Early Enzymatic Burn Debridement: Results of the DETECT Multicenter Randomized Controlled Trial

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Since 1970 surgeons have managed deep burns by surgical debridement and autografting. We tested the hypothesis that enzymatic debridement with NexoBrid would remove the eschar reducing surgery and achieve comparable long-term outcomes as standard of care (SOC). In this Phase 3 trial, we randomly assigned adults with deep burns (covering 3–30% of total body surface area [TBSA]) to NexoBrid, surgical or nonsurgical SOC, or placebo Gel Vehicle (GV) in a 3:3:1 ratio. The primary endpoint was complete eschar removal (ER) at the end of the debridement phase. Secondary outcomes were need for surgery, time to complete ER, and blood loss. Safety endpoints included wound closure and 12 and 24-months cosmesis on the Modified Vancouver Scar Scale. Patients were randomized to NexoBrid (n = 75), SOC (n = 75), and GV (n = 25). Complete ER was higher in the NexoBrid versus the GV group (93% vs 4%; P < .001). Surgical excision was lower in the NexoBrid vs the SOC group (4% vs 72%; P < .001). Median time to ER was 1.2 and 3.9 days for the NexoBrid and SOC respectively (P < .001). ER blood loss was lower in the NexoBrid than the SOC group (14 ± 512 mL vs 814 ± 1020 mL, respectively; P < .0001). MVSS scores at 12 and 24 months were noninferior in the NexoBrid versus SOC groups (3.7 ± 2.1 vs 5.0 ± 3.1 for the 12 months and 3.04 ± 2.2 vs 3.30 ± 2.76 for the 24 months). NexoBrid resulted in early complete ER in >90% of burn patients, reduced surgery and blood loss. NexoBrid was safe and well tolerated without deleterious effects on wound closure and scarring.

Key words: burns; enzymatic debridement; eschar; surgery; excision; grafting.

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Conflict of Interest: Y.S. is a consultant for MediWound and Vericel and owns stock in MediWound. L.R. is a consultant for MediWound and owns stock in MediWound. S.B.E. owns stock in Biomed Sciences. J.G. owns stock in MediWound and is a consultant and speaker for Vericel. W.H. received consulting fees from Access Pro Medium-C MO Burns and SiOx-Medical. A.J.S. is a speaker for AstraZeneca, Janssen and Abbott and is a consultant for AstraZeneca and Abbott. N.I., J.B.O., M.S., S.M. have no COI to disclose.

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INTRODUCTION

It is estimated that nearly 500 000 patients in the United States seek medical attention for burn injuries annually with about 40 000 requiring acute inpatient hospitalization.[1] These injuries lead to >3000 deaths in the United States alone.[1–3] Improvements in resuscitation have led to reductions in mortality.[4] However, management of the burn wound itself remains challenging.[5]

The current standard of care (SOC) for deep burns is removal of the eschar (debridement),[6,7] predominantly by surgical excision followed by skin grafting.[8] While reducing mortality and scarring, surgical excision is traumatic and requires specialized personnel and facilities. Early enzymatic and selective debridement of the eschar is an alternative, nonsurgical modality that may, in many cases, obviate the need for surgical excision with its inherent drawbacks and complications.[9,10] Anacaulase-bcdb (NexoBrid, MediWound Ltd, Yavne, Israel) has been developed and shown to reduce the overall need for and extent of surgery, while reducing blood loss and achieving long-term functional and cosmetic outcomes comparable to those with surgical excisional debridement.[9–14] While NexoBrid is approved for use in Europe and other regions outside of the United States, this study was required for US Food and Drug Administration approval. In addition, the study offered the potential for approval of a nonsurgical alternative for eschar removal (ER), with advantages in routine burn care and in burn mass casualty incidents, and funding was provided by the Biomedical Advanced Research and Development Authority (BARDA) within the Administration for Strategic Preparedness and Response (ASPR) in the US Department of Health and Human Services (HHS).

We conducted the Phase 3 DEbride and proTECT (DETECT) trial to assess the efficacy and safety of enzymatic debridement (ER) with NexoBrid when compared with placebo (Gel Vehicle [GV]), as well as reduction in surgical burden and blood loss compared with SOC in adults with deep burns.

METHODS

Trial oversight

The study was designed and initially funded by MediWound Ltd. (Yavne, Israel). Subsequent funding and oversight were provided by the Biomedical Advanced Research and Development Authority (BARDA) within the Administration for Strategic Preparedness and Response (ASPR) in the US Department of Health and Human Services (HHS).

Ethical considerations

The study was conducted according to Good Clinical Practice (GCP) guidelines and principles of the Declaration of Helsinki. Twenty-nine centers in 8 countries (United States, Belgium, Czech Republic, Germany, Romania, Israel, Italy, and Georgia) enrolled and randomized patients into the study. All study sites had written approval from their Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and local Competent Authority (as required locally), and all patients or their designees provided written informed consent before participating in the study. An independent data safety monitoring board (DSMB), consisting of two experienced burn specialists and a biostatistician, periodically convened in accordance with enrollment rate to assess safety data.

Patient selection and randomization

Adult patients (ages 18 years and older) suffering from deep partial or full thickness burns (caused by flame, scald, or contact) involving between 3% and 30% of their TBSA were eligible for the study. Only patients who could be consented within 84 h of injury were included. Study eligibility required that each patient have a target wound involving any area of the body except for the face and perineum, which was deep partial or full thickness and involved at least 0.5% TBSA. Exclusion criteria included patients with circumferential burns of the limbs, infected burns, inhalation injury, pregnancy, and a major comorbidity.

Study design and treatments

The DETECT study (NCT02148705; EudraCT 2014-001672-55) was a Phase 3, randomized, controlled, assessor blinded (2 endpoints), 3 arm, multicenter, international study designed to evaluate NexoBrid treatment compared to GV (placebo control) and SOC (nonsurgical and surgical). The study was conducted from May 2015 (first patient enrolled) to September 2019 (last patient completed).

An overview of the DETECT study design is shown in Figure 1. NexoBrid is a one- or two-time, 4-hour topical application with a short systemic exposure; therefore, primary efficacy and safety assessments were performed in the acute phase which was defined as up to 3 months post wound closure. In addition, as prespecified in the protocol, safety data were collected in the DETECT study in both the acute phase and in longer-term follow-up with a cutoff of 12 and 24 months after complete wound closure of all treated wounds.

Prior to treatment, eligible patients were randomly assigned in a 3:3:1 ratio to receive NexoBrid, SOC, or placebo (GV). Randomization was done in random and permuted blocks stratified by trial center and burn size by means of a GCP electronic data capture web-based service.

Treatments

An overview of the 3 treatment arms is depicted in Figure 2. All patients who met eligibility criteria were to receive ER treatment per the randomized treatment arm. Wound depth was assessed by clinical evaluation.[15] Patients in all treatment arms (NexoBrid, SOC, and GV) were treated in a similar way except for the ER stage. Prior to initiation of ER, patients were medicated with appropriate analgesia and underwent wound cleansing and dressing of all wounds with antibacterial solutions. Subsequently, patients underwent the ER process as per treatment assignment (NexoBrid, SOC, or GV).

NexoBrid treatment:

The overlying necrotic keratin layer (ie, the blisters) was removed and the burn was soaked in an antibacterial solution for at least 2 h. In patients assigned to NexoBrid the enzymatic agent was applied at a dose of 2-gram sterile

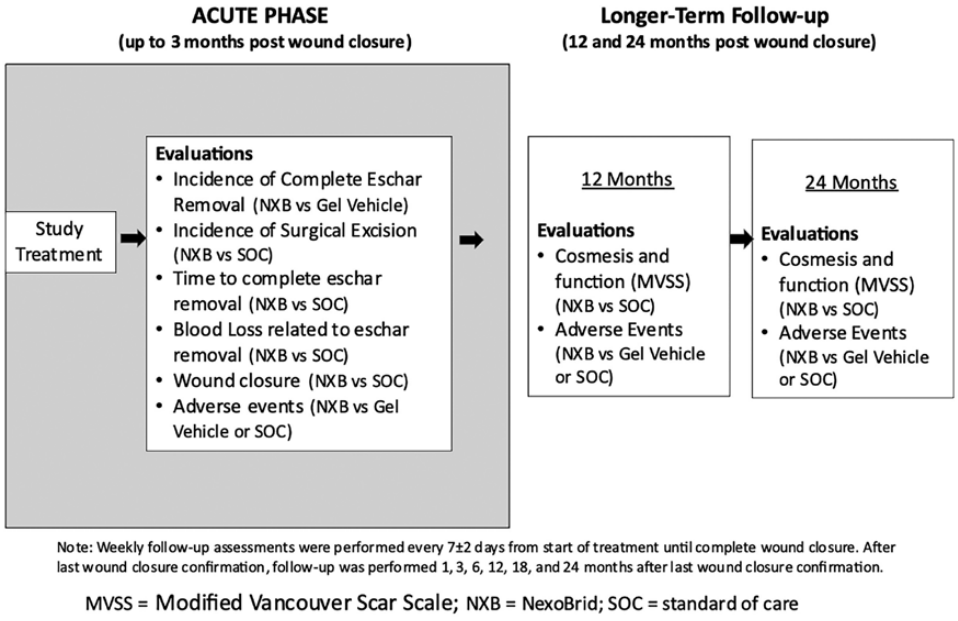

Figure 1. Overall Study Design and Key Endpoints for the DETECT (MW2010-03-02) Study

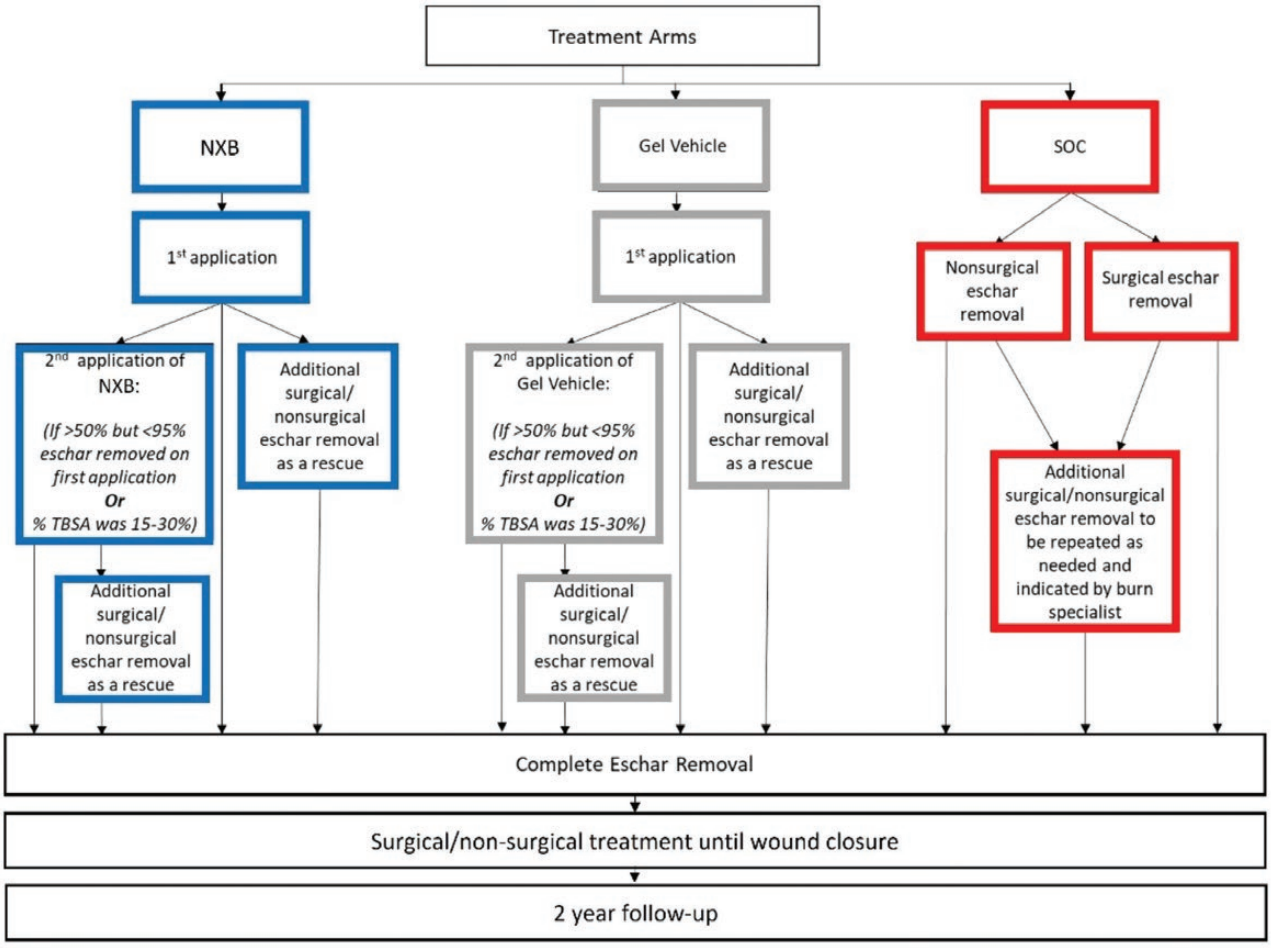

Figure 2. Summary of Treatment Interventions (NXB = NexoBrid, SOC = Standard of Care)

powder mixed with 20-gram sterile GV per 1% adult TBSA burn. A barrier of petrolatum gel was applied adjacent to the burn edges. The wound was then covered with an occlusive dressing in order to contain the enzymatic agent for 4 h. After 4 h, the dressings were removed and the enzymatic agent together with dissolved eschar was wiped with a wooden tongue depressor. The wounds were soaked in an antibacterial solution for an additional 2 h and then cleaned prior to assessment of ER. The amount of NexoBrid applied at any one session was limited to 15% TBSA. Patients with burns greater than 15% TBSA had the NexoBrid applied in two separate sessions. According to the study protocol, if ER was incomplete, NexoBrid could be reapplied one additional time.

GV (placebo control):

In patients assigned to the placebo (GV), all study interventions were as for NexoBrid except that only the topical gel, at a dose of 20 gram per 1% TBSA burns, was applied (without the active enzyme powder).

SOC:

Patients in the SOC arm may have been treated with a combination of surgical (eg, tangential excision, fascial excision, hydrosurgery, or dermabrasion) and nonsurgical (eg, collagenase ointment, antimicrobial solutions, or silver dressings) ER procedures according to the investigator's judgment. If nonsurgical SOC treatment did not result in complete ER, surgical SOC treatment may have been employed as a rescue procedure, according to the investigator's judgment. The procedures were repeated as needed until complete ER.

In case of failure of debridement in patients treated by NexoBrid or the placebo GV a rescue SOC treatment could be used at the discretion of the treating physician.

Wound closure

Following ER, the strategy used for wound bed closure was at the discretion of the burn surgeon. If enough viable dermis remained, the wound was allowed to re-epithelialize spontaneously. In patients with inadequate viable dermis to support spontaneous wound re-epithelialization, wound closure was achieved with autografting. Partial autografting of areas of deeper wounds or wounds with delayed epithelialization was done according to the burn surgeon's clinical judgment. Patients were then followed up for up to two years.

Data collection

We collected the data using standardized, structured data collection forms that included medical history, physical examination, pain levels (using a 100 mm unhatched visual analog scale [VAS] from 0 [none] to 100 [worst]), wound photographs, wound cultures, and central laboratory tests. Burn depth assessments were performed by clinical evaluation by experienced burn surgeons both before and after ER.[16,17] The %TBSA of the burn was assessed by a burn surgeon using Lund and Browder charts[18] or Wallace's Rule of Nine,[19] or for small burns: the patient's own palm (including the fingers), which was estimated as 1% TBSA,.[20] We also collected detailed information on all surgical procedures including blood loss and blood transfusions, percentage area of wound grafted, graft take, size of donor sites, and need for scar modulation.

Study endpoints/outcomes

An overview of the prespecified primary and secondary efficacy endpoints and key safety outcomes is provided in Table 1. The primary efficacy outcome was complete ER in the NexoBrid compared to GV (placebo) arm. The ER assessment was performed by a trained health professional who was not involved in the treatment of the patient or wound, as the treating physician could distinguish between treatments administered to each patient. For the topical arms (NexoBrid and GV), ER assessment was performed immediately following removal of the soaking dressing (6 h after start of first and second treatment and after any additional procedure until complete ER). The dressing was soaked with antibacterial solution, for example 3–5% Sulfamylon, 0.05–0.5% chlorhexidine, Dakin's solution, hypertonic 5–10% saline solution, or 0.9% saline, applied to the wound and left in place. The assessment included wound depth assessment and clinical assessment of the extent of ER. In all 3 treatment arms, ER was considered complete when more than 95% of the eschar was removed, as per the American Burn Association consensus guidelines.[7] Secondary efficacy outcomes included comparisons between NexoBrid and SOC in the need for surgical excision, time to ER, and estimated blood loss.[21]

Safety endpoints included time to wound closure, and long-term assessments of scar appearance and function. Wounds were considered closed when fully re-epithelialized without any drainage or need for outer dressings and confirmed at least two weeks later. Scar appearance was assessed using the Modified Vancouver Scar Scale[22] ranging from 0 to 15 from best to worst. All wound assessments were performed by observers blinded to all treatment assignments. Additional safety assessments included pain (VAS and adverse events), level of sedation, and adverse events.

Statistical analysis

The study was powered at 90% to detect a difference between groups for the primary and secondary endpoints based on data obtained in earlier studies.[23] The total sample size was determined to be 121 patients (65 NexoBrid, 13 GV, and 43 SOC); however, the enrolled patient number was increased to a total of 175 to provide adequate information on safety outcomes.

All statistical analysis was predefined in a Statistical Analysis Plan. Demographics and relevant baseline information are presented and summarized with appropriate descriptive statistics. Chi-square tests (or, in case of small, estimated cell counts, Fisher's exact test) for categorical variables and one-way analysis of variance for continuous variables were used to assess the comparability of the baseline characteristics between the treatment arms. If any of the baseline characteristics were found to be significantly different between the treatment arms, then the factor was included as an extra adjusting covariate in the supportive analysis models. Burn center was a covariate in secondary and sensitivity analyses of the primary and secondary endpoints.

Table 1. Primary and Secondary Efficacy Endpoints and Key Safety

Primary efficacy endpoint		
Complete Eschar Removal in the topical treatment arms	NexoBrid vs GV (placebo); assessor blinded to treatment	The main analysis was based on the binary variable (yes/no): "has complete eschar removal been achieved in all TWs."
Secondary efficacy endpoints		
Time to complete eschar removal (days)	NexoBrid vs SOC	Time (days) when complete eschar removal was achieved for each patient from the time of randomization.
Reduction in surgical needs	NexoBrid vs SOC	Incidence of surgical eschar removal (tangential/minor/avulsion/ Versajet, and/or dermabrasion excision) in the NexoBrid compared with SOC arm.
Amount of blood loss during eschar removal process	NexoBrid vs SOC	Actual blood loss (ABL), changes in hemoglobin during the eschar removal procedures, and units of blood transfused.
Safety endpoints and assessments		
Wound Closure	NexoBrid vs SOC Assessor blinded to treatment	Time to reach complete wound closure, assessed in days from randomization. A noninferiority margin of 7 days was used in the analysis.
Cosmesis and Function (MVSS)	NexoBrid, SOC, and GV Assessor blinded to treatment	Used to assess the quality of the wound closure scar at 1, 3, 6, 12, and 24 months post wound closure
Level of Sedation	NexoBrid, SOC, and GV (placebo)	Number and percentage of patients per each level of sedation and each eschar removal procedure (in topical arms: first and second topical application, surgical rescue procedures, and nonsurgical rescue procedures; in SOC arms: surgical procedures and nonsurgical procedures)
Pain assessment	NexoBrid, GV (placebo), and SOC	Pain was assessed as a patient reported outcome using visual analog scale [VAS], and as reported as an adverse event
Adverse Events	NexoBrid, SOC, and GV (placebo)	Treatment emergent adverse events

GV = Gel Vehicle; MVSS = Modified Vancouver Scar Scale; SOC = Standard of Care.

For the primary and secondary endpoints all patients randomized were included in the analysis in the group in which they were randomized (full analysis set [FAS] =intention-to-treat principle). For safety summaries, patients were included in the treatment arm in which they were treated.

For the primary efficacy endpoint, the proportions of patients who reached complete ER at the end of the topical agent soaking period were compared using logistic regression. The primary analysis was based on the binary variable (yes/no): "has complete eschar removal been achieved in all TWs" (as defined in study endpoints). The primary efficacy comparison was between the NexoBrid and GV arms. The statistical test was based on Fisher's exact test because of the small numbers expected in the GV treatment arm. The odds ratio of achieving complete ER for NexoBrid versus GV and its 95% confidence interval (CI) were estimated using exact distribution methods. If assessment data of complete ER were missing, the patient was counted as having failed the endpoint (ie, as not having achieved complete ER).

Time until complete ER was defined as the time from randomization date (in days) until complete ER had been achieved at a patient level (ie, for all TWs of an individual patient). For patients who did not reach complete ER, time was censored at the last nonmissing ER assessment (typically the last debridement procedure). Kaplan-Meier curves were presented graphically to display the distribution of time to complete ER under the 2 treatments (NexoBrid versus SOC). Median time to complete ER was estimated for each treatment arm with a 95% CI. Additionally, time to complete ER was analyzed descriptively with number of units, number of missing values, mean, standard deviation, min, max, median, and quartiles. The treatment arms were compared using a Cox regression model.

The incidence of surgical excision was a binary yes/no variable and the proportion of patients who needed excision for ER were compared using logistic regression. The explanatory variables in the model included treatment and the following variables: overall TW depth (all TWs FT, mixed TWs, and all TWs DPT), "Total % TBSA per patient," and number of TWs (1, 2, and ≥3). The odds ratio of requiring surgery for NexoBrid versus SOC was estimated from the model, as well as 95% CIs and the level of statistical significance.

The measure of actual blood loss (ABL) was computed for each patient as described in the results section on blood loss, and the distribution in the NexoBrid arm was compared with that in the SOC arm. Means, standard deviations, medians, and interquartile ranges were calculated. The normality of the data was tested on each treatment arm using the Shapiro-Wilk test. If the normal distribution hypothesis was not rejected at the 0.5% significance level in either arm, then differences in distribution between NexoBrid and SOC were tested using a *t*-test. If the normal distribution hypothesis was rejected either in the NexoBrid arm or in the SOC arm, then the differences in distribution between the treatment arms were tested using a Mann-Whitney test. Missing values were handled by the method of multiple imputation.

To preserve the overall significance level of each efficacy endpoint, a hierarchical test procedure was implemented. Since highly statistically significant results were obtained for all primary and secondary endpoints, the testing procedure did not stop, implying that all statistical tests of the primary and secondary endpoints primary analyses can be considered as confirmatory.

The safety endpoint of time to wound closure was analyzed using the FAS. Time to reach complete wound closure (time from randomization to confirmation of wound closure) was compared between NexoBrid and SOC at a wound level using a method of survival analysis with clustered data that is based on appropriate assumptions. "Clustered data" refers to the multiple TWs that can occur in a patient. A noninferiority (NI) margin was incorporated into the analysis that represented a 7-day advantage to the SOC arm. After that, the proportional hazards assumption was checked in the same way as in the analysis of the timely ER endpoint.

The means and standard errors of the MVSS scores at 12 and 24 months were estimated for each treatment arm. The treatment arms were compared using a linear model with MVSS scores as the dependent variable. A clinically meaningful noninferiority margin was incorporated into the analysis that represented 1.9 units or more advantage to the SOC treatment arm for the MVSS analysis. No statistical analysis was planned or performed for the pain assessment, level of sedation, or for adverse events.

The data were analyzed with SAS (SAS Institute, Cary, North Carolina), version 9.4.

RESULTS

Patient disposition and characteristics

A patient disposition consort diagram is shown in Figure 3. One-hundred and seventy-five patients were randomized in the DETECT study: 75 to the NexoBrid arm, 75 to the SOC arm, and 25 to the GV arm (FAS equivalent to intention to treat group). Of the 175 randomized patients, 169 received the study treatment; 77 patients were treated with NexoBrid, 68 with SOC, and 24 with GV (safety set).

A similar percentage of patients across treatment arms completed each phase of the study with most patients completing the acute phase (84%–92% in all arms), and more than 75% completing the 12-month follow-up phase (76%–80% in all arms). At 24 months, the study completion rates were, as expected, lower (57% in NexoBrid, 48% in the SOC, and 40% in the GV). The higher drop-out rate is not uncommon among the burn population in long-term trials.[24]

Table 2 provides a summary of patient demographics and burn characteristics. Patient characteristics and burn etiologies at baseline were similar across treatment groups. Most patients were White (79%–84%) males (60%–79%), with mean age of 41 years and body mass index of 27. The average time from injury to informed consent was from 33 to 38 h, and the majority of patients had burns with fire/flame burn etiology (59%–84%). Mean %TBSA was similar across treatment groups (8.3%–9.0%);and the distribution of all target wounds by %TBSA was similar across treatment groups for SPT, DPT, and FT wounds. Representative images of a burn treated with NexoBrid are shown in Figure 4.

Efficacy results

Incidence of complete ER (NexoBrid vs GV)

More than 93% of the patients treated with NexoBrid achieved complete debridement following 1 application of NexoBrid compared with 4% in the GV arm ($P < .0001$). All supportive, exploratory, and subgroup analyses (results not shown) consistently supported the primary analysis result. These consistent results demonstrate that NexoBrid is a highly effective enzymatic debriding agent.

Time to complete ER (NexoBrid vs SOC)

The Kaplan-Meier estimates for time to complete ER (defined as time from the time of randomization until date of complete ER) for the NexoBrid and SOC treatment arms in the FAS (main analysis) are shown in Table 3. The estimated median time to complete ER was 1.0 and 3.8 days for the NexoBrid and SOC treatment arms, respectively ($P < .0001$).

Reduction in surgical needs (incidence of surgical excision) (NexoBrid vs SOC)

The proportion of patients who needed any surgical excision for ER was compared in the NexoBrid and SOC treatment arms using logistic regression. Surgical excision was required for ER in 72% of SOC and 4% of NexoBrid patients. The calculated OR was 0.011 ($P < .0001$) (Table 4), meaning the NexoBrid group had a 98.9% [(1 – 0.011) × 100] decrease in the odds of having surgical excision compared to the odds of excision in the SOC group. The results of the sensitivity analyses (results not shown: per protocol [included patients without major protocol violations], complete cases [only patients without missing values], and positive analyses [missing information counted as no surgical excision]) were similar to the results of the main analysis (4.0%–4.05% incidence rates of surgical excisions and odds ratios of 0.010–0.015 for patients in the NexoBrid treatment arm).

ABL related to ER (NexoBrid vs SOC)

The ABL formula takes into account the changes in hemoglobin before and after the first debridement period as well as the volume of whole blood/PRBC transfused.

The ABL that occurred for each patient during ER was calculated as:

$$ABL = \frac{EBV * \left(Hb_{before} - Hb_{after}\right)}{\left(Hb_{before} + Hb_{after}\right)/2} + V_{WB} + \frac{5}{3}V_{PC}$$

EBV = estimated blood volume assumed to be 70 cm^3/kg, ($Hb_{before} - Hb_{after}$) = Changes in hemoglobin (Hb) following each ER procedure, V_{WB} = Volume [mL] of whole blood transfused, V_{PC} = Volume [mL] of packed red blood cells transfused, 5/3 = factor derived from Transfusion Medicine, 4th Edition (Chapter 5); compensates for comparison of whole blood and packed red blood cells.

There was significantly less ABL related to ER in the NexoBrid compared with the SOC treatment arm. The mean ABL during ER for patients in the NexoBrid arm was approximately 14 mL compared with over 800 mL in the SOC arm (*P*-value < .0001). Sensitivity analyses supported this primary analysis.

Safety results

Wound closure and cosmesis and function were included in the DETECT study as safety endpoints. Adverse events and level of sedation are standard clinical trial summaries. Adverse events are reported for the entire length of follow-up (up to 24 months).

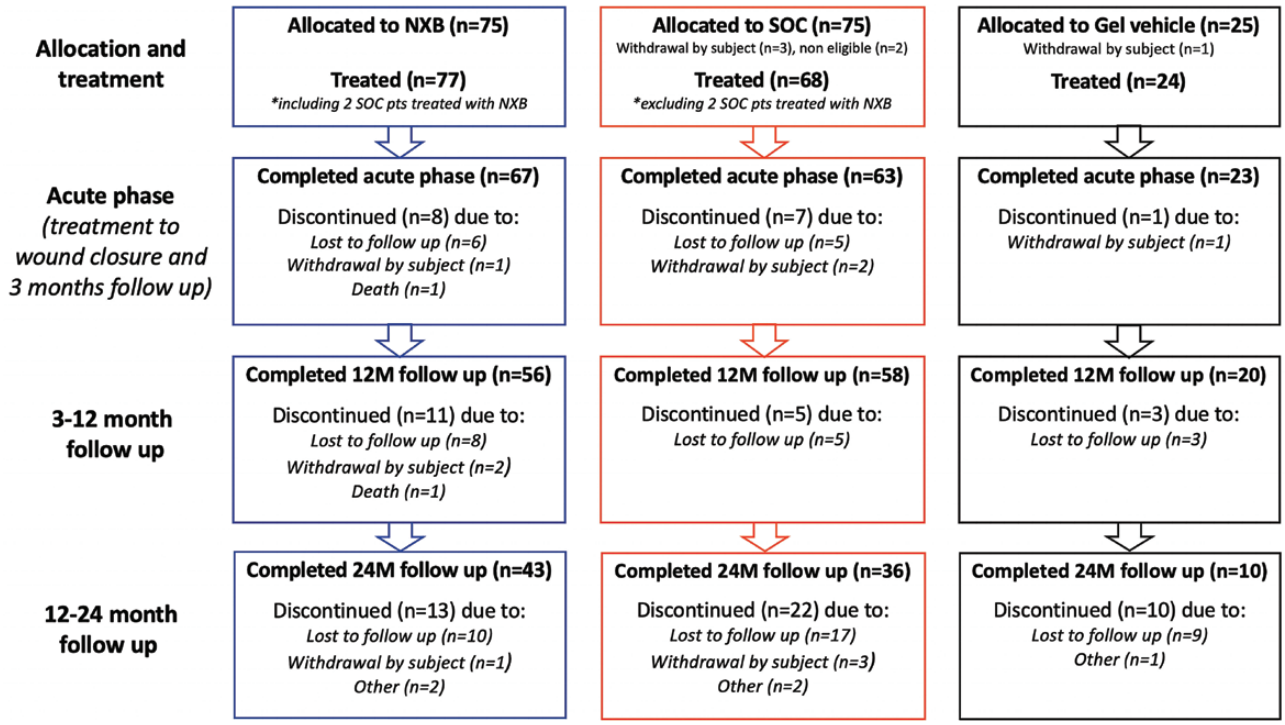

Figure 3. Patient Disposition Consort Diagram. Details Regarding Randomization and Numbers of Patients Completing Each of the 3 Phases of the Study (Acute [Primary Efficacy and Safety ≥3 Months Post Wound Closure], 12 Month [Long-term Safety Follow-up at 12 Months Post Wound Closure], and 24 Month [Long-term Safety Follow-up at 12 Months Post Wound Closure]). For Efficacy Endpoints, All Patients Randomized were Included in the Analysis in the Group in which They were Randomized (Full Analysis Set [FAS] = Intention-to-treat principle). For Safety Summaries, Patients Were Included in the Treatment Arm in Which They were Treated (Safety Set)

Table 2. Patients' and Wounds' Baseline Characteristics

	NexoBrid (N = 75)	SOC (N = 75)	Gel (N = 25)
Patients			
Age, mean (SD)	41.28 (15.03)	40.91 (15.16)	40.68 (17.30)
Sex, male, *n* (%)	49 (65.33)	59 (78.67)	15 (60.00)
Race, White *n* (%)	61 (81.3)	59 (78.7)	21 (84.0)
BMI, mean (SD), kg/m^2	27.64 (4.90)	26.56 (4.42)	27.02 (4.38)
Wounds			
Mean (SD) time from injury to informed consent, hours	37.62 (20.09)	37.98 (17.95)	33.35 (17.28)
Etiology of injury, *n* (%)[a]			
Fire/flame	44 (58.7)	44 (58.7)	21 (84.0)
Scald	22 (29.3)	18 (24.0)	2 (8.0)
Contact	8 (10.7)	12 (16.0)	2 (8.0)
Mean (SD) % TBSA per person all wounds	8.97 (5.18)	8.34 (4.24)	8.93 (3.63)
Mean (SD) % TBSA per person all target wounds	6.28 (3.68)	5.91 (3.06)	6.53 (3.60)
Wound distribution			
Mean (SD) %TBSA SPT	0.49 (0.85)	0.52 (0.90)	0.89 (1.33)
Mean (SD) %TBSA DPT	2.24 (1.59)	2.20 (1.70)	2.07 (1.60)
Mean (SD) %TBSA FT	0.95 (1.67)	0.71 (1.23)	0.84 (1.33)

BMI = body mass index; DPT = deep partial thickness; FT = full thickness; SD = standard deviation; SOC = standard of care, SPT = superficial partial thickness TBSA = total body surface area.

Wound closure (NexoBrid vs SOC)

The evaluation of wound closure as a safety endpoint was designed as a noninferiority test comparing time to wound closure between NexoBrid and SOC to ensure that enzymatic debridement of burn wounds using NexoBrid had no deleterious effect on the time to wound closure.

Time to reach complete wound closure was comparable in the NexoBrid and SOC treatment arms. The

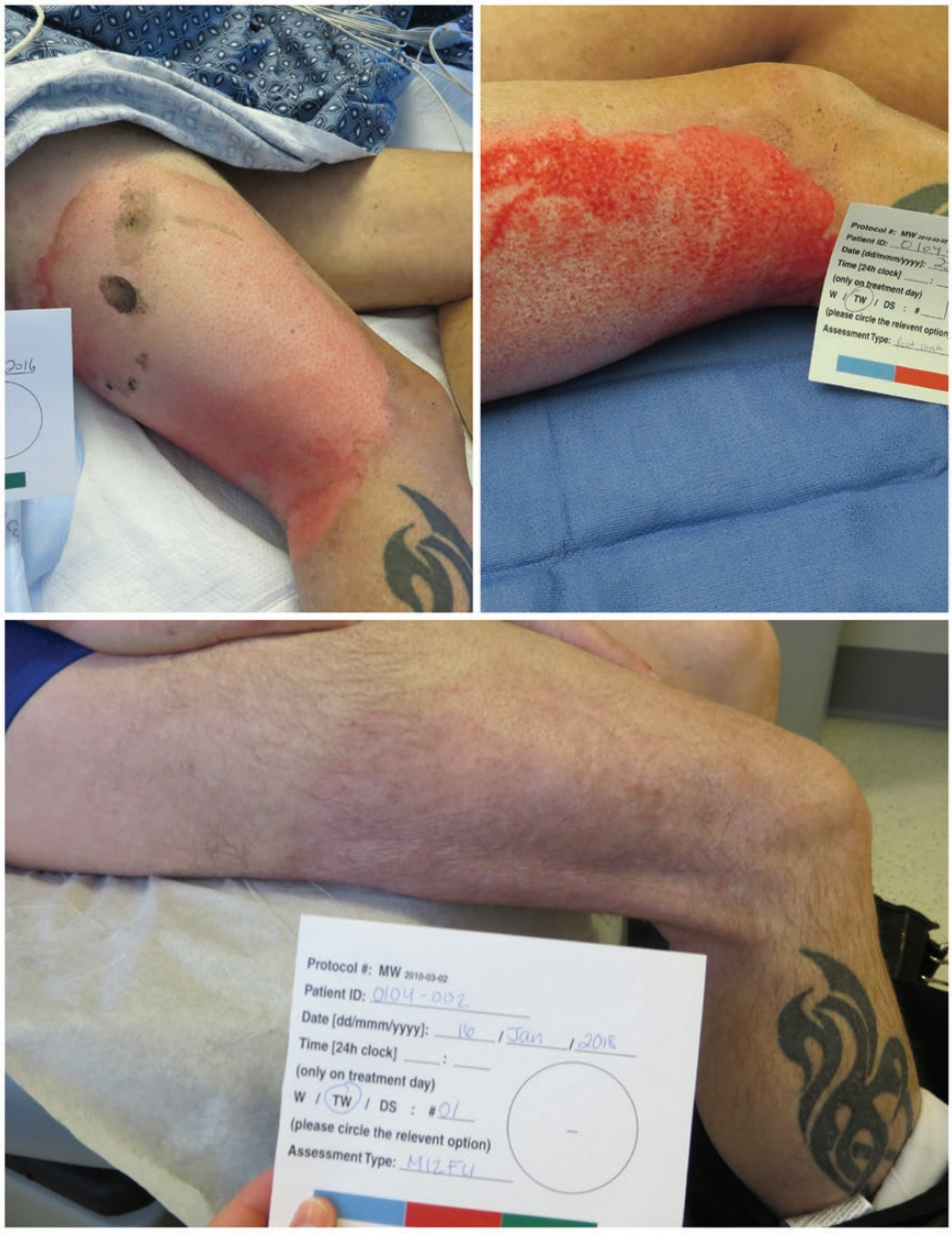

Figure 4. Representative Images of a Deep Partial Thickness Burn Treated With NexoBrid. The Upper Images Show a Burn of the Thigh Before (left) and After (Right) Enzymatic Debridement. The Lower Image Shows the Appearance of the Wound 1 Year after Injury

Table 3. Kaplan–Meier Estimates for Time to Complete Eschar Removal NexoBrid vs SOC

Treatment	Median (days)	Lower 95% confidence bound	Upper 95% confidence bound
NexoBrid (75 patients)	1.0232	0.9827	1.0799
SOC (75 patients)	3.8279	1.9872	5.9849

FAS, full analysis set; SOC, standard of care.
$P < .0001$ (Generalized Wilcoxon-Gehan test adjusted for overall treated wound dept, TBSA group, center group, and number of treated wounds).

Kaplan-Meier estimated median time to complete wound closure for NexoBrid and SOC, was 27 and 28 days, respectively. Statistical analysis established the noninferiority of NexoBrid compared with SOC when incorporating a 7-day advantage for the SOC group ($P < .01$).

Cosmesis and function (NexoBrid, SOC, and GV)

The 12-month follow-up mean MVSS scores were lower (better) for the NexoBrid group (3.7 ± 2.1) than for the SOC (5.1 ± 3.1) and Gel groups (5.6 ± 3.0). A regression analysis showed that NexoBrid had a 1.4 MVSS point advantage

Table 4. Incidence of Surgical Excision for Eschar Removal NexoBrid vs SOC

n	Surgical excision incidence rate	Odds ratio[a]	Test	2-sided *P*-value	Lower 95% confidence bound	Upper 95% confidence bound
150 Patients:	4.0%/72.0%	0.011	Wald χ^2	<.0001	0.003	0.044
75 NexoBrid						
75 SOC						

The main analysis of this endpoint used the FAS, which included 5 patients in the SOC group who were randomized but did not receive treatment. As detailed in the SAP, the missing values for these patients were included as having had an excision. FAS, full analysis set; SOC, standard of care.
[a]Adjusted for the other variables in the model.

over SOC after adjustment for all other variables in the model (*P*-value = .0027). The 95% CI for this treatment excludes the predefined noninferiority margin of 1.9 points, thus establishing noninferiority of NexoBrid treatment compared with SOC. Similar trends were observed in the 24-month follow up mean MVSS scores. Results were slightly lower (better) for the NexoBrod group (3.04 ± 2.2) than the SOC (3.30 ± 2.76).

Level of sedation (acute phase), NexoBrid vs SOC (exploratory endpoint)

The extent of analgesia and anesthesia use by the level of sedation in the NexoBrid, surgical SOC (nonsurgical SOC is not expected to require sedation), and GV groups during the Acute Phase is summarized in Table 5. Most patients treated with NexoBrid required minimal or moderate sedation. The use of general anesthesia was higher for patients treated with SOC during surgical ER than for patients treated with NexoBrid during first application (SOC = 87.5% [42/48] compared with NexoBrid = 5% [4/77], respectively). Patients treated with GV who required subsequent surgical excision also required general anesthesia (12/13 [92%] patients).

Assessment of pain

Pain intensity was collected by VAS patient reported outcomes scoring. Post first topical application, the VAS pain score was slightly higher in the NexoBrid (39.8) compared to the placebo (33.8) group. The incidence of pain was also collected as an adverse event. The incidence of pain was slightly less frequent in the NexoBrid (6.5%) compared to the SOC (8.3%) group.

Adverse events (NexoBrid, SOC, and GV)

Acute phase:

Treatment-emergent adverse events were observed across all treatment groups. The most frequent adverse events (≥3% of patients) in each treatment arm are shown in (Figure 5): A total of 12 patients experienced serious adverse events during the acute phase (6 NexoBrid, 4 SOC, and 3 GV patients). All patients in all 3 treatment arms had serious events that were mild to moderate with the exception of severe events of sepsis and acute respiratory failure in patients treated with NexoBrid; acute respiratory distress syndrome, and septic shock in patients treated with the SOC; and seizure and infusion site thrombosis in patients treated with the GV. One patient died due to a respiratory complication, assessed by the Investigator and DSMB as not related to NexoBrid.

Twelve-month follow-up:

As expected with a 1- or 2-time administration of a topical treatment with short systemic exposure, there was a reduced frequency of TEAEs past the first 3 months following wound closure. Only 2 patients (both in the NexoBrid arm) experienced an adverse event (folliculitis [mild] and pruritus [moderate]) assessed by the investigator as related to study drug in the 3- to 12-month period. One patient in the NexoBrid arm died 8 months post wound closure period due to an unknown cause following a second burn that underwent surgical excision. The Investigator and DSMB assessed the death as not related to study treatment.

Table 5. Level of Sedation per First Topical Application and Surgical Excision (Safety Analysis Set)

	Treatment/Procedure				
Level of sedation	**NexoBrid/first application**	**NexoBrid/surgical excision**	**SOC/surgical excision**	**GV/first application**	**GV/surgical excision**
Overall, *N*	77	3	48	24	13
Minimal Sedation, *n* (%)	39 (51%)	0	4 (8%)	14 (58%)	1 (8%)
Moderate Sedation, *n* (%)	20 (25%)	0	2 (4%)	2 (8%)	0
Deep Sedation, *n* (%)	13 (17%)	0	0	1 (4%)	0
General Anesthesia, *n* (%)	4 (5%)	3 (100%)	42 (87.5%)	0	12 (92%)
Missing	1 (1.3%)	0	0	7 (29%)	0

Surgical excision and eschar removal are used interchangeably. Percentages are calculated as percentage within treatment arm and procedure. *N* = number of patients within a treatment arm, *n* = number of observed patients within a treatment arm.

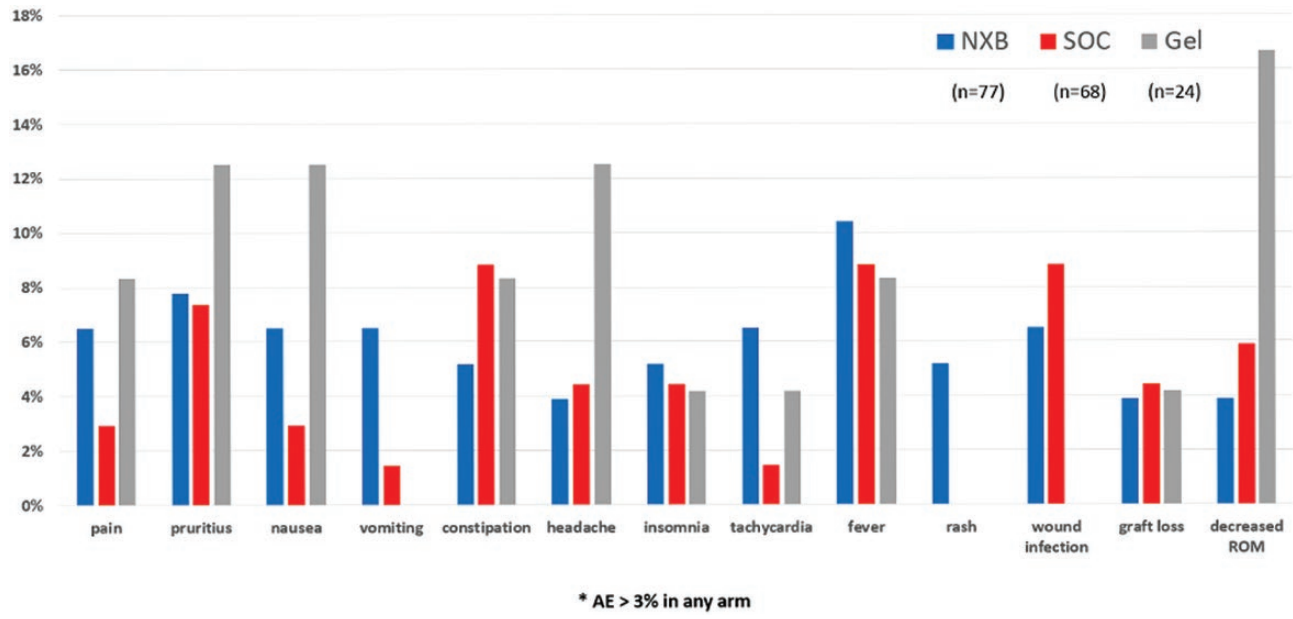

Figure 5. Treatment Emergent Adverse Events >3% Incidence in Any Arm (Acute Phase)

Twenty-Four-month follow-up:
There were no treatment related adverse events reported between 12 and 24 months of follow-up. There were no deaths reported in the 24-month follow-up.

DISCUSSION

The DETECT study was conducted as part of the post approval commitments to the European Medicines Agency (EMA) and to gain US FDA approval. As a result, its design and endpoints included the combined requirements of both authorities. The results presented in this manuscript encompass the primary and secondary efficacy and main safety and exploratory endpoints.

In this assessor-blinded (2 end points), controlled trial involving adult patients with deep burns covering 3–30% TBSA, enzymatic debridement with NexoBrid was more effective than its GV in removing the burn eschar, achieving complete ER in over 90% of patients. Compared with SOC, NexoBrid significantly reduced the need for surgery (number needed to treat 1.47; 95% CI, 1.28–1.85) as well as the associated blood loss. Complete ER was achieved at least 2 days earlier with NexoBrid than with SOC. The time to complete wound closure was similar in both NexoBrid and SOC arms though excision and autografting is expected to close wounds faster than the slower process of epithelialization over dermis. Long-term scar appearance in the NexoBrid arm, as reflected by lower MVSS scores, was better at 1-year when compared to the SOC and GV arms, and was similar at 24 months meeting the noninferiority test. The results of the current study are in line with previous reports[11–13,23,25–30] while adding a placebo control arm and blinded assessment of the primary outcome.

Introduction of rapid enzymatic debridement as a nonsurgical alternative for many deep burns is a significant advance in burn care. Early ER and autologous skin grafting of deep burn wounds are considered one of the cornerstones of modern burn care as this reduces early complications and late sequelae, mainly scarring.[8,31,32] Surgical debridement/

excision is currently recognized as the SOC for removal of the eschar, however, this technique requires a high level of expertise in order to differentiate between viable and nonviable tissue. Surgical debridement is also associated with significant blood and heat loss, and poor operator-dependent selectivity also results in viable tissues being sacrificed along with the eschar.[10] Consequentially, surgical debridement is often delayed until an accurate diagnosis of burn depth is reached confirming the necessity for surgery, thus compromising the advantages of early ER. Alternatively, these disadvantages may lead clinicians to use traditional nonsurgical ER methods which are known to be slow and much less effective than surgery, thus leading to an increased complication rate and inferior long-term results.

An important advantage of rapid enzymatic debridement is its selectivity exposing the underlying wound bed and allowing visual assessment of depth and viability of the dermis and its potential for spontaneous closure by epithelialization with less need for skin grafting.[33] This reduces or eliminates the morbidity associated with the skin graft donor wound (eg, pain and scarring). Earlier ER also reduces the release of inflammatory mediators and the risk of infection. Concerns that spontaneous re-epithelialization of the debrided wound bed would be delayed (as opposed to immediate wound closure by autografting the surgically excised wound bed) and contribute to hypertrophic scarring were unsubstantiated as wound closure and 1-year cosmesis were similar in burns treated with NexoBrid or the SOC.

Strengths of our study include the relatively large sample size and long-term follow-up, as well as the use of multiple, well-validated outcomes. However, our study has several limitations that need to be noted. Despite the relatively large number of burns, we could not fully account for several potential confounding variables such as anatomical location, skin type, genetic predilection to scarring, and surgeon treatment preferences and experience. Finally, results in a well-controlled study may not reflect those seen in real world settings.

In conclusion, among adult patients with deep burns involving 3–30% of their TBSA, NexoBrid was safe and effective at removing the burn eschar, reducing the need for surgery and blood loss while achieving 1-year cosmetic outcomes at least as good as with surgery. The results of this study have recently led to US FDA approval.

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