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Supplementary appendix

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Liposuction versus conservative therapy for patients with lipoedema:
A randomised controlled multi-centre investigator-blinded clinical trial

Supplementary Appendix

Supplement to:

“Liposuction versus conservative therapy for patients with lipoedema: A randomised controlled multi-centre investigator-blinded clinical trial”

This appendix has been provided by the authors to give readers additional information about the work.

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Sponsor and Data Monitoring Committee (DMC)

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List of Sites and Investigators by Liposuction Technique

Sites using power assisted technique

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5. Professor Lukas Prantl, M.D., University Center for Plastic and Aesthetic, Hand and Reconstructive Surgery of the University of Regensburg, Caritas Hospital St. Josef, Regensburg, Germany
6. Zaher Jandali, M.D., Department of Plastic, Aesthetic, Reconstructive, and Hand Surgery, Protestant Hospital Oldenburg, Oldenburg, Germany
7. Boris Müller, M.D., Dermatology Practice Mühlthal, Nieder-Ramstadt, Germany
8. Diana Rajewski, M.D., Dermatology Practice Diana Rajewski, Cologne, Germany

Sites using the water-jet assisted technique

9. Kay-Hendrik Busch, M.D., Institute: Plastic, Reconstructive, and Aesthetic Surgery, Wald Hospital Bonn, Germany
10. Zia Taufiq, M.D., Clinic and Outpatient Clinic for Plastic Surgery, Cologne, Germany
11. Mojtaba Ghods, M.D., Department of Plastic, Aesthetic, and Reconstructive Microsurgery, Ernst von Bergmann Hospital, Bad Belzig, Germany

List of ethics committees which approved the trial

- Ethics Committee of the Hesse State Chambers of Physicians (corresponding Ethics Committee; reference number Az. 2019-1377-evBO)
- Ethics Committee of the Medical Association of North Rhine (reference number: 2019316)
- Ethics Committee of the Saxon State Chambers of Physicians (reference number: EK-BR-76/ 19-1)
- Ethics Committee of the Brandenburg State Chambers of Physicians (reference number: AS 117(bB)/ 2019)
- Medical Ethics Committee of the University of Oldenburg (reference number: 2020-009)
- Ethics Committee of the Baden-Württemberg State Chambers of Physicians (reference number: B-F-2019-075)

The ethics committees of the University of Regensburg and of the Bavarian Medical Association do not require an additional ethics vote, after the study protocol has been approved by other German ethics boards.

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Supplementary Methods

Categorisation of pre-specified adverse events

Category	(Preferred) Term of AE
Surgical site abscess	Abscess
	Abscess on limbs
	Boil
	Infected hematoma
Post-surgical decrease in haemoglobin	Postoperative anaemia
	Anaemia
	Low haemoglobin
	Iron deficiency anaemia (if occurred after 1 st liposuction)
Erysipelas	Erysipelas
	Skin infection
	Skin ulcer
	Localized infection
	Soft tissue inflammation
	Peripheral swelling
Seroma	Serom
Pulmonary embolism	Lung disease (with details: pulmonary artery thrombosis)
	Pulmonary embolism
Venous thrombosis	Thrombosis
	Postoperative thrombosis

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Table S1: Further body measurements and distribution across the sites (ITT)

	Liposuction (n=278)	Conservative therapy (n=132)
Further body measurements		
Ankle, right (cm)	26.2 (3.4)	26.5 (3.9)
Ankle, left (cm)	26.2 (3.4)	26.5 (3.9)
Calf, right (cm)	43.9 (5.3)	44.4 (5.2)
Calf, left (cm)	43.8 (4.9)	44.4 (6.4)
Knee, right (cm)	43.6 (5.6)	43.9 (5.2)
Knee, left (cm)	42.8 (5.3)	43.8 (6.4)
Groin, right (cm)	65.9 (9.0)	66.7 (9.1)
Groin, left (cm)	64.9 (9.1)	65.8 (9.2)
Upper arm, right (cm)	35.5 (5.0)	35.6 (5.1)
Forearm, right (cm)	27.8 (2.9)	28.0 (3.3)
Upper arm, left (cm)	35.7 (6.3)	36.0 (7.4)
Forearm, left (cm)	27.7 (2.9)	27.8 (3.3)
Skin surface		
No abnormalities	1 (0.4%)	0 (0%)
Smooth skin surface with uniformly thickened, homogeneous	90 (33%)	41 (31%)
Uneven, predominantly undulating skin surface, nodules	108 (39%)	53 (40%)
Marked increase in circumference with overhanging tissue	77 (28%)	38 (29%)
Centres (Patients (%); surgeons)		
Potsdam	86 (31%); n _{surgeons} = 1	43 (33%)
Duesseldorf	62 (22%); n _{surgeons} = 8	32 (24%)
Koeln-1	35 (13%); n _{surgeons} = 1	16 (12%)
Bonn	28 (10%); n _{surgeons} = 4	15 (11%)
Koeln-2	22 (8%); n _{surgeons} = 2	11 (8%)
Darmstadt	17 (6%); n _{surgeons} = 2	6 (5%)
Freiburg	12 (4%); n _{surgeons} = 1	6 (5%)
Oldenburg	6 (2%); n _{surgeons} = 2	1 (1%)
Regensburg	4 (1%); n _{surgeons} = 1	2 (2%)
Bad Soden	3 (1%); n _{surgeons} = 2	0 (0%)
Muehlthal	3 (1%); n _{surgeons} = 1	0 (0%)
Data are n (%), median (IQR) or mean (SD), collected at randomisation. Taking the leg measurements was optional; the measurements were missing in less than 2% of cases.		

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Table S2: Relevant Pain Reduction

	Liposuction % (n/N)	Conservative therapy % (n/N)	Odds ratio (95% CI), liposuction to conservative therapy p-value ^{b, c}
Overall	68.3 (190/278)	7.6 (10/132)	26.2 (13.1 to 52.5) < 0.0001
Stage I	67.8 (61/90)	9.5 (4/42)	20.0 (6.5 to 61.3) < 0.0001
Stage II	72.6 (69/95)	6.7 (3/45)	37.2 (10.6 to 130.3) < 0.0001
Stage III	64.5 (60/93)	6.7 (3/45)	25.5 (7.3 to 88.5) < 0.0001

Relevant pain reduction (primary endpoint) 12 months of conservative therapy after randomisation or last liposuction in the Intention-to-treat population. Primary end point defined as a reduction of 'average pain intensity during the last 4 weeks' by ≥ 2 points, German pain questionnaire.¹

^a A missing primary endpoint was considered a failure, conservative therapy: 12/132, liposuction: 41/278

^b Cochran-Mantel-Haenszel² test stratified by stage

^c P-value per stage from Fisher's exact test

Abbreviations: n: number of patients with relevant improvement, N: total number in the group, CI: confidence interval

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Table S3: Relevant improvement in patient-reported outcomes

	Liposuction % (n/N)	Conservative therapy, % (n/N)	Odds ratio (95% CI) (liposuction to conservative therapy)	p-value ^{a, b}
SF-36, physical component ³ (relevant improvement: ≥ 6 points)				
All stages	73.7 (171/232)	13.4 (16/119)	18.4 (10.0 to 33.8)	< 0.0001
Stage I	72.9 (51/70)	12.8 (5/39)	18.3 (6.2 to 53.6)	< 0.0001
Stage II	68.2 (58/85)	11.6 (5/43)	16.3 (5.8 to 46.1)	< 0.0001
Stage III	80.5 (62/77)	16.2 (6/37)	21.4 (7.5 to 60.4)	< 0.0001
SF-36, mental component (relevant improvement: ≥ 6 points)				
All stages	44.8 (104/232)	23.5 (28/119)	2.6 (1.6 to 4.3)	0.0002
Stage I	41.4 (29/70)	25.6 (10/39)	2.0 (0.9 to 4.9)	0.1441
Stage II	44.7 (38/85)	18.6 (8/43)	3.5 (1.5 to 8.5)	0.0037
Stage III	48.1 (37/77)	27.0 (10/37)	2.5 (1.1 to 5.9)	0.0423
DLQI ⁴ (relevant improvement: ≥ 4 points)				
All stages	49.6 (117/236)	14.2 (17/120)	6.0 (3.4 to 10.7)	< 0.0001
Stage I	50.7 (35/69)	15.4 (6/39)	5.7 (2.1 to 15.2)	0.0004
Stage II	43.7 (38/87)	11.6 (5/43)	5.9 (2.1 to 16.4)	0.0003
Stage III	55.0 (44/80)	15.8 (6/38)	6.5 (2.5 to 17.3)	0.0001
PHQ9 ⁵ (relevant improvement: ≥ 5 points)				
All stages	36.7 (87/237)	5.0 (6/120)	11.0 (4.6 to 26.1)	< 0.0001
Stage I	35.7 (25/70)	5.1 (2/39)	10.3 (2.3 to 46.7)	0.0004
Stage II	35.6 (31/87)	4.7 (2/43)	11.3 (2.6 to 50.1)	0.0001
Stage III	38.8 (31/80)	5.3 (2/38)	11.4 (2.6 to 50.7)	0.0001
Haematoma proneness (assessed using the modified questionnaire of Schmeller ⁶ , relevant improvement: ≥ 2 points)				
All stages	78.1 (185/237)	9.2 (11/120)	35.3 (17.6 to 70.7)	< 0.0001
Stage I	77.1 (54/70)	10.3 (4/39)	29.5 (9.1 to 95.7)	< 0.0001
Stage II	78.2 (68/87)	4.7 (2/43)	73.4 (16.2 to 331.3)	< 0.0001
Stage III	78.8 (63/80)	13.2 (5/38)	24.5 (8.3 to 72.2)	< 0.0001
WHOQOL-BREF rating quality of life (G1) ⁷ (relevant improvement ≥ 20%)				
All stages	58.6 (139/237)	14.2 (17/120)	8.3 (4.7 to 14.7)	< 0.0001
Stage I	55.7 (39/70)	12.8 (5/39)	8.6 (3.0 to 24.5)	< 0.0001
Stage II	52.9 (46/87)	18.6 (8/43)	4.9 (2.0 to 11.8)	0.0003
Stage III	67.5 (54/80)	10.5 (4/38)	17.7 (5.7 to 55.0)	< 0.0001
WHOQOL-BREF content with quality of life (G4) (relevant improvement ≥ 20%)				
All stages	65.0 (154/237)	20 (24/120)	7.3 (4.3 to 12.3)	< 0.0001
Stage I	65.7 (46/70)	15.4 (6/39)	10.5 (3.9 to 28.7)	< 0.0001
Stage II	60.9 (53/87)	25.6 (11/43)	4.5 (2.0 to 10.2)	0.0002
Stage III	68.8 (55/80)	18.4 (7/38)	9.7 (3.8 to 25.1)	< 0.0001
WHOQOL-BREF physical health (Domain 1) (relevant improvement ≥ 20%)				
All stages	49.4 (117/237)	1.7 (2/120)	63.9 (14.7 to 278.1)	< 0.0001
Stage I	52.9 (37/70)	5.1 (2/39)	20.7 (4.6 to 92.8)	< 0.0001
Stage II	44.8 (39/87)	0.0 (0/43)	70.9 (4.2 to 1187.8) ^c	< 0.0001
Stage III	51.2 (41/80)	0.0 (0/38)	80.9 (4.8 to 1362.1) ^c	< 0.0001
WHOQOL-BREF psychological health (Domain 2) (relevant improvement ≥ 20%)				
All stages	31.4 (74/236)	1.7 (2/120)	26.8 (6.4 to 111.8)	< 0.0001
Stage I	32.9 (23/70)	0.0 (0/39)	39.1 (2.3 to 664.2) ^c	< 0.0001

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Stage II	29.1 (25/86)	0.0 (0/43)	36.1 (2.1 to 608.7) ^c	< 0.0001
Stage III	32.5 (26/80)	5.3 (2/38)	8.7 (1.9 to 38.8)	0.0009
WHOQOL-BREF social relationships (Domain 3) (relevant improvement ≥ 20%)				
All stages	16.9 (40/237)	5.9 (7/119)	3.2 (1.4 to 7.5)	0.0069
Stage I	12.9 (9/70)	10.3 (4/39)	1.3 (0.4 to 4.5)	0.7675
Stage II	17.2 (15/87)	0.0 (0/42)	18.2 (1.1 to 311.5) ^c	0.0025
Stage III	20.0 (16/80)	7.9 (3/38)	2.9 (0.8 to 10.7)	0.1135
WHOQOL-BREF environment (Domain 4) (relevant improvement ≥ 20%)				
All stages	13.1 (31/237)	1.7 (2/120)	9.0 (2.1 to 39.1)	0.0010
Stage I	11.4 (8/70)	0.0 (0/39)	10.7 (0.6 to 191.4) ^c	0.0486
Stage II	10.3 (9/87)	0.0 (0/43)	10.5 (0.6 to 185.3) ^c	0.0294
Stage III	17.5 (14/80)	5.3 (2/38)	3.8 (0.8 to 17.7)	0.0873
LEFS ^b (relevant improvement: ≥ 4 points)				
All stages	70.0 (166/237)	10.0 (12/120)	21.0 (10.8 to 40.7)	< 0.0001
Stage I	62.9 (44/70)	7.7 (3/39)	20.3 (5.7 to 72.6)	< 0.0001
Stage II	64.4 (56/87)	11.6 (5/43)	13.7 (4.9 to 38.5)	< 0.0001
Stage III	82.5 (66/80)	10.5 (4/38)	40.1 (12.2 to 131.2)	< 0.0001
General impairment of the legs (assessed using the modified questionnaire of Schmeller ⁶ , relevant improvement: ≥ 2 points)				
All stages	80.2 (190/237)	2.5 (3/119)	196.0 (52.7 to 729.7)	< 0.0001
Stage I	88.6 (62/70)	5.1 (2/39)	143.4 (28.9 to 711.6)	< 0.0001
Stage II	78.2 (68/87)	0.0 (0/42)	18.2 (1.1 to 311.5) ^c	< 0.0001
Stage III	75.0 (60/80)	2.6 (1/38)	111.0 (14.3 to 862.0)	< 0.0001
Additional end point, relevant improvement	Liposuction % (n/N)	Conservative therapy % (n/N)	Odds ratio (95% CI) (liposuction to conservative therapy)	
Weight (relevant improvement ≥ 10%)				
All stages	17.7 (42/237)	3.3 (4/120)	6.2 (2.2 to 17.8)	0.0003
Stage I	14.3 (10/70)	5.1 (2/39)	3.1 (0.6 to 14.9)	0.2058
Stage II	18.4 (16/87)	2.3 (1/43)	9.5 (1.2 to 74.0)	0.0112
Stage III	20.0 (16/80)	2.6 (1/38)	9.3 (1.2 to 72.6)	0.0112

Results for secondary and additional end points: relevant improvement 12 months of conservative therapy after randomisation or last liposuction (ITT population, as randomised).

^a Odds ratio with 95% confidence interval and p-value according to Cochran-Mantel-Haenszel² test stratified by stage

^b P-value per stage derived from exact Fisher's test

^c Odds ratios with confidence intervals were computed using the Haldane–Anscombe correction,⁹ whereby 0.5 was added to each cell in contingency tables containing empty cells.

Abbreviations: n: number of patients with relevant improvement, N: total number in the group, CI confidence interval, SF-36: 36-Item Short Form Health Survey, DLQI: Dermatology Life Quality Index, PHQ9: Patient Health Questionnaire-9, LEFS: Lower Extremity Functional Scale, WHOQOL-BREF: World Health Organization Quality of Life - Brief Version

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Table S4: Adverse events prior to randomisation (all patients)

	System organ class	Stage I	Stage II	Stage III	All stages
Serious	Ear and labyrinth disorders	0	0	1 (0)	1 (0)
	Gastrointestinal disorders	0	3 (0)	0	3 (0)
	Hepatobiliary disorders	1 (0)	0	0	1 (0)
	Infections and infestations	0	1 (0)	1 (0)	2 (0)
	Injuries, poisoning, and procedural complications	1 (0)	1 (0)	0	2 (0)
	Musculoskeletal and connective tissue disorders	0	2 (1)	1 (0)	3 (1)
	Nervous system disorders	0	1 (0)	3 (0)	4 (0)
	Renal and urinary disorders	0	0	1 (0)	1 (0)
	Surgical and medical procedures	0	1 (0)	0	1 (0)
	Vascular disorders	1 (0)	0	0	1 (0)
	Total	3 (0)	9 (0)	7 (0)	19 (0)
Non-serious	Cardiac disorders	0	0	1 (0)	1 (0)
	Eye disorders	0	2 (0)	0	2 (0)
	General disorders and administration site conditions	0	1 (0)	0	1 (0)
	Immune system disorders	0	1 (0)	0	1 (0)
	Infections and infestations	7 (0)	7 (0)	7 (0)	21
	Injuries, poisoning, and procedural complications	1 (0)	1 (0)	1 (0)	3 (0)
	Musculoskeletal and connective tissue disorders	0	1 (0)	2 (0)	3 (0)
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0)	0	0	1 (0)
	Nervous system disorders	0	3 (0)	0	3 (0)
	Pregnancy, puerperium and perinatal conditions	2 (0)	1 (0)	1 (0)	4 (0)
	Renal and urinary disorders	0	1 (0)	0	1 (0)
	Reproductive system and breast disorders	0	0	1 (0)	1 (0)
	Respiratory, thoracic and mediastinal disorders	0	1 (0)	0	1 (0)
	Skin and subcutaneous tissue disorders	0	1 (1)	0	1 (1)
	Surgical and medical procedures	1 (0)	1 (0)	0	2 (0)
	Vascular disorders	0	1 (0)	1 (0)	2 (0)
	Total	12 (0)	22 (1)	14 (0)	48 (1)
All adverse events		15 (0)	31 (2)	21 (0)	67 (2)

Absolute frequency of serious and non-serious adverse events prior to randomisation; safety population, all patients, n=450 (number of events related to the treatment is given in brackets)

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Table S5: Adverse events after randomisation or liposuction (safety population, as treated)

	Preferred term	Liposuction All stages (n=265)	Stage I (n=85)	Stage II (n=92)	Stage III (n=88)	Conservative therapy All stages (n=145)	Stage I (n=47)	Stage II (n=48)	Stage II (n=50)
Serious	Anaemia	3 (3)	2 (2)	1 (1)	0	0	0	0	0
	Abdominal discomfort	1 (0)	1 (0)	0	0	0	0	0	0
	Abscess	2 (1)	1 (1)	0	1 (0)	0	0	0	0
	Acinic cell carcinoma of salivary glands	1 (0)	1 (0)	0	0	0	0	0	0
	Adnexal torsion	0	0	0	0	1 (0)	0	1 (0)	0
	Benign adenoma	1 (0)	1 (0)	0	0	0	0	0	0
	Boil	1 (1)	1 (1)	0	0	0	0	0	0
	Colitis	1 (0)	1 (0)	0	0	0	0	0	0
	Diarrhoea	1 (0)	0	1 (0)	0	0	0	0	0
	Disc protrusion	0	0	0	0	1 (0)	0	0	1 (0)
	Dizziness	1 (0)	0	0	1 (0)	0	0	0	0
	Dysmenorrhea	1 (0)	0	0	1 (0)	0	0	0	0
	Erysipelas	2 (1)	0	0	2 (1)	0	0	0	0
	Implantation of a medical device	0	0	0	0	1 (0)	0	0	1 (0)
	Iron deficiency anaemia	1 (1)	1 (1)	0	0	0	0	0	0
	Ligament rupture	1 (0)	1 (0)	0	0	0	0	0	0
	Mammary gland abscess	0	0	0	0	1 (0)	1 (0)	0	0
	Multiple sclerosis	0	0	0	0	1 (0)	0	1 (0)	0
	Myocardial infarction	0	0	0	0	1 (0)	0	0	1 (0)
	Pain	1 (1)	0	1 (1)	0	0	0	0	0
	Peripheral swelling	1 (1)	0	0	1 (1)	0	0	0	0
	Respiratory insufficiency	1 (0)	1 (0)	0	0	0	0	0	0
	Vertigo	1 (1)	0	1 (1)	0	0	0	0	0
	Total	21 (10)	11 (5)	4 (3)	6 (2)	6 (0)	1 (0)	2 (0)	3 (0)
Non-serious	Abdominal discomfort	2 (0)	2 (0)	0	0	0	0	0	0
	Abdominal hernia	1 (0)	0	0	1 (0)	0	0	0	0
	Abscess	1 (1)	0	0	1 (1)	0	0	0	0
	Anaemia/postoperative anaemia	14 (12)	2 (2)	6 (6)	6 (4)	0	0	0	0
	Appendicitis	0	0	0	0	1 (0)	1 (0)	0	0
	Arrhythmia	0	0	0	0	1 (0)	0	1 (0)	0
	Arthralgia	1 (0)	0	1 (0)	0	0	0	0	0
	Arthropod bite	1 (0)	0	0	1 (0)	0	0	0	0
	Bankart lesion	1 (0)	0	0	1 (0)	0	0	0	0
	Benign adenoma	1 (0)	0	0	1 (0)	0	0	0	0
	Bleeding	1 (0)	1 (0)	0	0	0	0	0	0
	Bronchitis	3 (0)	0	3 (0)	0	0	0	0	0
	Contusion	1 (0)	1 (0)	0	0	0	0	0	0
	Coronavirus infection	60 (0)	26 (0)	18 (0)	16 (0)	10 (0)	0	8 (0)	2 (0)
	Craniofacial fracture	1 (0)	1 (0)	0	0	0	0	0	0
	Cyst removal	2 (1)	1 (1)	1 (0)	0	0	0	0	0
	Depression	2 (0)	0	2 (0)	0	0	0	0	0
	Diabetes mellitus	1 (0)	0	0	1 (0)	0	0	0	0

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Diarrhoea	1 (0)	0	1 (0)	0	0	0	0	0
Disc protrusion	1 (0)	1 (0)	0	0	0	0	0	0
Dysmenorrhea	0	0	0	0	1 (0)	1 (0)	0	0
Elevated C-reactive protein	1 (1)	0	0	1 (1)	0	0	0	0
Endometrial hyperplasia	1 (0)	0	1 (0)	0	0	0	0	0
Endometriosis	0	0	0	0	2	1 (0)	1 (0)	0
Erysipelas	9 (8)	0	7 (6)	2 (2)	0	0	0	0
Eyelid surgery	1 (0)	0	0	1 (0)	0	0	0	0
Extremity surgery (hand)	0	0	0	0	1 (0)	0	0	1 (0)
Fever	1 (0)	0	1 (0)	0	0	0	0	0
Fever after surgery	1 (1)	0	1 (1)	0	0	0	0	0
Fibroadenoma of the mammary gland	1 (0)	0	0	1 (0)	0	0	0	0
Foot fracture	1 (0)	1 (0)	0	0	1 (0)	0	1 (0)	0
Haemangioma of the liver	1 (0)	0	0	1 (0)	0	0	0	0
Hypercalcemia	1 (0)	0	0	1 (0)	0	0	0	0
Hypercholesterolemia	1 (0)	1 (0)	0	0	0	0	0	0
Infection	3 (0)	1 (0)	2 (0)	0	0	0	0	0
Infected hematoma	1 (1)	0	0	1 (1)	0	0	0	0
Infectious thyroiditis	1 (0)	0	0	1 (0)	0	0	0	0
Inflammation of the upper respiratory tract	1 (0)	1 (0)	0	0	0	0	0	0
Influenza	4 (0)	1 (0)	2 (0)	1 (0)	1 (0)	0	0	1 (0)
Iron deficiency	0	0	0	0	1 (0)	1 (0)	0	0
Iron deficiency anaemia	1 (0)	0	1 (0)	0	0	0	0	0
Joint injury	1 (0)	1 (0)	0	0	0	0	0	0
Left bundle branch block	1 (0)	0	0	1 (0)	0	0	0	0
Ligament strain	1 (0)	0	1 (0)	0	0	0	0	0
Lipoedema	2 (1)	1 (1)	1 (0)	0	0	0	0	0
Liver cyst	1 (0)	0	0	1 (0)	0	0	0	0
Localized infection	1 (1)	0	0	1 (1)	0	0	0	0
Low blood pressure	1 (0)	0	1 (0)	0	0	0	0	0
Low haemoglobin	1 (1)	0	0	1 (1)	0	0	0	0
Lung disease	1 (0)	0	0	1 (0)	0	0	0	0
Meniscus injury	0	0	0	0	1 (0)	0	0	1 (0)
Mental disorder	0	0	0	0	1 (0)	1 (0)	0	0
Nasopharyngitis	3 (0)	2 (0)	0	1 (0)	1 (0)	1 (0)	0	0
Obstructive sleep apnoea syndrome	1 (0)	0	1 (0)	0	0	0	0	0
Osteochondrosis	1 (0)	0	0	1 (0)	0	0	0	0
Ovarian cyst	1 (0)	0	1 (0)	0	0	0	0	0
Pain during surgery	1 (1)	0	0	1 (1)	0	0	0	0
Paronychia	1 (0)	0	0	1 (0)	0	0	0	0
Patella fracture	1 (0)	1 (0)	0	0	0	0	0	0
Peripheral venous disease	0	0	0	0	1 (0)	0	0	1 (0)
Pregnancy	4 (0)	1 (0)	1 (0)	2 (0)	3	2 (0)	0	1 (0)
Pulmonary embolism	0	0	0	0	1 (0)	0	0	1 (0)
Retinal detachment	0	0	0	0	1 (0)	0	1 (0)	0
Seborrheic keratosis	1 (0)	0	1 (0)	0	0	0	0	0
Seroma	11 (11) ^a	3 (3)	4 (4)	4 (4)	0	0	0	0
Sinusitis	1 (0)	0	1 (0)	0	0	0	0	0

Liposuction versus conservative therapy for patients with lipoedema:
A randomised controlled multi-centre investigator-blinded clinical trial

	Skin infection	1 (1)	1 (1)	0	0	0	0	0	0
	Skin ulcer	1 (1)	0	1 (1)	0	0	0	0	0
	Soft tissue inflammation	1 (1)	0	0	1 (1)	0	0	0	0
	Tachycardia	1 (0)	1 (0)	0	0	0	0	0	0
	Thrombosis/postoperative thrombosis	3 (3)	1 (1)	0	2 (2)	0	0	0	0
	Tinea pedis	1 (0)	0	1 (0)	0	0	0	0	0
	Tonsillitis	2 (0)	0	1 (0)	1 (0)	0	0	0	0
	Urinary tract infection	1 (0)	0	1 (0)	0	0	0	0	0
	Urticaria	1 (0)	0	1 (0)	0	0	0	0	0
	Total	173 (46)	52 (9)	64 (18)	57 (19)	28 (0)	8 (0)	12 (0)	8 (0)
All adverse events		194 (56)	63 (14)	68 (21)	63 (21)	34 (0)	9 (0)	14 (0)	11 (0)

Absolute frequency of serious and non-serious adverse events after first liposuction in patients with liposuction (safety population, n=265) and after randomisation in patients with conservative therapy (without liposuction; n=145); Number of events with possible causal relation to the intervention (liposuction or conservative therapy, respectively) are given in brackets). Nota bene: Between randomisation and the first liposuction 23 adverse events (one of which was serious) occurred in patients who underwent liposuction.

Supplementary Analyses: Results from Partially Nested Logistic Regression (Fixed effects)

1. Primary Endpoint

Relevant pain reduction ≥ 2 points (primary endpoint) (12M)

Predictor	Odds Ratio	Lower limit (95%-CI)	Upper limit (95%-CI)	p-value
(Intercept)	0.086	0.041	0.179	0.000
liposuction group	42.912	16.861	109.213	0.000
stage II	1.074	0.570	2.025	0.824
stage III	0.807	0.434	1.500	0.498

Variance of surgeon effect (τ^2): 1.2432

ICC for partially nested group (liposuction group): 0.2742

Explanation:

Reference categories are the control group or stage I, respectively.

The odds ratio for the relevant reduction in pain in the liposuction group compared to the conservative therapy group is 42.9 95%-CI (16.9 to 109.2); With the lower border of the confidence interval being 16.9 this is exceeding the anticipated OR of 6.

In a figurative sense, this means, that the chance to experience a relevant reduction is about 43 times higher in the liposuction group than in the control.

So, when partial nesting is taken into account, the results become even more clear than in the previously defined (more conservative) primary analysis according to the Cochran-Mantel-Haenszel test, stratified by stage (26.2; 95%- CI 13.1 to 52.5, see Figure 2a).

2. SF-36, physical component

Relevant improvement of ≥ 6 points in physical component at 12 months

Predictor	Odds Ratio	Lower limit (95%-CI)	Upper limit (95%-CI)	p-value
(Intercept)	0.145	0.075	0.280	0.000
liposuction group	25.984	12.203	55.327	0.000
stage II	0.840	0.442	1.595	0.594
stage III	1.444	0.738	2.826	0.284

Variance of surgeon effect (τ^2): 0.2828

ICC for partially nested group (liposuction group): 0.0792

3. SF-36, mental component

Relevant improvement of ≥ 6 points in mental component at 12 months

Predictor	Odds Ratio	Lower limit (95%-CI)	Upper limit (95%-CI)	p-value
(Intercept)	0.289	0.168	0.497	0.000
liposuction group	3.019	1.705	5.348	0.000
stage II	0.996	0.568	1.747	0.989
stage III	1.218	0.689	2.152	0.498

Variance of surgeon effect (τ^2): 0.2305

ICC for partially nested group (liposuction group): 0.0655

4. DLQI

Relevant improvement of ≥ 4 points in DLQI at 12 months

Predictor	Odds Ratio	Lower limit (95%-CI)	Upper limit (95%-CI)	p-value
(Intercept)	0.177	0.095	0.328	0.000
liposuction group	6.911	3.609	13.234	0.000
stage II	0.741	0.410	1.341	0.322
stage III	1.095	0.605	1.982	0.765

Variance of surgeon effect (τ^2): 0.2789

ICC for partially nested group (liposuction group): 0.0781

5. PHQ-9

Relevant improvement of ≥ 5 points in PHQ9 at 12 months

Predictor	Odds Ratio	Lower limit (95%-CI)	Upper limit (95%-CI)	p-value
(Intercept)	0.051	0.021	0.126	0.000
liposuction group	11.412	4.679	27.833	0.000
stage II	0.987	0.527	1.849	0.967
stage III	1.119	0.593	2.112	0.729

Variance of surgeon effect (τ^2): 0.0255

ICC for partially nested group (liposuction group): 0.0077

6. Haematoma proneness

Relevant improvement of ≥ 2 points in haematoma proneness at 12 months

Predictor	Odds Ratio	Lower limit (95%-CI)	Upper limit (95%-CI)	p-value
(Intercept)	0.101	0.048	0.212	0.000
liposuction group	42.282	19.536	91.511	0.000
stage II	0.916	0.461	1.821	0.803
stage III	1.105	0.542	2.253	0.783

Variance of surgeon effect (τ^2): 0.2002

ICC for partially nested group (liposuction group): 0.0574

7. WHOQOL-BREF rating quality of life (G1)

Relevant improvement of ≥ 20 % in rating quality of life (G1) at 12 months

Predictor	Odds Ratio	Lower limit (95%-CI)	Upper limit (95%-CI)	p-value
(Intercept)	0.146	0.078	0.272	0.000
liposuction group	8.639	4.854	15.375	0.000
stage II	1.000	0.566	1.768	0.999
stage III	1.429	0.798	2.559	0.230

Variance of surgeon effect (τ^2): 0

ICC for partially nested group (liposuction group): 0

8. WHOQOL-BREF content with quality of life (G4)

Relevant improvement of ≥ 20 % in content with quality of life (G4) at 12 months

Predictor	Odds Ratio	Lower limit (95%-CI)	Upper limit (95%-CI)	p-value
(Intercept)	0.236	0.134	0.415	0.000
liposuction group	7.413	4.402	12.484	0.000
stage II	1.016	0.579	1.783	0.957
stage III	1.171	0.658	2.084	0.592

Variance of surgeon effect (τ^2): 0

ICC for partially nested group (liposuction group): 0

9. WHOQOL-BREF physical health (Domain 1)

Relevant improvement of ≥ 20 % in physical health (Domain 1) at 12 months

Predictor	Odds Ratio	Lower limit (95%-CI)	Upper limit (95%-CI)	p-value
(Intercept)	0.021	0.005	0.088	0.000
liposuction group	66.488	15.678	281.967	0.000
stage II	0.636	0.336	1.205	0.165
stage III	0.819	0.429	1.561	0.544

Variance of surgeon effect (τ^2): 0.0995

ICC for partially nested group (liposuction group): 0.0293

10. WHOQOL-BREF psychological health (Domain 2)

Relevant improvement of ≥ 20 % in psychological health (Domain 2) at 12 months

Predictor	Odds Ratio	Lower limit (95%-CI)	Upper limit (95%-CI)	p-value
(Intercept)	0.018	0.004	0.077	0.000
liposuction group	30.528	7.169	130.003	0.000
stage II	0.793	0.391	1.607	0.520
stage III	1.057	0.527	2.122	0.875

Variance of surgeon effect (τ^2): 0.2177

ICC for partially nested group (liposuction group): 0.0621

11. WHOQOL-BREF social relationships (Domain 3)

Relevant improvement of ≥ 20 % in social relationships (Domain 3) at 12 months

Predictor	Odds Ratio	Lower limit (95%-CI)	Upper limit (95%-CI)	p-value
(Intercept)	0.059	0.024	0.145	0.000
liposuction group	3.299	1.365	7.972	0.008
stage II	0.905	0.400	2.046	0.810
stage III	1.320	0.602	2.894	0.489

Variance of surgeon effect (τ^2): 0.2166

ICC for partially nested group (liposuction group): 0.0618

12. WHOQOL-BREF environment (Domain 4)

Relevant improvement of ≥ 20 % in environment (Domain 4) at 12 months

Predictor	Odds Ratio	Lower limit (95%-CI)	Upper limit (95%-CI)	p-value
(Intercept)	0.013	0.003	0.062	0.000
liposuction group	8.894	2.067	38.269	0.003
stage II	0.902	0.330	2.466	0.841
stage III	1.933	0.779	4.802	0.155

Variance of surgeon effect (τ^2): 0.0023

ICC for partially nested group (liposuction group): 7e-04

13. LEFS

Relevant improvement of ≥ 4 points in LEFS at 12 months

Predictor	Odds Ratio	Lower limit (95%-CI)	Upper limit (95%-CI)	p-value
(Intercept)	0.076	0.037	0.159	0.000
liposuction group	22.532	11.494	44.170	0.000
stage II	1.139	0.618	2.099	0.677
stage III	2.365	1.227	4.562	0.010

Variance of surgeon effect (τ^2): 0

ICC for partially nested group (liposuction group): 0

14. General impairment of the legs

Relevant improvement of ≥ 2 points in General impairment of the legs at 12 months

Predictor	Odds Ratio	Lower limit (95%-CI)	Upper limit (95%-CI)	p-value
(Intercept)	0.044	0.013	0.146	0.000
liposuction group	192.149	54.368	679.095	0.000
stage II	0.414	0.176	0.977	0.044
stage III	0.373	0.156	0.889	0.026

Variance of surgeon effect (τ^2): 0.0191

ICC for partially nested group (liposuction group): 0.0058

15. Body weight

Relevant improvement of ≥ 10 % in weight at 12 months

Predictor	Odds Ratio	Lower limit (95%-CI)	Upper limit (95%-CI)	p-value
(Intercept)	0.030	0.010	0.091	0.000
liposuction group	6.213	2.171	17.778	0.001
stage II	1.182	0.530	2.639	0.683
stage III	1.314	0.587	2.943	0.507

Variance of surgeon effect (τ^2): 0

ICC for partially nested group (liposuction group): 0

Supplementary Analyses: Results from Partially Nested Mixed Model for Repeated Measures

1. Pain intensity

MMRM: Marginal means at 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	2.34	0.15	379.42	2.05	2.63
conservative group	6.38	0.20	368.50	5.98	6.77

MMRM: Group comparison at 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	-4.04	0.23	354.73	-4.49	-3.59	<0.001

MMRM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	-3.63	0.15	379.42	-3.92	-3.33
conservative group	0.41	0.20	368.50	0.02	0.81

MMRM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	-4.04	0.23	354.73	-4.49	-3.59	<0.001

LMM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	-3.77	0.20	13.77	-4.20	-3.34
conservative group	0.51	0.21	382.77	0.09	0.93

LMM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	-4.29	0.28	35.07	-4.86	-3.71	<0.001

=== Variance Components ===

Variance surgeon (τ^2_{surgeon}): 0.238

Variance patient (τ^2_{patient}): 2.546

Residual variance (σ^2): 1.6695

=== Intraclass Correlation Coefficients (ICC) ===

ICC surgeon (only liposuction group): 0.0534

ICC patient (liposuction group): 0.5717

ICC patient (conservative group): 0.604

2. SF-36 mental component

MMRM: Marginal means at 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	46.69	0.87	386.07	44.97	48.41
conservative group	40.33	1.19	372.88	37.99	42.67

MMRM: Group comparison at 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	6.35	1.35	359.20	3.71	9.00	<0.001

MMRM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	5.86	0.87	386.07	4.13	7.58
conservative group	-0.50	1.19	372.88	-2.84	1.84

MMRM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	6.35	1.35	359.20	3.71	9.00	<0.001

LMM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	5.85	0.94	9.44	3.74	7.95
conservative group	-0.51	1.24	208.91	-2.94	1.92

LMM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	6.36	1.50	17.98	3.20	9.51	<0.001

=== Variance Components ===

Variance surgeon (τ^2_{surgeon}): 0

Variance patient (τ^2_{patient}): 96.9442

Residual variance (σ^2): 43.5622

=== Intraclass Correlation Coefficients (ICC) ===

ICC surgeon (only liposuction group): 0

ICC patient (liposuction group): 0.69

ICC patient (conservative group): 0.69

3. SF-36 physical component

MMRM: Marginal means at 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	49.10	0.52	378.95	48.08	50.12
conservative group	36.94	0.71	366.01	35.55	38.33

MMRM: Group comparison at 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	12.16	0.80	351.30	10.59	13.73	<0.001

MMRM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	10.51	0.52	378.95	9.49	11.54
conservative group	-1.65	0.71	366.01	-3.04	-0.25

MMRM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	12.16	0.80	351.30	10.59	13.73	<0.001

LMM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	10.97	0.73	14.16	9.41	12.54
conservative group	-1.77	0.74	380.97	-3.23	-0.31

LMM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	12.74	1.00	35.03	10.70	14.78	<0.001

=== Variance Components ===

Variance surgeon (τ^2_{surgeon}): 3.8221

Variance patient (τ^2_{patient}): 31.7039

Residual variance (σ^2): 17.9235

=== Intraclass Correlation Coefficients (ICC) ===

ICC surgeon (only liposuction group): 0.0715

ICC patient (liposuction group): 0.5932

ICC patient (conservative group): 0.6388

4. DLQI total score

MMRM: Marginal means at 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	3.45	0.36	377.68	2.74	4.16
conservative group	9.18	0.49	366.83	8.21	10.16

MMRM: Group comparison at 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	-5.73	0.56	356.55	-6.83	-4.64	<0.001

MMRM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	-5.48	0.36	377.68	-6.20	-4.77
conservative group	0.25	0.49	366.83	-0.72	1.22

MMRM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	-5.73	0.56	356.55	-6.83	-4.64	<0.001

LMM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	-5.75	0.51	13.72	-6.84	-4.66
conservative group	0.50	0.52	366.72	-0.53	1.52

LMM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	-6.25	0.70	34.14	-7.67	-4.83	<0.001

=== Variance Components ===

Variance surgeon (τ^2_{surgeon}): 1.7417

Variance patient (τ^2_{patient}): 16.6519

Residual variance (σ^2): 7.7693

=== Intraclass Correlation Coefficients (ICC) ===

ICC surgeon (only liposuction group): 0.0666

ICC patient (liposuction group): 0.6365

ICC patient (conservative group): 0.6819

5. PHQ9 total score

MMRM: Marginal means at 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	5.28	0.32	393.89	4.66	5.90
conservative group	8.90	0.43	380.22	8.06	9.75

MMRM: Group comparison at 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	-3.62	0.49	364.29	-4.58	-2.66	<0.001

MMRM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	-3.76	0.32	393.89	-4.39	-3.14
conservative group	-0.14	0.43	380.22	-0.98	0.70

MMRM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	-3.62	0.49	364.29	-4.58	-2.66	<0.001

LMM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	-3.76	0.33	9.31	-4.51	-3.02
conservative group	-0.15	0.43	210.49	-1.01	0.70

LMM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	-3.61	0.53	17.54	-4.72	-2.51	<0.001

=== Variance Components ===

Variance surgeon (τ^2_{surgeon}): 0

Variance patient (τ^2_{patient}): 13.1567

Residual variance (σ^2): 4.3153

=== Intraclass Correlation Coefficients (ICC) ===

ICC surgeon (only liposuction group): 0

ICC patient (liposuction group): 0.753

ICC patient (conservative group): 0.753

6. Haematoma proneness

MMRM: Marginal means at 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	3.82	0.19	359.90	3.45	4.19
conservative group	8.47	0.25	349.63	7.97	8.97

MMRM: Group comparison at 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	-4.65	0.29	337.50	-5.21	-4.08	<0.001

MMRM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	-4.46	0.19	359.90	-4.82	-4.09
conservative group	0.19	0.25	349.63	-0.31	0.69

MMRM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	-4.65	0.29	337.50	-5.21	-4.08	<0.001

LMM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	-4.66	0.28	15.27	-5.26	-4.06
conservative group	0.25	0.27	399.68	-0.27	0.77

LMM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	-4.91	0.37	36.58	-5.66	-4.15	<0.001

=== Variance Components ===

Variance surgeon (τ^2_{surgeon}): 0.686

Variance patient (τ^2_{patient}): 4.1415

Residual variance (σ^2): 2.1416

=== Intraclass Correlation Coefficients (ICC) ===

ICC surgeon (only liposuction group): 0.0984

ICC patient (liposuction group): 0.5943

ICC patient (conservative group): 0.6592

7. WHOQOL-BREF rating quality of life (G1)

MMRM: Marginal means at 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	72.13	1.31	400.45	69.54	74.71
conservative group	56.24	1.79	383.78	52.72	59.77

MMRM: Group comparison at 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	15.88	2.06	356.81	11.82	19.94	<0.001

MMRM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	16.28	1.31	400.45	13.70	18.86
conservative group	0.40	1.79	383.78	-3.13	3.92

MMRM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	15.88	2.06	356.81	11.82	19.94	<0.001

LMM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	16.70	1.51	13.61	13.46	19.94
conservative group	0.04	1.77	377.75	-3.45	3.53

LMM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	16.65	2.24	35.50	12.10	21.20	<0.001

=== Variance Components ===

Variance surgeon (τ^2_{surgeon}): 7.591

Variance patient (τ^2_{patient}): 142.42

Residual variance (σ^2): 157.7257

=== Intraclass Correlation Coefficients (ICC) ===

ICC surgeon (only liposuction group): 0.0247

ICC patient (liposuction group): 0.4628

ICC patient (conservative group): 0.4745

8. WHOQOL-BREF content with quality of life (G4)

MMRM: Marginal means at 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	59.61	1.53	390.80	56.60	62.62
conservative group	39.79	2.08	377.59	35.69	43.88

MMRM: Group comparison at 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	19.82	2.37	357.02	15.16	24.49	<0.001

MMRM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	22.54	1.53	390.80	19.53	25.55
conservative group	2.71	2.08	377.59	-1.38	6.81

MMRM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	19.82	2.37	357.02	15.16	24.49	<0.001

LMM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	23.00	1.76	12.26	19.18	26.82
conservative group	2.46	2.14	328.99	-1.75	6.68

LMM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	20.54	2.67	30.27	15.09	25.99	<0.001

=== Variance Components ===

Variance surgeon (τ^2_{surgeon}): 7.2367

Variance patient (τ^2_{patient}): 235.8899

Residual variance (σ^2): 200.1387

=== Intraclass Correlation Coefficients (ICC) ===

ICC surgeon (only liposuction group): 0.0163

ICC patient (liposuction group): 0.5322

ICC patient (conservative group): 0.541

9. WHOQOL-BREF physical health (domain 1)

MMRM: Marginal means at 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	72.33	1.15	395.83	70.08	74.58
conservative group	53.23	1.56	381.99	50.16	56.31

MMRM: Group comparison at 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	19.10	1.77	362.61	15.61	22.59	<0.001

MMRM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	17.18	1.15	395.83	14.93	19.43
conservative group	-1.92	1.56	381.99	-4.99	1.16

MMRM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	19.10	1.77	362.61	15.61	22.59	<0.001

LMM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	18.60	1.68	14.46	15.00	22.19
conservative group	-2.46	1.57	369.25	-5.56	0.64

LMM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	21.06	2.22	33.10	16.54	25.57	<0.001

=== Variance Components ===

Variance surgeon (τ^2_{surgeon}): 24.772

Variance patient (τ^2_{patient}): 166.8814

Residual variance (σ^2): 53.2303

=== Intraclass Correlation Coefficients (ICC) ===

ICC surgeon (only liposuction group): 0.1012

ICC patient (liposuction group): 0.6815

ICC patient (conservative group): 0.7582

10. WHOQOL-BREF psychological health (domain 2)

MMRM: Marginal means at 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	68.20	1.06	388.13	66.13	70.28
conservative group	56.33	1.43	375.68	53.51	59.15

MMRM: Group comparison at 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	11.87	1.62	360.65	8.68	15.06	<0.001

MMRM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	12.58	1.06	388.13	10.51	14.66
conservative group	0.71	1.43	375.68	-2.11	3.53

MMRM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	11.87	1.62	360.65	8.68	15.06	<0.001

LMM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	13.25	1.31	11.87	10.40	16.11
conservative group	0.26	1.47	322.94	-2.62	3.15

LMM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	12.99	1.88	29.42	9.14	16.84	<0.001

=== Variance Components ===

Variance surgeon (τ^2_{surgeon}): 7.7512

Variance patient (τ^2_{patient}): 144.0385

Residual variance (σ^2): 54.6981

=== Intraclass Correlation Coefficients (ICC) ===

ICC surgeon (only liposuction group): 0.0375

ICC patient (liposuction group): 0.6976

ICC patient (conservative group): 0.7248

11. WHOQOL-BREF social relationships (domain 3)

MMRM: Marginal means at 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	72.87	1.25	383.89	70.41	75.32
conservative group	64.24	1.71	373.54	60.89	67.59

MMRM: Group comparison at 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	8.63	1.93	357.37	4.83	12.42	<0.001

MMRM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	5.62	1.25	383.89	3.16	8.08
conservative group	-3.01	1.71	373.54	-6.36	0.34

MMRM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	8.63	1.93	357.37	4.83	12.42	<0.001

LMM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	6.17	1.46	10.95	2.95	9.39
conservative group	-3.35	1.75	293.86	-6.79	0.08

LMM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	9.52	2.18	26.40	5.03	14.01	<0.001

=== Variance Components ===

Variance surgeon (τ^2_{surgeon}): 6.156

Variance patient (τ^2_{patient}): 201.4827

Residual variance (σ^2): 81.4785

=== Intraclass Correlation Coefficients (ICC) ===

ICC surgeon (only liposuction group): 0.0213

ICC patient (liposuction group): 0.6969

ICC patient (conservative group): 0.7121

12. WHOQOL-BREF environment (domain 4)

MMRM: Marginal means at 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	79.20	0.77	379.25	77.68	80.71
conservative group	73.69	1.06	370.30	71.61	75.77

MMRM: Group comparison at 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	5.51	1.19	355.79	3.16	7.85	<0.001

MMRM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	6.05	0.77	379.25	4.53	7.57
conservative group	0.54	1.06	370.30	-1.53	2.62

MMRM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	5.51	1.19	355.79	3.16	7.85	<0.001

LMM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	6.06	0.84	9.76	4.18	7.95
conservative group	0.55	1.12	233.71	-1.65	2.75

LMM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	5.51	1.35	19.98	2.69	8.33	<0.001

=== Variance Components ===

Variance surgeon (τ^2_{surgeon}): 0

Variance patient (τ^2_{patient}): 73.1748

Residual variance (σ^2): 42.0073

=== Intraclass Correlation Coefficients (ICC) ===

ICC surgeon (only liposuction group): 0

ICC patient (liposuction group): 0.6353

ICC patient (conservative group): 0.6353

13. LEFS total score

MMRM: Marginal means at 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	66.36	0.87	385.14	64.65	68.07
conservative group	47.29	1.19	373.38	44.96	49.62

MMRM: Group comparison at 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	19.07	1.34	357.31	16.43	21.70	<0.001

MMRM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	16.70	0.87	385.14	14.99	18.41
conservative group	-2.37	1.19	373.38	-4.70	-0.03

MMRM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	19.07	1.34	357.31	16.43	21.70	<0.001

LMM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	17.83	1.43	16.45	14.80	20.86
conservative group	-2.67	1.23	405.00	-5.08	-0.26

LMM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	20.50	1.83	35.16	16.79	24.22	<0.001

=== Variance Components ===

Variance surgeon (τ^2_{surgeon}): 21.9476

Variance patient (τ^2_{patient}): 91.978

Residual variance (σ^2): 39.707

=== Intraclass Correlation Coefficients (ICC) ===

ICC surgeon (only liposuction group): 0.1429

ICC patient (liposuction group): 0.5987

ICC patient (conservative group): 0.6985

14. Total leg impairment (Schmeller)

MMRM: Marginal means at 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	3.38	0.14	368.04	3.10	3.66
conservative group	7.37	0.19	359.63	6.99	7.74

MMRM: Group comparison at 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	-3.99	0.22	348.30	-4.41	-3.56	<0.001

MMRM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	-4.19	0.14	368.04	-4.46	-3.91
conservative group	-0.20	0.19	359.63	-0.57	0.18

MMRM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	-3.99	0.22	348.30	-4.41	-3.56	<0.001

LMM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	-4.19	0.15	9.20	-4.52	-3.85
conservative group	-0.20	0.20	246.45	-0.59	0.19

LMM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	-3.99	0.24	20.87	-4.48	-3.49	<0.001

=== Variance Components ===

Variance surgeon (τ^2_{surgeon}): 0

Variance patient (τ^2_{patient}): 2.6398

Residual variance (σ^2): 0.932

=== Intraclass Correlation Coefficients (ICC) ===

ICC surgeon (only liposuction group): 0

ICC patient (liposuction group): 0.7391

ICC patient (conservative group): 0.7391

15. Body weight

MMRM: Marginal means at 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	85.75	0.51	386.44	84.75	86.74
conservative group	91.14	0.69	376.53	89.79	92.50

MMRM: Group comparison at 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	-5.39	0.78	363.27	-6.92	-3.87	<0.001

MMRM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	-4.41	0.51	386.44	-5.41	-3.42
conservative group	0.98	0.69	376.53	-0.37	2.34

MMRM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	-5.39	0.78	363.27	-6.92	-3.87	<0.001

LMM: Marginal means of change from randomisation to 12 months

Group	Estimate	Std Error	DF	Lower CI	Upper CI
liposuction group	-4.46	0.54	8.11	-5.70	-3.22
conservative group	0.92	0.70	186.74	-0.46	2.31

LMM: Group comparison of change from randomisation to 12 months

Comparison	Estimate	Std Error	DF	Lower CI	Upper CI	p-value
liposuction group - conservative group	-5.38	0.85	15.01	-7.20	-3.57	<0.001

=== Variance Components ===

Variance surgeon (τ^2_{surgeon}): 0

Variance patient (τ^2_{patient}): 38.4081

Residual variance (σ^2): 7.06

=== Intraclass Correlation Coefficients (ICC) ===

ICC surgeon (only liposuction group): 0

ICC patient (liposuction group): 0.8447

ICC patient (conservative group): 0.8447

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Trial Protocol - Summary of changes

Version Trial Protocol	Changes
V01_0	unpublished draft of the protocol for initial ethics submission
V02_0 (17.12.2019)	1st published study protocol = original study protocol, approved by the Ethics Committee
V03_0	unpublished draft of the protocol submitted as amendment to ethics committees
V04_0 (01.02.2023)	2nd published study protocol = amended study protocol, approved by the Ethics Committee <u>Repetitive modifications in the protocol</u> - NCT-Number was added. - Addresses of Sponsor and Coordinating Investigator were updated. - Time plan has been adjusted. - Explanation on how to proceed in the event of a pandemic was added to the individual chapters. - In addition to the substantive changes listed below, minor editorial changes (e.g., adjustment of the list of abbreviations) were made, such as spelling errors (e.g., primary → Primary) or punctuation errors and formatting adjustments (e.g., adjustment of the version number and date). <u>Further modifications in the protocol</u> <i>Explanation: Changes are crossed out if they have been removed and underlined if they have been added.</i> 2.3 Secondary and other objectives: Change in the leg circumference of the left and right leg using a measuring tape at five predefined measuring points: • Lower leg ankles • Thigh, 10 cm below the groin • Hips (the widest point on the hip is measured) 3.7.1 Requirements for principal investigators and trial sites <u>This means that the surgeon must have operated on at least 15 patients per year (or 30 patients in the last 24 months).</u> 4.1.1 Schedule and Visit From the 1st patient to completion of the last patient <u>The duration for each individual participant is: max. 498.25-months</u> Recruitment period: 618 months Duration of the entire trial: 5766 Monate Random assignment of patients to one of the two treatment groups (EXP or CON) is performed centrally via a 24/7 internet service (ALEA, FormsVision BV, Abcoude, NL) in a ratio of 2:1 (EXP:CON) on the basis of permuted blocks <u>from ALEA using pseudorandom numbers.</u> 4.2 Discussion of the trial design Random assignment of patients to one of the two treatment groups (EXP or CON) is performed centrally via a 24/7 internet service (ALEA, FormsVision BV, Abcoude, NL) in a ratio of 2:1 (EXP:CON) on the basis of permuted blocks from ALEA <u>using pseudorandom numbers.</u> 4.4.1 Definitions <u>Screening:</u> <u>Active efforts by the trial physician to identify trial patients who may be eligible for participation in a clinical trial. The full screening process includes a visit to the trial site where health status is appropriately assessed. It includes a series of questions, including general, health-related and anamnestic questions. Trial-related measures can only be carried out after informed consent is signed.</u> <u>Screening Failure:</u> <u>Trial patients with signed informed consent who have not met one or more criteria for participation in the trial.</u> <u>Enrolment:</u> <u>The process of enrolling a participant into the clinical trial. Once the trial patients has signed the informed consent form and completed all screening assessments and is eligible according to the inclusion/exclusion criteria, she can be enrolled in the trial.</u> <u>Drop-out:</u>

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<u>Trial patients who withdraw from the trial before the end of their trial period.</u> <u>The reasons for this may be:</u> • <u>Exclusion by the trial physician or the sponsor due to an exclusion criterion, failure to meet an inclusion criterion at the P2 visit or failure to comply with the trial protocol requirements;</u> • <u>Premature termination of the trial at the trial participants own request by withdrawing consent to participate in the trial. This case is referred to as withdrawal;</u> • <u>Trial participants informs that she no longer wishes to participate in the trial without withdrawing her consent to participate in the trial.</u> • <u>Contact with the trial participant is lost. This case of premature termination of trial participation is referred to as lost to follow-up.</u> <u>The withdrawal of consent to participate in the trial (withdrawal) results in the immediate deletion of all data collected up to that point (GDPR Art. 17 para. 1 lit. b) In the event of a drop-out for other reasons, the data collected up to that point will not be deleted and can be used accordingly.</u> <u>Replacement of Drop-outs/Screening Failures:</u> • <u>Screening failures à are replaced;</u> • <u>Drop-outs before randomization à are only replaced if the drop-out rate is greater than 10%;</u> • <u>Drop-outs after randomization à will not be replaced.</u> <u>End of Trial (EOS)</u> • <u>For trial participants who have regularly completed the trial: Date of completion of all assessments required by the trial protocol in this trial for the trial participant.</u> <u>For drop-outs: Date of the last documented visit/assessment of the trial participants required by the trial protocol.</u> 4.4.2 Main exclusion criteria 4. „Weight>120,0 kg“ listed as a separate item; 13. <u>Plans to use a lymphomat during the trial</u> 4.5 Termination criteria The trial is discontinued for an individual participant if: <u>the participant has not undergone CDT for more than 30 days during the run-in phase.</u> 4.6.2 Method for allocating patients to the treatment groups <u>Allocation is stratified by stage and site. Randomization can be performed by all trial members except the blinded trial physician and the blinded trial personnel.</u> 4.6.4 Previous therapy and concomitant therapy <u>Further liposuctions are prohibited for the entire duration of the trial, with the exception of liposuctions on the arms (diagnosis: lipoedema), which can be performed at the earliest 12 months after the last liposuction on the legs - in the intervention group after visit V2, in the control group after visit V4. However, this is not a trial measure and the costs must be paid by the patients themselves.</u> 4.7.1.2 Secondary and other outcome measures • <u>Thigh, 10 cm below the groin</u> • <u>Hips (the widest point on the hip is measured)</u> 4.7.1.4 Description of the individual visits <u>Screening/baseline visit (for all recruited patients)</u> <u>After the participant has been pre-selected (telephone interview (pre-screening)), the investigator provides both verbal and written information about the trial and liposuction during the <u>baseline visit</u>.</u> <u>The inclusion and exclusion criteria are checked (screening) and after inclusion of the participant in the trial (enrollment) the following characteristics are documented and recorded in the eCRF: Master data, diagnosis, medical history, pregnancy test (urine), previous conservative treatment, weight, concomitant medications, body fat percentage, body fat distribution, leg circumference on the upper and lower leg of the left and right leg, occurrence of leg edema, the arm circumference of both arms and the skin appearance.</u> <u>If the inclusion criteria are not fully met or an exclusion criterion is violated, the participant cannot be included in the trial (screening failure).</u> <u>Run-in phase (up to 7 months) for all recruited patients</u> <u>(Note: excluding possible pandemic-related delays)</u>

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	<u>The starting point of the initiation phase is the first CDT treatment after inclusion in the trial. For this purpose, the participant informs her trial site promptly (e.g. by telephone) of the date of the first CDT performed after the baseline examination, as the further visits will depend on this.</u> At visits P1 (by week 4 at the latest) and P2 (by week 28 at the latest), body fat percentage, body fat distribution, weight, concomitant medication, leg and arm circumference, occurrence of leg edema, skin appearance, optional leg volume measurement by the investigator are recorded and checked. If these criteria are not met, the patient is excluded from the trial and a new patient must be recruited. If all inclusion and exclusion criteria are met, randomization into the intervention and control arm (2:1) takes place at P2. If an inclusion criterion is violated or an exclusion criterion is met, the participant is excluded from the trial (drop-out). <u>The participant will not be replaced unless the drop-out rate is more than 10% (approximately = 5% drop-out + 5% CDT success).</u> If all inclusion and exclusion criteria are met, randomization into the intervention and control arm (2:1) takes place at P2. Further course of the trial after randomization: Intervention group ECG and laboratory tests can also be carried out by the general practitioner if necessary.. Table 2 and 3 have been adapted to the amendment. Duration of the clinical trial The duration for each individual participant is a maximum of 49 8,25 months <u>after the start of the initiation phase (defined as the start of the 1st CDT).</u> 6.1 Statistical and analytical plan Intention-to-treat (ITT) population: All eligible randomized patients are evaluated without exception. <u>In particular, patients whose treatment could only be completed with a delay under pandemic conditions also remain part of this population.</u> 6.1.2 Primary endpoint To limit the influence of individual trial sites, a maximum of 50 patients per site per stage should be included. In each stage, 16 participating surgeons will treat 5-6 patients in the intervention group. <u>If possible, at least 5 patients per surgeon per stage should be treated (liposuction) to illustrate the effects of surgery</u> <u>A possible effect modification or bias due to delays in the implementation of liposuction (e.g. pandemic-related) is explored (stratification, regression models, subgroup analyses). The following two cases are to be distinguished: (1) The delay occurs before randomization. (2) The delay occurs after randomization. Case (1) does not result in bias, as both trial arms are equally affected. Effect modification is possible (and is being explored). Case (2) *may* result in bias as the trial arms are affected differently. In the control arm, the follow-up period starts immediately after randomization, in the intervention arm only after completion of the (delayed) liposuction. However, in view of the planned CDT duration of 6 months before randomization, a maximum effect of this measure can be assumed ("saturation"), so that the extension of the CDT duration in the intervention arm cannot have any further relevant influence on the efficacy. Possible effects are being explored.</u> 6.2 Determination of the number of cases If a drop-out rate higher than 10% (5% drop-out + 5% CDT success) becomes apparent in the course of the recruitment period over 6 month, more patients should be included in the run-in phase in the remaining time in order to be able to randomize at least 405 (135 patients per stage) with a high probability. 7.2 Documentation and reporting period of (serious) adverse events (AEs and SAEs) • <u>Possible causal</u> relationship to CDT or intervention (yes, no) 9. Changes to the trial protocol
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Liposuction versus conservative therapy for patients with lipoedema:
A randomised controlled multi-centre investigator-blinded clinical trial

	These will only be made after mutual agreement between the sponsor, the sponsor's <u>authorized</u> representative, the PCI and the biometrician as well as all signatories (authors) of this trial protocol.
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(Translated from German)

Trial PROTOCOL

A RANDOMIZED CONTROLLED MULTICENTRE INVESTIGATOR-BLINDED CLINICAL
TRIAL COMPARING EFFICACY AND SAFETY OF SURGERY VERSUS COMPLEX
DECONGESTIVE THERAPY FOR LIPEDEMA

(LIPLEG)

Sponsor

Department of Dermatology
Klinikum Darmstadt
64283 Darmstadt

Principal Coordinating Investigator and sponsor representative

PD Dr. Maurizio Podda
Department of Dermatology, Medical Center
Klinikum Darmstadt

Grafenstraße 9
64283 Darmstadt

Protocol-Code: LIPLEG-3806

ClinicalTrials.gov ID: NCT04272827

Version dated 01.02.2023, Version 04_0

The information in this trial protocol is strictly confidential. It is for the use of the sponsor, principal investigator, trial personnel, ethics committee and trial subjects only. This trial protocol may not be passed on to third parties without the express agreement of the sponsor or the Principal Coordinating Investigator (PCI).

I. Signatures

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Datum

Prof. Dr. med. Oliver Cornely

Consortium Leader
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Datum

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Statistician
Institute for Medical Statistics and Bioinformatics (IMSB),
Faculty of Medicine, University of Cologne

Unterschrift

Datum

II. Synopsis

Sponsor:	Department of Dermatology, Medical Centre Klinikum Darmstadt 64283 Darmstadt
Principal Coordinating Investigator:	PD Dr. Maurizio Podda Department of Dermatology, Medical Centre Klinikum Darmstadt Grafenstraße 9 64283 Darmstadt
Title of the clinical trial:	A randomized controlled multicentre investigator-blinded clinical trial comparing efficacy and safety of surgery versus complex decongestive therapy for lipedema (LIPLEG)
Short title	Liposuction for lipedema
Acronym:	LIPLEG
Indication:	E88.20, Lipedema, Stadium I E88.21, Lipedema, Stadium II E88.22, Lipedema, Stadium III
Phase:	Non-AMG/Non-MDR
Type of trial:	Randomized controlled multicentre investigator-blinded trial with two therapy groups.
Number of patients:	Number of pre-screened trial patients: > 1600 Number of trial patients screened: n = max. 985 Number of trial patients to be enrolled: n = 450 Number of trial patients to be randomized and evaluated: n = 405 (ITT)
Primary trial objective:	Reduction of pain
Outcomes:	<u>Primary end point:</u> Relevant reduction in average leg pain intensity over the last 4 weeks (stage I, II or III; ≥ 2 points on a numerical rating scale; German pain questionnaire) at 12 months after completion of

	liposuction (intervention group) or at 12 months after randomization (control group) <u>Secondary end points</u> (Change at 12 months after completion of liposuction treatment (intervention group) or at 12 months after randomization (control group)): • Change in average leg pain intensity (stage I, II or III) • Change in health-related quality of life according to SF- 36, DLQI and WHOQOL-BREF • Change in general impairment • Change in susceptibility to depression, Patient Health Questionnaire-9 (PHQ-9) • Change in hematoma proneness • Prevalence of edema • Modification in the scope of physical therapy • Change in body fat percentage • Change of leg circumference on the left and right leg using a measuring tape at five predetermined measuring points: - Lower leg ankles - Mid-calf - Knee - Thigh, 10 cm below the groin - Hips (the widest point at the hip is measured) • Relevant reduction in movement restriction in lower extremity functional scale (LEFS cumulative score) • Number of recurrent surgeries • Number of (serious) adverse events during the trial • Therapy discontinuation resulting from (serious) adverse events • Optional: Change in leg volume of the left and right leg (e.g. using perometry)
Diagnosis, main inclusion criteria, main exclusion criteria:	<u>Main</u> Inclusion criteria: 1. Signed informed consent form 2. Female 3. Age ≥ 18 years 4. Confirmed lipedema of the legs stage I-III 5. Average leg pain of ≥ 4 on a numerical rating scale 6. Documentation of insufficient symptom relief with conservative treatment

	7. Willingness and ability to undergo measurements according to the trial protocol before, during and, if necessary, after the liposuction treatment 8. Full legal capacity <u>Main</u> exclusion criteria: 1. Concurrent lipedema of the arms interfering with the primary end point of leg pain, at the decision of the investigator 2. Previous liposuctions 3. Diseases affecting operability (e.g. cardiac diseases, coagulation disorders, metabolic diseases,, active infectious diseases, epilepsy, diseases requiring immunosuppression or anticoagulation, allergies to drugs used before and during surgery), at the decision of the investigator 4. Weight >120.0 kg 5. Diseases affecting conservative therapy CDT (e.g. heart failure (volume stress), lack of physical ability to wear compression stockings (e.g. joint disease, neurological deficits)), at the decision of the investigator 6. Primary obesity without disproportion and unrelated to lipedema 7. Secondary obesity 8. Other fat distribution disorders than lipedema (e.g. painless lipo-hypertrophy, benign symmetrical lipomatosis or lipomatosis dolorosa) 9. Causes of edema other than lipedema (e.g. lymphedema, phlebedema or myxedema) 10. Un willingness to use contraception 11. Pregnancy 12. Breast feeding 13. Plans to use a lymphomat during the trial 14. Participation in other clinical trials 15. Cosmetic motivation to participate in the trial
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Intervention	<i>Run-In-Phase:</i> In order to establish same starting conditions for all patients before randomization, the trial patients initially receive CDT as recommended by the investigator in a run-in phase. The first part (phase I) of the run-in phase serves to eliminate edema within a maximum period of 4 weeks, followed by the second part (phase II), in which patients are treated with standardised CDT for a further 6 months to maintain the results achieved in phase I. Patients are then randomly assigned to one of the two treatment groups (treatment A: liposuction, treatment B: CDT) provided that all inclusion criteria are still met (and no exclusion criterion is fulfilled). The allocation ratio is 2:1 (intervention: control). <i>Intervention:</i> In the liposuction group, patients receive liposuction treatment using the wet technique. Techniques such as vibration (PAL) or water jet (WAL) can support the procedure depending on the amount of fat that is to be removed. A maximum of 4 surgical sessions is possible. CDT therapy is continued to the necessary extent for progression prophylaxis. <i>Control-intervention:</i> The CDT group is treated with CDT alone for further 12 months upon randomization to maintain at least the results obtained at the end of the run-in phase. After this period, patients will be offered liposuction treatment provided all inclusion and exclusion criteria are still valid. The primary end point will be assessed after an observation period of 12 months after randomization in the control group and after 12 months after final liposuction surgery in the intervention arm. This is followed by a further follow-up period of 24 months.		
Time plan	Inclusion of first patient (first patient first visit, FPFV)	Q1/2021	
	Last patient included (last patient first visit, LPFV)	Q3/2022	
	End of trial of last patient (last patient last visit, LPLV)	Q3/2026	
	Final clinical trial report:	Q3/2027	

Statistician:	Prof. Dr. Martin Hellmich Institute for Medical Statistics and Bioinformatics (IMSB), AG Medizinische Statistik, Faculty of Medicine and University Hospital Cologne, University of Cologne Robert-Koch Str. 10, Gebäude 55 50931 Köln
Statistical methods:	The primary analysis is performed according to the intention-to treat principle, where a missing primary end point or change of the randomly assigned treatment is counted as failure. Note: Since the primary end point can also be determined by mail or telephone if necessary, less than 20% of missing values are assumed. First, a joint evaluation of all 405 included patients will be performed using the Mantel-Haenszel test stratified by stage at two-sided significance level of 5% (H_0: OR = 1 vs. H_1: OR $\neq$ 1). If this test is statistically significant, the equality of the success rates in the separate stages will be evaluated by Fisher's exact test (hierarchical test strategy), also at two-sided significance level of 5%. 95% confidence intervals are calculated for the difference in success rates. <u>Safety analyses:</u> The information on adverse events will be assessed (according to severity, intensity of symptoms, causal relationship to CTD or intervention), coded and summarized (contingency tables; number of events and patients affected). This applies in particular to adverse events during the follow-up period (24 months). <u>Analysis of the secondary end points:</u> Parametric or non-parametric methods will be used to evaluate the secondary end points, depending on the distribution type. Quantitative variables are analysed descriptively with mean, standard deviation and percentiles (0, 25, 50, 75, 100), qualitative variables with absolute and relative frequency. Details of all planned analyses are described in the Statistical Analysis Plan (SAP).
GCP compliance	The present trial will be conducted in accordance with the current version of the trial protocol and the internationally recognized

	guideline Good Clinical Practice (ICH-GCP) including the archiving of essential documents.
Initiator and funding	GBA (Gemeinsamer Bundesausschuss=Federal Joint Committee). The project management agency is the DLR (Deutsches Zentrum für Luft- und Raumfahrt= German Aerospace Center) – Projektträger.

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III. List of abbreviations

Abbreviation	Meaning
AE	Adverse Event
AMG	German Medicinal Products Act
AT	As-treated
eCRF	electronic Case Report Form
DLQI	Dermatology Life Quality Index
DLR	Deutsches Zentrum für Luft- und Raumfahrt (=German Aerospace Center)
DMC	Data Monitoring Committee
FPFV	Einschluss erste Participant (First Participant First Visit)
GBA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GCP	Gute Klinische Praxis (Good Clinical Practice)
IMSB	Institute for Medical Statistics and Bioinformatics
ITT	Intention-to-treat
CDT	Complex decongestive therapy
LEFS	Lower Extremity Functional Scale
PCI	Principal Coordinating Investigator;
LPFV	Last Participant First Visit
LPLV	Last Participant Last Visit
MDR	Medical Devices Regulation
PAL	Power/Vibrations-assistierte Liposuktion
PHQ-9	Participant Health Questionnaire-9
PP	Per Protocol Analysis
RBQM	Risk-Based Quality Management
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF-36	Short Form (SF)-36 Health questionnaire

TA	Tumescent anesthesia
TMF	Trial Master File
WAL	Water-jet assisted liposuction
WHO	World Health Organization
WHOQOL- BREF	WHO-Quality of Life BREF
CTCC	Clinical Trials Centre Cologne
cQC	Central quality control

1. Introduction

Lipedema was first described by Allen and Hines in 1940 [1]. In 2017, it was then listed in the International Statistical Classification of Diseases and Related Health Problems (ICD-10) and coded according to stage (ICD10-E88.20, E88.21, E88.22 and E88.28) [2]. Lipedema is a symmetrical, , excessive increase in adipose tissue on the legs, which occurs almost exclusively in women, is not diet-related and therefore cannot be removed by diet and exercise [3] [4]. The majority of patients also have involvement of the arms [5]. Lipedema is associated with increased sensitivity to touch, a feeling of tension and pressure in the affected regions of the extremities and an increased hematoma proneness after minor trauma [6]. The data on the prevalence of lipedema in the medical literature are very imprecise. They vary between 10-18% in different studies[7] [8] [9] and are estimated by Child et al. at 1 in 72,000 [3] . However, it is noted that lipedema is frequently misdiagnosed and therefore incorrectly treated [3] [5], as not all physician are currently familiar with the condition, therefore a reliable differential diagnosis is essential. Despite significant clinical characteristics, lipedema is often misdiagnosed as obesity or, in particular, as lymphoedema and manifestations caused by other internal diseases. Shivat et al. developed an algorithm for diagnosing lipedema and published it in 2018 [10].

A genetic disposition is also assumed, as several members of a family often have lipedema. X-linked dominant or sex-limiting autosomal dominant inheritance is assumed [3]. An important factor in the pathophysiology of lipedema is the increased capillary permeability, which leads to orthostatic edema. This, and not the amount of adipose tissue, appears to be responsible for the increased sensitivity of the tissue to touch and pressure. The increased capillary fragility could also explain the hematoma proneness [11].

The course of the disease is very individual; some patients develop lipedema to a lesser extent, which stabilizes and shows no progression of pain. In other patients, there is a gradual progression of lipedema or an exacerbation after a stressful situation such as pregnancy or surgery [12]. It is generally reported that the onset of lipedema occurs during puberty, pregnancy or menopause [3] [13].

Three stages of lipedema are described. In stage I, the skin is smooth with an increase in subcutaneous adipose tissue . In stage II, nodules appear in the adipose tissue, the overlying skin is predominantly wavy and uneven, while in stage III the tissue is significantly coarser and more nodular and shows deforming fat flaps, especially on the thighs and knees [4].

Complex decongestive therapy (CDT) is used as a conservative treatment strategy [6].

Originally developed for the treatment of lymphoedema, progress has also been seen in patients with lipedema using CDT with regard to a reduction in the circumference of the leg and a reduction in tension and pressure pain has been reported. Conservative therapy alone, particularly in the form of CDT, is the current standard treatment for patients with lipedema due

to the lack of alternative treatments, without representing a causal therapy for lipedema. However, there is no reliable evidence and only the lymphatic component of lipedema is usually treated in this group of patients. One disadvantage of CDT is that it must be carried out regularly, as the edema returns if it is discontinued [4] [12].

CDT consists of the combined application of lymphatic drainage (manual, possibly using equipment), compression therapy (usually flat-knit compression stockings for legs and arms), skin care and exercise therapy. This treatment must be carried out permanently, consistently and with consistently high intensity as a whole-body treatment and aims to reduce the pressure pain associated with lipedema in the affected extremities. Whether this has any effect on the progression of the pain remains to be elucidated. However, the specific fat accumulation and distribution with the accompanying pain and the hematoma proneness remain [5]. The accompanying exercise therapy, possibly also in combination with a change in diet, serves to reduce or prevent possible accompanying obesity, which appears to have a negative prognostic influence on the development of lipedema [6] [10].

In the 1990s, people began to surgically remove pathologically altered subcutaneous adipose tissue sparing the lymphatic system. Liposuction using tumescent local anesthesia (TA) is a surgical procedure in which several liters of an anesthetic solution containing a mixture of lidocaine and prilocaine are first infiltrated into the subcutaneous space ("wet technique"). The subcutaneous adipose tissue (fat-solution mixture) is then suctioned using very fine, blunt, vibrating cannulas (2-4 mm). This method is a much more tissue-sparing surgical method and minimizes the risk of injury to surrounding vascular and nerve structures [4] [14] [15] [16] [17]. TA has established itself in liposuction to this day and is considered the standard low-risk local anesthetic method, which is also recommended as the method of choice in the guidelines for lipedema [10]. Liposuction itself is recommended and performed for lipedema using power/vibration-assisted liposuction (PAL) or water-jet-assisted liposuction (WAL). In PAL, the fat cells are suctioned using a motorized, vibrating cannula that is gentle on the blood vessels and connective tissue.

The vibration technique is used as the standard method in most lipedema centres worldwide. In water-assisted liposuction (WAL), instead of vibration, a jet of water loosens the fat cells and a mixture of fat cells, water and tumescent solution is suctioned out. Overall, a slightly smaller volume of tumescent anesthetic solution is usually injected in advance [18] [19].

Experience to date has shown that liposuction surgery not only reduces specific fat deposits and fat distribution, but also significantly reduces the sensitivity of the tissue to pain, which manifests itself as pressure or spontaneous pain, edema, restricted mobility and the hematoma proneness [4] [20]. Based on data collected using questionnaires before and after liposuction surgery, an improvement in general quality of life was also demonstrated [4] [11] [20]. CDT could either be reduced or completely omitted in the long term. The results and

participant satisfaction were maintained for years [20]. Various publications have discussed whether liposuction should be included as part of standard therapy in order to prevent possible late effects such as the occurrence of secondary lymphoedema and the progression of pain, improve quality of life and, if necessary, reduce the need for CDT, particularly in the early stages of lipedema [4] [11] [20] [21] [22].

In summary, numerous case reports as well as smaller, mostly monocentric, uncontrolled data collections and studies clearly demonstrate the positive results in terms of pain, freedom of movement and general quality of life as well as the low risk of liposuction for the treatment of lipedema. However, the risk of bias is considerable.

To date, however, no large multicentre, controlled, randomized clinical trial with validated methods has been conducted to investigate and compare the treatments in a large statistically meaningful collective on a stage-specific basis. As a result, there is a lack of evidence to prove the potential superiority of surgical treatment of lipedema with regard to the outcome of pain in stage I, II or III compared to conservative treatment with CDT alone. Scientific results from a randomized, controlled, clinical trial are required to evaluate the benefits of establishing this therapy in standard care.

2. Objectives of the clinical trial

2.1 Rationale of the clinical trial

Lipedema is accompanied by reduced quality of life in patients due to persistent pain (in stage I, II or III). Because the biological cause of lipedema is not known, there is no specific therapy. Treatment with Complex decongestive therapy (CDT) is lengthy and usually does not lead to a significant improvement in lipedema of the legs. Surgical treatment by means of liposuction may be an alternative. However, there is currently only limited meaningful data from published studies that suggest a potential for the effectiveness of surgical treatment of lipedema. A direct comparison of liposuction with CDT in a randomized, controlled, multicentre trial is necessary in order to establish a meaningful data situation.

For a detailed assessment of the risks and benefits, see also Chapter 4.3.

2.2. Primary objective

The objective is to determine whether surgical treatment of lipedema (stage I, II or III) by means of liposuction significantly improves leg pain compared to the use of CDT.

The primary end point is the relevant reduction of the average leg pain intensity in the last 4 weeks (≥ 2 points on a Numerical Rating Scale; German Pain Questionnaire) at 12 months after completion of liposuction treatment (intervention group) or after randomization (control group) compared to the time of randomization.

Hypotheses: The probabilities of success π of both types of treatment are the same (null hypothesis: $H_0: \pi_{Op} = \pi_{CDT}$) or different (alternative hypothesis: $H_A: \pi_{Op} \neq \pi_{CDT}$).

2.3. Secondary and other objectives

In order to comprehensively assess the possible superiority of surgical treatment of lipedema (stage I, II or III) by means of liposuction compared to the use of CDT, the following measures should also be considered (change at 12 months after completion of liposuction treatment (intervention group) or after randomization (control group) compared to the time of randomization:

- Change in average leg pain intensity in the last 4 weeks according to von Korff et al. (1992) [23] [stage I, II or III; (classes 0 = no pain) to 4 = high, pain-related impairment, severely limiting); German Pain Questionnaire [24]]

- Change in health-related quality of life according to SF-36, DLQI (a clinically relevant change corresponds to ≥ 4 points change in the DLQI cumulative score [25] and WHOQOL-BREF
- Change in general impairment according to Schmeller et al. (2010) (modified form) [26]
- Change in susceptibility to depression according to PHQ-9 (a clinically relevant improvement corresponds to ≥ 5 points reduction in the PHQ-9 cumulative score [27])
- Change in hematoma proneness according to Schmeller et al. (2010) [26] (modified form)
- Changed prevalence of edema
- Change in the extent of physical therapy
- Change in body fat percentage, determined according to the formula by Wright et al. (1981) [28] using a measuring tape at the following points:
 - Abdominal circumference: Measurement at the level of the navel. The tape measure is placed horizontally around the body.
 - Neck circumference: measurement below the larynx
 - Body height
 - Hip circumference: the widest part of the hip is measured.
- Change in the leg circumference of the left and right leg using a measuring tape at five predefined measuring points:
 - Lower leg ankles
 - mid-calf
 - knee
 - Thigh, 10 cm below the groin
 - Hips (the widest point on the hip is measured)
- Relevant movement restriction in lower extremity functional scale (stage I, II or III; ≥ 9 points improvement in LEFS cumulative score) [29]
- Number of recurrent surgeries
- Number of (serious) adverse events
- Treatment discontinuation caused by (serious) adverse events
- Optional: change in the leg volume of the left and right leg (e.g. using perometry etc.)

3. Organizational structure

3.1 Sponsor

Sponsor: Department of Dermatology,
Medical Center, Klinikum Darmstadt,
64297 Darmstadt/Eberstadt

Represented by: PD Dr. Maurizio Podda
Grafenstraße 9
64283 Darmstadt

3.2 Principal Coordinating investigator

Principal Coordinating investigator (PCI) s.o.

Statistician: Prof. Dr. Martin Hellmich
Institute for Medical Statistics and Bioinformatics (IMSB)
University of Cologne
Robert-Koch-Str.10, Building 55
50931 Cologne

3.3 Data Monitoring Committee

A Data Monitoring Committee (DMC) consisting of independent experts will be set up. It consists of two physicians and one statistician who are not involved in the conduct of the trial. The task of the DMC is to monitor the safety of the trial patients in the clinical trial by regularly assessing the safety of the trial therapy. Based on the available data (especially data on adverse events), the DMC makes recommendations to the sponsor/PCI for the continuation of the trial (with/without modification) or, if necessary, premature termination. Details are described in a separate DMC manual.

3.4 Other committees

Not applicable.

3.4.1. Management committee

Not applicable.

3.4.2. Advisory committee

Not applicable.

3.4.3 Review Board

Not applicable.

3.5 Test laboratories and other technical facilities

Not applicable.

3.6 Central organizational units

Project management, Monitoring, Data management:

Clinical Trials Centre Cologne (CTCC)

Faculty of Medicine of the University of Cologne

Gleueler Str. 269

50935 Cologne

3.7 Trial physicians and trial sites

The trial will be conducted as a national multicentre trial (> 10 trial sites) at several locations in Germany. If necessary, additional qualified trial sites can be recruited for the trial.

A list of trial sites, principle investigators and other trial staff will be kept in a separate list and will be continuously updated. Only principle investigators and participating trial sites that meet the necessary requirements, with qualifications and experience to conduct a clinical trial, will be selected for the trial. The sponsor appoints the principal investigator at each trial site, who in turn selects qualified and experienced personnel to conduct the trial.

3.7.1 Requirements for principal investigators and trial sites

PCI/principle investigators:

The PCI and principal investigators at the respective trial site are experienced dermatologists or plastic surgeons and must have received training in ICH-GCP before the start of the trial (e.g. GCP certificate, proof of investigator course).

Trial sites:

Trial site is either a medical practice or clinic specializing in dermatology and venereology and/or plastic and aesthetic surgery, which participates in outpatient (=ambulant) medical care, or a hospital approved according to §108 SGB V.

The trial site must perform liposuction using the “wet technique”. The procedure should be performed under tumescent anesthesia (TA). Supporting techniques such as vibration (PAL, power/vibration-assisted liposuction) or water-jet (WAL; water-jet-assisted liposuction) can be used. The trial site must also offer CDT in-house or via cooperation. If necessary, CDT can also be performed by a local physiotherapist (e.g. if patients have to travel long distances).

- a. In the case of trial sites with included cooperation centres or local physiotherapy practices, these must have at least one treating physiotherapist with a certificate in lymphatic drainage and at least two years of experience in lipedema treatment using CDT (at least 10 patients/year).

The trial site must have appropriate experience in the surgical treatment of lipedema patients and conservative CDT with at least 30 patients/year in the last 24 months. This means that the surgeon must have operated on at least 15 patients per year (or 30 patients in the last 24 months).

The trial site must have the appropriate personnel and material infrastructure (e.g. study nurse, study coordinator; premises e.g. for monitoring visits) and be able to demonstrate this.

The requirements for the trial sites are set out in a separate feasibility form and are collected and documented for each trial site.

Before the start of the trial, these requirements are checked by the CRA during selection visits.

3.8. Funding

The study is funded by the GBA.

The project management agency is the DLR (- Projektträger).

4 Trial conduct

4.1 General trial design

The trial is a multicentre, randomized, two-arm, investigator-blinded, controlled clinical trial. The aim is to include 450 patients.

4.1.1 Schedule and visits

After a run-in phase lasting up to seven months to eliminate edema and maintain the results using CDT, patients are randomized to one of the two treatment groups via internet randomization, provided that all inclusion and exclusion criteria are still met. Randomization takes place in a 2:1 ratio (intervention: control). In the intervention arm, patients will receive liposuction treatment (number of surgeries at the decision of the treating trial physician: maximum of 4 surgical procedures, with a minimum of 5 and a maximum of 7 weeks between each surgery) with possible accompanying CDT to maintain the surgical results as required by the participants. The primary end point (regarding leg pain in stage I, II or III) is assessed after an observation period of 12 months following the final liposuction surgery. This is followed by a further follow-up period of 24 months to observe and document the further course.

NOTE: Possible pandemic-related changes in the schedule and visit interval as well as the effects on the informed consent form and the statistical evaluation are described in chapters (4.3/4.6.1/4.7.1.4/5.5/6).

For a description of the individual visits, see Chapter 4.7.1.4 and Tables 2 and 3

Table 1: Schedule of the trial (note: without taking into account possible pandemic-related delays)

The duration for each individual participant is: max. 49 months

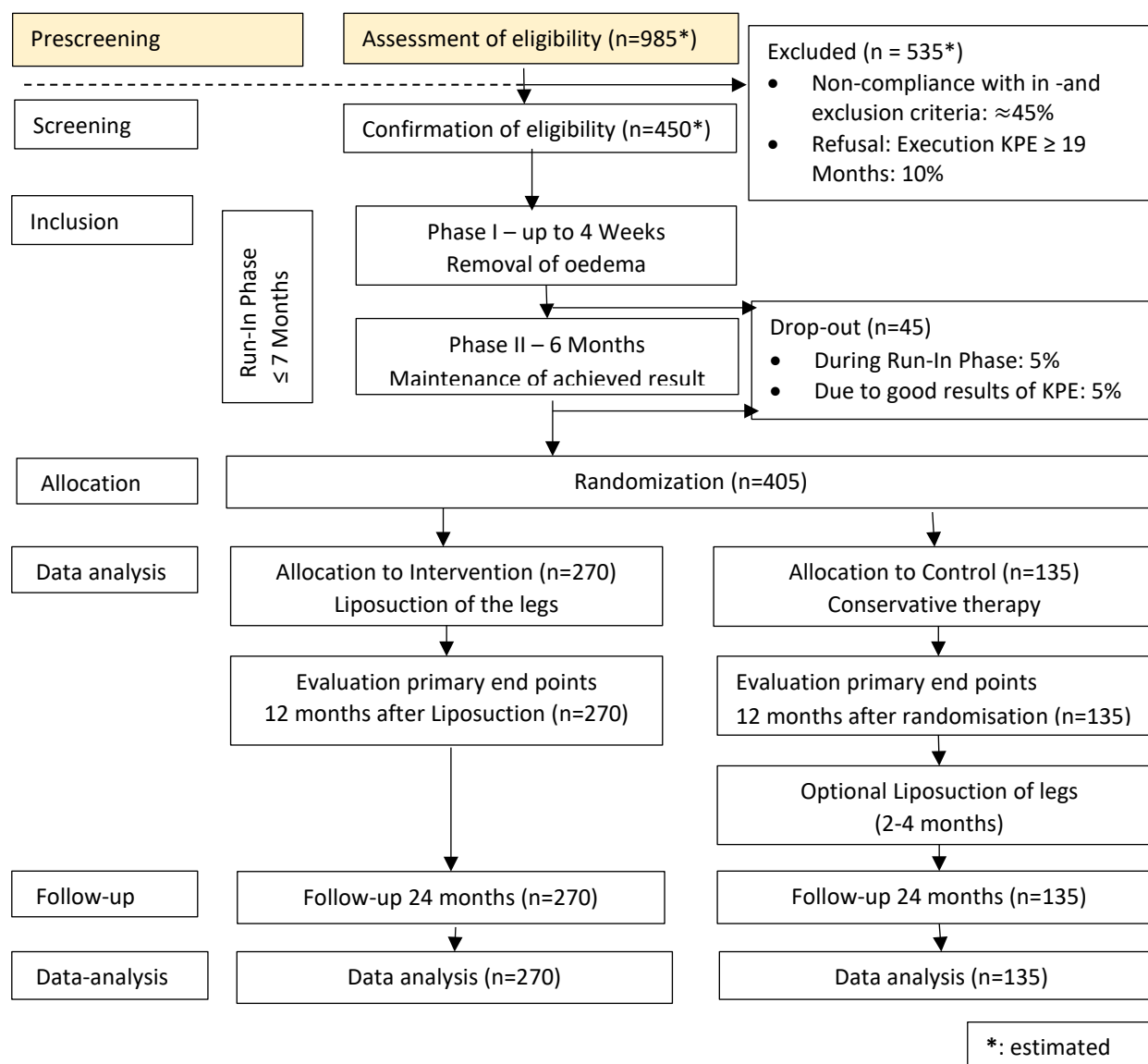
Recruitment period: 18 months

Duration of the entire trial: 66 months

Inclusion of first patient (first patient first visit, FPFV)	Q1/2021
Last patient included (last patient first visit, LPFV)	Q3/2022
End of trial of last patient (last patient last visit, LPLV)	Q3/2026
Final clinical trial report:	Q3/2027

End of the trial

The end of the trial is defined as the last visit of the last patient (LPLV).

Figure 1: Flowchart of the clinical trial

4.2 Discussion of the trial design

The clinical trial is a multicentre, controlled, randomized and investigator-blinded trial investigating the efficacy and safety of surgical treatment of lipedema compared to complex decongestive therapy (CDT) alone.

The risk of bias due to selection is minimized by randomization stratified by stage and site. Random assignment of patients to one of the two treatment groups (EXP or CON) is performed centrally via a 24/7 internet service (ALEA, FormsVision BV, Abcoude, NL) in a ratio of 2:1 (EXP:CON) on the basis of permuted blocks from ALEA using pseudorandom numbers. Blinding of the trial treatments is only possible to a limited extent. Surgical scars will be taped (dummy patch in the control group) and patients will be asked not to disclose the treatment received to the investigator. The statistical analysis is carried out by a blinded

statistician. In addition, the risk of bias as a result of the trial conduct or outcome determination must be minimized by careful standardization and control of the essential processes.

Since the primary end point could also be determined by mail or telephone, if necessary, less than 20% of missing values are assumed (reduced risk of bias due to attrition).

4.3 Benefit/risk assessment

The procedures of the trial are not expected to harm patients or pose a significant risk to patients. Patients participating in this trial will receive either the standardized surgical method of liposuction used in the guideline or the control intervention. The risk for the participating patients during the intervention is estimated to be negligible. Liposuction is limited to a maximum of 4 surgical procedures. It is performed by experienced dermatologists or plastic surgeons. There are general surgical risks that can occur with any surgical procedure (e.g. bleeding, wound healing disorder, infection, skin, nerve/vascular damage, scars, allergic reactions, thrombosis, embolism). Special risks of this surgery may include: swelling, oversuction, contour irregularities and surface depressions, recurrences of the disease, hematomas, seromas, cardiovascular effects.

The expected benefit is a short and long-term improvement in the clinical symptoms of lipedema [17].

Due to the low risk rates of liposuction for lipedema using the TA technique, a high benefit can be assumed [30].

The control interventions are carried out by experienced physiotherapists. CDT is adapted to the participants individual situation.

There are no risks associated with CDT, as diseases for which CDT may be contraindicated are taken into account by the exclusion criteria.

The principal investigators will ensure that the trial is conducted in accordance with the principles of Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki. At each visit, any adverse events that may have occurred will be documented (see also Chapter 3.3. DMC and Chapter 7 Safety).

NOTE: Should the pandemic situation lead to a postponement of elective procedures so that the liposuctions cannot be performed at the planned time in accordance with the trial protocol, the affected patients will continue to receive CDT, which corresponds to standard care. The risk for patients is not increased by a possible extension of CDT.

4.4 Selection of the trial population

Only females may participate in this study. Although lipedema-like changes occasionally also occur in men, these are attributed to hormonally effective therapies or pronounced hormonal disorders (e.g. hypogonadism or liver cirrhosis) and are therefore to be treated differently.

Due to the special need to protect minors in clinical trials, only females of legal age are included in the trial. Lipedema of the legs is considerably the more common and typical form of the disease and can be accompanied by other impairments such as lipedema of the arms. Patients with concomitant lipedema of the arms can only participate if it can be ensured that the co-affection of the arms has no influence on the primary end point (i.e. pain in the legs).

In order to keep the complexity of the trial design within reasonable limits, liposuction will only be performed on the legs as part of the trial.

The inclusion and exclusion criteria are designed in such a way that the results can be transferred to the target population in standard care.

4.4.1 Definitions

Screening:

Active efforts by the trial physician to identify trial patients who may be eligible for participation in a clinical trial. The full screening process includes a visit to the trial site where health status is appropriately assessed. It includes a series of questions, including general, health-related and anamnestic questions. Trial-related measures can only be carried out after informed consent is signed.

Screening Failure:

Trial patients with signed informed consent who have not met one or more criteria for participation in the trial.

Enrolment:

The process of enrolling a participant into the clinical trial. Once the trial patients has signed the informed consent form and completed all screening assessments and is eligible according to the inclusion/exclusion criteria, she can be enrolled in the trial.

Drop-out:

Trial patients who withdraw from the trial before the end of their trial period.

The reasons for this may be:

- Exclusion by the trial physician or the sponsor due to an exclusion criterion, failure to meet an inclusion criterion at the P2 visit or failure to comply with the trial protocol requirements;
- Premature termination of the trial at the trial participants own request by withdrawing consent to participate in the trial. This case is referred to as withdrawal;
- Trial participants informs that she no longer wishes to participate in the trial without withdrawing her consent to participate in the trial.
- Contact with the trial participant is lost. This case of premature termination of trial participation is referred to as lost to follow-up.

The withdrawal of consent to participate in the trial (withdrawal) results in the immediate deletion of all data collected up to that point (GDPR Art. 17 para. 1 lit. b) In the event of a drop-out for other reasons, the data collected up to that point will not be deleted and can be used accordingly.

Replacement of Drop-outs/Screening Failures:

- Screening failures → are replaced;
- Drop-outs before randomization → are only replaced if the drop-out rate is greater than 10%;
- Drop-outs after randomization → will not be replaced.

End of Trial (EOS)

- For trial participants who have regularly completed the trial: Date of completion of all assessments required by the trial protocol in this trial for the trial participant.
- For drop-outs: Date of the last documented visit/assessment of the trial participants required by the trial protocol.

4.4.2 Inclusion criteria

1. signed informed consent for participation in the trial
2. female sex
3. age $\geq$ 18 years
4. confirmed lipedema of the legs stage I, II or III
5. average leg pain of $\geq$ 4 points on a numerical scale within the last 4 weeks
6. documentation of an insufficient symptom relief with conservative treatment
7. willingness and ability to undergo measurements according to the trial protocol before, during and, if necessary, after the liposuction treatment
8. full legal capacity

4.4.3 Exclusion criteria

1. Concurrent lipedema of the arms interfering with the primary end point (i.e. average leg pain), at the decision of the investigator
2. Previous liposuction
3. Diseases affecting operability at the decision of the investigator, e.g. cardiac diseases, coagulation disorders, metabolic diseases, active infectious diseases, epilepsy, diseases requiring drug immunosuppression or anticoagulation; allergies to drugs used before and during surgery
4. Weight >120.0 kg
5. Diseases affecting conservative therapy, at the decision of the investigator, e.g. heart failure (volume stress), lack of physical ability to wear compression stockings (e.g. joint diseases, neurological deficits)
6. Primary obesity without disproportion and unrelated to lipedema
7. Secondary obesity
8. Other fat distribution disorders than lipedema (e.g. painless lipo-hypertrophy, benign symmetrical lipomatosis or lipomatosis dolorosa)
9. Causes of edema other than lipedema (e.g. lymphedema, phleboedema or myxedema)
10. Unwillingness to use adequate contraception
11. Pregnancy
12. Breast feeding
13. Plans to use a lymphomat during the trial
14. Participation in other clinical trials
15. Purely cosmetic motivation to participate

Note:

Methods with a Pearl Index of less than 1% are considered safe contraceptive measures:

- a. Oral hormonal contraception ("pill")
- b. Dermal hormonal contraception
- c. Vaginal hormonal contraception (NuvaRing®)
- d. Contraceptive patches
- e. Long-term effective, injectable contraceptives
- f. Progesterone-releasing implant (Implanon®)
- g. Tubal ligation (female sterilization)
- h. Hormone-releasing intrauterine device ("hormone coil")
- i. Double barrier methods

The following are therefore not considered reliable: Condom plus spermicide, simple barrier methods (vaginal pessary, condom, female condom), copper IUD, rhythm methods, basal body temperature method, coitus interruptus.

4.5 Termination criteria

The sponsor/CI has the right to terminate the trial prematurely if there are relevant medical or ethical concerns or if it is no longer certain that the trial will be conducted in accordance with the trial protocol. The reasons for discontinuing the trial must be documented in detail. All trial patients who are still undergoing treatment at the time of discontinuation should, if possible, take part in a final visit (assessment of the parameters documented at V6), which must be documented.

The sponsor must be informed immediately if an investigator has ethical concerns regarding the continuation of the clinical trial. The participant has the right to discontinue the trial at any time (even without giving reasons). She will not suffer any disadvantages as a result.

The trial is discontinued for an individual participant if:

- the investigator does not consider it justifiable for the participant to continue participating in the trial;
- if the inclusion and exclusion criteria are no longer met after the initiation phase (run in phase)
- the participant does not comply with the trial visits and treatments specified in the trial protocol (in particular if two or more consecutive visits are missed and/or the primary end point cannot be assessed);
- the participant repeatedly fails to follow the instructions of the treating investigator and thus fails to comply with the signed informed consent form for trial participation;
- the general state of health deteriorates so severely due to the accumulation of adverse events or other circumstances that continued participation is not medically justifiable and/or cannot be guaranteed;
- the participant becomes pregnant before reaching the primary end point;
- the participant can no longer be contacted after several attempts;
- the participant moves and cannot be transferred to another trial sites.
- the participant has not undergone CDT for more than 30 days during the run-in phase.

The trial can be discontinued at a trial site if:

- the site does not recruit adequately in consultation with the sponsor after implementation of appropriate measures;

- there is no adequate replacement in the event of a change of principal investigator;
- the site regularly violates the trial protocol and the implementation of corrective and preventive measures does not improve the situation;
- the principal investigator no longer wishes to continue participation in the trial at his/her own trial site after consultation with the sponsor;
- the trial site does not include and treat participant in accordance with ethical principles and ICH-GCP.

Early termination of the trial will be considered if:

- the risk-benefit ratio for the participant changes significantly;
- it is no longer ethically justifiable to continue the treatment;
- the DMC recommends discontinuation of the trial;
- it is no longer practicable to complete the trial.

4.6 Treatments

4.6.1 Treatments used

Run-in phase:

In order to create the same starting conditions for all patients before randomization, all patients should initially receive conservative treatment as part of a “run-in phase” (introductory phase). This involves the use of CDT. In accordance with the recommendation of the S1 guideline [6], this consists of manual lymphatic drainage, compression therapy, movement exercises and skin care. The run-in phase is divided into phase I to eliminate edema, followed by phase II of CDT to maintain the results achieved. Phase I lasts up to 4 weeks and phase II up to 6 months. CDT should be performed by physiotherapists in the trial site as far as possible, taking into account the S1 guideline, which serves as a manual [6]. CDT can also be carried out outside the centre via cooperation with medical practices or by local physiotherapy practices (e.g. in the case of long journeys), whereby the examinations must take place at the trial site in accordance with the visit schedule. One third of the patients will be allocated to the control arm after randomization.

NOTE: If the pandemic situation leads to a postponement of elective procedures so that the liposuctions cannot be performed at the planned time according to the trial protocol, the P2 visit and thus also the randomization must be postponed until it becomes foreseeable that the liposuctions can be performed en bloc with the necessary time intervals (1st surgery after 4 weeks at the latest, all further liposuctions at least 5 to max. 7 weeks later). In this case, all

patients will continue to be treated with CDT, which may extend the duration of the run-in phase. If necessary, patients will come to the trial site between trial visits to receive a new prescription for CDT in accordance with standard care. No parameters are recorded during this visit.

Liposuction intervention group:

Liposuction is carried out using the “wet technique” and should be performed under local tumescent anesthesia (TA). Supporting techniques such as vibration or water jet can be used. TA can also be combined with sedation or general anesthesia, depending on the findings and concomitant diseases. In TA, the subcutaneous area to be treated is infiltrated with a solution of a local anesthetic. The resulting fat-solution mixture is then suctioned off. This procedure is considered the standard to avoid injury to subcutaneous blood and lymph vessels and nerves as far as possible [17]. As a rule, several liters of tumescent solution are introduced into the treatment area. The large volume that is infused and later aspirated, poses hemodynamic risks due to the stress to the circulation. In addition, the transfer of large quantities of the local anesthetic into the systemic circulation can have systemic pharmacological effects. For this reason, maximum volumes for the tumescent solution and the amount of fat to be suctioned off per session have been defined.

The tumescent solution before each liposuction or, in the case of WAL, during liposuction is limited to a maximum volume of 10% of the participant's body weight. The absolute maximum of the infused solution must not exceed 8 liters per procedure. The maximum volume of liposuctioned fat tissue must not exceed 6 L for a body weight ≤ 80 kg per procedure. With a body weight > 80 kg, this volume of liposuctioned fatty tissue can be increased to a maximum of 8 L per procedure. This is particularly important for patients in stage III. These specified volumes are based on the usual volumes currently used in surgical lipedema centres and on the safety-relevant published data on liposuction in tumescent anesthesia [11] [29].

The surgeries are performed in accordance with the local applicable standard of the respective trial site. For this purpose, the trial sites receive a guideline explaining the surgical methods and volumes for the tumescent solution to be infused as well as the amount of adipose tissue to be aspirated with recommendations for execution. The eCRF records and documents the liposuction method selected, the volume of tumescent solution used for liposuction and the amount of fat aspirated. The localization of the procedure is also documented.

The chosen liposuction method for a participant must be retained by the surgeon for further procedures (max. 4 procedures with an interval of 5-7 weeks).

Continuation of CDT following the intervention is carried out as required by the participant and serves to maintain the treatment result.

Control group CDT

The control group is treated with CDT for 12 months from randomization in order to maintain at least the results achieved at the end of the run-in phase. At each trial visit, the trial physician assesses the treatment progress of patients in the control arm and adapts the CDT to the individual participant. For this purpose, trial physicians receive an information sheet in accordance with the S1 guideline and the Therapeutic Products Ordinance, which describes how to prescribe CDT. The frequency, duration and applied CDT are documented during the trial visits. Any necessary changes are communicated to the physiotherapist in charge of the CDT.

After these 12 months, patients can decide to undergo liposuction treatment, in case the inclusion and exclusion criteria are still met.

4.6.2. Method for allocating patients to the treatment groups

Patients are randomly allocated to one of the two treatment groups (EXP or CON) centrally via a 24/7 internet service (ALEA, FormsVision BV, Abcoude, NL) in a ratio of 2:1 (EXP: CON) on the basis of permuted blocks. Allocation is stratified by stage and site. Randomization can be performed by all trial members except the blinded trial physician and the blinded trial personnel.

4.6.3 Blinding

Blinding of the trial treatments is only possible to a limited extent. The patients are aware of the treatment performed. Nevertheless, the surgical scars are taped by unblinded trial personnel before each visit (dummy plaster in the control group) and the patients are asked not to disclose the treatment received to the blinded investigator. The blinded examination of the participant must not be performed by an operating/unblinded physician. The blinded investigator is not given access to the database and is informed that he/she may not inspect the participant file of the participant examined by him/her (with the exception of emergencies). The data by the blinded investigator will be documented on working sheets and entered into the eCRF by unblinded trial personnel in a timely manner. The statistical analysis is carried out by a blinded statistician.

4.6.3.1. Unblinding

Not applicable

4.6.4 Previous therapy and concomitant therapy

Physical activities, in particular water sports, are permitted as an optional supportive treatment for lipedema, as recommended in the guidelines. However, the type and intensity of these activities should not be changed for the duration of the trial. The supportive use of lymphomats, on the other hand, is not permitted due to the desire for a homogeneous participant population.

Further liposuctions are prohibited for the entire duration of the trial, with the exception of liposuctions on the arms (diagnosis: lipedema), which can be performed at the earliest 12 months after the last liposuction on the legs - in the intervention group after visit V2, in the control group after visit V4. However, this is not a trial measure and the costs must be paid by the patients themselves.

4.6.4.1 Emergency evasive therapy

Not applicable.

4.6.5 Further treatment after the end of the clinical trial

Further treatment after the end of the clinical trial is provided as part of standard care.

4.7 Efficacy and safety parameters

4.7.1 Measurement of efficacy and safety parameters

4.7.1.1 Primary outcome measure

The primary outcome measure is the relevant reduction of the average leg pain intensity (stage I, II or III; ≥ 2 points on a numerical rating scale) over the last 4 weeks 12 months after completion of liposuction treatment (intervention group) or 12 months after randomization (control group) compared to the time of randomization, respectively. The average leg pain over the last 4 weeks is recorded as part of the German Pain Questionnaire:

Figure 2: Assessment of average pain over the last four weeks using the German Pain Questionnaire

Please indicate the intensity of your pain below. Please mark on the scales below how strong your pain has been (while taking your usual medication). A value of 0 means you have no pain, a value of 10 means you are experiencing pain as bad as you can imagine. The numbers in between represent increasing levels of pain.										
Now please indicate your average pain intensity during the past 4 weeks:										
[0]	[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]
no pain										worst imaginable pain

4.7.1.2 Secondary and other outcome measures

In order to comprehensively assess the possible superiority of surgical treatment of lipedema (stage I, II or III) by means of liposuction compared to the use of CDT, the following outcome measures should also be considered (change in each case 12 months after completed liposuction treatment (intervention group) or 12 months after randomization (control group) compared to the time of randomization, respectively):

- Change in intensity according to von Korff et al. regarding leg pain (stage I, II or III). The severity is calculated based on the questions of the German Pain Questionnaire according to von Korff et al [23]. The assessment of pain intensity, impairment and additional information on the days of impairment are included in the calculation of the severity.
- Change in health-related quality of life according to SF-36, DLQI (a clinically relevant change corresponds to ≥ 4 points change in the DLQI cumulative score [25] and WHOQOL-BREF
- Change in general impairment according to Schmeller et al. (2010) (modified form) [26]
- Change in susceptibility to depression according to PHQ-9 (a clinically relevant improvement corresponds to ≥ 5 points reduction in the PHQ-9 cumulative score [27])
- Changed in hematoma proneness according to Schmeller et al. (2010), (modified form)
- Changed prevalence of edema
- Modification in the scope of physical therapy
- Change in body fat percentage, determined according to the formula by Wright et al. (1981) using a measuring tape at the following points:
 - Abdominal circumference: Measurement at the level of the navel. The tape measure is placed horizontally around the body.
 - Neck circumference: measurement below the larynx
 - Body height
 - Hip circumference: the widest part of the hip is measured
- Change in the leg circumference of the left and right leg using a measuring tape at five predetermined measuring points:
 - Lower leg ankles
 - mid-calf
 - knee
 - Thigh, 10 cm below the groin
 - Hips (the widest point on the hip is measured)
- Relevant reduction in movement restriction (stage I, II or III; ≥ 9 points improvement in the LEFS cumulative score [29])

The data for the other time points V1, V3 to V6 are considered analogously. The following are also recorded:

- Number of recurrent surgeries
- Number of (serious) adverse events
- Treatment discontinuation caused by (serious) adverse events
- Optional: change in leg volume of the left and right leg (e.g. using perometry etc.)

4.7.1.3 Safety analysis

All adverse events are documented and recorded in the eCRF. See chapter 7.

4.7.1.4 Description of the individual visits

The visits are conducted at the following times (see Table 3).

Recruitment procedure

After potential trial patients have been identified by a central registration office, the patients are contacted by the trial sites and summoned.

Screening/baseline visit

After the participant has been pre-selected (telephone interview (pre-screening)), the investigator provides both verbal and written information about the trial and liposuction during the baseline visit. The participant is informed about the objectives of the clinical trial, the benefits and risks as well as the potential side effects of the treatment. In addition to the participant information sheet, the participant receives a centre-specific information sheet describing the procedure and risks of liposuction. If the participant decides to participate in the clinical trial after an appropriate period of reflection, both the investigator and the participant sign and date the informed consent form personally. Written consent is given before the start of the trial. It explicitly includes consent to the collection of participant data and pseudonymized forwarding of participant data to the sponsor and the trial management team (e.g. to CTCC and biometrics) and evaluation of participants data in pseudonymized form.

The inclusion and exclusion criteria are checked (screening) and after inclusion of the participant in the trial (enrollment) the following characteristics are documented and recorded

in the eCRF: Master data, diagnosis, medical history, pregnancy test (urine), previous conservative treatment, weight, concomitant medications, body fat percentage, body fat distribution, leg circumference on the upper and lower leg of the left and right leg, occurrence of leg edema, the arm circumference of both arms and the skin appearance. Measurement of leg volume is optional. No CDT must have taken place at least two days before this examination, as this could falsify the circumference values. The participant will be informed of this in advance when making an appointment for this visit.

Quality of life is assessed using the Short Form (SF)-36 health questionnaire with reference to the previous 4 weeks, the Dermatology Life Quality Index (DLQI) and the WHO Quality of Life BREF (WHOQOL-BREF) [31, 32]. Pain is assessed using the German Pain Questionnaire ("Questionnaire at the start of treatment" [33]), and the change in general impairment using a questionnaire (modified according to Schmeller). To record the pain in the legs, the patients are asked to complete the German Pain Questionnaire with regard to their pain in the legs. To determine the primary end point, the average pain over the last 4 weeks is recorded using the German Pain Questionnaire. In addition, the proneness to hematoma is assessed using a questionnaire modified according to Schmeller et. al [26].

Functional limitations are assessed using the Lower Extremity Functional Scale (LEFS) [29]. A proneness towards depression is recorded using the Participant Health Questionnaire-9 (PHQ-9) [32]. The mentioned questionnaires are completed by the patients. The above-mentioned trial-specific assessment will be documented by the investigator or, from visit V1 on, by the blinded investigator.

If the inclusion criteria are not fully met or an exclusion criterion is violated, the participant cannot be included in the trial (screening failure).

Run-in phase (up to 7 months) for all recruited patients

(Note: excluding possible pandemic-related delays)

The patients then undergo a run-in phase (initiation phase) in which edema elimination is initiated for up to 4 weeks (phase I), which is continued by 6 months of standardized conservative therapy, in particular CDT (phase II), in order to maintain the result achieved. The starting point of the initiation phase is the first CDT treatment after inclusion in the trial. For this purpose, the participant informs her trial site promptly (e.g. by telephone) of the date of the first CDT performed after the baseline examination, as the further visits will depend on this.

The prescribed, standardized, conservative treatment measures are documented in the eCRF. No CDT must have taken place at least two days before these visits. At visits P1 and P2, body fat percentage, body fat distribution, weight, concomitant medication, leg and arm circumference, occurrence of leg edema, skin appearance, optional leg volume measurement

by the investigator are recorded and checked. In addition, pain is recorded using a numerical rating scale (patients are instructed to indicate only the pain in their legs); pain progression questionnaire [35], general impairment, functional limitations, hematoma proneness and adverse events. The above-mentioned questionnaires (see screening/baseline visit) on quality of life and depression symptoms are also collected. Furthermore, all inclusion and exclusion criteria are checked again. If an inclusion criterion is violated or an exclusion criterion is met, the participant is excluded from the trial (drop-out). The participant will not be replaced unless the drop-out rate is more than 10% (approximately = 5% drop-out + 5% CDT success).

If all inclusion and exclusion criteria are met, randomization into the intervention and control arm (2:1) takes place at P2.

If necessary, the patients come to the trial site between the trial visits to receive a new prescription for CDT. No parameters will be documented.

NOTE: If the pandemic situation leads to a postponement of elective procedures so that the liposuctions cannot be performed at the planned time according to the trial protocol, the P2 visit and thus also the randomization must be postponed until it becomes foreseeable that the liposuctions can be performed en bloc with the necessary time intervals (1st surgery after 4 weeks at the latest, all further liposuctions at least 5 to max. 7 weeks later). In this case, all patients will continue to be treated with CDT, which may extend the duration of the run-in phase. Patients must again consent to the modified trial procedure in order to continue participation (5.5). As soon as it becomes apparent that elective procedures can take place again, the P2 visit is planned and implemented so that all further measures can be implemented in accordance with the trial protocol.

Patients who have already undergone the P2 visit and have therefore also been randomized will continue to receive CDT, provided they have been assigned to the intervention group, until the liposuction(s) can be performed again en bloc according to the trial protocol. Before these patients can undergo liposuction(s), their operability must be checked again in accordance with the trial protocol (ECG and blood count). The patients must consent to the modified trial procedure for further participation (see point 5.5).

As soon as the liposuctions can be performed again, the patients are operated. It should be noted that for patients who have not yet been affected by the postponement of liposuctions, the time windows defined in the trial protocol must be adhered to in accordance with the trial protocol. Patients who are affected by the postponement must be operated en bloc at the first possible opportunity. If possible, the patients with the greatest deviation from the initial time window should be operated first. In addition, trial patients should be given priority over other liposuction patients, and patients assigned to the control group will implement the measures and visits specified in the trial protocol.

Further course of the trial after randomization:**Intervention group**

Two thirds of the patients subsequently undergo liposuction surgery(ies). The number varies according to need (maximum of 4 surgeries) with a 5-7 week interval between each surgery. For this purpose, the patients are informed again about the surgery in accordance with the clinical routine and tested for their operability (ECG, blood test, pregnancy test (blood/urine). Information on the respective surgeries and any adverse events are documented in the database (OP-V1-4). ECG and laboratory tests can also be carried out by the general practitioner if necessary.

Further visits (V1, V2) in the intervention group during the 12-month observation period take place 6 and 12 months after completion of the last liposuction surgery. Body fat percentage, body fat distribution, weight, leg and arm circumference, optional volume measurement of the legs, the occurrence of leg edema, skin appearance, functional limitations, hematoma proneness, pain, general impairment, adverse events and concomitant conservative therapy applications are documented. Pain will be recorded using the German Pain Questionnaire (Course of pain-Questionnaire to be filled out with regard to the legs [35]). To determine the primary end point, the average pain over the last 4 weeks is recorded using the German Pain Questionnaire. In addition, the concomitant medications are checked and changes documented, and the SF- 36 questionnaires with reference to the last 4 weeks, DLQI and WHOQOL-BREF, PHQ-9 are recorded. No CDT must have taken place for at least two days prior to these visits.

If CDT is prescribed between and after the last surgery as an accompanying measure, prescriptions are issued according to standard care on or between visits, whereby no parameters are recorded when prescriptions are issued outside the specified trial visits.

Control group

After randomization, prescriptions for CDT are issued according to standard care, depending on the patient's needs, with no parameters being recorded outside of visits V1 and V2.

Visits V1 and V2 for the control group take place after 6 and 12 months and body fat percentage, body fat distribution, weight, leg and arm circumference, optional volume measurement of the legs, the occurrence of leg edema, skin appearance, functional limitations, hematoma proneness, pain, general impairment, adverse events and conservative therapy applications are documented. No CDT must have taken place for at least two days prior to

these visits. Pain is recorded using the German Pain Questionnaire (pain progression-questionnaire to be filled out with regard to the legs [35]). To determine the primary end point, the average pain over the last 4 weeks is recorded using the German Pain Questionnaire. In addition, the concomitant medications are checked and changes documented and the questionnaires SF-36 with reference to the last 4 weeks, DLQI and WHOQOL-BREF, PHQ-9 are recorded.

At visit V2, the inclusion and exclusion criteria are checked again. If these criteria are met, patients from the control arm can opt for liposuction after 12 months. For this purpose, the patients are again informed about the surgery in accordance with the clinical routine and their operability is checked (ECG, blood test, pregnancy test (blood/urine)). Information on the respective surgeries and any adverse events are documented in the database (OP-V1-4). If concomitant CDT is ordered after surgery, the prescription must be issued according to standard care (i.e. no examinations are recorded when prescriptions are issued outside the trial visits).

If the inclusion and exclusion criteria are not met, the participant cannot undergo liposuction but can remain in the trial.

Follow-up of both groups

During the subsequent 24-month follow-up period, 4 visits (V3-6) are scheduled every 6 months. At these visits, body fat percentage, body fat distribution, weight, leg and arm circumference, optional volume measurement of the legs, the occurrence of leg edema, skin appearance, functional limitations, hematoma proneness, pain, general impairment, adverse events and concomitant conservative therapy applications are documented. No CDT must have taken place for at least two days prior to these examinations. In addition, the data from the questionnaires on quality of life (SF-36, DLQI and WHOQOL-BREF) and proneness to depression (PHQ-9) are recorded. During all visits, the concomitant medication is also checked and changes documented. Pain is recorded using the German Pain Questionnaire (pain progression-questionnaire to be filled out with regard to the legs [35]).

If necessary, the patients come to the trial site between the trial visits to receive a new prescription for CDT. No parameters are recorded during this visit.

Table 2: Visits during the trial and follow-up of the intervention group (Note: without taking into account possible pandemic-related delays)

Intervention Group						12 months observation		24 month follow-up			
Visits	B V	Start- time	P1 ^a	P2 ^a	OP-V (1-4) ^a	V1 ^a	V2 ^a	V3 ^a	V4 ^a	V5 ^a	V6 ^a
						Months after completion of OPs		Months after observation period			
Time	0	Start 1. CDT	After max. 4 weeks (28 days) after the start of the 1st CDT	After 6 Month (180 days) after P1	After max. 4 weeks 1st OP, then after 5-7 weeks max. 3 further OPs	6 Month (180 days) after last OP	12 Month (360 days) after last OP	6 Month (180 days) after V2	12 Month (360 days) after V2	18 Month (540 days) after V2	24 Month (720 days) after V2
Time frame			± 4 Days	± 14 Days		± 14 Days	± 14 Days	± 14 Days	± 14 Days	± 14 Days	± 14 Days
Examination											
Informed consent	x										
Clarification prior to Op	x				x**						
In- and exclusion criteria	x			x							
Background data	x										
Diagnosis	x										
Anamnesis	x										
Preliminary treatment, conservative	x										
Weight	x		x	x		x	x	x	x	x	x
Supplementary medication	x		x	x	x	x	x	x	x	x	x
Leg circumference [§] (UL, LL, left, right)	x		x	x		x	x	x	x	x	x
Occurrence of leg edema	x		x	x		x	x	x	x	x	x
Determination of body fat percentage and distribution [¶]	x		x	x		x	x	x	x	x	x
OPTIONAL: measuring leg volume	x		x	x		x	x	x	x	x	x
Arm circumference [§]	x		x	x		x	x	x	x	x	x
Skin image [°]	x		x	x		x	x	x	x	x	x
Quality of life (SF-36, DLQI, WHOQOL-BREF)	x		x	x		x	x	x	x	x	x
Depression (PHQ-9)	x		x	x		x	x	x	x	x	x
Hematoma proneness (modified according to Schmeller et al. 2010)	x		x	x		x	x	x	x	x	x
General impairment (modified according to Schmeller et al. 2010)	x		x	x		x	x	x	x	x	x
Pain (German Pain questionnaire) ^{xxx}	x		x	x		x	x	x	x	x	x
Functional limitations ^b (LEFS)	x		x	x		x	x	x	x	x	x
Randomization				x							
ECG (at least 1 time before 1st OP)					x						

Blood work (incl. thrombocytes, creatinine, GFR, electrolytes, GGT, GOT, GPT, Quick, INR, CRP)					x						
Pregnancy test (Urine at BV; otherwise blood or urine)	x			x	x						
Adverse events			x	x	x	x	x	x	x	x	x
OP†					x						
Recurrence of treatment						x	x	x	x	x	x
Standardized conservative therapy ¥ including prescription § (including therapy report)	x		x	x	x	x	x	x	x	x	x

BV = baseline visit, P1 = run-in phase 1, P2 = run-in phase 2, OP-V = surgical visit, V = visit, CDT = complex decongestive therapy, a) Note: 1 week corresponds to 7 days, 1 month corresponds to 30 days, UL= upper leg (thigh), LL = lower leg, SF-36 = Short Form 36, DLQI = Dermatology Life Quality Index, WHOQOL-BREF = World Health Organization Quality of Life-abbreviated version of the WHOQOL 100, PHQ-9 = Participant Health Questionnaire-9, LEFS = Lower Extremity Functional Scale, ** Patients are informed about the risks of liposuction according to clinical standards before the first surgery, ° Hematomas, lumps,† Surgical data, method, volume [mL] of tumescent solution, liposuction volume [mL], localization, ¥ In particular, use of CDT (manual lymphatic drainage, skin care, compression therapy, exercise therapy), frequency, duration - after last surgery, if necessary a) up to -3 weeks, b) mobility, hygiene, § NOTE: Prescriptions may be issued between trial visits for CDT according to standard care at the trial sites. No parameters are documented for prescriptions issued outside the specified trial visits. . xxx For BV "Questionnaire at the start of treatment" for all subsequent visits Pain progression questionnaire, § Note: no CDT must have taken place at least 2 days before this visit, # Note on recurrent surgeries: these are not permitted within the scope of the trial, Ω Body fat distribution measurement using a measuring tape (in cm) : Abdominal circumference: height of belly button, hip circumference: widest point of hip

Tabelle 1: Visits during the trial and follow-up of the control group (note: not taking into account possible pandemic-related delays)

Control Group					12 months Observation			24 months follow-up			
Visits	BV	Start-time	P1 ^a	P2 ^a	V1 ^a	V2 ^a	OP-V (1-4) ^{a,*}	V3 ^a	V4 ^a	V5 ^a	V6 ^a
					Months after randomization			Months after completion of surgery or observation period			
Time	0	Start 1 st CDT	max. 4 weeks (28 days) after the start of the 1 st CDT	6 Month (180 days) after P1	6 Month (180 days) after P2	12 Month (360 days) after P2	After max. 4 weeks 1 st OP, then after 5-7 weeks max. 3 further OPs	6 Month (180 days) after last OP	12 Month (360 days) after last OP	18 Month (540 days) after last OP	24 Month (720 days) after last OP
Time Frame			± 4 Days	± 14 Days	± 14 Days	± 14 Days		± 14 Days	± 14 Days	± 14 Days	± 14 Days
Examination											
Informed consent	x										
Clarification prior to OP	x						x**				
In- and exclusion criteria	x			x		x					
Reference data	x										
Diagnosis	x										
Anamnesis	x										
Preliminary treatment, conservative	x										
Weight	x		x	x	x	x		x	x	x	x
Supplementary medication	x		x	x	x	x	x	x	x	x	x
Leg circumference (UL, LL, left, right) [§]	x		x	x	x	x		x	x	x	x
Occurrence of leg edema	x		x	x	x	x		x	x	x	x
Determination of body fat percentage and distribution [¶]	x		x	x	x	x		x	x	x	x
OPTIONAL: measuring leg volume	x		x	x	x	x		x	x	x	x
Arm circumference [§]	x		x	x	x	x		x	x	x	x
Skin pattern [°]	x		x	x	x	x		x	x	x	x
Quality of life (SF-36, DLQI, WHOQOL-BREF)	x		x	x	x	x		x	x	x	x
Depression (PHQ-9)	x		x	x	x	x		x	x	x	x
Hematoma proneness (modified according to Schmeller et al. 2010)	x		x	x	x	x		x	x	x	x
General impairment (modified according to Schmeller et al. 2010)	x		x	x	x	x		x	x	x	x
Pain (German Pain questionnaire xxx)	x		x	x	x	x		x	x	x	x
Functional limitations ^b (LEFS)	x		x	x	x	x		x	x	x	x
Randomization				x							
ECG (at least 1 time before 1 st OP)							x				
Blood work							x				

(incl. thrombocytes, creatinine, GFR, electrolytes, GGT, GOT, GPT, Quick, INR, CRP)											
Pregnancy test (Urine at BV; otherwise blood or urine)	x					x	x				
Adverse events			x	x	x	x	x	x	x	x	x
OP†							x				
Recurrence of treatment								x	x	x	x
Standardized conservative therapy including prescription (including therapy report)	x		x	x	x	x	x	x	x	x	x

BV = baseline visit, P1 = run-in phase 1, P2 = run-in phase 2, OP-V = surgical visit, V = visit, CDT = complex decongestive therapy, a) Note: 1 week corresponds to 7 days, 1 month corresponds to 30 days, UL = upper leg (thigh), LL = lower leg, SF-36 = Short Form 36, DLQI = Dermatology Life Quality Index, WHOQOL-BREF = World Health Organization Quality of Life - abbreviated version of the WHOQOL 100, PHQ-9 = Participant Health Questionnaire-9, LEFS = Lower Extremity Functional Scale, ** = Patients are informed about the risks of liposuction according to clinical standards before the first surgery. Hematomas, lumps, † Surgical data, method, volume [mL] of tumescent solution, liposuction volume [mL], localization, ¥ In particular application of CDT (manual lymphatic drainage, skin care, compression therapy, exercise therapy), frequency, duration a) up to -3 weeks b) mobility, hygiene § NOTE: If necessary, prescription for CDT according to standard care between the trial visits at the trial site. No parameters are recorded when prescriptions are issued outside the specified trial visits. xxx For BV "Questionnaire at the start of treatment", for all subsequent visits pain progression questionnaire, § Note: no CPD must have taken place at least 2 days prior to this visit t# Note on recurrent surgeries: these are not permitted within the scope of the trial, Ω Body fat distribution: measurement using a measuring tape (in cm): Abdominal circumference at navel height, hip circumference: widest point of hip

Duration of the clinical trial

(Note: without taking into account possible pandemic-related delays)

The duration for each individual participant is a maximum of 49 months after the start of the initiation phase (defined as the start of the 1st CDT).

4.7.2 Rationale of the measurement methods

The three stages of the disease were taken into account when selecting the outcomes in order to show that participants in different stages can benefit from liposuction in different ways: In stages I and II, general functional impairment is less relevant than in stage III. In stages I and II, the main aspect is the participant's pain. Pain is no longer the most important aspect for stage III participants, as the pain can often no longer be completely resolved. In stage III, the main aspect is primarily on combating functional limitations (e.g. mobility, hygiene). In consideration to these differing main aspects of the various stages, pain was chosen as the primary end point, and the secondary end point were aligned in such a way that, in addition to pain, the aspects of restricted movement, etc. were also taken into account. The primary end point, the average leg pain over the last 4 weeks, is recorded using the validated German pain questionnaire "Questionnaire at the start of treatment" [33] and "pain progression questionnaire" [35]).

The secondary end point „movement restriction“ is recorded using the LEFS and Schmeller et al. 2010 questionnaires (modified form). The secondary end point change in average leg pain intensity (stage I, II or III) is based on the validated questions of the German Pain Questionnaire and is calculated according to von Korff et al [23]. This calculates information on pain intensity, pain-related impairment and the days on which patients were unable to perform their usual activities.

Various aspects of quality of life are assessed on the basis of validated questionnaires, as lipedema causes a reduction in patients' quality of life. The questionnaires have been validated for various questions and have already been used in clinical studies.

The Dermatology Life Quality Index (DLQI) [25] is a questionnaire validated for dermatological diseases. The Short Form (SF)-36 and the WHO Quality of Life BREF (WHOQOL-BREF) [31] [32] are validated questionnaires of general quality of life in patients with chronic diseases. Patients with lipedema suffer more from depressive moods, and successful treatment could lead to an improvement. The Participant Health Questionnaire-9 (PHQ-9) [32] is used to map this outcome. This has been validated for use in concomitant depression and has also been published for lipedema. Movement restrictions are assessed using the Lower Extremity Functional Scale (LEFS) [29].

The selection of these measurement instruments is justified by the fact that lipedema has far-reaching effects on various areas of the participant's life, including socially relevant areas, which are recorded by these measurement instruments.

There is currently no validated questionnaire that specifically measures quality of life in relation to lipedema.

A disease-specific questionnaire is therefore used in the trial to assess the specific aspects of lipedema with regard to quality of life. (Change in general impairment according to Schmeller et al. (2010) in modified form) [26]). This is also used to record hematoma proneness and movement restrictions. The assessment of the secondary end point "change in general impairment" is highly relevant for all three stages of the disease. Successful treatment could lead to an improvement.

The volume of the legs in lipedema patients is associated with pain sensitivity and, in particular, movement restriction. The optional secondary end point "change in leg volume, e.g. by volumetry" takes this into account. A change in leg volume is to be expected as a result of the surgical and/or CDT measures. A reduction in leg volume could be accompanied by an improvement in pain sensitivity and movement restriction.

4.8 Ensuring data quality

4.8.1 Quality assurance and monitoring

The trial sites will be monitored to ensure data quality. The CRAs will review the informed consent forms, check the completeness and accuracy of the collected participant data and ensure that the trial is conducted in accordance with the trial protocol, the principles of ICH-GCP and local laws. Monitoring of the trial is performed according to a risk-based quality management (RBQM) procedure using a risk assessment and categorization tool (RACT). Monitoring is risk-adapted. The monitoring strategy is described in a monitoring plan.

In order to monitor risks and ensure the data quality of the trial, the performance, documentation rate, recruitment rate and data clarity of the various trial sites are monitored centrally by a central quality control (cQC). In the event of conspicuous data (e.g. incorrect or insufficient documentation), this tool makes it possible to intervene at an early stage and to correct errors. The exact procedure for cQC is described in a separate cQC manual.

All principal investigators agree that the CRA will visit the trial site at regular intervals and will be supported by the trial site in an appropriate manner. A corresponding passage is included in the informed consent form, which grants the CRA the right to compare the recorded data in the case report form (eCRF) with the source data (medical records, ECG, laboratory printouts,

etc.) in compliance with the Data Protection Regulation. The investigators allow the CRA direct access to all necessary documents for trial-related monitoring.

A monitoring report is prepared for each monitoring over the last 4 weeks visit, documenting the progress of the trial and reporting any difficulties encountered.

4.8.2 Audits

The sponsor has the right to conduct audits at the trial sites and other facilities involved in the trial as part of quality assurance. The aim of audits is to check the validity, verifiability and completeness of the data and the credibility of the clinical trial as well as to check the safeguarding of participant rights and the guarantee of participant safety. The sponsor may appoint persons who are not otherwise involved in the clinical trial (auditors) for this purpose. These persons are permitted to inspect all trial-related documents (in particular: trial protocol, data collection forms, participant files, trial-related correspondence).

The sponsor and all participating trial sites oblige to support auditors and, in this context, to grant the authorized persons access to the source data.

All persons conducting audits obligeto treat personal data and other data confidentially.

4.9 Documentation

All data relevant to the clinical trial are recorded in the trial-specific electronic case report form (eCRF) shortly after the assessment or visit is performed by the principle investigator or a person authorized by him. The eCRFs of the individual visits are signed by an investigator in a timely manner to confirm the accuracy of the data. The eCRFs will be signed by the principle investigator at the end of a participant's participation in the trial to confirm the accuracy of the data.

The eCRF provides specific sections in which the data must be documented. All members of the trial team involved in documenting the data will receive individual login details, with the exception of the blinded trial physician, who will not have access to the database.

The principal investigator is responsible for ensuring that the data entered into the eCRFs are complete and accurate and that they are entered and updated in a timely manner.

4.9.1 Data management

The IT infrastructure and data management system are provided by CTCC Cologne. The trial database is developed and validated on the basis of standard operating procedures at CTCC Cologne. The data management system is based on a commercial trial software (TrialMaster®,

Omnicom, Inc.). For traceability, all changes to the data are documented in an audit trail. The trial software has a user and role concept that can be customized for specific studies.

The trial data is entered web-based at the trial site. Automatic plausibility checks are carried out during data entry to identify discrepancies immediately. The data management of the CTCC carries out checks for completeness and plausibility of the trial data and clarifies all queries with the trial site electronically via the trial software. These queries must be answered promptly by the trial site. Further details are described in the data management plan.

A pdf version of the eCRF will be provided to the trial site for interim documentation if the trial software is temporarily unavailable.

The database is integrated into an IT infrastructure and security concept with a firewall and backup system. The data is backed up daily. After completion and cleansing of the data, the database is closed and the data exported for statistical analysis.

CTCC Data Management will produce regular reports on the cQC to provide information to project management and to identify trial sites within the scope of risk-based quality management that could benefit from additional quality assurance measures such as risk-adjusted monitoring. Details are defined in the cQC manual.

4.9.2 Archiving

The originals of all central trial documents are stored in the trial sites for 10 years after completion or discontinuation of the trial, the medical records for at least 10 years after the final report has been prepared.

The TMF, the eCRFs, the code envelopes and other material provided for the implementation are archived by the CI for 10 years after completion or discontinuation of the trial.

5 Ethical and regulatory aspects

5.1 Ethics committee

The trial will only be started after the trial sites has received professional advice by the ethics committee responsible for the trial sites. For this purpose, the correspondingly required documents are submitted to the ethics committees for consultation.

Any changes to the trial documents that become necessary in the course of the trial will be resubmitted to the ethics committees for consultation.

5.2 Ethical conduct of the clinical trial

This trial protocol and any subsequent amendments to the trial protocol are/will be written in accordance with the currently valid version of the Declaration of Helsinki.

5.3 Legal provisions and guidelines taken into account

This clinical trial will be conducted in accordance with the principles of the Good Clinical Practice (ICH-GCP) guideline. These principles include ethics committee procedures, participant information and informed consent, trial protocol compliance, administrative documents, data collection, participant records (source documents), adverse event (AE) recording, audit preparation and record keeping. All investigators and other personnel directly involved in the trial are informed that personnel authorized by the sponsor of the clinical trial are entitled to view trial documents and participant files after notification.

5.4 Notification of the authorities and registration of the trial

As the provisions of the German Medicinal Products Act (AMG) or the German Medical Devices Regulatory (MDR) do not apply to this trial, notification of the authorities is not required.

Prior to the start of the clinical trial, the clinical trial will be registered with clinical trials.gov or another WHO-recognized trial registry.

The trial protocol is submitted for publication in a scientific journal.

5.5 Informing and consenting trial patients

A participant can only be included in the clinical trial if she has given her written consent to this after she has been informed verbally and in writing by an investigator about the nature, significance and scope of the clinical trial and about the liposuction procedure and the potential side effects in an appropriate and comprehensible manner. At the same time as giving consent, the participant must have declared that he/she agrees to the recording of data as part of the clinical trial and its review by persons appointed by the sponsor (e.g. CRA, auditor) and by the responsible supervisory or federal authority.

The participant may withdraw her consent at any time and without giving reasons, without suffering any disadvantages as a result.

The original version of the written consent will be kept in the trial folder of the trial site. The participant will be given a copy of the signed informed consent form, the written participant information and a copy of the insurance confirmation together with the insurance conditions.

The participant information and consent form, all other documents received by the patients and any recruitment notifications are submitted to the responsible ethics committee before use. As part of the monitoring process, it is checked whether the current consent form has been signed and dated by the participant and the investigator prior to the start of the clinical trial.

NOTE: If the pandemic situation leads to a postponement of elective procedures so that the liposuctions cannot be performed at the planned time according to the trial protocol, the P2 visit and thus also the randomization must be postponed until it becomes foreseeable that the liposuctions can be performed with the necessary time intervals according to the trial protocol. Patients must consent again to the modified trial procedure in order to continue participation

5.6 Participant insurance

Participant insurance is taken out for all included patients. The registered office, insurance number, telephone and fax number of the insurance company will be included in the participant information sheet (see patient information sheet).

In addition, travel accident insurance will be taken out for all enrolled patients to cover visits to the trial site.

5.7 Data protection

The provisions of the EU General Data Protection Regulation and data protection laws are observed. It is ensured that all trial materials and data are adequately pseudonymized in accordance with data protection regulations prior to scientific use.

The trial patients are informed about the transfer of their pseudonymized data to the recipients named therein as part of the documentation and notification obligations according to ICH-GCP. Persons who do not consent to the transfer will not be included in the clinical trial.

6 Statistical methods and determination of the number of cases

6.1 Statistical and analytical plan

The main aspects of the planned statistical analysis are described below. Further details are laid out in the statistical analysis plan (SAP).

Analysis populations

Intention-to-treat (ITT) population: The primary statistical analysis is performed according to the intention-to-treat principle, where a missing outcome or change of randomly assigned therapy is considered a failure ([36] [37]). All randomized patients are evaluated. In particular, patients whose treatment could only be completed with a delay under pandemic conditions also remain part of this population.

Per trial protocol (PP) population: The analysis of the patients treated and observed essentially in accordance with the trial protocol (i.e. completion of liposuction treatment in the intervention group; $\geq 80\%$ of the planned CTD treatments in the intervention and control group were performed; primary end point present) is secondary.

As treated (AT) population: In addition to the data from the primary observation period (12 months after randomization or after the last liposuction treatment), the analysis according to the treatment actually received also includes all data on the outcomes and adverse events that are collected on patients after the change of trial arm. This evaluation is also secondary.

6.1.1 Description of the participant population

Quantitative variables are descriptively analysed with mean value, standard deviation and percentiles (0, 25, 50, 75, 100), qualitative variables with absolute and relative frequency. They are analysed separately according to the stage of the disease.

6.1.2 Primary end point

The primary treatment success is defined as an individual reduction of the average leg pain (stage I, II or III) over the last 4 weeks by 2 points or more on a numerical rating scale. This difference represents a relevant improvement in the participant's symptoms [20, 26, 38]. Note: Since the primary end point can also be determined by mail or telephone if necessary (number between 0 and 10), a proportion of missing values of less than 20% is assumed.

First, a joint evaluation of all 405 included patients is performed using the Mantel-Haenszel test [39] stratified by stage at two-sided significance level of 5% (H_0 : OR=1 vs. H_A : OR $\neq$ 1). The

homogeneity of the common odds ratio is tested using the Breslow-Day test [40]. If the Mantel-Haenszel test is significant ($p < 0.05$), the equality of the success rates in the individual stages (stage-separated evaluation) is tested downstream using Fisher's exact test, also at two-sided significance level of 5%. This staged test procedure controls the multiple error for at least one false rejection (closed testing principle [41]). 95% confidence intervals are calculated for the difference in success rates (Newcombe's method 10; [42]). To limit the influence of individual trial sites, a maximum of 50 patients per site per stage should be included. If possible, at least 5 patients per surgeon per stage should be treated (liposuction) to illustrate the effects of surgery. The presentation of the variability of the results between the trial sites or surgeons is based on the relevant extension of the CONSORT recommendations [43], both descriptively and by means of multilevel analysis to take nesting into account. The influence of missing values and the lack of treatment adherence (especially in patients in the control group) is examined in sensitivity analyses (single/multiple imputation).

A possible effect modification or bias due to delays in the implementation of liposuction (e.g. pandemic-related) is explored (stratification, regression models, subgroup analysis). The following two cases are to be distinguished: (1) The delay occurs before randomization. (2) The delay occurs after randomization. Case (1) does not result in bias, as both trial arms are equally affected. Effect modification is possible (and is being explored). Case (2) *may* result in bias as the trial arms are affected differently. In the control arm, the follow-up period starts immediately after randomization, in the intervention arm only after completion of the (delayed) liposuction. However, in view of the planned CDT duration of 6 months before randomization, a maximum effect of this measure can be assumed ("saturation"), so that the extension of the CDT duration in the intervention arm cannot have any further relevant influence on the efficacy. Possible effects are being explored.

6.1.3 Secondary target variable

Parametric or non-parametric methods are used to evaluate the secondary target variable, depending on the type of distribution. These analyses are performed without controlling for multiple testing.

6.1.4 Safety variables

The information on adverse events is assessed (according to severity, intensity, causal relationship), coded and summarized (contingency tables; number of events and patients affected). This applies in particular to late complications during the follow-up period (24 months).

6.1.5 Subgroup analyses

A subgroup analysis is performed according to age, trial site and surgeon.

6.1.6 Interim evaluation

Not applicable.

6.2 Determination of the number of cases

According to the results of Schmeller et al [20, 26], the success rate of the intervention in each stage is assumed to be at least 40% and that of the control at most 10%. In order to detect this difference per stage with a power (1-beta) of 90% and a two-sided significance level of $\alpha=5\%$, 111 patients (74 vs. 37) are required (corrected chi-square test; Stata 15.1, StataCorp LLC, College Station, TX, USA; power twoproportions). To compensate for the influence of dropouts and stratification in the analysis, 135 patients per stage should be included, rounded slightly (this corresponds to an increase of approx. 20%). In this way, proof of the assumed effect can be ensured in each of the three relevant subgroups (stage I, II or III) (with alpha and beta errors as stated above). A total of 405 patients will be treated in the trial according to the randomization.

According to the “Supporting reasons for the decision of the Federal Joint Committee on a guideline for the testing of liposuction in lipedema” of January 18, 2018, it is expected “that no data on the primary end point can be collected for about 20% of patients” according to Schmeller et al. (2010) [26] report on 165 (of 255, i.e. 65%) patients who had completed the surgical treatment in full and had an interval of at least 6 months after the last procedure. In this trial plan (paid treatment, selected patients, controlled trial conditions), a lower proportion (<20%) can be expected, especially as the primary end point can also be recorded by mail or telephone if necessary.

Assuming a lack of eligibility of approx. 45% and a further 10% refusal to undergo CDT over a period of ≥ 19 months, the number of patients to be screened is 985. In addition, 5% are expected to drop out during the run-in phase and a further 5% due to good CDT results after completion of the run-in phase. A total of 450 patients are to be included in order to be able to randomize 405 patients. If more than 405 patients successfully complete the run-in phase, they will still be randomized in the corresponding stratum for ethical reasons (over-running). If a drop-out rate higher than 10% (5% drop-out + 5% CDT success) becomes apparent in the course of the recruitment period, more patients should be included in the run-in phase in the remaining time in order to be able to randomize at least 405 (135 patients per stage) with a high probability.

7 Safety

This chapter describes the documentation and reporting of adverse events.

7.1 Adverse events (AEs)

Although this trial is not subject to the German Medicinal Products Act (AMG) or the German Medical Devices Regulatory (MDR), the definitions of the ICH-GCP are used as a basis for the documentation of adverse events.

7.1.1 Definition of adverse event

An adverse event (AE) is any adverse medical event that occurs in a patient in this clinical trial within a defined documentation period and that is not necessarily causally related to the intervention. An adverse event can be any unfavorable and unintended reaction including an abnormal and clinically significant laboratory finding, any symptom or any associated disease.

7.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse medical event that

1. is fatal or life-threatening,
2. requires hospitalization or prolongation of hospitalization,
3. leads to permanent or severe disability or incapacity,
4. results in a congenital anomaly or birth defect
5. and any other event that fulfills a comparable criterion (as determined by the evaluating investigator).

Events are considered life-threatening in the above context if there was a risk of death at the time of the event.

A hospital admission is considered to be any inpatient stay of a subject that lasted at least one night (0 - 6 am). Planned hospital admissions are not considered serious adverse events, but require appropriate documentation in the participant record and eCRF.

7.2 Documentation and reporting period of (serious) adverse events (AEs and SAEs)

The recording of AEs/SAEs for each individual patient begins with the signing of the informed consent form and ends with the last follow-up visit of the individual patients.

The participant is asked about the occurrence of AEs during her visits. Adverse events are documented in the eCRF and must be followed up until they are resolved (maximum 4 weeks after the last visit) or there is a plausible explanation for the symptoms.

Ineffective therapy is not an adverse event. Furthermore, symptoms that already exist at the time of inclusion in the trial and do not worsen during the course of the trial are not considered AE/SAE. The data from the questionnaires used in the trial (see primary end point and secondary end points) are recorded as outcomes and are excluded from the AE documentation.

All AEs are documented in the eCRF with the following parameters

- Date and time of occurrence
- Date and time of end
- Outcome (resolved, resolved with sequelae, ongoing, etc.)
- Intensity of symptoms

Mild: Clinical symptom or sign that is well tolerated.

Moderate: Clinical symptom or sign that is sufficient to interfere with normal activity.

Severe: Clinical symptom or sign leading to severe impairment or inability to work or perform daily activities.

- Possible causal relationship to CDT or intervention (yes, no)
- Severity (yes, no)
- Measures

All AEs must be documented in the eCRF. In addition, SAEs are immediately sent directly from the database to the PCI by means of an automatic e-mail notification.

The risk-benefit ratio is reviewed by the PCI using a list of adverse events that have occurred up to that point, which is provided by the CTCC at regular intervals.

A pregnancy test must be carried out before each surgery and the result documented. In the event of pregnancy, the participant cannot continue to participate in the trial, regardless of her group affiliation (intervention group/control group), unless the primary end point has already been determined. If a participant in the control group wishes to undergo liposuction after the primary end point has been assessed at the end of the 12-month observation phase, pregnancy means that liposuction surgery cannot be performed, but the participant can remain in the follow-up phase.

A pregnancy must be documented as an AE in the eCRF as soon as it becomes known. In this case, the PCI receives an automatic e-mail notification directly from the database.

Patients who become pregnant after the primary end point has been assessed may remain in the trial.

7.2.1 Information to the Data Monitoring Committee

Details of the DMC procedures are described in the DMC manual (see chapter 3.3).

8 Trial results and publication

8.1 Reports

8.1.1. interim reports

Interim reports based on an interim analysis are not planned.

8.1.2 Final report

The ethics committee will be informed within 90 days that the trial has officially ended. Within one year of the end of the trial, the ethics committee will receive a summary of the final report or an appropriate publication of the clinical trial with the most important results.

8.2 Publication

It is planned to publish the results of the clinical trial in a scientific journal and/or present them at German and international congresses in consultation with the PCI. In principle, preference should be given to a complete publication of the clinical trial. The "Uniform requirements for manuscripts submitted to biomedical journals" of the "International Committee of Medical Journal Editors" (ICMJE) [44] are taken into account.

The clinical trial is registered in a public register in accordance with the recommendations of the ICMJE (see also 5.4).

For all publications, data protection is ensured for all data of data subjects as well as for the data of the members of the trial team.

The publication or presentation of the results of this clinical trial requires prior notification and prior comment and approval by the sponsor and the initiator.

9. Changes to the trial protocol

In order to ensure largely comparable conditions in all trial sites and in the interest of proper data evaluation, no changes to the agreed examination conditions laid down in the trial protocol are planned. In exceptional cases, however, changes to the examination conditions are possible. These will only be made after mutual agreement between the sponsor, the sponsor's authorized representative, the PCI and the biometrician as well as all signatories (authors) of this trial protocol. Any change to the trial procedures provided in the trial protocol must be made in writing, stating the reasons for the change, and must be signed by all authors of this trial protocol (amendment) and submitted to the ethics committees for consultation (see Chapter 5.1).

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Statistical Analysis Plan

Title of clinical trial:	A randomised controlled multicentre investigator blinded clinical trial comparing efficacy and safety of surgery versus complex physical decongestive therapy for lipedema (LIPLEG)
ClinicalTrials.gov ID:	NCT04272827
Indication:	E88.20, Lipedema, grade I E88.21, Lipedema, grade II E88.22, Lipedema, grade III
Experimental intervention:	Liposuction
Comparator:	Physical complex decongestive therapy (CDT)
Sponsor (or representative):	Dermatology clinic, Klinikum Darmstadt
Consortium leader:	Prof. Dr. med. Oliver Cornely Clinical Trials Centre Cologne (CTCC), Faculty of Medicine, University of Cologne
Financial support:	G-BA / DLR
Protocol-Code:	LIPLEG-3806
Trial phase (if applicable):	Non-AMG/Non-MDR
Principal Coordinating Investigator (PCI):	PD Dr. Maurizio Podda Department of Dermatology Medical Center, Klinikum Darmstadt
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1 Background

This statistical analysis plan (SAP) was prepared prior to data analysis and database lock and is based on the trial protocol, version V04_0 (version dated 01.02.2023), the DSMB charter, version V01_0 (version dated 31.08.2020) and the database specification, version V06_0 (28.09.2023).

The statistical analysis is carried out by the Institute of Medical Statistics and Bioinformatics, Medical Informatics Group. The responsible statistician is Prof. Dr. Martin Hellmich, deputies are Dr. Petra Schiller and Wiebke Müller.

This version V01 of the SAP includes a description of the main evaluation of the primary endpoint as well as the main secondary endpoints after 12 months and the follow-up evaluations at the later time points. Details of the follow-up evaluations can be provided in a second version of the SAP or in more detail if required. Additions and changes compared to the first version will then be marked in version V02.

1.1 Trial objective

Lipedema is accompanied by a reduced quality of life for patients due to persistent pain (in stages I, II or III). Because the biological cause of lipedema is not known, there is no basic specific therapy. Treatment with complex decongestive therapy (CDT) is lengthy and usually does not lead to a significant improvement in lipedema of the legs. Surgical treatment by means of liposuction may be an alternative. However, there is currently only limited meaningful data from published studies that suggest a potential for the effectiveness of surgical treatment of lipedema. A direct comparison of liposuction with CDT in a randomized, controlled, multicentre trial is necessary to establish a meaningful data situation.

The aim is to determine whether surgical treatment of lipedema (stage I, II or III) by means of liposuction significantly improves leg pain compared to the use of CDT. The primary endpoint is the clinically relevant reduction of the average pain in the legs over the last four weeks (≥ 2 points on a numerical rating scale; German pain questionnaire) 12 months after completion of liposuction (intervention group) or after randomization (control group) compared to the time of randomization.

Further measures of quality of life and changes in body measurements etc. will also be considered in order to comprehensively assess any superiority of surgical treatment of lipedema by means of liposuction compared to the use of CDT (for details see Chapter 4.3).

1.2 Study design

This is a multicenter, randomized, parallel group, investigator-blinded, controlled clinical trial. The schema is shown in Figure 1. The aim is to include 450 patients.

Randomisation

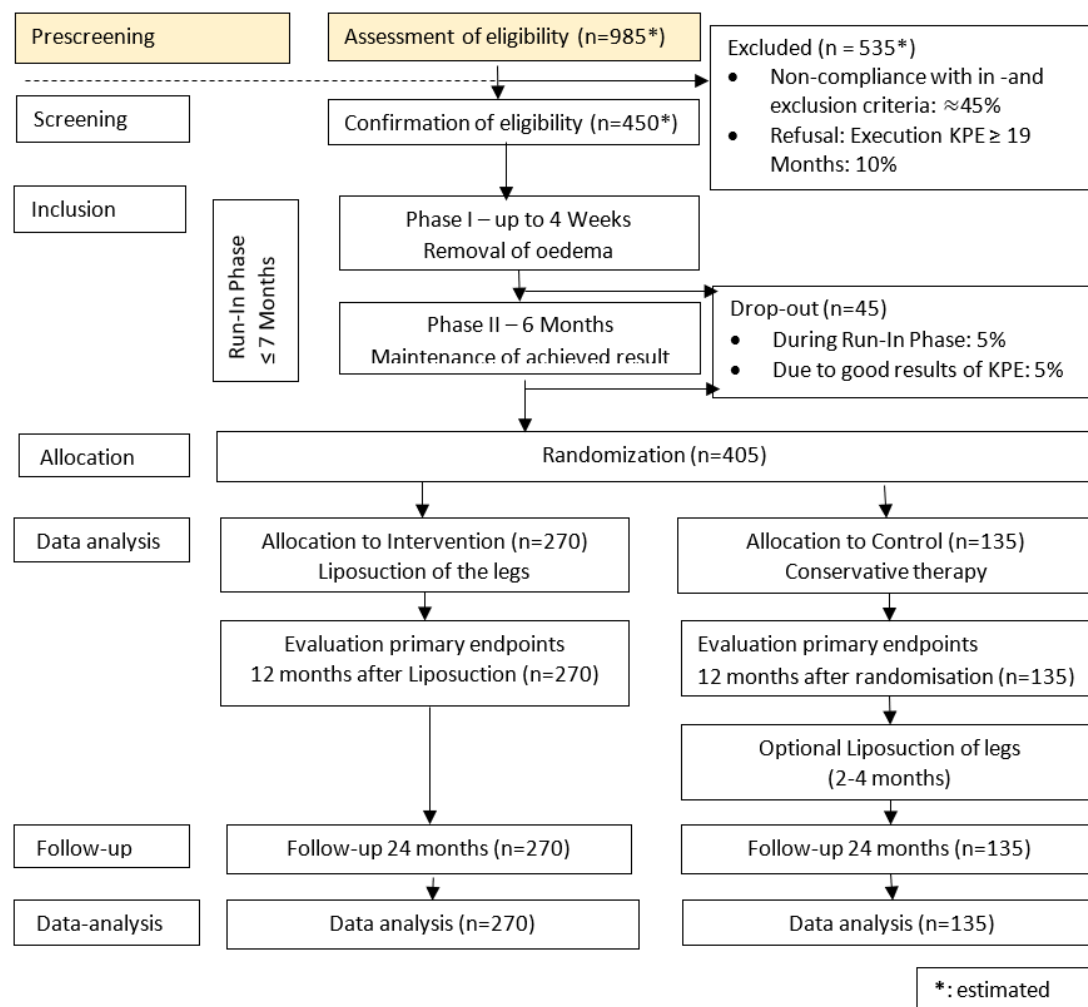
After a run-in phase lasting up to seven months for edema removal and maintenance of results using CDT, patients are randomly assigned to one of two treatment groups (EXP or CON) via a 24/7 internet service (ALEA, FormsVision BV, Abcoude, NL). Randomization is stratified by stage and surgeon in a 2:1 ratio (intervention : control) based on permuted blocks.

Intervention

In the intervention arm, patients receive liposuction operation (number of operations at the discretion of the treating trial physician: maximum of four surgical procedures, with a minimum of 5 and a maximum of 7 weeks between each liposuction) with, if necessary, accompanying

CDT to maintain the surgical results at the discretion of the investigator. Control patients receive CDT as standard therapy. Following a 12-month follow-up phase, they will also be offered the option of liposuction (see figure 1). Blinding of the trial treatments is only possible to a limited extent. Surgical scars are taped (dummy plaster in the control group) and patients are instructed not to communicate the treatment received to the investigator. The statistical analysis is carried out by a blinded statistician. The blinded study physician may not inspect either the patient file nor the eCRF. The data collected by this physician will be documented on working sheets and entered into the eCRF at the same time by unblinded trial personnel. The primary endpoint (regarding pain in the legs in stages I, II or III) will be determined after an observation period of 12 months after the final liposuction. This is followed by a further follow-up period of 24 months to observe and document the further course of the disease.

Figure 1: Flowchart of the clinical trial



1.3 Time planning

After completion of the last visit of the last patient, when, if possible, 405 patients have completed the entire trial, the data is cleaned by the CTCCologne in accordance with SOP and the database is locked. The first version of the statistical analysis plan (SAP) is finalized before the database is locked. The cleaned data is transmitted to the statistics department. The primary analysis of the primary outcome, the most important secondary outcomes and the safety parameters will take place as soon as possible at the same time after the primary outcome (12M) has been collected from the last patient (expected Q4 2024).

1.4 Sample Size

According to the results of Schmeller et al [1, 2], the success rate of the intervention (liposuction) in each stage is assumed to be at least 40% and that of the control (CDT) at most 10%. To detect this difference within each stage with a power (1-beta) of 90% and a two-sided type I error rate $\alpha=5\%$, 111 patients (74 vs. 37) are required (corrected chi-square test; Stata 15.1, StataCorp LLC, College Station, TX, USA; power twoproportions). To compensate for the influence of dropouts and stratification in the evaluation, 135 patients per stage should be included, rounded slightly (this corresponds to an increase of roughly 20%). In this way, proof of the assumed effect can be provided in each of the three relevant subgroups (stages I, II or III) (with alpha and beta errors indicated above). A total of 405 patients are to be treated in the trial in accordance with the randomization. In accordance with the specifications given in "Supporting reasons for the decision of the Joint Federal Committee on a guideline for testing liposuction in lipedema" of January 18, 2018, it is expected "that no data on the primary endpoints can be collected for about 20% of patients". Schmeller et al. (2010) [2] reported on 165 of 255 (65%) patients who had fully completed surgical treatment and had an interval of at least six months after the last procedure. In the LIPLEG trial (paid treatment, selected patients, controlled trial conditions), a lower proportion (<20%) can be expected, especially as the primary endpoint can also be recorded by post or telephone if necessary.

Assuming roughly 45% non-eligibility and a further 10% refusal to undergo CDT for ≥ 19 months results in the number of 985 patients to be screened. In addition, 5% drop-out during the run-in phase and a further 5% due to good results of the CDT after completion of the run-in phase are expected. A total of 450 patients are to be included in order to be able to randomize 405 patients. If more than 405 patients successfully complete the run-in phase, they will also be randomized in the corresponding stratum for ethical reasons (overrunning). If a drop-out rate higher than 10% becomes apparent during the recruitment period of 6 months, more patients should be included in the run-in phase in the remaining time in order to be able to randomize at least 405 (135 patients per stage) with a high degree of probability.

2 Analysis populations

2.1 Definitions

Note: Patients who did not comply with CDT as planned during the run-in phase will not be randomized and will not be included in the analysis (see trial protocol, pp. 7 and 28). The number of dropouts and the reasons for them will be reported in the flow chart.

Intention-to-treat (ITT) population: The primary statistical analysis is performed according to the intention-to-treat principle. A missing endpoint or change in randomly assigned therapy is considered a failure [3, 4]. All randomized patients are evaluated. In particular, patients whose treatment could only be completed with a delay due to pandemic conditions remain part of this population.

Per-protocol (PP) population: All patients from the ITT population who were treated and observed in accordance with the protocol form the PP population. The analysis of the PP population is secondary. A patient is considered to be protocol-compliant if all of the following criteria are met:

- Completion of liposuction treatment in the intervention group;
- Non-missing primary endpoint received;
- Patients whose visit to record the primary outcome (V2) takes place within the scheduled visit window (patients whose visit takes place more than 14 days before or after the scheduled window are excluded);

- No major protocol deviations in the period between the baseline visit and 12 months after randomization (control group) or after the last liposuction treatment (intervention group) - Major protocol deviations are:
 - Violation of at least one inclusion or exclusion criterion in the period between the baseline visit (BV) and the end of the 12-month follow-up (visit V2)
 - Intervention group: Liposuction treatment not completed (Note: for patients who have had visit V1, all surgeries have been completed)
 - Control group: Premature liposuction treatment (surgery date is before visit V2); visit V2 must have been conducted before surgery
 - Intervention and control group: <80% of planned CDT treatments performed between randomization (visit P2) and completion of the 12-month follow-up (visit V2)^a
 - Missing primary outcome measure (i.e., measurement of average pain in the legs over the past four weeks is missing for visit P2 and/or visit V2 (12 months after randomization (control group) or after the last liposuction treatment (intervention group)).

In addition to the protocol deviations listed, all recorded PDs are reviewed by the PI as part of a blind review and rated as “not significant” (=minor) or “significant” (=major), and patients’ inclusion into the PP set is determined.

^a Note: This is listed as a serious protocol deviation in the trial protocol: “< 80% of the planned treatments in the intervention and control groups were performed.” Based on the incomplete documentation available, it is not possible to determine for each patient how many of the protocol-mandated CDT treatments were actually performed and whether less than 80% were administered, thus constituting a protocol deviation.

Context: In the intervention group, CDT treatment is optional. In the CDT group, CDT is to be provided as needed for one year and is prescribed by a physician.

- (1) The number of prescribed CDT treatments is not documented completely; not all prescriptions and the scope of therapy specified thereon for patients are entered into the database. (The scope of therapy units per prescription can vary greatly, so it is not sufficient to consider the number of documented prescriptions)
- (2) The values for the variable “How many of the prescribed treatments did the patient receive?” [COMPNOTW] are not specified.

Procedure: Data completeness and quality are evaluated and presented. If documented by the local clinician that a patient has adhered to the prescription (see variable COMPLIA = patient has adhered to the prescription), this is interpreted as meaning that this patient has not violated the protocol in the performance of CDT and has performed at least 80% of the planned CDT treatments between randomization and the end of the 12-month follow-up period, see also Chapter 7).

Safety / As-treated (AT) population: The safety set includes all patients who were treated within the trial, from run-in (randomization) to last follow-up. This includes patients who changed treatment groups (see ITT analysis set). The evaluation is performed as treated and is also secondary.

Per-protocol 2 (PP-2) population: This second PP set includes all patients from the first defined PP set who were treated and observed in accordance with the protocol and who underwent surgery, i.e., patients from the intervention arm who underwent early surgery (in scenario A) and patients from the CPT arm who underwent (late) surgery after V2. All patients who did not receive surgery are excluded.

2.2 Application

Evaluation after 12 months

The primary analysis population is the ITT population. Based on the ITT population, the primary outcome measure and all secondary outcome measures are examined at 12 months after randomization in the control group and after the last surgery in the intervention group (V2). The primary variable and the secondary variables on efficacy and quality of life are additionally analyzed in the PP and AT populations.

Patients who were randomized but refuse or do not receive the respective treatment are not included in the analysis (see above, preliminary remark).

For the follow-up analyses, which consider the period from 12 months after randomization or surgery, the following evaluation groups are used:

- (1) ITT-set (as defined above for the evaluation of the primary outcome after 12 months)
- (2) additionally defined PP2-set (restriction to patients with surgery, early (intervention arm) or late (control)).

The treatment paths are presented in a separate document (see LIPLEG_treatment_paths_V01). This document illustrates the various possible outcomes of the treatments and the result in allocation to the analysis populations (available upon request).

3 Trial centres

Local	Site-Number	Site
Bad Belzig (Potsdam)	11	Klinikum Ernst von Bergmann, Klinik für Plastische, Ästhetische und Rekonstruktive Mikrochirurgie
Bad Soden am Taunus	03	Hautmedizin Bad Soden Part G
Bonn	04	Johanniter GmbH Waldkrankenhaus, Plastische, Rekonstruktive und Ästhetische Chirurgie
Darmstadt	01	Klinikum Darmstadt, Hautklinik
Düsseldorf	06	MVZ Hautarztpraxis Düsseldorf MVZ Corius Nordrhein GmbH
Freiburg	08	Venenzentrum Freiburg
Köln	10	Klinik und Praxisklinik für Plastische Chirurgie
Köln-Dellbrück	19	Hautarztpraxis Diana Rajewski
Mühlthal	18	Hautarztpraxis Mühlthal
Oldenburg	15	Evangelisches Krankenhaus Oldenburg, Klinik für Plastische, Ästhetische, Rekonstruktive und Handchirurgie
Regensburg	12	Hochschulzentrum für Plastische und Ästhetische, Hand- und Wiederherstellungs- chirurgie der Universität Regensburg, Standort Caritas-Krankenhaus St. Josef

4 Analysis variables

4.1 Visit schedules

The frequency and timing of measurements of the variables to be documented are specified separately for the intervention and control groups. The evaluation variables are specified in more detail in the following subchapters.

Table 1: Visit schedule during the trial and follow-up of the intervention group

Intervention Group						12 months observation		24 months follow-up			
Visits	B V	Start- time	P1 ^a	P2 ^a	liposuction -Visit (1-4) ^a	V1 ^a	V2 ^a	V3 ^a	V4 ^a	V5 ^a	V6 ^a
						Months after completion of OPs		Months after observation period			
Time	0	Start 1. CDT	After max. 4 weeks (28 days) after the start of the 1st CDT	After 6 months (180 days) after P1	After max. 4 weeks 1st liposuction , then after 5-7 weeks max. 3 further liposuct.	6 M (180 days) after last lipo.	12 M (360 days) after last lipo.	6 M (180 days) after V2	12 M (360 days) after V2	18 M (540 days) after V2	24 M (720 days) after V2
Time frame			± 4 Days	± 14 Days		± 14 Days	± 14 Days	± 14 Days	± 14 Days	± 14 Days	± 14 Days
Examination											
Informed consent	x										
Clarification prior to Op	x				x**						
In- and exclusion criteria	x			x							
Background data	x										
Diagnosis	x										
Anamnesis	x										
Preliminary treatment, conservative	x										
Weight	x		x	x		x	x	x	x	x	x
Supplementary medication	x		x	x	x	x	x	x	x	x	x
Leg circumference [§] (UL, LL, left, right)	x		x	x		x	x	x	x	x	x
Occurrence of leg edema	x		x	x		x	x	x	x	x	x
Determination of body fat percentage and distribution [¶]	x		x	x		x	x	x	x	x	x
OPTIONAL: measuring leg volume	x		x	x		x	x	x	x	x	x
Arm circumference [§]	x		x	x		x	x	x	x	x	x
Skin image [°]	x		x	x		x	x	x	x	x	x
Quality of life (SF-36, DLQI, WHOQOL-BREF)	x		x	x		x	x	x	x	x	x
Depression (PHQ-9)	x		x	x		x	x	x	x	x	x
Hematoma proneness (modified according to Schmeller et al. 2010)	x		x	x		x	x	x	x	x	x
General impairment (modified according to Schmeller et al. 2010)	x		x	x		x	x	x	x	x	x
Pain (German Pain questionnaire) ^{xxx}	x		x	x		x	x	x	x	x	x
Functional limitations ^b (LEFS)	x		x	x		x	x	x	x	x	x
Randomization				x							
ECG (at least 1 time before 1st OP)					x						
Blood work (incl. thrombocytes, creatinine, GFR, electrolytes, GGT, GOT, GPT, Quick, INR, CRP)					x						
Pregnancy test (Urine at BV; otherwise blood or urine)	x			x	x						
Adverse events			x	x	x	x	x	x	x	x	x

OP†					x						
Recurrence of treatment						x	x	x	x	x	x
Standardized conservative therapy ¥ including prescription § (including therapy report)	x		x	x	x	x	x	x	x	x	x

BV = baseline visit, P1 = run-in phase 1, P2 = run-in phase 2, LQ = quality of life, OP-V = surgical visit, V = visit, CDT = complex physical, Decongestive Therapy, M = month, OS = Upper Leg, US = Lower Leg, SF-36 = Short Form 36, DLQI = Dermatology Life Quality Index, WHOQOL-BREF = World Health Organization Quality of Life-abbreviated version of the WHOQOL 100, PHQ-9 = Patient Health Questionnaire-9, LEFS = Lower Extremity Functional Scale,

** Before the first operation, patients are informed about the risks of liposuction in accordance with clinical standards, ° hematomas, nodules,† Surgery data, method, volume [mL] tumescent solution, amount of liposuction [mL], location, ¥ In particular, application of CPT (manual lymphatic drainage, skin care, compression therapy, exercise therapy), frequency, duration – after last surgery, if necessary a) up to -3 weeks, b) mobility, hygiene, § NOTE: Prescriptions for CPT in accordance with standard medical care are issued outside of trial visits at the trial center as follows: 3 months after each P1; where necessary, also after the last surgical procedure and V1, as well as every three months after V2 in the intervention group. No examinations are conducted when prescriptions are issued outside of the specified trial visits. xxx For BV “Questionnaire at the start of treatment” [5], for all subsequent visits Pain history questionnaire [6].

Table 2: Visit schedule during the trial and follow-up of the control group

Control Group					12 months Observation			24 months follow-up			
Visits	BV	Start-time	P1 ^a	P2 ^a	V1 ^a	V2 ^a	liposuction-Visit (1-4) ^{a,*}	V3 ^a	V4 ^a	V5 ^a	V6 ^a
					Months after randomization			Months after completion of surgery or observation period			
Time	0	Start 1 st CDT	max. 4 weeks (28 days) after the start of the 1 st CDT	6 M (180 days) after P1	6 M (180 days) after P2	12 M (360 days) after P2	After max. 4 weeks 1 st liposuction, then after 5-7 weeks max. 3 further liposuctions	6 M (180 days) after last liposuct.	12 M (360 days) after last liposuct.	18 M (540 days) after last liposuct.	24 M (720 days) after last liposuct.
Time Frame			± 4 Days	± 14 Days	± 14 Days	± 14 Days		± 14 Days	± 14 Days	± 14 Days	± 14 Days
Examination											
Informed consent	x										
Clarification prior to OP	x						x**				
In- and exclusion criteria	x			x		x					
Reference data	x										
Diagnosis	x										
Anamnesis	x										
Preliminary treatment, conservative	x										
Weight	x		x	x	x	x		x	x	x	x
Supplementary medication	x		x	x	x	x	x	x	x	x	x
Leg circumference (UL, LL, left, right) [§]	x		x	x	x	x		x	x	x	x
Occurrence of leg edema	x		x	x	x	x		x	x	x	x
Determination of body fat percentage and distribution [¶]	x		x	x	x	x		x	x	x	x
OPTIONAL: measuring leg volume	x		x	x	x	x		x	x	x	x
Arm circumference [§]	x		x	x	x	x		x	x	x	x
Skin pattern [°]	x		x	x	x	x		x	x	x	x
Quality of life (SF-36, DLQI, WHOQOL-BREF)	x		x	x	x	x		x	x	x	x
Depression (PHQ-9)	x		x	x	x	x		x	x	x	x
Hematoma proneness (modified according to Schmeller et al. 2010)	x		x	x	x	x		x	x	x	x
General impairment (modified according to Schmeller et al. 2010)	x		x	x	x	x		x	x	x	x
Pain (German Pain questionnaire ^{xxx})	x		x	x	x	x		x	x	x	x
Functional limitations ^b (LEFS)	x		x	x	x	x		x	x	x	x
Randomization				x							
ECG (at least 1 time before 1 st liposuction)							x				
Blood work (incl. thrombocytes, creatinine, GFR, electrolytes, GGT, GOT, GPT, Quick, INR, CRP)							x				

Pregnancy test (Urine at BV; otherwise blood or urine)	x					x	x				
Adverse events			x	x	x	x	x	x	x	x	x
OP†							x				
Recurrence of treatment								x	x	x	x
Standardized conservative therapy including prescription (including therapy report)	x		x	x	x	x	x	x	x	x	x

BV = baseline visit, P1 = run-in phase 1, P2 = run-in phase 2, OP-V = surgical visit, V = visit, CDT = complex decongestive therapy, M = month;

a) Note: 1 week corresponds to 7 days, 1 month corresponds to 30 days, UL = upper leg (thigh), LL = lower leg, SF-36 = Short Form 36, DLQI = Dermatology Life Quality Index, WHOQOL-BREF = World Health Organization Quality of Life - abbreviated version of the WHOQOL 100, PHQ-9 = Participant Health Questionnaire-9, LEFS = Lower Extremity Functional Scale,

** = Patients are informed about the risks of liposuction according to clinical standards before the first surgery. Hematomas, lumps,

† Surgical data, method, volume [mL] of tumescent solution, liposuction volume [mL], localization, ¥ In particular application of CDT (manual lymphatic drainage, skin care, compression therapy, exercise therapy), frequency, duration a) up to -3 weeks b) mobility, hygiene

§ NOTE: If necessary, prescription for CDT according to standard care between the trial visits at the trial site. No parameters are recorded when prescriptions are issued outside the specified trial visits. xxx For BV "Questionnaire at the start of treatment", for all subsequent visits

pain progression questionnaire, § Note: no CPD must have taken place at least 2 days prior to this visit t# Note on recurrent surgeries:

these are not permitted within the scope of the trial, Ω Body fat distribution: measurement using a measuring tape (in cm): Abdominal circumference at navel height, hip circumference: widest point of hip

4.2 Demographics and baseline characteristics

The trial design has two timepoints for measuring baseline values: one at visit BV (screening/baseline) and the other at visit P2 after completion of the run-in phase. The baseline measurements at visit P2 are used to determine the primary outcome measure and the secondary outcome measures, which describe changes over time.

Demographics and baseline characteristics:

- Inclusion and exclusion criteria
- Demographics
- Diagnosis
- Medical history
- Conservative pre-treatment
- Concomitant medication
- Leg circumference (thigh, lower leg, left, right)
- Determination of body fat percentage
- OPTIONAL: Volume measurement of the legs
- Arm circumference
- Skin appearance°
- Quality of life (SF-36, DLQI, WHOQOL-BREF) [7, 8, 9]
- Depression (PHQ-9) [10]
- Tendency to hematoma (modified according to Schmeller et al. 2010)
- Overall impairment (modified according to Schmeller et al. 2010)
- Pain (German pain questionnaire: "Questionnaire at the start of treatment" [5])
- Functional limitations (Lower Extremity Functional Scale LEFS) [11]
- Standardized conservative therapy (in particular application of CPT (manual lymphatic drainage, skin care, compression therapy, exercise therapy), frequency, duration – after last surgery, if necessary) including prescription

4.3 Primary and secondary endpoints

The primary outcome measure is the clinically relevant reduction in average pain in the legs over the last 4 weeks (≥ 2 points on the numerical rating scale; German Pain Questionnaire) at visit V2, i.e., 12 months after completion of liposuction treatment (intervention group) or after randomization (control group), compared to the time of randomization (visit P2).

The primary endpoint and all other endpoints relevant to the early first evaluation are specified in the following table with information on the variable, definition of endpoint, summary measure, and time of measurement (Table 3).

For the follow-up evaluations, the differences or proportions are formed analogously (see section 6.6).

4.4 Additional endpoints

4.4.1 Safety /Tolerability

- (Serious) adverse events in the period between the baseline visit (BV) and the end of the 24-month follow-up (visit V6)

- Treatment discontinuation due to adverse events

4.4.2 Vital signs/Body measurements

- Körpermaße [Baseline, P1 und P2, V1 – V4] o Body measurements [baseline, P1 and P2, V1 – V4]
- Height [cm]
- Weight [kg]
- BMI
- Arm circumference on the left and right upper and lower arm [widest point, cm] o Leg circumference on the left and right leg [at the ankle, mid-calf, knee, 10 cm below the groin, hip; cm]
- Leg volume o Neck circumference [cm] o Abdominal circumference [cm] o Hip circumference [cm]
- Body fat percentage (calculated according to the US Navy formula) [%]
- Body fat distribution (waist-to-hip and waist-to-height ratio)

4.4.3 Health economics

Not applicable.

5 Handling of missing values and outliers

5.1 Missing Values

In the event that patients discontinue participation in the trial prematurely (drop-out), every effort should be made to collect follow-up data, particularly on the primary endpoint (exception: patient has withdrawn consent to data collection), and to enter all available data into the database.

Kaplan-Meier analyses (time to dropout, logrank test) will be performed to examine the dropouts in both groups in more detail.

It is assumed that missing values can be considered missing at random.

As described above, missing endpoints are considered treatment failure (see above, Chapter 2 and trial protocol p. 62; this applies to binary endpoints). Continuous endpoints are evaluated using mixed models for repeated measurements. This requires that the missing values can be considered missing completely at random (MCAR, i.e., the pattern of missing data is independent of the treatment). According to Verbeke and Molenberghs (2000), the statistical conclusions are also valid under assumptions that are somewhat weaker than MCAR [12].

The influence of missing values is also examined in sensitivity analyses (single or multiple imputation).

5.2 Outliers

An analysis of outliers is not planned.

6 Statistical Analyses/Methods

6.1 Patient/Subject disposition

Initially, the inclusion and exclusion criteria of all included patients are reviewed and their inclusion in the analysis populations is determined. Absolute and relative frequencies of patients are determined according to treatment arm and disease stage for the ITT population. The frequencies are also presented in a flow chart together with the number and reason for trial discontinuations.

6.2 Demographics and baseline characteristics

Demographics and basic characteristics are presented according to treatment arm and disease stage and overall for the ITT population using the following descriptive statistics: number of patients (n) as well as arithmetic mean, standard deviation, and percentiles (0, 25, 50, 75, 100) for quantitative variables and absolute and relative frequencies for qualitative variables.

6.3 Pre- treatment/concomitant therapy and concomitant diseases

Therapies (medicinal and/or physical) are considered pre-therapeutic if they are last administered no later than the day before the start of the intervention. This means the day before the first CDT during the 12-month follow-up period (control group) or the first surgery (intervention group).

Pre-existing conditions are defined as conditions that occur before the day of randomization. A further distinction is made between pre-existing therapies and conditions that occurred before the start of the run-in phase (before the start of the trial until BV) and those that occurred during the run-in phase (after BV until the day before (1) the first CDT during the 12-month follow-up period (control group) or (2) the first surgery (intervention group)). All therapies that are continued or initiated during the primary trial phase (between randomization (visit P2) and visit V2, i.e., 12 months after randomization (control group) or after completion of liposuction treatment (intervention group)) are considered concomitant therapy. All diseases that occur during the primary trial phase (between randomization (visit P2) and visit V2, i.e., 12 months after randomization (control group) or after completion of liposuction treatment (intervention group)) will be considered comorbidities.

The frequency and duration of prior/concomitant therapy and diseases are presented for the ITT population according to treatment arm, disease stage, and overall, classified by organ system (listing). Statistical tests are not performed.

6.4 Exposure to therapy/compliance

For the intervention arm of the ITT population, the number of patients (n) as well as the arithmetic mean, standard deviation, and percentiles (0, 25, 50, 75, 100) for the volume of the tumescent solution and the amount of fat removed, as well as the absolute and relative frequencies for the frequency of surgery and surgical method, are presented.

For the control arm of the ITT population, the number of patients (n) is presented in total and by type of CPT, along with the arithmetic mean, standard deviation, and percentiles (0, 25, 50, 75, 100) for the frequency and duration of CPT, as well as the absolute and relative frequencies of CPT.

All documented withdrawals and protocol deviations (PD) are summarized according to the reason for withdrawal or the type of protocol deviation (according to PD code) and treatment arm (absolute and relative frequencies). Listings are created indicating the treatment arm, time point, and reason for withdrawal or protocol deviation.

6.5 Primary analysis

The **primary treatment success** (after 12 months) is defined as an individual reduction of 2 points or more on a numerical rating scale for the average pain in the legs (stage I, II, or III) over the last four weeks. This difference represents a clinically relevant improvement in symptoms for patients [1, 2, 13]. Please note: Since the primary endpoint can also be determined by mail or telephone (number between 0 and 10) if necessary, a proportion of missing values of less than 20% is assumed.

Hypotheses: The probabilities of success π of both types of treatment are equal (null hypothesis: $H_0: \pi_{Op} = \pi_{KPE}$) or different (alternative hypothesis: $H_A: \pi_{Op} \neq \pi_{KPE}$).

First, a pooled analysis of all 405 included patients is performed using the Mantel-Haenszel test [14] stratified by stage at a two-sided level of 5% ($H_0: OR = 1$ vs. $H_A: OR \neq 1$). The homogeneity of the common odds ratio is tested using the Breslow-Day test [15]. If the Mantel-Haenszel test is significant ($p < 0.05$), the equality of the success rates in the individual stages (evaluation by stage) is tested using Fisher's exact test, also at a two-sided level of 5%. This stepwise test procedure controls the multiple error for at least one false rejection (closed testing principle [16]).

The difference in success rates is calculated using 95% confidence intervals (Newcombe's method 10; [17]).

According to the plan, 16 participating surgeons should treat 5-6 patients each in the intervention group for each stage.

The variability of the results between the surgeons is presented in accordance with the relevant extension of the CONSORT recommendations [18], both descriptively and by means of multilevel analysis to take nesting into account.

The influence of missing values and lack of adherence to therapy (especially in patients in the control group) is examined in sensitivity analyses (single/multiple imputation).

6.6 Secondary analyses

The secondary analyses include:

- (1) evaluation of the primary endpoint (survey after 12 months) based on the per-protocol and as treated sets (see trial protocol, p. 62)
- (2) evaluation of the secondary endpoints (survey after 12 months, ITT and per-protocol as sensitivity analysis)
- (3) follow-up evaluations of the primary endpoint and secondary endpoints at later time points (see evaluation strategies).

6.7 Analysis of endpoints 12 months after randomization

The secondary endpoints are analysed descriptively, numerical variables are presented with number of observations, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum; categorical variables with absolute and relative frequencies. For each time point, the overall results and results separated by treatment group are reported. The secondary analyses are performed without controlling for multiple testing.

The analysis of binary endpoints (see Table 3) is performed analogously to the analysis of the primary endpoint. Secondary continuous endpoints (see Table 3) are evaluated as changes from baseline to 12 months or later time points using a mixed model for repeated measurements (MMRM) with corresponding marginal means and contrast tests. Model specification: fixed effects: baseline pain score, age, stage, center, group, time, and group*time

interaction; ARH1-structured covariance matrix over time. Data from centers with low recruitment ($n < 10$ patients) are pooled.

As supplementary analysis, the corresponding model with center (fixed factor) and surgeon (random factor) is also evaluated. Only the first surgeon of a patient is considered. Data from surgeons who have operated on fewer than 5 patients are pooled. If the described models do not converge, they are simplified.

6.8 Follow-up analyses of the endpoints at later dates

The following strategies are used in the follow-up analysis of the endpoints at later time points (more than 12 months after randomization):

Strategy A: The first strategy examines the difference between early surgery (intervention group) and later surgery (after a longer CPG phase). The aim is to check whether the results of the previous “waiting group” (CPT group) align with the results of the intervention group. To this end, the entire time course up to 24 months after surgery (i.e., approx. 36 months follow-up from randomization) is considered, i.e., the starting point is the same for both groups, and the change from V2 to V4 is compared in both groups.

The analysis is performed according to the randomized assignment (ITT, by randomized treatment; patients from the CDT group who did not undergo surgery later in the course remain included). This evaluation is also performed in the per-protocol set.

Strategy B: In a second strategy, the time course from the operation onwards is considered and compared, i.e., the starting points are different for both groups, but the duration of physical therapy from the operation onwards is the same. In the intervention group (=early surgery), the changes from V1 to V4 are compared with the changes from V3 to V6 in the CDT group (patients who did not undergo surgery are not included in this analysis).

Note: If the evaluation shows no difference between patients with early and late surgery, the data from the two groups are pooled for analysis of strategy B.

6.8.1 Safety / Tolerability

6.8.1.1 Adverse events

Reported adverse events are summarized and analysed according to severity, intensity, and causal relationship (contingency tables; number of events and affected patients; all operated vs. non-operated (AEs up to 12 months), early (operated at Tx) vs. late (operated at Ty) (AEs 12 months after surgery), combined with outcome or action taken). In addition, late complications during follow-up (12-24 months) are summarized.

6.8.1.2 Vital signs and laboratory parameters

The vital signs and ECG results are analysed descriptively and summarized for all visits (in tables, box plots over time).

6.8.2 Quality of life

The change in health-related quality of life (according to SF-36, DLQI, WHOQOLBREF) or impairment according to Schmeller (overall impairment) at 12 and 24 months is evaluated using MMRM, analogous to the analysis described in 6.6.1. A Wilcoxon test is performed as sensitivity analysis (dependent samples, baseline and 12 or 24 months).

6.9 Planned subgroup analyses

Subgroup analyses is performed according to age (by median cutoff) and trial center and surgeon (prerequisite: $n \geq 10$ per subgroup; centers with fewer than 10 patients or surgeons (per center) with fewer than 5 patients are pooled).

In a further subgroup analysis, patients who complied with the requirement “no CDT in the 2 days prior to the visit” and those who did not comply with this requirement are analysed separately (the following visits are considered: P2 at the end of the run-in phase and V2 after 12 months) [Skin CDT].

6.9.1 Interim analysis

Not applicable.

7 Deviations from the test plan and data issues

Verification of CDT compliance is only possible to a limited extent, as the actual number of CDT treatments performed was not documented in many cases (in particular variable COMPNOTW, see section 2.1). Where possible, documentation on the prescription of remedies and treatment units as well as protocol violations is used to assess patient compliance. This requires the timely documentation of the following information [variables]: date of issue of the CPT prescription [COPLIDAT], remedy [KPEHeilm], treatment units [KPEBEHEI], treatment units different, please specify [KPEBEHAN]. Depending on the data quality, compression therapy [KPEPATS] may be used to check CDT compliance.

The endpoint “change in the scope of physical therapy” listed in the trial protocol is not recorded and therefore not evaluated.

According to the trial protocol, in order to limit the influence of individual centers, a maximum of 50 patients per stage should be included per center. To demonstrate surgeon effects, at least 5 patients per stage should be treated (liposuction) by each surgeon, if possible. The number of surgeons who actually performed surgery as part of the trial and the number of operations they performed as the primary surgeon will be examined.

Surgeons at a center who performed surgery on fewer than 5 patients will be pooled for the analysis of the surgeon effect. Surgeons at a center who have operated on fewer than 5 patients will be pooled for the analysis of the surgeon effect.

For the first evaluation (after V2), only some of the laboratory data has been cleaned. Nevertheless, listings will be created and parameters for the situation and dispersion over time will be provided. If the data is sufficiently complete and of sufficient quality, laboratory values are included in Table 1. During the course of the trial, it became apparent that the documentation of (S)AEs was sometimes late or incomplete. The responsible persons in the centers concerned received training and additional monitoring. The absolute and relative frequency of (S)AEs is therefore also stratified by site.

8 Software

Analyses are performed using IBM SPSS version 28 (or higher) [19], R version 4.2.1 (or higher) [20], or Stata version 18 (or higher) [21].

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10 Appendix

10.1 Abbreviations

Abbreviation	Meaning
AE / UE	Adverse Event
AMG	German Medicines Act
ARH(1)	Heterogeneous first-order autoregressive structure
AT	As-treated
BMI	Body Mass Index
BV	Baseline Visit
CONSORT	Consolidated Standards of Reporting Trials
eCRF	electronic Case Report Form
DB	Database
DLQI	Dermatology Life Quality Index
DLR	Deutsches Zentrum für Luft- und Raumfahrt
DSMB	Data Safety and Monitoring Board
G-BA	Common Federal Committee
GCP	Good Clinical Practice
IMSB	Institute for Medical Statistics and Bioinformatics
ITT	Intention-to-treat
CDT	Complex physical decongestive therapy
LEFS	Lower Extremity Functional Scale
MCAR	Missing completely at random
MDR	Medical device regulation
OP	Surgery
PD	Protocol deviation
PHQ-9	Patient Health Questionnaire-9
PP	Per-protocol
SAE / SUE	Serious Adverse Event
SF-36	Short Form (SF)-36 Health questionnaire
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
WHOQOL-BREF	WHO-Quality of Life BREF
CTC Cologne	Clinical Trial Centre Cologne

10.2 Miscellaneous

Tabelle 3: Specification of primary and secondary endpoints (efficacy, quality of life, and safety parameters; for details on the required forms and variables, see file LIPLEG_Endpunkte_V01.xlsx)

Objective	Variable	Endpoint	Summary measure	Measurement timepoint
Primary endpoint				
Clinically relevant reduction of the average pain in the legs over the last four weeks	numerical rating scale; German pain questionnaire	Clinically relevant reduction (≥ 2 points) yes/no (dichotomous)	Relative frequency	At baseline and 12 months (V2) after completion of liposuction (I) or after randomization (C)
Secondary endpoints				
Change of pain intensity in the legs	Pain intensity, German pain questionnaire	Difference (Pain intensity at 12 months – baseline)	Mean difference	At baseline and 12 months (V2) after completion of liposuction (I) or after randomization (C)
Change in health-related quality of life (total of 6 endpoints)	SF-36 summary scores (physical and mental component summaries based on 8 dimensions each; higher values correspond to higher QoL)	(a) Difference (SF-36 summary scores at 12 months – baseline)	Mean difference	At baseline and 12 months (V2) after completion of liposuction (I) or after randomization (C)
		(b) Clinically relevant change in SF-36 summary scales (≥ 5 points per component summary) $\rightarrow$ yes/no (dichotomous)	Relative frequency	as above
	DLQI-summary score	(a) Differenz (DLQI-summary score at 12 months – baseline)	Mean difference	At baseline and 12 months (V2) after completion of liposuction (I) or after randomization (C)
		(b) Clinically relevant reduction (≥ 4 points) $\rightarrow$ yes/no (dichotomous)	Relative frequency	as above

	WHOQOL-BREF (26 items)	(a) Difference (WHOQOL-BREF summary score at 12 months – baseline) (b) Clinically relevant reduction by 20% → yes/no (dichotomous)	Mean difference Relative frequency	At baseline and 12 months (V2) after completion of liposuction (I) or after randomization (C) as above
Change in total impairment	Total impairment according to Schmeller <i>et al.</i> (2010) (modified form; 7 dimensions, Likert scale 0 - 10)	(a) Difference of the average across 7 dimensions at 12 months – baseline (b) Clinically relevant reduction (≥ 2 Punkte) → yes/no (dichotomous; refer to primary endpoint)	Mean difference Relative frequency	At baseline and 12 months (V2) after completion of liposuction (I) or after randomization (C) as above
Change in susceptibility to depression	PHQ-9 summary score	Clinically relevant reduction (≥ 5 points) → yes/no (dichotomous)	Relative frequency of patients with clinically relevant reduction	At baseline and 12 months (V2) after completion of liposuction (I) or after randomization (C)
Change in hematoma proneness	hematoma proneness according to Schmeller <i>et al.</i> 2010 (modified form)	Susceptibility to hematoma → yes/no	Relative frequency of patients with susceptibility to hematoma	At baseline and 12 months (V2) after completion of liposuction (I) or after randomization (C)
Change in prevalence of edema	Documentation on form foedem (including number of edemas and location)	Edema yes/no (Edema count)	Relative frequency of patients with Edema Number of edemas per patient	At baseline and 12 months (V2) after completion of liposuction (I) or after randomization (C)
Change in body fat percentage	According to Wright <i>et al.</i> (1981) based on tape measurements at specific points	Change in calculated body fat percentage at 12 months – baseline	Mean difference	At baseline and 12 months (V2) after completion of liposuction (I) or after randomization (C)

Change in leg circumference	Right leg: Tape measurements at five points (Ankle, lower leg, knee, thigh 10 cm below	Difference of calculated circumference of the right leg at each measurement point (if total hip circumference only has been documented, it will be divided by two and each half will be attributed to one leg)	Mean difference	At baseline and 12 months (V2) after completion of liposuction (I) or after randomization (C)
	the groin, hip on widest point)			
	Left leg: Tape measurements at five points (as above)	as above	as above	as above
Clinically relevant reduction of movement restriction	LEFS (Lower extremity Functional Scale)	Clinically relevant reduction (≥ 9 points) from baseline to V2 yes/no (dichotomous)	Relative frequency	At baseline and 12 months (V2) after completion of liposuction (I) or after randomization (C)
Number of surgeries after relapse	Reported surgeries	Number of surgeries after relapse per patient	Absolute and relative frequency of patients with relapse and surgery	Between baseline and 12 months
Frequency of (S)AEs	Reported (S)AEs	Number of (S)AEs per patient	Absolute and relative frequency of patients with (S)AEs	Between baseline and 12 months
AEs leading to treatment discontinuation	Reported treatment discontinuation due to (S)AE	Treatment discontinuation due to (S)AE	Absolute and relative frequency of patients with treatment discontinuation due to (S)AE	Between baseline and 12 months