Full title	Mesenchymal stromal cells treatment in Lyell syndrome: A pilot phase 1-2 open trial.
Acronym	**LYSYME**
Coordinating Investigator	Saskia Oro Department of Dermatology Hospital Henri Mondor
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare acute life-threatening muco-cutaneous drug-adverse reactions. To date, no curative treatment has demonstrated its ability to promote SJS-TEN healing. MSCs, combining their immunomodulation effects and secretion of soluble factors implicated in wound repair, are a promising cell therapy strategy for promoting cutaneous healing in SJS-TEN syndrome and decrease the morbi-mortality.
Primary objective and outcome	To evaluate the safety and efficacy i.e., complete almost complete cutaneaous reepithelialisation at D7 after infusion of 2×10^6/kg ASCs in SJS-TEN patients. • **Safety:** The toxicity is defined as the observation of at least one adverse effect (please see primary outcome chapter) • **Efficacy:** Rate of complete almost complete reepithelialisation at D7 after infusion. This criterion is defined as at least 90% of cutaneous body surface area (BSA) healed at D7 in comparison to maximal cutaneous detachable-detached BSA observed.
Secondary objectives and outcomes	To evaluate the impact of ASCs treatment on SJS-TEN clinical course and immunological markers. - Rate of observed and predicted death at one month by the SCORTEN - Duration of hospitalisation according to our historical cohort related to BSA involved, onset of the disease and SCORTEN. - Duration of each mucous membrane healing i.e. (buccal, nasal, genital, eyes). - Rate of sepsis. - Rate of intensive care transfer - Rate of sequelae at M12 - Th1/Th2 immune response in the peripheral blood of the patients after injection at D0, D10, M1 - Evaluation of expression profile of Th1/Th2 associated chemokines and anti-inflammatory chemokines in the peripheral blood after injection at D0, D10, M1. - Epidermal chimerism research on healed skin biopsy at 1 month. - Rate of complete almost complete reepithelialisation at D5, D10 and D15 after infusion.
Experimental design	Single hospital open label phase 1-2 trial assessing the tolerance and efficacy of 2×10^6/kg of ASCs intravenously injected at D0 in patients with more than 10% detached-detachable body surface area.
Population of research participants	Patients: Adults diagnosed with SJS-TEN with at least 10% of body surface area involved Donors: Adults selected for a programmed plastic surgery of liposuction or aspiration in the abdominal wall under general anesthesia, in order to collect adipose tissue
Inclusion criteria	Patients: - Patients ≥ 18 years-old - Admission less than 10 days after onset of the reaction - Patient with confirmed SJS-TEN diagnosis hospitalized in the department of Dermatology or intensive care medicine - At least 10 % of detachable-detached body surface area at any time during the first 10 days after the index date - Written consent from patient or trustworthy person or legal representant or family member

	- Affiliated to a social security scheme Donors: - Patients ≥ 18 years-old - Admission for a programmed plastic surgery of liposuction or aspiration in the abdominal wall under general anesthesia - Selection criteria according to stem cell donor health history questionnaire from Agence de la Biomédecine - Written consent - Affiliated to a social security scheme
Exclusion criteria	Patients: - Pregnant or breastfeeding women - History of malignant disease within the past ten years and or presence of metastasis - Positive serology for HIV - Active infection for hepatitis B or C - Participation in other biomedical drug research - Patient deprived of freedom - Any psychological, familial, sociological or geographical condition potentially hampering compliance with the research protocol and follow-up schedule Donors: - Positive viral serology (HBV, HCV, HIV, syphilis, HTLV, active infection with IgM+ for toxoplasmosis, EBV, CMV) - Deprived of freedom - Significant comorbidities (according to stem cell donor health history questionnaire from Agence de la Biomédecine)
Investigational medicinal product(s)	Allogeneic mesenchymal stromal cells expanded from adipose tissue in suspension in human albumin Single Dose injected: $2x10^6$/kg injected intravenously at maximum three days after admission Phase I-II
Comparator treatment	Supportive standard care
Interventions added for the trial	Patients: 2×106/kg of ASCs intravenously injected at maximum three days after admission Donors: Collection of 60g of adipose tissue for research, during the liposuction carried out in the usual's care Viral serologies to verify the absence of blood contamination
Expected benefits for the participants and for society	Patients: Considering the roles of ASCs in promoting healing and decrease inflammation, the foreseeable benefits for the participants are an improvement of the rapidity of healing, that will be considered as a better rate of complete almost complete re-epithelialization at D7 after infusion
Other procedures added by the research	None
Risks added by the research	Patients: The potential risks associated to the research are related to ASCs intravenous injection. A recent meta-analysis focusing on the safety of cell therapy with MSC of clinical trials emphasizes a significant association between MSCs and transient fever. However, no other severe adverse events have been described with a significant frequency. There is no risk related to the clinical and biological exams, which are included in the usual care. Only one biopsy at M1 is performing for the research. The risk of biopsy may include local infection, transitory bleeding, and transitory pain. Donors: No risks Risk D

Practical implementation	Donors will be selected among those coming for liposuction or aspiration in the abdominal wall. ASCs will be expanded from several allogeneic donors and qualified in Good Manufacturing Procedures conditions by the Creteil GMP platform (EFS Ile de France). After inclusion of the patient, ASCs will be thawed and culture in GMP conditions following 24 hours in order to restore the immunosuppressive properties of MSCs. ASCs intravenously injected 3 days after inclusion in patients with more than 10% detached-detachable body surface area.
Number of participants included	Patients: 15 subjects (please see sample size section for more details) Donors: 5
Number of centres	National pilot research with participation of multicentric sites at hospital Henri-Mondor (reference center of toxic bullous diseases), with 4 hospital services: - Department of Dermatology and Intensive Care Unit for patients; - Plastic surgery and CIC for donors
Research duration	Inclusion period: 36 months Length of participation *(treatment 1 day + follow-up)*: total 12 months Total research period: 48 months
Number of inclusions expected per centre and per month	0.4 patient per month
Statistical analysis	The primary efficacy and safety endpoints will be analyzed using a Bayesian strategy. It provides a formal means of summarizing patient outcome by a single binary event (Toxicity or not, success or failure). It will allow continuous monitoring of outcomes throughout the trial and thus was expected to be more efficient in protecting patients from unsafe treatment. The efficacy endpoint will also be analyzed through a Bayesian strategy taking into account gain functions based on population cost regarding overall treatment success (see sample size section)
Funding source	The research is funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 2015 (Ministère de la Santé)
Data Safety Monitoring Board anticipated	Yes