NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of deep dermal injection of non-absorbable gel polymer for HIV-related lipoatrophy

Treating HIV-related lipoatrophy by injecting a non-absorbable gel polymer

HIV-related lipoatrophy is a loss of fat from the skin, often the face, which can occur as a side effect of antiretroviral drug treatment for HIV. Non-absorbable gel polymers are water-based synthetic substances that are not broken down by the body. The gel polymer is injected under the skin to restore the shape and volume of the areas where fat has been lost.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in March 2012.

Procedure name

- Deep dermal injection of non-absorbable gel polymer for HIV-related lipoatrophy

Specialty societies

- British Association of Dermatologists
- British Association of Plastic Reconstructive and Aesthetic Surgeons
- British Association of Aesthetic Plastic Surgeons
- British HIV Association.

Description

Indications and current treatment

Lipoatrophy is the localised loss of fat from within subcutaneous tissue. It can be a congenital condition or can occur locally at the site of injection as a result of subcutaneous injections for treatment for diabetes (for example, insulin) or multiple sclerosis (for example, copaxone), or can be a result of prolonged highly active antiretroviral therapy for HIV. HIV-related lipoatrophy is associated with loss of peripheral adipose tissue from the face, arms, legs and buttocks and central accumulation of fat on the body. It usually persists after HIV treatment has stopped. Facial lipoatrophy is commonly seen with HIV treatment. It involves wasting of the soft tissues of the cheeks, temples and around the eyes, which produces changes in appearance. This may have severe psychological and social consequences for some patients.

Current treatments for HIV-associated lipoatrophy include autologous fat transfer, dermal fat grafting, transfer of skin flaps and injection of temporary dermal fillers (such as collagen) or semi-permanent dermal fillers (such as polylactic acid).

What the procedure involves

Deep dermal injection of permanent or non-absorbable gel polymer aims to improve HIV-associated lipoatrophy and the related psychological effects.

The procedure is performed under general or local anaesthesia using aseptic technique. Non-absorbable gel polymer is injected with a needle, or cannula, deep into the subcutaneous tissue. Prophylactic antibiotics are used after injection. After injection the gel is massaged into position to give good aesthetic results. Once in place, the gel forms an external thin membrane or capsule that creates a liquid-filled endoprosthesis, isolating it from the surrounding tissues. The volume of gel injected depends on the body site to be treated and the degree of lipoatrophy. For facial treatment a few millilitres (for example, 1 ml at each treatment session) is typical. A course of injections over several weeks may be needed. A number of different products are available for this procedure, including gels made of liquid silicone, polyacrylamide gel, polyalkylimide gel and polymethylmethacrylate.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to deep dermal injection of non-absorbable gel polymer for HIV-related lipoatrophy. Searches were conducted of the following databases, covering the period from their commencement to 7 March 2012: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was

applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good-quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with HIV-related lipoatrophy.
Intervention/test	Deep dermal injection of non-absorbable gel polymer.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on 969 patients from 2 non-randomised comparative studies, 1 cohort study, 4 case series, 1 conference abstract and 1 case study.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on deep dermal injection of non-absorbable gel polymer for HIV-related lipoatrophy

Abbreviations used: AFT: autologous fat transfer; FLA, facial lipoatrophy; FLSS: facial lipoatrophy severity scores; HADS: Hospital Anxiety Depression Scale; IQR, interquartile range; MOS-HIV: M
Study HIV Health Survey; NAGP, non-absorbable gel polymer; NR: not reported; NS: not significant; PLA: polylactic acid; QoL, quality of life; sDQLS: slightly modified Dermatology Quality of Life
standard deviation

Study details

Orlando G (2007)[1]

Non-randomised comparative study

Italy

Recruitment period: 2005-2006

Study population: patients undergoing surgical interventions for HIV-related facial lipoatrophy.

n=**299 (130 vs 91 vs 24 vs 54)**

Age: 46 years (mean)

Sex: 71% male

Patient selection criteria: 18 years, documented HIV infection, on stable highly active antiretroviral therapy for at least 6 months, lipodystrophy diagnosis with moderate to severe facial wasting.

Technique: NAGP (polyacrylamide gel: Aquamid) (n=130): injected with a 1 ml syringe (27 gauge needle) into subcutaneous space every 4 weeks.

Key efficacy findings

Number of patients analysed: **299**

Change in skin thickness (measured by ultrasound)

Intervention	Right cheek		P-value	Left cheek		P-value
	Baseline*	Week 48*		Baseline*	Week 48*	
NAGP (Aquamid) n=130	3.7±1.3	10.0± 3.1	<0.0001	3.8±1.4	10.0± 3.2	<0.0001
PLA (Sculptra) n=91	4.3±2.0	8.7±2.8	<0.0001	4.5±2.4	8.9±2.9	<0.0001
AFT + PLA (Sculptra) n=24	5.1±2.5	9.5±3.3	<0.0001	5.5±2.3	9.5±3.5	<0.0001
AFT n=54	5.2±2.1	9.4±2.6	<0.0001	5.2±2.1	9.8±2.8	<0.0001
All patients n=299	4.3±1.9	9.5±3.0	<0.0001	4.4±2.0	9.6±3.1	<0.0001

*(mean mm± SD)

Aesthetic facial satisfaction (measured on a visual analogue scale)

Intervention	Baseline* (mean ±SD)	Week 48* (mean ±SD)	P-value
NAGP (Aquamid) n=130	2.7±2.0	6.5±2.2	<0.0001
PLA (Sculptra) n=91	3.3±2.1	6.2±2.0	<0.0001
AFT + PLA (Sculptra) n=24	1.9±1.9	5.0±2.4	0.002
AFT n=54	2.5±2.3	5.9±2.2	<0.0001
All patients n=299	2.9±2.1	6.2±2.1	<0.0001

Key safety findings

Adverse events

Adverse event	AFT n= 54	NAGP n= 130	PLA, PLA+ AFT (Sculptra) n=115	All patients n=299
Ecchymoses (transient and resolved spontaneously after 12 to 24 hours).				Reported as 'most frequent' (actual numbers not reported)
Non-visible subcutaneous micronodules.	0	0	45% (52/115)	
Abscess (2 weeks after last treatment; treated with antibiotics and filler removed. no resolution of the event).	0	1% (1/130)	0	

Comment

Follow-up

- Not sta
follow-

Study des

- Prospe
consec
- Single
- Those
subcut
selecti
transfe
given a
absorb
- Cheek
by ultra
- Psycho
evaluat
outcom
- Face a
by Visu
Patient
satisfie
facial i
on Visu
(0, poo
100, be
- Body i
the Ass
Chang
[ABCD
Questi
satisfie

Abbreviations used: AFT: autologous fat transfer; FLA, facial lipoatrophy; FLSS: facial lipoatrophy severity scores; HADS: Hospital Anxiety Depression Scale; IQR, interquartile range; MOS-HIV: M
Study HIV Health Survey; NAGP, non-absorbable gel polymer; NR: not reported; NS: not significant; PLA: polylactic acid; QoL, quality of life; sDQLS: slightly modified Dermatology Quality of Life
standard deviation

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comment</th></tr>
<tr>
<td>Polylactic acid (PLA) (Sculptra) (n=91): 4 l ml injected into deep dermis around the atrophied area in each cheek every 4 weeks.
Autologous Fat Transfer (AFT) (n=54): performed using Coleman’s technique, amount injected determined by surgeon and patient.
Some patients given AFT plus Sculptra (n=24)
No lidocaine given before injection. Cheeks were massaged after injection. Total number of treatments was dependent on physician’s opinion and patient’s desire.

Follow-up: 48 weeks

Conflict of interest/source of funding: not reported.</td>
<td>*(mean mm± SD);
Body image satisfaction (evaluated using the Assessment of Body Change and Distress [ABCD] question 7 and 8)
<table>
<tr><th rowspan="2">Intervention</th><th colspan="2">Question 7</th><th rowspan="2">P-value</th><th colspan="2">Question 8</th><th rowspan="2">P-value</th></tr>
<tr><th>Baseline*</th><th>Week 48*</th><th>Baseline*</th><th>Week 48*</th></tr>
<tr><td>NAGP (Aquamid) n=130</td><td>3.7±1.0</td><td>2.9±1.1</td><td><0.0001</td><td>72.6±16.9</td><td>78.2±18.4</td><td>0.002</td></tr>
<tr><td>PLA (Sculptra) n=91</td><td>3.7±0.9</td><td>3.0±0.9</td><td><0.0001</td><td>70.3±17.5</td><td>78.6±15.2</td><td>0.001</td></tr>
<tr><td>AFT + PLA (Sculptra) n=24</td><td>3.6±1.5</td><td>3.2±0.8</td><td>NS</td><td>62.5±16.1</td><td>69.2±21.9</td><td>NS</td></tr>
<tr><td>AFT n=54</td><td>4.2±0.9</td><td>3.7±0.9</td><td>0.0017</td><td>68.7±14.7</td><td>74.1±15.4</td><td>NS</td></tr>
<tr><td>All patients n=299</td><td>3.8±1.0</td><td>3.1±1.0</td><td><0.0001</td><td>40.7±16.7</td><td>77.2±17.2</td><td><0.0001</td></tr>
</table>
*(mean mm± SD);
Depression (assessed using Beck Depression Inventory Scale [BDI])
<table>
<tr><th>Intervention</th><th>Baseline*</th><th>Week 48*</th><th>P-value</th></tr>
<tr><td>NAGP (Aquamid) n=130</td><td>11.8±8.5</td><td>9.6±8.1</td><td>0.014</td></tr>
<tr><td>PLA (Sculptra) n=91</td><td>10.7±7.4</td><td>8.0±6.5</td><td>0.001</td></tr>
<tr><td>AFT + PLA (Sculptra) n=24</td><td>15.6±10.5</td><td>12.7±12.1</td><td>NS</td></tr>
<tr><td>AFT n=54</td><td>10.0±8.3</td><td>10.4±8.7</td><td>NS</td></tr>
<tr><td>All patients n=299</td><td>11.4±8.3</td><td>9.4±7.8</td><td>0.001</td></tr>
</table>
*(mean mm± SD</td>
<td></td>
<td>body lo
Respon
Likert s
satisfac
satisfac
about p
consec
change
weeks;
point L
greates
lipodys
impact
• Depres
Depres
higher
greater
depres
score r
63.).</td>
</tr>
</table>

Abbreviations used: AFT: autologous fat transfer; FLA, facial lipoatrophy; FLSS: facial lipoatrophy severity scores; HADS: Hospital Anxiety Depression Scale; IQR, interquartile range; MOS-HIV: M Study HIV Health Survey; NAGP, non-absorbable gel polymer; NR: not reported; NS: not significant; PLA: polylactic acid; QoL, quality of life; sDQLS: slightly modified Dermatology Quality of Life standard deviation

Study details	Key efficacy findings	Key safety findings	Comment

Negredo E (2006)[2]

Non-randomised comparative study

Spain

Recruitment period: 2002–2004

Study population: HIV-related facial lipoatrophy

n=149 (NAGP=115, PLA=26, AFT=8)

Age: (mean) NAGP: 43 years, PLA: 45 years, AFT: 39 years

Sex: NAGP: 80% male, PLA: 100% male, AFT: 100% male.

Inclusion criteria: facial lipoatrophy for more than 6 months confirmed by a clinician, antiretroviral treatment for 1 year, the nadir CD4 cell count greater than 100 cells/mm^3.

Technique: Injection of NAGP polyacrylamide gel: Aquamid) or autologous fat (AFT) or polylactic acid (PLA-New-Fill) in the perimalar area and nasolabial fold. Those with residual subcutaneous fat were given fat transfer under general anaesthesia. All others were offered intradermal PLA or NAGP injections Substance injected depended on availability and technical

Number of patients analysed: **138**

Mean volume of filler injected after first round of injections: NAGP (Aquamid) 5.5 ml, PLA (New-Fill) 6 ml, AFT-not reported

At 48 weeks, second round of injections were necessary in 33% (33/93) of patients (AFT 7/8, PLA 17/20, NAGP 5/65).

Observer ratings of appearance

	Baseline (n)	**1st round injections (n)**	**Week 48 (n)**
Degree of lipoatrophy	**0, 1, 2, 3, 4**	**0, 1, 2, 3, 4**	**0, 1, 2, 3, 4**
NAGP (Aquamid) (n=105)	-,11, 43, 41,10	19, 50, 28, 3, 1	15, 36, 14, -, -
PLA (New-Fill) (n=25)	-, 5, 9, 9, 2	7, 10, 7, 1, -	1, 8, 9, 2, -
AFT (n=8)	-, -, 3, 5, -	1, 4, 3, -, -	1, -, 2, 5, -

At baseline, almost 50% (67/138) of patients had grades 3 and 4 lipoatrophy, at week 48 only 7.5% (7/93) remained in these grades (no patients from the NAGP group).

Patient satisfaction

N		**1st round injection % (n)**	**Week 24 % (n)**	**Week 48 % (n)**
138	Satisfied	97% (134/138)	87% (120/138)	84% (116/138)
	Unsatisfied	3% (4/138)	NR	NR

Measured using a 5-point Likert scale (from not at all satisfied to completely satisfied)

Adverse events

Adverse event	**AFT n=24**	**PLA n=25**	**NAGP n=105**	**Total n=138**
Mortality (due to multifocal leukoencephalopathy unrelated to the treatment; unclear what stage of study the patient died).	0	0	1% (1/105)	1% (1/138)
Oedema (minimal and transient for 2–3 days, resolved spontaneously within 3–5 days)				100%
Ecchymosis (, resolved spontaneously within 3–5 days).	0	4% (1/25)	17% (18/105)	14% (19/138)
Palpable subcutaneous micronodules (timing not reported, treated with oral antibiotics.).	0	1.4% (2/25)	0	1.4% (2/138)
Superficial cutaneous infection (patients were treated with oral antibiotics, type of organism not identified..).	0	0	1.4% (2/105)	1.4% (2/138)
Overcorrection or excess of	0	0	1.4% (2/105)	1.4% (2/138)

Follow-up

- Intende 96 wee at wee presen
- 1 patie and 10 NAGP of follo interve include
- At wee lost to group a follow- The rea reporte

Study des

- Study p signs c but not correct
- Facial measu lipoatro scale fi facial li degree severe
- Unclea baselin betwee
- Study r combir groups

Abbreviations used: AFT: autologous fat transfer; FLA, facial lipoatrophy; FLSS: facial lipoatrophy severity scores; HADS: Hospital Anxiety Depression Scale; IQR, interquartile range; MOS-HIV: M
Study HIV Health Survey; NAGP, non-absorbable gel polymer; NR: not reported; NS: not significant; PLA: polylactic acid; QoL, quality of life; sDQLS: slightly modified Dermatology Quality of Life
standard deviation

Study details	Key efficacy findings	Key safety findings	Comment

feasibility. First round of injections consisted of 2 sessions, 2 weeks apart for NAGP group and 3 sessions, 2 weeks apart for PLA group. Second round of injections given at 1-year follow-up. Number of sessions for AFT group not reported.

Follow-up: 48 weeks

Conflict of interest/source of funding: Collaborated with private donors and Rotary club. Biotech Industries SA and Contura International donated products for study.

Quality of life

Follow-up (n=138)	General health perception*	Mental health*	Energy level*
Baseline	45.2±17.9	68.3±19.1	65.7±14.6
Week 24	55.7±19.2	75.9±17.2	75.8±17.8
P value	<0.001	0.002	<0.001
Week 48	58.2±14.1	75.1±19.7	72.3±19.6
P value	<0.001	0.009	0.003

*(mean ± SD), QoL measured with the medical outcomes study-HIV (MOS-HIV) questionnaire. MOS-HIV scores were transformed on a 0 to 100 scale, where higher scores indicated better health. Three aspects with lower scores at baseline were reported for all groups.

The impact of injections compared for all the psychological variables did not show any significant differences among the 3 treatment groups compared (p value not reported).

substance (resolved by withdrawal of substance).				

Abbreviations used: AFT: autologous fat transfer; FLA, facial lipoatrophy; FLSS: facial lipoatrophy severity scores; HADS: Hospital Anxiety Depression Scale; IQR, interquartile range; MOS-HIV: M Study HIV Health Survey; NAGP, non-absorbable gel polymer; NR: not reported; NS: not significant; PLA: polylactic acid; QoL, quality of life; sDQLS: slightly modified Dermatology Quality of Life standard deviation

Study details	Key efficacy findings	Key safety findings	Comment

Loufty MR (2011)[3]

Cohort study (combined RCT and pilot study)

Canada

Recruitment period: 2004–5.

Study population: HIV-positive patients with facial lipoatrophy.

n=36

(16 immediate vs15 delayed NAGP injections in RCT; 5 pilot study)

Age: RCT: 48 years (RCT); pilot study: 45 years (median)

Sex: 97% (35/36)male

Patient selection criteria: HIV FLA confirmed by physician assessment, 18 years or older, no prior corrective therapy.

Technique: NAGP (polyalkylimide gel: Bio-Alcamid Polymekon, Biotech Industrie, Italy) injections were administered into the subcutaneous plane using aseptic technique. Quantity of gel injected varied with severity of skin depression. Intraoral massage techniques were also used. Additional

Number of patients analysed: **32 (5 pilot and 27 RCT [14 vs 13] patients)**

Changes from baseline to year 4 in FLSS, QoL, depression and anxiety scores

	Total (n=32) Median (IQR)	P
FLSS scores		
Physician's grade (median of 3 physician's scores)	−2(−2, −1)	<0.001
Patient's grade	−1(−3, −1)	<0.001
MOS-HIV		
Quality of life	NR	NS
Physical health summary score	NR	NS
Mental health summary score	NR	0.02
HADS		
Depression	NR	<0.001
Anxiety	NR	<0.001
sDQLS	NR	<0.001

FLSS score: a validated five point Carruthers scale of FLA ranging from grade 0 (no FLA) to 4 (severe FLA) assessed by physicians and patients; MOS-HIV: assesses QoL and includes functional, mental health and QoL, subscales scored out of 600, 700 and 100, with higher numbers indicating better health; HADS: assesses anxiety and depression, each subscale is measured out of 21, high numbers representing greater degrees of depression and anxiety; sDQLS: measures the impact of HIV lipoatrophy on QoL, scored out of 30 with higher scores representing more impaired QoL caused by appearance.

At baseline, patients in the RCT had a median physician FLSS of 2 (IQR 1–3) and 23 (74%) of them had moderate to severe FLA (grade 2–4). Patients in the pilot study had moderate to severe FLA with a median physician FLSS of 4 (IQR 3–4).

Patient satisfaction with treatment at year 4

	Pilot study (n=5)	RCT (n=27)	P	Total (n=32)

Injection-related immediate adverse events

Immediate adverse events for patients in RCT	(n=31)
Swelling (mild and transient, resolved after 4 days)	77% (24/31)
Pain (median 2 [IQR 1,4] on a scale of 0–10, resolved after 1 day)	68% (21/31)
Bruising (mild and transient, resolved after 3 days)	58% (18/31)
Erythema(mild and transient, resolved after 3 days)	42% (13/31)

Injection-related adverse events through 4 years follow-up (for total patients in study)

Delayed adverse events	Total % (n=32)	Time since treatment (years)*	Peak severity in days*	Duration (days-onset to resolution)*
Pain	25% (8/32)	2.8 (1.8–3.7)	10(8–10)	7(4–30)
Oedema	25% (8/32)	3.2 (2.5–3.7)	10(7–10)	18(10–30)
Erythema	25% (8/32)	2.6 (2.1–3.1)	7(5–9)	5(4–7)
Bruise	3% (1/32)	NR	NR	NR
Nodules	25% (8/32)	NR	6(5–7)	ongoing and lasted more than 1 year
Bleeding	3% (1/32)	NR	NR	NR

Follow-up

- 11% (4 the RC follow- group.

Study des

- Single origina amend follow-
- Patient assign immed or dela 18) NA control short-t treatm years f groups
- Lack o observ FLSS s introdu
- QoL ar assess survey

Long-term asking pat experience (defined su

Other issu

- The ot associa was se
- Author prophy

Abbreviations used: AFT: autologous fat transfer; FLA, facial lipoatrophy; FLSS: facial lipoatrophy severity scores; HADS: Hospital Anxiety Depression Scale; IQR, interquartile range; MOS-HIV: M
Study HIV Health Survey; NAGP, non-absorbable gel polymer; NR: not reported; NS: not significant; PLA: polylactic acid; QoL, quality of life; sDQLS: slightly modified Dermatology Quality of Life
standard deviation

Study details	Key efficacy findings	Key safety findings	Comment

injections after 6 weeks given if the surgeon deemed necessary. Median volume injected was 16.0 ml.

Follow-up: 4 years

Conflict of interest/source of funding: the original study with 96 weeks follow-up was funded by a grant from Pur Medical Corporation. This analysis, received no funding.

Satisfied with overall treatment				
Very unsatisfied/ unsatisfied	0	0		0
Neither	20% (1/5)	4% (1/27)		6% (2/32)
Very satisfied/ satisfied	80% (4/5)	96% (26/27)		94% (30/32)
Satisfied with NAGP (Bio-Alcamid)				
Very unsatisfied/unsatisfied	20% (1/5)	15% (4/27)		16% (5/32)
Neither	0	19% (5/27)		16% (5/32)
Very satisfied/satisfied	80% (4/5)	67% (18/27)		69% (22/32)
Would recommend NAGP treatment	60% (3/5)	81% (22/27)	0.29	78% (25/32)

Satisfaction assessed on a five point Likert scale (very unsatisfied to very satisfied) and a binary question about treatment recommendation.

Confirmed infection*	16% (5/32)	2.8 (2.5–3.5)	10(9–10)	30(30–60)
Possible infection*	9% (3/32)	3.7 (1.5-4.4)	8(8–9)	10(4–30)

*results expressed as median (IQR), Peak severity was measured on a visual analogue scale of 0 to 10.

Management of infections:

- Oral antibiotics = 25% (8/32)
- IV antibiotics = 6% (2/32)
- Anti-inflammatories = 9% (3/32)
- Drainage of purulent material = 13% (4/32)
- Surgical removal of product = 19% (6/32)
- Visit to emergency department = 9% (3/32)
- Admission into hospital = 6% (2/32)

Infections classified as confirmed (presence of purulent material and confirmation of an infectious organism) and possible (presence of clinical signs with erythema, oedema and pain without purulent discharge or an infectious organism).

In 3 patients organisms isolated include *Staphylococcus aureus*, methicillin-resistant *S. aureus*, *Enterobacter cloacae* and 1 patient had an unspecified organism.

All patients with confirmed infections and 1 out of 3 patients with possible infection had dental procedures prior to developing an infection. The other variable associated with infection was more severe FLA.

prior to
or any
proced

- Data o
compli
mitigat
not gat

Abbreviations used: AFT: autologous fat transfer; FLA, facial lipoatrophy; FLSS: facial lipoatrophy severity scores; HADS: Hospital Anxiety Depression Scale; IQR, interquartile range; MOS-HIV: M Study HIV Health Survey; NAGP, non-absorbable gel polymer; NR: not reported; NS: not significant; PLA: polylactic acid; QoL, quality of life; sDQLS: slightly modified Dermatology Quality of Life standard deviation

Study details	Key efficacy findings	Key safety findings	Comment
Negredo E (2009)[4] **Case series** Spain Study period: 2002–2004 Study population: HIV patients with facial lipoatrophy. n=**145** Age: 47 years (mean) Sex: 83% male Patient selection criteria: patients who received NAGP at least 4 years before. To assess safety, also included all patients treated at the unit who presented with a local infection at any time after infiltration. Technique: NAGP (polyacrylamide gel: Aquamid) injected subcutaneously.. Quantity injected depended on severity of lipoatrophy. Further sessions done every 3 weeks until it successful. **Follow-up: 50 months (mean)** Conflict of interest/source of funding: none	Number of patients analysed: **145** Mean time to HIV infection (years): 16 Mean time with antiretroviral therapy (years): 9 Time with facial lipoatrophy (years): 5 Mean volume of Aquamid injected (ml): 5.5 **Patient satisfaction 4 years after procedure** 89% patients were 'satisfied' or 'very satisfied' with the cosmetic results. Patients with mild to moderate baseline facial lipoatrophy were 'very satisfied' with the long-term results compared with those with severe lipoatrophy (93% vs 87%). 17% of patients reported mild impairment of facial lipoatrophy after the injections. 9% of patients required further injections after the initial session. 76% would have liked more injections to improve the aesthetic results, although lipoatrophy in the malar area was absent.	**Complications in patients with 4-year follow-up** **Severe adverse event** / **% (n)** Local infection; (after 32 months inflammation and no signs of systemic involvement, resolved by removal of product and using antibiotics, no sequelae). / 1 (1/145) **Other adverse events** **Other adverse events** / **% (n)** Small palpable non-visible nodules (54% with severe baseline lipoatrophy) / 19 (28/145) Indurations (54% with severe baseline lipoatrophy) / 6 (9/145) An inverse association was observed between the presence of induration and severity of facial lipoatrophy (p=0.025) and the number of sets of infiltrations (p=0.006). **Complications in patients with less than 4-year follow-up** **Adverse event** / **% (n)** Local infection; 2 cases resolved by removal of product and using antibiotics. No sequelae, 1 patient with other comorbidities (vasculitis and severe systemic infection) died of multiorgan failure. / 1 (3/294) All cases of infection involved patients with severe lipoatrophy, Overall NAGP-associated local infection was 1% (4/439).	**Study des** • Evalua from o • Cases severe consid catego • Patient classe 'satisfi satisfie • Compli severe remova antibio interfe movem • Nodule small l indurat abnorm skin.

Abbreviations used: AFT: autologous fat transfer; FLA, facial lipoatrophy; FLSS: facial lipoatrophy severity scores; HADS: Hospital Anxiety Depression Scale; IQR, interquartile range; MOS-HIV: M Study HIV Health Survey; NAGP, non-absorbable gel polymer; NR: not reported; NS: not significant; PLA: polylactic acid; QoL, quality of life; sDQLS: slightly modified Dermatology Quality of Life standard deviation

Study details	Key efficacy findings	Key safety findings	Comment
George DA (2012)[5] **Case series** UK Recruitment period: 2003 to 2011 Study population: patients who had NAGP injections for HIV-lipoatrophy, facial defects secondary to maxillectomy, facial nasal cleft, acne, glandular fever, facial paralysis, vasculitis and Moh's procedure. n=**69** **90% (62/69) were patients with HIV-associated facial lipoatrophy**. Age: 47.2 years (mean) Sex: not reported Patient selection criteria: patients who had undergone correction of facial defects using NAGP: Bio-Alcamid. Technique: Variable amount of NAGP: Bio-Alcamid was injected in a subcutaneous plane. Follow-up arranged after 4–6 months to assess and discuss whether any further treatment required. Follow-up: **7 years** Conflict of interest/source of funding: not reported.	Number of patients analysed: **69** **Frequency of injections** 100% patients had injections to their cheeks and 29% (10/36) to their temples. Total number of procedures: 155 (138 insertions, 17 removals) Mean number of procedures per patient: 2.25 (range 1–9) 62% patients underwent further top-up procedures to further correct remaining contour defects. **Patient satisfaction and impact of procedure** 94% (34/36) stated an improvement in their cheek volume. 77% (28/36) stated an improvement in their temple volume. 78% (28/36) would undergo the procedure again. 86% (31/36) would recommend the treatment to a friend.	**Complications** 50.0% (18/36) of those responding to the questionnaire experienced at least one complication at a mean onset of 12 months. **Complication** / **% (n)** Death (due to HIV-related medical conditions but not as a direct effect of the procedure): 4 (3/65) Migration: 25 (9/36) Hardening: 22 (8/36) Irregularity: 19 (7/36) Asymmetry: 19 (7/36) infection*: 17 (6/36) inflammation*: 11 (4/36) Haematoma: 3 (1/36) Itching: 3 (1/36) Spots/acne: 3 (1/36) Pain with injection (rated on a scale 1–10, 10 indicating severe pain): 52 (18/36) * Bio-Alcamid removal was required in 25% (9/36) of patients (in 1 patient secondary to infection and in 8 patients due to superficial site of the gel resulting in a lump). Removal of the product from the cheek was more frequent (n=8) than from their temples (n=1). Five patients stated that the gel was not fully removed and 1 patient was uncertain. Two failed attempts to remove Bio-Alcamid from the left cheek using ultrasound guidance were reported.	**Follow-up** • 3 patie follow- lost to • Only 6 questio (36/65) • Individ were n 17 pati exclud **Study des** • Retros patient and pa survey were o yes/no boxes 1 to 10 • Possib recolle questio • Patient of onse compli respon point o compli **Populatio** • Site of 3 patie

Abbreviations used: AFT: autologous fat transfer; FLA, facial lipoatrophy; FLSS: facial lipoatrophy severity scores; HADS: Hospital Anxiety Depression Scale; IQR, interquartile range; MOS-HIV: M Study HIV Health Survey; NAGP, non-absorbable gel polymer; NR: not reported; NS: not significant; PLA: polylactic acid; QoL, quality of life; sDQLS: slightly modified Dermatology Quality of Life standard deviation

Study details	Key efficacy findings	Key safety findings	Comment

De Santis G (2012)[5]

Case series

Italy

Study period: 2002–2010

Study population: HIV-related facial lipoatrophy patients treated with NAGP and had minimum 5 years follow-up.

Mean HIV duration: 13 years.

n=38

Age: 42.6 years (mean)

Sex: 84% male

Inclusion criteria: HIV-related moderate to severe facial lipoatrophy (according to Fontdevila classification), adulthood, stable highly active antiretroviral therapy for 6 months, platelet count greater than 50,000 cells/ml, and willingness to participate in follow-up.

Technique: Injection of NAGP (polyacrylamide gel: Aquamid) 1 ml into subcutaneous tissue

Number of patients analysed: **38**

Physician-related outcomes

Cheek soft-tissue thickness

Mean cheek thickness (measured with ultrasound) increased from a pretreatment mean of 3.68 mm (range 0 to 9.45 mm) to 13.33 mm (range 2.05 to 17.45 mm) at 5 years follow-up (p<0.0001).

Aesthetic improvement

Aesthetic improvement (measured using Global Aesthetic Improvement scale) on selected photographs evaluated was judged 'very much improved' in 12% 'much improved' in 47% and 'improved' in 41%.

Patient related outcomes at 5 years from end of treatment

Assessment item	Scoring	Baseline (median IQR)	Follow-up (median IQR)	p
Visual Analogue Scale face: how do you judge your appearance?	0 to100, with 0=worst appearance possible and 100=best appearance possible.	30 (0–100)	65 (20–90)	<0.0001
Assessment of Body Change and Distress question 7: satisfaction with personal body appearance	1 to 5, with 1=best satisfaction and 5=poorest satisfaction.	4 (2–5)	2.5 (1–5)	<0.0001
Assessment of Body Change and Distress	Total score from 20–100, with	66.5 (24–95)	89.5 (42–100)	<0.0001

Acute adverse events (within 1 week)

Adverse event	% (n)
Temporary swelling	18 (7/38)
Subcutaneous haematoma (spontaneous resolution in 1 week)	8 (3/38)
Localised accumulation of NAGP (camouflaged by subsequent injections)	3 (1/38)

Early postoperative period (between 1 week and 1 month)

Adverse event	% (n)
Localised accumulation of NAGP (camouflaged by subsequent injections)	3 (1/38)

Midterm postoperative period (between 1 month and 1 year)

Adverse event	% (n)
Swelling (resolved spontaneously in 2 months)	3 (1/38)

Late adverse events (after 1 year)

Adverse event	% (n)
Localised permanent gel indurations (blebs non-visible, mild and did not require corrective treatment)	11 (4/38)
Caudal migration of the injected material (mild and did not require corrective treatment)	8 (3/38)
Progressive worsening of initial result (reported subjectively by patients, difficult to prove objectively, even by comparing baseline and follow-up photographs)	(4/38)

Total adverse events including patients who did not complete 5 year follow-up

Adverse events	% (n)
Localised infection and abscess (in	5

Follow-up

- Longes

Study des

- Single patient
- Aesthe assess pretrea treatme
- Self-ev related (satisfa psycho
- Advers classifi midterm
- Only 1 injecte formati ease a tissues
- To ass include at the s presen any tim
- Incons about t patient

Abbreviations used: AFT: autologous fat transfer; FLA, facial lipoatrophy; FLSS: facial lipoatrophy severity scores; HADS: Hospital Anxiety Depression Scale; IQR, interquartile range; MOS-HIV: M
Study HIV Health Survey; NAGP, non-absorbable gel polymer; NR: not reported; NS: not significant; PLA: polylactic acid; QoL, quality of life; sDQLS: slightly modified Dermatology Quality of Life
standard deviation

Study details	Key efficacy findings					Key safety findings		Comment
in each cheek (every 4 weeks), until adequate correction was obtained. Injection done with the linear threading technique and a fanning distribution. The mean number of treatment sessions was 7, performed over a mean period of 8 months. **Follow-up: 5.22 years (median)** Conflict of interest: no commercial associations.	question 8: psychological consequences of body changes in the last 4 weeks (20 questions)	20=greatest adverse impact of FLA and 100=no impact on everyday habits, adherence to antiretroviral therapies and social relationships.				6 patients, *Staphylococcus epidermidis* was isolated, in 2 patients no bacteria were found; 2 patients rapidly developed a definite abscess 2 weeks after last injection, 6 patients had a very slow progression to a subcutaneous abscess in months, treated by incision and drainage approximately 2 years after the last injection. All patients had antibiotics for 3 weeks until culture was obtained).	(8/146)	
	Assessment of Body Change and Distress face questionnaire (18 questions):	Total score from 18 to 85, with 18=maximal impact of FLA and 85=no impact of FLA on the life of the patient.		80 (34–85)				
	Beck Depression Inventory score (21 questions)	0–63, with 9–17=mild depression, 18–29=moderate depression, and >30=severe depression.	9(0–36)	3(0–29)	<0.0001			

Abbreviations used: AFT: autologous fat transfer; FLA, facial lipoatrophy; FLSS: facial lipoatrophy severity scores; HADS: Hospital Anxiety Depression Scale; IQR, interquartile range; MOS-HIV: M
Study HIV Health Survey; NAGP, non-absorbable gel polymer; NR: not reported; NS: not significant; PLA: polylactic acid; QoL, quality of life; sDQLS: slightly modified Dermatology Quality of Life
standard deviation

Study details	Key efficacy findings	Key safety findings	Comment
Nadarajah J (2010)[6] Conference abstract **Case series** Canada Recruitment period: not reported Study population: HIV patients with facial lipoatrophy. n=**264** Age: 55 years (median) Sex: 96% male Patient selection criteria: HIV diagnosed prior to 2000 and on treatment, 76% had CD4 counts greater than 350/mm^3, and 80% had suppressed viral loads <50 copies/ml at the time of the initial procedure. Technique: NAGP (polyalkylimide gel: Bio-Alcamid injection. 83% needed at least one touch-up treatment (further details not available). **Follow-up: 5 years** Conflict of interest/source of funding: not reported.	Number of patients analysed: **264**	**Infection** Infection occurred in 24 patients (majority had well-controlled HIV). Infection occurred 1, 2, 3, 4, and 5 years after the procedure in 8% (2/24), 17% (4/24), 38% (9/24), 25% (6/24), and 12% (3/24), respectively. There were no significant events identified preceding onset of infection in 73% (17/24) of patients. 25% (6/24) had preceding dental work and 2% (1/24) had preceding facial trauma. All infections were treated with antibiotics. **Surgical procedures** 96% (23/24) had further surgical procedures: 5 patients had open drainage and debridement, 11 required open drainage, and 7 had needle aspiration. **Product removal** 71% (17/24) patients with infections eventually needed full removal of the product. **Non-infectious complications** Product migration and breaking up of product producing a lumpy appearance that was frequently confused with infection was also described (actual numbers not reported).	**Study des** • Aims to incider of infec • Retros patient clinics

Abbreviations used: AFT: autologous fat transfer; FLA, facial lipoatrophy; FLSS: facial lipoatrophy severity scores; HADS: Hospital Anxiety Depression Scale; IQR, interquartile range; MOS-HIV: M
Study HIV Health Survey; NAGP, non-absorbable gel polymer; NR: not reported; NS: not significant; PLA: polylactic acid; QoL, quality of life; sDQLS: slightly modified Dermatology Quality of Life
standard deviation

Study details	Key efficacy findings	Key safety findings	Comment

Mansor (2011)[7]

Case series

Denmark

Recruitment period: not reported

Study population: treatment-experienced HIV patients with facial lipoatrophy

n=**42**

Age: 53 years (mean)

Sex: 95% male

Patient selection criteria: age 18 years or older, HIV with a CD4 count above 100 mio/l, stable antiretroviral therapy for 1 year, facial lipoatrophy for 6 months and available for 1 year follow-up.

Technique: patients injected with NAGP (polyacrylamide gel: Aquamid) in both cheeks into the subcutaneous plane in small deposits (a total of 4.5–17 ml of gel in 0.3–6 ml per visit) over several visits in 2-week intervals. Patients with no subcutaneous fat, heavy wrinkles and with low body mass index required large

Number of patients analysed: **34**

Patient satisfaction with reconstruction results

Follow-up	Very satisfied	Satisfied	Not satisfied	Very dissatisfied
24 months (n=34)	31	3	0	0
12 months (n=34)	31	3	0	0
3 months (n=6)	6	0	0	0

3 patients were not 'very satisfied' because after full restoration of the midface, lipoatrophy of the temples became more obvious. These areas were not part of the study so they were not injected.

Quality of life before and after treatment

	Before injection (n=31)	After injection (n=31)
Very good (could hardly be better)	6	8
Good	13	18
Neutral	9	3
Bad	2	2
Very bad (could hardly be worse)	1	0

Injector satisfaction

Follow-up	No deformity (100% natural appearance and feel)	Minimal deformity (contracture can be seen but not felt by injector)	Moderate deformity (seen and felt by both patient and injector)	Severe deformity (obvious by inspection and feel)
24 months (n=34)	26	8	0	0
12 months (n=34)	27	7	0	0

There were no short or long-term filler-associated complications.

Irregularity
In 7 patients with very little subcutaneous tissue, the injector noted a slight diffuse firmness or irregularity but appearance was normal and did not have an influence on satisfaction rating (patient could not feel or see it).

Abscess
1 patient presented with an emptied tooth abscess (timing and treatment not reported). Further injections were only given when all signs of infection had disappeared.

Follow-up

- 2 patie
from st
treatme
NAGP
not cor
- 2 years
85% (3
up. 1 p
metast
after 3
5 patie
follow u

Study des

- Outcor
subject
tools. F
was as
scale r
satisfie
unsatis
- Quality
assess
ranging
very ba
- Satisfa
evalua
ranging
to seve
- Aesthe
judged
photog
and aft
Degree
correla
body m
judged

Abbreviations used: AFT: autologous fat transfer; FLA, facial lipoatrophy; FLSS: facial lipoatrophy severity scores; HADS: Hospital Anxiety Depression Scale; IQR, interquartile range; MOS-HIV: M
Study HIV Health Survey; NAGP, non-absorbable gel polymer; NR: not reported; NS: not significant; PLA: polylactic acid; QoL, quality of life; sDQLS: slightly modified Dermatology Quality of Life
standard deviation

Study details	Key efficacy findings	Key safety findings	Comment
volume of NAGP. Follow-up: **2 years** Conflict of interest/source of funding: Polyacrylamide gel used in this study was donated by manufacturer.			none to need fo was as

3 months (n=6)	6	0	0	0

Aesthetic improvement (judged by an independent plastic surgeon) at 12 months follow-up

Degree of atrophy before treatment		**Degree of atrophy after treatment**		**Need for filler in other areas (n=34)**		**Need for more filler in same area (n=34)**		**Need for more filler in same and other areas (n=34)**	
Grade	**n= 34**	**Grade**	**n= 34**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
0		0	19	3		2		9	
1	2	1	14		20				
2	21	2	1						
3	11	3	0						

Abbreviations used: AFT: autologous fat transfer; FLA, facial lipoatrophy; FLSS: facial lipoatrophy severity scores; HADS: Hospital Anxiety Depression Scale; IQR, interquartile range; MOS-HIV: M
Study HIV Health Survey; NAGP, non-absorbable gel polymer; NR: not reported; NS: not significant; PLA: polylactic acid; QoL, quality of life; sDQLS: slightly modified Dermatology Quality of Life
standard deviation

Study details	Key efficacy findings	Key safety findings	Comment
Nelson L and Stewart KJ (2011) [8] **Case series** UK Study period: 2005 to 2007 Study population: HIV-related facial lipoatrophy **n=18** Age: not reported Sex: not reported Inclusion criteria: not reported Technique: NAGP (polyalkylimide gel: Bio-Alcamid) was injected into the subcutaneous tissue under general or local anaesthesia using aseptic technique. Prefilled 3 ml syringes and an 18 gauge needle were used. A blunt needle was used to create a pocket by fanning in the hypodermis of affected areas. The gel was injected until the desired volume was obtained. Antibiotic prophylaxis with co-amoxiclav was administered intra-operatively. **Follow-up: 2 months to 3 years**	No efficacy results reported.	**Complications** 39% (7/18) of patients developed complications, 33% (6/18) patients developed more than one type of complication.	**Study des** • Retros • Extend patient treatme within a • Report compli • Onset ranged years. • Demog charac treated were n **Other issu** • Migrati patient revisio

Complication	Co-complication	Management	% (n)
Asymmetry (after 1 month in 4 patients, details for 5 patients were not reported).	None	Corrected by minor revisions (aspiration and further injections in 3 patients and removal by needle puncture in 1 patient).	50 (9/18)
Infection (after 2 months in 1 patient, after 6 months in another patient and 1 week after a revision procedure in another patient).	Asymmetry (corrected 1 month after injection in 1 patient).	3 patients were treated with intravenous antibiotics.	22 (4/18)
Chronic inflammation leading to abscess (2 years after a revision procedure at 3 sites in 1 patient; [isolated *Clostridium perfringes*)]	Asymmetry corrected at 1 month after injection.	After unsuccessful antibiotic therapy, product was surgically removed by stab incisions, curettage and irrigation, resulting in undesirable facial scarring. Long-term antibiotics given.	
Inferior product migration from malar region to jowls (at 12 months in 1 patient, 16 months	1 patient had infection at 2 months, and another had infection at 6 months.	Expression of product by stab incision in 1 patient, removal of product and Coleman fat	17 (3/18)

Abbreviations used: AFT: autologous fat transfer; FLA, facial lipoatrophy; FLSS: facial lipoatrophy severity scores; HADS: Hospital Anxiety Depression Scale; IQR, interquartile range; MOS-HIV: M
Study HIV Health Survey; NAGP, non-absorbable gel polymer; NR: not reported; NS: not significant; PLA: polylactic acid; QoL, quality of life; sDQLS: slightly modified Dermatology Quality of Life
standard deviation

Study details	Key efficacy findings	Key safety findings				Comment
Conflict of interest/source of funding: study funded by 4 charities.		in 1 patient and 3 years in 1 patient).		transfer in 1 patient and removal of product in 1 patient.		
		Excessive capsule formation (at 3 months in 1 patient and 12 months in 1 patient)	Asymmetry corrected by further injections at 1 month in 1 patient. Infection treated at 2 months in 1 patient.	No further treatment. Expression of gel by stab incision.	11 (2/18)	
		Intra-oral extrusion to buccal mucosa (at 12 months in 1 patient).	Asymmetry corrected by 2 revision procedures at 1 month.	Manual expression and antibiotic treatment was unsuccessful. Product surgically removed by stab incisions and curettage.	1 (1/18)	

Abbreviations used: AFT: autologous fat transfer; FLA, facial lipoatrophy; FLSS: facial lipoatrophy severity scores; HADS: Hospital Anxiety Depression Scale; IQR, interquartile range; MOS-HIV: M
Study HIV Health Survey; NAGP, non-absorbable gel polymer; NR: not reported; NS: not significant; PLA: polylactic acid; QoL, quality of life; sDQLS: slightly modified Dermatology Quality of Life
standard deviation

Study details	Key efficacy findings	Key safety findings	Comment
MHRA correspondence	The MHRA has had 8 adverse events reported regarding NAGP (polyalkylimide gel: Bio-Alcamid). The root cause of infection in 2 cases could not be attributed to the device (no further details provided).		

Efficacy

Changes in facial lipoatrophy severity, quality of life, depression and anxiety scores

A non-randomised comparative study of 299 patients (130 treated by NAGP injection, 91 by polylactic acid [PLA] injection, 54 by autologous fat transfer [AFT] only and 24 by AFT plus PLA injection) reported a significant improvement in depression score (assessed using the Beck Depression Inventory scale) for all the patients (p=0.001), for the NAGP group (p=0.014) and for the PLA group (p=0.001) at 48-week follow-up compared with baseline[1].

A non-randomised comparative study of 138 patients that compared NAGP, PLA and AFT in HIV patients with facial lipoatrophy reported significant improvement in quality of life domains (measured by the Medical Outcomes Study-HIV [MOS-HIV] health survey, with scores of 0–100, higher scores indicating better health). The improvement was reported in general health perception (p<0.001), mental health (p=0.009) and energy level (p=0.003) at 48 weeks compared with baseline for patients in all 3 groups. There were no significant differences among the 3 groups when the impact of treatment was compared for all the psychological variables (p value not reported)[2].

A cohort study of 32 patients (5 treated by NAGP injection in a pilot study, 27 treated by immediate or delayed NAGP injection in an RCT) reported significant improvements in scores for median physician and patient-graded facial lipoatrophy severity (−2 [interquartile range −2, −1; p<0.001] and −1 [interquartile range −3, −1; p<0.001]). The study also reported significant improvements in scores for anxiety (p<0.001) and depression (p<0.00) on the Hospital Anxiety Depression scale, the slightly modified Dermatology Quality of Life Survey, (p<0.001) and the mental health domain (p=0.02) of the Medical Outcomes Study-HIV (MOS-HIV) health survey from baseline to 4-year follow-up when the whole group was assessed as a single cohort. Changes in the quality of life and physical health domains of the MOS-HIV scale at 4 years relative to baseline were not significantly different (scores and p values not reported)[3].

Patient satisfaction

The non-randomised comparative study of 299 patients reported significantly better patient facial aesthetic satisfaction (on a visual analogue scale) for patients in the NAGP,PLA and AFT groups at 48-week follow-up relative to baseline (p<0.0001)[2]. At 48 weeks compared with baseline, there were significant improvements for body image satisfaction for all patients (p<0.0001) and for the NAGP and PLA groups. There was a significant decrease in negative and psychological and behavioural consequences for all patients (p<0.0001), for the NAGP group (p=0.002), and for the PLA group (p=0.001; measured using the Assessment of Body Change and Distress questionnaire)[1] at 48 weeks compared with baseline.

The non-randomised comparative study of 138 patients reported that 84% (116/138) patients were completely satisfied with treatment at 48-week follow-up (outcome reported collectively for all patients; measured using a scale ranging from not all satisfied to completely satisfied)[2].

The cohort study of 32 patients reported that 94% of patients were satisfied with their overall treatment, but only 69% were satisfied with NAGP treatment specifically (assessed using a scale ranging from very unsatisfied to very satisfied) at 4-year follow-up. In the study, 78% of patients responded that they would recommend NAGP injections[3].

A case series of 145 patients reported that 89% of patients were 'satisfied' or 'very satisfied' with the results 4 years after receiving NAGP injections (assessed using a 3 point scale ranging from not satisfied to very satisfied). Patients with mild to moderate facial lipoatrophy were 'very satisfied' with the long-term results compared with those with severe lipoatrophy (93% compared with 87%). In the study, 76% of patients would have liked more injections to improve the aesthetic results and 17% reported mild impairment of lipoatrophy over time[4].

A case series of 38 patients treated by NAGP for moderate to severe facial lipoatrophy reported highly significant improvement ($p<0.0001$) for facial appearance, satisfaction with personal body experience, psychological consequences of body changes in the last 4 weeks, and depression (measured using a visual analogue scale, Assessment of Body Change and Distress questions 7 and 8 and the Beck Depression Inventory score) at 5 years compared with baseline. Aesthetic improvement (measured using the Global Aesthetic Improvement scale on selected photographs) was judged as 'very much improved' in 12%, 'much improved' in 47% and 'improved' in 41%[6].

A retrospective case series of 69 patients (90% with HIV-related facial lipoatrophy) reported high patient satisfaction in a patient satisfaction questionnaire survey at 7 years follow-up (only 55% of patients responded). In this case series 94% (34/36) of the patients responding confirmed an improvement in their cheek volume, 78% (28/36) would undergo the procedure again and 86% (31/36) would recommend the treatment to a friend[5].

Change in cheek thickness

The non-randomised comparative study of 299 HIV-related facial lipoatrophy patients reported significant increases in mean left and right cheek thickness measurements ($p<0.0001$) using ultrasound for all groups at 48-week follow-up compared with baseline[1].

The case series of 38 patients reported significant improvement in cheek thickness (measured with ultrasound) from a pretreatment mean of 3.7 mm to 13.3 mm ($p<0.0001$) at a mean follow-up of 5 years[6].

Observer rating of appearance

The non-randomised comparative study of 138 patients reported that at baseline about 50% (67/138) of the patients had grade 3 or 4 facial lipoatrophy (measured using the facial lipoatrophy intensity ordinal scale, with 0 as no facial lipoatrophy and 4 as severe lipoatrophy). Improvement in lipoatrophy score at 48 weeks follow-up was reported in all groups and only 7.5% (7/93) of patients remained in grades 3 and 4. There were no patients from the NAGP group in these grades[2].

A case series of 34 patients reported aesthetic improvement evaluated by independent specialists after treatment in all patients, with a reduction in lipoatrophy from grade 2 to1 (moderate to mild) in 11 patients, from grade 3 to 1 (severe to mild) in 20 patients and from grade 3 to 0 (severe to none) in 3 patients at 12-month follow-up[8].

Safety

Infection and abscess formation

Confirmed infections (defined as presence of purulent material and confirmation of an infectious organism by culture) were reported in 16% (5/32) of patients (with severe facial lipoatrophy) in the cohort study of 32 patients at 4 year follow-up. The median interval between NAGP injection and occurrence of infection was 2.8 years and the median duration between onset and resolution was 30 days. An additional 9% (3/32) of patients (with severe facial lipoatrophy) had possible infection (defined as presence of clinical signs with erythema, oedema, and pain without purulent discharge or an infectious organism) with a median time of occurrence of 3.7 years from baseline. The median time between onset and resolution was 10 days. All patients with confirmed infections and 1 patient with possible infection were treated with antibiotics and needed surgical removal of the NAGP. Possible infection in 2 patients resolved with only antibiotics. The organisms isolated in confirmed infections included *Staphylococcus aureus*, methicillin-resistant *S. aureus*, and *Enterobacter cloacae* in 3 patients; 1 patient had an unspecified organism[3].

Superficial cutaneous infection (not otherwise defined) was reported in 1% (2/105) of patients in the NAGP group in the non-randomised comparative study of 138 patients at 48-week follow-up. This was treated with oral antibiotics; the specific type of bacteria was not identified. None of the patients in the AFT and PLA groups reported this complication[2].

Local infection in the injected area (inflammation and no signs of systemic involvement 32 months after NAGP injection) was reported in 1 patient (1/145) in the case series of 145 patients at a mean follow-up of 50 months. This resolved without sequelae on removal of NAGP by needle aspiration and treatment with antibiotics. In this case series, 1% (3/294) of patients with less than 4-year follow-up reported local infection in the injected area. This resolved without sequelae on

removal of the NAGP and treatment with antibiotics, except in 1 patient who had other comorbidities (panarteritis nodosa) and died because of multiorgan failure. Overall, NAGP-related local infection was 1% and occurred in patients with severe lipoatrophy (4/439)[4].

Infections occurred in 24 patients (most of whom had well-controlled HIV infection) in a case series of 264 patients with 5-year follow-up. Infection occurred 1, 2, 3, 4 and 5 years after the procedure in 8% (2/24), 17% (4/24), 38% (9/24), 25% (6/24) and 12% (3/24) of patients respectively. There were no events prior to onset of infection in 73% (17/24) of patients. All infections were treated with antibiotics and 96% (23/24) of patients needed further surgical procedures. These included open drainage and debridement in 5 patients, open drainage in 11 patients and needle aspiration in 7 patients. Eventually the NAGP was removed in 17 of the 24 patients[7].

Infections and facial abscess requiring intervention or drainage were not reported in the case series of 38 patients with a median follow-up of 5 years. However, in this case series, 5% (8/146) of patients, with less than 5-year follow-up, reported infection. Two of these patients rapidly developed a definite subcutaneous abscess requiring drainage within 2 weeks of the last injection and 6 patients had subclinical infection that slowly progressed to an abscess, treated approximately 2 years after the last injection. Infection resolved on drainage and treatment with antibiotics. In 6 patients, *Staphylococcus epidermidis* was isolated, in 2 patients no organism was found [6].

A local cheek abscess 2 weeks after the last treatment was reported in 1 patient (1/130) in the NAGP group in the non-randomised comparative study of 299 patients at 48-week follow-up. This resolved on removal of NAGP and treatment with antibiotics[1].

Infections after treatment were reported in 22% (4/18) of patients in a case series of 18 patients with follow-up of 2 months to 3 years. These were treated by antibiotics in 3 patients and by surgical removal of NAGP in 1 patient[9].

Infection was reported in 17% (6/36) of patients in a case series of 69 patients at 7 years follow-up: its mean time of onset was 12 months. This was treated by removal of NAGP. Inflammation was also reported in 11% (4/36) of patients[5].

Infections occurred as a result of dental procedures in all patients with confirmed infections 16% (5/32) and 1 patient with possible infection in the cohort study of 32 patients at 4-year follow-up[3]. Infections occurred as a result of dental work in 2% (6/264) of patients and facial trauma in 1 patient in a case series of 264 patients at 5 year follow-up[7]. Infections occurred as a result of revision procedures near the site of infection for correction of asymmetry in 11% (2/4) patients in a case series of 18 patients with follow-up of 2 months to 3 years[5].

Granuloma formation and indurations

Nodules were reported in 25% (8/32) patients in the cohort study of 32 patients at 4-year follow-up. Development of these nodules was ongoing and they lasted more than 1 year[3].

Small palpable, hidden or non-visible nodules (defined as a small lump or swelling) were found in 19% (28/145) of patients in the case series of 145 patients at a mean follow-up of 50 months after NAGP injection. In the same study indurations (defined as an abnormal hard spot on the skin) were observed in 6% (9/145) of patients. In this case series, 54% of non-visible nodules and indurations were observed among patients with severe baseline facial lipoatrophy (no further details reported)[4].

Localised permanent NAGP indurations (non-visible blebs) were reported in 11% (4/38) patients in the case series of 38 patients after 1-year follow-up. They were mild with no noticeable aesthetic or functional consequences and needed no corrective treatment[6].

Migration, breakage and extrusion of NAGP

Migration of the NAGP was reported in 25% (9/36) of patients at 7 year follow-up in a retrospective case series of 69 patients: its mean time of onset was 12 months. This was treated by removal of the implant in 22% (8/36) patientspatients[5].

Caudal migration of the injected material after 1 year was reported in 8% (3/38) of patients in the case series of 38 patients with 5-year follow-up (they were mild with no noticeable aesthetic or functional consequences and needed no corrective treatment)[6].

NAGP migration and breaking up of the NAGP producing a lumpy appearance that was frequently confused with infection was also reported in the case series of 264 patients with 5-year follow-up (absolute numbers and details not reported)[7].

Inferior migration of the NAGP from the malar region to the jowls was reported in 17% (3/18) of patients in the case series of 18 patients at follow-up ranging from 2 months to 3 years. This was treated by surgical removal of the NAGP in 1 patient; surgical removal and Coleman fat transfer in 1 patient and expression of the NAGP by stab incision in 1 patient. 2 of these patients had prior infections[9].

Intra-oral extrusion of the NAGP through the buccal mucosa of the cheek was reported in 1 patient in the case series of 18 patients at 12-month follow-up. This was removed surgically by stab incisions and curettage[9].

Excessive capsule formation

Hardening of the NAGP was reported in 22% (8/36) of patients at 7 year follow-up (no further details reported) in the case series of 69 patients: its mean time of onset was 12 months[5].

Excessive capsule formation was reported in 11% (2/18) patients in the case series of 18 patients at follow-up of between 3 months and 1 year. One patient was treated by expression of the NAGP by stab incision and 1 patient received no further treatment[9].

Asymmetry and irregularity

Asymmetry of treated areas was reported in 50% (9/18) of patients in the case series of 18 patients at 1-month follow-up. This was corrected by aspiration and further injections in 3 patients and removal of the NAGP by needle puncture in 1 patient; no details reported for 5 patients[9]. Asymmetry was reported in 19% (7/36) of patients at 7 year follow-up (no further details reported) in the case series of 69 patients: its mean time of onset was 12 months[5].

Irregularity was reported in 19% (7/36) of patients at 7 year follow-up (no further details reported) in the case series of 69 patients: its mean time of onset was 12 months[5]. A slight irregularity of NAGP compared with normal fat tissue without any hardening or difference in appearance was felt by the injector in 21% (7/34) patients in the case series of 34 patients at 2-year follow-up. These patients could not see or feel this complication[8].

Hypercorrection or excess substance in the malar area was reported in 1% (2/105) of patients treated by NAGP in the non-randomised comparative study of 138 patients at 48-week follow-up. This resolved on removal of the NAGP. None of the patients in the AFT and PLA groups reported this complication[2].

Bleeding

Bleeding was reported in 1 patient (1/32) in the cohort study of 32 patients treated by NAGP injections at 4-year follow-up (no further details reported)[3].

Validity and generalisability of the studies

- As prolonged follow-up is important to detect rare adverse events after a procedure, priority was given to studies that included larger numbers of patients and longer and complete follow-up. Non-randomised studies and case series that are more informative about safety events were included in table 2.
- Most of the patients were male.
- Follow-up ranged from 1 year to 5 years.

- Different non-absorbable dermal fillers were used across studies, some reporting touch-up sessions.
- In some studies validated subjective scales or objective measurements were used to assess efficacy outcomes.
- Two studies provided comparative data relating to AFT, PLA and NAGP.
- There might be some overlap of patients in some studies.

Existing assessments of this procedure

The Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP–S) review group published a systematic review on safety and efficacy of permanent and semi-permanent dermal fillers for age-related wrinkles and HIV-associated facial lipoatrophy in February 2009. The results of the review indicate that semi-permanent and permanent fillers are more efficacious than temporary fillers and at least as safe as temporary fillers in the short term in those studies that compared them. The dermal fillers appeared to decrease the effects of age-related changes and HIV-associated lipoatrophy, with high patient satisfaction. The most common adverse events were mild, appeared to be related to the injection process and resolved within few days. Palpable lumps were reported in many studies but received little follow-up. Long-term efficacy and safety was limited and has not been determined. The report concluded that the small number of well-designed studies limited the ability to draw any firm conclusions.

The ASERNIP–S review group recommended further research into long-term efficacy and safety of permanent and semi-permanent fillers including the facial changes, quality of life and nature of outcome of lumps in the long term. The review group also recommended the development of valid assessment tools for use in studies and training standards to aid physicians with injection techniques and product placement.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Deep dermal injection of non-absorbable gel polymer for HIV-related lipoatrophy. NICE interventional procedures guidance 291 (2009). (Current guidance). Available from www.nice.org.uk/guidance/IPG291

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Mr Ken Stewart (The British Association of Plastic and Reconstructive and Aesthetic Surgeons, BAPRAS), Dr T Griffiths (British Association of Dermatologists).

- One Specialist Adviser who regularly performs and carries out clinical research on this procedure considered it to be a dangerous practice that should be banned immediately and subjected to a product recall. One Specialist Advisor with limited experience in the use of NAGP considered it to be an established practice and no longer new.
- Two Specialist Advisers listed the standard comparators for this procedure as autologous fat transfer, hyaluronic acid injection, polylactic acid injection.
- Two Specialist Advisers stated that less than 10% of specialists are engaged in this work.
- The Specialist Advisers stated that the key efficacy outcomes were restoration of appearance, volume augmentation and psychometric evaluation of satisfaction. One Specialist Adviser noted that early results suggested the product was very efficacious, however, long-term results were far less satisfactory and the complication rate was unacceptable.
- One Specialist Adviser had concerns regarding the aseptic technique as an outpatient procedure and difficulties in training the dermatologists.
- The Specialist Advisers stated that anecdotal adverse events included infection of product needing multiple surgical procedures and prolonged antibiotic therapy, extrusion of product through buccal sculus, capsulation of product leading to very undesirable aesthetic outcomes, inferior migration of product leading to undesirable cosmetic outcomes and granuloma formation.
- One Specialist Adviser listed theoretical adverse events as vascular occlusion, delayed granuloma formation, unsatisfactory cosmetic appearance and short

duration of effect. One Specialist Adviser stated that there are many more complications than theoretical adverse events reported in the literature.

- One Specialist Adviser stated that advanced training in facial reconstructive surgery and an aseptic clinical environment or operating theatre is required to carry out the procedure. Even with such precautions, one Specialist Adviser noted major complications and suggested that the use of permanent non-encased injectable fillers should be banned completely outside of approved clinical trials. One Specialist Adviser expressed concerns about the use of dermal fillers for cosmetic indications in the private sector as they have been deregulated in the UK and only a voluntary register exists.
- One Specialist Adviser who has published a paper on Bio-Alcamid complications noted that many more complications have been seen in the same patient cohort since publication.
- One Specialist Adviser noted that the initial dissemination of evidence to support the use of Bio-Alcamid was inappropriate and with the benefit of hindsight, lacked sufficient evidence. He believes that the principal proponent may have failed to disclose a financial interest.
- One Specialist Adviser noted that this procedure is likely to be done in district general hospitals and could have a moderate impact on the NHS even from procedures done in the private sector.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme sent xxx questionnaires to xxx trusts for distribution to patients who had the procedure (or their carers). NICE received xxx completed questionnaires.

Section to be inserted where Patient Commentary was not gathered

NICE's Patient and Public Involvement Programme was unable to gather patient commentary for this procedure.

Section to be inserted where Patient Commentators raised no new issues

The Patient Commentators' views on the procedure were consistent with the published evidence and the opinions of the Specialist Advisers.

Section to be inserted where Patient Commentators raised new issues

The Patient Commentators raised the following issues about the safety/efficacy of the procedure which did not feature in the published evidence or the opinions of Specialist Advisers, and which the Committee considered to be particularly relevant:

- [insert additional efficacy and safety issues raised by Patient commentators and highlighted by IPAC, add extra rows as necessary].
- [Last item in list].

Issues for consideration by IPAC

- Non-English language studies were excluded.
- The procedure was considered to fit the criteria of the IP programme because a permanent bulking agent is used to alter physiology.
- The scope for the procedure was limited to HIV-related lipoatrophy. Most of the studies included patients with facial lipoatrophy resulting from antiretroviral drug use.
- Long-term efficacy and safety was considered.
- Bio-Alcamid and Aquamid are the two main non-absorbable gel polymers used.
- It is unclear whether some safety events (infection, abscess, migration, granuloma formation) are attributable to the NAGP or injection technique or the stage of HIV.

References

1. Orlando G, Guaraldi G, De Fazio D et al. (2007) Long term psychometric outcomes of facial lipoatrophy therapy: forty-eight-week observational, non-randomized study. AIDS Patient Care and STDs 21: 833–842

2. Negredo E, Higueras C, Adell X et al. (2006) Reconstructive treatment for antiretroviral-associated facial lipoatrophy: a prospective study comparing autologous fat and synthetic substances. AIDS Patient Care and Standards 20: 829–37

3. Loufty MR, Brunetta J, Kovacs C et al. (2011) Four-year follow-up of polyalkylimide gel use for the treatment of HIV-associated lipoatrophy. HIV Clinical Trials 12: 323–32

4. Negredo E, Puig J, Aleda D et al. (2009) Four-year safety with polyacrylamide hydrogel to correct antiretroviral-related facial lipoatrophy. AIDS Research & Human Retroviruses 25: 451–455

5. George DA, Erel E, Waters R (2010) Patient satisfaction following Bio-Alcamid injection for facial contour defects. Journal of Plastic, Reconstructive & Aesthetic Surgery Jun 30 [Epub ahead of print].

6. De Santis G, Pignatti M, Baccarani A et al. (2012) Long-term efficacy and safety of polyacrylamide hydrogel injection in the treatment of human immunodeficiency virus-related facial lipoatrophy: a 5-year follow-up. Plastic & Reconstructive Surgery 129: 101–109

7. Nadarajah J, Collins M, Loufty M et al. (2010) Infectious complications of Bio-Alcamid soft tissue endoprosthesis treatment of HIV-associated facial lipoatrophy. Antiviral Therapy Conference: 12th International Workshop on Adverse Drug Reactions and Co-Morbidities in HIV London United Kingdom. Conference Start: 20101104 Conference End: 20101106. Conference Publication: A22–A23. 2010

8. Mansor S, Breiting VB, Dahlstrom K et al. (2011) Polyacrylamide gel treatment of antiretroviral therapy-induced facial lipoatrophy in HIV patients. Aesthetic Plastic Surgery 35: 709–716

9. Nelson L, Stewart KJ (2011) Early and late complications of polyalkylimide gel (Bio-Alcamid). Journal of Plastic, Reconstructive and Aesthetic Surgery: JPRAS 64: 401–405

Appendix A: Additional papers on deep dermal injection of non-absorbable gel polymer for HIV-related lipoatrophy

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Antoniou T, Raboud JM, Kovacs C et al. (2009) Long-term efficacy and safety of polyalkylimide gel for the treatment of HIV-associated liopatrophy. AIDS Care 21: 1247–1252	RCT n=31 FU= 96 weeks (n=28) HIV patients with facial lipoatrophy Immediate (weeks 0 and 6) or delayed (weeks 12 and 18) polyalkylimide gel (PAIG) (Bio-Alcamid) injections.	Adverse events including swelling, redness, bruising and pain were mild and resolved after a median of 3 days. At week 96 median change in physician and patient facial liopatrophy severity scores were −2 (IQR −3; p<0.001 vs baseline) and −2 (IQR −2, −1; p<0.001 vs baseline), respectively. They were not significantly different between groups. Significant improvements in patient anxiety (p<0.001), depression (p<0.001) and mental health (p=0.01) were observed from baseline to week 96. Treatment with PAIG was associated with sustained improvements in both the physical and psychological components of FLA through 96 weeks follow-up.	Longer follow-up study included in table 2.
Campana M, Lazzeri D, Rosato L (2010) Late-onset gluteal Escherichia coli abscess formation 7 years after soft tissue agumentation with Bio-Alcamid in a HIV positive patient. Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS 63:e709-e710.	Case report n=1 (41 year old woman) Follow-up=7 years Severe buttock lipodystrophy resulting from highly active antiretroviral therapy. single session of an unidentified quantity of polyalkylamide 4% (Bio-Alcamid)	Patient presented with redness and swelling of the buttock area. The area was hard, extremely painful to touch. Antibiotic therapy led to temporary relief. The abscess was drained by inserting a 20 gauge IV cannula in the thin collagen capsule surrounding the gel. Irrigation was done with 10% providone iodine solution 3 times daily. Antibiotics were given intravenously. Microbiologic culture demonstrated growth of Escherica coli susceptible to antibiotic treatment. Inflammation subsided; infection resolved 3 days after admission, discharged with a 7 day course of antibiotics. Follow-up at	Abscess formation in buttock area in HIV patient, not facial lipoatrophy.

		1, 3, 10 and 18 weeks showed no signs of granuloma formation or inflammation. No further treatment was required.	
De Santis G, Jacob V, Baccarani A et al. (2008) Polyacrylamide hydrogel injection in the management of human immunodeficiency virus-related facial lipoatrophy: a 2-year clinical experience. Plastic & Reconstructive Surgery 121: 644–653	Case series n=50 Follow-up= 13 months (mean) HIV-related facial lipoatrophy. Polyacrylamide - Aquamid injection (mean of 6.1 sessions).	Mean cheek thickness increased significantly at 6 months follow-up. Patient satisfaction and aesthetic results improved. No significant side effects were reported up to 12 months follow-up, including no infection, alteration in skin colour or granuloma formation. Transitory swelling or redness of treated area occurred in 4% of patients.	Larger and longer follow-up studies included in table 2.
Giorgini S, Martinelli C, Carocci A et al. (2010) Facial corrections for lipoatrophy in HIV-infected patients: treatment with polyacrylamide hydrogel injections. Journal of Applied Cosmetology 28: 49–58	Case series n=36 Follow-up=48 weeks HIV patients with different levels of facial lipoatrophy. Polyacrylamide hydrogel (Aquamid)	All patients were pleased with the aesthetic result, judged excellent elasticity and consistency in treated area after 12 and 48 months. Patients were satisfied and had diminished levels of anxiety and depression. No serious complications and adverse events were observed except for pain during injection. During follow-up there were no events like migration, palpable regional lymph nodes, scar tissue, oedema, hematomas, pain at palpitation, hyperemia, wrinkles, scratch marks rash or polish like skin.	Larger studies with longer follow-up included in table 2.
Guaraldi G, Orlando G, De Fazio D et al. (2005) Comparison of three different interventions for the correction of HIV-associated facial lipoatrophy: a prospective study. Antiviral Therapy 10: 753–9	Randomised controlled study. n=59 (n=15 non-absorbable) Follow-up: 24 weeks. HIV-related facial lipoatrophy. Polyacrylamide hydrogel (Aquamid)	24 patients received AFT and 35 were randomised to PLA (20) or polyacrylamide hydrogel (PAAG) (15) infiltrations. PLA and PAAG groups received a mean of 5 and 6 injections (P=NS). The mean change in dermal thickness was 3.3±4.1mm, 3.5±4.0mm, 2.1±3.0mm (p=0.687) respectively. The mean change in ABCD score	Short term efficacy and safety (24 weeks). Longer follow-up studies included in table 2.

		result was poorer in the AFT arm, but there were no differences in other factors. Four serious adverse events were documented in AFT arm only.	
Honig J (2008) Cheek augmentation with Bio-Alcamid in facial lipoatrophy in HIV seropositive patients. Journal of Craniofacial Surgery 19:1085–1088	Case series n=9 FU=2 years (median) HIV patients with facial liopatrophy. Bio-Alcamid for cheek augmentation.	All patients had an immediate modest inflammatory reaction which subsided within 24–36 hours. Oedema after surgery diminished and vanished after 2–3 days. No migration, dislocation, granulomas, intolerance were observed. Corrections remained unchanged throughout follow-up period. Bio-Alcamid maintained the form and blend with the surrounding tissues. Level of satisfaction was 'excellent' in 63%, 'good' in 32%, and 'poor' in 5%.	Larger studies included in table 2.
Ivanovic J, Bellaamba R, Fracasso L et al. (2009) Treatment options for facial HIV-related lipoatrophy: Intradermal injections of poly-l-lactic acid and polyacrylamide hydrogel. Infection Conference: Italian Conference on AIDS and Retroviruses, ICAR 2009 Milan Italy. Conference publication: 72	Comparative case series n=151 Follow-up=12 months (n=143; 60 PLA, 82 PAIG) Patients with moderate or severe HIV related facial lipoatrophy. 2 different fillers: polylactic-acid (PLA) (Sculptra) vs polyacrylamide gel (PAIG) (Aquamid)	The maximum aesthetic result was achieved by 52 patients from PAIG group and 48 patients from PLA group. Self-reported satisfaction with PAIG or PLA was 4.5 (+/-0.6) and 4.2 (+/-0.6) respectively. Pain related to the injection was reported by all. A mean level of measured pain was 4 (+/-1.7) for PLA group and 5 (+/-2) for PAIG group. No serious complications and adverse events were observed during the treatment and follow-up.	Conference abstract.
Jones DH, Carruthers A, Fitzgerald R et al. (2007) Late-appearing abscesses after injections of non-absorbable hydrogel polymer for HIV-associated facial lipoatrophy. Dermatologic Surgery 33 Suppl. 8: S193–8	Case series n=5 FU=3 years HIV associated lipoatrophy Polyalkylimide -Bio-Alcamid	Safety data reported a late appearing streptococcal bacteria abscess formation after dental work. Abscess resolved with incision and drainage and antibiotic therapy.	Larger series included in table 2. Complication relates to subsequent dental procedure rather than the index gel polymer injection procedure.

Jones DH, Carruthers A, Orentreich D et al. (2004) Highly purified 1000-cSt silicone oil for treatment of human immunodeficiency virus-associated facial lipoatrophy: an open pilot trial. Dermatologic Surgery 30:1279–1286	Case series n=77 HIV-associated facial lipoatrophy. Liquid silicone (Silikon 1000 or VitreSil 1000) Follow-up=mean 58.9 weeks since first treatment and 27.1 weeks since their last treatment.	The volume of silicone, number of treatments, and time required to reach complete correction were directly related to initial severity of lipoatrophy ($p<0.0001$). Facial contours were routinely restored with all patients tolerating treatments well. Most patients' experienced mild erythema, oedema, mild tenderness which resolved within 3 days. Ecchymoses were occasionally noted in temporal areas, resolved within 14 days. Majority of patients reported mild to moderate discomfort related to needle punctures.	Longer follow-up studies included in table 2.
Karim RB, de Lint CA, van Galen SR et al. (2008) Long-term effect of polyalkylimide gel injections on severity of facial lipoatrophy and quality of life of HIV-positive patients. Aesthetic Plastic Surgery 32: 873–78	Case series n=17 FU=48 weeks HIV patients with grade 2 and grade 3 facial lipoatrophy. Polyalkylimide gel injections (Bio-Alcamid)	The severity of facial lipoatrophy decreased significantly from baseline over 48 weeks. Quality of life improved significantly from baseline over 48 weeks for mental health and social functioning. Depression at week 48 was significantly correlated with the extent to which lipoatrophy had disappeared at week 48. 4 patients reported complications, infection at injection site requiring surgical drainage (n=1); capsule formation or gel migration that did not need additional intervention (n=3).	Larger studies with longer follow-up included in table 2.
Karim RB, de Lint CA, van Galen SR et al. (2008) Long-term effect of polyalkylimide gel injections on severity of facial lipoatrophy and quality of life of HIV-positive patients. Aesthetic Plastic Surgery 32:873–878	Case report n=1 Follow-up: 2 years. Patient with HIV-related severe facial lipodystrophy. Bio-Alcamid injection.	Post-treatment course uneventful. At 2 years follow-up patient had partial removal of gel at the left temporal area where it was bulging. Few weeks later patient had inflammation in the area (redness, swelling, hard and painful to touch) treated by antibiotics. Additionally a small swelling was present in the nasal	Larger studies with longer follow-up included in table 2.

		corner of the right upper eyelid and no treatment was given. A 'localised festering mass' was surgically removed from the left side of the head. A small incision over the swelling in the eyelid yielded approximately 0.25 ml of gel.	
Lafarge Claoue BL and Rabineau P (2004) The polyalkylimide gel: experience with Bio-Alcamid. Seminars in Cutaneous Medicine & Surgery 23: 236–40	Case series n=65 (50 face, 15 body) Follow-up=not reported. Healthy or HIV-related facial lipoatrophy. Non-absorbable gel polymer -polyalkylimide (Bio-Alcamid)	No efficacy outcomes reported. In patients with HIV facial lipoatrophy immediate reactions included moderate oedema or bruising. Infection (not otherwise defined) occurred in 4% (2/50) of patients following dental treatment several months after treatment. Sequelae not described.	Follow-up not reported. Mixed cohort of HIV and healthy patients. Longer follow-up studies included in table 2.
Lahiri A, Waters R (2007) Experience with Bio-Alcamid, a new soft tissue endoprosthesis. Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS 60: 663–667	Case series n=34 (15 HIV facial lipoatrophy patients) Follow-up=1 to 18 months (mean 7.5 months) Patients of different indications as HIV treatment-associated facial lipoatrophy, chest wall deformities in reconstructed breasts, Poland syndrome and pectus excavatum. Polyalkylimide – Bio-Alcamid injections	Results have been good and satisfactory. Patients tolerated the treatment very well and reported some functional improvement in terms of ease of chewing food and shaving. Corrections lasted in the follow-up period. All patients reported some degree of pain and swelling in the short term. One patient with HIV lipoatrophy developed an infection with *Staphylococcus aureus* which resulted in small area of skin breakdown and spontaneous discharge of the injected material which settled with a course of antibiotics. Another patient felt over correction of temporal hollows.	Larger studies included in table 2.
Loufty MR, Raboud JM, Antoniou T et al. (2007) Immediate versus delayed polyalkylimide gel injections to correct facial lipoatrophy in HIV-positive patients. AIDS 21: 1147–1155	RCT n=31 FU=48 weeks HIV patients with facial lipoatrophy Immediate (weeks 0 and 6) or delayed (weeks 12 and 18) polyalkylimide gel (PAIG) (Bio-Alcamid)	Median volume of product injected was 16.0 ml. Adverse events including swelling, redness, bruising and pain were mild and resolved after a median of 3 days. There were no cases of necrosis,	Longer follow-up study included in table 2.

	injections.	nodules or infection. At week 12, compared with patients in delayed treatment group, patients in the immediate treatment group had significantly lower physician-rated facial lipoatrophy scores (0 versus 2; P<0.0001), improved QoL (P=0.01) and lower anxiety (P=0.02). At week 48, median physician and patient facial lipoatrophy scores were 0 and 1 for the entire cohort and were not significantly different between groups. Significant improvements in patient anxiety and depression were observed from baseline to week 48.	
Mole B (2005) Long-term treatment for lipoatrophy associated or not with HIV infection using ePTFE implants and polyacrylamide gel. Aesthetic Surgery Journal 25:561–70.	Case series n=65 Follow-up=16 months (mean) Healthy or HIV-related facial lipoatrophy. Non-absorbable gel polymer (Eutrophill).	No efficacy outcomes reported because patients were still undergoing treatment. 5% (3/65) of patients displayed roughness of filler under oblique angle lighting conditions in patients with thin skin. No blending of the non-absorbable polymer gel with other filler products was reported.	Longer follow-up studies included in table 2.
Narciso P, Bucciardini R Tozzi V et al. (2009) Immediate versus delayed surgical intervention for reconstructive therapy of HIV-associated facial lipoatrophy: a randomized open-label study. AIDS Research & Human Retroviruses 25: 979–87	RCT n=134 Follow-up=Mean 27 weeks (immediate group) and 25 weeks (delayed group) HIV patients with severe facial lipoatrophy. Immediate versus delayed injections of polylactic acid (PLA) or polyacrylamide gel (Aquamid)	Adverse events were mild and resolved after a mean of 4 days. Compared to the delayed group, patients in the immediate group had significantly lower physician rated (0.0 vs −3.0; p<0.0001) and patient rated (0.1 vs −1.8; p<0.0001) FLA severity scores. There was no significant difference in HRQoL and anxiety measures between the groups.	Mixed reporting of results for biodegradable (poly lactic acid) and non-biodegradable (polyacrylamide gel-Aquamid) facial fillers.
Nelson L, Stewart KJ (2007) Plastic surgical options for HIV associated lipodystrophy. Journal of Plastic, Reconstructive &	Review	Describes various treatment options and evidence for problems of fat distribution in patients with HIV lipodystrophy.	Review.

Aesthetic Surgery 61: 359–65			
Nelson L, Stewart KJ (2008) Experience in the treatment of HIV-associated lipodystrophy. Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS 61:366–71	Case series n=7 Follow-up=2 to 12 months HIV-related facial lipoatrophy. Polyalkylimide gel- Bio-Alcamid	Results with treatment were good and overall mean satisfaction was 8/10. Intraoperative bleeding and bruising occurred in 1 patient and bruising and swelling persisted up to 1 month. Minor asymmetry requiring corrective procedure occurred in 2 of 7 patients.	Larger studies included in table 2.
Nelson L, Stewart KJ (2012) Psychological morbidity and facial volume in HIV lipodystrophy: Quantification of treatment outcome. Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS 65:439–447	Comparative case series n=48 12 (AFT) vs 20 (Sculptra) vs 16 (Bio-Alcamid) Follow-up=12 months HIV lipodystrophy patients. Autologus fat transfer vs Sculptra vs Bio-Alcamid	Mean injected volume of Bio-Alcamid was 25.5 cc which was comparable to the measured volume change at follow-up. Changes in facial volume compared with baseline were observed in all 3 groups. There was no difference in psychological outcomes between groups. There was a significant improvement in DAS 24 scores compared with baseline for all 3 groups. No correlation between change in facial volume and psychological measures were demonstrated.	Only efficacy results reported. Studies with long-term safety data were included in table 2.
Orentreich D, Leone AS (2004) A case of HIV-associated facial lipoatrophy treated with 1000-cs liquid injectable silicone. Dermatologic Surgery 30: 548–51	Case report n=1 Follow-up=not reported Patient with HIV-associated facial lipoatrophy Silikon 1000 Liquid injectable silicone oil (8 sessions, 1 month apart) using microdroplet serial puncture technique.	Satisfactory improvements of areas of facial lipoatrophy. The treatment time, limited patient discomfort and morbidity were minimal and results long lasting. Patient reported satisfaction with treatment. No adverse events reported.	Larger studies included.
Protopapa C, Sito G, Caporale D et al. (2003) Bio-Alcamid in drug-induced lipodystrophy. Journal of Cosmetic & Laser Therapy 5: 226–30	Case series n=73 Follow-up=up to 3 years (only 5 patients were followed up to 3 years) Drug-induced facial lipodystrophy. Bio-Alcamid	No objective efficacy outcomes reported. Aesthetic results were deemed excellent by both physicians and patients. Oedema resolved after 3 to 4 days. There were no instances of gel dislocation, migration, granuloma, allergic reaction or intolerance.	Only 5 patients followed up to 3 years. Larger studies with longer follow-up included in table 2.
Ramon Y, Fodor L,	Case series	Overcorrection occurred	Larger studies included

Ullmann Y (2007) Preliminary experiences with Bio-Alcamid in HIV facial lipoatrophy. Dermatology 214: 151–4	n=13 Follow-up=1–2 years HIV-related facial lipoatrophy Polyalkylimide -Bio-Alcamid injection.	in 2 patients and some filler was removed 3 months after the injection. Local oedema was present for up to 1 week in all patients. No major complications such as gel migration, infection or granulomas. A small haematoma was seen in 1 patient. Most of the patients felt they had good to excellent results.	in table 2.
Rauso R, Freda N, Parlato V et al. (2011) Polyacrylamide gel injection for treatment of human immunodeficiency virus-associated facial lipoatrophy: 18 months follow-up. Dermatologic Surgery 37: 1584–1589	Case series n=32 Follow-up: 18 months Patients with HIV-associated facial lipoatrophy Polyacrylamide gel (Aquamid)	Pain and discomfort during the procedure were common in all patients. Ecchymosis and oedema observed in all and persisted for approximately 6 days. Local infection, foreign body reaction, and migration were not observed during 18 months follow-up. Small, palpable, non-visible nodules were recorded in 13 cases at the end of follow-up.	Larger studies included in table 2.
Rauso R, Gherardini G, Parlato V et al. (2012) Polyacrylamide gel for facial wasting rehabilitation: how many millilitres per session? Aesthetic Plastic Surgery 36: 174–179	Comparative case series n=31 Follow-up=12 months Different volume of Aquamid gel injected. Group A: 8 ml in first session retreated every 8th week with touch-up until corrected. Group B: 2 ml per session retreated every 8th week with touch-up until corrected.	Patients in group A noted a great improvement after the first filling procedure. Patients in group B noted improvement after 4 filling procedures on average. Local infection, foreign body reaction and migration of the product were not observed in either group during follow-up. In group A ecchymosis occurred in all patients after 1st injection except for one patient. In touch-up sessions in group A and filling sessions in group B ecchymosis was not seen. Small palpable non-visible nodules were recorded in 6 and 3 patients in group A and B at the end of follow-up.	Larger studies with longer follow-up included in table 2.
Rauso R, Curinga G, Santillo V et al. (2011) Comparison between lipofilling and a non-absorbable filler for	Comparative case series n=23 Follow-up=1 year HIV positive patients affected by facial	There were no major complications. No infections or other complications were observed. A light	Larger studies with longer follow-up included in table 2.

facial wasting rehabilitation in HIV positive patients. The Journal of Craniofacial Surgery 22: 1684–1688	wasting. Group A: Facial lipofilling (n=14) Group B: Aquamid injection (n=9)	swelling and oedema was observed for a week in the postoperative period for patients in group A. Haematomas for a week, on average, were observed after Aquamid injection inpatients in group B. According to Global Aesthetic Improvement Scale, group A obtained significantly higher ratings than group B after baseline ($p<0.05$).	
Sturm Lp, Cooter RD, Mutimer KL et al. (2009) A systematic review of permanent and semipermanent dermal filler for HIV-associated lipoatrophy. AIDS Patient Care and STDs 23:699–714	Systematic review		Not comprehensive and includes evidence on both permanent and semi-permanent dermal fillers.
Treacy PJ, Goldberg DJ (2006) Use of a biopolymer polyalkylimide filler for facial lipodystrophy in HIV positive patients undergoing treatment with antiretroviral drugs. Dermatologic Surgery 32: 804–808	Case series n=11 FU=18 months HIV patients with severe facial lipodystrophy. Polyalkylimide gel (Bio-Alcamid)	All patients received an immediate acceptable therapeutic aesthetic effect. Injections well tolerated with only 3 adverse events (swelling and bruising) recorded. Patients assessed at 3 and 18 months follow-up continued to show improvement. No patient reported evidence of migration or nodules at 3 months follow-up.	Larger studies included in table 2.

Appendix B: Related NICE guidance for deep dermal injection of non-absorbable gel polymer for HIV-related lipoatrophy

Guidance	Recommendations
Interventional procedures	**Deep dermal injection of non-absorbable gel polymer for HIV-related lipoatrophy. NICE interventional procedure guidance 291 (2009)** **(Current guidance)** 1.1 Current evidence on the efficacy and safety of deep dermal injection of non-absorbable gel polymer (NAGP) for HIV-related facial lipoatrophy is based on small patient numbers but shows that the procedure is efficacious in the short term and there are no major short-term safety concerns. However, there are uncertainties about both efficacy and safety in the longer term. Therefore, this procedure should be performed with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake deep dermal injection of NAGP for HIV-related facial lipoatrophy should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy. In particular, patients should be informed that repeated injections may be required; that there is a risk of inflammation, infection or deterioration in the long term; and that the gel polymer may be difficult to remove. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended. • Audit and review clinical outcomes of all patients having deep dermal injection of NAGP for HIV-related facial lipoatrophy (see section 3.1). 1.3 Clinicians using this procedure should be trained in the correct placement of deep dermal injections. 1.4 Further research should take the form of randomised controlled trials with long-term follow-up, comparing the procedure with alternative treatments. NICE may review the procedure on publication of further evidence.

Appendix C: Literature search for deep dermal injection of non-absorbable gel polymer for HIV related lipoatrophy

Database	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	07/03/2012	Issue 2 of 12, Feb 2012
Database of Abstracts of Reviews of Effects – DARE (CRD website)	07/03/2012	n/a
HTA database (CRD website)	07/03/2012	n/a
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	07/03/2012	Issue 2 of 12, Feb 2012
MEDLINE (Ovid)	07/03/2012	1946 to February Week 4 2012
MEDLINE In-Process (Ovid)	07/03/2012	March 06, 2012
EMBASE (Ovid)	07/03/2012	1980 to 2012 Week 09
CINAHL (NLH Search 2.0/EBSCOhost)	07/03/2012	n/a
BLIC (Dialog DataStar)	07/03/2012	n/a

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE search strategy

1 Gels/

2 Polymers/

3 Biopolymers/

4 Hydrogels/

5 Acrylic Resins/

6 Electrophoresis, Polyacrylamide Gel/

7 Imides/

8 Biocompatible Materials/

9 Injections/

10 (derma* adj3 inject*).tw.

11 (Gel$ adj3 polymer$).tw.

12 Biopolymer$.tw.

13 (biocompatib* adj3 material*).tw.

14 Hydrogel$.tw.

15 (Acrylic$ adj3 resin$).tw.

16 Polyacrylamide$.tw.

17 Polyalkylimide$.tw.

18 Imide$.tw.

19 Alkylimide$.tw.

20 Endoprosthe$.tw.

21 (BioAlcamid$ or Bio-Alcamid$).tw.

22 Polymekon$.tw.

23 or/1-22

24 HIV-Associated Lipodystrophy Syndrome/

25 exp Lipodystrophy/

26 Subcutaneous Fat/

27 Lipodystroph$.tw.

28 Lipoatroph$.tw.

29 (Subcutaneou$ adj3 fat$).tw.

30 or/24-29

31 23 and 30

32 Animals/

33 Humans/

34 32 not (32 and 33)

35 31 not 34