Supplementary table 02

Evaluation of clinical trials and the status on the primary and secondary endpoints

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| Study ID | Primary objective | Achieved results | References |
| NCT01759823 |  To examine the efficacy and safety of autologous bone marrow-derived mononuclear cell (ABM-MNCs) transplantation in T2DM, and to explore mechanism of stem cell action through metabolic studies. | 1. Six out of 7 (90%) patients achieved the primary end-point. 2. Significant reduction in insulin requirement by 51% at 6 months compared to baseline (p < 0.003). 3. Significant increase in the 2nd phase C-peptide response during hyperglycaemic clamp (p = 0.018 but no significant alteration in insulin sensitivity or glucose disposal rate during hyperinsulinemic-euglycemic clamping, relative to baseline. 4. Other measures of β-cell indices like HOMA-β, and stimulated C-peptide response to glucagon and mixed meal tolerance test were non-contributory | (1)  |
| NCT00883870 |  The primary objective was to determine the safety of BM- MSCs in patients with Critical limb ischemia (CLI); two arms- placebo, and BM-MSC | 1. Improvement was observed in rest pain scores in both the arms.
2. Significant increase in ABPI and ankle pressure in BM-MSC arm compared to placebo.
3. Incidence of AEs in the BM-MSC arm was higher in … (13 vs. 45) in the placebo arm, whereas SAEs were similar in both arms (5 in BM-MSC and 4 in the placebo group); SAEs were related to disease progression and not to stem cells.
4. BM-MSCs are safe when injected IM at a dose of 2 million cells/kg body weight. Encouraging results in ABPI and ankle pressure warrant further studies.
 | (2) |
| NCT00883727 | Recently developed investigational new drug named Stempeucel that contains bone marrow-derived allogeneic mesenchymal stromal cells. For use in patients with acute myocardial infarction (AMI) with ST-segment elevation. A phase I/II randomized, double-blind, single-dose study was conducted to assess the safety and efficacy of intravenous administration of Stempeucel versus placebo (multiple electrolyte injection). | **1.** Number of treatment-emergent adverse events were similar (18 in Stempeucel vs. 21 in placebo groups). 2. None of the adverse events were related to Stempeucel, according to the investigators and the independent data safety monitoring board. 3. There were no serious adverse events in the Stempeucel group but there were three serious adverse events in the placebo group, of which one had a fatal outcome. 4. Ejection fraction, determined using echocardiography, showed improvement in both Stempeucel (43.06% to 47.80%) and placebo (43.44% to 45.33%) groups at 6 months (P = 0.26). 5. Perfusion scores measured by use of single-photon emission tomography and infarct volume measured by use of magnetic resonance imaging showed no significant differences between the two groups at 6 months.**Conclusions:**Stempeucel was safe and well-tolerated when administered intravenously in AMI patients 2 days after percutaneous coronary intervention. The optimal dose and route of administration need further evaluation in larger clinical trials. | (3) |
| NCT02425670 | The efficacy and safety of autologous BMSCs in subacute ischemic stroke was evaluated as pilot studies have suggested benefit from intravenous administration of bone marrow mononuclear stem cells (BMSCs) in stroke. | 1. Fifty-eight patients received 280.75 million BMSCs (mean value) at median 18.5 days after stroke onset.
2. At day 180, there was no significant difference between the BMSCs and control arms in the Barthel Index score (63.1 versus 63.6; P=0.92), modified Rankin scale shift analysis (P=0.53) or score >3 (47.5% versus 49.2%; P=0.85), NIHSS score (6.3 versus 7.0; P=0.53), change in infarct volume (-11.1 versus -7.36; P=0.63).
3. Adverse events were similar in both arms, and no patient showed any new area of (18)fluorodeoxyglucose uptake.

**Conclusions:**With the methods used, while intravenous infusion of BMSCs is safe, there is no beneficial effect of treatment on stroke outcomes. | (4) |
| NCT01453738 |  In the clinical study, cell-based therapy was explored to address the repair of damaged articular cartilage in the knee joint. | 1. IA administration of Stempeucel® was safe, and a trend towards improvement was seen in the 25-million-cell dose group in all subjective parameters (VAS, ICOAP, and WOMAC-OA scores); however, this was not statistically significant when compared to placebo. 2. Adverse events were predominant in the higher dose groups (50, 75, and 150 million cells). Knee pain and swelling were the most common adverse events. The whole-organ magnetic resonance imaging score of the knee did not reveal any difference from baseline or the placebo group.**Conclusion:**Intra-articular administration of Stempeucel® is safe. A twenty-five-million-cell dose may be the most effective among the doses tested for pain reduction. Clinical studies with a larger patient population are required to demonstrate robust therapeutic efficacy of Stempeucel® in OA. | (5) |
| ID No: CTRI/2008/091/000232 | Acute myocardial infarction (AMI) can result in reduced left ventricular ejection fraction (LVEF), which is a major determinant of short and long term morbidity and mortality. This phase III prospective, open-labelled, randomized, multicentric trial was undertaken to evaluate the efficacy of autologous mononuclear cells (MNC) in improving LVEF over a period of six months. A predefined dose of 5-10 × 10 [8] cells were injected by the intra-coronary route in patients at 1-3 weeks post STEMI, in addition to standard medical therapy. | 1. **I**ntention-to-treat analysis showed no positive impact of MNCs infusion on LVEF improvement of ≥ 5 per cent. 2. The improvement in LVEF after six months was 5.17 ± 8.90% in non-SCT group and 4.82 ± 10.32 per cent in SCT group. 3. The adverse effects were comparable between both groups. Post-hoc analysis showed that cell infused at the dose of ≥ 5 X 10 [8] (n=71) had a positive impact. 4. This benefit was noted upto three weeks post AMI. There were 38 trial deviates in the SCT group which was a limitation of the study.**Interpretation & conclusions: Even though** the procedure was safe, infusion of stem cells was found to have no benefit in STEMI. A possible benefit was seen when a predefined cell dose was administered and this effect was noted up to three weeks post AMI. However, this was not significant and needs confirmation by larger trials. | http://ctri.nic.in/ |
| CTRI/2021/01/030327 | This was a single arm trial to explore the potential of bone marrow-derived mononuclear stem cells in improving neurological deficits and muscle power in patients affected by poliomyelitis in India. The pattern of neurological involvement and EMG changes were evaluated in all. The primary outcome was EMG changes at 6 months. The secondary outcome was muscle charting and Physical handicap at 1-60 months. Significant improvement was defined as improvements in PH, MC by > 1 grade and in EMG/NCV studies. | 1. Five patients (4 males), median age 23 years (range, 16-25) were recruited.
2. P1 crawled with hand support. P2, P5 limped. P3, P4 had tilted pelvis and used calipers. P5 used support. 2 had bilateral involvement, 3 had left limb involvement.
3. Median MNCs injected 3 million cells (range, 1.44-68). At follow up of 6 months, all (n=5) had significant improvement in PH, MC; EMG/NCV. PH, MC improved by 3 months follow up and remained consistent till 60 months after injection.

**Conclusion:** MNC count was lower in patients with reduced mobility. BMNCs have the potential to heal damaged neurons and muscle fibres in poliomyelitis. | http://ctri.nic.in/ |
| CTRI/2017/12/011046 | Various methods have been tried to induce operational tolerance in organ transplantation. We present a single-centre experience using 6 tolerance induction protocols (TIP) in living-related renal transplantation. | We evaluated 6 TIP protocols that used: (1) peripheral blood stem cells (n = 38); (2) modified protocol with portal infusion (n = 292); (3) second protocol plus TIP+DST+BM+intra-thymic and intra-marrow infusion plus low-dose nonmyeloablative conditioning (n = 174), (4) the third protocol of TIP plus cultured hematopoietic stem cells (HSC) with target-specific irradiation (n = 290); (5) TIP 4 plus thymus, intra-marrow infusion, and target-specific irradiation converted to total lymphoid irradiation (TLI) (n = 366); and(6) TIP 5 plus bortzomib-TLI (n = 165). Patient/donor demographics were comparable.Patient and graft survival, rejection episodes, recurrence, drug toxicity, and chimerism, were evaluated.**Results:** 1. Patients with protocols 4 and 5 showed better survival, graft function, and chimerism, and decreased rejection episodes, compared to other protocols.
2. In groups 1-6, serum creatinine (mg/dL) at 1 year was 1.5, 1.39, 1.5, 1.51, 1.46, and 1.41, respectively, and at 5 years it was 1.69, 1.72, 1.82, and 1.59, respectively. Chronic rejection episodes were seen in 10.5%, 14.1%, 10.4%, 9.3%, 3.5%, 1.7%, and 1.8% of the population, respectively.
3. Patient survival in groups 1, 2, and 3 at 1, 5, and 10 years was 86.5%, 56.8%, and 40.1%; 89.4%, 69.1%, and 56.4%; and 89.6%, 67.7%, and 64.6%, respectively. The same for group 4 at 1 and 5 years was 92.4% and 81.8%, and that for groups 5 and 6 at 1 year was 94% and 96.3%, respectively.
4. Death-censored graft survival in groups 1, 2, and 3 at 1, 5, and 10 years was 91.9%, 70.3%, and 64.7%; 89%, 66%, and 57.6%; and 86.7%, 67%, and 42.5%, respectively. The same in group 4 at 1 and 5 years was 87.9% and 74.7%; and in groups 5 and 6 at 1 year was 94% and 96.5%, respectively.

**Conclusion:** TIP results showed improved graft/patient survival and minimum immunosuppression along with fewer episodes of rejection or recurrence. | http://ctri.nic.in/ |

References

1. Bhansali S, Dutta P, Yadav MK, Jain A, Mudaliar S, Hawkins M, et al. Autologous bone marrow-derived mononuclear cells transplantation in type 2 diabetes mellitus: effect on β-cell function and insulin sensitivity. Diabetol Metab Syndr. 2017;9:50.

2. Gupta PK, Chullikana A, Parakh R, Desai S, Das A, Gottipamula S, et al. A double blind randomized placebo controlled phase I/II study assessing the safety and efficacy of allogeneic bone marrow derived mesenchymal stem cell in critical limb ischemia. J Transl Med. 2013 Jun 10;11:143.

3. Chullikana A, Majumdar AS, Gottipamula S, Krishnamurthy S, Kumar AS, Prakash VS, et al. Randomized, double-blind, phase I/II study of intravenous allogeneic mesenchymal stromal cells in acute myocardial infarction. Cytotherapy. 2015 Mar;17(3):250–61.

4. Prasad K, Sharma A, Garg A, Mohanty S, Bhatnagar S, Johri S, et al. Intravenous autologous bone marrow mononuclear stem cell therapy for ischemic stroke: a multicentric, randomized trial. Stroke. 2014 Dec;45(12):3618–24.

5. Gupta PK, Chullikana A, Rengasamy M, Shetty N, Pandey V, Agarwal V, et al. Efficacy and safety of adult human bone marrow-derived, cultured, pooled, allogeneic mesenchymal stromal cells (Stempeucel®): preclinical and clinical trial in osteoarthritis of the knee joint. Arthritis Res Ther. 2016 Dec 20;18(1):301.