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Original Research Article

Post-marketing safety evaluation of recombinant anti-Rho (D) immunoglobulin for the prevention of maternal Rh-isoimmunization: A prospective, multi-centre, phase IV study

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ABSTRACT

Background: AntiD® is a recombinant anti-D immunoglobulin approved as an immunoprophylaxis treatment in Rh-negative mothers carrying an Rh-positive fetus. This study was conducted to assess the safety and tolerability of AntiD in clinical settings.

Materials and Methods: This was a prospective, multicenter, phase IV, post-marketing safety study of AntiD. The study was conducted at 29 hospitals in India as per regulatory requirements. Three hundred eligible Rh-negative women were administered a single intramuscular dose of either 150 mcg or 300 mcg AntiD within 72 hours of a sensitizing event as per the approved indication. Safety and tolerability were evaluated based on the assessment of adverse events (AEs) and serious adverse events (SAEs) reported during the study.

Results: Out of the 300 participants enrolled, 290 completed the study procedures. A total of 54 AEs and 34 treatment-emergent adverse events (TEAEs) were reported by 47 (15.7%) and 30 (10.0%) participants, respectively. Most reported TEAEs were mild, unrelated to the study drug, and were completely resolved during the study. Except for two participants with clinically significant hematological and urinalysis findings consistent with their underlying medical conditions, none of the participants exhibited abnormal clinical or laboratory parameters.

Conclusion: Based on the assessment of the different safety parameters, AntiD administered at a dose of either 150 mcg or 300 mcg did not raise any new or significant safety concerns. The current study demonstrated that AntiD is well-tolerated and safe to use for anti-D prophylaxis as per product label indications for the prevention of Rh-isoimmunization in a clinical setting.

1. Introduction

Maternal Rh-isoimmunization occurs when an Rh-negative mother carrying an Rh-positive fetus is exposed to fetal Rh-positive red blood cells (RBCs), and maternal anti-RhD

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antibodies are produced against the RhD antigen present on fetal RBCs. This is also known as sensitization and can occur during any sensitizing event such as childbirth, abortion, invasive obstetric testing, antepartum hemorrhage (APH), ectopic pregnancy, external cephalic version, fall or abdominal trauma, and intrauterine death.[1,2] The anti-RhD antibodies can penetrate the placenta and destroy fetal RBCs, leading to serious conditions such as erythroblastosis fetalis, hemolytic disease of the fetus and newborn (HDFN), hydrops fetalis, and even fetal death.[3] While the fetal risk for a first pregnancy is low, a perinatal mortality rate of 24% has been reported for subsequent pregnancies in sensitized Rh-negative women.[4] The incidence of Rh-negative pregnancies in India is at about 5% of the total reported pregnancies, with an isoimmunization rate of 10.7% among the Rh-negative pregnancies.[5]

Anti-Rho(D) immunoglobulin (anti-D IgG) therapy is a prophylaxis treatment option to prevent Rh-sensitization.[5] In 2014, it was reported that the routine postpartum administration of anti-D IgG decreased the incidence of Rh-isoimmunization in subsequent pregnancies from 16% to 2%; this was further reduced to <0.1% by introducing an additional dose prenatally.[6,7] Chilcott et al.[8] noted that routine anti-D IgG injections should prevent future hemolytic diseases in infants. Routine antenatal anti-D prophylaxis (RAADP) for Rh-negative women has been recommended as a prevention strategy by various authorities worldwide such as the American College of Obstetricians and Gynecologists (ACOG) in the United States,[9] the National Institute of Health and Clinical Optimization (NICE; https://www.nice.org.uk/guidance/TA156) and British Committee for Standards in Hematology (BCSH) in the United Kingdom,[7] the National Blood Authority (NBA) and Royal Australian and New Zealand College of Obstetricians and Gynecologists (RANZCOG) in Australia (https://www.blood.gov.au/anti-d-0), and the New Zealand Blood Service (NZBS) in New Zealand (https://www.nzblood.co.nz/).[10] In India, the Federation of Obstetric and Gynecological Societies of India (FOGSI) recommends both antenatal and postnatal use of anti-D prophylaxis in non-sensitized Rh-negative women (https://icogonline.org/gcpr/).

Conventionally, polyclonal anti-Rho D (poly-anti-D), isolated from the blood of Rh-isoimmunized individuals has been used for anti-D prophylaxis.[11] However, poly anti-D is associated with issues such as the limited availability of donors and the risk of transmission of viral/prion diseases.[12,13] In some European countries, the procedure for obtaining polyclonal immunoglobins from repeatedly immunized donors has been banned in view of donor safety.[14] Monoclonal anti-D immunoglobulins (mono-anti-D), manufactured using the hybridoma technique, were introduced to mitigate these problems.[11,13,15] However, the maintenance of hybridoma cultures and the generation of monoclonal antibodies is a time-consuming and laborious process. Moreover, the limited availability of hybridoma growth supplements such as fetal bovine serum is a major obstacle to the adequate production of mono-anti-D.[16,17] The development of recombination anti-D immunoglobulins (R-anti-D) has provided a viable option to overcome the obstacles associated with mono-anti-D. Attempts to produce R-anti-D antibodies have been reported as early as 1997.[18,19] The yields, stability, and reliability of R-anti-D have been reported to be superior to that of mono-anti-D.[20] Mayekar et al.[21] have reported that R-anti-D is well-tolerated and effective in both mother and fetus as its polyclonal counterparts, and is non-immunogenic in nature.

In India, Bharat Serums and Vaccines Ltd. (BSV) has developed AntiD® (Trinbelimab, BSV, Mumbai, India), a recombinant anti-Rho(D) immunoglobulin, for prophylactic use in Rh-negative mothers. The product has been approved for clinical use in India since December 2020 based on the results of a Phase III clinical trial which showed that AntiD is comparable in efficacy to conventional poly-anti-D, is well-tolerated, and non-immunogenic.[21] The present study is a prospective, multi-center, Phase IV study for the post-marketing safety evaluation of recombinant AntiD in the prevention of maternal Rh-isoimmunization, and was conducted as mandated by the Central Drugs Standard Control Organization (CDSCO). The results of this study showed that AntiD is well-tolerated with no severe or unexpected safety concerns for use as a prophylactic agent in Rh-negative mothers in a clinical setting to prevent Rh-isoimmunization.

2. Materials and Methods

2.1. Trial design

This was a prospective, multicenter, phase IV, post-marketing safety study of recombinant anti-Rho(D) immunoglobulin (AntiD®; Trinbelimab, BSV, India) when administered as prophylaxis to prevent maternal isoimmunization in Rh-negative women after a sensitizing event. The study duration for each participant was a maximum of 31 days which included a screening period (within 48 hours after the sensitizing event), AntiD administration (within 72 hours of the sensitizing event), and a follow-up period of 28 days (± 3 days) post-AntiD administration.

The study protocol was approved by the Drugs Controller General of India (DCGI) and the institutional ethics committees of all the participating hospitals/institutions. The study was conducted following the New Drugs and Clinical Trials Rules, 2019, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline for Good Clinical Practice E6(R2), and the World Medical Association's Declaration of Helsinki, 2013.

2.2. Participants

The study participants were enrolled as per the following inclusion criteria: Rh-negative women; age ≥ 18 years; negative indirect Coomb's test (ICT); eligible to receive AntiD injection as per approved indication; and provided informed consent. Participants were excluded from the study if they had any medical condition that could compromise their ability to participate in the trial, a history of anaphylactic or other severe systemic reactions to immunoglobulins, or if they required blood transfusion. Participants were withdrawn from the study in any of the following conditions: participant withdrew consent to participate; the investigator deemed that withdrawal was in the participant's best interest; occurrence of an adverse event (AE) that did not justify continuation in the study; occurrence of a major violation; or the participant was unable to follow the study protocol.

2.3. Sensitizing events

Childbirth and abortion are the main sensitization events considered in this study. However, other sensitizing events including but not limited to invasive obstetric testing (for example, amniocentesis or chorionic villus sampling), antepartum hemorrhage (APH), ectopic pregnancy, external cephalic version, fall or abdominal trauma, intrauterine death, and termination of pregnancy, were also considered.

2.4. Randomization and blinding

Randomization was not performed as this was a non-randomized, single-arm study; hence, blinding was not required. Participants were administered a single dose of AntiD (intramuscular injection) at 300 mcg or 150 mcg, as per the prescription.

2.5. Intervention

After obtaining written and signed informed consent, the participants were screened for their eligibility as per the inclusion and exclusion criteria within 48 hours of the sensitizing event and enrolled as per eligibility. Enrolled participants were then administered either 150 mcg or 300 mcg of AntiD intramuscularly within 72 hours of the sensitizing event, as per pre-defined criteria. The 300 mcg AntiD dose was administered post-delivery to participants who delivered Rh-positive infants and did not exhibit serum anti-D antibodies, and to participants who miscarried in advanced stages of pregnancy. The 150 mcg AntiD dose was administered in cases of abortion or pregnancy termination if the pregnancy duration was < 12 weeks. Participants at risk of transplacental hemorrhage with other sensitizing events and not known to have been sensitized were administered 150 mcg or 300 mcg of AntiD.

2.6. Outcomes

The primary outcome of the study was safety, which was evaluated based on the reporting of AEs and serious adverse events (SAEs). Data on the following were collected on enrolment day (pre-treatment): demography (age, height, weight); medical history; details of the sensitizing event; vital signs; physical examination; and concomitant medication. Blood and urine samples were collected and analyzed for hematology, blood biochemistry, indirect Coombs test (ICT), and urinalysis. On the day of AntiD administration, on follow-up day (day 28 post-AntiD administration), and at appropriate times during the study, data on the following were obtained: vital signs; physical examination; AE assessment; concomitant medication; and laboratory assessments (as above). Telephonic follow-up was performed on day 3 post-AntiD administration to enquire about the participant's health status and any AEs. All AEs, SAEs, and AEs of special interest that occurred during the study were documented and reported according to the governing regulatory requirements.

2.6.1. Statistical analysis

Descriptive statistics (number of observations, mean, standard deviation [SD], median, and range) were provided for all the continuous variables. Frequency count (n) and percentage (%) of participants were provided for the categorical variables. The demographic data and baseline characteristics were summarized using the intent-to-treat (ITT) population by AntiD dose. The IIT population comprised all participants who were eligible and received the study drug. AEs were analyzed in the safety population, which comprised all participants who received the study drug. AEs were coded using the Medical Dictionary of Regulatory Activities (MedDRA version 24.1) and summarized. Subgroup analysis was also performed for participant disposition and overall AEs. The following subgroups were defined:

Cohort A: Rh-negative women who had delivered Rh-positive infant(s).

Cohort B: Rh-negative women with abortion or other sensitizing events. This cohort was further divided into three subgroups as follows:

1. **Cohort B1**: Participants with abortion or termination of pregnancy (pregnancy duration < 12 weeks).
2. **Cohort B2**: Participants with miscarriage at an advanced stage (> 12 weeks) of pregnancy.
3. **Cohort B3**: Participants with other sensitizing events during the pregnancy.

3. Results

3.1. Participant flow

This trial was conducted from 23 December 2021 to 1 August 2022 across 29 hospitals/institutions in India. A total of 316 participants were screened, of whom 300 were enrolled in the study and received either 300 mcg (229 participants) or 150 mcg (71 participants) of AntiD® within 72 hours of the sensitizing event. Of the 300 enrolled participants, 290 completed the study, whereas 10 discontinued due to reasons such as withdrawal, loss to follow-up, and other reasons (Figure 1). As all the 300 enrolled participants received the study drug, they were included in the study analysis as the ITT population as well as the safety population.

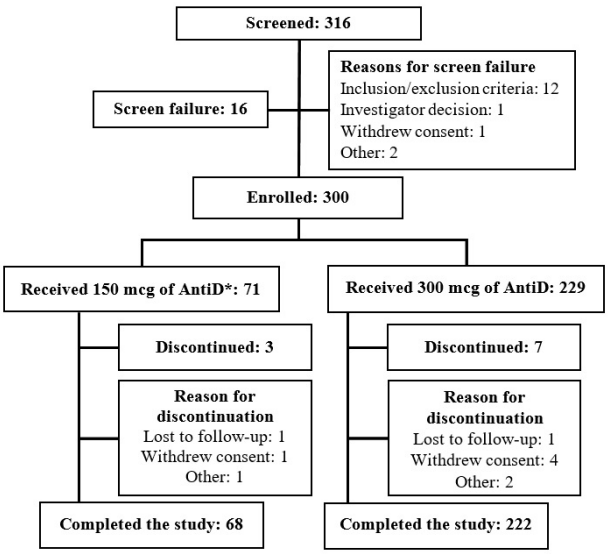

Figure 1: Participant flow *AntiD: Trinbelimab (Recombinant Anti Rho-DImmunoglobulin)

3.2. Demographics and baseline characteristics

All the enrolled participants were Rh-negative women who had experienced a sensitizing event that may lead to feto-maternal hemorrhage (FMH). The mean age of the participants was 25.5 years (range 18 to 39 years). The mean gestational age was 29.2 weeks (range 3 to 42 weeks), and 285 (95.0%) participants had a regular menstruation history (Table 1). Medical history (Table S1) and concomitant or prior medications (Table S2) of the participants were aligned with their underlying obstetrical condition or were prescribed by the investigators for the management of AEs. None of the participants consumed prohibited medications during the study.

3.3. Safety evaluation

Overall, 54 AEs were reported in the study, of which 34 events reported by 30 (10.0%) participants were TEAEs. All the AEs were also analyzed based on the pre-defined cohorts (A, B1, B2, and B3); the results are presented in Table 2. The distribution of the 34 TEAEs according to the AntiD dosage was as follows: 300 mcg dose: 29 events reported by 25 (10.9%) participants; and 150 mcg dose: 5 events reported by 5 (7.0%) participants. The TEAEs are listed in Table 3 according to the system organ class and preferred term for the safety population.

As per the investigator's decision, 19 TEAEs (16 events in 14 participants and 3 events in 3 participants administered 300 mcg and 150 mcg AntiD, respectively) were considered to be related to the study drug, which included injection site erythema (6 events in 6 participants), injection site pain (3 events in 3 participants), or injection site swelling (1 event in 1 participant) (Table S3). However, none of the participants had SAEs or serious TEAEs, and no deaths were reported during the study.

The majority of the TEAEs were mild in severity, whereas two TEAEs (injection site swelling and anemia in two participants administered 300 mcg of AntiD) were of moderate severity. All the TEAEs were completely resolved during the study, and none of the participants were discontinued from the study due to any AE or TEAE.

Laboratory findings for most of the participants were within the normal or clinically non-significant range except for the findings in two participants (administered 300 mcg of AntiD). On day 28 (follow-up visit), one participant was reported to have low levels of lymphocyte counts while the other participant was diagnosed with a urinary tract infection; however, these findings were coherent with the underlying medical condition of the participants.

Vital signs were within clinically acceptable limits for all but one participant (administered 300 mcg of AntiD) who showed abnormal clinically significant levels of systolic and diastolic blood pressure (gestational hypertension) during the study. None of the participants showed any abnormal clinically significant physical examination findings.

4. Discussion

Different research groups are working on the development of mono- and/or R-anti-D immunoglobulins that can replace conventional poly-anti-D and provide a safe and sustainable source for anti-D prophylaxis.[14] Various studies (Phase I to III clinical trials) have been conducted on the pharmacokinetics, efficacy, and safety of mono- and R-anti-D antibodies. Varying efficacies have been reported across products concerning the clearance rate of Rh-positive RBCs from blood circulation.[22–25] Chauhan et al.[15] reported similarities between Rhoclone®, a monoclonal anti-D antibody product (Bharat Serums and Vaccines Ltd.,

Table 1: Demographic and baseline characteristics

Characteristic	Response	AntiD* 150 mcg (N = 71) n= 71 (100%)	AntiD 300 mcg (N = 229) n= 229 (100%)	Overall (N = 300) n= 300 (100%)
Age (years)Mean ± SD		27.5 ± 4.65	24.9 ± 4.92	25.5 ± 4.97
Height (cm)Mean ± SD		158.5 ± 7.08	156.1 ± 5.63	156.7 ± 6.09
Weight (Kg)Mean ± SD		59.2 ± 10.75	59.0 ± 10.11	59.0 ± 10.24
Mensuration history [n (%)]	Regular	65 (91.5)	220 (96.1)	285 (95.0)
	Irregular	6 (8.5)	9 (3.9)	15 (5.0)
	Other	0	0	0
Gestational age (Weeks)Mean ± SD		8.4 ± 2.48	35.6 ± 6.21	29.2 ± 12.86
Any Sensitizing Event for FMH [n (%)]	Yes	71 (100.0)	229 (100.0)	300 (100.0)
	No	0	0	0
Indirect Coombs test [n (%)]	Positive	0	0	0
	Negative	71 (100.0)	229 (100.0)	300 (100.0)

***AntiD**: Trinbelimab (Recombinant Anti Rho-D Immunoglobulin)
N = Total number of participants in each AntiD dose group; **n** = Number of participants with complete data within the specific category

Table 2: Subgroup analysis of overall adverse events

Cohorts [#]	Adverse events (AEs)		Treatment-emergent AEs (TEAEs)		Treatment-related	
	No. of events	n (%)	No. of events	n (%)	No. of events	n (%)
Overall (N=300)	54	47 (15.7)	34	30 (10.0)	19	17 (5.7)
AntiD* of 150 mcg						
A (N=0)	NA	NA	NA	NA	NA	NA
B1 (N=58)	9	6 (10.3)	5	5 (8.6)	3	3 (5.2)
B2 (N=1)	0	0	0	0	0	0
B3 (N=12)	0	0	0	0	0	0
Total (N=71)	9	6 (8.5)	5	5 (7.0)	3	3 (4.2)
AntiD of 300 mcg						
A (N=196)	42	38 (19.4)	27	23 (11.7)	14	12 (6.1)
B1 (N=4)	0	0	0	0	0	0
B2 (N=9)	1	1 (11.1)	1	1 (11.1)	1	1 (11.1)
B3 (N=20)	2	2 (10.0)	1	1 (5.0)	1	1 (5.0)
Total (N=229)	45	41 (17.9)	29	25 (10.9)	16	14 (6.1)

[#]**Cohort A**: Participants who had delivered Rh-positive infants; **Cohort B1**: Participants with abortion or termination of pregnancy (pregnancy duration: < 12 weeks); **Cohort B2**: Participants with miscarriage at an advanced stage (> 12 weeks) of pregnancy; **Cohort B3**: Participants with other sensitizing events during pregnancy; Other sensitizing events included invasive obstetric testing (e.g., amniocentesis or chorionic villus sampling), antepartum haemorrhage (APH), ectopic pregnancy, external cephalic version, fall or abdominal trauma, and intrauterine death.
***AntiD:** Trinbelimab (Recombinant Anti Rho-D Immunoglobulin)
N = Total number of participants in each AntiD dose group; **n** = Number of participants with complete data within the specific category; **NA**= not applicable.

India), and its poly-anti-D counterpart with reference to clinical effects in a large number of women requiring anti-D in the clinical setting. It is noteworthy that in all studies, the safety profiles for both mono- and R-anti-D immunoglobulins have been consistent and comparable with that of poly-anti-D.[14,26]

AntiD is a recombinant anti-D product that has been approved for use as an anti-D prophylaxis treatment in Rh-negative women carrying an Rh-positive fetus and who had experienced a sensitizing event during pregnancy. As per our knowledge, this is the only R-anti-D product that has been approved and launched in India for clinical use for eligible Rh-negative pregnant women. AntiD has been assessed for its efficacy and safety in a Phase III clinical trial. In that study, none of the 215 participants (144 in the AntiD group and 77 in the poly-anti-D group) was reported to develop anti-D antibodies at the end of 6 months; less than 1% of the participants reported mild or non-serious AEs; and none of the participants developed anti-AntiD antibodies. This showed that AntiD is as effective, safe, and non-immunogenic as poly-anti-D.[21]

Table 3: Treatment-emergent adverse events (TEAEs) by system organ class and preferred term for the safety population

System Organ Class	AntiD 150 mcg (N = 71) Number of Events	AntiD 150 mcg (N = 71) n (%)	AntiD 300 mcg (N = 229) Number of Events	AntiD 300 mcg (N = 229) n (%)	Overall (N = 300) Number of Events	Overall (N = 300) n (%)
Number of Participants with at least one TEAE	**5**	**5 (7.0)**	**29**	**25 (10.9)**	**34**	**30 (10.0)**
Blood and lymphatic system disorders	**0**	**0**	**2**	**2 (0.9)**	**2**	**2 (0.7)**
Anemia	0	0	1	1 (0.4)	1	1 (0.3)
Leukocytosis	0	0	1	1 (0.4)	1	1 (0.3)
Cardiac disorders	**0**	**0**	**1**	**1 (0.4)**	**1**	**1 (0.3)**
Tachycardia	0	0	1	1 (0.4)	1	1 (0.3)
Gastrointestinal disorders	**0**	**0**	**4**	**4 (1.7)**	**4**	**4 (1.3)**
Abdominal pain	0	0	1	1 (0.4)	1	1 (0.3)
Gastritis	0	0	2	2 (0.9)	2	2 (0.7)
Vomiting	0	0	1	1 (0.4)	1	1 (0.3)
General disorders and administration site conditions	**3**	**3 (4.2)**	**11**	**11 (4.8)**	**14**	**14 (4.7)**
Injection site erythema	2	2 (2.8)	4	4 (1.7)	6	6 (2.0)
Injection site pain	1	1 (1.4)	2	2 (0.9)	3	3 (1.0)
Injection site swelling	0	0	1	1 (0.4)	1	1 (0.3)
Pyrexia	0	0	4	4 (1.7)	4	4 (1.3)
Infections and infestations	**0**	**0**	**1**	**1 (0.4)**	**1**	**1 (0.3)**
Bacterial infection	0	0	1	1 (0.4)	1	1 (0.3)
Investigations	**0**	**0**	**1**	**1 (0.4)**	**1**	**1 (0.3)**
White blood cell count increased	0	0	1	1 (0.4)	1	1 (0.3)
Musculoskeletal and connective tissue disorders	**1**	**1 (1.4)**	**2**	**2 (0.9)**	**3**	**3 (1.0)**
Back pain	1	1 (1.4)	1	1 (0.4)	2	2 (0.7)
Flank pain	0	0	1	1 (0.4)	1	1 (0.3)
Nervous system disorders	**0**	**0**	**2**	**2 (0.9)**	**2**	**2 (0.7)**
Headache	0	0	2	2 (0.9)	2	2 (0.7)
Pregnancy, puerperium , and perinatal conditions	**0**	**0**	**1**	**1 (0.4)**	**1**	**1 (0.3)**
Pre-eclampsia	0	0	1	1 (0.4)	1	1 (0.3)
Renal and urinary disorders	**0**	**0**	**1**	**1 (0.4)**	**1**	**1 (0.3)**
Dysuria	0	0	1	1 (0.4)	1	1 (0.3)
Reproductive system and breast disorders	**1**	**1 (1.4)**	**2**	**2 (0.9)**	**3**	**3 (1.0)**
Nipple disorder	0	0	2	2 (0.9)	2	2 (0.7)
Vaginal discharge	1	1 (1.4)	0	0	1	1 (0.3)
Skin and subcutaneous tissue disorders	**0**	**0**	**1**	**1 (0.4)**	**1**	**1 (0.3)**
Hyperhidrosis	0	0	1	1 (0.4)	1	1 (0.3)

***AntiD:** Trinbelimab (Recombinant Anti Rho-D Immunoglobulin)
N = Total number of participants in each AntiD dose group; **n** = Number of participants with complete data within the specific category.

AntiD has been in the market since July 2021, and more than 700,000 units have been utilized till February 2023. In the current Phase IV post-marketing safety evaluation study, AntiD was used as per the approved indication and directions and was assessed for its safety and tolerability in the clinical setting for the prevention of maternal Rh-isoimmunization.

The compliance rate of the study was high, as 290/300 participants completed the study procedures. The majority of the reported TEAEs were mild and unrelated to the study drug. All the reported TEAEs were completely resolved during the study. Except for two participants with clinically significant hematological and urinalysis findings consistent with their underlying medical conditions, none of the participants exhibited abnormal clinical or laboratory parameters. Thus, based on the assessment of the different safety parameters (adverse events, vital signs, physical examination, and laboratory parameters), AntiD administered at a dose of either 300 mcg or 150 mcg did not raise any new or significant safety concerns. Overall, AntiD exhibited a favorable safety profile and no new safety signals were identified in this study.

5. Conclusion

In conclusion, the current study demonstrated that AntiD is well-tolerated and safe for clinical use as anti-D prophylaxis under the approved directions for the prevention of Rh-isoimmunization in a clinical setting. AntiD is thus a viable alternative to conventional poly-anti-D and provides a robust, replicable, and non-limiting source for anti-D prophylaxis.

6. Supplementary Materials

Table S1: Summary of Medical or Surgical History Classified byMedDRA System Organ Class and Preferred Term (in the Safety Population), Table S2: Summary of Prior and Concomitant Medication by Anatomical Therapeutic Chemical (ATC) Class and Preferred Term (in the Safety Population), Table S3: Summary of Treatment-Emergent Adverse Events Classified by System Organ Class, Preferred Term, and Relationship to Study Drug (in the Safety Population).

7. Author Contributions

Shilpa N. Naik, Srinivas Gadappa, Swati Kochar, Lakshmikantha G., Sweety Saigal, and Ravindra Pukale have made substantial contributions to the study investigation, patients' identification and enrolment, and data acquisition. Kishma Vinod and Pratik Shah have contributed to the conceptualization, formal analysis, methodology, supervision, reviewing, editing, and designing of the manuscript.

8. Data Availability Statement

The data that support the findings of this study are available within the article and its supplementary materials; and are also available in CTRI/2021/11/038206.

9. Conflict of Interest

The authors declare no conflicts of interest.

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References

1. Costumbrado J, Mansour T, Ghassemzadeh S. Rh Incompatibility [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.
2. Fyfe TM, Ritchey MJ, Taruc C, Crompton D, Galliford B, Perrin R, et al. Appropriate Provision of Anti-D Prophylaxis to RhD Negative Pregnant Women: A Scoping Review. *BMC Pregnancy Childbirth*. 2014;14(1):411.
3. Sahoo T, Sahoo M, Gulla KM, Gupta M. Rh Alloimmunisation: Current Updates in Antenatal and Postnatal Management. *Indian J Pediatr*. 2020;87(12):1018–28.
4. Bhutani VK, Zipursky A, Blencowe H, Khanna R, Sgro M, Ebbesen F, et al. Neonatal Hyperbilirubinemia and Rhesus Disease of the Newborn: Incidence and Impairment Estimates for 2010 at Regional and Global Levels. *Pediatr Res*. 2013;74(Suppl 1):86–100.
5. Agarwal S, Seema S, Sharma S, Chaudhary V, Bala S, Umesh U. Rh negative pregnancy: Maternal and perinatal outcome in Bundelkhand region. *J Evol Med Dent Sci*. 2016;5(71):5165–8.
6. Delaney M, Matthews DC. Hemolytic Disease of the Fetus and Newborn: Managing the Mother, Fetus, and Newborn. *Hematology Am Soc Hematol Educ Program*. 2015;2015(1):146–51.
7. Qureshi H, Massey E, Kirwan D, Davies T, Robson S, White J, et al. BCSH Guideline for the Use of Anti-D Immunoglobulin for the Prevention of Haemolytic Disease of the Fetus and Newborn: Guidelines. *Transfus Med*. 2014;24(1):8–20.
8. Chilcott J, Jones ML, Wight J, Forman K, Wray J, Beverley C, et al. A Review of the Clinical Effectiveness and Cost-Effectiveness of Routine Anti-D Prophylaxis for Pregnant Women Who Are Rhesus-Negative. *Health Technol Assess*. 2003;7(4):62.
9. Practice Bulletin No. 181: Prevention of Rh D Alloimmunization. *Obstet Gynecol*. 2017;130(2):57–70. doi:10.1097/AOG.0000000000002232.
10. Xie X, Fu Q, Bao Z, Zhang Y, Zhou D. Clinical Value of Different Anti-D Immunoglobulin Strategies for Preventing Rh Hemolytic Disease of the Fetus and Newborn: A Network Meta-Analysis. *PLoS One*. 2020;15(3):e0230073.
11. Haas MD, Finning K, Massey E, Roberts DJ. Anti-D prophylaxis: past, present and future. *Transfus Med*. 2014;24(1):1–7.
12. Brinc D, Lazarus AH. Mechanisms of Anti-D Action in the Prevention of Hemolytic Disease of the Fetus and Newborn. *Hematology Am Soc Hematol Educ Program*. 2009;(1):185–91. doi:10.1182/asheducation-2009.1.185.
13. Lazarus AH. Monoclonal versus Polyclonal Anti-D in the Treatment of ITP. *Expert Opin Biol Ther*. 2013;13(10):1353–6.
14. Zipursky A, Bhutani VK, Odame I. Rhesus disease: a global prevention strategy. *Lancet Child Adolesc Health*. 2018;2(7):536–42.
15. Chauhan AR, Nandanwar YS, Ramaiah A, Yelikar KA, Rashmi MD, Sachan R, et al. Randomized, Open-Label Trial Comparing the

Efficacy and Safety of Monoclonal Anti-Rh (D) Immunoglobulin with Polyclonal Anti-Rh (D) Immunoglobulin for the Prevention of Maternal Rh-Isoimmunization. *J Obstet Gynaecol India*. 2019;69(5):420–5.
16. Holzlöhner P, Hanack K. Generation of Murine Monoclonal Antibodies by Hybridoma Technology. *J Vis Exp*. 2017;119:54832. doi:10.3791/54832.
17. Gstraunthaler G, Lindl T, Van Der, Valk J. A Plea to Reduce or Replace Fetal Bovine Serum in Cell Culture Media. *Cytotechnology*. 2013;65(5):791–3.
18. Edelman L, Margaritte C, Chaabihi H, Monchâtre E, Blanchard D, Cardona A, et al. Obtaining a Functional Recombinant Anti-Rhesus (D) Antibody Using the Baculovirus-Insect Cell Expression System. *Immunology*. 1997;91(1):13–9.
19. Miescher S, Zahn-Zabal M, Jesus MD, Moudry R, Fisch I, Vogel M, et al. CHO Expression of a Novel Human Recombinant IgG1 Anti-RhD Antibody Isolated by Phage Display: CHO Expression of Human Recombinant Anti-RhD Antibodies. *Br J Haematol*. 2000;111(1):157–66.
20. Siegel DL. Recombinant Monoclonal Antibody Technology. *Transfus Clin Biol*. 2002;9(1):15–22.
21. Mayekar RV, Paradkar GV, Bhosale AA, Sachan R, Beeram S, Anand AR, et al. Recombinant Anti-D for Prevention of Maternal-Foetal Rh(D) Alloimmunization: A Randomized Multi-Centre Clinical Trial. *Obstet Gynecol Sci*. 2020;63(2):315–22.
22. Kumpel BM, Goodrick MJ, Pamphilon DH, Fraser ID, Poole GD, Morse C, et al. Human Rh D Monoclonal Antibodies (BRAD-3 and BRAD-5) Cause Accelerated Clearance of Rh D+ Red Blood Cells and Suppression of Rh D Immunization in Rh D- Volunteers. *Blood*. 1995;86(5):1701–9.
23. Miescher S, Spycher MO, Amstutz H, Haas MD, Kleijer M, Kalus UJ, et al. A Single Recombinant Anti-RhD IgG Prevents RhD Immunization: Association of RhD-Positive Red Blood Cell Clearance Rate with Polymorphisms in the FcgammaRIIA and FcgammaIIIA Genes. *Blood*. 2004;103(11):4028–35.
24. Bichler J, Spycher MO, Amstutz HP, Andresen I, Gaede K, Miescher S. Pharmacokinetics and Safety of Recombinant Anti-RhD in Healthy RhD-Negative Male Volunteers. *Transfus Med*. 2004;14(2):165–71.
25. Beliard R, Waegemans T, Notelet D, Massad L, Dhainaut F, Romeuf C, et al. A Human Anti-D Monoclonal Antibody Selected for Enhanced FcgammaRIII Engagement Clears RhD+ Autologous Red Cells in Human Volunteers as Efficiently as Polyclonal Anti-D Antibodies. *Br J Haematol*. 2008;141(1):109–19.
26. Kumpel BM. Lessons Learnt from Many Years of Experience Using Anti-D in Humans for Prevention of RhD Immunization and Haemolytic Disease of the Fetus and Newborn. *Clin Exp Immunol*. 2008;154(1):1–5.

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