that patients in the treatment arm and external control arms are as similar as possible in terms of known confounders (eg, baseline characteristics, disease severity) that may affect the treatment choices and outcome under investigation.[15] Rigorous assessment of the extent of confounding from such factors and sources of bias as well as statistical methods to reduce the impact of such bias are critical to study involving external control arms, even if unmeasured confounding may not be completely eliminated.[15] This study matched extensively on confounders and found a well-matched cohort as evaluated by <0.1 absolute SMD. It also used a Rosenbaum sensitivity analysis to assess potential hidden biases after match. The gamma of 1.29 found in this study indicated that ATT might be sensitive to unmeasured covariates (eg, different practice patterns in different burn centers). However, the result is consistent with findings from previous research, which showed that it is common to see a bias of gamma between 1 and 2 in social science studies.[27]

This study builds on previous discussions using external control arms, and it is novel because it balanced many confounders and found that treatment with BACC significantly reduced inpatient LOS over Autograft, the current standard of care. It is interesting to see that other researchers used a similar approach to evaluate other burn treatments. One study used electronic medical records to match adult patients who received inpatient burn treatment with autologous skin cell suspension (ASCS) ± split-thickness skin grafting (STSG) to patients treated with STSG alone on the basis of patient characteristics including sex, age, %TBSA, and comorbidities. ASCS ± STSG was associated with a numeric reduction in LOS compared with STSG alone.[28] In another publication, patients receiving inpatient treatment with ASCS ± STSG for burns <20% TBSA was matched to patients receiving STSG using baseline characteristics, and statistically insignificant reductions in LOS were observed.[29] Neither study showed whether confounders were balanced after matching, nor did they quantify the impact of hidden biases on the study results. In contrast, the rigorous analytic approach employed in the present study bolsters confidence in the finding that treatment with BACC significantly reduces inpatient LOS over Autograft.

The primary strength of this study is the counterfactual framework, which can be used to prove causality without randomization in observational studies.[17] A matching technique developed by Abadie and Imbens was implemented following the counterfactual framework to ensure comparable study populations in the StrataCAT expanded-access study arm and the NBR external control arm.[16] It is widely accepted that the increase in the number of matches (possibly resulting from a wider match distance) introduces additional bias while effectively reducing variance (sampling variation) in assessing treatment effects.[30,31] Austin found matching with 2 patients could be optimal in terms of the mean squared error.[30] In this study, some BACC patients were matched with more than 2 Autograft patients as ties were allowed. Nearest-neighbor matching on Mahalanobis distance with replacement may lower bias[19] and was therefore used in this study. Overall, the presence of multiple matches allows for reduced variance in assessing treatment effects.

In addition to the rigorous study design and analytic approach that bolster confidence in cause-and-effect finding, strengths of this study include the use of data from an expanded-access trial, StrataCAT. Study sites participating in the expanded-access study were able to leverage the experience gained from conducting the DPT pivotal clinical study.[4] The StrataCAT study allowed for an increase in the number of constructs utilized; therefore, the data from StrataCAT may more closely resemble the potential use of BACC in the real world. Additionally, while the StrataCAT study population was older, with greater %TBSA burned and more comorbidities than the general NBR population before matching, the StrataCAT inclusion/exclusion criteria were strictly applied to the NBR data collected during the same time period to find potential eligible patients who closely matched with the StrataCAT study and eliminate potential confounders. Indeed, the BACC and Autograft cohorts in this analysis were comparable after matching.

A further strength of this study is its use of a concurrent control versus a historic control group. Concurrent control groups are generally preferred, as use of historical controls tends to overestimate the effect of the more current treatment.[32] The use of a concurrent control group was especially important in this study because the StrataCAT study was conducted during an unusual time, the COVID-19 pandemic.

Limitations of this study included the challenges inherent in emulating randomized controlled trials. Well-designed real-world studies with non-randomized patients can lead to strong conclusions when design and measurements can be closely emulated, but this may be difficult to achieve, as residual confounding can be challenging to disentangle.[33] Even with the best efforts to align the external control arm with the StrataCAT experimental arm, not all StrataCAT trial inclusion/exclusion criteria were applicable to the NBR data because some required information that was not available from the NBR. Furthermore, there may have been potential sources of unmeasured bias (eg, differences in practice patterns among treatment centers and geographic regions) as this was an observational study. Additionally, the BACC cohort had a sample size of 47 participants, which may be considered small.[34]

Despite such limitations, this study highlights a clear benefit in terms of LOS when adults with DPT burns are treated with BACC versus autografting. More real-world data are required to increase the robustness of these observations.

## Conclusion

The clinical benefit of BACC over autografting, including the benefit with respect to reducing or eliminating autograft, has been demonstrated in several clinical trials. In this study, which compared real-world data from a well-matched external control arm from the NBR with data from the single-arm StrataCAT trial, LOS was statistically significantly shorter for BACC compared with a weighted Autograft cohort, with an average of 4.84 days ($P$ = 0.0127) reduction, among adults with DPT burns. A reduced LOS decreases the burden on the healthcare system, reduces costs for inpatient burn treatment, and provides clinical and quality-of-life benefits for patients. Additional real-world data are needed to further enhance the robustness of these findings.

## Abbreviations

ASCS, autologous skin cell suspension; ATT, average treatment effect on the treated; BACC, bioengineered allogeneic cellularized construct; DPT, deep partial-thickness; ECA, external control arm; FDA, US Food and Drug Administration; FT, full-thickness; IRB, Institutional Review Board; LOS, length of stay; NBR, National Burn Repository; SMD, standardized mean differences; SPT, superficial partial-thickness; STSG, split-thickness skin grafting; TBSA, total body surface area.

## Data Sharing Statement

Deidentified patient data will not be shared due to data use agreements.

## Ethics Approval and Informed Consent

This was a secondary data analysis involving deidentified patient and registry data and was therefore exempt from IRB review.[35–37] Under the Common Rule (45 CFR 46), research/secondary data analysis involving deidentified data is generally not considered "human subjects research," because it does not involve "a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual, or identifiable private information." (45 CFR 46.102[e])[35] The Office for Human Research Protection provides guidance stating that if the data are deidentified to the extent that subjects cannot be readily ascertained directly or through identifiers linked to them, then the data do not involve human subjects research as defined by the Common Rule.[36] Further, the HIPAA Privacy Rule indicates that once data are deidentified according to HIPAA standards (removing all 18 identifiers), it is no longer subject to HIPAA regulations.[37]

## Acknowledgments

The authors would like to thank the patients who participated in StrataCAT, their families, and all clinical staff at each study site. Medical writing and editorial support, conducted in accordance with Good Publication Practice 2022 and the

International Committee of Medical Journal Editors recommendations, were provided by Oxford PharmaGenesis Inc., Newtown, PA, and funded by Mallinckrodt Pharmaceuticals, plc., Bridgewater, NJ.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This work was supported by Stratatech, a Mallinckrodt Company.

## Disclosure

T-CY, HH, and RR are former employees of Mallinckrodt Pharmaceuticals, Bridgewater, NJ. F-SH and ZZ are employees of KMK Consulting Inc., Morristown, NJ, whose activities on research projects are funded by various pharmaceutical/biotech/medical device companies. ZZ also reports grants from Kyowa Kirin, Genmab US, and Teva Pharmaceutical Industries, outside the submitted work. The authors report no other conflicts of interest in this work.

## References

1. Bittner EA, Shank E, Woodson L, Martyn JA. Acute and perioperative care of the burn-injured patient. *Anesthesiology*. 2015;122(2):448–464. doi:10.1097/ALN.0000000000000559
2. Kagan RJ, Peck MD, Ahrenholz DH, et al. Surgical management of the burn wound and use of skin substitutes: an expert panel white paper. *J Burn Care Res*. 2013;34(2):e60–79. doi:10.1097/BCR.0b013e31827039a6
3. Chukamei ZG, Mobayen M, Toolaroud PB, et al. The length of stay and cost of burn patients and the affecting factors. *Int J Burn Trauma*. 2021;11(5):397–405.
4. Gibson ALF, Holmes J, Shupp JW, et al. A phase 3, open-label, controlled, randomized, multicenter trial evaluating the efficacy and safety of StrataGraft(R) construct in patients with deep partial-thickness thermal burns. *Burns*. 2021;47(5):1024–1037. doi:10.1016/j.burns.2021.04.021
5. Asuku M, Yu TC, Yan Q, et al. Split-thickness skin graft donor-site morbidity: a systematic literature review. *Burns*. 2021;47(7):1525–1546. doi:10.1016/j.burns.2021.02.014
6. American Burn Association. Burn Incidence Fact Sheet. Available from: https://ameriburn.org/resources/burn-incidence-fact-sheet/. Accessed March 6, 2024.
7. Yu TC, Zhang X, Smiell J, et al. Healthcare resource utilization, treatment patterns, and cost of care among patients with thermal burns and inpatient autografting in two large privately insured populations in the United States. *Burns*. 2020;46(4):825–835. doi:10.1016/j.burns.2019.10.019
8. Hahn H, Yu TC, Teng CC, Tan H. Holistic view of autografting patients by percentage of total body surface area burned: medical record abstraction integrated with administrative claims. *Clinicoecon Outcomes Res*. 2023;15:251–267. doi:10.2147/CEOR.S401003
9. Siddique SM, Tipton K, Leas B, et al. Interventions to reduce hospital length of stay in high-risk populations: a systematic review. *JAMA Network Open*. 2021;4(9):e2125846. doi:10.1001/jamanetworkopen.2021.25846
10. Lagoe RJ, Abbott JH, Littau SA. Reducing hospital lengths of stay: a five-year study. *Case Rep Clin Med*. 2021;10(06):160–167. doi:10.4236/crcm.2021.106020
11. Gibson ALF, Joe V, Carson J, et al. Open-label, expanded-access study of a bioengineered allogeneic cellularized construct in adults with deep partial-thickness burns. Paper presented at: American Burn Association 55th Annual Meeting 2023; Dallas, TX.
12. Holmes IV JH, Schurr MJ, King BT, et al. An open-label, prospective, randomized, controlled, multicenter, phase 1b study of StrataGraft skin tissue versus autografting in patients with deep partial-thickness thermal burns. *Burns*. 2019;45(8):1749–1758. doi:10.1016/j.burns.2019.07.021
13. Ziedins E, Corona A, McLawHorn M Long term scarring assessment of burn wounds treated with bioengineered allogeneic cellularized construct. Paper presented at: American Burn Association 55th Annual Meeting 2023; Dallas, TX.
14. American Burn Association. *2021 Full Burn Dataset*. Data Dictionary and Technical Documentation. 2021.
15. U.S. Food and Drug Administration. *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products: Guidance for Industry*. Silver Spring, MD: U.S. Department of Health and Human Services; 2023.
16. Abadie A, Imbens G. *Simple and Bias-Corrected Matching Estimators for Average Treatment Effects*. Cambridge, MA: National Bureau of Economics Research; 2002.
17. Glymour MM, Spiegelman D. Evaluating public health interventions: 5. causal inference in public health research-do sex, race, and biological factors cause health outcomes? *Am J Public Health*. 2017;107(1):81–85. doi:10.2105/AJPH.2016.303539
18. Song JW, Chung KC. Observational studies: cohort and case-control studies. *Plast Reconstr Surg*. 2010;126(6):2234–2242. doi:10.1097/PRS.0b013e3181f44abc
19. Abadie A, Drukker D, Herr JL, Imbens GW. Implementing matching estimators for average treatment effects in Stata. *Stata J*. 2004;4(3):290–311. doi:10.1177/1536867X0400400307
20. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46(3):399–424. doi:10.1080/00273171.2011.568786

21. Normand ST, Landrum MB, Guadagnoli E, et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. *J Clin Epidemiol*. 2001;54(4):387–398. doi:10.1016/S0895-4356(00)00321-8
22. Rosenbaum PR. Sensitivity analysis in observational studies. In: Everitt BS, Howell DC, editors. *Encyclopedia of Statistics in Behavioral Science*. Vol. 4. Chichester, England: John Wiley & Sons, Ltd.; 2005:1809–1814.
23. Sekhon JS. Multivariate and propensity score matching software with automated balance optimization: the matching package for R. *Journal of Statistical Software*. 2011;42(7):1–52. doi:10.18637/jss.v042.i07
24. Haddad LM, Annamaraju P, Toney-Butler TJ. Nursing Shortage. In: *StatPearls*. FL: Treasure Island; 2023.
25. Jahanshahi M, Gregg K, Davis G, et al. The use of external controls in FDA regulatory decision making. *Ther Innov Regul Sci*. 2021;55 (5):1019–1035. doi:10.1007/s43441-021-00302-y
26. U.S. Food and Drug Administration. FDA approves first treatment for Friedreich's ataxia. Aavialable from: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-first-treatment-friedreichs-ataxia. Accessed October 17, 2023.
27. Keele L. An Overview of Rbounds: an R Package for Rosenbaum Bounds Sensitivity Analysis with Matched Data. *White Paper*, Ohio State University, Columbus, OH. 2010.
28. Carter JE, Carson JS, Hickerson WL, et al. Length of stay and costs with autologous skin cell suspension versus split-thickness skin grafts: burn care data from US centers. *Adv Ther*. 2022;39(11):5191–5202. doi:10.1007/s12325-022-02306-y
29. Carson JS, Carter JE, Hickerson WL, et al. Analysis of real-world length of stay data and costs associated with use of autologous skin cell suspension for the treatment of small burns in U.S. centers. *Burns*. 2023;49(3):607–614. doi:10.1016/j.burns.2022.11.007
30. Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. *Am J Epidemiol*. 2010;172(9):1092–1097. doi:10.1093/aje/kwq224
31. Rosenbaum PR. Impact of multiple matched controls on design sensitivity in observational studies. *Biometrics*. 2013;69(1):118–127. doi:10.1111/j.1541-0420.2012.01821.x
32. Malay S, Chung KC. The choice of controls for providing validity and evidence in clinical research. *Plast Reconstr Surg*. 2012;130(4):959–965. doi:10.1097/PRS.0b013e318262f4c8
33. Wang SV, Schneeweiss S, Initiative R-D, et al. Emulation of randomized clinical trials with nonrandomized database analyses: results of 32 clinical trials. *JAMA*. 2023;329(16):1376–1385. doi:10.1001/jama.2023.4221
34. Rosenbaum PR. Two R packages for sensitivity analysis in observational studies. *Observational Studies*. 2015;1(2):1–17. doi:10.1353/obs.2015.0000
35. US Department of Health and Human Services. Basic HHS Policy for Protection of Human Subjects. 45 CFR § 46.102(e):2018.
36. Office for Human Research Protections. Guidance on Research Involving Coded Private Information or Biological Specimens. U.S. Department of Health and Human Services. https://www.hhs.gov/ohrp/coded-private-information-or-biospecimens-used-research.html. Accessed July 29, 2024.
37. US Department of Health and Human Services. Standards for privacy of individually Identifiable Health Information. 45 CFR §164:514;2013.