



Research Article

# A Randomized, Single-blind, Comparison Trial of Beractant (Beraksurf™) versus Poractant Alfa (Curosurf®) in the Treatment of Respiratory Distress Syndrome in Preterm Infants

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## Article Info

### Article History:

Received: 05 Sep 2021

Accepted: 13 Feb 2022

ePublished: 21 Feb 2022

### Keywords:

- Beractant
- Poractant alfa preterm
- Respiratory distress syndrome
- Surfactant
- Surfactant replacement therapy

## Abstract

**Background:** Neonatal respiratory distress syndrome (NRDS) affects approximately up to 7% of all term newborns. This study aimed to assess the efficacy and safety of investigational beractant (Beraksurf™, Tekzima Company) in comparison with poractant alfa (Curosurf®, Chiesi Pharmaceuticals) as surfactant replacement therapy in NRDS.

**Methods:** This trial was a randomized, controlled, single-blind, phase III study of two natural surfactants which was conducted in NICU of Alzahra hospital in Tabriz for 8 months. 220 infants were enrolled in 2 groups to receive either 100 mg/kg Beraksurf™ or 200 mg/kg Curosurf® as an initial dose endotracheally. Additional doses were given if needed. Infants' gestational age, birth weight, discharge weight and other demographic information were recorded. Efficacy outcomes were changes in fraction of inspired oxygen (FiO<sub>2</sub>) and the number of infants who reached FiO<sub>2</sub> less than 0.3 (treatment success rate) which were compared between both groups with analysis of covariance (ANCOVA).

**Results:** The results showed that the treatment success rate was 92% and 72% in Beraksurf™ and Curosurf® groups, respectively ( $P$ -value < 0.001). In addition, no difference was observed in the efficacy of these two treatments in terms of binary outcomes and incidence of complications such as mortality.

**Conclusion:** The result analysis of current study implies Beraksurf™ has same beneficial impact on clinical management of RDS as Curosurf® among infants below 32 weeks. However, larger studies are needed to evaluate further efficacy and safety outcomes of this surfactant in comparison with the reference products in other subgroups.

## Introduction

Preterm delivery is defined as delivery occurrence before 37 weeks of gestational age. The incidence of preterm deliveries is increasing despite significant advancements in prenatal care. It has been claimed that the preterm delivery rate in developed countries varies between 5-13%.<sup>1,2</sup> Respiratory distress syndrome (RDS) is the leading cause of mortality in premature infants. RDS, also called hyaline membrane disease, is related to structural and functional pulmonary immaturity.<sup>3</sup> There is reliable evidence that pulmonary surfactant deficiency is the leading cause of RDS regarding its pathophysiology.<sup>4</sup>

Surfactants contains mixture of lipids and proteins,

which reduce surface tension. For four decades, surfactant replacement therapy (SRT) has been an established RDS treatment in neonatology.<sup>5</sup>

Surfactant also contains proteins including protein A, B, C, and D. Surfactant protein A (SP-A) and SP-D activate immune function. SP-B, an highly hydrophobic protein, stabilize the phospholipid bilayer surface and SP-C play an important role in adsorption of DPPC (dipalmitoyl-phosphatidyl-choline) and other phospholipids.<sup>6</sup>

Randomized controlled trials (RCTs) on the available surfactants were conducted to assess the treatment or prevention of RDS in preterm infants. The results demonstrated that surfactant administration decreases

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RDS severity, pneumothorax incidence and increases survival rate. The Cochrane Library also encompasses systematic reviews indicating the benefits of multiple doses over a single dose.<sup>7,8</sup>

According to the 2019 update of European consensus guidelines on RDS management, continuous positive airway pressure (CPAP) initiation and oxygen titration should be implemented immediately after the preterm neonate's birth. Furthermore, surfactant replacement therapy is a crucial part of the RDS management.<sup>9</sup>

There were thousands of randomized controlled trials on various types of natural and synthetic surfactants, which demonstrated the superiority of the natural ones to the synthetic ones. Recently, different natural surfactants have been compared in randomized trials.<sup>10-12</sup> An study which was compared beractant and poractant alfa showed that there was no significant difference between two groups but we have investigated a larger sample size and evaluate  $FiO_2$  changes.<sup>13</sup>

Available exogenous pulmonary surfactants in Iran for neonatal RDS management are poractant alfa (Curosurf®, Chiesi, Italy), beractant (Survanta®, AbbVie, USA), calfactant (Infasurf, ONY Inc, USA), bovine lipid extract surfactant (BLES, BLES Biochemical Inc, Canada).<sup>7</sup> Except for BLES®, all mentioned surfactants have FDA approval.

Beraksurf™ (beractant), the bovine lung extract is the generic form of Survanta® that has been produced by Tekzima Company (Alborz, Iran) since 2018. Each milliliter of Beraksurf™ consists of 25 mg phospholipids (mostly dipalmitoyl-phosphatidyl-choline (DPPC)), surface-active proteins including SP-B and SP-C, tripalmitin, and palmitic acid. If the amount of each was not sufficient in the drug substance, DPPC, tripalmitin, and palmitic acid would be added in order to standardize the product based on pharmacopeia.

This study was the first randomized clinical trial conducted to assess the efficacy and safety of Beraksurf™ (Biosimilar of Survanta®) vs. Curosurf in infants with RDS in a standard management setting by measuring a quantifiable variable compared to other previous studies.<sup>7,13,14</sup>

## Methods

This randomized study was performed during eight months on 200 premature infants with RDS hospitalized in Neonatal Intensive Care Unit (NICU) of Alzahra Hospital in Tabriz, Iran.

Inclusion criteria were infants with gestational age up to 32 weeks, birth weight under 2000 g, definitive diagnosis of RDS based on clinical symptoms or radiographic evidence, fraction of inspired oxygen ( $FiO_2$ )  $\geq 0.3$  to maintain oxygen saturation between 88-96%, requirement of surfactant administration within 6 hours from birth at the time of randomization and written informed consent form signed by a parent or legal guardian. Infants with respiratory failure due to other causes except for RDS, lung hypoplasia, 5-minute Apgar score  $\leq$  four, prior treatment

with an exogenous surfactant, untreated pneumothorax, prolonged rupture of membranes (3 weeks), hypotension, hypoglycemia, using High-Frequency Ventilation (HFV) before the first dose of surfactant, Intra Ventricular Hemorrhage (IVH) were excluded from this study.

Infants' demographic data such as gestational age (in weeks), birth weight, discharge weight, types of delivery, and gender were recorded.

Therapeutical interventions, dose and intervals of the administrated surfactant, maternal information including age, risk factors, and using antenatal steroids were also documented.

## Randomization

Infants were randomly assigned to two groups. The block randomization technique with a 1:1 ratio was used to achieve balanced group sizes. A randomized block sheet was prepared, and AABB, ABAB, ABBA, BBAA, BABA, BAAB codes were allocated to the participants. Each of the sequences converted to alphabetic and numeric codes. Due to the difference in volumes and dosing between two surfactants and their administration by the neonatologists, double blinding was not possible and only the neonates were blinded to the treatment.

## Procedures

After resuscitation, infants were transferred to the intensive care unit, receiving CPAP. Within the first 6 hours from birth, in case of  $FiO_2 \geq 30\%$ , infants were randomized in a ratio of 1:1 to receive either 100 mg/kg of Beraksurf or 200 mg/kg of Curosurf as an initial dose. Both were administered by neonatologists intratracheally. Additional doses of surfactant were given if the infant  $FiO_2$  was  $\geq 0.30$  or continued to require mechanical ventilation to maintain an oxygen saturation of 88% or greater using pulse oximetry. If necessary, repeated doses were given 100 mg/kg every 6 to 12 hours up to 4 doses for Beraksurf™, or 100 mg/kg every 12 hours up to 3 doses for Curosurf.

## Outcomes

This study's primary outcomes were the  $FiO_2$  changes and treatment success rate. Infants with final  $FiO_2 \leq 30$  were considered as neonates with treatment success.  $FiO_2$  variation was measured every six hours. The total dose and the frequency of surfactants administration during the study, duration of hospitalization, reintubation need, and the occurrence of adverse events were also evaluated as secondary outcomes.

## Statistical analysis

The distribution of continuous variables was checked by Shapiro-Wilk test for normality, within-group comparison was performed via Wilcoxon signed ranks test or paired t-test, if applicable.

In practice, given the limited sample size, the random nature of RCTs, any important prognostic factors and baseline score may not be balanced between arms. RCTs

of small or moderate sample sizes are particularly prone to such imbalances.<sup>15</sup> As the primary outcome is a post-score change, in case of any imbalance, it should always be adjusted for baseline scores using analysis of covariance (ANCOVA); otherwise, the estimated treatment effect may be biased.<sup>15,16</sup> Therefore, between groups, comparisons were done using ANCOVA in three steps: Model I, the crude effect of the treatment group, Model II, adjusted for the initial FiO<sub>2</sub>, and in Model III due to the potential confounding effect of birth weight and gestational age, the effects of these two variables as well as treatment and the initial FiO<sub>2</sub> were evaluated.

The effect of treatment on the final FiO<sub>2</sub> was also assessed via logistic regression. Since the birth weight is a potentially influential factor in treatment efficacy, sensitivity analysis by excluding six infants with a birth weight under 800 grams was also done.

All statistical analyses were performed with STATA Statistical Software Release 15.0 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.) and significance level was considered 0.05.

## Results

### Patients

A total of 270 infants were screened, and 220 infants were enrolled in the study from October 2019 to May 2020.

Eleven infants in the Beraksurf group, and nine infants in the curosurf group were excluded because of complications such as hypotension. The remaining 200 subjects treated with surfactant composed the entire study population. In this study, 101 infants received 200 mg/kg of poractant alfa and 99 infants received 100 mg/kg of beractant for the initial dose (Figure 1).

The characteristics of the study population and mothers/infants-related risk factors are shown in Table 1, and the comparison of evaluated variables between groups is shown in Table 2.

There were no significant differences among the study groups in the 1-minute Apgar score, mode of delivery, mother-related risk factors such as the mother's underlying diseases, maternal age, the incidence of Premature Rupture of Membranes (PROM), and preeclampsia. There was a significant difference in the use of antenatal steroids in the two groups; 73 participants in the Beraksurf<sup>TM</sup> group and 83 participants in the Curosurf group received antenatal steroids. Gestational age and birth weight were significantly higher in the Beraksurf<sup>TM</sup> group.

### Primary outcome

#### Treatment effect on the FiO<sub>2</sub>

The result of each treatment group's effect on the difference of FiO<sub>2</sub> is shown in Table 3. According to ANCOVA results, the efficacy of Curosurf was higher than Beraksurf<sup>TM</sup>

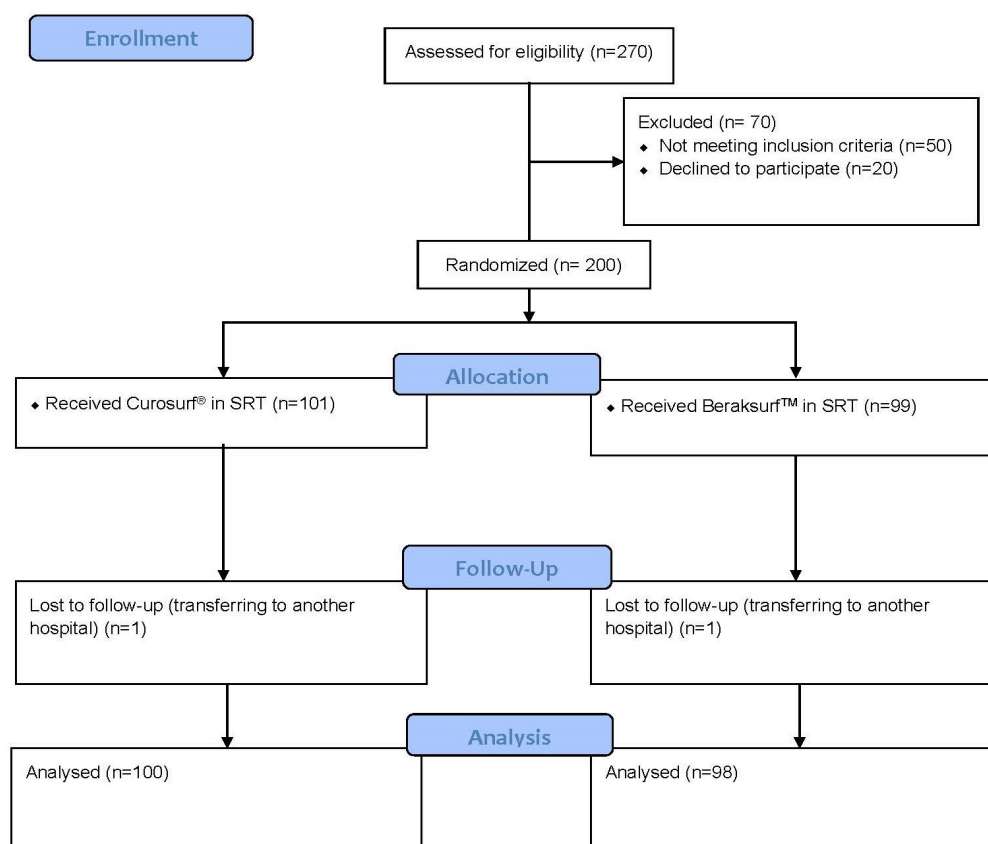


Figure 1. Flow chart of the study population.

**Table 1.** Baseline characteristics and Risk factors of infants.

Variables		Beraksurf™ (N:99) Mean (±SD)	Curosurf (N:101) Mean (±SD)	P-value
Gestational age (week)		32.9 (±2.6)	30.3 (±2.6)	<0.001 <sup>a</sup>
Birth weight (g)		1957.2 (±675.2)	1566.2 (±672.3)	<0.001 <sup>a</sup>
Maternal age (year)		29.9 (±5.7)	31 (±7.2)	0.21
Apgar score at 1 min		6.6 (±2.1)	5.9 (±2.3)	0.30
Apgar score at 5 min		8.3 (±1.4)	7.7 (±1.7)	0.01 <sup>a</sup>
		<b>n (%)</b>	<b>n (%)</b>	
Delivery method	NVD <sup>b</sup>	15 (15.2)	16 (15.8)	1
	C/S <sup>c</sup>	84 (84.8)	85 (84.2)	
Gender	Male	50 (50.5)	68 (67.3)	0.021 <sup>a</sup>
	Female	49 (49.5)	33 (32.7)	
Mother's underlying diseases	Diabetes	14 (14.1)	20 (19.8)	0.34
	Hypertension	23 (23.2)	33 (32.7)	0.15
PROM <sup>d</sup>		21 (21.2)	32 (31.7)	0.11
Antenatal steroid use	No	25 (25.5)	18(17.8)	0.01 <sup>a</sup>
	Partial	41(41.8)	30(29.7)	
	Complete	32(32.7)	53(52.5)	
Preeclampsia		11 (11.1)	18 (17.8)	0.22
History of previous infant death		4 (4)	3 (3)	0.72
Infertility history		8 (8.1)	6 (5.9)	0.59
IVF <sup>e</sup>		5 (5.1)	5 (5)	1

<sup>a</sup>P-Value statistically significant at P<0.05

<sup>b</sup>NVD: Natural Vaginal Delivery

<sup>c</sup>CS: Caesarean Section

<sup>d</sup>PROM: Premature Rupture of Membrane

<sup>e</sup>IVF: In-Vitro Fertilization

regarding dFiO<sub>2</sub> of patients, without considering the imbalanced nature of baseline data in two groups (model I) (*P*-value: 0.002). By considering the imbalanced initial FiO<sub>2</sub> in analysis, to eliminate the effect of that imbalance on the analysis result (model II), the Beraksurf™ group significantly had a better outcome (*P*-value: 0.03). Considering the imbalance of initial FiO<sub>2</sub>, birth weight, and gestational age in analysis (model III), the Beraksurf™ group's outcome was better than the Curosurf group (*P*-value: 0.02). This analysis showed that the confounding effect was negligible.

#### Treatment effect on success rate

The result of each treatment group's effect on treatment

success rate is shown in Table 4.

Based on the chi-square test results, the treatment success rate was significantly different between groups; this proportion was 92% and 72% in Beraksurf™ and Curosurf groups, respectively (*P*value <<0.001).

As mentioned in last guidelines of RDS treatment, the threshold of FiO<sub>2</sub> to administer surfactants is 0.3 and in this study, we considered this measurement to repeat administration of surfactants up to their limitation according to their monographs.<sup>17</sup>

#### Safety outcomes

The statistical analysis showed that the incidence of Treatment-Emergent Adverse Events (TEAEs) was not

**Table 2.** Comparison of evaluated variables between groups.

Variables		Beraksurf™ (N:99) mean (±SD)	Curosurf® (N:101) mean (±SD)	P-value
FiO <sub>2</sub> (%)	Initial	75.9 (±9.6)	81.9 (±12.4)	<0.001 <sup>a</sup>
	Final	25.9 (±0.321)	27.9 (±0.4)	<0.001 <sup>a</sup>
Duration of hospitalization(hour)		11.6(±10.3)	23.9(±17.5)	<0.001 <sup>a</sup>
Discharge weight (g)		2000.4 (±5.16.6)	1773 (±525.2)	<0.01
		<b>n (%)</b>	<b>n (%)</b>	
Number of surfactant doses	2nd dose	22 (22.2)	46 (45.5)	<0.001 <sup>a</sup>
	3rd dose	2 (2)	10 (9.9)	0.019
	4th dose	0 (0)	1 (1%)	0.321

<sup>a</sup>P-Value Statistically significant at P<0.05

**Table 3.** Treatment effect on the difference of FiO<sub>2</sub> using ANCOVA.

Beraksurf vs Curosurf	Model I	P-Value	Model II	P-Value	Model III	P-Value
		-4.1(-6.8, -1.49)	0.002 <sup>a</sup>	0.9(0.07,1.82)	0.03 <sup>a</sup>	1.07(0.14,2.01)
Initial FiO <sub>2</sub>			0.81(0.77, 0.8)	<0.001 <sup>a</sup>	0.80(0.75,0.85)	<0.001 <sup>a</sup>
Birth weight					~0	0.77
Gestational age					-0.14(-0.47, 0.18)	0.38

<sup>a</sup>Statistically significant at P<0.05**Table 4.** Treatment success rate using logistic regression.

Beraksurf™ vs Curosurf®	OR (95% CI)					
	Model I	P-value	Model II	P-value	Model III	P-value
	4.37 (1.88,10.18)	<0.01 <sup>a</sup>	1.74 (0.63, 4.83)	0.28	2.26 (0.75, 6.81)	0.14
Initial FiO <sub>2</sub>			0.82 (0.76, 0.88)	0.01 <sup>a</sup>	0.79 (0.72,0.87)	0.01 <sup>a</sup>
Birth weight					1.00 (0.99, 1.00)	0.80
Gestational age					0.82 (0.59,1.14)	0.24

<sup>a</sup>Statistically significant at P<0.05

significantly different. There was no significant difference in the respiratory support requirement between the two groups; overall mortality was higher in the Curosurf group. The incidence of adverse events is summarized in Table 5.

## Discussion

Due to the proven role of SRT in the treatment of neonatal RDS, this study was conducted to compare the therapeutic effects of the two natural surfactants which are regularly used in Iran: Curosurf (poractant alfa, Cheisi, Italy) and Beraksurf™, (beractant, Tekzima, Iran).

In this study, 50 of 89 infants in the Beraksurf™ group and 68 of 101 infants in the Curosurf group were males. The other studies showed that the male gender was considered an RDS risk factor due to hormonal differences.<sup>18</sup> However, we checked the effect of gender in a model, and it was not statistically significant (beta=0.01, p=0.81).

Another independent risk factor in the studies for RDS occurrence was the mode of delivery by cesarean section.<sup>17</sup> Most of the infants in both groups in this study were born

by cesarean section as well.

Results of the logistic regression showed that the crude treatment effect difference was statistically significant, and Beraksurf™ outperformed Curosurf in terms of maintaining FiO<sub>2</sub> at a low threshold (FiO<sub>2</sub> ≤ 30). However, when we considered the effect of initial levels of FiO<sub>2</sub>, birth weight, and gestational age, the effect did not remain significant. It could be said that the efficacy of these two treatments was equal in terms of a binary outcome. In the study conducted by Dilli *et al.*<sup>19</sup> in 2019, infants in both of the poractant alfa and beractant group had shown a similar effect on decreasing oxygen requirement.<sup>19</sup> Despite this study, in another study conducted by Malloy *et al.*<sup>20</sup> in 2005, the FiO<sub>2</sub> requirement in the first 48 hours in the poractant alfa (Curosurf) group was significantly lower than the beractant (Survanta<sup>®</sup>) group.<sup>20</sup>

Eventually, FiO<sub>2</sub> is one of the most critical factors to assess the efficacy of surfactants in RDS. As demonstrated by the current study, Beraksurf™ could play a significant role in decreasing it. Comparing Curosurf® and Survanta® in the pulmonary outcomes and evaluating the complications,

**Table 5.** Pulmonary and other outcomes.

Variables	Beraksurf™ (N:99)	Curosurf® (N:101)	P-value
	n (%)	n (%)	
Nasal CPAP <sup>a</sup>	96 (97)	96 (95)	0.42
IPPV <sup>b</sup>	29 (29.3)	60 (59.4)	0.24
NIV <sup>c</sup>	0	6 (5.9)	0.99
HFNC <sup>d</sup>	96 (97)	93 (92.1)	0.93
Pulmonary bleeding	0	0	-
Pneumothorax	0	0	-
Sepsis	0	0	-
Death	2 (2)	8 (7.9)	0.66

<sup>a</sup>CPAP: Continuous Positive Airway Pressure<sup>b</sup>IPAV: Intermittent Positive Airway Ventilation<sup>c</sup>NIV: Non-Invasive Ventilation<sup>d</sup>HFNC: High Flow Nasal Cannula

Najafian *et al.*<sup>21</sup> in their clinical study in 2016, found that more patients in the subgroup below 28 weeks of gestational age needed nasal CPAP and more patients with IVH and Necrotizing enterocolitis (NEC) incidence were observed in the age of 29 to 32 weeks subgroup in the Curosurf group; other complications were not significantly different between the Curosurf and Survanta groups,<sup>21</sup> which consistent with the result of this study. However, Dizdar *et al.*<sup>22</sup> in 2012 reported equal complications in both Curosurf and Survanta groups in their study.

There were no reports of pulmonary hemorrhage, sepsis, and pneumothorax between two groups, and it represents that there was no significant difference between surfactants. Also, in the study performed by Saeedi *et al.*,<sup>23</sup> two groups of surfactant were equal in terms of occurrence of side effects.

The duration of hospitalization was longer in the Curosurf group. The same result was concluded in the study conducted by Baroutis *et al.*<sup>24</sup> when they compared three treatment regimens of natural surfactant in 2003. Despite this result, in the study conducted by Gharehbaghi *et al.*<sup>25</sup> in 2010, infants who received poractant alfa had a shorter intubation duration than infants treated with beractant, without any difference in oxygen therapy or hospitalization duration.

The result of the current study showed that the mortality rate was lower in the Beraksurf<sup>TM</sup> group. On the other hand, Najafian *et al.*<sup>21</sup> and Zhang *et al.*<sup>26</sup> found a similar effect on the mortality rate in the beractant and poractant alfa groups.

### Limitation

Despite studying in Tabriz's most important neonatal intensive care unit, it is better to evaluate these drugs in a multicenter study with a longer follow-up duration to obtain more accurate outcomes.

### Conclusion

No statistically significant difference was observed between two groups of surfactants in term of side effects. Also, Beraksurf<sup>TM</sup> has showed significantly reduced FiO<sub>2</sub> in comparison with poractant alfa among infants < 32 weeks. However, larger studies are needed to evaluate further efficacy and safety outcomes of this surfactant in comparison with the reference products in other subgroups.

### Ethical Issues

Ethical approval was obtained from the Ethics committee of Tabriz University of Medical Sciences. The study protocol was registered at the Iranian Registry of Clinical Trials (IRCT) (IRCT20180404039187N4) prior to subject recruitment.

### Acknowledgments

This research was not funded. The authors would like to appreciate all the NICU staff of Alzahra Hospital.

### Data Sharing

The data is available from the corresponding author on reasonable request.

### Author Contributions

ES: Conceptualization, data curation, validation, investigation, visualization, methodology, supervision, writing—original draft and editing, data collection; MMG: Conceptualization, writing—original draft, writing—review and editing; MH: Resources, supervision, validation, investigation, methodology, data collection; PS: Methodology, analysis, writing—original draft and editing.

### Conflict of Interests

The authors have no financial interests related to the materials mentioned in the manuscript.

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