MEDICAL DEVICE MATERIAL PERFORMANCE STUDY

Poly (2-Hydroxyethyl Methacrylate) (pHEMA) Safety Profile

Report Details

Date of Submission

5/03/2021

Prepared For

U.S. FDA Center for Devices and Radiological Health

Submitted to

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Executive Summary

Key Points

1. Searches identified 1,022 citations; 38 articles were selected for inclusion.
2. The local response reported in the largest number of studies was migration, and it was associated with moderate to very low quality of evidence. Local responses for polyacrylamide dermal fillers, ocular implants, implantable intraocular lens (IOLs), and contact lenses (no evidence) were associated with very low quality of evidence.
3. Evidence for systemic responses was reported for poly(2-hydroxyethyl methacrylate) (pHEMA) as a material, polyacrylamide dermal fillers, and HEMA dermal fillers although the direct association with pHEMA is uncertain in all cases.
4. No reports were found within the accident investigation, Problem Reporting Network (PRN), or Patient Safety Organization (PSO) data. The Healthcare Technology Alerts database returned 24 alerts. These consisted of package mislabeling, incorrect materials and particulates in packaging, and compromised sterility, as well as more serious hazards such as residual toxins (IOLs), leaking fluid during procedure (injectable agents for gastro-urology use), and high levels of diluting agent causing discomfort and redness (daily wear soft contact lens).
5. Evidence gaps:
    a) Long-term human randomized controlled trials (RCTs) for all pHEMA device categories. Of the 38 human studies, 30 (78%) studies were uncontrolled (low quality evidence).
    b) Long-term animal RCTs for pHEMA as a material. No animal studies were identified in this category.
    c) Additional research on systemic responses, including patient or material factors, for all pHEMA device categories. Systemic responses were investigated only in 7 (18%) studies, with no studies investigating pHEMA for urethral bulking, ocular implants, or IOLs.
    d) Evidence for dermal fillers was based mostly on facial injection applications. Information is lacking in various anatomic sites, in younger adults, and in males. One nonrandomized comparative study addressing both dermal filler types examined only DermaLive (HEMA) and Aquamid (polyacrylamide) in fewer than 10 patients each.

Overview - pHEMA

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. Additionally, data derived from ECRI's Patient Safety Organization (PSO), accident investigations, Problem Reporting Network (PRN), and Healthcare Technology Alerts were analyzed. This report focuses on answering 5 key questions provided by FDA and summarized below, regarding a host's local and systemic response to pHEMA. If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research.

1. What is the typical/expected local host response to pHEMA?

Local responses/device events varied somewhat across different device categories (see specific responses/events under 1a. below). The only ECRI surveillance data available were healthcare technology alerts that consisted of package mislabeling, incorrect materials and particulates in packaging, and compromised sterility as well as more serious hazards such as residual toxins (IOLs), leaking fluid during procedure (injectable agents for gastro-urology use), and high levels of diluting agent causing discomfort and redness (daily wear soft contact lens).

a. Can that response vary by location or type of tissue the device is implanted in or near?

i. Several studies evaluating pHEMA as a material addressed polyacrylamide hydrogel (PAHG) and polyacrylamide gel (PAAG) injections for breast augmentation and reported migration, pain, induration (area of hardened tissue), and deformities. Swelling/edema, breast lump/mass, local inflammation, and fistula were reported less frequently. Malignant tumors were a rare occurrence.

i. Studies of urethral bulking most frequently reported hematuria, implantation site pain, and urinary retention. Injection site rupture of the urethral mucous membrane and transurethral catheterization were rarely reported.

ii. Studies of polyacrylamide dermal fillers reported various local responses, with only 3 (37%) studies reporting induration and migration, and 2 (25%) studies reporting ecchymosis, diffused distribution of product/localized accumulation, hematoma, and swelling. Palpable nodules, local inflammation, and pain were less frequently reported.
iii. No local responses overlapped in studies of ocular implants. Stromal melt had the highest occurrence (n=9), while migration had the lowest occurrence (n=1).
iv. Studies of HEMA dermal fillers reported similar complications to polyacrylamide dermal fillers, however migration with HEMA dermal fillers was reported less frequently.
v. Studies of IOLs most commonly reported opacification and local inflammation. Corneal edema occurred more frequently than macular edema (21.1% vs. 2%) in 1 study.
vi. The overall quality of evidence related to local host responses was moderate to very low, with variation across different device categories.
vii. Very little evidence was included regarding local host response for ocular implants, HEMA dermal fillers, and IOLs.
viii. No evidence was included regarding local host responses for contact lenses.

b. Over what time course does this local host response appear?

i. Follow-up time varied for different device categories and outcomes. Studies detected local inflammation, migration, and other local responses following pHEMA material exposure at 3 months to 20 years. Studies evaluating urethral bulking reported intraoperative complications (injection site bleeding, pain, and rupture) and complications at 8 years follow-up (cystitis, stranguria). Studies evaluating polyacrylamide dermal fillers reported induration from 0.5 months to 36 months, and migration from 6 months to 18 months. Some local responses (ecchymosis, edema, hematoma, localized accumulation of product) occurred within 1 week, while 1 response (pain) occurred 36 months postimplantation. Studies evaluating ocular implants reported mild posterior capsule opacification at 2 months and 9 years and optic deposition and stromal melt at 42 months. Most studies evaluating HEMA dermal fillers reported delayed onset (>1 year) of abscess, inflammation, and migration; however, 1 study reported fistula formation and palpable nodules at 4 months. Lastly, studies evaluating IOLs reported edema up to 60 days and opacification up to 22 months.

2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?

a. What evidence exists to suggest or support this?

Overall, 7 studies investigated systemic responses; studies addressed pHEMA as a material (4), polyacrylamide dermal filler (1), and HEMA dermal filler (2). Six studies identified persistent or exaggerated immune responses, while 31 (81%) studies did not investigate systemic responses.

b. What are the likely systemic manifestations?

For pHEMA as a material, evidence was limited to 4 single-arm studies investigating PAHG for breast augmentation. One study examining autoimmune syndrome induced by adjuvants (ASIA) confirmed ASIA in 15 (50%) patients; however, only 8 patients undergoing removal reported complete resolution of symptoms. Authors reported the following systemic responses in ≥20% of patients: recurrent fever (43.3%), numbness/tingling of upper extremities (33.3%), chronic fatigue and major depressive disorder (MDD) symptoms (30%), lymph node enlargement (26.7%), and limitation/numbness of upper extremity movements (20%). Arthralgia, body weight loss, breathing disorders, increased sweating, morning joint stiffness, and Raynaud's phenomenon were reported in fewer than 10% of patients. The 3 remaining studies also reported upper limb numbness and fever, in addition to hypodynamia, palpitations, and pain but the percentage of patients affected per complication was not reported.

For polyacrylamide dermal filler, 1 nonrandomized comparative study reported fever in 1 patient from Amazingel.

For HEMA dermal filler, 1 study reported severe systemic infection in 2 patients.

c. What is the observed timeline(s) for the systemic manifestations?

For pHEMA as a material, timing from injection to complications was 12 to 57 months for arthralgia, 1 to 60 months for chronic fatigue and MDD, and mean 17.8 months for numbness/tingling of upper extremities. Two other studies both reported headaches, upper limb numbness, and palpitations at mean 5.1 years from injection to PAHG removal and 6 months to 10 years postimplantation.

For polyacrylamide dermal filler, fever in 1 patient from Amazingel occurred at 36 months.

For HEMA dermal filler, severe systemic infection in 2 patients occurred at 8 months and 12 months.

d. Have particular cellular/molecular mechanisms been identified for such manifestations?

No studies investigated cellular/molecular mechanisms for systemic responses.

3. **Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?**

   No studies investigated patient-related factors that may predict, increase, or decrease the likelihood of an exaggerated, sustained immunological/systemic response.

4. **Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?**

   No studies investigated material-related factors that may predict, increase, or decrease the likelihood of an exaggerated, sustained immunological/systemic response.

5. **What critical information gaps exist and what research is needed to better understand this problem?**

   All gaps listed here could benefit from future research.

   a. Long-term human and animal RCTs for local responses to pHEMA as a material and for all device categories to better ascertain associations with these responses to pHEMA.
   b. Additional research on systemic responses, including those on patient or material factors, for all pHEMA device categories. Systemic responses were only investigated in 7 (18%) studies with no studies investigating pHEMA for urethral bulking, ocular implants, or IOLs.

Project Overview

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. Specific materials or topics were selected by FDA based on current priority. For the first quarter of 2021, the following six topics were chosen:

1. Magnesium (Mg)
2. Complications associated with Polypropylene Mesh in Pre-, Peri-, and Post-Menopausal Women
3. Polytetrafluoroethylene (PTFE)
4. Acrylics 1: PMMA
5. Acrylics 2: pHEMA
6. Acrylics 3: Cyanoacrylates

The systematic review was guided by key questions mutually agreed upon by FDA and ECRI. Data were extracted from literature articles and ECRI surveillance databases accordingly.

Key Questions

1. What is the typical/expected local host response to pHEMA?

a. *Can that response vary by location or type of tissue the device is implanted in or near?*
b. *Over what time course does this local host response appear?*

2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?

    a. *What evidence exists to suggest or support this?*
    b. *What are the likely systemic manifestations?*
    c. *What is the observed timeline(s) for the systemic manifestations?*
    d. *Have particular cellular/molecular mechanisms been identified for such manifestations?*

3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

4. Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

5. What critical information gaps exist and what research is needed to better understand this problem?

If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research.

Safety Profiles were written for the six materials listed above to include the summary of key findings from the systematic review and surveillance search and are included in this report.

Literature Search and Systematic Review Framework

The ECRI-Penn Evidence-based Practice Center (EPC) conducts research reviews for the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care (EHC) Program. ECRI's scientific staff within our Center for Clinical Excellence has authored hundreds of systematic reviews and health technology assessments on 3,500+ technologies/interventions for ECRI's public- and private-sector clients. In addition to this work, ECRI staff have coauthored several methods papers on evidence synthesis published on the AHRQ Effective Health Care website and in peer-reviewed journals.

For this project, the clinical and engineering literature was searched for evidence related to biocompatibility of each material. Searches of PubMed/Medline and Embase were conducted using the Embase.com platform. Scopus was used initially to search nonclinical literature; however, it was determined that the retrieved citations did not meet inclusion criteria and that database was subsequently dropped from the search protocol. Search limits included publication dates between 2010 and 2020 and English as the publication language. ECRI and FDA agreed on appropriate host and material response search concepts as follows:

- **Material Response**
    - Strength
    - Embrittlement
    - Degradation
    - Migration
    - Delamination
    - Leaching
- **Host Response**
    - Local
        - Inflammation
        - Sensitization
        - Irritation
        - Scarring/fibrosis
            - *Keloid formation*
            - *Contracture*

        - Ingrowth
        - Erosion
    - Systemic
        - Cancer
            - *Lymphoma*
        - Inflammation
        - Immune Response
        - Fatigue
        - Memory Loss
        - Rash
        - Joint Pain
        - Brain Fog

Search strategies were developed for each concept and combined using Boolean logic. Several search approaches were used for comprehensiveness. Strategies were developed for devices of interest as indicated by FDA as well as the material-related strategies. Each of these sets were combined with the material and host response strategies. Detailed search strategies and contextual information are presented in Appendix B. Text mining, logistic regression, and a search for "random" and "systematic" in titles and abstracts were used to prioritize only the top 35%-40% of the identified literature. This subset was screened against the inclusion criteria, first by title/abstract review, and then by full article review. An evidence prioritization scheme was used to ensure the inclusion of no more than 50 studies. Data were extracted from the resulting articles.

ECRI Surveillance Search Strategy

There are 4 key ECRI sources for medical device hazards and patient incidents. These databases were searched by key terms and device models. Relevant data were extracted to address the key questions agreed upon by FDA and ECRI. Patient demographics were extracted when available. All data presented were redacted and contain no protected health information (PHI).

ECRI surveillance data comprise ECRI Patient Safety Organization (PSO) event reports, accident investigations, Problem Reporting Network (PRN) reports, and alerts. The PSO, investigations, and PRN reports included in this report include mostly acute patient events. We rarely find chronic conditions or patient follow-up reports, which are more prevalent in the clinical literature. Complications are reported directly by clinical staff, thus reports vary greatly in the level of detail provided.

ECRI Patient Safety Organization (PSO)

ECRI is designated a Patient Safety Organization by the U.S. Department of Health and Human Services and has collected more than 3.5 million serious patient safety events and near-miss reports from over 1,800 healthcare provider organizations around the country. Approximately 4% of these reports pertain to medical devices. Most of these reports are acute (single event) reports and do not include patient follow-up. These data were filtered by complication, and relevant reports were included in the analysis. "Harm Score" refers to the National Coordinating Council Medication Error Reporting and Prevention (NCC MERP) taxonomy of harm, ranging from A to I with increasing severity (see Figure 1). The entire PSO database was included in the search, with reports ranging from year 2004 through May 2020, unless otherwise noted.

Figure 1. NCC MERP "harm score," which is now regularly used by patient safety organizations.

Category A (No Error)

Circumstances or events that have the capacity to cause error.

Category B (Error, No Harm)

An error occurred but the error did not reach the patient (An" error of omission" does reach the patient).

Category C (Error, No Harm)

An error occurred that reached the patient but did not cause patient harm.

Category D (Error, No Harm)

An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to prelude harm.

Category E (Error, Harm)

An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention

Category F (Error, Harm)

An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization.

Category G (Error, Harm)

An error occurred that may have contributed to or resulted in permanent patient harm.

Category H (Error, Harm)

An error occurred that required intervention necessary to sustain life.

Category I (Error, Death)

An error occurred that may have contributed to or resulted in the patient's death.

Definitions

Harm – Impairment of the physical, emotional, or psychological function or structure of the body and/or pain resulting therefrom

Monitoring – To observe or record relevant physiological or psychological signs

Intervention – May include change in therapy or active medical/surgical treatment

Intervention Necessary to Sustain Life – Includes cardiovascular and respiratory support (e.g., CPR, defibrillation, intubation)

Accident Investigation

ECRI has performed thousands of independent medical-device accident investigations over more than 50 years, including on-site and in-laboratory investigations, technical consultation, device testing and failure analysis, accident simulation, sentinel event and root-cause analyses, policy and procedure development, and expert consultation in the event of litigation. Our investigation files were searched by keywords, and the search was limited to the past 10 years unless we found landmark investigations that are particularly relevant to biocompatibility.

Problem Reporting Network (PRN)

For more than 50 years, ECRI's Problem Reporting Network (PRN) has gathered information on postmarket problems and hazards and has been offered as a free service for the healthcare community to submit reports of medical device problems or concerns. Each investigation includes a search and analysis of the FDA MAUDE database for device-specific reports. Based on our search findings, we may extend our analysis to all devices within that device's FDA-assigned product code. The PRN database was searched by keywords, and the search was limited to the past 10 years.

Healthcare Technology Alerts

We regularly analyze investigation and PRN data to identify trends in use or design problems. When we determine that a device hazard may exist, we inform the manufacturers and encourage them to correct the problem. ECRI publishes the resulting safety information about the problem and our recommendations to remediate the problem in a recall-tracking management service for our members. The Alerts database contains recalls, ECRI exclusive hazard reports, and other safety notices related to Medical Devices, Pharmaceuticals, Blood Products, and Food Products. This database was searched by keywords and specific make and model, and the search was limited to the past 10 years.

Safety Profile - pHEMA

Full Name: Poly (2-hydroxyethyl methacrylate)
CAS Registry Number: [25249-16-5]

Safety Brief - Systematic Review Results

The systematic review included clinical and engineering literature on biocompatibility (i.e., host response and material response) of poly (2-hydroxyethyl methacrylate) (pHEMA) used in medical devices. In addition to fundamental material biocompatibility, we focused on specific devices known to be made of pHEMA. The devices in **Table 1** were recommended by FDA CDRH to guide ECRI in searching this literature and ECRI's surveillance data. In the latter, only those devices listed in **Table 2** were included.

Table 1: Medical Devices Containing pHEMA provided by FDA to Guide ECRI Searches

Regulatory Description	Product Code	Class
Intraocular Lens	HQL	3
Lens, Intraocular, Phakic	MTA	3
Phakic Toric Intraocular Lens	QCB	3
Keratoprosthesis, Permanent Implant	HQM	2
Lenses, Soft Contact, Daily Wear	LPL	2
Lenses, Soft Contact, Extended Wear	LPM	3
Lens, Contact (Other Material) - Daily	HQD	2
Lens, Contact (Orthokeratology)	MUW	2

The Safety Brief summarizes the findings of the literature search on toxicity/biocompatibility of pHEMA. Inclusion/exclusion criteria and quality of evidence criteria appear in Appendix A in the Appendices document. Quality of evidence ratings reflected a combination of the quality of comparative data (study designs), quantity of evidence (number of relevant studies), consistency of evidence, magnitude of effect, directness of evidence, and evidence for a dose response or response over time. The search strategy appears in Appendix B, and a flow diagram documenting inclusion/exclusion of studies appears in Appendix C. Summary evidence tables with individual study data appear in Appendix D, and a reference list of studies cited in the Safety Brief appears in Appendix E.

A summary of our primary findings is shown in Table 2. We then turn to a detailed discussion of research on pHEMA as a material as well as research on the various device categories.

Table 2: Summary of Primary Findings from our Systematic Review

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
pHEMA as a material (12 human studies)	Breast deformities, breast induration, breast pain, migration, swelling/edema, breast lump/mass, fistula, local inflammation, malignant tumors	Moderate for migration and pain Low for other local responses/device events	Arthralgia, ASIA, body weight loss, breathing disorders, chronic fatigue, general weakness, headache, hypodynamia, increased sweating, limitation/numbness of upper extremities, lymph node enlargement, MDD symptoms, morning joint stiffness, numbness/tingling, pain, palpitations, Raynaud's phenomenon, recurrent fever	Low
Urethral bulking (8 human studies)	Hematuria, urinary retention, implantation site pain, injection site rupture of the urethral mucous membrane, de novo urgency, dysuria	Low for urinary retention and hematuria Very low for other local responses/device events	No studies investigated systemic responses.	Very low
Polyacrylamide, dermal filler – (8 human studies)*	Ecchymosis, induration, migration, hematoma, swelling, diffused distribution of product or localized accumulation, edema, palpable	Very low	Fever	Very low

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
	nodules, abscess, local inflammation, pain, leakage			
Ocular implants (4 human studies)	Stromal melt, iris incarceration, microhyphema, migration, mild posterior capsule opacification, optic deposition, microperforation of the trabeculo-Descemet's membrane	Very low	No studies investigated systemic responses.	Very low
HEMA, dermal filler (4 human studies)*	Abscess, erythema, fistula, induration, inflammation, migration, pain, palpable nodules, swelling	Low	Of 2 studies investigating, 1 study reported severe systemic infection that may not be associated with pHEMA.	Very low
IOLs (3 human studies)	Edema (corneal and macular), local inflammation, opacification, macular degeneration, vitreous detachment	Very low	No studies investigated systemic responses.	Very low
Contact lenses (no studies)	No studies	Very low (no evidence)	No studies	Very low (no evidence)

*1 study (Kadouch et al. 2013{1101550}) addresses both HEMA and polyacrylamide dermal fillers.

ASIA: autoimmune syndrome induced by adjuvants; IOL: intraocular lens; MDD: major depressive disorder; pHEMA: poly (2-hydroxyethyl methacrylate)

pHEMA as a Material

12 human studies (1 systematic review,[1] and 11 single-arm studies[2-12]). For further information see Table 1 in Appendix D.

Local Responses (human studies)

Materials examined included polyacrylamide hydrogel (PAHG),[2-7,11,12] polyacrylamide gel (PAAG),[1,9,10] and polyacrylamide (PAM).[8] Sample size ranged from 3 patients[2,12] to 409 patients;[1] 7 (58%) studies examined fewer than 100 patients.[2,4-6,8,11,12] Follow-up ranged from 3 months to 20 years; 10 studies (83%) reported at least 2 year follow-up. When reported, administrations were multiple in 4 studies, and single in 3 studies.

Nine (75%) studies addressed PAHG or PAAG injections for breast augmentation and reported similar complications.[2-5,7,9-12]

The most commonly reported local responses were migration,[2-5,7,9,10,12] pain,[2-5,7,9-11] induration (area of hardened tissue),[3,5,7,10,12] and breast deformities.[3,4,7,9,10]

Migration rates ranged from 6.2%[3] to 54%,[9] and occurred as late as 7 years.[2] Acrylics were detected in the abdomen,[7] sternum,[10] and perineum.[3] Pain rates ranged from 37.5%[7] to 80%[10] and occurred as late as 12 years after injection.[2]

Breast induration rates ranged from 4.6%[5] to 77.5% (after initiation of breastfeeding)[7] and breast induration was detected as late as 6 years.[12]

Less frequently reported local responses were swelling/edema,[2,4,11,12] breast lump/mass,[5,9,12] and fistula.[4,9,10] 1 study reported that malignant tumors were detected in 2 (2.33%) patients 12 years postimplantation.[5]

The remaining studies reported inflammation from 1.5% PAM,[8] and bruising and palpable nodules from PAAG injections for HIV-associated facial lipoatrophy.[1] No complications were reported from PAHG to treat vesicoureteral reflux.[6]

Local Responses (animal studies)

We did not identify any animal studies investigating local responses for pHEMA as a material.

Systemic Responses

4 single-arm studies reported systemic responses from PAHG injections for breast augmentation.[3,4,7,11] The 1st study (n=325) reported headaches, hypodynamia, palpitations, and upper limb numbness in 11 (3.4%) patients at mean 5.1 years from injection to PAHG removal.[3]

The 2nd study (n=30) examining autoimmune syndrome induced by adjuvants (ASIA) reported recurrent fever (43.3%), numbness/tingling of upper extremities (33.3%), chronic fatigue and major depressive disorder (MDD) symptoms (30%), lymph node enlargement (26.7%), limitation of upper extremities movements (20%), arthralgia (6.7%),and body weight loss (6.7%). Increased sweating, morning joint stiffness, Raynaud's phenomenon, and breathing disorders were reported in 1 (3.3%) patient each. Mean months from injection to complications were 34.5 for arthralgia, 27.6 for chronic fatigue, 25.8 for MDD, and 17.8 for numbness/tingling. ASIA was confirmed in 15 (50%) patients. 8 patients undergoing PAHG removal reported complete resolution of symptoms.[4]

The 3rd study (n=200) reported headache, upper limb numbness, and palpitations in 34 (17%) patients at 6 months to 10 years after injections.[7] The 4th study (n=58) reported fever, pain, and weakness after contact duration of 1 to 7 years.[11]

Factors Associated with Systemic Responses

No included studies reported whether there are patient-related factors or material-related factors that may affect systemic responses.

Overall Quality of Evidence

The evidence for migration and pain was mostly consistent with reporting across studies and with other pHEMA devices (PAM and HEMA dermal fillers, ocular implants); however, because of the low quality of the human studies, the quality of evidence is moderate. For other local responses/events and systemic responses, the quality of evidence is low.

Urethral bulking

8 human studies (2 systematic reviews (SRs),[13,14] 1 nonrandomized comparative study,[15] and 5 single-arm studies[16-20]). For further information see Table 2 in Appendix D.

The only product in this category is Bulkamid (Contura International). Follow-up for the SRs (n=1,242) was up to 1 year[13] and 5 years.[14] Mean follow-up for the remaining studies (n=454 patients) was 24 months.

We included two SRs. One (Kasi et al 2016[13]) reported on 8 studies of 767 patients, all of whom received Bulkamid (1 study also included a group who received a different bulking agent, but those patients are not included in the SR). The other SR (Capobianco et al. 2020[14]) reported on 21 studies of 1,890 patients receiving 10 different bulking agents; Bulkamid was examined in 4 of the studies (475 patients received Bulkamid). The majority of studies included in these SRs were observational, and both SRs reported relevant adverse event (AE) rates by each study individually. Herein, for each AE, data from the SRs are presented as the range of rates reported in the individual studies, along with the total number of studies that reported rates for that AE.

Two studies of Bulkamid were included in both SRs (along with a 3rd study for which the SRs reported no AEs). For those studies, we give the rates reported in Capobianco et al., which reported on a wider range of AEs than Kasi et al. It should be

noted that 1 of those studies reported rates of different types of AEs among the subset of patients who experienced any treatment-related AE. The sum of those rates thus totaled 100% by definition, resulting in rates markedly higher than those reported by other studies in which the rates are based on all patients in the study.

Local Responses/Device Events (human studies)

2 studies reported on bleeding; 1 reported a single case (1%) of trickling bleeding after injection,[20] and the other noted no cases of major bleeding.[17]

One study reported cystitis rate (29%) and stranguria rate (4%) at 8 years follow-up.[16]

One SR reported a 1% dysuria rate based on a single study;[14] 1 other study reported that no cases of dysuria occurred.[16]

The SRs reported hematuria rates ranging from 1% to 6%, based on 5 studies.[13,14]

The SRs reported implantation site pain rates ranging from 6% to 14%, based on 3 studies.[13,14] One SR reported an overall postoperative pain rate of 28% based on 1 study;[14] 1 other study reported a 3% rate of pain, not further specified.[19]

One SR reported a 3% rate of injection site rupture, based on a single study;[14] 1 other study reported a 2% rate of injection site rupture.[17]

One SR reported a 6% transurethral catheterization rate, based on a single study.[14]

One SR reported rates of aggravated urge incontinence of 0.4% to 6%, based on 2 studies; rates of de novo urge incontinence of 1% to 6%, also based on 2 studies; and a 20% overall rate of urge incontinence, based on a single study.[14]

One SR reported a 4% rate of de novo urgency, based on a single study;[14] 1 other study noted no cases of de novo urgency.[17] One SR reported a 1% rate of urgency, not further specified, based on a single study.[14]

The SRs reported rates of urinary retention ranging from 1% to 15%, based on 8 studies;[13,14] 1 other study reported a 2% rate.[19] One SR reported rates of voiding dysfunction of 1%, based on 2 studies;[14] one other study noted no cases of urinary retention or voiding dysfunction.[17]

One of the studies we reviewed reported that no complications occurred,[15] and another reported that no AEs thought to be treatment-related occurred.[18]

Local Responses/Device Events (animal studies)

We did not identify any animal studies investigating local responses to PAM for urethral bulking.

Systemic Responses

We did not identify any studies reporting systemic responses to polyacrylamide for urethral bulking.

Overall Quality of Evidence

The evidence for urinary retention and hematuria was low due to the low quality of studies and inconsistency with other pHEMA devices. For other local responses/events, the quality of evidence is very low. Since systemic responses were not investigated in any study, the quality of evidence was also very low.

Polyacrylamide, dermal filler

8 human studies (1 randomized controlled trial (RCT),[21] 2 nonrandomized comparative studies,[22,23] and 5 single-arm studies.[24-28]) One study[22] is also presented in HEMA, dermal filler. For further information see Table 3 in Appendix D.

Local Responses (human studies)

One RCT[21] evaluated complications arising from different amounts and frequencies of PAAG injection (Aquamid). All 31 patients were HIV-positive and affected by facial wasting. Group A (n=18) was injected once with 8 to 14 mL, whereas, Group B (n=13) was injected multiple times with 2 mL. Group A reported ecchymosis in 17 patients and small palpable nodules in 6 patients. Group B reported only small palpable nodules in 3 patients. AEs presented either directly after injection or 12 months following an injection.

One nonrandomized comparative study[22] examined fillers composed of PAM (Bio-Alcamid and Aquamid), hydroxyethyl methacrylate and ethylmethacrylate (HEMA; DermaLive), polymethylmethacrylate (PMMA; Artecoll), and liquid injectable

silicone (LIS). Of the 85 patients examined, 66 (78%) patients received Bio-Alcamid. Migration mostly occurred with LIS (50%), Bio-Alcamid (45%), and Artecoll (43%), while low-grade inflammation mostly occurred with LIS (75%) and Artecoll (57%). Noninflammatory nodules were more common with DermaLive (88%) and Aquamid (67%), while abscesses only occurred with Bio-Alcamid (38%). Mean onset of any AE was 10 months for Aquamid, 38 months for Bio-Alcamid and LIS, 40 months for DermaLive, and 57 months for Artecoll.

The other nonrandomized comparative study[23] examined Aquamid and Amazingel and reported similarly few cases experiencing all AEs. This study, however, did not include non-polyacrylamide fillers and thus did not investigate the impact of the material on possible adverse events. Induration was the most common event with 5 cases (71%) for Amazingel and 4 cases (50%) for Aquamid. Migration, swelling, pain, and leakage occurred in ≤2 patients in each study. Mean onset of any adverse event was 15 months (range 0.5 to 60 months).

The remaining 5 single-arm studies reported highly variable AEs related to Aquamid dermal filler.[24-28] One study[24] with the shortest follow-up time of 12 months reported no serious AEs. Two studies[25,27] with follow-ups of 18 months[27] and 10 years[25] reported diffused distribution of product,[25] general fibrosis,[25] ecchymosis,[27] and edema[27] in all patients.

The 2 remaining studies[26,28] had a maximum follow-up of 5 years. The most common AEs for these studies included gel induration/blebs, swelling, and hematoma. A less frequently occurring event was migration after 1 year in 3 (2%) patients.[26]

Local Responses (animal studies)

We did not identify any animal studies investigating local responses to PAM as a dermal filler.

Systemic Responses

1 nonrandomized comparative study reported fever in 1 (14%) patient receiving Amazingel.[23]

Factors Associated with Systemic Responses

No included studies reported whether there are patient-related factors or material-related factors that may affect systemic responses.

Overall Quality of Evidence

The evidence for most outcomes was inconsistent across studies and based on low quality studies, so the quality of evidence is very low. For systemic responses, the quality of evidence is also very low.

Ocular implants

4 human studies (4 single-arm studies[29-32]). For further information see Table 4 in Appendix D.

Local Responses/Device Events (human studies)

4 single-arm studies[29,30,32,33] examined 4 different ocular implants (Esnoper V2000, AlpaCor, Clareon CNA0T0, and Alphasphere). 3 (75%) studies examined ≤20 patients.[29,30,32]

Two studies[32,33] had low AE rates with high variation in follow-up of 14 months[32] and 9 years.[33] The 1st study reported mild posterior capsule opacification in 4 (3.6%) eyes occurring from 2 months to 9 years with Clareon CNA0T0.[33] The 2nd study reported migration in 1 (8%) patient with Alphasphere.[32]

The other two studies[29,30] had follow-ups of 12 months[29] and 67 months.[30] The most common adverse events in these studies were stromal melt (n=9) occurring 12 months to 36 months postimplantation with AlphaCor;[30] and microperforation of trabeculo-Descemet's membrane (n=4) with ESNOPER V2000.[29]

Local Responses (animal studies)

We did not identify any animal studies investigating local responses to HEMA as an ocular implant.

Systemic Responses

We did not identify any studies reporting systemic responses to HEMA as an ocular implant.

Overall Quality of Evidence

The 4 human observational studies examined various ocular implants and were inconsistent in reporting outcomes (migration, opacification, stromal melt, and microperforation of trabeculo-Descemet's membrane) so we rated the quality of evidence for these outcomes as very low. Since systemic responses were not investigated in any study, the quality of evidence is also very low.

HEMA, dermal filler

4 human studies (1 systematic review,[34] 1 nonrandomized comparative study[22] and 2 single-arm studies[35,36]). One study[22] was also presented under Polyacrylamide, Dermal Filler. For further information see Table 5 in Appendix D.

Local Host Responses (human studies)

All studies addressed multiple injections of DermaLive (Dermatech) as a facial dermal filler. Patients were more commonly female, with a mean age of 47 to 54 years. The largest sample size was 25 patients (60 patients overall).

AEs associated with this treatment tended to have a delayed onset after injection, with local reactions typically occurring 14 to 40 months after injection. The most commonly reported complications included the formation of palpable nodules, induration, inflammation, erythema, pain, and swelling. Less commonly reported complications included migration and abscess formation.

One nonrandomized comparative study[22] examined fillers composed of HEMA (DermaLive), PAM (Bio-Alcamid and Aquamid), PMMA (Artecoll), and LIS. Of the 85 patients enrolled, DermaLive was injected in 8 (9%) patients. See the section on Polyacrylamide Dermal Filler for results for DermaLive.

One single-arm study reported erythema, fistula formation, and red induration in 1 patient at 4 months, and multiple bulging or palpable hard nodules in 21 (100%) patients at 18.6 mean months postimplantation.[35]

Local Host Responses (animal studies)

We did not identify any animal studies investigating local responses to HEMA as a dermal filler.

Systemic Responses

One study reported history of severe systemic infections (severe bronchitis, acute abdominal infection) in 2 (10%) patients at 8 months and 12 months after pHEMA implantation, although it is unclear whether this response can be linked to pHEMA.[35] Another study reported but did not identify systemic responses to HEMA as dermal fillers.[34]

Factors Associated with Systemic Responses

No included studies reported whether there are patient-related factors or material-related factors that may affect systemic responses.

Overall Quality of Evidence

The evidence for most outcomes was consistent across studies, and consistent with polyacrylamide dermal fillers, but 50% of studies were observational, so the quality of evidence was low. Of 2 studies examining systemic responses, 1 small observational study identified severe systemic infections however due to the unclear association to pHEMA, the quality of evidence was very low.

IOLs

3 human studies (3 single-arm studies[37-39]). For further information see Table 6 in Appendix D.

Local Responses/Device Events (human studies)

The type of HEMA IOL implant varied across studies (pHEMA IOL with ultraviolet absorber,[37] Clareon 3-piece MA60NM,[38] and Rayner C-flex 1-piece 570C[39]). Additionally, 1 study focused on IOL complications in children with a mean age of 7 years,[37] while the other 2 studies described complications in adult patients with a mean age of 75 years. Sample size ranged from 120 patients to 3,461 patients.

Two studies reported opacification as a complication.[37,39] One study reported opacification in 7 (3.9%) eyes.[37] The other study focused on Nd:YAG capsulotomy after IOL implantation as a means of assessing symptomatic opacification.[39] Reported

capsulotomy rates were 0.6% and 1.7% at 12 and 24 months, respectively. Time to Nd:YAG capsulotomy ranged from 1.3 to 22.7 months.

Other complications reported include membrane inflammation, edema (corneal and macular), and vitreous detachment. Corneal edema occurred more frequently than macular edema, (21.1% vs. 2%),[38] while inflammatory membrane[37] and macular degeneration[38] occurred similarly (10.1%). Edema was reported as a shorter-term complication, resolving after an average of 60 days, while other complications presented at a longer-term follow-up on average of 9 to 14 months postimplantation.

Local Responses/Device Events (animal studies)

We did not identify any animal studies investigating local responses to HEMA as implantable IOLs.

Systemic Responses

We did not identify any studies investigating systemic responses to HEMA as implantable IOLs.

Overall Quality of Evidence

The quality of evidence is very low for all local responses due to the inconsistency in reported outcomes, and low quality of studies. Since systemic responses were not investigated in any study, the quality of evidence is also very low.

Contact lenses

Our literature searches did not identify any studies of these devices that met inclusion criteria.

ECRI Surveillance Data

Refer to Appendix F for a list of devices that guided our searches of ECRI Surveillance Data. No reports were found within the accident investigation, PRN, or PSO data. The Healthcare Technology Alerts database returned 24 alerts. These consisted of package mislabeling, incorrect materials and particulates in packaging, and compromised sterility as well as more serious hazards such as residual toxins (intraocular lens), leaking fluid during procedure (injectable agents for gastro-urology use), and high levels of diluting agent causing discomfort and redness (daily wear soft contact lens).

Patient Safety Organization

Search Results: ECRI PSO identified 0 reports that involved pHEMA materials.

Accident Investigations

Search Results: No investigations were recovered that involved pHEMA materials.

ECRI Problem Reports

Search Results: The search returned 0 reports submitted by ECRI members.

Healthcare Technology Alerts

Search Results: The search returned 24 manufacturer-issued alerts describing problems with labelling, packaging, sterility, IFU clarifications, refraction errors, residual toxins, leaking, presence of foreign matter, malformed product, discoloration, high levels of salinity, patient discomfort, and product not manufactured to specifications, summarized in Table 3.

Table 3: Summary of Regulatory Manufacturer Alerts

Device Type	# Alerts	Reported Problem
HQL (Intraocular Lens)	5 Manufacturer-Issued	• Incorrect raw materials and particulates visible in packaging • Incorrect IFU • Post-op refractive errors • Residual toxins • Mislabeling
LNM (Agent, Bulking, Injectable for Gastro-Urology Use)	2 Manufacturer-Issued	• Updated IFU • Leaking fluid during procedure
LPL (Lenses, Soft Contact, Daily Wear)	17 Manufacturer-Issued	• High salinity solution • Compromised sterility • High levels of diluting agent causing discomfort and redness • Mislabeling • Packaging • Not manufactured to cylinder axis specifications • Malformed product

Potential Gaps

ECRI surveillance searches reflect mostly acute patient incidents that involved medical devices made of pHEMA. Areas of particular concern involve incidents that result in direct tissue exposure to the material if there is moderate to high-quality evidence of acute or systemic reaction to this exposure, as determined by the systematic review. Topics with very low or low quality of evidence represent areas of potential gaps in the literature. If the literature revealed areas of new concern (e.g., systemic response to long-duration contact) and there is little supporting evidence, these are considered gaps.

pHEMA as a material

Evidence for pHEMA as a material mostly focused on PAHG and PAAG for breast augmentation in females. The quality of evidence was considered low for most local responses and for systemic responses, although 1 study reported malignant tumors and 3 studies reported upper limb numbness. Limitations include the lack of studying pHEMA in animals and lack of controlled studies (11 [92%] studies were single-arm) thus precluding any conclusions regarding a direct association of these responses with pHEMA.

Urethral bulking

8 human studies (5 single-arm) examined Bulkamid for urethral bulking. The quality of evidence was considered low for urinary retention and hematuria; very low for other local responses and systemic responses (because pf lack of studies investigating them). Rates for urinary retention ranged from 1% to 15% so the direct association with Bulkamid and urinary retention is questionable. Evidence of migration was not reported; however, this could be because of follow-up ≤1 year in most studies.

Polyacrylamide, dermal filler

Evidence for Aquamid, Amazingel, and Bio-Alcamid was rated very low quality for all local and systemic responses. Outcomes were mostly inconsistent across studies, and based on low quality studies. Only 1 study reported injections in various sites (e.g., cheeks, breasts, nasal root, eyelid, penis), and fewer than 5 patients received fillers in these areas. Systemic responses were limited to fever from Amazingel in 1 patient. Seven studies did not investigate systemic responses.

Ocular implant

Local responses varied across ocular implants (Esnoper V2000, AlpaCor, Clareon CNA0T0, or Alphasphere) in 4 human studies. The quality of evidence for local responses and systemic responses (no studies investigating) was very low. 3 (75%) studies examined ≤20 patients.

HEMA, dermal filler

4 human studies examined DermaLive only as a facial dermal filler in mostly females aged 47 to 54 years. 60 patients total were examined. In 1 nonrandomized comparative study, also addressing PAM dermal filler, rates for some complications (e.g., noninflammatory nodules, low-grade inflammation, migration) were similar with 2 PAM dermal fillers (Aquamid and Bio-Alcamid); however, fewer than 10 patients each received DermaLive or Aquamid. 1 study reported severe systemic infections in 2 patients; however, there is an unclear association with pHEMA.

IOLs

Evidence from 3 human studies was rated very low quality for local and systemic responses (no studies investigating). One study focused on children implanted with a pHEMA IOL with ultraviolet absorber, while 2 studies focused on adults using Clareon 3-piece MA60NM, or Rayner C-flex 1-piece 570C. Local responses were not consistently reported.

Contact lenses

There were no studies that met inclusion criteria for pHEMA contact lens devices indicating an area of future research.

Appendix A. Inclusion/Exclusion Criteria and Quality of Evidence Criteria

Inclusion Criteria

1	English language publication
2	Published between January 2011 and May 2021
3	Human and animal studies
4	Systematic reviews, randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, case series
5	Studies that evaluate toxicity/biocompatibility of pHEMA or priority devices that include this material

Exclusion Criteria

1.	Foreign language publication
2.	Published before January 2010
3.	Not a study design of interest (e.g., in vitro lab study, case report, narrative review, letter, editorial)
4.	Off-topic study
5.	On-topic study that does not address a key question
6.	No device or material of interest
7.	No relevant outcomes (adverse events or biocompatibility not reported)
8.	Study is superseded by more recent or more comprehensive systematic review

Quality of Evidence Criteria

1.	**Quality of comparison –** is there evidence from systematic reviews including randomized and/or matched study data and/or randomized or matched individual studies?
2.	**Quantity of data** – number of systematic reviews and individual studies providing relevant data.
3.	**Consistency of data** – are the findings consistent across studies that report relevant data?
4.	**Magnitude of effect** – what is the likelihood of adverse effects compared to controls (with no device, lower dosage, shorter exposure time), and possibly number of patients likely to have harms.
5.	**Directness of evidence** – do human studies isolate the effect of the device (i.e. can the adverse effects be attributed to the device)?
6.	Is there evidence of a **dose response or time response** (e.g., adverse effects increase with longer exposure time)?

Appendix B. Search Summary

Strategies crafted by ECRI's medical librarians combine controlled vocabulary terms and free-text words in conceptual search statements that are joined with Boolean logic (AND, OR, NOT).

Most medical bibliographic databases such as Medline and Embase include detailed controlled vocabularies for medical concepts accessible through an online thesaurus. Controlled vocabularies are a means of categorizing and standardizing information. Many are rich ontologies and greatly facilitate information transmission and retrieval. Frequently seen examples of controlled vocabularies include ICD-10, SNOMED-CT, RxNorm, LOINC, and CPT/HCPCS.

Citations in PubMed are indexed with MeSH terms and those in Embase are indexed with terms from EMTREE. These terms are assigned either by a medical indexer or an automated algorithm. Several terms are selected to represent the major concept of the article – these are called "major" headings. This "major" concept can be included in search strategies to limit search retrieval. The syntax in Embase for this is /mj. We have used this convention in our strategies sparingly since indexing is subjective and we are using a sensitive search approach which errs in the direction of comprehensiveness.

Database providers build functionality into their search engines to maximize the usefulness of indexing. One of the most frequently used shortcuts is term explosion. "Exploding" in the context of hierarchical controlled vocabularies means typing in the broadest (root or parent) term and having all the related more specific terms included in the search strategy with a Boolean OR relationship. We use term explosions whenever feasible for efficiency. Feasibility depends on whether you wish to include all of the related specific terms in your strategy. For example, in one of our approaches we explode the Emtree concept mechanics. This explosion automatically added the all the following terms (n = 174) and their associated entry terms (lexical variants and synonyms) to the strategy using an "OR" without the searcher having to type them in. That's one of the major advantages to searching using controlled vocabularies. We don't rely exclusively on controlled vocabulary terms since there are possible limitations such as inconsistent indexing and the presence of unindexed content. That's why we also include free text words in our strategies.

Set Number	Concept	Search Statement
Material		
1	pHEMA	'polyacrylamide'/de OR 'polyacrylamide gels'/de OR 'polyacrylamide gel'/de OR 'poly acrylamide*' OR 'polyacrylamide' OR 'polyacrylamide*' OR 'poly acrylamide' OR 'poly-1-carbamoylethylene' OR 'poly 1-carbamoylethylene' OR 'poly 1 carbamoylethylene' OR 'poly-2-propenamide' OR 'poly 2-propenamide' OR 'poly 2 propenamide'
2.		poly NEAR/10 ('propenamide' OR 'carbamoylethylene' OR 'carbamoyl ethylene')
3		'2 hydroxyethyl methacrylate'/exp OR '2 hydroxyethylmethacrylate' OR 'hydroxyethylmethacrylat*' OR 'glycolmethacrylate' OR 'glycolmethacrylat*' OR 'hydroxyethyl methacrylate polymer' OR 'poly 2 hydroxyethyl methacrylate*' OR 'poly hydroxyethyl methacrylate*' OR 'polyhydroxyethyl methacrylate*' OR 'polyhydroxyethylmethacrylat*' OR 'polyhydroxyethylmethylacrylat*' OR 'poly hydroxy ethyl methacrylat*' OR 'poly hydroxyethylmethacrylat*' OR 'polymacon'/exp OR 'polymacon'
4		'phema' OR 'phema*' OR 'hema' OR 'poly-hema' OR 'polyhema' OR 'poly hema'
5		(poly OR 'p') NEAR/4 'hema'
6		#1 OR #2 OR #3 OR #4 OR #5
7	Trade Names	'bulkamid'/de OR 'dermalive'/de OR 'bulkamid' OR 'dermalive' OR 'derma live' OR 'aquiamid' OR 'elasto-gel' OR 'elastogel' OR 'elasto gel'

8		'allvue' OR 'biomedics*' OR 'clearview' OR 'customeyes*' OR 'epconsoft' OR 'esstechps' OR 'hydron*' OR 'sofblue*' OR 'metrosoft*' OR 'simulvue*' OR 'sof-form*' OR 'sof form*' OR 'soflens*' OR 'softics' OR 'softview' OR 'unilens' OR 'vistakon' OR 'acuvue' OR 'surevue' OR 'esstech' OR 'ideal soft' OR 'lifestyle xtra' OR 'lifestyle mv2' OR 'lifestyle 4vue' OR 'lifestyle toric bifocal' OR 'unilens 38' OR 'westhin toric' OR 'abafilcon*' OR 'acquafilcon*' OR 'amfilcon*' OR 'astifilcon*' OR 'balafilcon*' OR 'bisfilcon*' OR 'bufilcon*' OR 'comfilcon*' OR 'crofilcon*' OR 'cyclofilcon*' OR 'darfilcon*' OR 'delefilcon*' OR 'deltafilcon*' OR 'dimefilcon*' OR 'droxifilcon*' OR 'efrofilcon*' OR 'elastofilcon*' OR 'enfilcon*' OR 'epsiflcon*' OR 'esterifilcon*' OR 'etafilcon*' OR 'focofilcon*' OR 'galyfilcon*' OR 'genfilcon*' OR 'govafilcon*' OR 'hefilcon*' OR 'hilafilcon*' OR 'hioxifilcon*' OR 'hydrofilcon*' OR 'iberfilcon*' OR 'lenefilcon*' OR 'licryfilcon*' OR 'lidofilcon*' OR 'lotrafilcon*' OR 'mafilcon*' OR 'mesifilcon*' OR 'methafilcon*' OR 'mipafilcon*' OR 'narafilcon*' OR 'nelfilcon*' OR 'nesofilcon*' OR 'netrafilcon*' OR 'ocufilcon*' OR 'ofilcon*' OR 'omafilcon*' OR 'oxyfilcon*' OR 'pentafilcon*' OR 'perfilcon*' OR 'petrafocon a-hem-larafilcon*' OR 'pevafilcon*' OR 'phemfilcon*' OR 'polymacon*' OR 'senofilcon*' OR 'shofilcon*' OR 'sifilcon*' OR 'silafilcon*' OR 'siloxyfilcon*' OR 'surfilcon*' OR 'tasfilcon*' OR 'tefilcon*' OR 'tetrafilcon*' OR 'trifilcon*' OR 'uvifilcon*' OR 'vasurfilcon*' OR 'vifilcon*' OR 'xylofilcon*'
9		'cemex' OR 'cortoss' OR 'jectos' OR 'osteo-firm' OR 'osteo firm' OR 'vertebroplastic'
10		'bicon' OR 'grafton'
11		'morcher ctr' OR 'ophtec ctr' OR 'symblepharon ring*' OR 'keraring*' OR 'intacs' OR 'intralase' OR 'myoring*' OR 'verisyse' OR 'auro kpro' OR 'auro k pro' OR 'aurokpro' OR 'b kpro' OR 'bi kpro' OR 'boston keratoprosth*' OR 'boston kpro*' OR 'boston type i*' OR 'boston type 1*' OR 'boston type 2*' OR 'm kpro'
12		#7 OR #8 OR #9 OR #10 OR #11
13	Devices	'implant'/exp OR implant OR implantation OR implanted OR implant*
14		'orbit implant'/exp OR 'orbital floor implant'/de OR 'orbital rim implant'/de OR 'orbital tissue expander' OR 'orbit* implant*' OR 'orbital implant*'
15		'injectable implant'/exp OR 'filler' OR 'injectable implant' OR 'subdermal filler' OR 'subdermal implant' OR 'hyrdogel' OR 'bulking agent'
16		'external urethral occluder'/dv OR 'urethral occlusion device'/exp OR 'external urethral occluder'/de OR 'urethral occlusion device' OR 'external urethral occluder'
17		'bone cement'/exp OR 'acrylic cement'/de OR 'bone cement*' OR 'acrylic cement*' OR 'orthopaedic cement*' OR 'orthopedic cement*'
18		(bone OR orthopaedic OR orthopedic OR acrylic) NEAR/3 (cement OR glue)
19		'tooth implant'/exp OR 'dental implant*' OR 'tooth implant*' OR 'teeth implant*'

20		(dental OR teeth OR tooth) NEAR/3 implant*
21		'cataract'/exp OR 'cataract*' OR 'intrastromal corneal ring segment'/dv OR 'intrastromal corneal ring segment' OR 'capsular tension ring'/dv OR 'capsular tension ring*'
22		#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
23	Combine and Limit by language and publication date	(#6 OR #12 OR #21) AND [english]/lim AND [2011-2021]/py
24	Limit by publication type	#23 NOT ('book'/it OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it OR 'tombstone'/it)

Material Response

25		'biocompatibility'/de OR biocompat* OR tribolog* OR 'bio compat*' OR 'biological* compat*' OR 'biological* evaluation'
26		'degradation'/exp OR degrad* OR biodegrad* OR bioabsorb* OR bioadsorb* OR absorbable OR adsorbable OR split OR splitting OR split* OR wear OR deteriorat* OR atroph* OR migrat* OR movement OR shift* OR transfer* OR 'delamination'/exp OR delamina* OR leach* OR filtrate OR filter* OR seep* OR evaginat* OR subsidence
27		Leachable* OR extractable*
28		(swell* OR shrink* OR contract* OR stretch* OR retract* OR extension OR extend* OR deform* OR creep OR plasticity OR degrad* OR disintegrat* OR fail*) NEAR/3 (graft? OR endograft? OR stentgraft? OR stent? OR suture OR catheter? OR microcatheter?)
29		'mechanics'/exp
30		'device material'/exp/mj
31		'Biomedical and dental materials'/exp/mj
32		'glistening'/exp OR 'surface whiten*' OR 'nanoglisten*' OR 'glisten*' OR 'degradation'/exp OR degrad* OR adsorbable OR split* OR wear OR deteriorat* OR atroph* OR migrat* OR distend* OR distension OR 'delamination'/exp OR delamina* OR leach* OR filter* OR seep* OR evaginat* OR subsidence OR 'glistening*' OR 'nanoglistening*' OR 'whitening' OR discolor* OR opacificat*
33	Combine sets	#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32
34	**pHEMA + Material Response**	**#24 AND #33**

Host Response

35		Host NEAR/2 (reaction* OR response*)
36		'toxicity'/exp OR toxic*:ti OR cytotox* OR teratogenic* OR genotox* 'carcinogenicity'/exp OR carcinogen*:ti
37		'immune response'/exp OR 'immunity'/exp/mj OR 'hypersensitivity'/exp OR 'immunopathology'/exp/mj
38		(immun*:ti OR autoimmun*:ti OR hypersens*:ti) NOT immunofluorescenc*:ti

39		'inflammation'/exp OR inflamm*
40		'foreign body' OR granuloma* OR 'foreign body'/exp OR (fibro*NEAR/2 capsule*)
41		'adhesion'/exp OR 'tissue adhesion'/exp OR 'tissue response' OR 'bone response'
42		(protrude* OR protrus*)
43		'thrombosis'/exp OR 'stenosis, occlusion and obstruction'/exp OR 'stent complication'/exp OR restenosis OR thromb*
44	Combine sets	#35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43
45	**pHEMA + Material Response+ Host Response**	**#24 AND #45**
46	**Final set**	**#34 AND #45**

Example Embase Explosion

Mechanics/exp

- Biomechanics
- Compliance (physical)
    - Bladder compliance
    - Blood vessel compliance
        - Artery compliance
        - Vein compliance
    - Heart muscle compliance
        - Heart left ventricle compliance
        - Heart ventricle compliance
    - Lung compliance
- Compressive strength
- Dynamics
    - Compression
    - Computational fluid dynamics
    - Decompression
        - Explosive decompression
        - Rapid decompression
        - Slow decompression
    - Gravity
        - Gravitational stress
        - Microgravity
        - Weight
            - Body weight
                - Birth weight
                    - High birth weight
                    - Low birth weight
                        - Small for date infant
                        - Very low birth weight
                            - Extremely low birth weight
            - Body weight change
                - Body weight fluctuation

        - Body weight gain
            - Gestational weight gain
        - Body weight loss
            - Emaciation
        - Body weight control
        - Fetus weight
        - Ideal body weight
        - Lean body weight
        - Live weight gain
    - Dry weight
    - Fresh weight
    - Molecular weight
    - Organ weight
        - Brain weight
        - Ear weight
        - Heart weight
        - Liver weight
        - Lung weight
        - Placenta weight
        - Spleen weight
        - Testis weight
        - Thyroid weight
        - Uterus weight
    - Seed weight
    - Tablet weight
    - Thrombus weight
- Weightlessness
- Hydrodynamics
    - Hypertonic solution
    - Hypotonic solution
    - Isotonic solution
    - Osmolality
        - Hyperosmolality
        - Hypoosmolality
        - Plasma osmolality
        - Serum osmolality
        - Urine osmolality
    - Osmolarity
        - Blood osmolarity
        - Hyperosmolarity
        - Hypoosmolarity
        - Plasma osmolarity
        - Serum osmolarity
        - Tear osmolarity
        - Urine osmolarity
    - Osmosis
        - Electroosmotic
        - Osmotic stress
            - Hyperosmotic stress
            - Hypoosmotic stress
- Photodynamics
    - Photoactivation
        - Photoreactivation
    - Photodegradation

        - Photoreactivity
            - Photocytotoxicity
            - Photosensitivity
            - Photosensitization
            - Phototaxis
            - Phototoxicity
        - Photostimulation
    - Proton motive force
    - Shock wave
        - High-energy shock wave
    - Stress strain relationship
    - Thermodynamics
        - Adiabaticity
        - Enthalpy
        - Entropy
- Elasticity
    - Viscoelasticity
    - Young modulus
- Force
- Friction
    - Orthodontic friction
- Hardness
- Kinetics
    - Adsorption kinetics
    - Flow kinetics
        - Electroosmotic flow
        - Flow rate
        - Gas flow
        - Laminar airflow
        - Laminar flow
        - Powder flow
            - Angle of repose
            - Hausner ration
        - Pulsatile flow
        - Shear flow
        - Thixotropy
        - Tube flow
        - Turbulent flow
        - Vortex motion
        - Water flow
    - Motion
        - Coriolis phenomenon
        - Rotation
        - Vibration
            - Hand arm vibration
            - High frequency oscillation
            - Oscillation
            - Oscillatory potential
            - Whole body vibration
    - Velocity
        - Acceleration
        - Deceleration
        - Processing speed
        - Wind speed

- Mass
    - Biomass
        - Fungal biomass
        - Immobilized biomass
        - Microbial biomass
    - Body mass
    - Bone mass
    - Dry mass
    - Fat free mass
    - Fat mass
    - Heart left ventricle mass
    - Kidney mass
- Materials testing
- Mechanical stress
    - Contact stress
    - Contraction stress
    - Shear stress
    - Surface stress
    - Wall stress
- Mechanical torsion
- Molecular mechanics
- Plasticity
- Pliability
- Quantum mechanics
    - Quantum theory
- Rigidity
- Torque
- Viscosity
    - Blood viscosity
        - Plasma viscosity
    - Gelatinization
    - Shear rate
    - Shear strength
    - Shear mass
    - Sputum viscosity

Viscoelasticity

Appendix C. Study Flow Diagram

I. 1022 citations identified by searches

- **a. 662 citations not screened manually due to likely irrelevance** (based on text mining, logistic regression, etc.)
- b. 360 citations screened for potential inclusion at title/abstract level.
  - i. 321 citations selected by text mining in Distiller (306 (30%), plus 15 over)
  - ii. 39 additional citations: 37 citations by logistic regression (5%), 2 citations for including "random" or "systematic" in the title or abstract
    - **1. 219 citations excluded at the title/abstract level** Citations excluded at this level were off-topic, not published in English, did not address a Key Question, did not report a device of interest, or did not report an outcome of interest
    - 2. 141 full-length citations reviewed
      - **a. 96 citations excluded at 1st pass full article level** Citations excluded at this level were off-topic, or not published in English, or did not address a Key Question, or did not report a device of interest, or did not report an outcome of interest, or were not available
      - b. 45 citations reviewed (No evidence prioritization necessary due to number of studies)
        - **i. 7 citations excluded at 2nd pass full article review** Citations excluded at this level were not a device or material of interest, not a focus of interest (e.g., focused on use of antibiotics postimplantation), narrative review, and duplicate reporting of adverse events
        - ii. 38 citations included

Appendix D. Evidence Tables

Table 4: pHEMA as a Material - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Qian et al. 2020[3]

Study Design: Single-arm study
Device or Material: PAHG injection for breast augmentation*
Contract Duration: Mean 5.1 years from implantation to removal (based on age)
Dose: Mechanics/Morphology: 50 to 500 mL (unilateral), 140 to 1,000 mL (bilateral)
Frequency/Duration: NR
Response:

- Deformation
- Deposition milk
- Displacement
- Induration
- Pain

Patient characteristics (gender, mean age): 100% female; mean age 33.13 years at injection, 38.23 at removal. All patients received PAHG injections for breast augmentation and had it removed.
Number per group: 325 (650 breasts).
Observed adverse effects: Deformation (atrophy, ptosis, and asymmetry), 20.6%; deposition milk, 1.5%; displacement, 6.2%; induration (single, multiple, and diffuse), 33.2%; pain (stabbing pain, distending pain, pressing pain, and referred pain in the breast, axilla, chest, and back), 45.5%.
Timing of adverse effects: NR
Factors that predict response: NR

Source Citation: Woźniak-Roszkowska et al. 2020[4]

Study Design: Single-arm study
Device or Material: PAHG injection for breast augmentation*
Contract Duration: Median 18.2 months (IQR 34.5) from implantation to onset of complications
Dose: Median 300 mL (IQR 190)
Frequency/Duration: Median number of injections 1 (IQR 0.75)
Response:

- Axilla pain
- Breast deformities
- Breast edema
- Breast pain
- Fistula
- Migration
- Skin discoloration

Patient characteristics (gender, mean age): 100% female; mean (SD) age 39.54 (8.50). Presence of complications (n = 28) or anxiety about potential future complications (n = 2) was an eligibility criterion.
Number per group: 30
Observed adverse effects: Axilla pain, 36.7%; breast deformities/lumps, 63.3%; breast edema, 36.7%; breast pain, 73.3%; fistula, 36.7%; clinically detectable hydrogel migration, 53.3%; skin discoloration, 10%
Timing of adverse effects: Average intervals in months from injection: Breast deformities/lumps, 12.7
Factors that predict response: NR

Source Citation: Yang et al. 2020[5]

Study Design: Single-arm study

Device or Material: PAHG injection for breast augmentation*
Contract Duration: Mean 11.51 years from implantation to removal; range <1 year to 20 years
Dose: NR
Frequency/Duration: NR
Response:
- Abscesses
- Adenosis
- Atrophy
- Deformation
- Fibroadenoma
- Fibrosis
- Induration
- Inflammation
- Malignancy
- Mass
- Migration
- Pain/discomfort

Patient characteristics (gender, mean age): 100% female; mean age 44 years (range 30 to 64). All patients had received PAHG injections for breast augmentation and had it removed.
Number per group: 90 (86 with clinical data)
Observed adverse effects: Deformation, 18.6%; induration (breast turned hard or rubbery), 4.6%; malignant tumor, 2.3%; mass, 75.6%; migration (presented in infraclavicular, hypochondria, abdominal wall, anterior sternum, axilla, and posterior chest wall), 22.1%; pain/discomfort (uncomfortable included foreign body sensation, feeling of being swollen, difficulty breathing), 45.4%. Chronic inflammation, reported in 70 (77.8%) patients, included infiltration of lymphocytes and plasma cells. Acute inflammation with neutrophilic infiltration was noted in 9 (10%) patients; 2 patients also had abscesses. Fibrosis (proportion of fibrous component exceeding 90%) was more likely in patients experiencing masses vs. patients without masses (30.7% vs. 24.0%), patients with pain vs. without pain (38.4% vs. 21.5%), while patients with gel migration were less likely to present obvious fibrosis (10.5% vs. 33.8%). The mammary gland around the gel displayed atrophy (20%), adenosis (36%) and fibroadenoma (1.1%).
Timing of adverse effects: Malignant tumors in 2 (2.33%) patients occurred after 12 years postimplantation.
Factors that predict response: NR

Source Citation: Jin et al. 2018[2]
Study Design: Single-arm study
Device or Material: PAHG injection for breast augmentation*
Contract Duration: 8 years, 10 years, 12 years
Dose: NR
Frequency/Duration: Single application
Response:
- Diffusion
- Migration
- Pain
- Swelling

Patient characteristics (gender, mean age): 100% female; age NR
Number per group: 3 case reports selected to illustrate 3 proposed categories of complication profiles.
Observed adverse effects: Swelling (1 patient); diffusion, pain, and swelling (1 patient); migration (1 patient)
Timing of adverse effects: 8 years (swelling), 12 years (swelling and pain), and 7 years (chest wall masses due to migration to lateral chest wall) postimplantation
Factors that predict response: NR

Source Citation: Ramsay et al. 2017[6]
Study Design: Single-arm study
Device or Material: PAHG to treat vesicoureteral reflux
Contract Duration: Median 36 months follow-up

Dose: Median per refluxing renal unit 1.0 mL (range 0.6 to 2.5)
Frequency/Duration: 1 or 2 administrations (6 patients had 2)
Response:
- None reported

Patient characteristics (gender, mean age): 53 female, 23 male. Median age at surgery 45 months
Number per group: 76 patients (123 refluxing renal units). At time of report, 70 patients were eligible for 12-month follow-up, of whom 68 had provided data, and 46 were eligible for 36-month follow-up, of whom 40 had provided data.
Observed adverse effects: No calcifications or de novo or worsening hydronephrosis
Timing of adverse effects: NR
Factors that predict response: NR

Source Citation: Chen & Song 2016[7]
Study Design: Single-arm study
Device or Material: PAHG injection for breast augmentation*
Contract Duration: 6 months to 10 years
Dose: Average 150 mL per side
Frequency/Duration: NR
Response:
- Asymmetry
- Deformation
- Deposition milk
- Galactorrhea
- Induration
- Inflammation
- Pain
- Migration

Patient characteristics (gender, mean age): 100% female; average age 36.5 years (range 25 to 48). All patients had received PAHG injections for breast augmentation and had it removed.
Number per group: 200
Observed adverse effects: Asymmetry, 24%; deformation, 8.5%; deposition milk, 1%; induration, 77.5%; inflammation, 2%; pain, 37.5%; migration (movement to abdomen in 1 patient), 25%; galactorrhea, 1%
Timing of adverse effects: NR
Factors that predict response: NR

Source Citation: Karaca et al. 2016[8]
Study Design: Single-arm study
Device or Material: Polyacrylamide 1.5% (Medilon; Mediphacos)
Contract Duration: 3 months
Dose: NR
Frequency/Duration: Single application
Response:
- Increase in IOP
- Inflammation (iritis)

Patient characteristics (gender, mean age): 12 males, 8 females; mean (SD) age 54.7 (17.7) years; left in the anterior chamber at the end of combined phacoemulsification with IOL implantation and PPV
Number per group: 20
Observed adverse effects: 2 cases had inflammation (iritis). Clinical significant but transient increase in IOP in 4 (20%) patients.
Timing of adverse effects: Iritis noted at 24-hour follow-up visit; had disappeared by day 7 visit. Elevation in IOP 4 hours postoperatively gradually decreased to preoperative levels at 24 to 96 hours.
Factors that predict response: NR

Source Citation: de Vries and Geertsma 2013[1]

Study Design: Systematic review
Device or Material: PAAG injections for facial lipoatrophy
Contract Duration: 12 and 24 months follow-up
Dose: NR
Frequency/Duration: NR
Response:
- Ecchymosis
- Nodules
- Papules
- Transient local inflammatory reactions

Patient characteristics (gender, mean age): HIV patients
Number per group: 3 studies met publication criteria (≥2010) or were not included as individual studies. 1 study of 31 patients (12 month f/u); 1 study of 88 patients (24 months f/u); and 1 study of 290 patients (24 months follow-up).
Observed adverse effects: Ecchymosis (58%) and small palpable but not visible nodules (29%) reported in 1 study (n=31). Subcutaneous nodules (n=3) and transient local inflammatory reactions (n=3) were reported in 1 study (n=88). Injection-site nodules (8.3%) and papules (8.6%) were reported in 1 study (n=290).
Timing of adverse effects: Follow-up through 12 and 24 months
Factors that predict response: NR

Source Citation: Patlazhan et al. 2013[9]
Study Design: Single-arm study
Device or Material: PAAG injection for breast augmentation
Contract Duration: NR
Dose: NR
Frequency/Duration: NR
Response:
- Asymmetry
- Consistency changes
- Deformity
- Discoloration
- Enlargement
- Fever
- Fistula
- Hyperemia
- Mastalgia
- Migration
- Palpable lumps
- Ptosis
- Range of motion limitation
- Rejection reaction

Patient characteristics (gender, mean age): 100% female, 36 years (range 18-52).
Number per group: 154 patients: Group I (immediate breast reconstruction, no acute inflammation), n=121 (79%); Group II (delayed breast reconstruction due to acute inflammation), n=33 (21%)
Observed adverse effects: The most prevalent complaints before surgery included breast asymmetry (100%), breast deformity (90%), mastalgia (breast pain, 63%), and gel migration outside the breast contour (54%). Other noninflammatory complaints included: palpable lumps (79%) and breast ptosis (sagging, 12%). Inflammatory complaints included skin color changes (30%), breast consistency changes (25%), hyperemia (23%), fever (21%), breast enlargement (18%), upper-extremity motion limitations (17%), and breast fistula (10%).
Timing of adverse effects: NR
Factors that predict response: NR

Source Citation: Unukovych et al. 2012[10]

Study Design: Single-arm study
Device or Material: PAAG injection for breast augmentation
Contract Duration: Mean 6.1 years (SD 4.1)
Dose: Mean gel volume 230 mL (SD 66 mL)
Frequency/Duration: 12% unilateral; 88% bilateral
Response:
- Breast deformity
- Breast hardening
- Fistulas
- Gel leakage
- Gel migration
- Lumps
- Pain

Patient characteristics (gender, mean age): 100% female; mean age at injection 29 (SD 6.7)
Possible overlap with patients from Patlazhan et al. 2013[9]
Number per group: 136 (199 breasts)
Observed adverse effects: Breast deformity (n=77, 73%), breast hardening (n=79, 74%), fistulas (n=17, 16%), gel leakage (n=12, 11%), lumps (n=57, 54%), and pain (n=85, 80%). Gel migration affected 39 (37%) patients, spreading to the following areas: submammary (n=12), axilla (n=10), sternum (n=3), abdominal wall (n=1), or two or more zones (n=13).
Timing of adverse effects: Mean time between injection and debridement was 51 months (2 to 160 months).
Factors that predict response: NR

Source Citation: Wang et al. 2012[11]
Study Design: Single-arm study
Device or Material: PAHG injection for breast augmentation
Contract Duration: 1 to 7 years
Dose: NR
Frequency/Duration: Multiple administration (50 unilateral, 8 bilateral)
Response:
- Autoinflation
- Fever (local)
- Galactocele
- Nipple bulging
- Pain
- Swelling

Patient characteristics (gender, mean age): 100% female, 31 ± 12 years.
Number per group: 58 patients reporting infection during breastfeeding.
Observed adverse effects: Serious manifestations included local fever, breast swelling, nipple bulging, tenderness, and pain up to 1 month. Galactocele formed gradually thereafter.
Timing of adverse effects: The maximum interval to intervention was 7 years 2 months and the minimum was 1 year 2 months. Mean interval was 4 years 1 month; median interval was 5 years 3 months. Complications occurred 1 week to 1 month after initiation of breastfeeding.
Factors that predict response: NR

Source Citation: Khedher et al. 2011[12]
Study Design: Single-arm study
Device or Material: PAHG injection for breast augmentation*
Contract Duration: 6 years, 2 years, 4 years
Dose: NR
Frequency/Duration: Single administration (all 3 bilateral)
Response:
- Discharge
- Induration

- Mass/lumps
- Migration
- Redness
- Swelling/edema/ enlargement
- Tenderness/ discomfort

Patient characteristics (gender, mean age): 100% female; 32 years, 35 years, 40 years.
Number per group: Case reports of 3 symptomatic patients.
Observed adverse effects: Induration, nipple discharge, redness, swelling, tenderness, and migration (1 patient); enlargement, induration, edema, discomfort (1 patient); mass/lumps, and migration of the gel into different layers of the mammary gland (1 patient).
Timing of adverse effects: 6 years (patient 1), 2 years (patient 2), and 4 years (patient 3) from injection to presentation with symptoms
Factors that predict response: NR

Systemic Response/ Toxicity

Source Citation: Qian et al. 2020[3]

Study Design: Single-arm study
Device or Material: PAHG injection for breast augmentation*
Contract Duration: Mean 5.1 years from injection to removal (based on age)
Dose: 50 to 500 mL (unilateral), 140 to 1,000 mL (bilateral)
Frequency/Duration: NR
Response:

- Headaches
- Hypodynamia
- Palpitations
- Upper limb numbness

Patient characteristics (gender, mean age): 100% female; mean age 33.13 years at injection, 38.23 at removal. All patients had received PAHG injections for breast augmentation and had it removed.
Number per group: 325 (650 breasts)
Observed adverse effects: Headaches, palpitations, hypodynamia, upper limb numbness, and additional symptoms (not defined), 11 (3.4%) patients
Timing of adverse effects: NR
Factors that predict response: NR

Source Citation: Woźniak-Roszkowska et al. 2020[4]

Study Design: Single-arm study
Device or Material: PAHG injection for breast augmentation*
Contract Duration: Median 18.2 months (IQR 34.5) from implantation to onset of complications
Dose: Median 300 mL (IQR 190)
Frequency/Duration: Median number of injections 1 (IQR 0.75)
Response:

- Arthralgia
- Body weight loss
- Chronic fatigue
- Limitation of movement
- Lymph node enlargement
- Major depressive disorder symptoms
- Numbness/tingling
- Recurrent fever

Patient characteristics (gender, mean age): 100% female; mean (SD) age 39.54 (8.50). Presence of complications (n=28) or anxiety about potential future complications (n=2) was an eligibility criterion.
Number per group: 30
Observed adverse effects: Arthralgia, 6.7%; body weight loss, 6.7%; chronic fatigue, 30%; limitation of upper extremity movements, 20%; lymph node enlargement, 26.7%; major depressive disorder symptoms, 30%;

numbness/tingling of upper extremities, 33.3%; recurrent fever, 43.3%; 5 other symptoms (increased sweating, morning joint stiffness, Raynaud's phenomenon, increased infection incidence, breathing disorders) reported by 1 patient (3.3%) each. All patients undergoing surgical PAHG removal (n=8) reported alleviation of complete resolution of ASIA symptoms.

Timing of adverse effects: Average intervals in months from injection: arthralgia, 34.5 (12 to 57 months); chronic fatigue, 27.6 (1 to 60 months); major depressive disorder, 25.8 (1 to 60 months); numbness/tingling, 17.8

Factors that predict response: NR

Source Citation: Chen & Song 2016[7]

Study Design: Single-arm study

Device or Material: PAHG injection for breast augmentation*

Contract Duration: 6 months to 10 years

Dose: Average 150 mL per side

Frequency/Duration: NR

Response:

- Back pain
- Headache
- Palpitation
- Upper limb numbness

Patient characteristics (gender, mean age): 100% female; average age 36.5 years (range 25 to 48). All patients received PAHG injections for breast augmentation and had it removed.

Number per group: 200 (400 breasts); 135 patients with breast shrinkage after breastfeeding; 65 females had not breastfed.

Observed adverse effects: Headache, back pain, upper limb numbness, palpitation and others (not described), 17%

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Wang et al. 2012[11]

Study Design: Single-arm study

Device or Material: PAHG injection for breast augmentation

Contract Duration: 1 to 7 years

Dose: NR

Frequency/Duration: Multiple administration (50 unilateral, 8 bilateral)

Response:

- Fever
- Pain
- Weakness

Patient characteristics (gender, mean age): 100% female, 31 ± 12 years.

Number per group: 58 patients reported infection during breastfeeding.

Observed adverse effects: Systemic responses included pain, weakness, and fever-related symptoms.

Timing of adverse effects: The maximum interval to intervention was 7 years 2 months and the minimum was 1 year 2 months. Mean interval was 4 years 1 month; median interval was 5 years 3 months. Complications occurred 1 week to 1 month after initiation of breastfeeding.

Factors that predict response: NR

*Reported as polyacrylamide hydrogel (PAAG)

ASIA: Autoimmune syndrome induced by adjuvants; IOP: intraocular pressure; IQR: interquartile range; mL: milliliter; NR: not reported; PAAG: polyacrylamide gel: PAHG: polyacrylamide hydrogel; PPV: para plana vitrectomy; SD: standard deviation

Table 5: Urethral bulking - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Capobianco et al. 2020[14]

Study Design: Systematic review and meta-analysis
Device or Material: Bulkamid (Contura International), 9 other agents
Contract Duration: 1 to 60 months
Dose: NR
Frequency/Duration: Single or repeated administration
Response:

- Dysuria
- Hematuria
- Pain
- Rupture
- Transurethral catheterization
- Urge incontinence (aggravated, de novo, overall)
- Urgency
- Urinary retention
- Voiding dysfunction

Patient characteristics (gender, mean age): 100% female; NR (mean age ranged from 50 to 77 years).
Number per group: 21 studies of 1,890 patients; 475 patients in 4 studies received Bulkamid. 3 of these 4 studies are in Kasi et al. 2016.[13]
Observed adverse effects: Dysuria, 1% (1 study), hematuria, 1% to 6% (2 studies), implantation site pain, 12% (1 study) overall postoperative pain, 28% (1 study), rupture, 3% (1 study), transurethral catheterization, 6% (1 study), aggravated urge incontinence, 0.4% to 6% (2 studies), de novo urge incontinence, 1% to 6% (2 studies), overall urge incontinence, 20% (1 study), urgency, 1% to 4% (2 studies), voiding dysfunction, 1% (studies); urinary retention, 2% to 6% (3 studies); 1 study noted no occurrences of excreted bulking material, nocturia, outlet obstruction, or urinary frequency, and reported a 3% rate of "other" AEs not appearing in this list. (Note: Meta-analyses of AEs pooled data for all agents; percentages given here are from individual studies of Bulkamid.).
Timing of adverse effects: NR
Factors that predict response: NR

Source Citation: Altman et al. 2017[20]

Study Design: Single-arm study
Device or Material: Bulkamid (Contura International)
Contract Duration: 6 months
Dose: 0.9-1.2 mL
Frequency/Duration:
Response: 1 or 2 administrations

- Bleeding

Patient characteristics (gender, mean age): 100% female; mean (SD) age 69.8 (13.0) years, median 71 (range 32 to 92).
Number per group: 81
Observed adverse effects: 1 case of trickling bleeding postinjection. No serious adverse events.
Timing of adverse effects: NR
Factors that predict response: NR

Source Citation: Mohr et al. 2017[19]

Study Design: Single-arm study
Device or Material: Bulkamid (Contura International)
Contract Duration: 3 months
Dose: NR
Frequency/Duration: 1 or 2 administrations
Response:
- Pain
- Urinary retention

Patient characteristics (gender, mean age): 100% female; median age 68 years (range 29 to 93)
Number per group: 154 enrolled; 138 provided data at follow-up.
Observed adverse effects: "The overall complication rate was 13% due to lower UTIs (n=12), temporary retention <48 h (n=3), and pain requiring additional pain medication (n=4)."
Timing of adverse effects: NR
Factors that predict response: NR

Source Citation: Kasi et al. 2016[13]
Study Design: Systematic review
Device or Material: Bulkamid (Contura International)
Contract Duration: 1 year
Dose: NR
Frequency/Duration: Single or repeated administration
Response:
- Hematuria
- Injection site pain
- Urinary retention

Patient characteristics (gender, mean age): 100% female; NR
Number per group: 8 studies of 767 patients, all of whom received Bulkamid. 3 of these 8 studies (n=475) are in Capobianco et al. 2020.[14]
Observed adverse effects: Hematuria (1% to 5%, 5 studies), injection site pain (4% to 14%, 3 studies), transient urinary retention (1% to 15%, 5 studies), chronic urinary retention (0% to 1%, 2 studies)
Timing of adverse effects: NR
Factors that predict response: NR

Source Citation: Zhao et al. 2016[15]
Study Design: Nonrandomized comparative study
Device or Material: PAHG (Bulkamid), collagen, hyaluronic acid, ethylene vinyl alcohol
Contract Duration: 12 months
Dose: NR
Frequency/Duration: 1 to 3 administrations (median 1)
Response: None reported
Patient characteristics (gender, mean age): 100% female. Overall median age 79 years, equally distributed in all 4 groups
Number per group: 44 PAHG, 312 collagen, 54 hyaluronic acid, 104 ethylene vinyl alcohol
Observed adverse effects: Overall complication rate for PAHG, 0%. (Rates for other materials: collagen, 3.2%; hyaluronic acid, 5.6%; ethylene vinyl alcohol, 5.7%.)
Timing of adverse effects: N/A
Factors that predict response: N/A

Source Citation: Martan et al. 2014[17]
Study Design: Single-arm study
Device or Material: Bulkamid (Contura International)
Contract Duration: 6 months
Dose: Mean 1.39 mL

Frequency/Duration: Single administration (5 patients had reinjection)
Response:
- Rupture

Patient characteristics (gender, mean age): 100% female; mean age 70 years
Number per group: 51
Observed adverse effects: Rupture of urethral mucous membrane during procedure (n=1); no major bleeding, urinary retention, or de novo urgency
Timing of adverse effects: Intraoperative rupture
Factors that predict response: NR

Source Citation: Mouritsen et al. 2014[16]
Study Design: Single-arm study (long-term follow-up of 2006 study)
Device or Material: PAHG injection for female SUI
Contract Duration: 8 years
Dose: NR
Frequency/Duration: NR
Response:
- Cystitis
- Stranguria

Patient characteristics (gender, mean age): 100% female; median age 74 years (range 43 to 92)
Number per group: 24
Observed adverse effects: Recurrent cystitis (7/24; 29.1%), stranguria (1/24; 4.1%); no dysuria or vaginal discharge. Of 11 women who underwent pelvic examination, none had granulomas, indurations, or fistulas.
Timing of adverse effects: NR
Factors that predict response: NR

Source Citation: Toozs-Hobson et al. 2012[18]
Study Design: Single-arm study (long-term follow-up of 2010 study)
Device or Material: Bulkamid (Contura International)
Contract Duration: 2 years
Dose: Mean 1.53 mL
Frequency/Duration: Single administration (35% of patients had reinjection)
Response: No treatment-related AEs
Patient characteristics (gender, mean age): 100% female; age NR.
Number per group: 116 (original n = 135)
Observed adverse effects: "16 new nonserious AEs and four new serious adverse reactions were reported, none of which was thought to be related to the treatment."
Timing of adverse effects: N/A
Factors that predict response: N/A

AE: adverse event; mL: milliliter; N/A: not applicable; NR: not reported; PAHG: polyacrylamide hydrogel; SUI: stress urinary incontinence; UTIs: urinary tract infections

Table 6: Polyacrylamide, Dermal Filler - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Kastner et al. 2018[25]

Study Design: Single-arm study
Device or Material: Aquamid (Contura International)
Contract Duration: 2 to 10 years
Dose: NR
Frequency/Duration: NR
Response:
- Diffused distribution of product/migration
- General fibrosis
- Occlusion and fibrogenous alteration of labial artery
- Upper lip paresthesias

Patient characteristics (gender, mean age): 90.9% female; age range 31 to 53 years
Number per group: 11
Observed adverse effects: Diffused distribution of product/migration (n=11), general fibrosis (n=11), occlusion and fibrogenous alteration of a labial artery (n=5), upper lip paresthesias (n=1)
Timing of adverse effects: 2 to 10 years
Factors that predict response: NR

Source Citation: Kadouch et al. 2013[22]

Study Design: Nonrandomized comparative study
Device or Material: Aquamid (Contura International), Bio-Alcamid (Polymekon), DermaLive (Dermatech), Artecoll (Suneva Medical Inc.), and liquid injectable silicone (Alcon Pharmaceuticals)
Contract Duration: Minimum 2 weeks
Dose: NR
Frequency/Duration: Some patients (n=5) were injected with more than one permanent filler in the same area.
Response:
- Abscess
- Low-grade inflammation
- Migration
- Noninflammatory nodule

Patient characteristics (gender, mean age): 85 patients (40 male, 45 female); mean age 54 (range 27 to 79); 5 patients received more than one permanent filler.
Number per group: 66 (78%) received Bio-Alcamid, 8 (9%) received DermaLive, 6 (7%) received Aquamid, 7 (8%) received PMMA (Artecoll), and 4 (5%) received liquid injectable silicone (LIS). 60% underwent soft-tissue augmentation for facial rejuvenation, 40% had HIV and were treated for CART-induced facial lipoatrophy.
Observed adverse effects: Bio-Alcamid: abscesses in 25 (38%), noninflammatory nodules in 20 (30%), low-grade inflammation in 25 (38%), and migration in 30 (45%);
DermaLive: abscesses in 0 (0%), noninflammatory nodules in 7 (88%), low-grade inflammation in 2 (25%), and migration in 1 (13%);
Aquamid: abscesses in 0 (0%), noninflammatory nodules in 4 (67%), low-grade inflammation in 2 (33%), and migration in 1 (17%)
Artecoll: abscesses in 0 (0%), noninflammatory nodules in 2 (29%), low-grade inflammation in 4 (57%), and migration in 3 (43%)
LIS: abscesses in 0 (0%), noninflammatory nodules in 0 (0%), low-grade inflammation in 3 (75%), and migration in 2 (50%)

Timing of adverse effects: Mean onset was 38 months for Bio-Alcamid and LIS, 10 months for Aquamid, 57 months for PMMA, and 40 months for DermaLive.
Factors that predict response: NR

Source Citation: De Santis et al. 2011[26]
Study Design: Single-arm study
Device or Material: Aquamid (Contura International)
Contract Duration: 5 years
Dose: NR
Frequency/Duration: 1 mL injections monthly;
Mean number of injection 7 (SD 2.56, Range 2 to 13)
Response:
- Caudal migration
- Facial abscesses requiring drainage
- Gel indurations/ blebs
- Localized accumulation of PAAG
- Subcutaneous hematoma
- Swelling

Patient characteristics (gender, mean age): 15.79% female; mean age 42.61 (range 32.99 to 64.72)
Number per group: 141 completed treatment, 38 available for 5 year follow-up
Observed adverse effects: Caudal migration (n=3), facial abscesses requiring drainage (n=2), gel indurations/blebs (n=4), localized accumulation of PAG (n=2), subcutaneous hematoma (n=3), swelling (n=8)
Timing of adverse effects: Caudal migration: after 1 year (n=3); facial abscesses requiring drainage: approximately 2 years after injection (n=2); gel indurations/blebs: after 1 year (n=4); localized accumulation of PAAG: within 1 week (n=1), between 1 week and 1 month (n=1); subcutaneous hematoma: Within 1 week (n=3); temporary swelling: within 1 week (n=7), 1 month to 1 year (n=1).
Factors that predict response: N

Source Citation: Rauso et al. 2011[21]
Study Design: RCT
Device or Material: Aquamid (Contura International)
Contract Duration: 12 months
Dose: Group A: 8 mL to 14 mL
Group B: 2 mL
Frequency/Duration: Group A: 1 injection
Group B: multiple injections
Response:
- Ecchymosis
- Small palpable nodules

Patient characteristics (gender, mean age): All 31 patients HIV+ receiving antiretroviral therapy and affected by facial wasting.
Group A: 33.3% female; Group B: 30.8% female.
Number per group: Group A: 18, Group B: 13.
Observed adverse effects: Group A: Ecchymosis (n=17) and small palpable nodules (n=6). No foreign body reactions or migration of product.
Group B: Small palpable nodules (n=3). No ecchymosis, foreign body reactions, or migration of product.
Timing of adverse effects: Up to 12 months.
Factors that predict response: NR.

Source Citation: Rauso et al. 2011[27]
Study Design: Single-arm study
Device or Material: Aquamid (Contura International)
Contract Duration: 18 months
Dose: NR

Frequency/Duration: Variable administration (average 2.3 injections)
Response:
- Ecchymosis
- Edema
- Nodules

Patient characteristics (gender, mean age): NR
Number per group: 32
Observed adverse effects: All patients experienced ecchymosis and edema (n=32). Small, palpable, nonvisible nodules were also recorded (n=13). No patients experienced foreign body reactions or migration of product.
Timing of adverse effects: Ecchymosis and edema experienced directly after surgery. Nodules occurred within follow-up period.
Factors that predict response: NR

Source Citation: Giorgini et al. 2010[24]
Study Design: Single-arm study
Device or Material: Aquamid (Contura International)
Contract Duration: 12 months
Dose: 1 to 2 vials
Frequency/Duration: Injection every 4 weeks for 3 months
Response: None Reported
Patient characteristics (gender, mean age): 36.2% female; mean age 45.5 years (SD 6.4)
Number per group: 36
Observed adverse effects: No serious AEs reported
Timing of adverse effects: N/A
Factors that predict response: N/A

Source Citation: Ono et al. 2010[23]
Study Design: Nonrandomized comparative study
Device or Material: Aquamid (Contura International) and Amazingel (FuHua High Molecular Matter Company)
Contract Duration: Mean 15 months (range 0.5 to 60 months)
Dose: NR
Frequency/Duration: Injection sites included the cheeks (n=4), breasts (n=4), nasal root (n=4), eyelid (n=2), and penis (n=1).
Response:
- Decensus
- Gel leakage
- Induration
- Pain
- Redness
- Swelling
- Uncomfortable feeling

Patient characteristics (gender, mean age): 93.3% female, mean age 37.3 years (22 to 56 years)
Number per group: 15; Aquamid (n=8), Amazingel (n=7)
Observed adverse effects: Amazingel: Decensus caused by migration (n=1), induration (n=5), swelling (n=1), uncomfortable feeling (n=1), pain (n=1). No gel leakage or redness observed.
Aquamid: Decensus caused by migration (n=2), induration (n=4), gel leakage (n=1), redness (n=2), pain (n=1). No swelling or uncomfortable feeling observed.
Timing of adverse effects: Amazingel: Decensus caused by migration: 6 months (n=1), 18 months (n=1); induration: 12 months (n=3), 18 months (n=1), 36 months (n=1); pain: 36 months (n=1); redness: 18 months (n=1); swelling: uncomfortable feeling: 60 months (n=1)
Aquamid: Decensus caused by migration: 6 months (n=1); gel leakage: 1 month (n=1); induration: 0.5 month (n=1), 5 months (n=1), 6 months (n=1), 12 months (n=1); pain: 1 month (n=1); redness: 6 months (n=1); swelling: 12 months (n=1).
Factors that predict response: NR

Source Citation: Pallua et al. 2009[28]

Study Design: Single-arm study
Device or Material: Aquamid (Contura International)
Contract Duration: 12 months to 60 months
Dose: Average 4.3 mL
Frequency/Duration: Average 2.4 injections (range 1 to 8 sessions)
Response:
- Discoloration
- Edema
- Gel induration/ blebs
- Hematoma
- Pain
- Tingling/itching
- Treatment-related AEs

Patient characteristics (gender, mean age): 92.0% female; mean age 46 (range 19 to 70)
Number per group: 251
Observed adverse effects: Discoloration (n=4 cases, 4 patients), edema (n=4 cases, 4 patients), gel induration/blebs (n=13 cases, 9 patients), hematoma (n=5 cases, 5 patients), pain (n=5 cases, 5 patients), tingling/itching (n=7 cases, 3 patients), treatment-related AEs (n=53 cases, 40 patients)
Timing of adverse effects: NR
Factors that predict response: NR

Systemic Response/Toxicity

Source Citation: Ono et al. 2010[23]

Study Design: Nonrandomized comparative study
Device or Material: Aquamid (Contura International) and Amazingel (FuHua High Molecular Matter Company)
Contract Duration: Mean 15 months (range 0.5 to 60 months)
Dose: NR
Frequency/Duration: Injection sites included the cheeks (n=4), breasts (n=4), nasal root (n=4), eyelid (n=2), and penis (n=1).
Response:
- Fever

Patient characteristics (gender, mean age): 93.3% female; mean age 37.3 years (22 to 56 years)
Number per group: Aquamid (n=8), Amazingel (n=7).
Observed adverse effects: Amazingel: Fever (n=1)
Aquamid: No systematic adverse events
Timing of adverse effects: Amazingel: Fever: 36 months (n=1)
Factors that predict response: NR

AE: adverse events; CART: combination antiretroviral therapy; HIV+: human immunodeficiency virus positive; mL: milliliter; NR: not reported; PAAG: polyacrylamide gel; PAHG: polyacrylamide hydrogel; PMMA: polymethylmethacrylate; RCT: randomized controlled trial; SD: standard deviation

Table 7: Ocular Implant - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Bonilla et al. 2012[29]

Study Design: Single-arm study
Device or Material: ESNOPER V2000 (AJL Ophthalmic)
Contract Duration: 12 months
Dose: NR
Frequency/Duration: Single administration (15 unilateral, 4 bilateral)
Response:

- Iris incarceration
- Microhyphema
- Microperforation of the trabeculo-Descemet's membrane
- Positive Seidel test

Patient characteristics (gender, mean age): 16 patients completing 12-month follow-up: 31.3% female; mean age 76.
Number per group: 19 patients enrolled (23 eyes), 16 patients (20 eyes) provided data at follow-up.
Observed adverse effects: For all enrolled 19 patients: iris incarceration (n=2 patients), microhyphema (n=3 patients), microperforation of the trabeculo-Descemet's membrane (n=4 patients), positive Seidel test (n=2 patients).
Timing of adverse effects: Seidel test positivity confirmed within 24 hours after surgery.
Factors that predict response: NR

Source Citation: Jiraskova et al. 2011[30]

Study Design: Single-arm study
Device or Material: AlphaCor (Argus Biomedical)
Contract Duration: 12 months to 67 months
Dose: NR
Frequency/Duration: Single administration (all unilateral)
Response:

- Optic deposition
- Retroprosthetic membrane formation
- Stromal melt
- Trauma

Patient characteristics (gender, mean age): 93.3% female; mean age 57 years
Number per group: 15
Observed adverse effects: Optic deposition (n=3 patients, 6 cases), retroprosthetic membrane formation (n=3 patients, 4 cases), stromal melt (n=9 patients, 9 cases), and trauma (n=3 patients, 6 cases) observed. No endophthalmitis, glaucoma progression, inflammation, or retinal detachment
Timing of adverse effects: Optic deposition: 24 months (n=2), 30 months (n=2), 36 months (n=1), 42 months (n=1); retroprosthetic membrane formation: 6 months (n=1), 12 months (n=2), 18 months (n=1); stromal melt: 12 months (n=4), 18 months (n=2), 36 months (n=1), 42 months (n=1), timing NR (n=1); trauma: 6 months (n=3), 18 months (n=1)
Factors that predict response: NR

Source Citation: Oshika et al. 2020[33]

Study Design: Single-arm study
Device or Material: Clareon CNA0T0 (Alcon Research)
Contract Duration: 1 year to 9 years
Dose: Single administration (all unilateral)
Frequency/Duration:

Response:
- Mild posterior capsule opacification

Patient characteristics (gender, mean age): 1 year: 64.5% female; mean age 72.4 years (6.6 SD)
9 year: 70% female; mean age 80.1 years (7.4 SD)
Number per group: 1 year: 110 patients (110 eyes)
9 year: 20
Observed adverse effects: Mild posterior capsule opacification (n=4 eyes, 3 at 1-year follow-up, 1 at 9-year follow-up). No glistening or surface light scattering.
Timing of adverse effects: 1 year: mild posterior capsule opacification: 2 months (n=1 eye), 6 months (n=2 eyes)
9 years: No glistening. No surface light scattering. 1 posterior capsule opacification.
Factors that predict response: NR

Source Citation: Shevchenko et al. 2013[32]
Study Design: Single-arm study
Device or Material: AlphaSphere (Argus Biomedical)
Contract Duration: 2 weeks to 14 months
Dose: NR
Frequency/Duration: Single surgery (all unilateral)
Response:
- Migration

Patient characteristics (gender, mean age): 58.3% female; mean age 40 years (range 8 to 82)
Number per group: 12
Observed adverse effects: Slight implant migration (n=1). No other adverse events.
Timing of adverse effects: 2 weeks to 14 months
Factors that predict response: NR

NR: not reported

Table 8: HEMA_Dermal Filler - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Alijotas-Reig et al. 2013[34]

Study Design: Systematic review
Device or Material: pHEMA injection DermaLive/DermaDeep (Dermatech, Novamedical)
Contract Duration: 14 to 30 months
Dose: NR
Frequency/Duration: Multiple administration
Response:
- Edema
- Induration
- Inflammatory nodules

Patient characteristics (gender, mean age): NR.
Number per group: 25.
Observed adverse effects: Patients developed delayed-type hypersensitivity reactions characterized by inflammatory nodules, induration, and facial edema following injections of fillers.
Timing of adverse effects: Average latency period to beginning of symptoms was 14 months; n=6 patients had recurrent bouts after an average of 16 months of follow-up.
Factors that predict response: NR.

Source Citation: Demir et al. 2013[35]

Study Design: Single-arm study
Device or Material: pHEMA injection DermaLive (Dermatech, Novamedical)
Contract Duration: 4 to 48 months
Dose: 1.94 ± 0.9 mL
Frequency/Duration: Single and multiple administration
Response:
- Edema/swelling
- Erythema
- Fistula formation
- Induration
- Infection
- Lesions
- Nodules, palpable
- Pain
- Scar tissue

Patient characteristics (gender, mean age): 19 female, 2 male, 47 years
Number per group: 21
Observed adverse effects: One patient presenting with intermediate-stage adverse effects at 4 months after nasolabial fold injection, including erythema, fistula formation, palpable hard and visible nodules, and red induration. All 21 patients reported late-stage adverse effects with multiple bulging or palpable hard nodules. Other reported late-stage adverse effects included: lesions symptomatic with discomfort (n=9), recurrent pain (n=10), and swelling and edema formation (n=6); discolored nodules or erythema (n=12); swelling (n=6), and scar tissue formation (n=1).
Timing of adverse effects: Intermediate-stage (2 to 6 months); late-stage (>6 months). Mean delay after injection = 18.6 months
Factors that predict response: NR

Source Citation: Kadouch et al. 2013[22]

Study Design: Nonrandomized comparative study
Device or Material: Aquamid (Contura International), Bio-Alcamid (Polymekon), DermaLive (Dermatech), Artecoll (Suneva Medical Inc.), and liquid injectable silicone (Alcon Pharmaceuticals)
Contract Duration: Minimum 2 weeks
Dose: NR
Frequency/Duration: Some patients (n=5) were injected with more than one permanent filler in the same area.
Response:

- Abscess
- Low-grade inflammation
- Migration
- Noninflammatory nodule

Patient characteristics (gender, mean age): 85 patients (40 male, 45 female); mean age 54 (range, 27 to 79)); 5 patients received more than one permanent filler.
Number per group: 66 (78%) received Bio-Alcamid, 8 (9%) received DermaLive, 6 (7%) received Aquamid, 7 (8%) received PMMA (Artecoll), and 4 (5%) received liquid injectable silicone (LIS). 60% underwent soft-tissue augmentation for facial rejuvenation, 40% had HIV and were treated for CART-induced facial lipoatrophy.
Observed adverse effects: Bio-Alcamid: abscesses in 25 (38%), noninflammatory nodules in 20 (30%), low- grade inflammation in 25 (38%), and migration in 30 (45%)
DermaLive: abscesses in 0 (0%), noninflammatory nodules in 7 (88%), low-grade inflammation in 2 (25%), and migration in 1 (13%)
Aquamid: abscesses in 0 (0%), noninflammatory nodules in 4 (67%), low-grade inflammation in 2 (33%), and migration in 1 (17%)
Artecoll: abscesses in 0 (0%), noninflammatory nodules in 2 (29%), low-grade inflammation in 4 (57%), and migration in 3 (43%)
LIS: abscesses in 0 (0%), noninflammatory nodules in 0 (0%), low-grade inflammation in 3 (75%), and migration in 2 (50%)
Timing of adverse effects: Mean onset was 38 months for Bio-Alcamid and LIS, 10 months for Aquamid, 57 months for PMMA, and 40 months for DermaLive.
Factors that predict response: NR.

Source Citation: Bachmann et al. 2010[36]
Study Design: Single-arm study (Injectable Filler Safety Study)
Device or Material: pHEMA injection DermaLive (Dermatech)
Contract Duration: 29 months
Dose: NR
Frequency/Duration: Multiple administration
Response:

- Abscess formation
- Discoloration
- Erythema
- Nodules
- Pain
- Pruritus
- Swelling

Patient characteristics (gender, mean age): 153 female, 8 male, 49.6 years
Number per group: N=6 patients whose adverse reactions were attributable to pHEMA alone
Observed adverse effects: Adverse reactions attributable to pHEMA due to symptoms and reaction latency. Pruritus and nodules seen in all 6 patients; 5 patients with erythema; 4 patients reporting discoloration; 3 patients reporting swelling; and 2 patients with pain and abscess formation.
Timing of adverse effects: 29±16.3 months
Factors that predict response: NR

CART: combination antiretroviral therapy; HIV: human immunodeficiency virus; NR: not reported; pHEMA: Poly(2-hydroxyethyl methacrylate); PMMA: polymethylmethacrylate

Table 9: IOL - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Adhikari and Shrestha 2018[37]

Study Design: Single-arm study
Device or Material: pHEMA IOL with UV absorber (Fred Hollows IOL lab, Tilganga Institute of Ophthalmology)
Contract Duration: 13.7 months
Dose: 80% to 100% IOL power
Frequency/Duration: Single application per eye (58 unilateral, 62 bilateral)
Response:

- Endophtalmitis
- Inflammation
- Opacification

Patient characteristics (gender, mean age): 58.3% male, 6.9 years
Number per group: 178 eyes of 120 children
Observed adverse effects: Post-op complications present in 18.3% of eyes. 18 (10.1%) eyes developed inflammatory membrane; 7 (3.9%) eyes developed visual axis opacification; and 2 (1.1%) eyes developed endophtalmitis.
Timing of adverse effects: 13.7 months
Factors that predict response: NR

Source Citation: Maxwell and Suryakumar 2018[38]

Study Design: Single-arm study
Device or Material: pHEMA IOL Clareon 3-piece MA60NM (Alcon Laboratories)
Contract Duration: 3 years
Dose: 15.0 to 29.0 diopter
Frequency/Duration: Single application per eye (138 unilateral)
Response:

- Corneal edema
- Inflammation
- Macular degeneration
- Macular edema
- Vitreous detachment

Patient characteristics (gender, mean age): 61.9% female, 74.1 years
Number per group: 179 (one-year follow-up); 138 (three-year follow-up)
Observed adverse effects: No observed serious adverse events were considered related to IOL. Non-serious adverse events through one year were corneal edema (21.2%), macular degeneration (10.1%), vitreous detachment (3.2%), macular edema (2%), and "other" (40.2%, not specified). Vitreous detachment and macular degeneration were not associated with cataract surgery. Edema was not observed beyond the 30 to 60 day post-op visit. Visual outcomes maintained at 3 years.
Timing of adverse effects: 1 year; 3 years. Edema up to 60 days.
Factors that predict response: NR

Source Citation: Mathew and Coombes 2010[39]

Study Design: Single-arm study
Device or Material: pHEMA IOL Rayner C-flex 1-piece 570C (Rayner Intraocular Lens, Ltd.)
Contract Duration: 5.3 to 29.0 months
Dose: OD 5.75 mm; RI 1.46
Frequency/Duration: Single application per eye
Response:

- Posterior capsule opacification

Patient characteristics (gender, mean age): 1.8:1 female to male (64.3% female), 76 years

Number per group: 58 Nd:YAG capsulotomies performed out of 3,461 patients receiving IOL
Observed adverse effects: An indirect method of studying symptomatic posterior capsule opacification is to look at Nd:YAG capsulotomy rates associated with an IOL. The Nd:YAG capsulotomy rate was 0.6% at 12 months and 1.7% at 24 months. Mean time to Nd:YAG capsulotomy was 9.3±5.5 months (range: 1.3 to 22.7 months).
Timing of adverse effects: 5.3 to 29.0 months
Factors that predict response: NR

IOL: intraocular lens; mm: millimeter; ND:YAG: neodymium-doped yttrium aluminum garnet; NR: not reported; OD: optic diameter; pHEMA: Poly (2-hydroxyethyl methacrylate); RI: refractive index; UV: ultraviolet

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Appendix F. Surveillance Event Reports - PSO and Accident Investigation

Provided with this report as separate Excel spreadsheet.

Appendix G. Regulatory and Manufacturer Safety Alerts

Provided with this report as a separate PDF.