SAFETY, EFFICACY, AND OUTCOMES OF CURRENT STANDARD OF CARE IN PREGNANT INDIVIDUALS AND THEIR OFFSPRING AT HIGH RISK OF EARLY-ONSET SEVERE HEMOLYTIC DISEASE OF THE FETUS AND NEWBORN: RESULTS FROM THE PROSPECTIVE OBSERVATIONAL CLARITY STUDY

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BACKGROUND

- Pregnancies at risk of early-onset severe hemolytic disease of the fetus and newborn (EOS-HDFN) develop fetal anemia at ≤24 weeks gestational age (GA) and are at high risk of poor outcomes, including severe morbidity and mortality for the fetus and newborn[1-3]
- Standard of care (SOC) for pregnancies at risk of EOS-HDFN includes monitoring of middle cerebral artery peak systolic velocity (MCA-PSV) by Doppler ultrasound to detect fetal anemia and intrauterine blood transfusions (IUTs) once fetal anemia is confirmed by cordocentesis[4-6]
- Intravenous immunoglobulin G (IVIG) or plasmapheresis has sometimes been administered to delay the onset of fetal anemia and the need for IUT[7-9]

OBJECTIVE

- The CLARITY trial aims to characterize the current SOC, clinical course, and outcomes for pregnant individuals and their offspring at high risk for EOS-HDFN at global HDFN referral centers

METHODS

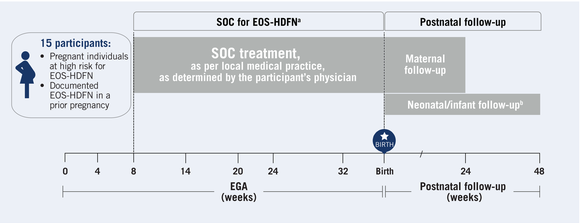
Inclusion Criteria

- Singleton pregnancy with an estimated GA ≥8 weeks
- Previous pregnancy with a gestation that included ≥1 of the following at ≤24 weeks GA:
  - Severe fetal anemia, defined as hemoglobin ≤0.55 multiples of the median (MoM) for GA
  - Hydrops fetalis with an MCA-PSV MoM ≥1.5
  - Stillbirth indicative of severe HDFN
- Maternal alloantibody titers for anti-D ≥32 or anti-Kell ≥4
- Confirmation of an antigen-positive fetus in the current pregnancy based on 1 of the following available laboratory test results:
  - Father is homozygous for D or Kell antigen
  - Free fetal DNA test results
  - Fetal antigen status, as documented by amniocentesis for the mother

Study Design

- CLARITY is an ongoing prospective, global, multicenter, observational study that enrolled 15 alloimmunized pregnant individuals (**Figure 1**)
  - Interim data reported here are for the primary analysis (cut-off date October 20, 2022), and are subject to change upon study completion

Figure 1. CLARITY Study Design



EGA, estimated gestational age; EOS-HDFN, early-onset severe hemolytic disease of the fetus and newborn; GA, gestational age; SOC, standard of care.
[a]Participants who were pregnant at a GA of ≥8 weeks were screened for inclusion during the current pregnancy and enrolled in the study at any time during the current pregnancy prior to delivery.
[b]Treatments received for EOS-HDFN per SOC up to 3 months of age and outcomes of interest through 1 year.

Outcomes

- The primary outcome is the proportion of participants with a live birth at ≥32 weeks GA without an IUT
- Secondary outcomes can be found in **Table 1**

Table 1. Primary and Secondary Outcomes

Primary outcome
The proportion of participants with a live birth at or after GA Week 32 without an IUT
Secondary outcomes (antenatal)
Percentage of participants with a live birth
GA at first IUT
Number of IUTs required
Percentage of participants at GA Week 24 without an IUT
Percentage of participants with hydrops fetalis
Percentage of participants treated with plasmapheresis and/or IVIG
GA at delivery
Secondary outcomes (postnatal)[a]
Percentage of neonates requiring phototherapy
Number of hours of phototherapy required
Percentage of neonates requiring simple transfusions in the first 3 months of life
Number of simple transfusions required in the first 3 months of life
Percentage of neonates requiring exchange transfusions
Safety outcomes[b]
Serious AEs (grade 3 per CTCAE v5.0 criteria)
AESIs (ie, infections requiring anti-infectives, hypoalbuminemia, and unexpected/unusual childhood illnesses)

AE, adverse event; AESI, adverse event of special interest; CTCAE, Common Terminology Criteria for Adverse Events; GA, gestational age; IUT, intrauterine transfusion; IVIG, intravenous immunoglobulin G.
[a]Other perinatal and neonatal outcome variables were evaluated up to Day 28 postpartum of the last maternal participant.
[b]Safety data were only collected for serious AEs and AESIs.

CONCLUSIONS

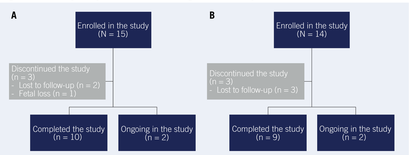
- **This prospective observational study demonstrates that the majority of maternal participants at high risk of EOS-HDFN did not achieve the primary efficacy outcome of a live birth at 32 weeks GA or later without any IUTs**
- **Almost all study pregnancies required multiple IUTs, often starting <24 weeks GA, even if IVIG was administered**
- **All neonates/infants required hospitalization related to EOS-HDFN, and almost all required NICU hospitalization**
- **More than half of neonates/infants required simple transfusions and one-fifth required exchange transfusions even if IVIG was administered**
- **These results highlight the significant unmet medical need for an effective, noninvasive intervention for the treatment and management of pregnant individuals and their offspring at high risk for EOS-HDFN**

RESULTS

Participants

- The study enrolled 15 pregnant participants, and 14 live births occurred (**Figure 2**)

Figure 2. Study Disposition of (A) Pregnant Participants and (B) Neonates/Infants



- Most pregnant participants were White (73%) and had alloantibody titers for RhD (93%); median (range) age was 36.0 (29-42) years (**Table 2**)

Primary and Antenatal Outcomes

- Of the 15 pregnant participants enrolled, 2 (13%) achieved the primary outcome; both participants received IVIG during the study (**Table 3**)
- Fourteen of 15 (93%) pregnancies resulted in a live birth, with a median GA at delivery of 36.3 weeks
- One pregnancy resulted in fetal demise, occurring at 16.7 weeks
- Thirteen of 15 (87%) participants required IUTs, with a median of 4 IUTs
- The median GA at first IUT was 24.0 weeks
- There was 1 (7%) case of hydrops fetalis
- Four of the 13 (31%) maternal participants treated with IUTs experienced complications, including fetal bradycardia (2/13), cord bleeding (1/13), preterm premature rupture of membranes (1/13), and other (2/13; "unable to get posttransfusion samples due to the needle migrating after transfusion" and "mild ascites compatible with a small intraperitoneal transfusion")

Table 2. Demographic and Baseline Characteristics

Characteristic	Participants (N = 15)
Age (years), median (range)	36.0 (29-42)
18-34 years, n (%)	5 (33.3)
≥35 years, n (%)	10 (66.7)
Race, n (%)	
White	11 (73.3)
Black or African American	1 (6.7)
Asian	1 (6.7)
Unknown/not reported	2 (13.3)
Country of site, n (%)	
Australia	1 (7.1)
Canada	1 (7.1)
The Netherlands	4 (28.6)
Spain	1 (7.1)
Sweden	2 (14.3)
United Kingdom	2 (14.3)
United States	3 (21.4)
Missing	1 (7.1)
Qualifying antibody type, n (%)	
RhD	14 (93.3)
Kell	1 (6.7)

Table 3. Summary of Antenatal Outcomes

	Participants (N = 15)
Primary outcome	
Participants with a live birth at ≥32 weeks GA without an IUT, n (%)	2 (13.3)
Secondary outcomes	
Participants with a live birth at any time, n (%)	14 (93.3)
GA at delivery, median (range)	Week 35.7 (16.7-38.0)
GA at first IUT, median (range)	Week 24.0 (13.0-28.3)
Participants with a fetus with hydrops fetalis, n (%)	1 (6.7)
Participants with ≥1 IUT, n (%)	13 (86.7)
IUTs per participant, median (range)	4.0 (1-11)
Participants with a live birth and ≥1 IUT, n (%)	12 (80.0)
IUTs per participant, median (range)	4.5 (2-11)
Participants with fetal demise and ≥1 IUT, n (%)	1 (6.7)
IUTs per participant, median (range)	1.0 (1-1)

GA, gestational age; IUT, intrauterine transfusion.

Post Hoc Subgroup Analysis by IVIG Usage

- Seven of 15 (47%) maternal participants received IVIG
- None of the 8 maternal participants who did not receive IVIG met the primary outcome
- Of the 7 maternal participants who received IVIG, 2 met the primary outcome (**Table 4**)
- Three of the 7 (43%) maternal participants receiving IVIG experienced IVIG-related complications, including headache (2/7), abnormally rapid heart rate (2/7), lower back pain (1/7), nausea (1/7), and other (1/7)
- One of the 7 (14%) maternal participants receiving IVIG developed aseptic meningitis likely related to IVIG as per the investigator's judgment, which occurred during pregnancy prior to study enrollment

Table 4. Post Hoc Subgroup Analysis by IVIG Usage

	Participants receiving IVIG (n = 7)
Primary outcome	
Participants with a live birth at ≥32 weeks GA without an IUT, n (%)	2 (28.6)
IVIG-related complications	
Participants with IVIG-related complications, n (%)[a]	3 (42.9)
Headache	2
Abnormally rapid heart rate	2
Lower back pain	1
Nausea	1
Other	1

GA, gestational age; IUT, intrauterine transfusion; IVIG, intravenous immunoglobulin G.
[a]Some participants may have >1 complication.

Postnatal Outcomes

- Postnatal simple transfusions were required by 8 of 14 (57%) neonates/infants, and exchange transfusions were required by 3 of 14 (21%) neonates/infants (**Table 5**)

Antenatal and Postnatal Outcomes by Participant

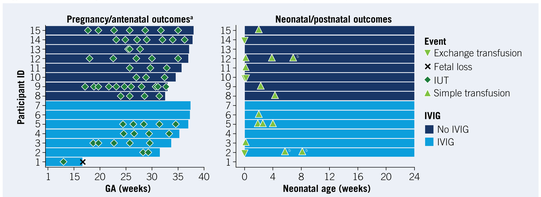
- Five of 7 (71%) pregnant participants who received IVIG required ≥1 IUT, which is similar to pregnant participants who did not receive IVIG (13/15; 86%; **Figure 3A**)
- Three of the 6 (50%) neonates who received IVIG required ≥1 simple transfusion, which is similar to neonates who did not receive IVIG (8/14; 57%; **Figure 3B**)

Table 5. Summary of Postnatal Outcomes

	Neonates/infants (N = 14)
Phototherapy	
Infants requiring ≥1 phototherapy session, n (%)	14 (100)
Number of hours of phototherapy, median (range)	116.5 (12.0-216.0)
Simple transfusion in the first 12 weeks of life	
Infants requiring ≥1 simple transfusion, n (%)	8 (57.1)
Number of simple transfusions, median (range)	1.0 (1-3)[a]
Exchange transfusion	
Infants requiring ≥1 exchange transfusion, n (%)	3 (21.4)
Number of exchange transfusions, median (range)	1.0 (1-2)

[a]Does not include transfusions that occurred after data cut-off, as depicted in Figure 3.

Figure 3. Summary of Antenatal and Postnatal Outcomes by Participant



GA, gestational age; IUT, intrauterine transfusion; IVIG, intravenous immunoglobulin G.
[a]Bars extend to GA at delivery.
[b]Transfusion occurred after data cut-off. Data are subject to change upon completion of the final analysis.

Safety

- Serious adverse events were reported in 2 of 15 (13%) maternal participants and 1 of 14 (7%) neonates/infants (**Table 6**)

Table 6. Serious AEs

Serious AEs by preferred term[a]	Total
Maternal participants, N	**15**
Participants with ≥1 serious AE, n (%)	2 (13.3)
Abortion spontaneous	1 (6.7)
Scar pain	1 (6.7)
Neonates/infants, N	**14**
Participants with ≥1 serious AE, n (%)	1 (7.1)
Blood bilirubin increased	1 (7.1)

AE, adverse event; MedDRA, *Medical Dictionary for Regulatory Activities*.
[a]AEs are coded using MedDRA v25.0.

- All 14 neonates/infants required hospitalization related to EOS-HDFN, with a median (range) of 7 (3-65) days; 13 (93%) required neonatal intensive care unit (NICU) hospitalization, with a median (range) of 5 (2-34) days

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