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Map of Pre-Clinical and Clinical Expertise on Cell Therapy from Adipose Tissue for Wounds in Austria and Italy

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1. Introduction

Over the last two decades, the therapeutic use of adipose-derived stem/stromal cells (ASCs) has emerged as a central pillar of regenerative medicine. Adipose tissue represents a particularly attractive cell source due to its abundance, accessibility, and the regenerative potential of the stromal vascular fraction (SVF) and isolated mesenchymal progenitors. In the European Union, cell-based medicinal products are regulated under the framework of Advanced Therapy Medicinal Products (ATMPs). Despite increasing global activity, the number of clinically approved ATMPs remains limited, and regulatory, manufacturing, and standardization challenges continue to hinder widespread adoption.

Within Europe, Austria and Italy stand out as countries with significant expertise in ASC-based clinical research. Austria has developed concentrated know-how in industry-driven, multicentric clinical trials—particularly for Crohn's disease–related fistulas through products such as darvadstrocel (Alofisel). Italy, by contrast, has developed a broader translational portfolio ranging from Crohn's disease and gastrointestinal fistulas to systemic sclerosis–related digital ulcers and diabetic foot wounds. Mapping the expertise in both countries highlights their complementary roles: Austria as a hub for standardized, phase-driven ASC drug development, and Italy as a fertile ground for investigator-initiated translational innovation in wound healing.

This review synthesizes the pre-clinical and clinical expertise on adipose tissue–derived cell therapy for wounds in Austria and Italy, based on clinical trial registries, regulatory reports, and peer-reviewed publications. It discusses the biological rationale, regulatory and methodological frameworks, and compares the trial portfolios of the two countries.

2. Methods

The review was based on a structured literature and clinical trial database search. First, reviews on adipose-derived stem/stromal cell (ASC) applications in wound healing and skin-related conditions

were screened to provide background and identify product characterization requirements relevant for Advanced Therapy Medicinal Products (ATMPs), such as sterility, identity, and potency criteria.

To capture clinical activity, two major registries were consulted: *ClinicalTrials.gov* (US NIH) as the most comprehensive international database, and **EudraCT**, which lists all interventional clinical trials on medicinal products submitted to National Competent Authorities within the EU/EEA. The search strategy focused on:

1. **Austria and Italy**: ASC trials in wound healing and, given their scarcity, in other disease areas where wound healing may be relevant.
2. **Global context**: ASC trials in wound healing broadly, including wounds secondary to systemic diseases.

Products with EU market authorization, particularly **darvadstrocel (Alofisel®, Takeda)**, were highlighted as benchmarks, since they represent the most advanced stage of ASC-based clinical development.

A known limitation is that trials performed under the **hospital exemption framework** are rarely captured in these registries. Such interventions are only traceable through published reports, if outcomes are formally disseminated and indexed with appropriate keywords in PubMed or other databases. This gap complicates systematic mapping and underlines the fragmented reporting standards in the field.

3. Results

3.1 Biological Basis and Rationale for ASCs in Wound Healing

Properties of adipose-derived stem/stromal cells

Adipose tissue contains a heterogeneous stromal vascular fraction (SVF), including ASCs, endothelial progenitors, pericytes, and immune cells (1). Isolated ASCs share core features with mesenchymal stem/stromal cells (MSCs) from bone marrow and other tissues, including multipotency, clonogenicity, and secretion of trophic factors. They differ, however, in surface marker profile and relative abundance, with adipose tissue yielding higher numbers of stem cells per gram compared to bone marrow aspirates (2).

ASCs exert regenerative functions mainly through paracrine mechanisms: secretion of vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), fibroblast growth factors (FGFs), and platelet-derived growth factor (PDGF), among others, which promote angiogenesis, re-epithelialization, and modulation of inflammation (3). This trophic activity has positioned ASCs as strong candidates for chronic wound therapy, where impaired angiogenesis, persistent inflammation, and defective matrix remodeling represent critical bottlenecks(4).

Mechanistic evidence from pre-clinical studies

Pre-clinical work has consistently shown ASC efficacy in models of cutaneous wounds, burns, diabetic ulcers, and ischemic injury. In burn wounds, ASC treatment improved re-epithelialization and

reduced scarring (5). In diabetic mice, ASC secretome accelerated wound closure, promoted neovascularization, and enhanced collagen organization (6). ASCs also modulate immune responses by reducing pro-inflammatory cytokines such as TNF-α and IL-1β while enhancing regulatory T cell responses (7).

Although the molecular pathways are increasingly understood, clinical translation has been slowed by the heterogeneity of ASC preparations (enzymatic vs. mechanical isolation, expanded vs. minimally manipulated tissue), lack of standardized release criteria, and variable endpoints across trials (8).

Global and European Clinical Trial Landscape of ATMPs

Advanced Therapy Medicinal Products (ATMPs) have gained prominence over the last 15 years, though their presence remains modest compared with conventional drugs. Since 2009, 14 ATMPs have been authorized in Europe, but only 9 remain on the market; withdrawals were due to commercial, not safety, reasons.

Worldwide, ~1,900 ATMP clinical trials have been registered, including 112 phase III studies—mainly industry-led. Europe hosts ~360 ATMP trials, with 50 in the pre-authorization phase. Italy plays a leading role, having tested the first four EMA-approved ATMPs and 23 trials are underway, according to data provided by AIFA (the Italian Medicines Agency) up to 2022 (*AboutPharma web version, 22/05/24*). Globally, development exceeds 2,500 products with >2,000 clinical trials and $3.2 billion invested, dominated by North America, followed by Asia-Pacific, and, only third, Europe (NCF, gennaio 2024, 22-23).

Despite growth, ATMPs still accounted for only ~7% of trials in 2021, with dermatology indications—relevant for wound healing—representing just 2.3 (ATMP forum "Quinto report italiano sulle Advanced Therapy Medicinal Product", 2022). The field remains dynamic but fragmented, with ongoing challenges in regulation and standardization.

3.2 Regulatory and Methodological Framework

EU regulatory context

In the European Union, ASCs fall under the ATMP regulation when subjected to substantial manipulation or when intended for use in a non-homologous manner. Thus, enzymatically isolated and expanded ASCs qualify as ATMPs, while mechanically processed autologous adipose tissue (e.g., Lipogems®, nanofat) may be considered minimally manipulated and not subject to the same regulatory framework. Austria and Italy, both EU member states, adhere to this framework, but differ in the degree of clinical application under hospital exemption versus industry-sponsored multicentric trials.

Characterization of ASC products

Key parameters for ASC product release include:

- **Identity and purity**: phenotypic confirmation against ISCT minimal criteria for MSCs (plastic adherence; trilineage potential; ≥95% expression of CD73, CD90, CD105; ≤2% expression

of hematopoietic markers such as CD34 and CD45 for expanded MSCs) as the baseline framework, with explicit tissue-of-origin reporting per updated ISCT guidance (9) (10).

- **Viability**: Many regulatory submissions for MSC products target high viability at lot release; ≥90% is commonly accepted for fresh products in regulatory reviews, while some programs set thresholds in the ≥80–90% range depending on formulation and logistics (11).
- **Sterility and endotoxin testing**: In accordance with European Pharmacopoeia.
- **Potency assays**: So far, no universally accepted ASC-specific potency assay exists. ISCT recommends a matrix of mechanism-informed functional assays (e.g., immunomodulation such as macrophage/lymphocyte suppression; angiogenic/trophic readouts), qualified to the product's intended mechanism of action (MOA) and clinical indication. Blinded/limited disclosure of specific assays is common in industry dossiers; sometimes inferred from angiogenic or immunomodulatory readouts (12).

A major unmet need is the lack of universally accepted ASC-specific markers and potency assays. This complicates trial comparability and regulatory harmonization.

Endpoints for wound healing trials

Clinical trials have employed heterogeneous endpoints, including:

- **Objective wound scores**: Bates-Jensen Wound Assessment (BJWA), a 15-item objective measure designed to assess wound status and track healing. Measures size, depth, edges, undermining, necrotic tissue type, necrotic tissue amount, exudate type, exudate, amount, skin color surrounding the wound, peripheral tissue edema and induration, granulation tissue, and epithelialization. Patient and Observer Scar Assessment Scale (POSAS).
- **Morphometric outcomes**: Time to 50% wound area reduction, time to complete re-epithelialization.
- **Patient-reported outcomes**: Pain scores, cosmesis evaluation.
- **Biological correlates**: VEGF, TGF-β levels, histological evaluation of angiogenesis (PROMOS report).

The lack of standardization across trials in Austria and Italy complicates the construction of a uniform evidence base.

3.3 Clinical Expertise in Austria

Austria's expertise is characterized by its **participation in large, multicentric, phase-driven clinical trials**, almost exclusively centered on **darvadstrocel (Alofisel, Takeda)**, which contains allogenic expanded adipose stem cells (5 million cells/mL, 30 million cells per ampoule) to improve the healing process of complex perianal fistulas in patients with Crohn's disease. Four major trials have been conducted in Austrian centers such as Medizinische Universität Wien, Innsbruck Universität-Klinik, and St. Veit/Glan Krankenhaus.

Trials on Crohn's disease fistulas

- **FATT trial (NCT01378390; EudraCT 2008-004286-25)**
  This pivotal **phase III**, multicenter trial evaluated the use of allogeneic expanded adipose-derived stem/stromal cells (eASCs) for the treatment of complex perianal fistulas in Crohn's disease. The Austrian contribution was coordinated at **MedUni Wien**. The study demonstrated both **safety** and a **clinically meaningful improvement in fistula closure rates** compared to placebo, laying the groundwork for later EU approval of darvadstrocel.

- **ADMIRE-CD trial (NCT01541579)**
  A large **phase III, randomized, placebo-controlled study** sponsored by TiGenix (later Takeda), involving multiple Austrian centers (Innsbruck, St. Veit/Glan, Wien). The trial established the **clinical efficacy** of eASCs, showing **50% combined remission at 24 weeks** versus 34% with placebo, thereby providing the critical evidence base for EMA authorization (13). Study Details-clinicaltrials.gov | NCT01541579 |.

- **EMPIRE trial (NCT04118088; EudraCT 2017-002491-10)**
  A **phase IV post-authorization study** designed to assess the **long-term safety and repeat administration** of darvadstrocel. The Austrian arm is conducted at **AKH Wien**. This trial emphasizes **MRI-based fistula assessment** and **immunological monitoring**, addressing key questions about durability of remission and safety in repeated dosing. Study Details-clinicaltrials.gov | NCT04118088 |

- **Cx601 national study (NCT05322057)**
  An **academic, multicenter Austrian study** led by **MedUni Wien**, focusing on darvadstrocel in perianal fistulizing Crohn's disease. Unlike the large industry-led programs, this trial provides **independent validation** of efficacy and feasibility within the Austrian healthcare setting. Study Details-clinicaltrials.gov | NCT05322057 |

Translational significance

Although Austria's clinical trial portfolio appears narrow, focused solely on Crohn's fistulas, this concentration has enabled Austrian centers to accumulate substantial expertise in **GMP-grade ASC handling, standardized trial methodology, and long-term safety monitoring**. This expertise is directly translatable to wound healing indications, particularly in standardizing ASC product release criteria and trial conduct.

Austria's alignment with industry-sponsored multicentric trials ensures exposure to harmonized regulatory practices, making it an important contributor to Europe-wide ASC drug development.

3.4 Clinical Expertise in Italy

Italy has developed a **broad, more heterogeneous portfolio** of ASC-based clinical investigations, spanning Crohn's disease, gastrointestinal fistulas, digital ulcers in systemic sclerosis, diabetic foot amputations, and reconstructive indications. This reflects the country's strong translational research culture and network of academic medical centers.

Crohn's disease and gastrointestinal fistulas

Italy has participated in international darvadstrocel trials (ADMIRE-CD, Cx601, long-term follow-up studies), with sites in Bologna, Firenze, Milano, Napoli, Padova, Roma, Udine, and Verona (PROMOS report). In addition, Italian investigators have explored **autologous adipose therapies**:

- **NCT04326907 (University Hospital of Ferrara)**: Use of centrifuged autologous adipose tissue (CAT) containing progenitor cells for complex anal fistulas (excluding Crohn's). This approach bypasses cell expansion, relying on minimally manipulated autologous material. Study Details | NCT04326907 | Treatment of Complex Anal Fistulas Using Centrifuged Adipose Tissue Containing Progenitor Cells | ClinicalTrials.gov

- **NCT04670276 (Fondazione Policlinico Gemelli, Roma)**: Endoscopic injection of emulsified stromal vascular fraction (tSVFem) for gastrointestinal fistulas. This inexpensive, mechanically isolated product avoids enzymatic digestion, exemplifying Italy's emphasis on practical, cost-effective regenerative strategies. Study Details | NCT04670276 | Conservative Treatment of Gastrointestinal Fistulas by Endoscopic Injection of tSVFem | ClinicalTrials.gov

Systemic sclerosis and digital ulcers

- **NCT03406988 (ASST Gaetano Pini-CTO, Milano)**: Randomized trial on autologous adipose tissue grafting for systemic sclerosis–related digital ulcers. Building on pilot data (Del Papa et al., PMID: 27159987), this trial tests whether autologous fat grafts accelerate ulcer healing and reduce ischemic pain. Preliminary evidence suggests improved neovascularization and pain reliefhttps://clinicaltrials.gov/study/NCT03406988. Study Details | NCT03406988 | Autologous Adipose Tissue in the Treatment of Systemic Sclerosis Digital Ulcers | ClinicalTrials.gov

This trial illustrates Italy's focus on **autoimmune-related chronic wounds**, expanding ASC therapy beyond Crohn's disease.

Diabetic foot wounds

- **NCT03276312 (University of Modena and Reggio Emilia)**: Randomized trial using the Lipogems® system (micro-fragmented autologous adipose tissue) for minor diabetic foot amputations. Endpoints include healing time, pain, relapse rates, and quality of life. This trial directly addresses a major public health burden where chronic wounds often lead to amputations. Study Details | NCT03276312 | Autologous Micro-fragmented Adipose Tissue in the Treatment of Minor Amputations of Diabetic Foot | ClinicalTrials.gov.

Reconstructive and other indications

- **NCT00616135 (Università di Firenze)**: Post-marketing study of autologous fat augmented with adipose-derived regenerative cells (ADRCs) for breast deformities after lumpectomy. Although reconstructive, it contributes to expertise in ASC-based graft enhancement Study Details | NCT00616135 | Study of Autologous Fat Enhanced w/ Regenerative Cells Transplanted to Reconstruct Breast Deformities After Lumpectomy | ClinicalTrials.gov.

- **NCT04223622 (IRCCS Galeazzi-Sant'Ambrogio, Milano)**: Evaluation of ASC secretome on osteochondral explants—illustrating Italian interest in **cell-free biological products** as next-generation therapies Study Details | NCT04223622 | Effects of ASC Secretome on Human Osteochondral Explants | ClinicalTrials.gov

Methodological characteristics

Italian trials often use **mechanically processed autologous adipose products (Lipogems®, nanofat, CAT, tSVFem)**, which are minimally manipulated and thus fall outside strict ATMP regulation. This facilitates clinical use but reduces standardization and comparability. Conversely, industry-sponsored darvadstrocel trials in Italy follow strict ATMP standards, aligning with EU regulatory requirements.

3.5 Comparative Analysis: Austria vs. Italy

The Austrian and Italian landscapes of adipose-derived cell therapy for wound-related indications reveal markedly different but complementary profiles. Austria has concentrated almost exclusively on **darvadstrocel** for Crohn's-related perianal fistulas. This narrow focus has yielded clear strengths: Austrian centers are well-integrated into **multicenter, industry-sponsored trials**, operate under strict **GMP and regulatory frameworks**, and have developed a reputation for **standardization and methodological rigor**. The limitation, however, is the lack of breadth; Austria has not substantially engaged in ASC applications beyond Crohn's fistulas, leaving innovation and exploration of other wound-related conditions largely unexplored.

Italy, by contrast, has pursued a **broad and heterogeneous portfolio** of ASC-based interventions. Clinical activity ranges from Crohn's disease and gastrointestinal fistulas to **systemic sclerosis–related digital ulcers, diabetic foot wounds, and reconstructive applications**. Many of these efforts have been **investigator-initiated**, highlighting Italy's translational dynamism and strong clinical innovation. However, this diversity comes with challenges: **heterogeneity of products** (expanded allogeneic ASCs vs. mechanically processed autologous adipose tissue), **variable trial endpoints**, and **regulatory fragmentation** between hospital exemption and ATMP pathways.

Taken together, Austria and Italy appear **complementary rather than redundant**. Austria contributes **depth** in industrialized clinical development, offering a model of rigor and harmonization. Italy contributes **breadth**, driving translational exploration across multiple indications of unmet need. Coordinated collaboration could combine Austria's strengths in standardization with Italy's innovation-driven clinical scope, advancing the field of ASC therapy for wounds in Europe.

4. Challenges and Knowledge Gaps

Despite promising data, several obstacles continue to constrain the field. First, there is no **universally accepted set of ASC markers or potency assays**. This hampers regulatory comparability and trial harmonization, as studies rely on differing definitions of cell identity and function. Second, the field suffers from **product heterogeneity**: some trials employ expanded, allogeneic ASCs produced under GMP, while others use minimally manipulated autologous adipose products. This variability makes it difficult to aggregate findings across studies.

Another challenge is the **diversity of clinical endpoints**. Trials use wound closure rates, composite scores, imaging, or patient-reported outcomes, leading to inconsistent measures of success and limiting meta-analytical approaches. Moreover, **regulatory heterogeneity**—particularly the coexistence of hospital exemption pathways with ATMP classification—adds further fragmentation, especially in Italy, where minimally manipulated adipose tissue products are frequently employed outside the full ATMP framework. Finally, **manufacturing and GMP compliance** remain critical bottlenecks. The need for reproducible, scalable processes is essential for commercialization, yet still poses cost and infrastructure challenges.

5. Future Perspectives

Several priorities will shape the next phase of ASC-based wound therapies. The foremost is **harmonization of standards**, including validated potency assays, consistent viability thresholds, and immune-phenotyping criteria tailored to adipose-derived cells. This would improve comparability across trials and provide regulators with a clearer framework for approval.

Cross-border collaboration between Austria and Italy could be particularly powerful: Austria brings experience with standardized, industry-grade clinical trial execution, while Italy contributes a wide spectrum of investigator-led studies in diverse wound indications. Integrating these strengths would accelerate both scientific and translational progress.

Another need is the **integration of biomarker-driven endpoints**. Beyond wound closure, angiogenic, inflammatory, and immunomodulatory markers could provide earlier and more sensitive measures of therapeutic benefit, enabling better trial design and mechanistic understanding.

Looking beyond cell-based products, **cell-free approaches** such as ASC-derived secretome or extracellular vesicles are gaining attention as safer and more scalable alternatives (PMID: 34859174). These products may circumvent some of the manufacturing and regulatory challenges that currently limit widespread adoption of live-cell therapies.

Finally, the **public health impact** should not be overlooked. In conditions like diabetic foot ulcers, where non-healing wounds often result in amputation, cost-effective and standardized ASC products could substantially reduce morbidity, healthcare burden, and long-term disability.

6. Conclusion

Austria and Italy represent two distinct but complementary hubs of ASC-based expertise for wound therapy. Austria has concentrated its efforts on standardized, multicentric trials of darvadstrocel for Crohn's fistulas, developing strong regulatory and industrial expertise. Italy has pursued a broader translational agenda, extending ASC applications to systemic sclerosis ulcers, diabetic foot, gastrointestinal fistulas, and reconstructive surgery.

The mapping of these efforts reveals both the progress and the challenges of ASC translation: lack of standardization, regulatory fragmentation, and heterogeneity of clinical endpoints. Moving forward, collaboration between Austria and Italy could help harmonize trial design and accelerate the development of adipose-derived therapies for chronic wounds, a field with pressing clinical and societal need.

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Attendum#1:

LIST OF CLINICAL TRIALS IN AUSTRIA AND ITALY ON ADIPOSE STEM CELLS

AUSTRIA

ClinicalTrials.gov ID	NCT01378390	EudraCT ID	2008-004286-25
Drug	Darvadstrocel		
Title	Safety and Efficacy of Adipose-Derived Stem Cells to Treat Complex Perianal Fistulas Patients With Crohn's Disease (FATT)		
Phase	3	Sponsor	Takeda
AT Center(s)	Wien, Medizinische Universität		
Other countries	The Netherlands, Spain		
Summary	The purpose of this study is to determine safety and efficacy of eASCs (expanded adult stem cells) for treatment of complex perianal fistulas in patients with Crohn's disease.		

ClinicalTrials.gov ID	NCT01541579	EudraCT ID	n.a.
Drug	n.a.		
Title	Adipose Derived Mesenchymal Stem Cells for Induction of Remission in Perianal Fistulizing Crohn's Disease (ADMIRE-CD)		
Phase	3	Sponsor	Tigenix SAU
AT Center(s)	Innsbruck, Universität–Klinik; St. Veit/Glan, Krankenhaus; Wien, Medizinische Universität		
Other countries	Belgium, France, Germany, Israel, The Netherlands, Spain, **Italy** **AOU Policlinico Sant'Orsola Malpighi, Bologna** **AOU Careggi, Firenze** **Istituto Clinico Humanitas IRCSS, Milano** **Seconda Università degli Studi di Napoli** **AO Padova** **AO San Camillo Formalini, Roma** **Università Cattolica del Sacro Cuore, Roma**		
Summary	The current multicentre phase III study is proposed to confirm in an add-on therapy design compared to a placebo-control group, the efficacy of adipose-derived stem cells (eASCs) from healthy donors for the treatment of complex anal fistulas in patients with Crohn's disease over a 24-week period and an extended follow-up period up to 104 weeks.		

ClinicalTrials.gov ID	NCT04118088	EudraCT ID	2017-002491-10
Drug	Darvadstrocel 120 million cells		
Title	A Study of Darvadstrocel in Adults With Crohn's Disease and Complex Perianal Fistula (EMPIRE)		

Phase	4	Sponsor	Takeda
AT Center(s)	AKH Wien		
Other countries	Czech Republic, France, Germany, Israel, Spain		
Summary	The main aim is to check the long term side effects of a repeat treatment of darvadstrocel and to see if that treatment improves symptoms of Crohn's disease and complex perianal fistula. Participants will attend 8 clinic visits and will receive 1 treatment of darvadstrocel at the third visit. A magnetic resonance imaging (MRI) will be performed several times during the study.		

ClinicalTrials.gov ID	NCT05322057	EudraCT ID	n.a.
Drug	Darvadstrocel		
Title	Efficacy of Cx601 (Darvadstrocel) for the Treatment of Perianal Fistulizing Crohn's Disease		
Phase	n.a.	Sponsor	Wien, Medizinische Universität
AT Center(s)	Wien, Medizinische Universität		
Other countries	none		
Summary	The use of mesenchymal stem cells is considered a novel and promising therapeutic option for patients with perianal fistulizing Crohn's disease. However, due to limited clinical data, this multicentre, nationwide study aimed to assess its clinical efficacy in closing complex anal fistula.		

ITALY

ClinicalTrials.gov ID	NCT04326907	EudraCT ID	n.a.
Drug	Autologous centrifuged adipose tissue (CAT) injection, harvested from abdominal subcutaneous adipose tissue		
Title	Treatment of Complex Anal Fistulas Using Centrifuged Adipose Tissue Containing Progenitor Cells		
Phase	n.a.	Sponsor	University Hospital of Ferrara
IT Center(s)	University Hospital of Ferrara		
Other countries	none		
Summary	In the treatment of complex anal fistulas transplant of freshly collected autologous adipose tissue mechanically fragmented or centrifuged adipose tissue (CAT) might be an alternative to in vitro expanded autologous or allogeneic adipose-derived stem cells, showing remarkable efficacy in diverse therapeutic indications. The aim of our study is to evaluate randomly the efficacy and safety of the use of CAT in the healing process of complex anal fistulas, except for Crohn's disease (CD) related fistulas.		

ClinicalTrials.gov ID	NCT02403232	EudraCT ID	n.a.
Drug	Autologous Adipose-derived Stem Cells (ASCs) prepared by LIPOGEMS system		

Title	Autologous Adipose-derived Stem Cells (ASCs) for the Treatment of Perianal Fistula in Crohn Disease: A Pilot Study		
Phase	n.a.	Sponsor	Papa Giovanni XXIII Hospital, Bergamo
IT Center(s)	Papa Giovanni XXIII Hospital, Bergamo		
Other countries	none		
Summary	Rationale for the trial: To evaluate the efficacy of the use of ACSS in Crohn related perianal fistulas by Lipogems® and Salvecoll®. Lipogems® product is a non-expanded and microfractured fat tissue ready for autologous settings. Salvecoll® is sterile bioplastic, equine derived, type I collagen material with a fully preserved fibrous structure (non-reconstructed) that ensures the regeneration of affected tissues. Type I collagen has zero risk of transmitting viral or microbial infections.		

ClinicalTrials.gov ID	NCT04670276	EudraCT ID	n.a.
Drug	Emulsified adipose tissue stromal vascular fraction		
Title	Conservative Treatment of Gastrointestinal Fistulas by Endoscopic Injection of tSVFem		
Phase	n.a.	Sponsor	Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma
IT Center(s)	Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma		
Other countries	none		
Summary	The aim of this study is to exploit the regenerative-tissue capacities of autologous emulsified adipose tissue-derived stromal vascular fraction (tSVFem, widely used in other medical fields - like plastic surgery -for different purposes) harvested and delivered locally by endoscopy to close the GI fistula. The proposed technique for the treatment of GI fistulas with tSVFem requires a minimal, inexpensive, easily reproducible mechanical manipulation of autologous adipose tissue without necessity of any enzymatic digestion or cell expansion.		

ClinicalTrials.gov ID	NCT04075825	EudraCT ID	2019-000333-39
Drug	Darvadstrocel		
Title	Long-term Follow-up Study With Darvadstrocel in the Treatment of Complex Perianal Fistula		
Phase	3	Sponsor	Takeda
IT Center(s)	AOU Policlinico di Modena; Università Cattolica del Sacro Cuore, Roma		
Other countries	USA, Belgium, Czech Republic, France, Hungary, Israel, Poland, Spain		
Summary	The main aim is to follow-up on long term side effect and symptom improvement of Darvadstrocel in the treatment of complex perianal fistula in adults. Participants will not receive any drug in this study.		

ClinicalTrials.gov ID	NCT03279081	EudraCT ID	2017-000725-12
Drug	Cx601 eASCs 120 million cells		
Title	Study to Assess Efficacy and Safety of Cx601, Adult Allogeneic Expanded Adipose-derived Stem Cells (eASC) for the Treatment of Complex Perianal Fistula(s) in Participants With Crohn's Disease (CD)		
Phase	3	Sponsor	Tigenix SAU
IT Center(s)	OU Policlinico Sant'Orsola Malpighi, Bologna; AOU Policlinico di Modena; Seconda Università degli Studi di Napoli; AO Palermo; Università degli Studi di Pisa; Policlinico Universitario Campus Bio-Medico, Roma; AO San Camillo Forlanini, Roma; Università Cattolica del Sacro Cuore, Roma; Policlinico Universitario Gemelli, Roma; AOU Santa Maria della Misericordia, Udine; AOUI Verona; Ospedale Santissima Annunziata Cento (FE); Istituto Clinico Humanitas IRCSS, Milano		
Other countries	USA, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Israel, Poland, Puerto Rico, Spain, Sweden, UK		
Summary	The purpose of this study is to evaluate the combined remission of complex perianal fistulas, defined as the clinical assessment at Week 24 of closure of all treated external openings that were draining at baseline despite gentle finger compression, and absence of collections greater than (>) 2 centimeter (cm) (in at least 2 dimensions) confirmed by blinded central magnetic resonance imaging (MRI) assessment at Week 24.		

ClinicalTrials.gov ID	NCT00616135	EudraCT ID	n.a.
Drug	(Adipose-derived regenerative cells) ADRC-enhanced autologous fat transplant		
Title	Study of Autologous Fat Enhanced w/ Regenerative Cells Transplanted to **Reconstruct Breast Deformities After Lumpectomy**		
Phase	4	Sponsor	Cytori Therapeutics
IT Center(s)	Università di Firenze		
Other countries	Belgium, Spain, UK		
Summary	A post-marketing study evaluating the transplantation of autologous fat augmented with Adipose Derived Regenerative Cells (ADRCs), in patients with functional and cosmetic breast deformities post segmental mastectomy or quadrantectomy (lumpectomy).		

ClinicalTrials.gov ID	NCT04223622	EudraCT ID	n.a.
Drug	ASC secretome		
Title	Effects of ASC Secretome on Human **Osteochondral Explants**		
Phase	n.a.	Sponsor	I.R.C.C.S Ospedale Galeazzi-Sant'Ambrogio
IT Center(s)	I.R.C.C.S Ospedale Galeazzi-Sant'Ambrogio, Milano		
Other countries	none		
Summary	Since the need of finding effective disease-modifying anti-osteoarthritis (OA) treatments is still unmet, with this study the investigators aim to gather further evidences of the therapeutic potential of Mesenchymal Stem/stromal Cell (MSC) secretome in order to pave the way to its future use as a cell-free biological product. In detail, the investigators predict to validate the		

	promising results obtained in vitro, ex vivo on osteochondral explants, an OA model more representative of the physiological situation.

ClinicalTrials.gov ID	NCT03158727	EudraCT ID	2015-002994-39
Drug	Cx611 (eASC)		
Title	Cx611-0204 SEPCELL Study		
Phase	1-2	Sponsor	Tigenix S.A.U.
IT Center(s)	Azienda Ospedaliera Sant'Andrea, Roma		
Other countries	Belgium, France, Lithuania, Norway, Spain		
Summary	The purpose of this randomised, multicentre, double-blind, placebo-controlled, phase Ib/IIa study is to assess the safety, tolerability and efficacy of eASCs (Cx611) administered intravenously as adjunctive therapy, therefore in addition to standard of care (SoC) therapy, to patients with severe community-acquired bacterial pneumonia (sCABP). The completion of this study will contribute to the basic knowledge on stem cells and their mode-of-action, and has a large translational character, i.e. to document the safety and explore the efficacy of Cx611 in patients with sCABP.		

ClinicalTrials.gov ID	NCT03406988	EudraCT ID	n.a.
Drug	Autologous Adipose Tissue (AT)		
Title	Regional Grafting of Autologous Adipose Tissue in the Treatment of **Systemic Sclerosis Digital Ulcers**: a Prospective Randomized Controlled Study		
Phase/Study Status	n.a./Recruiting	Sponsor	ASST Gaetano Pini-CTO
IT Center(s)	ASST Gaetano Pini-CTO, Milano		
Other countries	none		
Summary	A randomized controlled trial will be performed to confirm preliminary uncontrolled data indicating that regional adipose tissue grafting is effective in inducing digital ulcer healing in patients with systemic sclerosis. Systemic Sclerosis patients with digital ulcers will be randomized to be blindly treated with adipose tissue implantation or a sham procedure. Adipose tissue grafting will consist of injection at the base of the finger with digital ulcer of 0.5-1 ml of adipose tissue after centrifugation of fat aspirate. Sharm procedure will consist of false liposuction and local injection of saline solution. The primary end-point will be to compare the cumulative prevalence of healed digital ulcers in the two groups within the following 8 weeks.		
Description	Systemic sclerosis (SSc) is an autoimmune disease characterized by a multifactorial pathological process where a central role is played by the progressive loss of the microvascular bed, with the consequent fibrotic changes in the involved organs and tissues. The most advanced stages of capillary loss may induce the formation of digital ulcers (DUs) on the fingertips.The healing of DUs is often a lengthy process requiring accurate and intensive topical and systemic treatment. Nevertheless, in a significant number of cases this therapeutic approach is ineffective and distal necrosis with subsequent tissue loss or phalangeal amputation may eventually occur.		

	In a recent open pilot study performed by Del Papa et al., it has been demonstrated that autologous adipose tissue grafting (AT-G), which is known to contain both adipose-derived stem cells and a stromal/vascular fraction, was effective in inducing prompt healing of long lasting DUs localized in the fingertips of a small number of patients with SSc. The DU healing was accompanied by the rapid disappearance of local ischemic pain and evidence of a partial restoration of the capillary bed in the digits when assessed by nailfold videocapillaroscopy (NVC). With the purpose of confirming these preliminary results, the investigators have designed a monocentric randomized controlled study. In accordance with the study protocol, patients with a typical SSc-related DU on the fingertip will be randomized to undergo a regional AT-G with autologous fat as active therapy or a 'sham' procedure (SP) - that simulates the active treatment - as placebo treatment. All of the patients with SSc enrolled in both arms will be blind regarding the treatment received. Furthermore, during the study period all of the enrolled patients will receive the same systemic vasoactive and topical therapy.
Interventional model	Candidate SSc patients will have only one active DU of at least 6 mm in diameter, lasting for at least 6 weeks, despite conventional vascular therapy. Patients with severe visceral manifestations, diabetes and treated with immune-suppressors and endothelin inhibitors will be excluded. Active therapy: implantation of 0.5-1 ml of autologous AT at the base of the finger with DU. Autologous AT will be obtained by liposuction from abdominal fat. SP will be blindly performed in the control group to simulate the AT-G. A false liposuction will be performed followed by the injection of 0.5-1 ml of 0.9% saline solution at the base of the affected finger. Basal therapy: weekly iloprost infusion (0.5-2 ng/Kg/min), and calcium-channel blockers (oral nifedipine 20 mg daily) will be continued during the entire observation time in all of the patients recruited in both arms of the study. The administration of analgesics to alleviate the DU-related pain will be also allowed for each patient.
Inclusion criteria	M/F, 18 to 70 Years • Patients candidate for enrollment in the study have to meet the 2013 classification criteria of the American College of Rheumatology/European League Against Rheumatism for SSc; • Patients may have either the limited cutaneous or the diffuse cutaneous variants of SSc; • All of the candidate patients must have only one active DU (cardinal ulcer), lasting for at least 6 weeks prior to enrolment time and showing no tendency to heal despite intravenous iloprost (0.5-2 ng/Kg/min), the oral administration of calcium-channel blockers (nifedipine) and local medication with surgical removal of necrotic tissue.
Primary outcomes	Digital Ulcer healing. Prevalence of DU healing in the arm treated with autologous fat grafting in comparison with the prevalence of healing in the placebo group. 8 weeks after either autologus fat grafting or sham procedure.
Secondary outcomes	• Pain evaluation by Visual Analogue Scale (VAS) • Neovascularization evaluation

ClinicalTrials.gov ID	NCT03276312	EudraCT ID	n.a.
Drug	Device: Lipogems		
Title	Local Inoculation of Autologous Micro-fragmented Adipose Tissue in the Treatment of Minor Amputations of **Diabetic Foot**: A Randomized Controlled Trial		
Phase/Study Status	n.a./Recruiting	Sponsor	University of Modena and Reggio Emilia

IT Center(s)	University of Modena and Reggio Emilia
Other countries	none
Summary	This is a randomized controlled monocentric study on 114 diabetic patients with the aim of evaluating the efficacy of the lipofilling with Lipogems® system in diabetic patients that are candidates for a minor amputation in the foot. In particular, it will be evaluated whether the lipofilling will be able to shorten the healing times and to reduce the number of major amputations, with consequent positive impact on the quality of life. Patients will be randomized to the treatment group with Lipogems® (local injection of autologous micro-fractured adipose tissue) or to the control group, thus, treatment according to standard clinical practice.
Description	Primary objective of this study is the evaluation of the time of the healing of the lesions resulting from minor amputations (digital or forefoot) treated with Lipogems® technique. Secondary objectives are: 1) assessment of the safety of the lipofilling; 2) evaluation of the intensity of pain (VAS); 3) assessment of the skin tropism; 4) calculation of the relapse rate (defined as the occurrence of local infections, dehiscence and suffering of skin flaps that lead to a revision of the amputation stump or amputation at a higher level); 5) evaluation of the time of hospitalization and quality of life (QoL).
Interventional model	Routine clinical practice - Local injection of autologous micro-fragmented adipose tissue - Lipogems® is a system that, starting from minimum quantities of autologous lipoaspirate, provides, with a minimal manipulation, a micro-fragmented and non-expanded adipose tissue product. No Intervention: Control
Inclusion criteria	M/F, 18 to 70 Years • Patients with diabetes (diabetes mellitus type 1 and type 2). • Presence of irreversible gangrene digital or localized at forefoot (with X-ray of the foot negative or positive for osteolytic lesions at phalanges and/or metatarsus). • Patients with vascular problems absent or resolved (evaluated with Eco Color Doppler and ABI (Ankle Brachial Index, that calculates the ratio of the systolic pressure measured at the ankle and the systolic pressure in the arm, both measured in supine position using wave continue Doppler. If assessable, it has to be greater than/equal to 0.7) and pressure index finger/arm TBI (Toe Brachial Index, if assessable, it has to be greater than/equal to 0.6) and/or by the determination of the transcutaneous oxygen pressure (TcPO2 that needs to be equal to or greater than 30mmHg).
Primary outcomes	Healing time after the minor amputation intended as the complete healing of the amputation stump. Time frame 6 months.
Secondary outcomes	• Pain evaluation by Visual Analogue Scale (VAS) • Safety (Adverse events) • Incidence of relapse • Total time of hospitalization • Total time of immobility • Quality of Life using the Short Form 36 (SF-36) questionnaire