2 SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Biotest AG</td><td rowspan="3">Individual Trial Table Referring to Part of the Dossier: na

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<tr><td>Name of Finished Product:
Cytotect CP</td></tr>
<tr><td>Name of Active Substance:
Human cytomegalovirus immunoglobulin (CMVIG)</td></tr>
<tr><td colspan="3">Title of Trial: Prevention of maternal-fetal Cytomegalovirus transmission after primary maternal infection with gestational age ≤ 14 weeks – an open-label, single-arm, prospective trial investigating efficacy and safety of Cytotect CP Biotest (PreCyssion)

Short Title: PreCyssion</td></tr>
<tr><td colspan="3">Trial Number(s): 997
EudraCT/NCT Number: 2020-002383-32/NCT05170269
Last protocol version and date: Final Version 4.0, 03-NOV-2022</td></tr>
<tr><td colspan="3">Investigators:
Coordinating Investigator: Prof. Dr. med. Karl Oliver Kagan, Tübingen (site 4901)

Principal Investigators of active sites: Dr. med. Michael Oliver Schneider, Erlangen (site 4902), Prof. Dr. med. Annegret Geipel, Bonn (site 4903), Priv. Doz. Dr. med. Julia Jückstock, Wasserburg am Inn (site 4905), Dr. Jan-Peter Siedentopf, Berlin (site 4906).</td></tr>
<tr><td colspan="3">Trial Site(s): 5 sites in Germany</td></tr>
<tr><td colspan="3">Publication (references): n/a</td></tr>
<tr><td colspan="2">Studied Period (years):
(date of first enrollment) 17-NOV-2021
(date of last completed) 28-MAR-2024
(date of Early Trial Termination) 11-DEC-2023
Rationale for early trial termination: In Trial 997, 9 serious adverse events (SAEs) in fetuses with the MedDRA PTs ‘Vertical infection transmission’ and ‘Congenital cytomegalovirus infection’ diagnosed by amniocentesis and 1 SAE in a newborn with ‘Vertical infection transmission’ based on urine sample of the newborn were reported. Based on these SAE reports, the Biotest Product Safety Team (PST) for BT097 discussed on 15-SEP-2023 and 18-SEP-2023 that the number of maternal-fetal transmissions within Trial 997 is close to the transmission rates from the published historical control group defined in the protocol. This trend should be assessed by the Data and Safety Monitoring Board (DSMB) during the meeting scheduled for 27-SEP-2023, as it could be a hint for lack of efficacy. On 25-SEP-2023,</td><td>Clinical phase:
Phase III</td></tr>
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however, after receipt of one additional SAE 'vertical infection transmission' diagnosed by amniocentesis, the PST agreed on a temporary recruitment stop for Trial 997 with immediate effect.

The temporary recruitment stop for both subgroups was continued also after the DSMB had provided its assessment, based on a decision taken during another PST meeting held on 28-SEP-2023. Subsequently amniocenteses of all patients already included and willing to continue in Trial 997 were performed.

After all amniocentesis results were available, the PST recommended on 30-NOV-2023: "Despite the favorable safety profile, the benefit-risk balance for subjects enrolled in the trial remains questionable due to the unfavorable benefit data. Although a statistically non-significant result remains possible, continuation of the trial is no longer considered feasible, clinically relevant or ethically justifiable. Therefore, the PST recommends for early discontinuation of the trial."

This was implemented on 11-DEC-2023 by the sponsor and Trial 997 was discontinued early.

Objectives: The main purpose of the trial was to demonstrate efficacy and safety of Cytotect CP Biotest in preventing maternal-fetal transmission of cytomegalovirus (CMV)

Methodology: Open-label, single-arm, prospective, multicenter with historical control group

Number of Subjects planned: planned to have at least 66 evaluable subjects with valid assessments at amniocentesis

Diagnosis and Criteria for Inclusion and Exclusion:

Trial Population:

Pregnant women with confirmed recent primary CMV infection with gestational age ≤14 weeks. Subjects will be classified according to the timing of the maternal infection into 2 subgroups:

- Periconceptional subgroup (PSG): periconceptionally acquired infection (CMV infection at gestational age ≤8 weeks)
- First trimester subgroup (1TSG): infection acquired during first trimester (CMV infection at gestational age >8 to ≤14 weeks)

Inclusion criteria:

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1. Written informed consent obtained from subjects indicating that they understand the purpose of and procedures required for the trial and are willing to participate in it
2. Pregnant women, age 18 to 45 years
3. Pregnant women at trial entry with gestational age ≤14 weeks; pregnancy after in-vitro fertilization permitted
4. Detection of early primary CMV infection as defined by:
   - Low anti-CMV IgG level (Electro-chemiluminescence Immunoassay [ECLIA]) <60 U/mL
   - Lack of anti-CMV IgG reactivity, i.e., no positive reactivity (band intensity score 0 or 1) against recgB2 antigen (CMV Immunoblot [recIB] assay)
   - Anti-CMV IgG avidity
     - Anti-CMV IgG avidity (recIB assay: recombinant avidity antigens IE1, CM2, p150, gB2): low avidity
     - Anti-CMV IgG avidity index (AI) <45 Avi%, i.e., low avidity (ECLIA).

   If one test for determination of anti-CMV IgG avidity (ECLIA or recIB) is not evaluable, the other test must have low avidity.

   Subgroup definition:
     - Infection during periconceptional period:
       - Trial entry and blood sample for CMV serology taken prior or equal to 8 weeks' gestation
       - Trial entry and blood sample taken between >8 and ≤14 weeks' gestation: Anti-CMV IgG AI >20 Avi% and <45 Avi%
     - Infection during first trimester:
       - Trial entry and blood sample for CMV serology taken between >8 and ≤14 weeks' gestation and Anti-CMV IgG AI ≤20 Avi% or not measurable due to low anti-IgG levels
   - Borderline anti-CMV IgM index (≥0.7 Cutoff-index [COI]) or reactive IgM index ≥1.0 COI (ECLIA). If anti-CMV IgM index <0.7 COI, anti-rec IgM reactivity against p150 and additionally one or more reactivities against IE1, CM2, and p65 (recIB)

Exclusion criteria:

1. Women with current multiple pregnancy
2. History of severe pre-eclampsia or severe gestational hypertension (GHTN), which required medical intervention. Definition according to AWMF guideline (AWMF, 2019a)
3. Presence of severe disease impairing course of pregnancy (e.g., diabetes, epilepsy, cancer)
4. Clinically significant congenital or acquired autoimmune disease

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5. Known immunosuppressive (e.g., transplanted patients) or immunodeficient condition (e.g., congenital agammaglobulinemia or hypo-gammaglobulinemia, common variable immunodeficiency, severe combined immuno-deficiencies, Wiskott Aldrich syndrome) or immunosuppression
6. Known infection with hepatitis B or C, or HIV from the medical history or active infection at screening as assessed by respective virus serology
7. Maternal CMV infection prior to this pregnancy as defined by an IgG avidity index ≥45 Avi% (ECLIA) and/or positive anti-CMV IgG recgB2 reactivity in the presence of a negative IgM reactivity (recIB)
8. Covid-19 infection at time of inclusion (positive Polymerase Chain Reaction [PCR])
9. Any signs or symptoms indicating an increased risk of abortion or premature labor or has known negative effect on fetus with exception of a CMV infection
10. Active infection according to TORCH serology with exception of CMV in the assessment of the investigator
11. Known major fetal anomalies or demise
12. Intolerance to proteins of human origin or known allergic reactions to components of the trial product
13. Selective absolute IgA deficiency or known antibodies to IgA
14. Known pre-existing clinically relevant risk factors for thrombotic events (e.g., history of vascular disease or thrombotic episodes, women with clinically relevant acquired or inherited thrombophilic disorders e.g., deep vein thrombosis, severely hypovolemic women or women with diseases which increase blood viscosity)
15. Known renal insufficiency with serum creatinine levels >1.4 mg/dL and proteinuria (albuminuria) at screening (≥30 mg/dL or dipstick reading of 1+ and greater)
16. Participation in another clinical trial within 90 days before entering the trial or during the trial
17. Women who are dependent on trial site staff, on Biotest AG or its authorized representatives
18. Inability or lacking motivation to participate in the trial
19. Medical condition, laboratory finding, or physical examination finding that in the opinion of the investigator precludes participation
20. Eligibility for a subgroup where enrollment was stopped

Test Product, Dose and Mode of Administration, Batch Number(s): Cytotect CP Biotest 100 U/mL solution for infusion, 200 U per kg of maternal body weight (i.e., 2 mL/kg body weight (BW)) intravenously (IV) repeated every 2 weeks, Batches C797170 and C797101.

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Duration of Treatment: After seroconversion (≤14 weeks' gestation (GW)) until at least GW 17 (about 1-2 weeks prior to the amniocentesis between GW 19-22). Follow up until date of delivery (+3 days).

Control Product, Dose and Mode of Administration, Batch Number: not applicable

Criteria for evaluation

Efficacy Endpoints:

Primary Endpoint**:**

Overall rate of maternal-fetal transmission at the time of amniocentesis (week 20 [-1 week / +2 weeks] of gestation

Amniotic fluid (AF) was tested by

- quantitative real time PCR (q-rt PCR)
- short-term (18 to 24 h) microculture with CMV antigen staining, long-term (range 1 to 28 days) culture until generation of a cytopathic effect (CPE).

Maternal-fetal transmission was proven by detection of CMV-DNA above limit of detection (LOD) in combination with detection of CMV antigen in short-term. Maternal-fetal transmission was excluded if all 3 tests are unable to detect either viral DNA or viral infectivity.

The rate of maternal-fetal transmission was calculated based on subjects with proven viral transmission only and was compared to historical data (Chatzakis et al., 2020; Kagan et al., 2021).

Secondary Endpoints:

- Rate of maternal-fetal transmission at the time of amniocentesis (week 20 [-1 week / +2 weeks] of gestation) in the 2 subgroups:
  - Subjects with periconceptionally acquired infection
  - Subjects with infection acquired during first trimester
- CMV viral load in maternal blood at screening (VS), before each treatment (VTx) and at amniocentesis visit (VA) and follow-up visit (VF) in week 30
- Anti-CMV IgG levels by ECLIA at VS, before and after each treatment, at VA and VF
- Anti-CMV IgG avidity by recIB assay and AI by ECLIA and at VS, before the second and the fourth/last treatment (whichever occurs first) and at VA

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- Anti-CMV IgM index by ECLIA at VS and VA
- Soluble fms-like tyrosine kinase 1 (sFlt-1) concentration in maternal serum at VS, every 4 weeks from baseline and at VA
- Vitality, growth and heart rate of fetuses/ newborns including sonography results during pregnancy and weight, height, sex, Apgar-score, and head circumference at delivery
- Rate of congenital CMV infection at delivery or within the first 3 days after delivery (urine is screened for CMV-DNA)
- Number of CMV-DNA copies in urine of newborns (CMV viral load in newborns) at delivery or within the first 3 days after delivery, in case of a positive CMV test

Safety Endpoints:

- Number, severity, causality, outcome, and seriousness of all adverse events (AEs) and treatment-emergent AEs (TEAEs) until delivery (+3 days) in both mother and fetus/ newborn
- Number, severity, causality, outcome, and seriousness of all AEs of special interest until delivery (+3 days) in both mother and fetus/ newborn
- Number, severity, causality, outcome, and seriousness of all infusional AEs (AEs developing from start of infusion of investigational medicinal product (IMP) until 2 hours after end of infusion).
- Number, severity, causality, and outcome of all SAEs until delivery (+3 days) in both mother and fetus/newborn
- Number of withdrawals from the trial due to AEs
- Distribution and changes over time for safety parameters (outside reference range and clinically relevant)
- Changes in vital sign parameters
- Frequency of pre-eclampsia based on test results of sFlt-1/ Placental Growth Factor (PlGF)

The safety results of this trial were compared to historical data reported from:

- Use of Cytotect CP Biotest in this indication with the same dosage and timeframe evaluated by Kagan et al., 2021.
- Untreated control populations from other prospective clinical trials published by Nigro et al., 2005 (patients who had not undergone amniocentesis), Revello et al., 2014 (ClinicalTrials.gov number, NCT00881517; EudraCT no. 2008-006560-11), Biotest trial 963 (EudraCT number 2007-004692-19) and Cytogam clinical trial (ClinicalTrials.gov number, NCT01376778) based on present publications of Hughes, 2019 and Saade, 2020. The data of untreated control

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populations will serve as negative control providing the safety profile with standard of care except CMVIG treatment. (Biotest, 2018; Hughes, 2019; Nigro et al., 2005; Revello et al., 2014; Saade, 2020)

- Known Cytotect CP Biotest safety profile.

  The safety profile of the subjects in the trial was discussed in respect to pre-existing risk factors of subjects included in this trial and serious TEAEs detected in the trial population.

Statistical Methods: The primary endpoint was the overall rate of maternal-fetal transmission at the time of amniocentesis.

The overall transmission rate was compared with transmission rates from published historical control groups (periconceptionally acquired infection and infection during first trimester: 21% and 36.8% transmission rate, respectively). Considering a distribution of 2/3 of subjects in the PSG and 1/3 in the 1TSG (Kagan et al., 2021) an overall transmission rate of 26% was calculated.

We assumed a power of 80% and a significance level of 5%. The null hypothesis was that the primary endpoint is equal to the historical control.

With a sample size of at least 66 evaluable subjects (n=44 in the PSG and n=22 in the 1TSG) we wanted to show a difference of 14%-points in favor of Cytotect CP Biotest treatment for the primary endpoint, so that the proportion of maternal-fetal transmission at the time of amniocentesis of gestation was less or equal to 12%.

To account for a natural miscarriage rate or chromosomal abnormalities (12%) and drop outs (6%), we needed to enroll about 80 eligible subjects to have at least 66 evaluable subjects with valid assessments at amniocentesis.

A one group Chi-square test with a 5% two-sided significance level was applied.

Sample size was calculated with nQuery Version 8.6.1.0.

Summary of Results and Conclusions:

Subject Disposition:

Of 48 subjects treated with ≥1 dose of BT097 in this trial at 5 sites in Germany, 11 were infected with CMV in the first trimester and 37 periconceptionally.

At screening, subjects had a mean (SD) age of 31.3 (4.4) years, a mean (SD) Body Mass Index (BMI) of 23.84 (3.93) kg/m^2 and were in mean (SD) gestational week 9.4 (2.0). Overall, the profile of previous and concomitant diseases and of prior and concomitant medications was consistent with the profile expected for a population of pregnant women.

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Efficacy Results: Trial 997 was discontinued early. Despite the favorable safety profile, the benefit-risk balance for subjects enrolled in the trial remained questionable due to the unfavorable benefit data. Therefore, efficacy results were not evaluated.

The mean (SD) overall duration of BT097 exposure was 58.1 (12.3) days (median 57 days). The dose defined by protocol was 200 U/kg maternal BW. The mean (SD) actual dose was 199.7 (0.3) U/kg BW. The majority of subjects received all infusions as planned. For one subject (4903-15) in the PSG the maximum infusion rate was exceeded once (1.595 mL/kg BW/h at VT2) and recorded as 'Medication error'. The average (SD) duration of the first infusion was 177.2 (28.7) minutes for all subjects and the average (SD) duration of infusion was 175.4 (11.2) minutes.

Safety Results:

- Safety evaluations, including AEs, laboratory values, vital signs, physical examination, uterus sonography and newborn data did not uncover any unexpected safety issues.

- In total, 63 mothers, fetuses and newborns in this trial (65.6% of 96 total lives) experienced 390 AEs, including 386 TEAEs and 4 non-TEAEs predominantly of mild severity. The majority of AEs and TEAEs were observed in mothers. Frequent TEAEs by MedDRA Preferred term (PT) observed in >20% subjects were 'Nasopharyngitis', 'Anaemia', 'Headache'. 'Oropharyngeal pain' and 'Congenital cytomegalovirus infection'.

- Three TEAEs in 2 subjects were severe and also classified as serious. Two SAEs in the same mother (subject 4906-01/PSG) were life-threatening (one event of 'Postpartum haemorrhage' and one event of 'Prolonged labour'), and one event of 'Congenital cytomegalovirus infection' in a fetus (subject 4901-06/PSG) was classified as other medically important serious event. No TEAE of severe or moderate severity was assessed as related to the IMP.

- Of 27 serious TEAEs observed in 23 total lives (mother/fetus/newborn) none was assessed as related to the IMP and infusion. Serious TEAEs were mostly observed in the fetus (16 events in 13 fetuses, 9 events in 8 mothers, and 2 events in 2 newborns). All maternal fetal CMV transmissions were reported as SAE and coded as PT 'Congenital cytomegalovirus infection'. Overall, 11 fetuses (22.9%) in this trial experienced the serious TEAE 'Congenital cytomegalovirus infection', and 2 (4.2%) newborns experienced 1 (2.1%) event of 'Congenital cytomegalovirus infection' and 1 (2.1%) event of PT 'Hyperbilirubinaemia neonatal'. In mothers, the most frequent serious TEAEs by PT were 'Gestational diabetes' (3 events in 3 [6.3%] mothers) and 'Hyperemesis gravidarum' (2 events in 2 [4.2%] mothers).

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- Regarding the subgroups, 'Congenital cytomegalovirus infection' occurred in 10 (27.0%) fetuses or newborns in the PSG and 2 (18.2%) in the 1TSG. Of them, 2 (18.2%) cCMV infections in the 1TSG and 9 (24.3%) in the PSG were diagnosed by amniocentesis in the fetus. In newborn, 1 (2.1%) 'Congenital cytomegalovirus infection' in the PSG was diagnosed by newborn urine.

- No TEAEs were observed that led to death, trial withdrawal, IMP interruption, IMP infusion rate or dose reduction.

- No TEAE related to the IMP was reported for fetus or newborn, but 21 non-serious mild TEAEs related to the IMP occurred in 6 mothers. The most common PT was 'Headache' with 5 events in 4 (8.3%) mothers. Nine of these Adverse Drug Reactions (ADRs) were mild infusional AEs and are known adverse reactions to Cytotect CP Biotest infusion or to infusion of intravenous immunoglobulins. Twelve ADRs were related, non-infusional TEAEs. The most common PT was 'Headache' with 5 events in 4 (8.3%) mothers. All other ADRs were observed in only 1 subject each.

- Overall, 18 mothers experienced 30 infusional AEs, all of them non-serious and of mild severity. The most frequent infusional AE by PT was 'Headache' (8 events in 7 [14.6%] mothers, followed by 'Fatigue' and 'Nausea' with 2 events in 2 [4.2%] mothers). In Trial 997 the frequency of infusional AEs at first infusion of IMP in mothers was slightly increased (8 infusional AEs at first infusions vs. 30 infusional AEs for a mean of 5.1 infusion per subject). In total, 356 non-infusional AEs were reported.

- Four Adverse Events of Special Interest (AESIs) were recorded in 4 subjects, namely 'Pre-term delivery' with PT 'Premature baby', 'Eclampsia/ Preeclampsia' with PT 'Hypertension', 'Fetal growth retardation' with PT 'Small for dates baby' (2 events; fetus, reported term "small for gestational age (SGA) 8th percentile", newborn, reported term: "child under 3rd percentile"). All AESIs were of mild to moderate severity, not related to the IMP and had the outcome 'recovered/ resolved' or 'recovering/ resolving'. In the case of one fetus, 'fetal growth retardation' was considered serious because of hospitalization of the mother. The AESI posed no risk after birth to the neonate.

- Subjects in this trial showed no clinically significant abnormalities for clinical chemistry parameters, immunology parameters, most hematology parameters and in urinalysis. Clinically significant abnormalities were observed for hematocrit, hemoglobin and red blood cells (RBCs), consistent with the profile expected for a population of pregnant women. Abnormally low, clinically significant values for hematocrit were recorded in 3 (6.3%) subjects, for hemoglobin in 10 (20.8%) subjects, and for erythrocytes in 2 (4.2%) subjects and recorded as AEs but are within the expected decline of hemoglobin

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and associated parameters during pregnancy. Subjects showed no relevant changes of vital signs before infusions, and no abnormal, clinically significant findings in physical examination.

- The by protocol foreseen uterus sonography examinations were documented without any abnormal findings. However, uterus sonography examinations not foreseen in the protocol resulted in SAE reporting (e.g., 'Ultrasound head abnormal').

- The values for newborn head circumference, weight, length of the 3rd and 10th percentiles correspond to the epidemiological expected values for Germany (Voigt et al., 2014).

- Most pregnancies in this trial had a normal course and outcome. AESIs and SAEs reported for fetuses or newborns were not related to the IMP.

Conclusion: Trial 997 confirmed the safety profile of BT097, leaving its efficacy in the targeted indication undetermined.

Date and Version of this Report: Final 1.0, 25-FEB-2025