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**Table 1: The original Sarnat and Sarnat staging system**, which was published in their seminal paper in Archives of Neurology in 1976

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| --- | --- | --- | --- | --- | --- | --- |
| Therapeutic Target  | Study (Clinical Trials.gov ID) | Participants  | Experimental Protocol  | Primary Outcomes  | Secondary Outcomes  | Status  |
| **Xenon**  | CoolXenon3[NCT02071394] **UK**  | Infants with HIE> 36 weeks |  cooling + 18h xenon inhalation at 50% concentration | Death and moderate to severe disability at 18 months  | Brain MRI (within 2 weeks of birth) aEEG grading within 1 week of birth)Developmental Outcomes at 18-24 months  | Phase 2: Recruiting  |
| **Topiramate** | [NCT01765218]**USA** | Infants with HIE >=34 weeks | Cooling + Topiramate (5 mg/kg/day) for total of 5 doses | Seizures at 4 weeks or at discharge | HIE score at 4 weeks or at discharge Normalization of aEEG at 4 weeks or at discharge S100-beta levels at 1, 3 ,7 days MRI score at 5-7 days Developmental Outcomes at 9,18,27 months  | Phase 1,2: Completed  |
| **Allopurinol**  | ALBINO [NCT03162653]**Europe**  | Infants with HIE >=36 weeks | Cooling + Allopurinol (20mg/kg) within 30 minutes of birth and (10mg/kg) 12 h thereafter  | Death and moderate to severe disability at 24 months  | Incidence of Death and CP at 24 months GMFCS-score at 24 months Developmental outcomes at 24 months | Phase 3: Not yet recruiting  |
| **Melatonin** | [NCT02621944] **USA**  | Infants with HIE >=36 weeks | Cooling + melatonin (0.5mg/kg within 12 h after birth | MTD Pharmacokinetics of escalated doses Adverse events Developmental outcomes at 18-20 months | Developmental outcomes subscales at 18-20 months GMA at 3 and 23 months Brain MRI 7-12 days after birth  | Phase 1: Recruiting  |
| **Erythropoietin**  | PAEAN [NCT03079167]**Australia and New Zealand**  | Infants with HIE >=35 weeks | Cooling + erythropoietin (1000 IU/kg BW), on days 1,2,3,5,7 of age | Death and moderate/severe disability at 24 months  | Death and CP at 24 months Developmental outcomes at 24 months Epilepsy at 24 months Cost of healthcare Frequency of AED | Phase 3:Recruiting  |
| NEATO [NCT01913340]**USA**  | Infants with HIE >=36 weeks | Cooling + erythropoietin (1000 IU/kg BW) total of 5 doses  | Markers of organ function for 2 weeks  | Developmental and functional outcomes at 12 months  | Phase 1, 2: Not yet recruiting  |
| Neurepo [NCT01732146 ]**France**  | Infants with HIE >=36 weeks | Cooling + erythropoietin (1000-1500 IU/kg BW) total of 3 doses  | Survival without neurological sequelae At 2 years  | Death and Moderate/severe disability at 24 months Brain MRI within 6-12 days Tolerance at 2 years  | Phase 3: Recruiting  |
| PENUT [NCT01378273]**USA**  | Preterm infants 24-27 weeks of gestation  | Cooling + erythropoietin (1000 IU/kg BW) for total of 6 doses followed by 400 U/kg until 32 6/7 weeks of gestation  | Neurodevelopmental outcomes at 24-26 months  | Safety at term PMABrain MRI at 36 weeks PMAInflammation biomarkers at 24-26 months | Phase 3: Not yet recruiting  |
| **Cell-Based**  | [NCT02455830]**Japan**  | Infants with HIE >=36 weeks | Cooling +Autologous cord blood cell infusion (3 doses within 72 h) | Changes in cytokines and trophic factors level for 10 days  | Brain MRI at 12 months Developmental and functional outcomes at 18 monthsCorrelation with cytokines profile  | Phase 1: Recruiting  |
| [NCT02256618]**Japan**  | Infants with HIE >=36 weeks | Cooling + Autologous umbilical cord blood cells (3 doses within 72 h) | Adverse events at 30 days  | Neurodevelopmental function at 18 monthsBrain MRI at 12 months  | Phase 1: Recruiting  |
| **[NCT02551003]****China**  | Infants with HIE >=34 weeks | Cooling + Autologous umbilical cord blood cells (divided doses within 72 h) | Death and neurodevelopmental disability within 18 months  | Neurodevelopmental outcomes at 12 and 18 months Brain MRI at 7, 28 days and 12 monthsAdverse events within 72 hSerum SDF-1, TNF-alpha, IL-1 at 4 and 14 days  | Phase 1,2: Recruiting |
| [NCT02612155]**USA**  | Infants with HIE >=35 weeks | Cooling + Autologous umbilical cord blood cells (2 doses) | Survival at 1 year Neurodevelopmental outcomes at 1 year  | Mortality rate , seizures and AED, Need for iNO use, ECMO and G tube feeding at 12 months  | Phase 2: Recruiting  |
| [NCT02854579]**China**  | Infants with HIE >=34 weeks | Neural progenitor cells and/or paracrine factors intrathecal infusion  | Neurodevelopmental outcomes at 14 and 28 days Adverse events at 7 days  | Neurodevelopmental outcomes at 1 2 monthsDeath within 12 months Treatment-related CNS tumor within 5 years  | Phase 1: Recruiting  |

**Table (2): Description of active clinical trials pursuing new neuroprotective strategies for neonates with Hypoxic Ischemic Injury**. h: hour; MRI: Magnetic Resonance Imaging; aEEG: amplitude integrated EEG. S100-Beta: marker of neuronal injury; CP: cerebral palsy; MTD: maximum tolerated dose; GMA: generalized motor assessment; AED: anti-epileptic drugs; PMA: Post menstrual age; SDF-1, TNF-alpha and IL-1: Biomarkers for oxidative stress, Inflammation and immune response.