SUMMARY OF THE RESULTS
18 April 2024

Sponsor Name:

Kedrion S.p.A., Loc. Ai Conti – Castelvecchio Pascoli, Barga (Lucca) – Italy

Product Name:	**Active Ingredient Name:**
IMMUNOHBs UMAN BIG	Human Hepatitis B Immunoglobulin

Title of Study: Efficacy and Safety evaluation of Kedrion Human Hepatitis B Immunoglobulin for intramuscular use in the prevention of hepatitis B in the newborns of Hepatitis B Virus carrier-mothers: multi-centre, open-label, phase IV clinical trial

Principal Investigator: [redacted]

Coordinating Center: Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, UO Neonatologia e Terapia Intensiva Neonatale, Milan (Italy)

Study Sites: 4 sites in Italy enrolled at least one patient to the study

Study period:	**Study Phase**:
First Subject First Visit: 28 April 2012 Last Subject Last Visit: 23 February 2023 Study Early Termination*: 18 October 2023 **For the details, please refer to "Results" section*	Phase IV

Objectives:

The objective of this study was to evaluate the efficacy, safety of UMAN BIG/IMMUNOHBs* (Investigational Medicinal Product - IMP) in the prevention of hepatitis B in the newborn of hepatitis B virus carrier-mothers.

The ***Efficacy*** objective was to evaluate the efficacy of the IMP at the posology reported in the SmPC (30-100 IU/Kg) in preventing hepatitis B in the newborns of hepatitis B virus carrier-mothers.

The ***Safety*** objective was to evaluate the safety and tolerability of the IMP during the study period.

**UMAN BIG and IMMUNOHBs are different brand names for the same product; both products are manufactured and commercialized by Kedrion S.p.A.*

Methods:

This was a Phase IV, open-label, prospective, single-arm, multicenter study to evaluate the efficacy and safety of UMAN BIG/IMMUNOHBs.

At least 184 newborns of Hepatitis B virus carrier mothers were to receive a first dose of IMP at the posology recommended by the SmPC (30-100 IU/Kg) at birth (T_0) and anti-hepatitis B vaccine, according to clinical practice and Italian national law (Legge 27 Maggio 1991 N. 165 "Obbligatorieta' della vaccinazione contro l'epatite virale B" – "Requirement for Hepatitis B Vaccination").

During the study 2 different vaccination schemes were used, 3 doses and 4 doses. In 2019 the 3 doses scheme was removed from the protocol because it was not used by any of the study sites.

4 doses vaccination Scheme

Hepatitis B antibody levels were planned to be measured at 1 month (T_{1M}) ± 10 days, 3/4 months ($T_{3/4M}$) ± 10 days, and, if required as detailed below, 13 months ±10 days and 15 months ± 10 days.

Patients showing at the second observation (3/4 months – $T_{3/4M}$) a level of hepatitis B antibodies (Anti-HBsAb) higher than the one measured at 1 month (T_{1M}), were to undergo the end of study visit and exit the study.

Patients with Anti-HbsAb levels below 10 IU/L at $T_{3/4M}$, were to receive a second dose of IMP (8 IU/kg); if the measured Anti-HbsAb level was above 10 IU/L, the patient was not planned to be treated. In any case, a third Follow Up was to be performed at month 13 (T_{13M}).

Patients not showing an increase in antibodies T_{13M}, or whose level dropped below 10 IU/L, were to receive an additional dose of IMP of 8 IU/kg. A Follow Up was to be performed at month 15 (T_{15M}) to verify if protective levels above 10 IU/L were maintained.

Following the T_{15M} follow-up all patients were to exit the study.

The HBsAg status was to be assessed at study entry and again at study end.

A pre-treatment serum sample from each patient included in the clinical trial was to be stored at a temperature <-70°C for possible future viral testing.

Number of patients:

At least 184 patients were planned to be enrolled in the study, of which all were to be included in the efficacy analysis.

Subject Characteristics and Inclusion/Exclusion Criteria:

Inclusion Criteria:

1. Newborn of hepatitis B virus carrier-mothers
2. Newborn was eligible for Hepatitis B virus vaccination according to either the normal practice performed in every sites or the scheme recommended by National Health Authority
3. Parents/Legal Guardian consent to study participation
4. Information sheet for Data handling signed by at least one parent

Exclusion criteria:

5. Newborn from mother treated during pregnancy with Human Hepatitis B Immunoglobulins

Investigational Medicinal Product, dosage regimen, route of administration:

IMMUNOHBs 180 IU/ml vial of 180 IU/1 mL

IMMUNOHBs 180 IU/ml vial of 540 IU/3 mL

UMAN BIG 180 IU/ml vial of 180 IU/1 mL

UMAN BIG 180 IU/ml vial of 540 IU/3 mL

Posology - according to the product SmPCs: 30-100 IU/kg.

All subjects whose levels dropped below 10 IU/L at $T_{3/4M}$ and those who did not show an immune response (no measurable hepatitis B antibodies) after vaccination (at T_{13M}), and for whom continuous prevention was necessary, received a dose of 8 IU/kg to maintain a minimum protective antibody titre of 10 IU/L.

Route of administration - intramuscular

The first vaccine dose could be injected the same day as IMP, however in different sites.

Duration of treatment observation (per patient):

15 months maximum

Criteria for evaluation:

<u>Efficacy evaluation:</u>

Primary end points:

1. Absence of Hepatitis B infection in the newborns (HBsAg negative status).

Secondary end points:

1. Maintenance of a minimum protective antibody titre of 10 IU/L in children who did not show an immune response (no measurable hepatitis B antibodies) after vaccination.

Safety evaluation:

1. Percentage of newborns who experienced treatment-related (i.e., those classified as possibly, probably or certainly related to the IMP administration) Adverse Events (Adverse Drug Reactions – ADRs).
2. Percentage of newborns who experienced treatment-related immediate and/or delayed local tolerability at the injection site up to 72 hours after the drug administration.

RESULTS

At the date this summary of results was issued, the clinical database was not yet locked, and final data reconciliation was ongoing.

The study was planned to enroll at least 184 patients, to assess the efficacy and safety of the IMP.

The study enrolled 191 subjects, of which 5 were excluded from the analysis study due to issues in Informed Consent/Data handling collection and subsequent removal of all related data from the study database, and 17 were excluded from the Per Protocol Population because they withdrew from the study before the study completion and/or reported major protocol deviations with impact on the efficacy evaluation.

Therefore, 186 subjects were included in the safety analysis and 169 were included in the efficacy analysis.

Despite more than 10 years of enrolment the sample size was not achieved for the following reasons:

- Widespread use of anti-hepatitis B vaccination in Italy. The vaccination was introduced in Italy by Law n.165 dated May 27th, 1991, for all newborns within the first year of age and, for the 12 years following the entry into force of the law, for all subjects during the 12th year of age. By the time the study started a great number of women of childbearing potential were vaccinated.
- Hepatitis B is not endemic in Western Europe.

For this reason, Kedrion took the decision to terminate the study early, a decision that was supported by AIFA.

Efficacy Results

All subjects evaluated at study end for HBsAg status (169 subjects) were negative, confirming the absence of Hepatitis B infection.

Safety Results

All subjects receiving IMP were included in the safety analysis (186 patients). A total of 27 SAEs were reported, comprising 32 separate events. None of them was considered to be related to IMMUNOHBs/UMAN BIG by either the reporting investigators /or by Kedrion S.p.A. (See Appendix 1).

No other non-serious adverse events assessed as possibly, probably, or certainly related to the IMP were reported by either the reporting investigators or by Kedrion S.p.A.

Date of Report: 18 April 2024

APPENDIX 1

System Organ Class Preferred term	**SAE #**
Blood and lymphatic system disorders	**1**
Thrombocytopenia	1
Congenital, familial and genetic disorders	**1**
Vascular malformation	1
General disorders and administration site conditions	**1**
Pyrexia	1
Infections and infestations	**15**
Pneumonia	1
Pyelonephritis	2
Bronchitis	1
Rhinovirus infection	1
Upper respiratory tract infection	3
Nasopharyngitis	1
Bronchiolitis	4
Rhinitis	1
Viral infection	1
Gastrointestinal disorders	**1**
Incarcerated inguinal hernia	1
Hepatobiliary disorders	**1**
Jaundice	1
Surgical and medical procedures	**1**
Inguinal hernia repair	1
Investigations	**2**
Inflammatory marker increased	1
Protein C increased	1
Metabolism and nutrition disorders	**5**
Hypoglycaemia	3
Hypoglycaemia neonatal	1
C-reactive protein	1
Nervous system disorders	**1**
Brain injury	1
Respiratory, thoracic and mediastinal disorders	**3**
Acute respiratory failure	1
Neonatal asphyxia	1
Tachypnoea	1
TOTAL	**32**