Feasibility and safety of cellular therapy for in-utero repair of myelomeningocele (CuRe Trial): a first-in-human, phase 1, single-arm study

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Summary

Background The Management of Myelomeningocele Study (MOMS) trial established the benefit of in-utero repair of myelomeningocele, with a decreased need for ventriculoperitoneal shunt placement. However, although there was some improvement of motor function, over half of the patients were unable to ambulate independently. Live placenta-derived mesenchymal stem cells (PMSCs) seeded on an extracellular matrix have shown promise in rescuing neurological function in the fetal ovine model of myelomeningocele. We aimed to evaluate the safety of this novel, living, stem cell product to augment the prenatal repair of myelomeningocele.

Methods In this phase 1, first-in-human, single-dose, single-arm study, pregnant women who had fetuses diagnosed with myelomeningocele were enrolled in a staggered manner at University of California, Davis (UC Davis) School of Medicine, in Sacramento (CA, USA). Eligibility criteria were gestational age from 19 weeks to 26 weeks, upper boundary of the myelomeningocele defect between T1 and S1, hindbrain herniation shown by MRI, and normal karyotype. In-utero repair of the myelomeningocele was conducted with a single dose of topically applied allogeneic human PMSCs seeded on an extracellular matrix (Cook Biodesign Dural Graft [Cook Biotech; West Lafayette, IN, USA]). The PMSCs were generated from donated placentas collected from consented patients at the UC Davis Medical Center, and the cells were tested for identity, sterility, and viability 72 h before surgery. Primary safety endpoints included evaluation of the myelomeningocele repair site for healing, cerebrospinal fluid leak, infection, and unexpected abnormal growth or tumour formation. This study is registered with ClinicalTrials.gov (NCT04652908).

Findings Between June 21, 2021, and Dec 5, 2022, six women with fetuses with gestational ages from 24^{+5} weeks to 25^{+5} weeks were enrolled in the study. Newborns were delivered at a median gestational age of 34^{+5} weeks (range 33^{+2} weeks to 36^{+6} weeks) by caesarean delivery. At birth, all infants had an intact repair site with no evidence of cerebrospinal fluid leak, infection, or abnormal tissue growth. After treatment, MRIs showed reversal of hindbrain herniation and no evidence of tumour formation. No cell-mediated adverse events occurred.

Interpretation This first-in-human treatment consisting of allogeneic, live stem cells showed no cell-related adverse effects. The therapy was assessed as sufficiently safe to proceed with non-staggered enrolment of 35 patients in a phase 1/2a trial.

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Introduction

Neural tube defects, such as spina bifida, are a spectrum of congenital diseases with a substantial worldwide burden, ranging in severity from minor disability to lethality. Globally, nearly half a million babies are born every year with a neural tube defect.[1,2] This figure is likely to be an underestimation as there is variability in reporting across different countries.[3] Insight into disease mechanism drove worldwide preventive efforts in the form of vitamin fortification in foods,[4] with the discovery that folate supplementation in pregnancy reduced the risk of neural tube defects resulting in the introduction of an important public health protective measure.[5] However, children are still born daily with these catastrophic conditions and require lifelong and costly multidisciplinary care, leading to an enormous global disability burden. In 2014, spina bifida-related hospital charges were reported to be US$2 billion annually in the USA alone.[6] The incidence of spina bifida in the USA is one in every 2800 births,[7] with a higher prevalence in people of Hispanic ethnicity than in those of non-Hispanic White or non-Hispanic Black ethnicity.[8]

Myelomeningocele is the most severe form of spina bifida, whereby failure of neural tube closure early in fetal development results in leakage of cerebrospinal fluid and progressive damage to the fetal spinal cord from chemical and mechanical trauma caused by the amniotic fluid and

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Research in context

Evidence before this study

Myelomeningocele is the most severe type of spina bifida, a neural tube defect leading to substantial disability across the lifespan, including paralysis and bowel, bladder, and kidney failure. The Management for Myelomeningocele Study established that fetal surgery to repair the neural tube defect improved outcomes by reducing the need for shunting procedures for hydrocephalus. Although most prenatally operated children were still unable to walk, motor function of the legs was improved. This observation gave us hope that we could further advance neurological outcomes for these children using stem cells. Many studies have explored different surgical techniques, but there are no published human clinical trials evaluating the safety or efficacy of stem cells of any kind to treat spina bifida in utero, nor are there any commercially available stem cell products to treat fetuses for any condition. We have conducted numerous searches across several databases including PubMed, Embase, and Scopus, with no date limitations or language restrictions (most recently on Aug 1, 2025). Searches were comprised of terms such as "myelomeningocele", "spina bifida", "surgery", "in utero", "fetal", "prenatal", "stem cell", and "stem cell transplantation". Therefore, this trial began with more than a decade of preclinical work to identify the best stem cell source, rigorous translational research being required given the unknown effects of allogeneic stem cells on the fetal CNS.

Added value of this study

This study shows the safety of placenta-derived mesenchymal stem cells (PMSCs) to treat a CNS disorder before birth. To our knowledge, this trial is the first phase 1 study in humans to investigate the safety and feasibility of a tissue-engineering approach to treat myelomeningocele in utero. Allogeneic PMSCs seeded on an extracellular matrix graft applied topically to the exposed spinal cord at the time of in-utero repair of myelomeningocele had no unexpected adverse outcomes related to the stem cell product. Specifically, there were no difficulties with wound healing or any instances of abnormal tissue growth or tumour formation.

Implications of all the available evidence

Stem cell therapy at the time of standard prenatal surgery for myelomeningocele does not interfere with the known benefits of fetal surgery and is not associated with any cell-related adverse effects. Phase 1/2a is ongoing to evaluate the long-term safety and preliminary efficacy of the product.

uterine wall, respectively.[9] This damage results in numerous abnormalities in development, including Arnold-Chiari II malformation with hindbrain herniation, hydrocephalus, and other brain abnormalities, as well as loss of motor function below the level of the spinal cord lesion, leading to paralysis and bowel and bladder dysfunction. These outcomes are explained by a two-hit hypothesis—the first hit arising from abnormalities in the anatomical development of the spinal cord and the second from damage to the cord caused by chemical and mechanical trauma in utero.

Myelomeningocele remains the only nervous system defect that is routinely repaired in utero and the only non-lethal disease for which fetal surgery is offered. Historically, myelomeningocele was treated with postnatal closure of the defect to prevent infection. However, in 2011, the Management of Myelomeningocele Study (MOMS)[10] showed that in-utero repair of the myelomeningocele defect was safe, leading to decreased hindbrain herniation, reduced need for cerebrospinal fluid shunting, and improved distal neurological function. Nonetheless, 58% of the prenatally operated children were unable to independently ambulate at 30 months.[11] A considerable gap remains between the outcomes of the current standard of care and the goal of independent ambulation for all patients.

In-utero repair of myelomeningocele might protect against progressive spinal cord injury, but it does not reverse damage that has already occurred. An autopsy study showed that in human patients with myelomeningocele, the exposed fetal spinal cord has a distorted architecture and an increased number of apoptotic cells.[12] A murine model of myelomeningocele evaluated with scanning electron microscopy showed typical development of the spinal cord in the initial stages of myelomeningocele, with tissue damage progressing throughout gestation.[13] Together, these studies suggest that the root cause of disability is spinal cord injury in utero. Therefore, a reparative, regenerative, anti-apoptotic treatment could augment the in-utero surgical closure, repair the spinal cord damage, and prevent the catastrophic symptoms associated with myelomeningocele. This vision catalysed over a decade of preclinical work focused on developing a feasible and safe therapeutic approach that would complement—and not compromise—the known benefits of in-utero repair of myelomeningocele. The translational pathway leading to Investigational New Drug (IND) approval is outlined in figure 1.

The neurorestorative effects of mesenchymal stem cells are well documented and include promotion of neurite outgrowth, secretion of anti-apoptotic and neuroprotective factors, and regulation of inflammation.[20] Multiple cell types were investigated as therapeutic candidates, including induced pluripotent stem cell-derived neural crest stem cells[15] and placenta-derived mesenchymal stem cells (PMSCs).

The placenta is a unique, extra-embryonic tissue that has a fundamental role in orchestrating fetal development throughout gestation, regulating nutrient transfer, and modulating immunological tolerance.[29,30] Initially, the

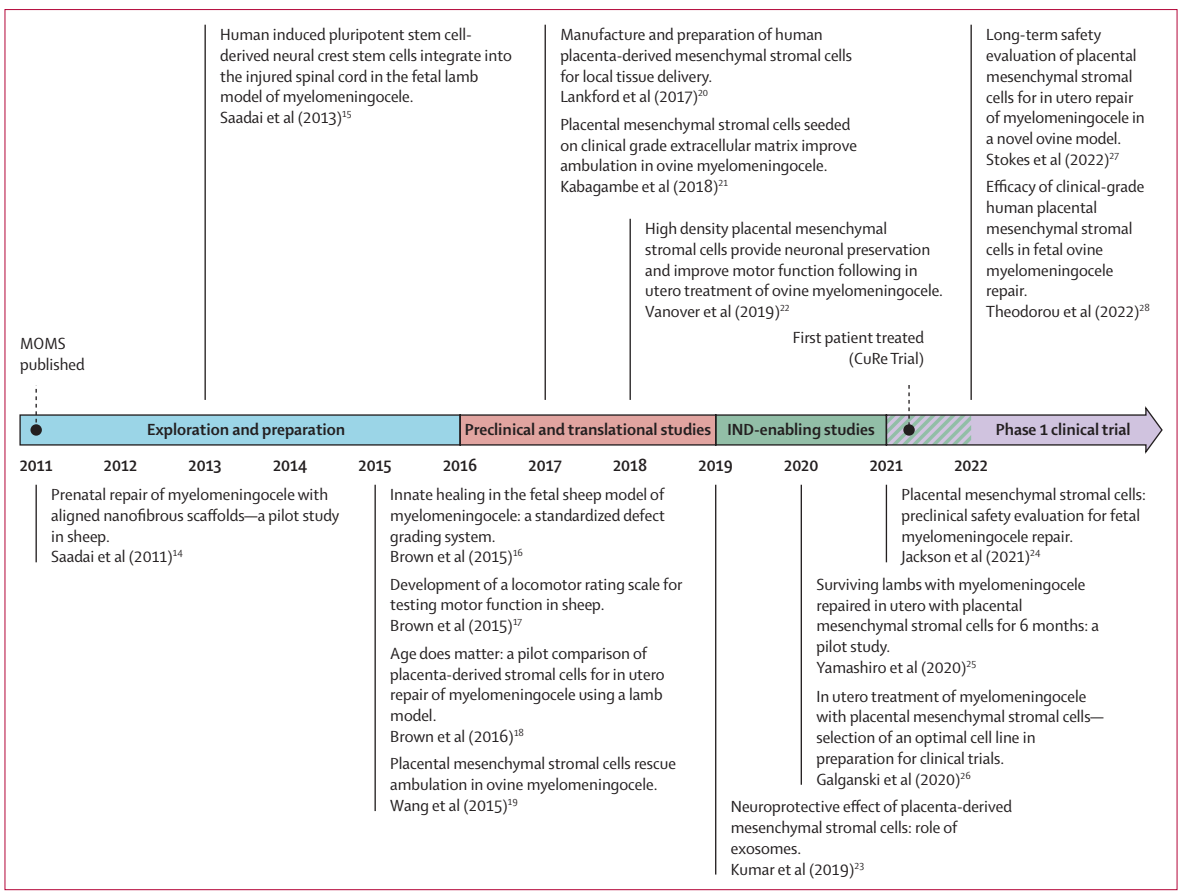

Figure 1: **Translational pathway and preclinical development timeline leading to the first-in-human in-utero stem cell therapy for spina bifida**
The schematic shows the preclinical work that led to IND approval, encompassing evaluation of different stem cell sources, including neural crest cells;[14,15] discovery of the benefits of placental tissue-derived stem cells; standardisation of an animal model for rigorous assessment of therapies;[16,17] assessment of the efficacy and neuroprotective mechanisms of PMSCs;[20,23] development of the PMSC-ECM product;[21] selection and manufacturing of clinical grade cell lines; and, finally, establishment of the safety and efficacy of the clinical-grade product in a fetal lamb model.[24–26,28] Timeline reflects online publication dates. CuRe=Cellular Therapy for In Utero Repair of Myelomeningocele. IND=Investigational New Drug. MOMS=Management of Myelomeningocele Study. PMSC=placenta-derived mesenchymal stem cells. PMSC-ECM=placenta-derived mesenchymal stem cells-extracellular matrix.

placenta was an attractive candidate as a source of autologous cells as the cells can be obtained readily through the well-established technique of chorionic villus sampling.[31] We discovered that PMSCs obtained in early gestation were an ideal therapeutic candidate due to their fetal origin, absent tumerogenicity, neuroprotective effect, and anti-apoptotic capability. When cultured in a specific neurogenic medium, they can be uniquely culture adapted to secrete higher concentrations of neurogenic growth factors and can rescue apoptotic neurons in vitro.[19,23] PMSCs also have immunomodulatory properties and potential for ex vivo expansion.[32,33] Compared with adult bone marrow-derived mesenchymal stem cells, PMSCs secrete higher quantities of key neurotrophic growth factors, including brain-derived neurotrophic factor and hepatocyte growth factor.[33] The engagement of cell surface receptors with matrix molecules when PMSCs are cultured on an extracellular matrix scaffold could further enhance the survival and biological functions of these cells. Although several dural substitutes have been reported in the literature, including biocellulose patches,[34] the product used in this study is distinct in that its primary purpose is to serve as a cellular delivery vehicle, with the added benefit of already being approved by the US Food and Drugs Administration (FDA).

Notably, PMSCs have rescued ambulation in an ovine model of spina bifida.[22] Overall, previous studies suggested that allogeneic stem cells were a reasonable choice to test in human fetuses and potentially preferable to further exploring autologous sources, with the added benefit of sparing pregnant individuals the known procedural risks of chorionic villus sampling (which include a small chance of pregnancy loss).[31] However, until now, the safety of allogeneic PMSCs for fetal applications was unknown.

In preclinical dose-escalating ovine studies and IND-enabling studies (IND 24097) using the most effective cell density, in-utero surgical repair of myelomeningocele with PMSCs seeded on an FDA-approved extracellular matrix (PMSC-ECM, using Cook Biodesign Dural Graft) resulted

in substantial improvements in motor function compared with extracellular matrix alone[22] and restored normal bowel and bladder function.[28,35] Here, we report the feasibility and safety results of Cellular Therapy for In Utero Repair of Myelomeningocele (CuRe Trial)—a phase 1, first-in-human study of PMSC-ECM with live cells topically applied over the exposed spinal cord during in-utero repair of myelomeningocele.

Methods

Study design

We conducted a phase 1, investigator-initiated, first-in-human, single-centre, single-dose study designed to evaluate the safety of the PMSC-ECM topically applied to the exposed spinal cord of eligible fetuses with myelomeningocele during fetal surgery. The protocol was approved by the University of California, Davis (UC Davis) Institutional Review Board (approval number 1617774). Written informed consent was obtained from participants before the start of the study. The study was overseen by the FDA (IND 24097), the California Institute for Regenerative Medicine (CIRM), and an independent data safety monitoring board (DSMB). The study was conducted through close cooperation between the study funder and the FDA. This study is registered with ClinicalTrials.gov (NCT04652908).

Study participants

See Online for appendix

Inclusion and exclusion criteria followed those used in MOMS[10] (appendix). In summary, patients between gestational ages 19 weeks and 26 weeks with a myelomeningocele defect (including myeloschisis) from T1 to S1, hindbrain herniation shown by MRI, and normal karyotype were eligible. Non-singleton pregnancy, fetal anomaly unrelated to myelomeningocele, maternal contraindications to surgery, conditions for increased risk of preterm birth, and psychosocial limitations were major reasons for exclusion.

Preparation of PMSCs

Human PMSC cell lines were generated from donated placentas collected from consented patients at the UC Davis Medical Center (CA, USA). Chorionic villus tissue was dissected from placentas, and PMSCs were expanded and cryopreserved following the IND protocol and all relevant standard operating procedures in the UC Davis Good Manufacturing Practice facility.

72 h before the scheduled fetal myelomeningocele repair, PMSCs were thawed and tested for identity, sterility, and viability. The PMSC-ECM product was formulated by seeding PMSCs onto Cook Biodesign Dural Graft (Cook Biotech; West Lafayette, IN, USA) at a density of 300 000 cells/cm² and incubating for 24 h at 37°C in 5% CO_2. Before use, the product underwent additional sterility testing.

	Expected event rate	Number to trigger DSMB review
Maternal death	0	1
Perinatal death	0·03	1
Cerebrospinal fluid leak	0·011	2
Dehiscence of myelomeningocele repair	0·13	3

DSMB=data safety monitoring board.

Table 1: **Expected rate of adverse events and numbers of events at which review by the DSMB would be triggered**

Surgical procedure

Patients underwent general anaesthesia with epidural placement, and a low transverse laparotomy was used to expose the uterus. The operative technique used in this trial follows the procedure described in MOMS,[10] which provides the only validated data and serves as our historical control group. The only addition was the placement of the PMSC-ECM product. Briefly, a 5–8 cm hysterotomy was made after confirming placental location with ultrasonography. The fetus was positioned to expose the myelomeningocele defect through the hysterotomy. The PMSC-ECM product was delivered sterilely to the operating room. After neurosurgical dissection of the neural placode, the PMSC-ECM was topically applied directly onto the neural placode, with the cells in contact with the exposed fetal spinal cord, followed by primary closure of the dura or duraplasty using the PMSC-ECM product, and closure of the fetal skin, hysterotomy, and maternal abdomen. An overview of the CuRe trial procedure and timeline is depicted in the appendix. After the surgery, weekly targeted ultrasonography was done until delivery to monitor the repair site and overall wellbeing of the fetus.

Primary outcomes

The primary endpoints were the safety and feasibility of the PMSC-ECM product. Feasibility was defined as the ability to administer the investigational treatment—ie, apply the product at the time of surgery—for all patients. Safety was defined as the absence of the following, assessed during birth hospitalisation: postnatal cerebrospinal fluid leak, evaluated by physical examination and spinal ultrasonography at birth; clinical evidence of infection at the fetal myelomeningocele repair site, evaluated by physical examination assessing for erythema or other visual signs of infection; failure of the myelomeningocele repair site to heal, evaluated by physical examination to assess for wound dehiscence; tumour formation, evaluated by contrast-enhanced MRI, assessing for abnormal tissue growth at the repair site; and any patient deaths. The myelomeningocele repair site was documented by photography within 24 h of birth and assessed at birth by physical examination by the treating neonatologist, paediatric neurosurgeons, fetal surgeons, and research team. MRI was done within 2 weeks of birth or as soon as the neonate was clinically stable.

	Maternal age (years)	Gravida, para	Lesion level*	Hindbrain herniation	Myeloschisis *vs* myelomeningocele	Fetal lateral ventricle size on MRI	Clubfoot	Gestational age at surgery
1	35	Gravida 4, para 3	L2/3	Yes	Myelomeningocele	7 mm (right), 12·5 mm (left)	No	25⁺⁵ weeks
2	23	Gravida 2, para 0	L1	Yes	Myelomeningocele	11 mm bilaterally	No	25⁺² weeks
3	28	Gravida 2, para 1	L4	Yes	Myelomeningocele	11 mm bilaterally	Yes	25⁺³ weeks
4	25	Gravida 1, para 0	S1	Yes	Myelomeningocele	13 mm bilaterally	No	25⁺¹ weeks
5	36	Gravida 5, para 4	S1	Yes	Myeloschisis	15 mm (right), 18 mm (left)	No	24⁺⁵ weeks
6	27	Gravida 5, para 2	L3	Yes	Myelomeningocele	12 mm bilaterally	Yes	25⁺⁵ weeks

*As ascertained by the cranial aspect of the lesion on prenatal ultrasonography.

Table 2: **Characteristics of patients at the time of surgery**

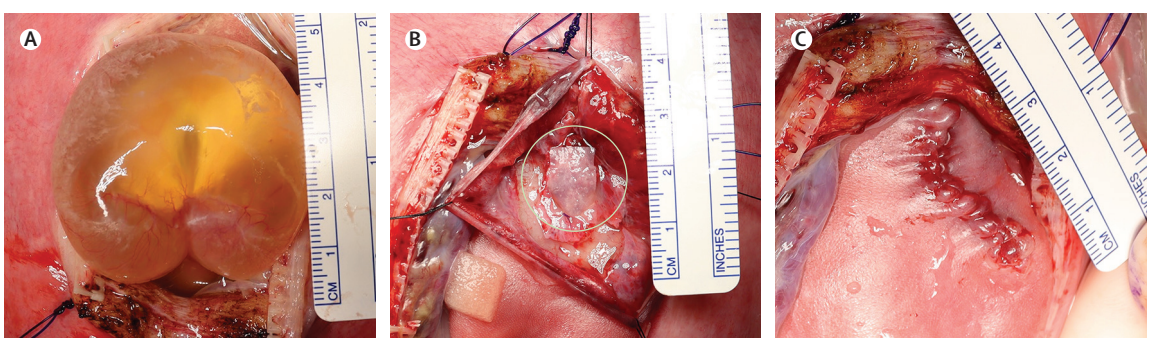

Figure 2: **Intraoperative steps of in-utero myelomeningocele repair using PMSC-ECM**
(A) Maternal laparotomy and hysterotomy are done to expose the fetal myelomeningocele lesion. (B) The spinal cord is dissected from the surrounding tissue, and the PMSC-ECM product is tailored to the size of the defect and applied topically, directly on the exposed spinal cord, cell side facing down (indicated by circle). (C) The fetal skin is closed over the dura. PMSC-ECM=placenta-derived mesenchymal stem cells-extracellular matrix.

Treatment of patients was staggered, as maximum caution was required, given the unknown outcomes of putting living stem cells into the fetal CNS. No subsequent patient was enrolled until the previous child was delivered and assessed for cell-related complications, as mandated by FDA-approved protocol. Data collection and enrolment was halted when the sixth patient reached the age of 3 months for data analysis and determination of sufficient safety of the PMSC-ECM to warrant continuation of the trial.

Statistical analysis

Data are outlined in a descriptive manner according to the prespecified primary endpoints of this phase 1 study. Our protocol and statistical plan mandated that accrual would be halted for DSMB review if the frequency of a specific adverse event exceeded the threshold that would be expected to occur with less than 5% probability, given an expected event rate based on the MOMS study.[10] Event rates required to trigger DSMB review are shown in table 1. It should be noted that although the risk of perinatal death in the MOMS trial was 3%,[10] we chose to have a single perinatal death trigger a DSMB review as any perinatal death must be investigated to ensure it is not due to the experimental treatment.

	PPROM	Gestational age at birth (weeks)	Birthweight (g)	Hindbrain herniation	PMSC-ECM related adverse events	Cerebrospinal fluid diversion procedure for hydrocephalus prior to discharge	Length of stay until discharge home (days)
1	No	36⁺⁶	3565	No	None	No	5
2	Yes	35⁺²	2575	No	None	No	9
3	No	36⁺⁴	2730	No	None	No	8
4	Yes	33⁺²	2320	No	None	No	28
5	Yes	34⁺⁰	2065	No	None	No	17
6	Yes	33⁺²	2075	No	None	No	30

PPROM=preterm premature rupture of membranes. PMSC-ECM=placenta-derived mesenchymal stem cells-extracellular matrix.

Table 3: **Characteristics of patients at birth**

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Annual reports to CIRM are submitted as a condition for ongoing milestone-based funding. CIRM continues to serve in an advisory capacity, assist with enrolment, and identify any concerns related to patients or trial conduct.

Results

Between June 21, 2021, and Dec 5, 2022, six pregnant patients assigned female sex at birth and of median age 27·5 years (range 23–36 years) were enrolled in the trial. All six patients were White (non-Hispanic). All had fetuses with myelomeningocele (except for one with myeloschisis) diagnosed on second trimester ultrasonography, with the lesion level ranging from L1 to S1 and presence of hindbrain herniation confirmed on fetal MRI (table 2).

Gestational age at surgery ranged from 24^{+5} weeks to 25^{+5} weeks. There were no technical complications preventing PMSC-ECM product from being applied or the fetal repair from being accomplished (figure 2). There were no intra-operative complications requiring maternal or fetal transfusions, maternal or fetal resuscitation, or emergent delivery of the fetus.

Newborns were delivered at a median gestational age of 34^{+5} weeks (range 33^{+2} weeks to 36^{+6} weeks) by caesarean delivery (table 3). Two infant patients were born before 34 weeks of gestation, with one infant requiring intubation because of transient respiratory distress syndrome related to prematurity. All infants were discharged without a requirement for home oxygen. All baseline characteristics were similar to those reported in the MOMS trial (table 4).

All newborns were found to have an intact repair site, with no evidence of cerebrospinal fluid leak, infection, skin separation, or abnormal tissue (tumour) growth on physical examination (figure 3). Postnatal MRI obtained as soon as the newborns were clinically stable showed reversal of hindbrain herniation (figure 4, tables 2, 3). No evidence of abnormal tissue proliferation or tumour formation was seen on postnatal imaging. No infant patients required a shunt to treat hydrocephalus before being discharged. The median corrected gestational age at discharge was 37^{+4} weeks (range 36^{+4} weeks to 37^{+5} weeks). Of note, all patient data and images are presented in a randomised order.

	CuRe (first six patients)	MOMS (prenatal repair group)[10]
Maternal age, years	23–36	29·3 (5·3)
Lesion level*		
Thoracic	0	4 (5%)
L1–L2	2 (33%)	21 (27%)
L3–L4	2 (33%)	30 (38)
L5–S1	2 (33%)	23 (29%)
Gestational age at surgery, weeks	24^{+5} to 25^{+5}	23·6 (1·4)†
Gestational age at birth, weeks	33^{+2} to 36^{+6}	34·1 (3·1)

Data are range, mean (SD), or n (%). CuRe=Cellular Therapy for In Utero Repair of Myelomeningocele. MOMS=Management of Myelomeningocele Study.
*As ascertained by the cranial aspect of the lesion on prenatal ultrasonography.
†Gestational age at random assignment.

Table 4: **Baseline maternal and fetal characteristics in CuRe and MOMS**

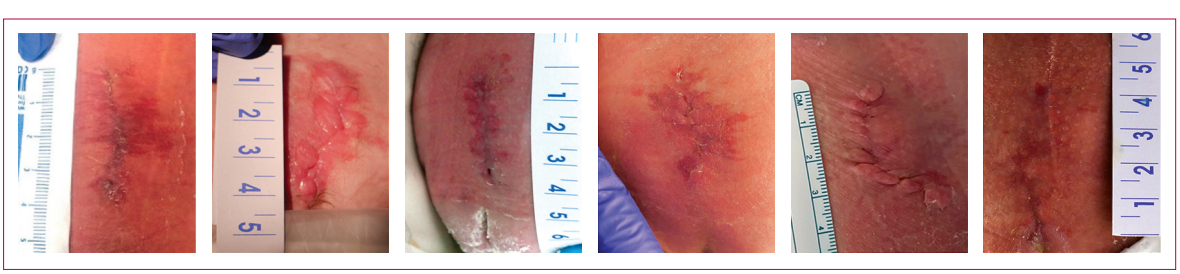

Figure 3: **Postnatal evaluation of the surgical repair site following in-utero myelomeningocele repair**
Each patient's repaired defect was evaluated at birth. Macroscopic images of the surgery site confirmed that all the patients had an intact repair site, with no evidence of cerebrospinal fluid leak or infection.

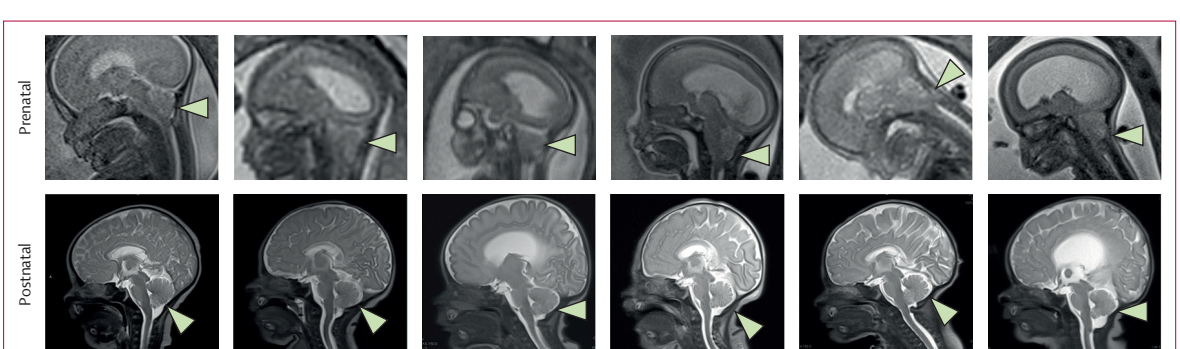

Figure 4: **Prenatal and postnatal MRI showing reversal of hindbrain herniation following in-utero myelomeningocele repair with PMSC-ECM**
Hindbrain herniation was confirmed by MRI in all six patients before repair (top row). Following repair of the myelomeningocele defect with the PMSC-ECM product, postnatal MRI within 2 weeks of birth showed reversal of hindbrain herniation (bottom row). Arrowheads in each image indicate the location of the hindbrain. PMSC-ECM=placenta-derived mesenchymal stem cells-extracellular matrix.

Discussion

This trial constitutes the translation of a rationally designed, mechanistically informed regenerative therapy into clinical application, leveraging PMSCs specifically engineered to modulate the intrauterine environment at the site of the exposed spinal cord in myelomeningocele. The PMSCs were designed to attenuate neuroinflammation, reduce neuronal apoptosis, and secrete neurotrophic and growth factors that support neural tissue preservation and spinal cord integrity. These therapeutic mechanisms were previously validated through in-vitro neuroprotection assays[23] and both small and large animal models.[19,21,25,27,36] PMSCs are intended to protect and regenerate the injured fetal spinal cord during a crucial window of fetal neurodevelopment, complementing the mechanical benefits of surgical repair with a biologically active strategy aimed at improving long-term neurological outcomes.

There was appropriate pretrial concern about the unknown effects of placing allogeneic PMSCs into the fetal CNS. Therefore, this phase 1 trial focused on the surgical feasibility and early safety of combining PMSC therapy with standard fetal myelomeningocele repair in a carefully monitored clinical cohort. The outcomes showed the safe application of PMSC-ECM, without interference with the known saltatory effects of fetal surgery or evidence of adverse events related to stem cell application in the fetal CNS during pregnancy. Specifically, all patients had reversal of hindbrain herniation. No patients had evidence of abnormal tissue growth or tumour formation on physical exam or postnatal imaging. At birth, the repair site appeared indistinguishable from those of patients who underwent prenatal repair without the stem cell product in the MOMS trial.[10] Evaluating these safety endpoints was crucial to confirm that the anti-inflammatory properties of the stem cell product did not impair fetal wound healing, particularly as previous studies in the ovine model showed that the anti-inflammatory characteristics of the amnion contributed to failed healing.[37] All six patients had complete healing of their fetal wound at birth and, as of Aug 1, 2025, no patients have had any wound complications attributable to the stem cell product.

The potential for tumour development in fetal patients receiving stem cell therapy is of concern in two potential scenarios: malignant or proliferative transformation of the transplanted PMSCs and exuberant growth of the cells of the fetus through the effects of PMSCs. To date, there are no reported cases in the literature of abnormal tissue or tumour growth after the use of mesenchymal stromal or stem cells in adult patients.[38,39] Our study is the first to show the feasibility and safety of PMSC-ECM for use in prenatal therapy for a CNS disorder, directly applied to the anatomical site of pathology. Although these phase 1 endpoints showed adequate safety to proceed to the phase 2a stage of the trial, we acknowledge the small initial sample size of six patients and the focus limited to birth outcomes in this report. Long-term follow-up of all enrolled patients (up to age 6 years) will provide a more definitive assessment of both safety and preliminary efficacy.

Currently, no regenerative stem cell products are commercially available to treat diseases in utero. The fetal environment contains numerous qualities that could facilitate stem cell therapy, including the natural receptivity of the developing fetus to regeneration and remodelling by stem cells.[40] Recently, two studies have evaluated the safety and efficacy of in-utero stem cell transplantation for the severe genetic disorders thalassaemia (a bleeding disorder) and osteogenesis imperfecta (a collagen disorder).[41,42] In-utero intravenous transplantation of maternal bone marrow-derived hematopoietic stem cells for thalassaemia and of allogeneic fetal liver-derived stem cell for osteogenesis imperfecta appeared safe, but long-term engraftment for genetic conditions is challenging and continues to be optimised. In contrast, long-term engraftment is not warranted for myelomeningocele, which is a structural birth defect with a defined anatomical area requiring transient regeneration and repair. PMSCs have shown immunomodulatory, neuroprotective, and wound-healing properties in vitro and efficacy in vivo in animal models of fetal myelomeningocele repair.[19,22,28] Until now, the use of PMSCs in human fetal patients, particularly with these cells in direct contact with the delicate and developing CNS, had not been studied.

In patients with myelomeningocele, prenatal repair has been shown to reduce hindbrain herniation and rates of ventriculoperitoneal shunt.[10] However, prenatal surgery does not fully address the mobility issues that arise from damage to lower motor neurons. The initial findings of this study indicated that PMSC-ECM directly applied to the fetal spinal cord during prenatal repair of myelomeningocele was without cell-related adverse events and that hindbrain herniation was reversed. The safety results of the first six patients have been deemed to be adequate by the DSMB and FDA to allow continuation of the trial with more aggressive, non-staggered enrolment.

Although some motor function observations can be made after birth, their clinical validity remains uncertain; therefore, these findings are not included in this phase 1 safety study report. In addition to routine care, follow-up assessments will be done at 3 months, 6 months, 9 months, 12 months, 18 months, 24 months, and 30 months and then annually, until age 6 years. Long-term outcomes include long-term safety; motor function, tested using validated tools (Test of Infant Motor Performance,[43] Alberta Infant Motor Scale,[44] Bayley Scale of Infant Development,[45] Peabody Developmental Motor Scales,[46] the WeeFIM test,[47] and the Ages & Stages Questionnaires); bowel and bladder function (assessed with anorectal manometry and urodynamics); and results of any imaging or procedures. The ongoing phase 1/2a study will continue

the assessment of the long-term safety and preliminary efficacy of the PMSC-ECM for improving motor function, as well as bowel and bladder function.

This trial establishes a scalable and clinically feasible platform for the targeted delivery of biological therapeutics to the fetus. The successful integration of cell-based therapy into fetal surgery, under stringent regulatory oversight and within a standardised surgical workflow, shows the feasibility and safety of delivering rationally designed biologics during gestation. By intervening at early stages of development, this approach has the potential to alter lifelong health trajectories, reducing the burden of chronic disability and minimising the long-term social and economic impact of these conditions.

Contributors

The following authors were responsible for aspects of study design pertinent to their expertise—medical and regulatory oversight: DLF, ABP, SYL, MZ, JAN, ASM, SH, PS, and EGB; product formulation and delivery: PK and AW; enrolment of study participants: DLF, ABP, SYL; and collection of data and analysis of findings: DLF, SYL, CDP, AW, and ER. All authors were engaged in manuscript preparation and confirm adherence to protocol, the completeness and accuracy of results, and the collective decision to publish the paper. DLF, AW, ER, SYL, CDP, and PK directly accessed and verified the data.

Declaration of interests

DLF and AW report the following disclosures: US patent number 10058572 (issued Aug 28, 2018) from US patent application 14/912066 (filed Aug 14, 2014); US patent number 11583557 (issued Feb 21, 2023) from US patent application 15/998529 (filed Aug 16, 2018); and US patent application 18/098631 (filed 18, 2023). All patents are assigned to the Regents of the University of California, Davis. All other authors declare no competing interests.

Data sharing

Study-related documents including study protocol, statistical analysis plan, informed consent form, and de-identified participant data can be made available on request at the conclusion of this trial and on publication of related manuscripts.

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