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Clinical Investigation Report

"Study of the viability of stem cells in adipose tissue samples collected using the Lipomatic®/evamatic® device and of autologous adipose tissue transplantation using the lipofilling n.l.f. system®kit"

Agreement number:

C-1420012-OFT

Wallonie

SPW
Service public de Wallonie

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1 ADMINISTRATIVE INFORMATION

1.1 Identification of the project

Title of the DGO6 Programme: Clinical Investigation Report

Title of project: "Study of the viability of Stem Cells in Adipose Tissue samples collected using the Lipomatic®/evamatic® device and of autologous adipose tissue transplantation using the Lipofilling NLF system®kit"

The study is divided into two parts:

- The first part concerns the viability study of the adipose tissue stem cells collected using the Lipomatic® device.
- The second part involves the transplantation of autologous adipose tissue in the breast region and/or other areas of the body (chest, upper and lower limbs, etc.) using the lipofilling NLF system®kit.

1.2 Agreement

Agreement RW: C-1420012-OFT

1.3 Dates

Agreement start date: 02/02/2016

1.4 Sponsors and investigators

Contact details of the clinical investigation sponsor:

Name	EUROMI SA
Address	Zoning Industriel de Lambermont 151, rue des Ormes 4800 VERVIERS BELGIUM
Tel.	+32 87 29 22 24

Contact details of the principal investigators in the clinical trial:

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Area of specialisation	Department of Plastic Surgery

Name	Dr. DENOËL Christophe
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Area of specialisation	Specialist in Plastic, Reconstructive and Aesthetic Surgery

Contact details of the principal investigators in the clinical trial:

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Area of specialisation	Head of the Clinical Haematology Department

Analytical Laboratory contact details

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Address	LTCG Tour 2 niveau -4E CHU Sart-Tilman 1 Avenue de l'hôpital 4000 Liège Belgium Tel.: Chantal Lechanteur: +32 4/366.85.91 Alexandra Briquet : +32 4/366.83.96 Laura Lambert (LTCG secretary): +32 4/366.83.90
Area of specialisation	Head of the Clinical Haematology Department

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Tel.	: +32 4/222.99.90

Contact details of the Clinical Trial Sites:

Name	Clinique Saint-Vincent CHC
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Name	Clinique André Renard
Address	1, Rue André Renard 4040 Herstal Belgium
Area of specialisation	Plastic, Reconstructive and Aesthetic Surgery

2 Introduction

This clinical investigation was carried out in conjunction with the Clinique André Renard d'Herstal, Hôpital Saint-Vincent de Rocourt and the University of Liège in accordance with ISO standard 14155. The study comprises two parts: The first part concerns the viability study of the adipose tissue stem cells collected using the Lipomatic® device. The second part involves the transplantation of autologous adipose tissue in the breast region and/or other areas of the body (chest, upper and lower limbs, etc.) using the lipofilling NLF system®kit. Both parts are carried out in parallel.

The purpose of this clinical investigation is to complete earlier studies carried out on the Lipomatic®/Evamatic® device and the N.I.L.® technique, on the one hand, and on publications related to adipose tissue sampling using the conventional Coleman technique, on the other hand. The study to be carried out aims to apply the conventional Coleman method with specimen collection using the Lipomatic®/Evamatic® device and the N.I.L.® technique, which is an automated, more effective, less traumatic technique generating optimum results with lipofilling and related applications.

3 Purpose of the study

The purpose of this study is to investigate the composition of adipose tissue collected using an eva sp® suction machine and Lipomatic®/Evamatic® hand-piece, which will be stored in the "NLF System" lipofilling kit produced by EUROMI s.a., on the one hand,

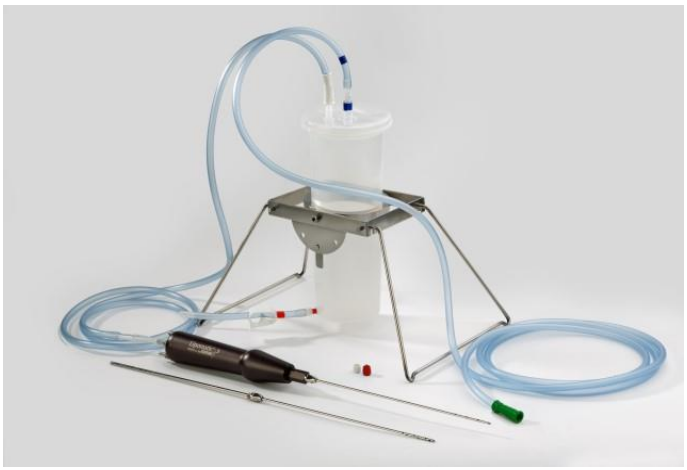
and to analyse patient follow-up for up to three months post-procedure, on the other hand. In fact, autologous adipose tissue transplantation is constantly increasing. This technique is used in reconstructive breast surgery after cancer or to correct breast malformation such as "tuberous breasts", Poland syndrome or simply asymmetrical breast volume. It is also used in the treatment of burn scars, congenital malformations, post-traumatic malformations, scleroderma and aesthetic surgery. The regenerating action of the tissues compliments the volume-enhancing effect. The action of autologous injected adipose tissue is ideal because it is biocompatible, polyvalent, natural, non-immunogenic, reasonably priced and rapidly available with very low donor site morbidity.

One of the main purposes of this clinical investigation is to prove that the device is fit-for-purpose and that its performance is consistent with the specification.

4 Material and method

The surgical technique comprises three parts; firstly, the initial infiltration phase. Then the initial adipose tissue sampling phase, firstly via a multi-perforated cannula, 3 mm in diameter. As soon as 500 ml of adipose tissue is collected, the surgeon can use other cannula with diameters of different dimensions. A User Guide on the investigational device has been given to doctors taking part in this investigation.

The lipofilling in this clinical investigation is carried out with the n.l.f. System® 1, which is supplied sterile and for single use. This device is used to harvest adipocytes via the NIL technique using the decantation method - a renowned lipofilling technique. In this investigation, 19 patients underwent surgery and were followed up after 1 month and 3 months.



At the same time, specimens collected from ten of these patients were sent to the Department of Cell and Tissue Therapy at CHU Liège. The stem cells derived from adipose tissue were initially isolated over time, according to the technique described, then placed in culture in an attempt to be cultured and expanded by successive trypsinisation up to passage 4.
On harvesting at passage 4, the cells were identified by their membrane marker profile using flow cytometry (CD105, CD90, CD73, CD45, CD14, CD34, CD3, HLADR) and by their capacity for bone, cartilage and adipose tissue differentiation (still in process).

Type of surgery and anatomical regions investigated:

Liposuction of the abdominal wall was performed. In the absence of any adipose tissues at this level, the specimen can be collected from the trochanter, hips, internal surface of the thighs or the knees.
The surgeon generally uses several different techniques during the adipose tissue reinjection process:
a) Colman technique with manual adipose sampling using a 10 cc syringe and a centrifugation stage prior to reinjection of the stromal part,
b) macrofill® technique,
c) simple decanting technique after manual aspiration
d) technique according to Dr. E DELAY (manual sampling kit which is commercially available).

The surgical technique used is:

a. For the initial infiltration phase: Absence of lidocaine is likely to affect the viability of the stem cells. The anaesthetic will not be injected until the end of the sampling phase.

Composition of the infiltration liquid:
1000 ml of 0.9% cold (6°) NaCl is prepared. Unless specified otherwise by the anaesthetist, the following are added:
- 1 ampoule of catapressan (clonidine) 0.150 mg/ml 1 ml,
- 1 ampoule of adrenaline (levorenin) 1 mg/ml

The litre of mixture is infiltrated via 4 orifices, each measuring 2 mm in diameter (2 located in the sub-pubic region, mid-way between the EIAS (external iliac arteries) and the median section, and 2 at the junction between the umbilical zone and the flanks).

b. For the initial adipose sampling phase, with a negative pressure of 0.5 bar. In fact, as described in the literature, this pressure does not damage the adipocytes collected since it preserves optimal tissue viability, which should be analysed in the laboratory. Suction will start with a multi-perforated cannula measuring 3 mm in diameter, with orifices measuring between 1.5 and 2.5 mm in diameter. Once an adequate quantity of adipose tissue has been collected, the surgeon can prepare the following specimens.

At this stage, 3 x 10-ml adipose tissue samples are collected at various heights from the harvesting jar in the afore-mentioned sampling kit:
- 2 from the intermediate stromal fraction (between the oily layer and the blood layer). Mid-way (fraction 1) and in the lower section of this layer (fraction 2).
- 1 from the blood level (fraction 3).

- 1 x 10-ml sample is also collected using the conventional Coleman technique (fraction 4).

The specimens were refrigerated at a temperature of 8° and transferred for analysis to the Department of Cell and Tissue Therapy led by Professor Yves BEGUIN (CHU Liège). Depending on the cell counts recorded in adipose specimens of identical volume, the harvested zones with the richest ASC content were determined.

c. For the adipose tissue reinjection phase, the characteristics of the reinjection cannula are described above, in point b.

Reinjection is carried out by collecting samples from the deep layer of the stromal fraction, in a closed circuit, which previously underwent decantation at negative pressure for 30 minutes. Reinjection is carried out via orifices, 2 mm in diameter (4 to 8 orifices), depending on the zone to be filled (tissue surface area and thickness).

Patient follow-up was carried out by Doctor Denoël, a specialist in plastic, reconstructive, and aesthetic surgery, for up to three months post-procedure - the length of time needed in order to obtain a conclusive result in terms of viability. In fact, from a safety perspective, checks are carried out to ensure that the patient has not sustained any injury since the procedure, or contracted any infection and/or contamination. From a performance standpoint, transplant survival will be confirmed by the absence of any complication such as steatonecrosis. The following aspects were monitored during patient follow-up:
- Visual appearance of the area
- Medical history
- Volumetric analysis using the VECTRA 3D system (powerful measuring tool to assess volumetric gain)
- Degree of patient satisfaction

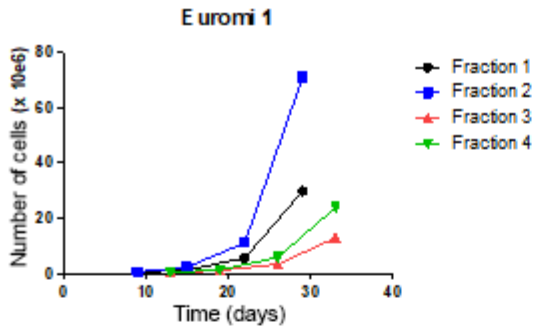
5 Results

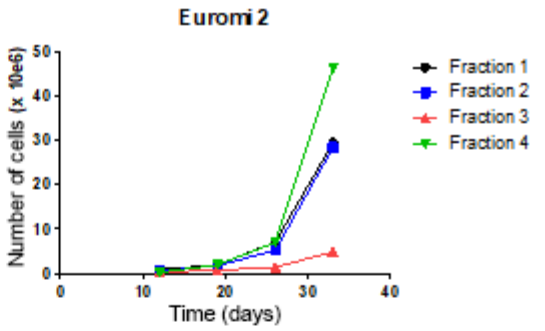
This clinical investigation is intended to complete earlier studies focusing on the Lipomatic®/Evamatic® and N.I.L.® technique on the one hand, and on publications related to adipose tissue sampling using the conventional Coleman technique, on the other hand.

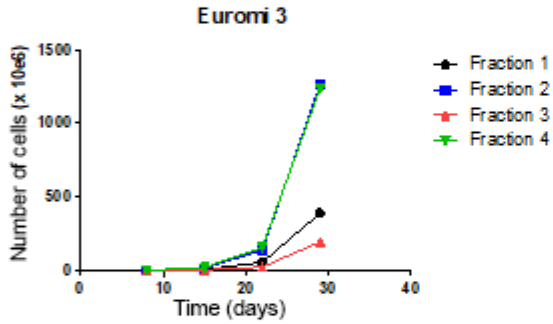
Phase I: Viability study of the adipose tissue stem cells collected using the Lipomatic®/Evamatic® device.

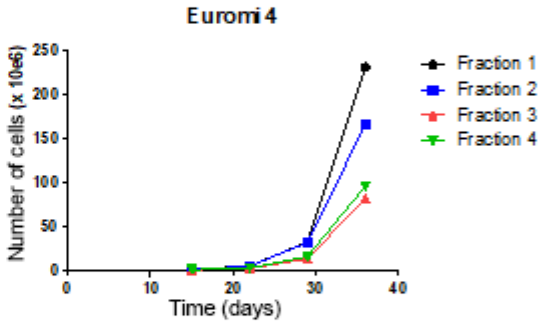
The study data were analysed using the 10 specimens and cultures provided for in an attempt to obtain a statistically significant set of samples.

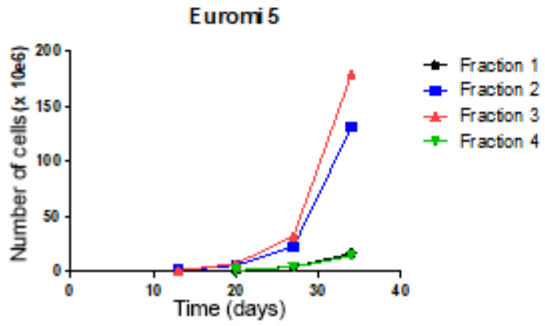
All fractions (from 1 to 4) of the 10 samples produced cultures (no culture failures) with proliferation that varied considerably from one fraction to the next for the same donor, and also from one donor to the next for the same fraction. The culture times were also adjusted from one culture to the next as well as from one fraction to the next within one culture from the same donor. All of the cultures were processed up to passage 4. These means that the times of the different passages varied from one culture to the next and from one fracture to the next; the latter were carried out when adequate cell confluence was obtained.

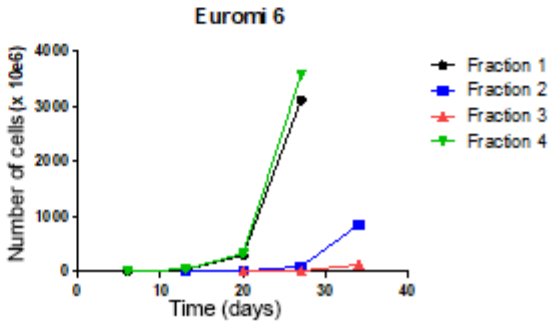

Euromi 1
Number of cells (x 10e6)
Time (days)
Fraction 1
Fraction 2
Fraction 3
Fraction 4

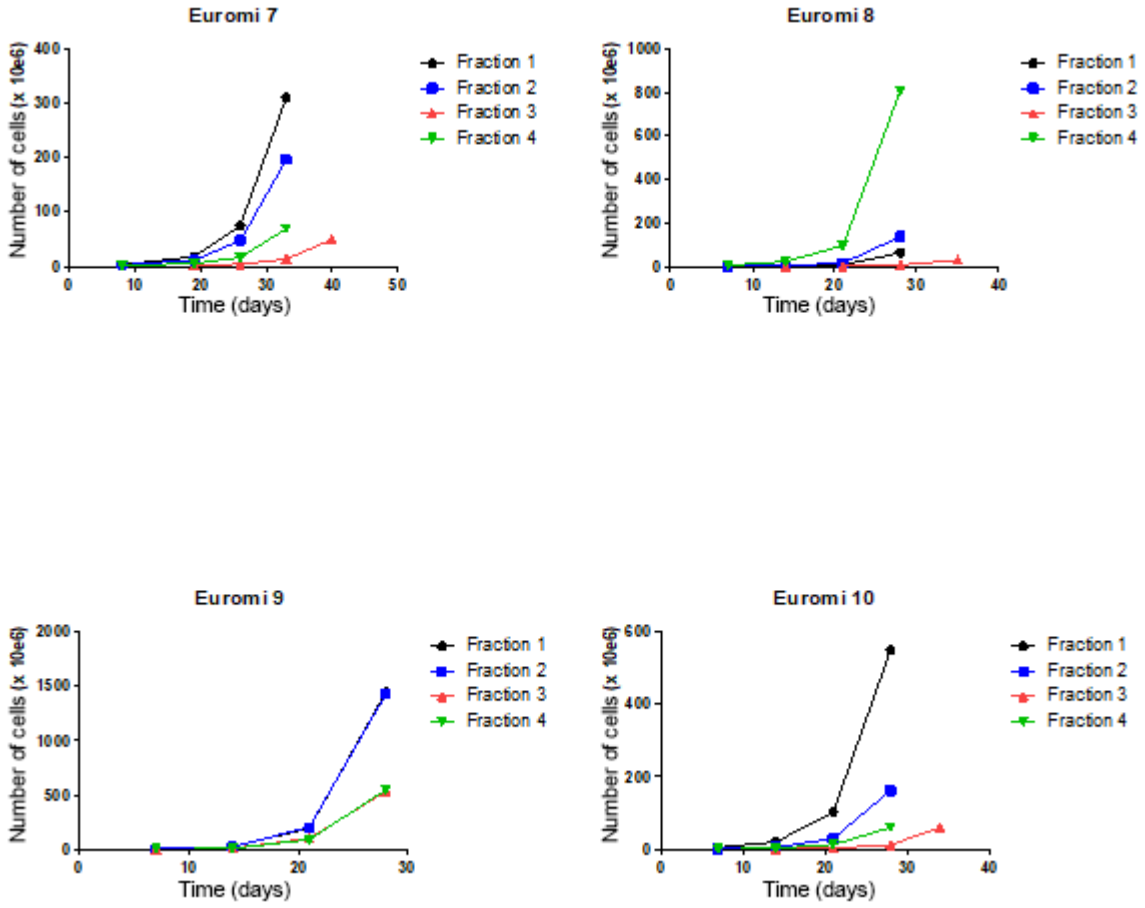

Euromi 2
Number of cells (x 10e6)
Time (days)
Fraction 1
Fraction 2
Fraction 3
Fraction 4


Euromi 3
Number of cells (x 10e6)
Time (days)
Fraction 1
Fraction 2
Fraction 3
Fraction 4


Euromi 4
Number of cells (x 10e6)
Time (days)
Fraction 1
Fraction 2
Fraction 3
Fraction 4


Euromi 5
Number of cells (x 10e6)
Time (days)
Fraction 1
Fraction 2
Fraction 3
Fraction 4


Euromi 6
Number of cells (x 10e6)
Time (days)
Fraction 1
Fraction 2
Fraction 3
Fraction 4



Although the results obtained are combined from the same fraction for the various cultures (see the following graphs comparing the fractions from the different passages):

- 16.4 x 10e6 (Euromi 5; 33 days) to 3112 x 10e6 cells (Euromi 6; 26 days) were harvested from all the cultures of the various 1 fractions, with culture periods ranging from 26 to 35 days.

An analysis of all the 1 fractions (10 cultures) at different passages shows that, on average, 617 x 10e6 cells can be harvested from a liposuction of 10 mL (median = 270 x 10e6 cells) at passage 4.

- 28.5 x 10e6 (Euromi 2; 33 days) to 1425 x 10e6 cells (Euromi 9; 28 days) were harvested from all the cultures of the various 2 fractions, with culture periods ranging from 28 to 36 days.

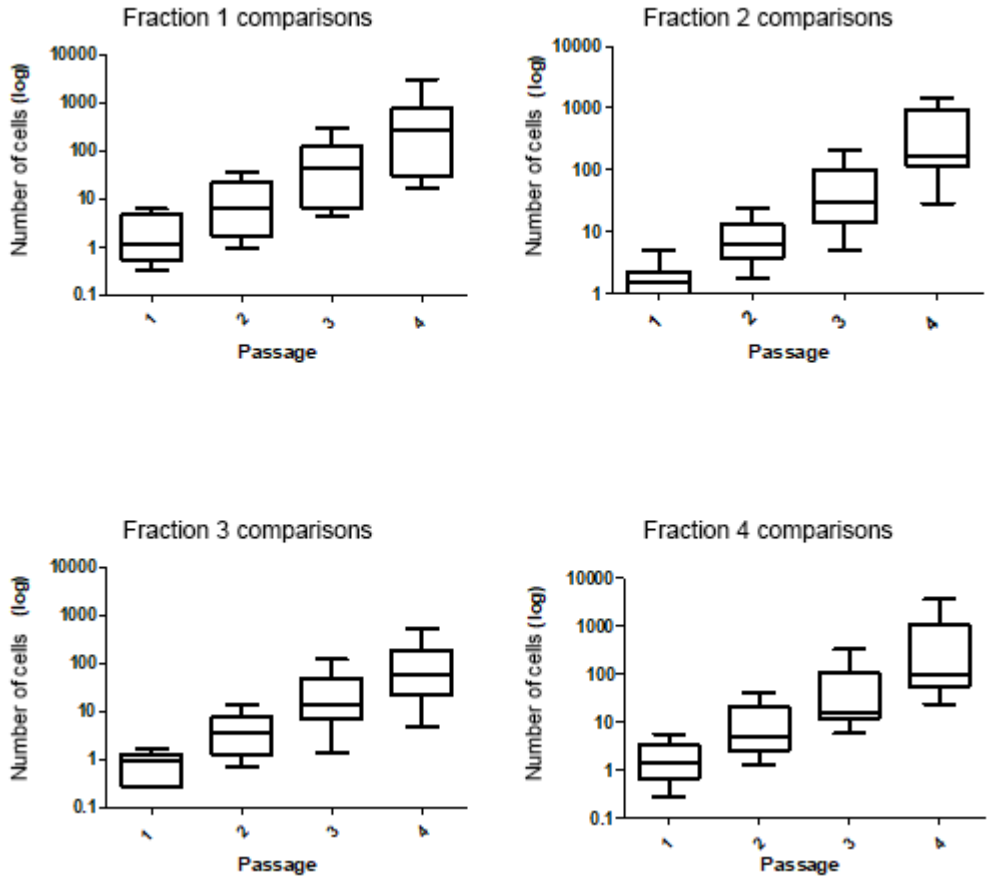
An analysis of all the 2 fractions at different passages shows that, on average, 443 x 10e6 cells can be harvested from a liposuction of 10 mL (median = 163.7 x 10e6 cells) at passage 4.

- 12.9 x 10e6 (Euromi 1; 33 days) to 179 x 10e6 cells (Euromi 5; 34 days) were harvested from all the cultures of the various 3 fractions, with culture periods ranging from 28 to 40 days.

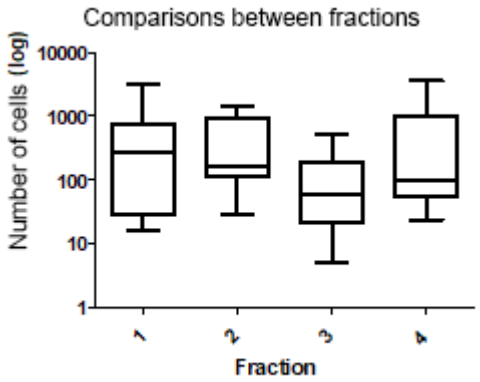
An analysis of all the 3 fractions at different passages shows that, on average, 127.5 x 10e6 cells can be harvested from a liposuction of 10 mL (median = 60.3 x 10e6 cells) at passage 4.

- 14 x 10e6 (Euromi 5; 34 days) to 3572 x 10e6 cells (Euromi 6; 27 days) were harvested from all the cultures of the various 4 fractions, with culture periods ranging from 27 to 36 days.

An analysis of all the 3 fractions at different passages shows that, on average, 718 x 10e6 cells can be harvested from a liposuction of 10 mL (median = 95.83 x 10e6 cells) at passage 4.



A comparative statistical analysis of the yields obtained at passage 4 in the various fractions did not highlight any significant difference: see graph below: comparison between fractions.
In fact, the yields compared via a Mann-Whitney test do not differ significantly between fractions 1 and 2 (p=0.9705), 1 and 3 (p=0.133), 1 and 4 (p=0.8421), 2 and 3 (p= 0.0947), 2 and 4 (p= 0.549) and 3 and 4 (p= 0.1615).

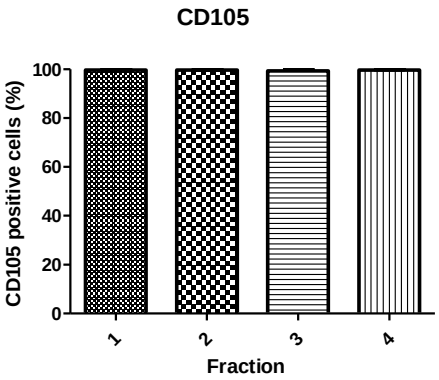


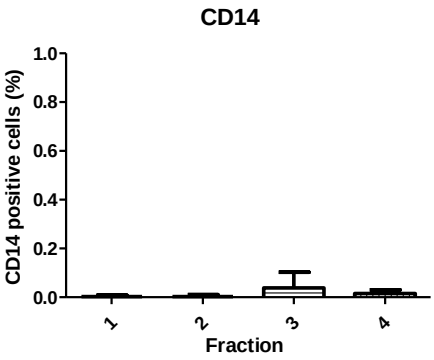
When harvesting (passage 4) from the 4 conditions of each culture one cell sampling session was used to:

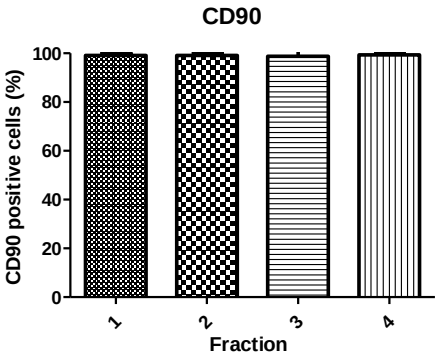
a) Create a phenotype (detection of cell membrane markers) to check the identity of the expanded population.
The graphs below compare the expression of each of the membrane markers for the 4 fractions of 10 cultures.

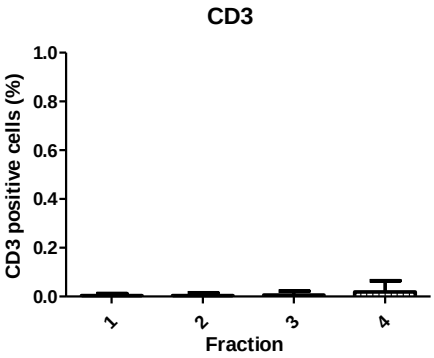
All of the expanded populations clearly present the phenotype that conforms to MSC, which is characterised by positivity (>95%) of markers CD90, CD105 and CD73, and negativity (<1%) of markers CD3, CD14, CD45, HLADR and CD34. Positivity of marker CD34 was, however, described for all MSCs expanded from adipose tissues.
In fact, slight positivity can be observed with this marker, which varies substantially from one culture to the next, with slightly greater, albeit insignificant, positivity in the cells obtained from sample fraction 3.

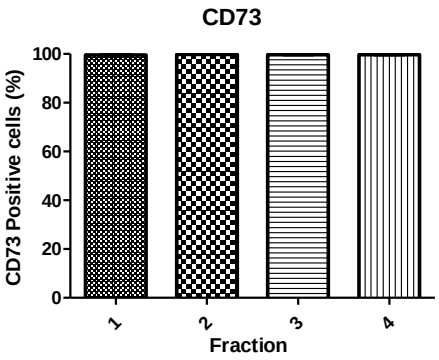
b) Induce the differentiation of the MSC obtained in adipocytes and osteoblasts by culturing them in a specific medium for 3 weeks. All of the populations harvested (4 fractions, 10 cultures) were tested with clear differentiation vis-à-vis the line induced.
This test is a purely qualitative test. A typical series of photos of an MSC population, with or without differentiation to osteoblastic or adipocyte lines, is shown below.

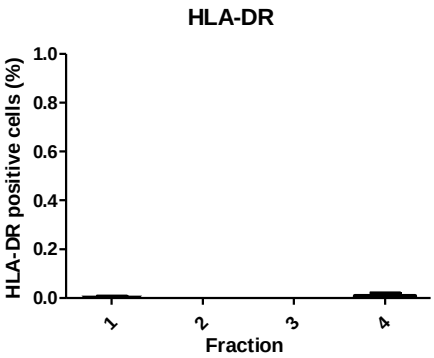

CD105
CD105 positive cells (%)
100
80
60
40
20
0
1
2
3
4
Fraction

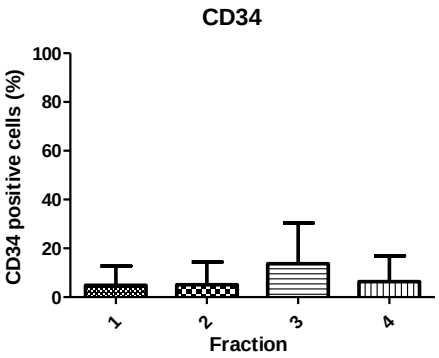

CD14
CD14 positive cells (%)
1.0
0.8
0.6
0.4
0.2
0.0
1
2
3
4
Fraction

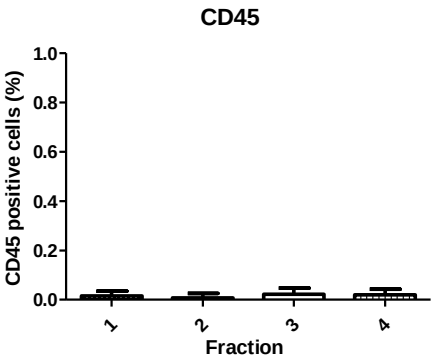

CD90
CD90 positive cells (%)
100
80
60
40
20
0
1
2
3
4
Fraction


CD3
CD3 positive cells (%)
1.0
0.8
0.6
0.4
0.2
0.0
1
2
3
4
Fraction


CD73
CD73 Positive cells (%)
100
80
60
40
20
0
1
2
3
4
Fraction

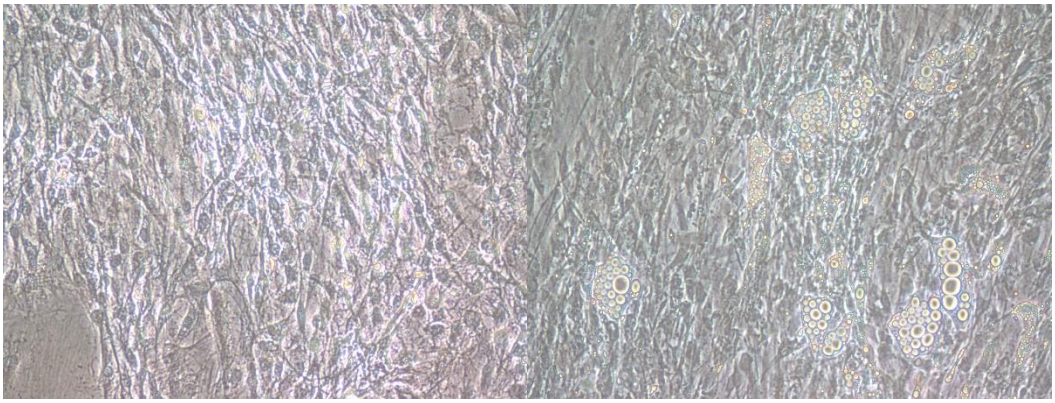

HLA-DR
HLA-DR positive cells (%)
1.0
0.8
0.6
0.4
0.2
0.0
1
2
3
4
Fraction

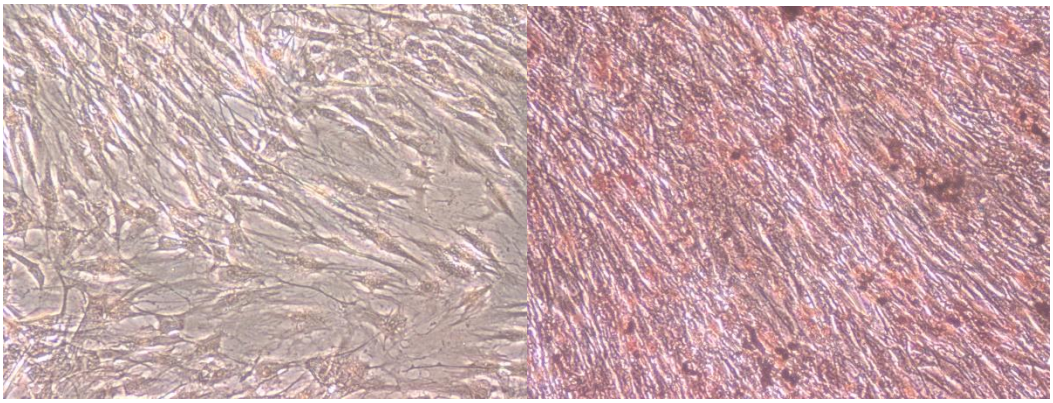

CD34
CD34 positive cells (%)
100
80
60
40
20
0
1
2
3
4
Fraction


CD45
CD45 positive cells (%)
1.0
0.8
0.6
0.4
0.2
0.0
1
2
3
4
Fraction

Non-differentiated

Differentiated in terms of adipocytes (lipid vesicles)





Non-differentiated (inclusions)

Differentiated in terms of osteoblast

Phase II: Transplantation of autologous adipose tissue using the lipofilling n.l.f. System®kit

Sampling - Reinjection	
Patient No. 1 Sampling - Reinjection	03-02-16
Patient No. 2 Sampling - Reinjection	17-02-16
Patient No. 3 Sampling - Reinjection	07-03-16
Patient No. 4 Sampling - Reinjection	07-03-16
Patient No. 5 Sampling - Reinjection	15-03-16
Patient No. 6 Sampling - Reinjection	16-03-16
Patient No. 7 Sampling - Reinjection	13-04-16
Patient No. 8 Sampling - Reinjection	14-04-16
Patient No. 9 Sampling - Reinjection	26-04-16
Patient No. 10 Sampling - Reinjection	27-04-16
Patient No. 11 Sampling - Reinjection	24-05-16
Patient No. 12 Sampling - Reinjection	07-06-16
Patient No. 13 Sampling - Reinjection	21-06-16
Patient No. 14 Sampling - Reinjection	22-06-16
Patient No. 15 Sampling - Reinjection	14-09-16
Patient No. 16 Sampling - Reinjection	14-09-16
Patient No. 17 Sampling - Reinjection	27-09-16
Patient No. 18 Sampling - Reinjection	08-11-16
Patient No. 19 Sampling - Reinjection	22-11-16
Patient follow-up - 1 month	

Patient No. 1 Patient follow-up - 1 month	03-03-16
Patient No. 2 Patient follow-up - 1 month	17-03-16
Patient No. 3 Patient follow-up - 1 month	07-04-16
Patient No. 4 Patient follow-up - 1 month	07-04-16
Patient No. 5 Patient follow-up - 1 month	15-04-16
Patient No. 6 Patient follow-up - 1 month	16-04-16
Patient No. 7 Patient follow-up - 1 month	13-05-16
Patient No. 8 Patient follow-up - 1 month	14-05-16
Patient No. 9 Patient follow-up - 1 month	26-05-16
Patient No. 10 Patient follow-up - 1 month	27-05-16
Patient No. 11 Patient follow-up - 1 month	24-06-16
Patient No. 12 Patient follow-up - 1 month	07-07-16
Patient No. 13 Patient follow-up - 1 month	21-07-16
Patient No. 14 Patient follow-up - 1 month	26-08-16
Patient No. 15 Patient follow-up - 1 month	29-09-16
Patient No. 16 Patient follow-up - 1 month	22-09-16
Patient No. 17 Patient follow-up - 1 month	10-10-16
Patient No. 18 Patient follow-up - 1 month	24-11-16
Patient No. 19 Patient follow-up - 1 month	16-12-16
Patient follow-up - 3 months	
Patient No. 1 Patient follow-up - 3 months	03-05-16
Patient No. 2 Patient follow-up - 3 months	17-05-16
Patient No. 3 Patient follow-up - 3 months	07-06-16
Patient No. 4 Patient follow-up - 3 months	07-06-16
Patient No. 5 Patient follow-up - 3 months	15-06-16
Patient No. 6 Patient follow-up - 3 months	16-06-16
Patient No. 7 Patient follow-up - 3 months	13-07-16
Patient No. 8 Patient follow-up - 3 months	14-07-16
Patient No. 9 Patient follow-up - 3 months	26-07-16
Patient No. 10 Patient follow-up - 3 months	27-07-16
Patient No. 11 Patient follow-up - 3 months	24-08-16
Patient No. 12 Patient follow-up - 3 months	07-09-16
Patient No. 13 Patient follow-up - 3 months	21-09-16
Patient No. 14 Patient follow-up - 3 months	13-10-16
Patient No. 15 Patient follow-up - 3 months	01-12-16
Patient No. 16 Patient follow-up - 3 months	16-03-17
Patient No. 17 Patient follow-up - 3 months	Not reviewed
Patient No. 18 Patient follow-up - 3 months	13-01-17
Patient No. 19 Patient follow-up - 3 months	13-03-17

No steatonecrosis-related complication was observed during follow-up for patients who underwent lipofilling. No painful nodules, no granuloma and no infection were detected for these cases. These various aspects are the main adverse reactions and/or complications observed following a lipofilling procedure.
The use of a foam cannula with a Lipomatic®/evamatic® head to create "pre-tunnels" in the receiving zone can limit haematomas compared to the manual method which is more traumatic and causes bleeding.

Cases with atrophic or irradiated skin are indicative of a filling defect. However, these comments are also reported with other filling techniques where the quality of the receiving site is poor. Most patients

were prepared to consider a second procedure to complete filling, which is current practice in these cases.

6 Difficulties encountered from a scientific and/or technical perspective

No technical or scientific difficulty was encountered.

7 Conclusion:

Phase I: Viability study of the adipose tissue stem cells collected using the Lipomatic®/Evamatic® device.

1) The Lipomatic®/Evamatic® device, like the so-called Coleman technique preserves the stem cells in the adipose tissue collected and allows MSC (mesenchymatous stem cells) to be collected successfully from all fractions tested.

The rapid proliferation of stem cells shows the quality of the adipose tissue collected, and therefore justifies the choice of maximum pressure applied, i.e. -0.5 bar.

2) No significant difference in culture yield was observed between the 3 fractions obtained using the Lipomatic®/Evamatic® device. However, fraction 3 is always far slower to start and generates lower yields overall than the other two fractions although these differences are not statistically significant if only the yield is considered. Fractions 1 and 2 are the most interesting in terms of stem cell extraction.

3) There is no significant difference in terms of yield between fractions 1, 2 and 3 obtained using the Lipomatic®/Evamatic® device and fraction 4 obtained with the conventional so-called Coleman technique. Both techniques seem to demonstrate the same efficacy in terms of obtaining MSC (mesenchymatous stem cells) from the liposuctions obtained. The same comment applies for fraction 3.

4) The MSC populations obtained by culturing the 4 fractions isolated in the 10 patients fully comply with MSC identification criteria.

Phase II: Transplantation of autologous adipose tissue using the lipofilling n.l.f. System®kit

Further to the data analysis, the performance and safety of the n.l.f. System kit are demonstrated. In fact, the follow-up of patients transplanted with Autologous Adipose Tissue using an eva sp® suction machine and its Lipomatic®/Evamatic® hand piece and stored with an "n.l.f. System® 1" kit from EUROMI S.A. in the breast region and/or other regions of the body (chest, buttocks and lower limbs) proved highly conclusive.

The quality of the adipose tissue is obtained using NIL® technology, which offers the following benefits:

For patients:

- less traumatic (less post-operative pain and kinder to peripheral tissues);
- less swelling on the donor site;
- less bruising on the donor site;
- faster recovery (reduction in post-surgical analgesic treatment).

For surgeons:

- less tiring;
- ease of execution;
- technical facility (easier tunnelling and reinjection)

Analysis of patient follow-up 3 months post-procedure confirms the performance and safety of the n.l.f. system kit associated with the NIL technique. Moreover, the quality and viability of the reinjected adipocytes are tested via the post-surgical control check performed 3 months post-procedure.

The fact that no adverse reaction (infection, contamination, foreign body granulomas) was observed is reassuring with regard to the aseptic status (sterile status maintained, biocompatibility) of the device.
The decanting system is used to facilitate separation from the residual liquid (sera-blood proportion).
The system is ideal for aspirating a volume greater than 100 ml and re-injecting more than 50 ml. Below this quantity, there is no gain in terms of time or quality of the result compared to the manual method.).
The n.l.f. System 2 kit should eliminate more liquid (as after centrifugation). Decantation in the n.l.f. System 1 kit is interesting but more time-consuming. The optimal decanting time is less than 20 minutes after the end of adipose tissue sampling time. The optimal indications are the unilateral corrections for one breast presenting with asymmetry (volume correction of the smallest breast) and the corrections of grade 2 and 3 tuberous breasts.

In conclusion, the n.l.f. System 1 kit satisfies all requirements in terms of anticipated performance and safety within a lipofilling procedure. The results obtained with this clinical investigation are conclusive and reassuring in terms of patient safety. Aseptic conditions with the n.l.f system kit outweigh the manual method as there is less handling before reinjection.

The protocol implemented (harvesting of adipose tissue, pressure applied, cannula model, purification of the adipose tissue by decanting) is therefore ideal and allows good-quality adipocytes to be harvested for reimplantation. Patient medical follow-up will be continued during the kit post-marketing period for up to 18 months after the procedure. This follow-up will be carried out by Doctor Denoël and will identify the very long-term adverse reactions.

DOCUMENT VALIDATION

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