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Triphasic biomaterial for augmentation of the osteoporotic femoral neck

Systematic Review

AIHTA Decision Support Document: 126 | ISSN-online: 1998-0469

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Vienna, February 2021

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This report should be referenced as follows:

Kheder, M., Vandepeer, M., Forel, D., Tivey, D. (2021). Triphasic biomaterial for augmentation of the osteoporotic femoral neck. AIHTA Decision Support Documents No. 126; 2021. Vienna: Austrian Institute for Health Technology Assessment GmbH.

Conflict of interest

All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org).

IMPRINT

Publisher:
HTA Austria – Austrian Institute for Health Technology Assessment GmbH
Garnisongasse 7/Top20 | 1090 Vienna – Austria
https://www.aihta.at/

Responsible for content:
Priv.-Doz. Dr. phil. Claudia Wild, managing director

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AIHTA Decision Support Documents are only available to the public via the Internet at http://eprints.aihta.at/view/types/hta_report.html.

AIHTA Decision Support Documents No.: 126

ISSN online 1998-0469

Content

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List of abbreviations

aBMD..... areal bone mineral density
ACROBAT-NRSI.... a Cochrane risk of bias assessment tool – for non-randomized studies of interventions
BMD..... bone mineral density
BTM ..... bone turnover markers
CI..... confidence interval
CRD ..... centre for reviews and dissemination
CT..... computed topography
CTX..... C-terminal telopeptide of type 1 collagen
DARE..... database of abstracts of reviews of effects
DF ..... Deanne Forel
DXA ..... dual energy X-ray absorptiometry
EU ..... European Union
FDA..... Food and Drug Administration
FEA ..... finite element analysis
GRADE..... Grading of Recommendations Assessment, Development and Evaluation
HRQoL ..... health-related quality of life
HTA ..... health technology assessment
ICD ..... International Classification of Diseases
INAHTA..... International Network of Agencies for Health Technology Assessment
LOEP ..... local osteo-enhancement procedure
MK ..... Murad Kheder
MV..... Meegan Vandepeer
N/A..... not applicable
NHS-EED..... National Institute for Health Research economic evaluation database
OPAQ..... osteoporosis assessment questionaire
PICO ..... population, intervention, comparator, outcome
P1NP ..... procollagen type 1 N propeptide
ROBINS-I..... risk of bias in non-randomized studies – of interventions
SD..... standard devation
UK..... United Kingdom
USA..... United States of America
WHO-ICTRP ..... World Health Organization International Clinical Trials Registry Platform

Executive Summary

Introduction

Health Problem

This systematic review focuses on patients with osteoporosis. This disease is a decline in bone mineral density causing the bone to weaken and become susceptible to fractures. Osteoporotic fractures typically occur in the hip, wrist or spine. This systematic review focuses on a minimally invasive procedure that aims to augment the femoral neck with a triphasic biomaterial to prevent or treat a hip fracture. The systematic review intends to answer the research question:

focus on patients with osteoporosis

- In patients with osteoporosis, is AGN1 LOEP more effective concerning changes in femoral bone mineral density, changes in femoral strength, changes in fragility fractures and health-related quality of life, compared with standard osteoporotic management?
- In patients with osteoporosis, is AGN1 LOEP as safe with respect to adverse events compared standard osteoporotic management?

research question: effectiveness and safety of AGN1 LOEP, a minimally invasive procedure

Description of Technology

OSSURE® Local Osteo-Enhancement Procedure (LOEP®) is a minimally invasive surgical procedure developed by AgNovos Healthcare (Rockville, Maryland, USA). It involves the injection of a calcium-based biomaterial (AGN1) into an area of osteoporotic bone loss, where it reportedly provides immediate strength and then is subsequently resorbed and replaced by bone. The intended outcome is increased bone strength and preventing fragility fractures.

OSSURE® Local Osteo-Enhancement Procedure (LOEP)-injection of a calcium-based biomaterial (AGN1) to prevent and treat osteoporotic hip fractures

Current clinical guidelines on the management of osteoporosis recommend lifestyle modifications (diet and exercise) and pharmacological interventions. However, the efficacy of these conservative management elements in preventing hip fractures is reportedly low due to poor compliance. Also, even if adhered to, they can take several months before they effectively reduce hip fracture risk. In comparison to these current interventions, AGN1 LOEP is a once-off minimally invasive surgical treatment that thought to resorb and replace the implant material with new bone. As a natural process of bone healing, as in a fracture, an initial step is an inflammatory response followed by resorption of bone.

main treatment alternatives – diet and lifestyle modification and pharmacotherapy

low compliance

Methods

A systematic review was conducted to answer the research question of the current literature on clinical utilisation of AGN1 LOEP to prevent and treat osteoporotic hip fractures in adults. Five biomedical databases (Medline, Embase, the Cochrane Library, the HTA databases of Centre for Reviews and Dissemination/CRD and INAHTA) were searched on 1st of February 2021. Two authors independently conducted the study selection, data extraction and quality appraisal.

literature search in 5 databases, RoB assessment qualitative synthesis according to GRADE

Results

outcomes: fragility fractures, change bone mineral density, AE/SAE

The outcomes used as evidence to derive a recommendation on the relative efficacy of AGN1 LOEP included: fragility fractures of the hip, change in femoral neck areal bone mineral density (aBMD) and femoral strength as estimated by finite element analysis (FEA). Procedure-related adverse events and complications were included to derive a recommendation on the relative safety of AGN1 LOEP.

available evidence: 1 prospective cohort study with 12 post-menopausal women first-in-human study

The review identified one prospective cohort study comparing AGN1 LOEP to no treatment to derive a recommendation on the effectiveness of AGN1 LOEP. The study included 12 Caucasian osteoporotic postmenopausal women without a previous hip fracture. Each patient received AGN1 LOEP augmentation of the left proximal femur while their right proximal femur served as an untreated control. This study is the first-in-human study of the procedure.

Clinical effectiveness

bone formation: post-procedure aBMD and femoral strength increased fragility fractures: lower in treated hips compared with control

aBMD in the AGN1 LOEP treated femoral necks increased from the baseline value and remained significantly higher than that of the untreated femoral necks at all post-treatment follow-up times (12 months through to 5-7 years; $p<0.001$). Further, femoral strength in the treated hips was significantly higher than in the untreated hips at all follow-up times (12 weeks through to 5-7 years; $p<0.01$). However, there were three post-treatment fragility hip fractures among the participants; two occurred in untreated hips and one in a treated hip.

Safety

no serious adverse events or complications

No serious procedure or device-related safety issues were reported. Minor adverse events possibly related to AGN1 LOEP included an irritation from the injection procedure and post-operative nausea. All were minor and resolved without additional medical intervention.

Upcoming evidence

2 ongoing single-arm clinical trials

There are two ongoing clinical trials investigating the effectiveness and safety of AGN1 LOEP in preventing and treating osteoporotic hip fractures. Both studies are single-arm and recruiting 60 patients each. The trials are due to be completed in May 2021 and December 2025, respectively.

Discussion and conclusion

1 study with 12 pts, low quality of evidence serious RoB due to co-medication of 50% pts.

Results from one prospective cohort study comparing the effectiveness of AGN1 LOEP to no treatment in 12 post-menopausal women without a previous hip fracture demonstrated that AGN1 LOEP significantly increased femoral neck aBMD and femoral strength compared to no treatment. According to GRADE (Grading of Recommendations Assessment, Development and Evaluation), the quality of the evidence was very low for all the reported outcomes. One specific area of bias related to the fact that half of the patients included in the study received pharmacological treatments for osteoporosis. Additionally the validity of an increase in femoral neck aBMD and femoral strength as surrogates for fracture risk has not been determined. An increase in BMD may not translate into a reduction in fractures.

evidence not sufficient
technology is in an early stage of implementation

The evidence presented in this review is not sufficient to determine whether AGN1 LOEP is as safe or more effective than conservative treatments in the prevention of fractures. Implementation of AGN1 LOEP is currently not recommended. The intervention is in an early stage of clinical implementation with too little data available. A re-evaluation is recommended only after robust data from RCTs are available. Such RCTs are not registered yet.

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

neues minimal-invasives Verfahren bei Osteoporose

Diese systematische Übersichtsarbeit befasst sich mit einem neuen minimal-invasiven Verfahren (AGN1 LOEP) für Patient*innen mit Osteoporose. Osteoporose verursacht eine Abnahme der Knochenmineraldichte, wodurch der Knochen schwächer und anfälliger für Frakturen wird. Frakturen treten typischerweise an der Hüfte, dem Handgelenk oder der Wirbelsäule auf. Diese systematische Übersichtsarbeit untersuchte das neue Verfahren, das darauf abzielt, den Schenkelhals mit einem dreiphasigen Biomaterial zu augmentieren, um eine Hüftfraktur zu verhindern oder zu behandeln.

Prävention und Behandlung von Hüftfrakturen

Typen von Osteoporose:

postmenopausale am häufigsten

Osteoporose-bedingte Fragilitätsfrakturen an Hüfte, Handgelenk oder Wirbelsäule

Osteoporose kann bei beiden Geschlechtern, allen Ethnien und allen Altersgruppen auftreten. Es gibt zwei Kategorien von Osteoporose: Die primäre Osteoporose steht im Zusammenhang mit der Veränderung der Keimdrüsenfunktion und deren Auswirkung auf die Knochenresorption und -bildung. Sie umfasst die postmenopausale (Typ-I-Osteoporose) und die senile Osteoporose (Typ-II-Osteoporose). Die Typ-I-Osteoporose ist die häufigste Form der Osteoporose und geht mit einem verstärkten Knochenabbau bei Frauen nach der Menopause durch den Verlust von Östrogen einher. Die senile oder Typ-II-Osteoporose kann bei Frauen und Männern auftreten, wobei Frauen doppelt so häufig betroffen sind wie Männer. Sie resultiert aus einem allmählichen altersbedingten Knochenverlust. Die sekundäre Osteoporose wird durch eine Grunderkrankung, Vitamin- und Mineralstoffmangel oder bestimmte Medikamente verursacht.

infolge Krankenhausaufenthalte, Pflegeheimunterbringung und auch Sterblichkeit

Frakturen infolge von Osteoporose werden als Fragilitätsfrakturen bezeichnet. Personen, die bereits eine Fragilitätsfraktur erlitten haben, haben ein fünfmal höheres Risiko, innerhalb der nächsten zwei Jahre eine zweite Fraktur zu erleiden. Diese Fragilitätsfrakturen führen zu Behinderungen, Krankenhausaufenthalten, Pflegeheimunterbringung und Sterblichkeit.

Beschreibung der Technologie

Verfahren AGN1 LOEP: Injizierung eines Biomaterials auf Kalziumbasis (AGN1) in betroffenen Bereich (Hüfte)

OSSURE® Local Osteo-Enhancement Procedure (LOEP®) ist ein minimalinvasives chirurgisches Verfahren, das von AgNovos Healthcare (Rockville, Maryland, USA) entwickelt wurde. Es beinhaltet die Injizierung eines Biomaterials auf Kalziumbasis (AGN1) in jenen Bereich mit osteoporotischem Knochenverlust, wo es – laut Hersteller – sofort für Festigkeit sorgt. Als natürlicher Prozess der Knochenheilung – wie bei einer Fraktur – ist ein erster Schritt eine Entzündungsreaktion, gefolgt von einer Resorption des Knochens. Das angestrebte Ergebnis ist eine erhöhte Knochenfestigkeit und die Vermeidung von Fragilitätsfrakturen. AGN1 LOEP wird einmalig verabreicht und ist minimalinvasiv. Alle Komponenten, die zur Durchführung des Verfahrens erforderlich sind, werden in einem Einweg-Kit bereitgestellt.

Europa CE-mark: 2017 USA: FDA Breakthrough Device Designation 2020

OSSURE LOEP ist in Europa mit dem CE-Kennzeichen (im Jahr 2017) für Knochenneubildung bei Indikationen der Hüfte, Becken und Extremitäten zugelassen. In den USA hat die Food and Drug Administration (FDA) OSSURE LOEP 2020 eine Breakthrough Device Designation zur Behandlung stabiler vertebraler Kompressionsfrakturen erteilt.

Aktuelle klinische Leitlinien zum Management der Osteoporose empfehlen Lebensstiländerungen (Ernährung und Bewegung), Vitamin D Supplementierung und pharmakologische Interventionen (Bisphosphonate). Die Wirksamkeit dieser konservativen Behandlungsmaßnahmen zur Vorbeugung von Hüftfrakturen ist jedoch Berichten zufolge aufgrund der schlechten Compliance gering.

Komparator: Lebensstiländerungen (Ernährung und Bewegung), Vit D, Bisphosphonate

Methoden

Folgende Forschungsfragen sollen in dem systematischen Review beantwortet werden:

Forschungsfrage: Wirksamkeit und Sicherheit von AGN1 LOEP

- Ist AGN1 LOEP bei Patient*innen mit Osteoporose effektiver in Bezug auf Veränderungen der femoralen Knochenmineraldichte, Veränderungen der Femurfestigkeit, Veränderungen der Fragilitätsfrakturen und der gesundheitsbezogenen Lebensqualität im Vergleich zur konservativen Osteoporosebehandlung?
- Ist AGN1 LOEP bei Patient*innen mit Osteoporose hinsichtlich unerwünschter Ereignisse genauso sicher wie konservativen Osteoporosebehandlungen?

Zur Beantwortung der Forschungsfragen wurde eine systematische Literatursuche durchgeführt. Es wurden fünf Datenbanken (Medline, Embase, die Cochrane Library und die HTA Datenbanken vom Centre for Reviews and Dissemination(CRD) und INAHTA) am 1. Februar 2021 durchsucht. Zwei Autor*innen führten unabhängig voneinander die Studienauswahl, Datenextraktion und Qualitätsbeurteilung durch. Nach Deduplikation wurden 1.150 Zitate nach Titel und Abstract gescreent und schließlich wurden 9 Zitate eingeschlossen. Um laufende und unveröffentlichte Studien zu identifizieren, wurde außerdem eine Suche in drei Studienregistern (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) durchgeführt, die am 8. Februar 2021 zwei potenziell relevante Studien identifizierte.

Literatursuche in 5 Datenbanken

nach Deduplikation 1.150 Zitate davon 9 ausgewählt

Suche in 3 Studienregistern: 2 laufende Studien

Das Verzerrungsrisiko wurde mit dem Risk of Bias In Non-Randomized Studies – of Interventions (ROBINS-I; früher ACROBAT-NRSI) Tool bewertet. Darüberhinaus wurde eine Synthese der vorhandenen Evidenz nach der „Grading of Recommendations Assessment, Development and Evaluation“ Schema (GRADE) Methode durchgeführt. Alle Arbeitsschritte wurden von zwei Wissenschafter*innen durchgeführt.

RoB mit ROBINS-I

GRADE

Ergebnisse

Zu den Endpunkten, die als Evidenz für die Ableitung einer Empfehlung zur relativen Wirksamkeit von AGN1 LOEP herangezogen wurden, gehörten: Fragilitätsfrakturen der Hüfte, Veränderung der Knochenmineraldichte (aBMD) des Schenkelhalses und die mittels Finite-Elemente-Analyse (FEA) eingeschätzte Femurfestigkeit.

Wirksamkeits-Endpunkte

Verfahrensbedingte unerwünschte Ereignisse und Komplikationen wurden für die Ableitung einer Empfehlung zur relativen Sicherheit von AGN1 LOEP herangezogen.

Sicherheits-Endpunkte

Verfügbare Evidenz

1 prosp. Studie mit 12 postmenopausalen Frauen, Intervention an linker Hüfte, Kontrolle an rechter Hüfte 1st-in-human Studie

Die Literatursuche identifizierte eine prospektive Kohortenstudie, die AGN1 LOEP mit keiner Behandlung verglich: die Studie schloss 12 osteoporotische postmenopausale Frauen ohne vorherige Hüftfraktur ein. Jede Patientin erhielt eine AGN1 LOEP-Augmentation des linken proximalen Femurs, während der rechte proximale Femur als unbehandelte Kontrolle diente.

Diese Studie ist die 1st In-Human-Studie zu diesem Verfahren.

Klinische Wirksamkeit

aBMD und Femurfestigkeit signifikant höher zu allen Messzeitpunkten, aber 3 Fragilitätsfrakturen: 1 x in Interventionshüfte, 2 x in Kontrollhüfte

Die Knochenmineraldichte (aBMD) in den mit AGN1 LOEP behandelten Femurhälsen stieg vom Ausgangswert an und blieb zu allen Nachuntersuchungszeitpunkten (12 Monate bis zu 5-7 Jahren; $p<0,001$) signifikant höher als bei den unbehandelten Femurhälsen. Ebenso war die Femurfestigkeit der behandelten Hüften zu allen Nachuntersuchungszeitpunkten (12 Wochen bis zu 5-7 Jahren; $p<0,01$) signifikant höher als in den unbehandelten Hüften. Allerdings gab es unter den Teilnehmerinnen drei Fragilitäts-Hüftfrakturen nach der Behandlung; zwei traten in unbehandelten Hüften und eine in einer behandelten Hüfte auf.

Sicherheit

keine SAE 3 AE: geringfügig

Es wurden keine schwerwiegenden Verfahrens- oder Interventions-bezogene Sicherheitsprobleme dokumentiert. Zu den drei geringfügigen unerwünschten Ereignissen gehörten Reizungen an der Einstichstelle und postoperative Übelkeit. Alle unerwünschten Ereignisse waren geringfügig und klangen ohne zusätzliche medizinische Intervention ab.

Laufende Studien

2 einarmige Studien im Laufen

Es konnten zwei laufende klinische Studien identifiziert werden, die die Wirksamkeit und Sicherheit von AGN1 LOEP bei der Prävention und Behandlung osteoporotischer Hüftfrakturen untersuchen. Beide Studien sind einarmig und rekrutieren jeweils 60 Patient*innen. Die Studien sollen im Mai 2021 bzw. im Dezember 2025 abgeschlossen werden.

Diskussion und Fazit

1 Studie mit 12 Pts zeigt signifikant verbesserte Ergebnisse im Vergleich zum Ausgangswert bei Knochendichte und Femurfestigkeit aber: 1 Fraktur trotz präventiver Behandlung

Die Ergebnisse einer prospektiven Kohortenstudie, in der die Wirksamkeit von AGN1 LOEP mit keiner Behandlung bei postmenopausalen Frauen ohne vorherige Hüftfraktur verglichen wurde, zeigten, dass AGN1 LOEP die aBMD des Oberschenkelhalses und die Femurfestigkeit im Vergleich zu keiner Behandlung signifikant erhöhte. Diese Ergebnisse wurden von 12 Monaten (als das AGN1 LOEP vollständig resorbiert war) bis zum erweiterten Follow-up von 5-7 Jahren nach der Behandlung beobachtet. Frakturen wurden in diesem Zeitraum an einer mit AGN1 LOEP behandelten Hüfte und zwei unbehandelten Hüften beobachtet. Es wurden drei leichte unerwünschte Ereignisse berichtet, die mit dem Verfahren in Zusammenhang standen, und alle ohne zusätzliche medizinische Intervention abklangen.

Qualität der Evidenz (GRADE): sehr niedrig

Gemäß GRADE (Grading of Recommendations Assessment, Development and Evaluation) war die Qualität der Evidenz für alle berichteten Outcomes sehr niedrig. Die wichtigsten Einschränkungen der Evidenzbasis bestanden aus dem Umstand, dass es sich um eine Studie mit einem ernsthaften Risiko für Verzerrungen und einer kleinen Stichprobengröße handelte.

Ein spezifischer Bereich der Verzerrung betraf die Hälfte der in die Studie eingeschlossenen Patientinnen, die pharmakologische Behandlungen für Osteoporose erhielten. Da sie als ihre eigene Kontrolle dienten, wobei eine Hüfte das AGN1 LOEP und die andere Hüfte keine Behandlung erhielt, könnte dies zu einem Risiko der Verzerrung gegen AGN1 LOEP führen. Die Effektgröße (beobachteter Unterschied zwischen der unbehandelten Hüfte und der mit AGN1 LOEP behandelten Hüfte) könnte aufgrund dieser Verzerrung größer sein als die in dieser Studie beobachtete.

Verzerrungsrisiko: Ko-Medikation bei 50% der Pts. ev. größerer Effekt

Die Validität eines Anstiegs der Knochendichte (BMD) des Schenkelhalses und der Femurfestigkeit (durch FEA bestimmt) infolge von AGN1 LOEP als Surrogate für eine Verringerung des Frakturrisikos ist ungewiss. Die BMD berücksichtigt nicht die Knochenqualität: daher kann von einer Erhöhung der BMD (aufgrund einer Intervention) nicht unbedingt eine Verringerung von Frakturen abgeleitet werden. Die Fragilitätsfrakturraten aus der eingeschlossenen Studie allein sind nicht ausreichend, um daraus zu schließen, ob AGN1 LOEP das Auftreten von Frakturen reduziert.

Surrogat-Endpunkte valide für Ableitung der Verringerung des Frakturrisikos ?

Außerdem war die eingeschlossene Studie nur für eine der beiden angegebenen Populationen relevant – Patient*innen ohne vorherige osteoporotische Hüftfraktur (elektive Anwendung). Die Übersichtsarbeit identifizierte keine Evidenz zur Anwendung von AGN1 LOEP bei Patient*innen mit einer frischen osteoporotischen Hüftfraktur. Zudem bezieht sich die Evidenz explizit auf kaukasische postmenopausale Frauen. Die Anwendbarkeit auf andere Geschlechter, Ethnien und Bevölkerungsgruppen und prämenopausale Frauen mit Osteoporose ist unbekannt.

nur 1 von 2 potentiellen Patientenpopulationen untersucht – zur Prävention, nicht aber Therapie

AGN1 LOEP wurde nicht mit den derzeit empfohlenen Behandlungsmodalitäten für Osteoporose (Diät- und Lebensstilmodifikationen und/oder pharmakologische Therapie) verglichen. Daher ist die in dieser Übersichtsarbeit präsentierte Evidenz nicht ausreichend, um zu bestimmen, ob AGN1 LOEP genauso sicher oder effektiver als diese Behandlungen in der Prävention von Frakturen ist.

keine Vergleichsgruppe

Evidenz nicht ausreichend

Empfehlung

Die in dieser Übersichtsarbeit präsentierte Evidenz reicht nicht aus, um Aussagen zu machen, ob AGN1 LOEP so sicher oder effektiv ist wie konservative Behandlungen in der Prävention von Frakturen ist. Zur Indikation der Behandlung der Osteoporose liegen gar keine Daten vor. Die Implementierung von AGN1 LOEP wird derzeit nicht empfohlen. Die Intervention befindet sich in einem frühen Stadium der klinischen Umsetzung mit einer zu geringen Datenlage. Eine Neubewertung wird erst empfohlen, wenn belastbare Daten aus RCTs vorliegen. Solche RCTs sind bisher nicht registriert.

Evidenz für Prävention: unzureichend
Evidenz für Behandlung: nicht vorhanden
Technologie in frühem Stadium

1 Background

1.1 Overview of the disease, health condition and target population[1]

Osteoporosis[2] is a chronic, progressive disease characterised by a reduction in bone mineral density (BMD) due to an imbalance between bone resorption and bone formation[1] [2]. As a result of reduced BMD, the bones in individuals with osteoporosis gradually become thinner and weaker and have an increased susceptibility to fracture [3].

Osteoporose: Reduktion der Knochendichte führt zu Anfälligkeit für Brüche

The most relevant International Classification of Disease (ICD)-10 codes for this application are:

ICD-10:

- M80.05 – Age-related osteoporosis with current pathological fracture, femur
- M81.0 – Age-related osteoporosis without current pathological fracture
- M81.8 – Other osteoporosis without current pathological fracture
- M80.85 – Other osteoporosis with current pathological fracture, femur

M80.05
M81.0
M81.8
M80.85

Osteoporosis can occur in both sexes, all races and all age groups [4]. There are two categories of osteoporosis: primary and secondary. Primary osteoporosis is related to the change in gonadal function that occurs with aging and its effect on bone resorption and formation. It includes postmenopausal (type I osteoporosis) and senile osteoporosis (type II osteoporosis). Postmenopausal or type I osteoporosis is the most frequently recognised form of osteoporosis and is associated with increased bone resorption in women following menopause due to the loss of oestrogen. Senile or Type II osteoporosis can occur in women and men, although women are twice as likely to suffer it than men [5]. It results from gradual age-related bone loss whereby, after the third decade of life, bone resorption exceeds formation [6]. Secondary osteoporosis is caused by an underlying disease, vitamin and mineral deficiency or certain drugs [2].

primäre und sekundäre Osteoporose

primäre:
postmenopausal (Typ1)
senile (Typ2)

sekundäre:
Grunderkrankung

Frauen häufiger betroffen

There are several risk factors for osteoporosis: factors that affect an individual's risk of developing osteoporosis include[3]:

Risikofaktoren:

- age (the incidence increases with age, >50 years)
- gender (the risk is greater for females)
- early menopause (before the age of 45 years), late menarche
- body size (slender, thin boned women are at greater risk)
- ethnicity (Caucasian or Asian ethnicity are at highest risk)
- a family history of osteoporosis
- diet (a diet low in calcium and vitamin D, excessive dieting or inadequate protein intake, calcium or vitamin D deficiency)

Alter
Geschlecht
frühe Menopause
Körpergröße
Ethnie

Ernährung
Lebensstil

---

[1] This section addresses the EUnetHTA Core Model® domain CUR.

[2] A0001 – For which health conditions, and for what purposes is the technology used?; A0002 – What is the disease or health condition in the scope of this assessment?

[3] A0003 – What are the known risk factors for osteoporosis?

Medikamentierungen Grunderkrankungen

- certain medical conditions, including thyroid disease or an overactive thyroid gland, rheumatoid arthritis, chronic liver and kidney disease [7], conditions that affect metabolism and the body's ability to absorb nutrients, such as coeliac disease, Crohn's disease and other inflammatory bowel conditions [2]
- medications (use of anticonvulsants, systemic steroids such as corticosteroids for rheumatoid arthritis, asthma and other conditions [8], thyroid supplement, heparin, insulin, chemotherapy agents)
- lifestyle (factors that contribute to bone loss include low levels of physical activity, excessive alcohol consumption and smoking) [4]

Knochenumbau ist lebenslang ablaufender Prozess

wenn Verlust größer ist als Aufbau: Anfälligkeit für Frakturen

Hüfte Wirbelsäule Handgelenk

Bone remodelling[4] occurs continuously during an individual's life, with new bone formation occurring after bone resorption. This remodelling occurs at discrete sites within the skeleton. Osteoporosis results from an imbalance in bone remodelling, where the rate of bone loss is greater than bone formation [2]. Without intervention to correct this imbalance, bones become weaker and more susceptible to fracture, typically the bones of the hip, vertebrae and wrist [4]. Individuals who have already suffered one osteoporotic fracture are at increased risk for developing additional osteoporotic fractures [2]. The reduction in BMD caused by osteoporosis generally occurs without symptoms, and thus, the disease is not usually diagnosed until a bone is fractured or one or more of the vertebrae collapse [9]. Fractures resulting from osteoporosis can occur in any bone but typically occur in bones of the hip, vertebrae and wrist [4]. Fractures at the hip and vertebrae are the most common and serious sites [10].

sog. Fragilitätsbrüche (unter Alltagsbedingungen, nicht Trauma)

Hospitalisierungen, Pflegebedarf

Fractures resulting from osteoporosis are termed fragility fractures as they result from mechanical forces that would not normally result in fracture. The World Health Organisation (WHO) has quantified this as forces equivalent to a fall from standing height or less [11]. Individuals who have already suffered a fragility fracture are five times more likely to experience a second fracture within the next two years [12]. These fragility fractures result in disability, hospitalisation, nursing home placement and mortality. The United Kingdom (UK) guidelines on osteoporosis note that approximately 53% of patients suffering a hip fracture can no longer live independently, and 28.7% die within 12 months of the fracture. They further note that only 54% of individuals admitted from home with a hip fracture return home within 30 days [13].

Konsequenz für Individuen: Verlust der Unabhängigkeit und Mobilität

Fractures resulting from osteoporosis have a significant impact on affected individuals' physical and mental health and quality of life[5]. Fractures can lead to reduced independence. One year after a hip fracture, 40% of individuals cannot walk independently, and 80% are restricted in other activities [12]. As a result of reduced mobility, individuals may rely on family and friends to care for them, placing stress on both the carer and the individual with osteoporosis [12]. Fractures of the hip are the most severe osteoporotic fracture and almost always lead to hospitalisation [15]. Many individuals do not rehabilitate completely following a hip fracture and so are placed in nursing homes [16]. Fractures are associated with increased mortality. Approximately 28.7% of patients with a hip fracture die within 12 months post fracture [13].

[4] A0004 – What is the natural course of osteoporosis?

[5] A0005 – What is the burden of disease for patients with osteoporosis?

In addition to having a significant impact on affected individuals' quality of life, fractures caused by osteoporosis have a major economic impact on society[6]. In 2017, the estimated costs associated with osteoporotic fracture across six European countries (France, Germany, Italy, Spain, Sweden and the UK) were € 37.5 billion and will increase to € 47.4 billion by 2030. Healthcare costs are highest with hip fractures, as this is the most severe fracture site [12].

Konsequenz für Gesellschaft: hohe Folgekosten

According to the Austrian Osteoporosis Guidelines the prevalence[7] of osteoporosis in Austria among people 50+ years of age was 460,000 (370,000 female vs 90,000 male) in 2010 [15]. One epidemiological study calculated the prevalence of osteoporosis in Austria based on current prevalence of the condition in Germany [18]. This study estimated the prevalence of osteoporosis in Austria to be approximately 740,000 of over 50-year olds in 2010, of whom around 617,000 are women. Further, more recent figures from an Austrian hospital website confirms the number of people with osteoporosis to be around 800,000, with around 14,000 patients suffering a hip fracture every year [19]. The incidence of proximal femoral fractures in this same population is reported to be one of the highest in the world after Denmark and Sweden. In 2008, 16,000 osteoporotic proximal femoral fractures were registered in Austria, corresponding to an age-standardised incidence of 605 per 100,000 women and 261 per 100,000 men [14]. In Austria, the economic burden resulting from osteoporotic fractures was estimated at € 685.2 million in 2008. Most of these costs were related to family care (30.2%) and hospitalisation (26.6%) [17].

Prävalenz in Ö: 800.000

Inzidenz: 14.000-16.000 Hüftfrakturen p.a.

There are two populations for this assessment[8] on AGN1 LOEP, a minimally invasive procedure used for the treatment of bone loss caused by osteoporosis:

2 Patient*innen-Population für Technologie (AGN1 LOEP) in diesem Assessment:

1. Patients without a current pathological fracture due to osteoporosis but who have had a previously treated fracture in the hip or at another site are at an increased risk of a hip fracture (either unilateral or bilateral). The intervention in this population aims to prevent bone loss and increase bone density and strength in the femoral neck, reducing the risk of a hip fracture. Treatment of this population is considered elective.

Pts, die bereits (Hüft-) Fraktur hatten und hohes Risiko auf weitere Frakturen

2. Patients who have a current osteoporotic hip fracture. The intervention in this population aims to treat the fractured site to prevent another femoral neck fracture in the same location. Further to treat the contralateral hip to avoid a fracture there. Treatment of this population is considered non-elective.

Pts, die aktuell Hüftfraktur haben zu Behandlung, aber auch Prävention bei kontralateraler Hüfte

6 A0006 – What are the consequences of osteoporosis for the society?

7 A0023 – How many people belong to the target population?

8 A0007 – What is the target population in this assessment?

1.2 Current clinical practice[9]

Diagnostik von Osteoporose:

Knochendichtemessung mit DXA

European guidance on diagnosis and management of osteoporosis[10] in postmenopausal women recommends that osteoporosis is diagnosed based on BMD as assessed by dual-energy X-ray absorptiometry (DXA) at the femoral neck or spine. This is based on the relationship between fracture risk and BMD. An individual with a BMD value that is 2.5 standard deviations (SD) or more below the mean BMD of a young female adult is classified as having osteoporosis (T-score equal or less than -2.5) [16]. The Endocrine Society Clinical Guidelines on osteoporosis in men also recommend that men be assessed for osteoporosis based on DXA measurement of BMD in the spine and hip [20]. The same cut-off value used for diagnosis of osteoporosis in women is also used for diagnosis of osteoporosis in men (a value of 2.5 SD or more below the average for young adult women) [13].

Management von Osteoporose:

Management of osteoporosis[11], as occurs in practice and as recommended by recent UK and European guidelines, is through dietary and lifestyle modifications as well as pharmacological interventions as follows:

Lebensstilmodifikationen: Bewegung und Ernährung Vit D Supplementierung

- **Exercise:** Exercise, especially weight-bearing exercise, is advised to increase BMD. This should be tailored to individuals need and abilities [13, 16].
- **Nutrition:** An adequate supply of calcium and vitamin D is important for maintaining BMD. A daily calcium intake of 700 to 1,200 mg is advised. This is ideally achieved through diet, but supplements may be necessary. Those postmenopausal women and older men (≥ 50 years) at a higher risk of fracture are advised a daily dose of 800 IU cholecalciferol (vitamin D). In postmenopausal women and older men receiving bone-protective therapy for osteoporosis, calcium supplementation is advised if dietary intake is low (below 700 mg/day). Vitamin D supplementation should also be considered in those at risk, or with evidence, of deficiency [13].

pharmakologische Interventionen:

orale Bisphosphonate

- **Pharmacological intervention:** Several types of pharmacological agents have been evaluated for osteoporosis. In postmenopausal women and men with osteoporosis, the oral bisphosphonates alendronate or risedronate are considered first-line treatments. In women and men who are intolerant or contraindicated to these, intravenous bisphosphonates or denosumab are recommended [13, 16]. In men, zoledronic acid or teriparatide is an additional option, while in postmenopausal women, raloxifene or hormone replacement therapy are additional options [13]. Women and men ≥70 years, with a previous fragility fracture or taking high doses of glucocorticoids (≥7.5 mg/day prednisolone) should be considered for bone protective therapy bisphosphonates alendronate and risedronate considered first-line options. Bone protective therapy may also be considered appropriate in some premenopausal women and younger men, particularly individuals with a previous fracture history or those receiving high doses of glucocorticoids [13].

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[9] This section addresses the EUnetHTA Core Model® domain CUR.

[10] A0024 – How is osteoporosis currently diagnosed according to published guidelines and in practice?

[11] A0025 – How is osteoporosis currently managed according to published guidelines and in practice?

1.3 Features of the intervention[12]

OSSURE Local Osteo-Enhancement Procedure (LOEP) (AgNovos Healthcare)[13] is a treatment aimed at preventing osteoporotic fractures. It involves injecting a triphasic, resorbable material consisting of calcium sulphate, brushite and β-tricalcium phosphate (AGN1) into osteoporotic bone. The implant material, which sets *in situ*, is designed to provide immediate strengthening of the bone. The brushite provides structural integrity to the implant material as it resorbs whilst the β-tricalcium phosphate, present as granules throughout the implant material, provides sites for new bone formation to improve bone density and strength and thus reduce fracture risk [21].

OSSURE = Local Osteo-Enhancement Procedure (LOEP)

einmalige lokale Injizierung von Implantatmaterial

As claimed by the manufacturer[14], the benefits of this product in comparison to dietary and lifestyle modifications as well as pharmacological therapy are:

- higher patient compliance [32]
- immediate bone strengthening and thus an immediate reduction in fracture risk [33]
- a single treatment involving a minimally invasive procedure [22].

Material ist Kalzium-basiert, resorbierbar, dreiphasig (AGN1)

minimal-invasiv

AGN1 LOEP involves a single treatment, it is minimally invasive, it provides immediate strengthening and the product gets resorbed and is replaced with new bone [22]. All the components necessary to perform the procedure are provided in a single-use kit [23]. Details regarding the procedure or the context of care were identified in the manufacturer's documents [24].

According to the applicant's proposal, no patients were treated with AGN1 LOEP in Austria so far[15]. Their estimated annual utilisation of this product in Austria is 500 treatments per year. However, based on the number of osteoporotic patients suffering a hip fracture each year (14, 000, as reported by an Austrian hospital website), the number of patients eligible for the AGN1 LOEP procedure could be much higher [19]. Further, this figure only pertains to population two outlined in chapter 1.1 (patients with a current osteoporotic hip fracture). It does not consider the number of patients from population one (patients without a current fracture but at increased risk due to having previously experienced a fracture in the contralateral hip or other areas) who would also be eligible for treatment.

bislang keine Anwendungen in Ö

aber hohe potentielle Nutzung der Technologie insb. bei Risikopatient*innen

For treatment, the patient is placed in the supine position with their femoral neck parallel to the floor [1, 23]. Patients are treated under local or general anaesthesia, laryngeal mask airway or short-acting spinal anaesthesia (personal communication, B. Huber, AgNovos Healthcare). Following anaesthesia, a 1-2 cm incision is made to access the proximal lateral femoral cortex, just below the trochanter. Under fluoroscopic guidance, a 2.5 mm guide pin is inserted into the apex of the femoral neck. Using the guide pin, a 5.3 mm cannulated drill accesses the site to be treated [1]. The treatment (or enhancement) site is divided into three zones: the proximal or apex zone (where the probe debrider stops), the mid or tubular zone (usually devoid of significant structural bone) and the funnel zone (between the greater and lesser trochan-

Patient*in Rückenlage Lokalanästhesie unter Fluoroskopie

Einführung der Injektionsnadel zum Schenkelhals

[12] This section addresses the EUnetHTA Core Model® domain TEC.

[13] B0001 – What is AGN1 LOEP?

[14] B0002 – What is the claimed benefit of AGN1 LOEP in relation to its conservative management comparators?

[15] A0011 – How much is AGN1 LOEP utilised?

ters and the proximal femoral canal) [23]. The enhancement site is debrided, irrigated with saline, and then aspirated to remove fat and other loose non-structural elements; a minimum of two full suction and irrigation cycles is used [1, 23].

AGN1 Implantatmaterial muss sofort verwendet werden (innerhalb von 5 Min nach Anmischung)

Volumen: 19 ± 2 cm³

The AGN1 implant material is prepared by combining its powder and liquid components. As the curing process begins immediately, premixing is not possible. The manufacturer advises the mixing process should take no longer than 90 seconds, and injection of the implant material should be completed ideally within 5 minutes of mixing [23]. Under fluoroscopic guidance, the prepared AGN1 is injected to fill the enhancement site, starting from the apex. It completely sets within 60 minutes after mixing. The injection cannula is removed, and the incision site closed [23]. The average volume of AGN1 injected per patient is 19 ± 2 cm^3 (range 15 to 22 cm^3). Howe et al. noted that patients could fully weight bear within four hours of the procedure, following recovery from anaesthesia [1].

orthopädischer Eingriff stationäre Aufnahme notwendig

An orthopaedic surgeon should carry out the AGN1 LOEP procedure in a sterile surgical theatre under anaesthesia [24][16, 17]. The type of anaesthesia may vary depending on the patient. Post-surgery care will require nurses and physiotherapists. Weight-bearing activity, which will commence approximately four hours after the surgery, may require a gym [1]. The applicant states that the procedure should be performed on a full inpatient basis.

notwendige Ausstattung an Medizinprodukten für AGN1 LOEP Verfahren

The OSSURE AGN1 LOEP kit includes the below elements[18]: Scalpel, Serrated tissue protector with cantering obturator, 2.5 mm guide pin, 5.3 mm cannulated drill, Working trough (2X), Blunt probe debrider, Suction/irrigator, Syringe for irrigation, Vacuum hose clamp, Injection cannula, Foil pouch with powder component container, Delivery syringes (2X), Mixer, Threaded extruder, Liquid components vial. Other required equipment not included in the kit includes a vacuum line, sterile saline, and a saline vessel. Further, the 2.5 mm guide pin provided requires a 2.5 mm-compatible pin collet chuck, and the 5.3 mm cannulated drill provided requires a 6.35 mm chuck [24]. The procedure also requires C-arm Fluoroscopy for guidance during the procedure [24].

2017 CE-Zertifizierung 2020 FDA Breakthrough Device Designation

OSSURE LOEP is CE-marked[19] (in 2017) for forming new bone in voids in the skeletal system with intended use in the hip, pelvis and extremities (personal communication, B. Huber, AgNovos Healthcare)[25]. In the United States, the Food and Drug Administration (FDA) has granted OSSURE LOEP Breakthrough Device Designation in 2020 to treat stable vertebral compression fractures [26, 27].

AGN1 LOEP völlig neue Technologie; andere Materialien wurden erprobt, aber waren nicht erfolgreich

The AGN1 LOEP procedure is a new treatment for increasing bone strength and reducing fracture risk in osteoporotic patients. Current treatments for reducing fracture risk include dietary and lifestyle modification and a range of pharmaceutical agents. While femoral bone augmentation using other non-resorbable agents (e.g. polymethylmethacrylate and silicone) has been inves-

16 B0004 – Who administers AGN1 LOEP and conservative management, and in what context and level of care are they provided?

17 B0008 – What kind of special premises are needed to use AGN1 LOEP and conservative management?;

18 B0009 – What supplies are needed to use AGN1 LOEP and conservative management?

19 A0020 – For which indications has AGN1 LOEP received marketing authorisation or CE marking?

tigated [21, 28], these treatments have not been clinically adopted due to inherent limitations, including the invasiveness of these treatments, safety issues and short-term effectiveness. [21].

sehr frühes Stadium der Einführung der Technologie: nur 1 klinische Studie mit 12 Patient*innen

To date, there is only one published in-human study that has investigated the effectiveness and safety of AGNI1 LOEP in 12 postmenopausal women with osteoporosis [1][20]. Dietary and lifestyle modifications and pharmacological agents have been recommended for osteoporosis patients by multiple evidence-based clinical guidelines in various countries [13, 16, 34][21]. The most common dietary and lifestyle modifications recommended by these guidelines are an increase in dietary intake of calcium and vitamin D and the promotion of exercise, especially weight-bearing activities. The most common pharmacological agents recommended by these guidelines are bisphosphonates, anabolic therapy, denosumab, selective oestrogen receptor modulators, and hormonal therapy.

Komparatoren wie Lebensstiländerungen (Bewegung, Ernährung) und

Vit D Supplementierung

in zahlreichen Leitlinien empfohlen

Dietary and lifestyle modification: Foods rich in calcium (including dairy products and green leafy vegetables) and vitamin D (from the sun and some foods) are essential in improving and maintaining bone health. People with osteoporosis will be advised to increase their intake of calcium and vitamin D (sun) exposure or to take dietary supplements. Exercise, particularly weight-bearing, is also vital for bone health. As well as maintaining a healthy weight, it is recommended to avoid smoking and limit the consumption of alcohol [29].

Arzneimitteltherapien:

Pharmaceutical agents: Several pharmacological agents are currently used to manage osteoporosis; they can be divided into antiresorptive and anabolic agents:

- **Antiresorptive agents:** These help to reduce bone loss, thereby slowing disease progression. This is achieved by inhibiting bone degeneration and promoting bone formation [30]. These agents include oral or intravenous bisphosphonates (such as alendronate and risodronte (oral) and zoledronate (intravenous)) as well as oestrogen replacement and selective oestrogen receptor modulators (such as oestrogen progestins, raloxifene, lasofoxifene and bazedoxifene) or denosumab, a human monoclonal antibody.

  Antiresorptive Therapie zur Verlangsamung des Abbaus der Knochendichte

  und

- **Anabolic agents:** These stimulate bone formation, improving bone quality and mass [31]. These agents include teriparatide, abaloparatide and romosozumab.

  Anabolische Therapie zur Stimulierung von Knochenaufbau

sequentielle oder Kombinationstherapien

Sequential or combination therapy describes the consecutive use (e.g. antiresorptive agent use following anabolic therapy) or joint use of these agents to increase BMD.

Currently, the procedure with AGNI1 LOEP is not included in the hospital benefit catalogue.[22] Pharmaceutical therapies are included in the drug benefit catalogue of the Austrian social insurances.

[20] B0003 – What is the phase of development and implementation of AGN1 LOEP and conservative management?

[21] B0001 – What is AGN1 LOEP and its comparators (dietary and lifesyle modification and pharmaceutical agents)?

[22] A0021 – What is the reimbursement status of AGN1 LOEP?

2 Objectives and Scope

2.1 PICO question

PIKO-Frage

In patients with osteoporosis, is AGN1 LOEP more effective concerning changes in femoral bone mineral density, changes in femoral strength, changes in fragility fractures and health-related quality of life, compared with standard osteoporotic management?

In patients with osteoporosis, is AGN1 LOEP as safe with respect to ad-verse events compared standard osteoporotic management?

2.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Table 2-1 provides a summary of the criteria for the inclusion of relevant studies.

Table 2-1: Inclusion criteria

Population	Patients with osteoporosis. Two osteoporotic populations are relevant to this PICO: ■ *Patients without a current pathological fracture* due to osteoporosis but who have had a previously treated fracture in the hip or at another site are *at an increased risk* of a hip fracture (either unilateral or bilateral). The intervention in this population aims to prevent bone loss and increase bone density and strength in the femoral neck, reducing the risk of a hip fracture. Treatment of this population is considered *elective*. ■ For *patients who have a current osteoporotic hip fracture*, the intervention aims to treat the current fracture and prevent future fractures in the same location. Further, the *contralateral hip* is treated to prevent a fracture in that location. Treatment of this population is considered *non-elective*. **Intended use of the technology:** Prevention and treatment of osteoporosis-related hip fractures. **Contraindications:** patients with ■ severe vascular or neurological disease, ■ uncontrolled diabetes, ■ severe degenerative bone disease, ■ hypercalcaemia, ■ pregnancy, ■ penal compromised patients, ■ a history of Pott's Disease, ■ who cannot/will not follow postoperative instructions (including those who abuse drugs and/or alcohol) [24]. **ICD-10 codes:** M80.05 – Age-related osteoporosis with current pathological fracture, femur; M81.0 – Age-related osteoporosis without current pathological fracture; M81.8 – Other osteoporosis without current pathological fracture; M80.85 – Other osteoporosis with current pathological fracture, femur **MeSH terms:** Osteoporosis, Femur, Hip, Osteoblast, Osteoclast **Rationale:** International guidelines on the recommended use of AGN1 are not currently available. Therefore, the population has been defined based on the suggested indications in the reimbursement application.

Intervention	OSSURE Local Osteo-Enhancement Procedure (LOEP) (AgNovos Healthcare) [21] **Contraindications:** OSSURE is contraindicated for use in articulating surfaces or for structural support in load-bearing bones instead of hardware, in closed voids/gaps capable of over-pressurisation during injection and spinal applications [24]. **MeSH term:** none identified
Control	Dietary and lifestyle modifications: Vitamin D and calcium supplementation, regular weight-bearing exercise. Pharmacological agents: bisphosphonates, anabolic therapy, denosumab, hormone therapy. Other comparators include no treatment or placebo. **MeSH terms:** diphosphonates, denosumab, oestrogen replacement therapy, selective oestrogen receptor modulators, cholecalciferol, calcium, alendronate, raloxifene hydrochloride, teriparatide* **Rationale:** Dietary and lifestyle modifications and pharmacological agents are recommended interventions for patients with osteoporosis to strengthen bones and prevent further fractures in several guidelines and guidance documents on osteoporosis including European, UK and Austrian.
Outcomes	
Efficacy	**Primary endpoints** ■ Hip fragility fractures ■ Post-operative mobilisation ■ Health-related quality of life (HRQoL) **Surrogate endpoints** ■ Bone mineral density in the proximal femur ■ Bone turnover markers ■ Femoral strength measured through finite element analysis ■ Fracture risk†
Safety	■ Mortality ■ Surgical or device-related adverse events ■ Withdrawal due to treatment-related adverse events ■ Other adverse events (non-device related) ■ Fragility fractures at sites other than hip
Study design	
Efficacy	Randomised controlled trials Prospective non-randomised controlled trials In the absence of comparative evidence, prospective case series will be included **Excluded:** narrative reviews, letters to the editor, author response, case reports, retrospective case series, conference abstracts
Safety	Randomised controlled trials Prospective non-randomised controlled trials Prospective case-series (n≥40) **Excluded:** narrative reviews, letter to the editor, author response, case reports, retrospective case series, conference abstracts

Abbreviations: HRQoL = health-related quality of life; ICD = international classification of diseases; LOEP = local osteo-enhancement procedure; MeSH = medical subject heading; PICO = population, intervention, comparator, outcome.

*Notes: *The MeSH terms for the comparator were not included in our search as they narrowed the search results too much; †Calculated using: age, BMD, body weight, number of falls in the last year, and number of fractures after the age of 50 [35].*

3 Methods

3.1 Research questions

Forschungsfragen nach EUnetHTA

Assessment elements from the EUnetHTA Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to this assessment's specific objectives [56].

Table 3-1: Health problem and Current Use

Element ID	Research question
A0001	For which health conditions, and for what purposes is the technology used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0004	What is the natural course of the disease or health condition?
A0005	What is the burden of disease for the patients with the disease or health condition?
A0006	What are the consequences of the disease or health condition for the society?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are the technologies utilised?

Table 3-2: Description of the technology

Description of the technology	
Element ID	**Research question**
B0001	What is the technology and the comparator(s)?
A0020	For which indications has the technology received marketing authorisation or CE marking?
B0002	What is the claimed benefit of the technology in relation to the comparators?
B0003	What is the phase of development and implementation of the technology and the comparator(s)?
B0004	Who administers the technology and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use the technology and the comparator(s)?
B0009	What supplies are needed to use the technology and the comparator(s)?
A0021	What is the reimbursement status of the technology?

Table 3-3: Clinical Effectiveness

Element ID	Research question
D0001	What is the expected beneficial effect of the technology on mortality?
D0003	What is the effect of the technology on the mortality due to causes other than the target disease?
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0011	What is the effect of the technology on patients' body functions?
D0016	How does the use of technology affect activities of daily living?
D0012	What is the effect of the technology on generic health-related quality of life?
D0013	What is the effect of the technology on disease-specific quality of life?
D0017	Was the use of the technology worthwhile?

Table 3-4: Safety

Element ID	Research question
C0008	How safe is the technology in comparison to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying the technology?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?
C0007	Are the technology and comparator(s) associated with user-dependent harms?

3.2 Clinical effectiveness and safety

3.2.1 Systematic literature search

Suche in 5 Datenbanken

The systematic literature search was conducted on the 1st of February 2021 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- Centre for Reviews and Dissemination (CRD: DARE, NHS-EED, HTA)
- International Network of Agencies for Health Technology Assessment (INAHTA)

1.150 Zitate identifiziert

9 Zitate inkludiert

The systematic search was limited to articles published in English or German, with no date limit. After the removal of duplicates, 1,150 citations were screened by title and abstract. Finally 9 citations were included. The specific search strategy employed for each database can be found in the Appendix.

Suche in 3 Studienregistern

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 8th of February 2021 that identified two potentially relevant trials (see Appendix).

By hand-search, no additional citations could be identified.

3.2.2 Flow chart of study selection

Literaturauswahl: 1 Studie für qualitative Synthese eingeschlossen

Overall 1,425 hits were identified. The references were screened by two independent researchers (MK, MV) and in case of disagreement a third researcher was involved to solve the differences. The selection process is displayed in Figure 3-1.

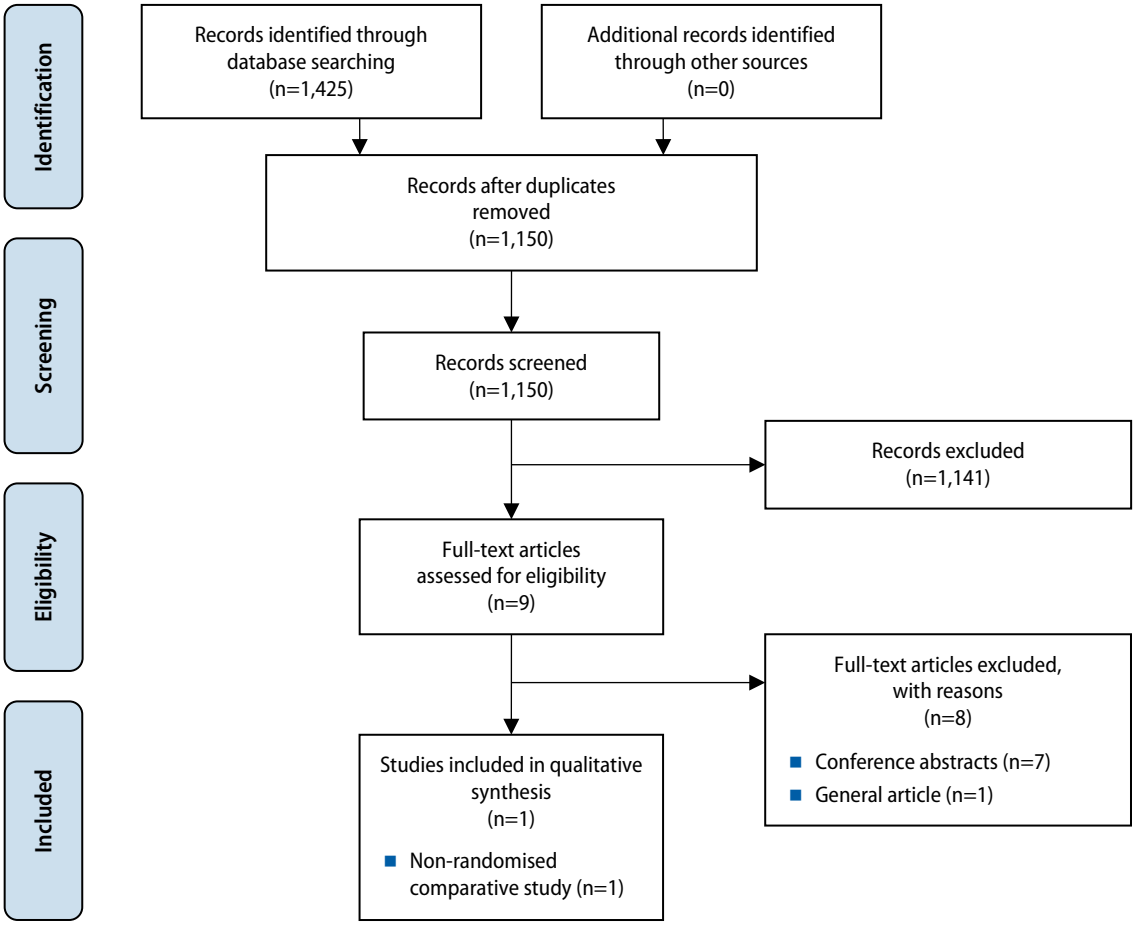

Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)

3.2.3 Analysis

RoB Assessment mit ROBINS-I

Quality was assessed using the Risk of Bias In Non-Randomized Studies – of Interventions (ROBINS-I; formerly the ACROBAT-NRSI) tool [36] (Table A-2).

Extraktion der Daten

Bewertung der Qualität der Evidenz mit GRADE

One reviewer systematically extracted relevant data from the included study into data extraction tables. A second reviewer cross-checked the data extraction tables with the data source and validated them for accuracy. As only one study was included in this review, further analysis of the data was not necessary. A reviewer analysed the quality of the data using GRADE [37], and a second reviewer validated the analysis for accuracy. Risk of bias was conducted by independent researchers and differences were settled via consensus.

3.2.4 Synthesis

nur qualitative Synthese der Evidenz

The questions were answered in plain text format with reference to GRADE evidence tables that are included in Appendix. Results were summarised in Table A-3. No quantitative analysis of outcomes was performed due to only one comparative trial being identified.

4 Results: Clinical effectiveness and Safety

4.1 Outcomes

4.1.1 Outcomes effectiveness

The following outcomes were defined as *crucial* to derive a recommendation:

entscheidende Endpunkte zur Beurteilung der Wirksamkeit:

- **Fragility fractures (hip):** Fragility fractures are the clinical outcome of osteoporosis [38]. Fractures harm patients' quality of life as they may result in significant pain, disability, loss of independence and increased risk of morbidity and mortality. Hip fractures in particular, are considered the most serious fragility fractures, almost always resulting in hospitalisation [38].

Fragilitätsbrüche an der Hüfte

- **Post-operative mobilisation:** AGN1 LOEP claims to result in faster and better mobilisation following femoral neck fracture treatment. Early post-operative mobilisation is commonly practiced to reduce post-operative complications, including thromboembolism, pneumonia, wound breakdown, pressure ulcers and delirium [39].

post-operative Mobilisation

- **Health-related quality of life (HRQoL):** osteoporosis and osteoporotic fractures have a substantial impact on a patient's quality of life. HRQoL is a patient-reported measure of a health condition's physical, mental, emotional and social impact [40]. The osteoporosis assessment questionnaire (OPAQ) is an HRQoL tool designed specifically for people with osteoporosis [41].

HRQoL

Additional *important* outcomes are:

weitere wichtige Endpunkte:

- **Bone mineral density (BMD) in the proximal femur:** BMD is measured by dual-energy x-ray absorptiometry (DXA). The X-ray beams' energy pass through the bones, and what is not absorbed is detected on the other side of the body – the denser the bones, the more energy that is absorbed. The radiation energy detected is converted into an areal density measured in g/cm [42]. BMD is an important outcome as it can measure bone strength and calculate fracture risk [43].

Knochendichte

- **Bone turnover markers (BTM):** BTMs measure the process of bone remodelling. The International Osteoporosis Foundation recommends the following reference markers for bone resorption (C-terminal telopeptide of type 1 collagen (CTX) and bone formation (procollagen type 1 N propeptide (P1NP) be reported in clinical trials [44].

Knochenumsatzmarker

- **Femoral strength:** A direct measurement of bone strength is not possible; therefore, strength is estimated from computed tomography (CT) imaging using finite element analysis (FEA) [45, 46]. In 2015, the International Society of Clinical Densitometry released a position paper stating that bone strength estimated by FEA can be used to predict fracture in postmenopausal women and elderly men, as well as to monitor age-related or treatment-related bone strength changes in the same populations [45].

Femurfestigkeit

- **Fracture risk:** Fracture risk is calculated using BMD scores and clinical factors to determine a patient's absolute fracture risk [47]. A common tool used to calculate fracture risk is the FRAX® fracture risk assessment tool which calculates a patient's 10-year probability of sus-

Frakturrisiko

taining an osteoporotic fracture [35]. In addition to BMD, the tool using the following factors to determine fracture risk: age, gender, body mass index, fracture history, smoking and alcohol use, glucocorticoid use, rheumatoid arthritis and secondary osteoporosis status [48].

4.1.2 Outcomes safety

entscheidende Endpunkte zur Beurteilung der Sicherheit:

Mortalität
Komplikationen und Nebenwirkungen

The following outcomes were defined as *crucial* to derive a recommendation:

- Mortality
- Surgical or device-related adverse events: These are any events related explicitly to AGN1 LOEP during or after its insertion.
- Withdrawal from the trial by patients due to adverse events relating to AGN1 LOEP
- Other adverse events (non-device related)
- Fragility fracture at a site other than the hip

4.2 Included studies

4.2.1 Included studies effectiveness

1 Studie (USA)

12 postmenopausale Frauen

= 1st-in-human-study/ proof-of-concept von AGN1 LOEP

Only one non-randomised comparative study met the predefined inclusion criteria, comparing AGN1 LOEP with no treatment [1]. This prospective cohort study conducted in the United States of America recruited 12 post-menopausal women diagnosed with osteoporosis. It is the first-in-human study of AGN1 LOEP. The authors noted that it was a proof-of-concept study designed to determine: 1) the initial and long-term safety of treating the proximal femur using AGN1 LOEP, 2) the rate and extent of resorption and replacement of AGN1 with new bone in the proximal femur, and 3) initial and long-term changes in proximal femoral aBMD and strength following AGN1 implantation [1].

Einschluss der Pts:
≥ 55 J (Ø 71,7 ± 10,1)
aBMD T-score > 2,5

Ko-Medikationen vor/während AGN1 LOEP:
6 Pts mit Bisphosphonaten
1 Pt mit HRT
FU Ø 6 Jahr

The study inclusion criteria included patient age ≥ 55 years and a femoral neck aBMD T-score of ≤-2.5 (as assessed by DXA). The authors note that one woman was admitted to the study with an aBMD T-score > 2.5. Patients were excluded if they had suffered a previous hip fracture, had creatine > 2.0 mg/100 mL or a glomerular filtration rate < 30 mL/min. The post-menopausal women were all Caucasian with an average age of 71.7 ± SD 10.1 years (range of 56 to 89 years). Pharmacological management of osteoporosis was not altered despite trial commencement. At the beginning of the trial, six participants were on bisphosphonates, and one was on hormone replacement therapy. It is not reported how long patients had been receiving these therapies. The authors noted that at the extension follow-up visit (5-7 years after treatment; average of 6 years) two women had prescriptions for bisphosphonate treatment. It is not clear whether these two women receiving bisphosphonates were in addition to the six women who were on this medication at the start of the trial.

All 12 women received AGN1 LOEP in their left hip. Their right hip was untreated and served as a control. The average aBMD scores of the left and right hips were similar at baseline (mean 0.527 ± SD 0.054 g/cm^2 and 0.530 ± SD 0.045 g/cm^2, respectively) or T-score (mean -2.9 ± SD 0.4 and -2.9 ± SD 0.5, respectively).

alle 12 Pts AGN1 LOEP in linker Hüfte rechte Hüfte Kontrolle aBMD + T-scores

Additional patient and study characteristics and results are presented in Table A-1.

4.2.2 Additional included studies safety

No additional studies were identified on safety for inclusion in this report.

4.3 Results

Mortality[23],[24]

Fractures resulting from osteoporosis can result in mortality, particularly hip-related fractures. Two patients developed hip fractures during the trial follow-up; one patient sustained fractures in both their right (untreated) and left (treated) hip, the other patient developed a fracture in their right (untreated) hip. No patients died during follow-up.

keine Todesfälle

weder Hüftfraktur-bedingt

noch aus anderen Ursachen

The expected beneficial effect of AGN1 LOEP on osteoporosis-related mortality is uncertain owing to data only being available from one trial with a very small number of patients. Further, any effect of AGN1 LOEP on mortality from this trial is confounded by the fact that each patient received the intervention (AGN1 LOEP) and comparator (no treatment).

It is unlikely that AGN1 LOEP would affect mortality other than through potentially reducing osteoporosis-related fractures.

Morbidity[25]

Answering this research question was based on the crucial and important effectiveness outcomes; hip fracture, aBMD in the femoral neck, and femoral strength reported in the one included study by Howe, et al. [1].

basierend auf entscheidenden und wichtigen Endpunkten

Hip fracture

Fractures occurred in one treated hip (1/12; 8%) and two control hips (2/12; 17%) during the 5-7 year follow up. Two of these fractures occurred in one patient (in their treated hip at 40 months follow-up and their control hip at 44 months follow-up). The other patient who sustained one fracture in their control hip occurred at 27 months follow-up. In the fracture that occurred in the treated hip, the cause was reported as unknown. In contrast, the two fractures associated with the control hips a fall was reported to be the cause.

Hüftfrakturen:
IG (linke Hüfte):
1/12; 8 %
KG (rechte Hüfte):
2/12; 17 %

FU 5-7 J

[23] D0001 – What is the expected beneficial effect of AGN1 LOEP on mortality?

[24] D0003 – What is the effect of AGN1 LOEP on the mortality due to causes other than osteoporosis?

[25] D0005 – How does AGN1 LOEP affect symptoms and findings (severity, frequency) of osteoporosis?

Effekt von AGN1 LOEP unsicher, wegen Studiengröße und Ko-Medikamentierung

Owing to the very small number of patients in this trial, the effect of AGN1 LOEP on hip fracture is uncertain. Also, the study authors reported hip fractures under safety outcomes. This review has deemed hip fracture as an important patient-relevant efficacy outcome.

Areal bone mineral density (aBMD)

Knochendichte am Oberschenkelhals

gleiche Scores zu Baseline s. s. größer zu allen Messzeitpunkten in IG

Femoral neck aBMD was assessed by DXA scans before and post-treatment at 1, 6, 12, 18 and 24 weeks; 12, 18 and 24 months and at the extension follow-up that occurred at 315 weeks (average of 6 years). Left (treated) and right (control) femoral necks did not differ in aBMD at baseline (mean 0.527 ± 0.054 g/cm^2 and 0.530 ± 0.045 g/cm^2, respectively). At all follow-up times, aBMD in the treated femoral necks was statistically greater than in the untreated corresponding hips ($p<0.0001$). This difference was reported to be 68 ± SD 22% at 12 months, 59 ± SD 24% at 24 months and 58 ±SD 27% at 315 weeks (Figure 4-1).

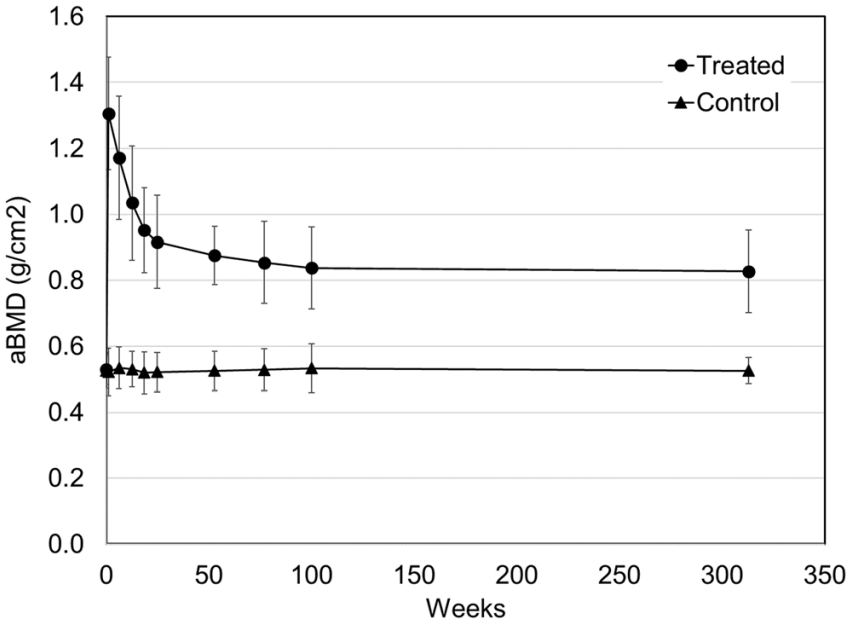

Figure 4-1: Femoral neck aBMD in treated and control hips as assessed by DXA.
Abbreviations: aBMD = areal bone mineral density.
Notes: N=12 except at 315 weeks N=10;
P<0.001 treated vs control for all time points [1]

AGN1 Resorption innerhalb von 1 J, anhaltender Effekt 5-7 J

The authors noted that the AGN1 was completely resorbed and made no contribution to aBMD from 1 year after treatment through to the 5-7 years extended follow-up. Thus, aBMD data should only be considered from one year onwards as previous aBMD measurements may be confounded by residual AGN1 that has not been resorbed and, due to its radiopacity, would be detected by DXA. These results demonstrate that from 12 months through to 5-7 years post-treatment AGN1 LOEP resulted in statistically significant greater aBMD in the femoral neck compared with no treatment.

Femoral strength

Femoral strength was estimated by finite element analysis (FEA). CT scans of treated and untreated hips were analysed at baseline, 12 and 24 weeks and 315 weeks post-treatment using VirtuOst Version 1.2 (O.N. Diagnostics). Pre-treatment values were 2028 ± SD 469 in control femurs and 2077 ± SD 469 in treated femurs. Two different scale factors (α) were applied in the calculation; one assuming 100% of the new tissue performed as normal load-bearing bone and the other assuming only 30% of the new tissue performed as normal load bearing bone. It should be noted that comparisons across all time points were limited to nine patients (25% loss to follow-up). Irrespective of the scale factor used, femoral strength was significantly higher in the treated compared with control femurs at 12 and 24 weeks and 5-7 years after treatment (p<0.01; Table 4-1).

Femurfestigkeit
Analyse von CTscans
nur 9/12 Pts auswertbar

s.s. in IG (linke Hüfte) vs. KG (rechte Hüfte)
zu allen Messzeitpunkten

Table 4-1: Femoral strength in sideways fall estimated from finite element analysis

Mean femoral strength ± SD* (% higher strength compared with control femur)	
Left proximal femur (treated) α† = 0.30 12 weeks: 2,820 ± 463 (41% higher) 24 weeks: 2,755 ± 402 (54% higher) 5-7 years: 2,420 ± 396 (36% higher) *Left proximal femur (treated) α† = 1.00* 12 weeks: 3,165 ± 432 (59% higher) 24 weeks: 3,101 ± 392 (41% higher) 6 years: 2,685 ± 403 (22% higher)	*Right proximal femur (control)* 12 weeks: 1,994 ± 425 24 weeks: 2,013 ± 425 5-7 years: 1,981 ± 338
P<0.01 treated vs control for all identical time points and both 30% and 100% scale factors (α)	

Abbreviations: SD = standard deviation

*Notes: *N=9 at all time points; †scale factor (α) was applied to implant region assuming either 30% or 100% of the new tissue performed as normal load bearing bone.*

No data was available on the other efficacy outcomes listed in the PICO (post-operative mobilisation, bone turnover markers and fracture risk).

keine Evidenz zu post-operativer Mobilisation, Knochenumsatz-marker, Frakturrisiko

Function[26],[27]

No data on the effect of AGN1 LOEP on patient's body functions were identified.

No data on the effect of AGN1 LOEP on activities of daily living were identified.

keine Evidenz zu Körperfunktionalität und ADL

Health-related quality of life (HrQoL)[28], [29]

No data on the effect of AGN1 LOEP on generic health-related quality of life were identified.

No data on the effect of AGN1 LOEP on disease-specific quality of life were identified.

keine Evidenz zu HrQoL, disease-specific QoL

[26] D0011 – What is the effect of AGN1 LOEP on patients' body functions?

[27] D0016 – How does the use of AGN1 LOEP affect activities of daily living?

[28] D0012 – What is the effect of AGN1 LOEP on generic health-related quality of life?

[29] D0013 – What is the effect of AGN1 LOEP on disease-specific quality of life?

Patient satisfaction[30]

keine Evidenz zu Patient*innen-Zufriedenheit

No data on the effect of AGN1 LOEP on patient satisfaction were identified.

Patient safety[31, 32, 33, 34, 35]

AGN1 LOEP vs. dietary and lifestyle modifications and/or pharmacological treatments

keine vergleichende Evidenz zu aktivem Komparator

No comparative data were available evaluating the safety of AGN1 LOEP compared with dietary and lifestyle modifications or pharmacological treatments.

AGN1 LOEP vs. no treatment

keine Prozedur- oder Produkt-induzierte schweren AE

Howe et al. reported that there were no procedure or device-related serious adverse events relating to the use of AGN1 LOEP, and no patient withdrew due to treatment-related adverse events [1].

3 Prozedur- oder Produkt-induzierte Nebenwirkungen; 10 (in 5 Pts) nicht Prozedur- oder Produkt-induzierte Beschwerden/ Erkrankungen

Howe et al described three minor adverse events related to the AGN1 LOEP procedure; a small area of wound breakdown, irritation at the injection site and anaesthesia-related post-operative nausea. These events were reported as mild and resolved without medical intervention [1]. The number of patients having these procedures related adverse events was not reported; thus, an adverse event rate per person cannot be calculated.

Ten other adverse events not related to the procedure were reported in five patients (5/12; 42%) and included pneuomia, shoulder pain and squamous cell carcinoma.

3 Frakturen an anderer Lokalisation

Fragility fractures that occurred in locations other than the hip, were reported in three patients. Details are provided in Table 4-2. One of these patients also had two hip fractures as reported above.

Table 4-2: Summary of fragility fractures suffered during follow-up, excluding those of the hip

Patient	Fracture location	Time post- procedrue	Age at fracture	Cause
1	Left proximal humerus Left patella	36 months	83	Fall
2*	Left patella Spine (level unknown)	8 months 73 months	93	Unknown
3	Spine (T8)	Unknown	Uknown	Unknown

*Notes: *Patient also suffered a fracture in the left and right hip*

[30] D0017 – Was the use of AGN1 LOEP worthwhile?

[31] C0008 – How safe is AGN1 LOEP in comparison to its comparators?

[32] C0002 – Are the harms related to dosage or frequency of applying AGN1 LOEP?

[33] C0004 – How does the frequency or severity of harms change over time or in different settings?

[34] C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of AGN1 LOEP?

[35] C0007 – Are AGN1 LOEP and comparator(s) associated with user-dependent harms?

keine Evidenz zu AE aufrund von Dosierung oder Frequenz/Schweregrad von AE über längere Zeit

No data is available on the harms related to dosage of applying AGN1 LOEP.

No data is available on change of frequency or severity of harms over time or in different settings.

Kontraindikationen

No independent and peer-reviewed data is available to answer this question, on susceptible patient groups that are more likely to be harmed through the use of AGN1 LOEP. However, the manufacturer advises caution when treating patients with pre-existing conditions these include; bleeding disorders of any aetiology, patients on long-term steroidal therapy, immunosuppression and high-dose radiation therapy [24].

Schäden durch Anwender

No data is available on user-dependent harms?

5 Quality of evidence

Risk of bias in the prospective cohort study included in this review was assessed by the ROBINS-I tool [36], and is presented in Table A-2 (Appendix). This study compared AGN1 LOEP with no treatment, with each patient receiving both AGN1 LOEP and no treatment. This was achieved by assigning the left hip to receive AGN1 LOEP and the right hip no treatment. More than half of the participants were taking anti-osteoporotic pharmacological agents at the time of the trial, which is a comparator treatment to AGN1 LOEP. The overall risk of bias for this study was serious. Biases identified related to the following domains: confounding, missing data at the long-term follow-up and selection of the outcome results.

RoB mit ROBINS-I bewertet: schwerwiegender RoB

Vergleich von AGN1 LOEP mit keiner Behandlung

>50% der Pts erhielt Ko-Medikation (eigentlich der Komparator)

The strength of evidence was rated according to GRADE for each endpoint individually [49]. The study was rated by two independent researchers (MK, MV). In case of disagreement a third researcher was involved to resolve the difference. A more detailed list of the criteria applied can be found in the recommendations of the GRADE Working Group [49].

GRADE uses four categories to rank the strength of evidence:

GRADE Bewertung der Qualität der Evidenz

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below (Table 5-1) and in the evidence profile in Table A-3 (Appendix).

The overall strength of evidence for the effectiveness and safety of AGN1 LOEP in comparison to no treatment was very low. The strength of evidence for the safety of AGN1 LOEP from this prospective cohort study was also very low.

sehr niedrige Stärke der Evidenz

Table 5-1: Summary of findings table of AGN1 LOEP (compared with no treatment) for the treatment and management of osteoporosis at last follow-up (5-7 years)

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute difference (mean ± SD)	Number of participants (studies)	Quality	Comments
	Risk with [comparison]	Risk with [intervention]					
EFFICACY							
aBMD of femoral neck **Follow-up (5-7 years)**	N/A	N/A	Not estimable	58 ± 27% higher in treated group	10 (1)	⨁⊙⊙⊙ VERY LOW [a,b,c]	Higher scores indicate increased bone formation
Femoral strength **Follow-up (5-7 years)**	N/A	N/A	Not estimable	**α = 1.00** 36% higher in treated group* **α = 0.30** 22% higher in treated group*	9 (1)	⨁⊙⊙⊙ VERY LOW [a,b,c]	Higher scores indicate improved femoral strength
Fragility fractures **Follow-up (5-7 years)**	NA	NA	Not estimable	3 (1 treated vs 2 control) hip fractures in 2 participants	12 (1)	⨁⊙⊙⊙ VERY LOW [a,b,c]	Higher scores indicate improved fragility fractures
SAFETY							
Serious adverse events **Follow-up (5-7 years)**	N/A	N/A	Not estimable	None	12 (1)	⨁⊙⊙⊙ VERY LOW [a,b,c]	-
Minor device-related adverse events **Follow-up (1 day to 6 weeks)**	N/A	N/A	Not estimable	3†	12 (1)	⨁⊙⊙⊙ VERY LOW [a,b,c]	Adverse events were resolved shortly after the procedure without any further medical intervention.
Non-device-related adverse events **Follow-up (5-7 years)**	N/A	N/A	Not estimable	3 adverse events in 5 participants	12 (1)	⨁⊙⊙⊙ VERY LOW [a,b,c]	-

Abbreviations: aBMD = areal bone mineral density; CI = confidence interval; N/A = not applicable; SD = standard deviation.

Notes:

* *Standard deviations not reported;*

† *number of patients who experienced these adverse events was not reported;*

[a.] *Serious risk of bias due to confounders (the lack of pre-specified statistical analysis plan, and the ability for results to be adjusted for potential confounders raise concern) and moderate risk of bias due to missing data and possible selection of reported results;*

[b.] *Some participants with various comorbidities and taking various osteoporosis medications;*

[c.] *Small sample size.*

6 Discussion

Individuals reaching the age of 50, especially post-menopausal women, may suffer from osteoporosis [1]. This disease occurs due to a progressive loss of BMD leading to an increased risk of fractures. The risk factors for osteoporosis include; genetics, age, gender, nutrition, inactivity, and endocrinal status [2]. Current management and treatment of osteoporosis include dietary and lifestyle modifications and pharmacological therapy. These treatments aim to increase bone strength, thereby reducing fracture risk. Limitations to these treatments include lack of compliance and the lengthy time required for them to affect.

Osteoporose ist häufig, insb. bei Frauen > 50 Jahre

Verlust an Knochendichte erhöht Risiko für Frakturen

herkömmliche Interventionen sind Lebensstilveränderungen und Arzneitherapien

AGN1 LOEP is a novel, once-off, surgical intervention that delivers a triphasic calcium-based material into an osteoporotic bone site, whereby it reportedly provides immediate strengthening and is then resorbed and replaced with new bone [1]. This procedure may provide a potential alternative treatment and prevention option for patients with osteoporosis, who are at an elevated risk of hip fractures.

AGN1 LOEP = neue Technologie, potentielle Alternative

This systematic review aimed to evaluate the safety and effectiveness of AGN1 LOEP in the prevention and treatment of osteoporosis-related hip fractures compared with currently recommended treatments (diet and lifestyle modifications and pharmacological therapy) and no treatment.

Übersichtsarbeit zur Wirksamkeit und Sicherheit von AGN1 LOEP

Summary of evidence and interpretation

Only one prospective cohort study (AGN1 LOEP vs. no treatment, 12 patients) was identified to inform clinical effectiveness and safety recommendations [1]. The study reported significantly greater femoral neck aBMD and femoral strength (estimated by FEA) in the AGN1 LOEP treated hips compared with the untreated hips at all follow-ups through to 5-7 years post-treatment. The authors note that as the AGN1 was completely resorbed by one year after treatment the sustained long-term significant increases in aBMD and femoral strength were due to newly formed bone and not residual AGN1. Two untreated hips and one treated hip experienced a fracture during the long-term follow-up. Also important is the manufacturer's (AgNovos Healthcare) sponsorship of the study. Many of the study's authors also had affiliations with the company either through employment, shareholdings or paid consultancy.

nur 1 klinische Studie mit 12 Pts: signifikante Verbesserung bei Knochendichte am Schenkelhals und bei Femurfestigkeit zu allen Messzeitpunkten

aber: 3 Hüftfrakturen, davon 1 trotz AGN1 LOEP

The overall risk of bias for this study was serious. Moderate to serious bias was identified in several domains including bias due to confounding, missing data, and possible selection of the outcome results. Owing to the small sample size this study would be underpowered to detect a significant difference which reduces the likelihood that a statistically significant result reflects a true effect [50, 51]. Thus, the results should be interpreted with caution.

Verzerrungsrisiko: schwerwiegend

Ergebnisse mit großer Vorsicht zu interpretieren

In the two untreated hips that sustained a fracture, they were fragility fractures due to a fall; however, the cause of the fracture in the treated hip was reported as unknown. While this fracture was documented in the table of 'fragility fractures', it is possible this fracture may have been a result of an event that would cause a fracture in a person without osteoporosis. In addition to the very small number of patients included in the trial, this uncertainty makes it difficult to draw any conclusions concerning the effect of AGN1 LOEP on fragility fractures.

große Unsicherheit bez. der Ursache der 3 Hüftfrakturen und möglicher SAE oder AE (Häufigkeit und Art der Nebenwirkungen)

Similarly, the very small patient sample size also leads to uncertainty regarding the number and types of adverse events resulting from the use of AGN1 LOEP as reported by the study. Recruitment of a matched control group (not undergoing the AGN1 LOEP procedure) may have been useful in determining if there were additional difficulties in dealing with subsequent fractures of the femur in patients who had undergone the procedure and those who had not.

schwerwiegender Confounder: Komedikation

In interpreting the results, it should be noted that half of the patients were receiving pharmacological therapy (bisphosphonates). This cotreatment may have resulted in a bias against the AGN1 LOEP. The actual effect size may be larger than that observed in the trial.

klinische Relevanz der signifikanten Endpunkte (aBMD) fraglich

Häufigkeit von Fragilitätsfrakturen hingegen klinisch relevanter Endpunkt

Despite the significant improvement in femoral neck aBMD and femoral strength observed in the trial, there is uncertainty regarding these outcomes' clinical relevance from a patient's perspective as they are surrogate measures of fracture risk. While actual BMD is used in the diagnosis of osteoporosis due to its correlation with fracture risk, the validity of an 'increase' in BMD owing to antiresorptive agents as a surrogate for fracture risk is unclear due to limited evidence [52]. That is, BMD, as measured by DXA, does not consider the quality of the bone; therefore, an increase in BMD may not translate into an actual reduction in fractures. The validity of using an increase in surrogate markers for reduced fracture risk (increased femoral neck aBMD and bone strength) that resulting from AGN1 LOEP has not been determined. In contrast, the number of fragility fractures is a highly relevant patient outcome. As noted above, the very small number of patients included in the trial makes it difficult to draw any conclusions concerning this outcome.

1 sehr kleine Studie: abschließende Beurteilung nicht möglich

This review included one published study on AGN1 LOEP, which investigated its effectiveness in treating bone loss in proximal femurs compared to no treatment in postmenopausal women. This is the first in-human study of this procedure. It is difficult to reach a definitive conclusion regarding the safety and effectiveness of AGN1 LOEP based on the results of a single prospective cohort study with a very limited sample size of 12 patients. Given the study's sample size, losses to follow-up at 315 weeks, although small (aBMD = 2 patients; femoral strength = 3 patients), may have affected the results.

The study's applicability, including population, interventions, comparators, and outcomes, is outlined in the Appendices (Table A-4).

Evidence gaps and ongoing studies

vorliegende (first-in-human) Studie ist unzureichend

2 laufende Studien: beide ein-armig werden auch nicht Evidenzlücke füllen

The AGN1 LOEP procedure has been trialled in animals and human cadaveric-based studies [53, 54]. There is currently only one published in-human clinical study on AGN1 LOEP compared to no treatment [1]. In the absence of trials comparing AGN1 LOEP to currently recommended osteoporotic treatment methods (dietary and lifestyle modifications and/or pharmacological therapy), it is difficult to determine its benefits in treating and preventing osteoporotic hip fractures. While two ongoing clinical trials were identified, they are single-arm studies, so will not fill this evidence gap (details of these trials and their estimated completion are reported in Table A-5 [Appendix]).

This study included Caucasian postmenopausal women. It is unknown whether the results apply to men, premenopausal women or other races with osteoporosis. There was a wide age range in the included patients (56 to 89 years). As the prognosis of patients with osteoporosis (fracture risk and recovery from surgery) is impacted by advancing age, the safety and efficacy of AGN1 LOEP might vary with age. This would not have been captured by the one study included in this review.

Evidenz zu unterschiedlichen Patienten-Populationen

This application sought to determine the safety and effectiveness of AGN1 LOEP in two populations; patients without a previous osteoporotic hip fracture but with an increased fracture risk (population 1 – elective use) and patients with a fresh osteoporotic hip fracture (population 2 – non-elective use). The single study identified pertained to population 1 only. No evidence was identified on population 2; therefore, the effectiveness of AGN1 LOEP at improving the speed of recovery and time to mobilisation after treatment of a femoral neck fracture is unknown.

vorliegende Studie ist nur zu 1 (der beiden) Patienten-Populationen

viele Fragen offen

Limitations to the report

Although the present report followed a transparent and systematic methodology including a systematic literature search according to the PICO scheme, it also has a few weaknesses. These include:

Schwachstellen des Berichts

- The absence of extensive grey literature searches. Clinical trial databases were searches, as well as the manufacturer's website; however, other sources of grey literature (including specialty society and hospital websites) were not searched. As such, some unreported cases might have been missed.
- Contact with the manufacturer specifically asking for further unpublished or ongoing studies. The manufacturer was contacted for further information about the product and its use, but additional patient data was not requested.
- Restrictions on language to English and German only.

Nevertheless, it is unlikely that additional unpublished data would have changed the conclusion that AGN1 LOEP is in an early stage of implementation with uncertain effects.

Conclusion

The effectiveness and safety of AGN1 LOEP compared with dietary and lifestyle modification and pharmacological therapy in treating and preventing osteoporotic hip fractures is unknown as no evidence has been published on these comparisons. Evidence comparing AGN1 LOEP with no treatment showed significantly greater femoral neck aBMD and femoral strength favouring AGN1 LOEP over a long-term follow-up. However, this evidence is derived from a single prospective cohort study on 12 postmenopausal women. Thus, these findings are highly uncertain. The evaluation of AGN1 LOEP requires further evidence (with large patient numbers and follow-up of at least 5 years) before a more robust conclusion on the effectiveness and safety of AGN1 LOEP in the prevention and treatment of osteoporosis-related hip fractures can be made.

1 kleine Studie, sehr unsichere Datenlage

robuste klinische Daten notwendig für eine Beurteilung der Wirksamkeit und Sicherheit

7 Recommendation

In Table 7-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 7-1: Evidence based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	The inclusion in the catalogue of benefits is **currently not recommended**.
	The **inclusion in** the catalogue of benefits is **not recommended**.

Reasoning:

The current evidence is not sufficient to prove that the assessed technology, AGN1 LOEP, is more effective and equally safe compared to the main comparators dietary and lifestyle modifications and pharmacological therapy in the prevention and treatment of osteoporotic hip fractures.

unzureichende Datenlage, sehr frühes Stadium der Technologie

The intervention is in an early stage of clinical implementation with too little data available. A re-evaluation is recommended only after robust data from RCTs are available. Such RCTs are not registered yet.

Re-Evaluierung, wenn RCTs vorliegen

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: AGN1 LOEP for patients with osteoporosis: Results from the comparative study

Author, year	**Howe, 2020**	
Country	USA	
Sponsor	AgNovos Healthcare, Rockville, MD, USA	
Intervention/Product	AGN1 LOEP injected into left femoral neck	
Comparator	No treatment of right femoral neck	
Study design	Prospective non-randomised comparative study	
Number of pts	12 (24 hips: 12 treated, 12 untreated)	
Inclusion criteria	Patients diagnosed with osteoporosis aged ≥ 55 years with femoral neck areal bone mineral density (aBMD) T-score ≤ -2.5* assessed by dual-energy X-ray absorptiometry (DXA)	
Exclusion criteria	Patients with previous hip fractures, creatinine >2.0mg/100mL or glomerular filtration rate <30mL/min	
Age of patients (years) (mean ± SD [range])	71.7 ± 10.1 (56-89)	
Baseline femoral neck T-score (mean ± SD [range])	*Left femoral neck (treated)* -2.9 ± 0.4 (-2.2 to -3.4)	*Right femoral neck (control)* -2.9 ± 0.5 (-2.3 to -4.1)
Baseline femoral neck aBMD (g/cm^2) (mean ± SD)	*Left femoral neck (treated)* 0.527 ± 0.054	*Right femoral neck (control)* 0.530 ± 0.045
Baseline femoral strength (N) (mean ± SD)†	*Left proximal femur (treated)* 2,077 ± 469	*Right proximal femur (control)* 2,028 ± 469
Baseline osteoporosis medication, n/N (%)	Bisphosphonate: 6/12 (50%) Hormone replacement therapy: 1/12 (8%)	
Follow-up (years)	5-7 years	
Loss to follow-up, n (%)	Early (0-24 months) follow-ups: femoral neck aBMD = 0/12 (0%); femoral strength = 3/12 (25%); medical history = 0/12 (0%) Late (5-7 year) follow-up: femoral neck aBMD = 2/12 (17%); femoral strength = 3/12 (25%); medical history = 0/12 (0%)	
Outcomes	**Efficacy**	
Femoral neck aBMD (g/cm^2) (mean ± SD)	*Left femoral neck (treated)* 12 months: 0.885 ± 0.065; 68 ± 22% higher‡ 24 months: 0.837 ± 0.066; 59 ± 27% higher‡ 5-7 years: 0.832 ± 0.068; 58 ± 27% higher‡	*Right femoral neck (control)* 12 months: NR 24 months: NR 5-7 years: NR
	P<0.001 treated vs control for all time points (n = 12 for all time points except 5-7 years where n = 10)	

Author, year	Howe, 2020	
Femoral strength (N) (mean ± SD)†	*Left proximal femur (treated) α = 0.30* 12 weeks: 2,820 ± 463; 41% higher‡ 24 weeks: 2,755 ± 402; 37% higher‡ 315 weeks: 2,420 ± 396; 22% higher‡ at 5-7 years *Left proximal femur (treated) α = 1.00* 12 weeks: 3,165 ± 432; 59% higher‡ 24 weeks: 3,101 ± 392; 54% higher‡ 315 weeks: 2,685 ± 403; 36% higher‡ at 5-7 years	*Right proximal femur (control)* 12 weeks: 1,994 ± 425 24 weeks: 2,013 ± 425 315 weeks: 1,981 ± 338
	P<0.01 treated vs control for all time points (n = 9 for all time points)	
Osteoporosis-related fragility fractures (hip), n (%)	Left (treated) hip: 1 (8%)	Right (control) hip: 2 (17%)
Outcomes	**Safety**	
Non-procedure-related AEs, n/N (%)§	5/12 (42%) 10 AEs (including pneuomia, shoulder pain and squamous cell carcinoma)	
Minor procedure-related AEs, n/N (%)	n/N (%) NR 3 AEs (including small area of wound breakdown, irritation at injection site and post-operative nausea)	
Major procedure-related adverse events, n/N (%)	0/12 (0%)	
Procedure-related mortality, n/N (%)	0/12 (0%)	
Osteoporosis-related fragility fracture (site other than hip), n/N (%)	4/12 (33%)	

Abbreviations: aBMD = areal bone mineral density; AGN1 = resorbable triphasic osteoconductive implant material; DXA = dual-energy X-ray absorptiometry; FEA = finite element analysis; LOEP = local osteo-enhancement procedure; MD = Maryland; NR = not reported; SD = standard deviation; USA = United States of America.

Notes:

* *One subject was admitted into the study with an aBMD T-score >-2.5.*

† *Femoral strength was estimated in simulated sideway fall loading condition using subject specific nonlinear finite element analysis. Within the implant, a scale factor (α = 0.30 or α = 1.00) was applied to represent 30% (conservative) or 100% of new tissue acting as normal load-bearing bone.*

‡ *Compared with right untreated hip.*

§ *The severity of these complications was not provided.*

Risk of bias tables and GRADE evidence profile

Two independent researchers judged the internal validity of the included studies. In case of disagreement, a third researcher was involved to resolve the differences. A more detailed description of the criteria used to assess the individual study designs' internal validity can be found in the Internal Manual of the AIHTA [2] and the Guidelines of EUnetHTA [3].

Table A-2: Risk of bias – study level (non – randomised studies comparing AGN1 LOEP *versus* no treatment)*, see [36]*

Study reference/ID	Bias due to confounding	Bias selection of participants into the study	Bias in measurement of interventione	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
Howe et al. 2020, [1]	Serious	Low	Low	Low	Moderate	Moderate	Serious	Serious	The outcome is objective yet the lack of pre-specified statistical analysis plan, and the ability for results to be adjusted for potential confounders raise concern.

Table A-3: Evidence profile: efficacy and safety of AGN1 LOEP in 12 post-menopausal patients.

Quality assessment							Summary of findings				
							Number of patients		Effect		Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Impression	Other considerations	[intervention]	[comparison]	Relative (95% CI)	Absolute (95% CI)	
Efficacy											
Bone formation (change in femoral neck aBMD)											
1	Observational study	Serious[a]	Not serious	Serious[b]	Serious[c]	-	10	10	-	-	⨁◯◯◯ VERY LOW
Femoral strength											
1	Observational study	Serious[a]	Not serious	Serious[b]	Serious[c]	-	10	10	-	-	⨁◯◯◯ VERY LOW
Fragility fractures											
1	Observational study	Serious[a]	Not serious	Serious[b]	Serious[c]	-	12	12	-	-	⨁◯◯◯ VERY LOW
Safety											
Serious adverse events											
1	Observational study	Serious[a]	Not serious	Serious[b]	Serious[c]	-	9	9	-	-	⨁◯◯◯ VERY LOW
Minor device-related adverse events											
1	Observational study	Serious[a]	Not serious	Serious[b]	Serious[c]	-	12	12	-	-	⨁◯◯◯ VERY LOW
Non-device-related adverse events											
1	Observational study	Serious[a]	Not serious	Serious[b]	Serious[c]	-	12	12	-	-	⨁◯◯◯ VERY LOW

Abbreviations: a BMD = areal bone mineral density; CI = confidence interval

Notes:

[a] *Serious risk of bias due to confounding, and moderate risk of bias due to missing data and selection of reported results. The lack of a pre-specified statistical analysis plan, and the ability for results to be adjusted for potential confounders raise concern.*

[b] *Some participants with various comorbidities and taking various osteoporosis medications.*

[c] *Small sample size.*

Applicability table

Table A-4: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The population in the one study included in this review was 12 postmenopausal Caucasian women age range of 56-89 years old (mean 71.7 ± SD 110.1 years) with a diagnosis of osteoporosis based on DXA scans of the femoral neck and no previous hip fractures. This population reflects one of the osteoporotic populations in clinical practice that would be eligible to receive this intervention. No evidence was identified on the safety and effectiveness of AGN1 LOEP in patients with a current hip fracture. Also, no evidence was identified on men or premenopausal women with osteoporosis.
Intervention	The AGN1 LOEP was conducted by injecting the AGN1 into the left proximal femur of patients who were positioned on a fracture table. Feedback from one of the authors of the study was: "we used a variety of anesthesia techniques. Local was used in all cases prior to incision and the procedures took between 15 and 30 minutes for completion. All patients were discharged the same day and were full weight bearing immediately. All patients had to perform weight-bearing execises four hours post-surgery" [55]. At enrollment into the trial 7/12 (58%) of patients were on pharmacological therapy (6 on bisphosphonates and 1 on hormone replacement therapy). These treatments were not altered as a result of participating in the study. At the extended follow-up, an additional two patients had prescriptions for bisphosphonates.
Comparators	The one study included in this review compared the effectiveness and safety of AGN1 LOEP with no treatment. Standard treatment for osteoporosis, based on published guidelines, are dietary and lifestyle modifications and or pharmacological therapy. Thus, the effectiveness and safety of AGN1 LOEP compared with treatment alternatives reflective of clinical practice is unknown.
Outcomes	The one study included in this review reported the following outcomes: femoral aBMD, femoral strength and fragility fractures of the hip. These outcomes, deemed as critical/important, were reported up to 5-7 years following treatment and thus can inform the long-term efficacy of AGN1 LOEP. Adverse events related to the LOEP procedure were documented but not reported clearly as it is not stated how many patients had the three LOEP-related adverse events. The patient-relevant outcome 'health-related quality of life' was not reported, and thus it is not known whether this is affected by AGN1 LOEP.
Setting	The one included comparative study was conducted in a community-based hospital in the USA. All procedures were completed by orthopaedic surgeons. The setting in which AGN1 LOEP was conducted is reflective of the intended use of the procedure in clinical practice.

Abbreviations: aBMD = areal bone mineral density; DXA = duel energy X-ray absorptiometry; LOEP = local osteo-enhancement procedure; SD = standard deviation; USA = United States of America.

List of ongoing randomised controlled trials

Table A-5: List of ongoing studies on AGN1 LOEP

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT04511364	60	AGN1 Femoral Local Osteo-Enhancement Procedure	Single-arm	Change in DXA score at 24 months [Time Frame: 24 months] Change in DXA score of treated hip from baseline pre-AGN1 LOEP to 24 months post-treatment.	December 2025	AgNovos Healthcare
NCT02916953	60	AGN1 Femoral Local Osteo-Enhancement Procedure	Single-arm	Number of participants with procedure-related or device-related adverse events [Time Frame: 42 Days] Adverse Events and Serious Adverse Events related to either the treatment or device.	May 2021	AgNovos Healthcare

Abbreviations: DXA = duel energy X-ray absorptiometry; LOEP = local osteo-enhancement.

Literature search strategies

Search strategy for Medline/Embase

Search Name: AGN1 LOEP	
Search date: 08.02.2021	
ID	Search
#1	Subject Heading: [Femur] explode all trees
#2	Subject Heading: [Hip] explode all trees
#3	Keyword: femur*
#4	Keyword: proximal femur*
#5	Keyword: femur neck
#6	Keyword: femoral neck
#7	Keyword: femoral bone*
#8	Keyword: thigh bone*
#9	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
#10	Subject Heading: [Osteoporosis] explode all trees
#11	Keyword: osteoporosis
#12	Keyword: osteoporotic
#13	Keyword: bone loss
#14	Keyword: osteopenia
#15	Subject Heading: [Osteoclast] explode all trees
#16	Keyword: osteoclast*
#17	Subject Heading: [Osteoblast] explode all trees
#18	Keyword: osteoblast*
#19	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18
#20	9 AND 19
#21	Keyword: resorbable triphasic osteoconductive implant
#22	Keyword: triphasic biomaterial
#23	Keyword: osteoconductive implant
#24	Keyword: AGN1
#25	Keyword: OSSURE
#26	Keyword: calcium sulfate
#27	Keyword: calcium sulphate
#28	Keyword: calcium phosphate
#29	26 OR 27 OR 28
#30	Keyword: implant*
#31	29 AND 20
#32	21 OR 22 OR 23 OR 24 OR 25 OR 31
#33	Keyword: local osteo-enhancement
#34	Keyword: local osteo enhancement
#35	Keyword: local osteoenhancement
#36	Keyword: LOEP
#37	Keyword: augmentation
#38	33 OR 34 OR 35 OR 36 OR 37
#39	32 OR 38
#40	20 AND 39
Total hits: 486 (Medline)/657 (Embase) Hits	

Search strategy for Cochrane

Search Name: AGN1 LOEP	
Search date: 08.02.2021	
ID	Search
#1	MeSH Descriptor: [Femur] explode all trees
#2	All Text: hip
#3	All Text: femur*
#4	All Text: proximal femur*
#5	All Text: femur neck
#6	All Text: femoral neck
#7	All Text: femoral bone*
#8	All Text: thigh bone*
#9	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
#10	MeSH Descriptor: [Osteoporosis] explode all trees
#11	All Text: osteoporosis
#12	All Text: osteoporotic
#13	All Text: bone loss
#14	All Text: osteopenia
#15	MeSH Descriptor: [Osteoclast] explode all trees
#16	All Text: osteoclast*
#17	All Text: osteoblast*
#18	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
#19	9 AND 18
#20	All Text: resorbable triphasic osteoconductive implant
#21	All Text: triphasic biomaterial
#22	All Text: osteoconductive implant
#23	All Text: AGN1
#24	All Text: OSSURE
#25	All Text: calcium sulfate
#26	All Text: calcium sulphate
#27	All Text: calcium phosphate
#28	25 OR 26 OR 27
#29	All Text: implant*
#30	28 AND 29
#31	20 OR 21 OR 22 OR 23 OR 24 OR 30
#32	All Text: local osteo-enhancement
#33	All Text: local osteo enhancement
#34	All Text: local osteoenhancement
#35	All Text: LOEP
#36	All Text: augmentation
#37	32 OR 33 OR 34 OR 35 OR 36
#38	31 OR 37
#39	19 AND 38
Total hits: 282	

Search strategy for York CRD

Search Name: AGN1 LOEP	
Search date: 08.02.2021	
ID	Search
#1	MeSH Descriptor: [Femur] explode all trees
#2	MeSH Descriptor: [Hip] explode all trees
#3	All Text: femur*
#4	All Text: proximal femur*
#5	All Text: femur neck
#6	All Text: femoral neck
#7	All Text: femoral bone*
#8	All Text: thigh bone*
#9	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
#10	MeSH Descriptor: [Osteoporosis] explode all trees
#11	All Text: osteoporosis
#12	All Text: osteoporotic
#13	All Text: bone loss
#14	All Text: osteopenia
#15	MeSH Descriptor: [Osteoclast] explode all trees
#16	All Text: osteoclast*
#17	MeSH Descriptor: [Osteoblast] explode all trees
#18	All Text: osteoblast*
#19	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18
#20	9 AND 19
#21	All Text: resorbable triphasic osteoconductive implant
#22	All Text: triphasic biomaterial
#23	All Text: osteoconductive implant
#24	All Text: AGN1
#25	All Text: OSSURE
#26	All Text: calcium sulfate
#27	All Text: calcium sulphate
#28	All Text: calcium phosphate
#29	26 OR 27 OR 28
#30	All Text: implant*
#31	29 AND 20
#32	21 OR 22 OR 23 OR 24 OR 25 OR 31
#33	All Text: local osteo-enhancement
#34	All Text: local osteo enhancement
#35	All Text: local osteoenhancement
#36	All Text: LOEP
#37	All Text: augmentation
#38	33 OR 34 OR 35 OR 36 OR 37
#39	32 OR 38
#40	20 AND 39
Total hits: 0	

Search strategy for INAHTA database

Search Name: AGN1 LOEP	
Search date: 08.02.2021	
ID	Search
#1	MeSH Search: [Femur] explode all trees
#2	MeSH Search: [Hip] explode all trees
#3	All: femur*
#4	All: proximal femur*
#5	All: femur neck
#6	All: femoral neck
#7	All: femoral bone*
#8	All: thigh bone*
#9	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
#10	MeSH Search: [Osteoporosis] explode all trees
#11	All: osteoporosis
#12	All: osteoporotic
#13	All: bone loss
#14	All: osteopenia
#15	MeSH Search: [Osteoclast] explode all trees
#16	All: osteoclast*
#17	MeSH Search: [Osteoblast] explode all trees
#18	All: osteoblast*
#19	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18
#20	9 AND 19
#21	All: resorbable triphasic osteoconductive implant
#22	All: triphasic biomaterial
#23	All: osteoconductive implant
#24	All: AGN1
#25	All: OSSURE
#26	All: calcium sulfate
#27	All: calcium sulphate
#28	All: calcium phosphate
#29	26 OR 27 OR 28
#30	All: implant*
#31	29 AND 20
#32	21 OR 22 OR 23 OR 24 OR 25 OR 31
#33	All: local osteo-enhancement
#34	All: local osteo enhancement
#35	All: local osteoenhancement
#36	All: LOEP
#37	All: augmentation
#38	33 OR 34 OR 35 OR 36 OR 37
#39	32 OR 38
#40	20 AND 39
Total hits: 0	

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH