HTA Austria
Austrian Institute for
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Allogeneic mesenchymal stem cells for Crohn's Disease-associated complex perianal fistulas

1. Update 2023
Systematic Review

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

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Content

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List of abbreviations

AE ..... Adverse event
AGA ..... American Gastroenterological Association
ATMPs ..... Advanced therapy medicinal product
BM ..... Bone marrow
CD ..... Crohn's disease
CDAI ..... Crohn's Disease Activity Index
EBV ..... Epstein-Barr virus
ECCO ..... European Crohn's and Colitis Organisation
EUnetHTA ... European Network for Health Technology Assessment
f/u ..... Follow-up
HTA ..... Health technology assessment
IBDQ ..... Irritable Bowel Disease Questionnaire
LPD ..... Lymphoproliferative disease
m(ITT) ..... Modified intention to treat
MC ..... Morbus Crohn
MRI ..... Magnetic resonance imaging
MSC ..... Mesenchymal stem cell
n ..... Number
p ..... P-value
PDAI ..... Perianal Disease Activity Index
QoL ..... Quality of life
RCT ..... Randomised controlled trial
RoB ..... Risk of Bias
s.s. ..... Statistically significant
SAE ..... Serious adverse event
SCT ..... Stem cell therapy
SF-36 ..... Short-fom 36 questionnaire
STEAE ..... Serious treatment-emergent adverse events
STRAE ..... Serious treatment-related adverse events
TEAE ..... Treatment-emergent adverse events
TRAE ..... Treatment-related adverse events

Executive Summary

Introduction

Health Problem

patients with complex perianal fistulas caused by Crohn's disease

The scope of this review includes patients with complex perianal fistulas caused by Crohn's disease (CD) that are refractory to conventional and/or biologic agents or intolerant to such treatments. Fistulas caused by CD occur when a fissure penetrates the gut wall, surrounded by granulation tissue with acute and chronic inflammation. In the case of perianal fistulas, an abnormal connection occurs between the anorectum and the perianal epithelium. The main symptoms of perianal fistulas are anal pain with defecation and associated swelling, perianal itching, bleeding, and/or discharge of pus or stool from cutaneous fistula openings. According to the American Gastroenterological Association (AGA), fistulas can be categorised as simple and complex.

estimated CD-incidence rate in Austria: 11.5 per 100,000 inhabitants

The highest number of CD patients is reported in the United States of America (USA), Canada, and Europe, with prevalence rates above 300 per 100,000 inhabitants. In Austria, incidence rates of 11.5 per 100,000 inhabitants were estimated, with 9.5 and 14.6 in the rural and urban areas, respectively. Perianal fistulas occur in about five to 40 percent of patients during the course of their CD disease.

Description of Technology

advantages of allogeneic mesenchymal stem cells (MSCs)

Allogeneic mesenchymal stem cells (MSCs) are assumed to prevent repeating surgeries that may lead to high morbidity (i.e. incontinence) and subsequently to a loss of quality of life (QoL) in patients with complex perianal fistulas caused by CD. Due to their less invasive character, especially for the anal sphincter apparatus, they may prevent the need for a permanent stoma.

locally injected in fistula tracts and internal openings

During the actual process, allogeneic MSCs are injected locally and distributed into the patient's tissue adjacent to all fistula tracts and internal openings via a fine long needle. If the fistula tracts are not successfully closed after a single injection, further injections may be necessary. Alofisel® (darvadstrocel/Cx601) was approved as an allogeneic MSCs therapy (as an ATMP) by the European Medicines Agency (EMA) in 2018. The treatment is approved for adult patients with perianal fistulas with non-active/mildly active Crohn's disease whose fistulas have responded inadequately to at least one conventional or biological therapy.

Alofisel® authorised in European Union since 2018

Methods

update of the 2018 assessment

In this report, we conducted an update assessment to evaluate the effectiveness and safety of allogeneic MSCs.

systematic literature search in 5 databases

A systematic literature search was conducted in five databases (Cochrane, CRD, Embase, Medline, INAHTA database). The systematic search was limited to English or German language and in time from 12.2017 to 12.2022.

selection, extraction & quality appraisal: conducted by 2 researchers

In addition, a manual search on the internet was performed, and information provided by the manufacturer were screened to identify further relevant studies. The study selection, data extraction and assessment of the methodological quality of the studies were performed by two independent researchers. GRADE (Grading of Recommendations, Assessment, Development and Evaluation) was further used, and the evidence was qualitatively synthesised.

Domain effectiveness

critical outcomes for effectiveness

The following efficacy-related outcomes were used as evidence to derive a recommendation: Quality of life, combined remission, and closure of external openings (response).

Domain safety

critical outcomes for safety

The following safety-related outcomes were used as evidence to derive a recommendation: any adverse events (AE) and serious adverse events (SAE).

Results

Available evidence

available evidence for effectiveness and safety: 2 RCTs with follow-up (f/u) publications 3 non-comparative studies

Two RCTs (n=233) comparing allogeneic MSCs with placebo – the ADMIRE-CD trial and a dose-escalation trial – and one single-arm study (n=24) from the previous report were included. In addition to the primary analyses of the RCTs, two follow-up publications for the ADMIRE-CD trial, one follow-up publication for the dose-escalation RCT, one single arm study (n=22) and one case-series (n=11) were newly available since 2018. The study populations represented patients with Crohn's Disease-associated complex perianal fistulas.

RoB of the included studies: low to high

The risk of bias of the two RCTs (f/u up to 24 weeks) was rated as moderate for the ADMIRE-CD study and high for the dose-escalation study. The single-arm study included in the previous report was judged to have a high risk, and the new non-comparative observational studies yielded a moderate and a low risk of bias.

Clinical effectiveness

statistically significant (s.s.) improvement in combined remission

The ADMIRE-CD indicated that allogeneic MCS statistically significantly improves the patient-relevant endpoint combined remission. After 24 weeks, combined remission was achieved in 53 (50%) out of 107 patients compared to 36 (34%) out of 105 patients in the intervention and control groups (p= 0.024), respectively. At 52-week follow-up, combined remission was achieved in 58 (56%) out of 103 subjects receiving MSCs compared to 39 (39%) out of 101 subjects receiving the placebo (p=0.021). For response, no significant changes were observable.

no relevant improvements in quality of life (QoL)

Available studies measured QoL by different questionnaires as a secondary endpoint and did not find statistically significant differences, except for some subscores of the dose-escalation study.

Safety

several (severe) adverse events

most common (s)AEs: (peri)anal abscesses

One RCT and two single-arm studies reported several severe adverse events. Severe anal abscesses/fistulas were reported more commonly in the MSC-groups than in the control groups of the RCT. In contrast, the control group only reported severe cases of Crohn disease, proctalgia, anal inflammation, and liver abscesses. In the single-arm studies, one case each of pyrexia, perianal abscess, intestinal obstruction, intestinal anastomosis complication, urinary calculus, Crohn's disease and tubulointerstitial nephritis were reported as SAEs. Adverse events were reported in all studies. In the RCTs, peri(anal) abscesses/fistulas, proctalgia and nasopharyngitis were most commonly reported in the intervention groups and the control groups most commonly reported abscesses/fistulas, proctalgia and abdominal pain. The ADMIRE-CD trial reported that 9% of patients in both study groups withdrew by week 52

due to adverse events. Further, one patient of the dose-escalation trial developed an adenocarcinoma and died two years after intervention, however this adverse event was not reported as related to treatment. In the non-comparative studies the most common adverse events were: (peri)anal abscesses and proctalgia.

Upcoming evidence

5 ongoing RCTs

The systematic search and the search in clinical trial registries yielded five ongoing RCTs, in which four different origins of stem cells are evaluated. The RCT (ADMIRE-CD-II) with the largest study population (554 patients), which will provide new information on the efficacy and safety of allogeneic MSCs compared to placebo, is expected to be completed in July 2023. In addition, a RCT (IRCT20210830052332N1) with a very small study population (24 patients) is investigating the efficacy and safety of allogeneic MSCs in combination with standard treatment compared to other comparators from clinical practice (e.g. conventional surgery). However, an expected end of the study is not yet known.

Discussion

placebo as the only comparator

Both included RCTs compared MSCs with a placebo. Based on clinical practice, for example, fistula plugs or fibrin glue can be used as another comparator. However, no evidence is currently comparing allogeneic MSCs with treatments other than placebo.

certainty of evidence: very low to moderate

The certainty of the available evidence in this report was very low to low due to the high imprecision (most studies were underpowered to detect a statistically significant difference or had a wide confidence interval) and the high RoB of some included studies.

MSCs not included in benefit catalogue in Austria

Allogeneic MSCs for perianal fistulas are currently not included in the hospital catalogue of benefits (LKF, leistungsorientierte Krankenanstaltenfinanzierung) and, hence not a fully reimbursed in the Austrian healthcare system.

Summary and recommendation

MSCs may be superior to placebo in terms of combined remission & as safe as placebo treatment

long-term research needed

inclusion of MSCs in the hospital benefit catalogue restricted in time and to selected patients & specialised centres

The current evidence of allogeneic mesenchymal stem cells for Crohn's Disease-associated complex perianal fistulas indicates modest benefit for combined remission over placebo: statistically significant differences favouring MSCs could be observed after 24 weeks (low certainty of evidence) and 52 weeks (very low certainty of evidence). However, in the outcomes of response and quality of life (measured as second outcomes) the evidence showed no statistically differences between the groups. Additional there is uncertainty on the long term benefits (more than 52 weeks) due to few data. In terms of safety, the occurrence of adverse events were similar in the treatment and the control group (placebo). No knowledge is available on the active comparison with treatments as used in clinical practice: e.g. fistula plugs or fibrin glue. Including MSCs for treatment of perianal fistulas in the hospital benefit catalogue should be restricted to adult patients with non-active/mildly active luminal Crohn's disease whose fistulas have responded inadequately to at least one conventional or biological therapy. Furthermore, the inclusion should be limited in time – until data on long-lasting effects are available – and to specialised centres.

results of the ADMIRE CD-II to be awaited

New study results from the ADMIRE-CD-II will potentially influence the effect estimate. Re-evaluation is recommended not before 2025.

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Patient*innen mit komplexen perianalen Fisteln aufgrund von Morbus Crohn (CD), können zu Analschmerzen mit Defäkation/perianaler Schwellung oder Juckreiz, Blutungen, Inkontinenz führen

Morbus Crohn (CD) ist eine chronisch-entzündliche Darmerkrankung, die durch eine transmurale Entzündung und durch einen diskontinuierlichen, segmentalen Befall der Darmschleimhaut (sog. skip lesions) gekennzeichnet ist. Fisteln treten gewöhnlich dann auf, wenn eine Fissur umgeben von Granulationsgewebe mit akuten und chronischen Entzündungen die Darmwand durchdringt. Bei perianalen Fisteln kommt es zu abnormen Verbindung zwischen dem Anorektum und dem Perianalepithel. Laut der Amerikanische Vereinigung für Gastroenterologie (American Gastroenterological Association, AGA) können perianale Fisteln in einfache und komplexe Fisteln eingeteilt werden. Komplexe Fisteln sind hoch und betreffen mehr als zwei Drittel des äußeren Schließmuskels. Sie beeinträchtigen die Lebensqualität der Patient*innen, insbesondere durch anale Schmerzen bei der Defäkation und damit verbundene Schwellungen, sowie perianalen Juckreiz, Blutungen und/oder Ausfluss von Eiter oder Stuhl aus kutanen Fistelöffnungen.

geschätzte Inzidenzrate für CD in Österreich: 11,5 pro 100.000 Einwohner*innen

Die häufigsten CD-Patient*innen werden aus den Vereinigten Staaten von Amerika (USA), Kanada und Europa, mit Prävalenzraten von über 300 pro 100.000 Einwohner*innen, berichtet. In Österreich wurden Inzidenzraten von 11,5 pro 100.000 Einwohner*innen geschätzt, mit 9,5 in den ländlichen bzw. 14,6 in den städtischen Gebieten. Bei etwa fünf bis 40 Prozent der Patient*innen treten im Verlauf ihrer CD-Erkrankung perianale Fisteln auf. Die kumulative Inzidenz von CD-assoziierten perianalen Fisteln beträgt 12 % nach einem Jahr und verdoppelt sich 20 Jahre nach der Diagnose. Etwa ein Drittel der Patient*innen mit CD-assoziierten perianalen Fisteln sprechen nicht auf medizinische Standardbehandlungen an. Der Fokus der vorliegenden Übersichtsarbeit liegt auf CD-bedingte komplexe, perianale Fisteln bei Patient*innen, die gegenüber konventionellen und/oder biologischen Wirkstoffen refraktär oder intolerant sind.

Beschreibung der Technologie

Vorteile von allogenen mesenchymalen Stammzellen (MSCs)

Allogene mesenchymale Stammzellen (MSCs) sollen bei Patient*innen mit CD-bedingten, komplexen perianalen Fisteln, wiederholte Operationen verhindern, da diese zu einer hohen Morbidität (z. B. Inkontinenz) und folglich zu einem Lebensqualitätsverlust führen können. Aufgrund ihres weniger invasiven Charakters, insbesondere für den analen Schließmuskelapparat, könnten MSCs die Notwendigkeit eines permanenten Stomas verhindern.

lokale Injektion in Fistelgänge und innere Öffnungen

2018: EMA-Zulassung von Alofisel®

Während des Eingriffs werden allogene MSCs lokal injiziert und mit einer feinen langen Nadel in das Gewebe im Bereich der Fistelgänge und inneren Öffnungen verteilt. Bei nicht erfolgreichem Verschluss der Fistelgänge nach einmaliger Injektionen können weitere Injektionen erforderlich sein. Alofisel® (Darvadstrocel/Cx601) wurde als allogene MSCs Therapie (als ATMP) 2018 von der Europäischen Arzneimittel-Agentur (EMA) zugelassen. Die Behandlung ist für erwachsene Patient*innen mit perianalen Fisteln mit einem nicht aktiven/leicht aktiven Morbus Crohn zugelassen, deren Fisteln auf mindestens eine konventionelle oder biologische Therapie nicht oder nur unzureichend angesprochen haben.

Methoden

Ziel der vorliegenden Arbeit war es, die in der systematischen Übersichtsarbeit aus dem Jahr 2018 dargelegte Evidenz zur klinischen Wirksamkeit und Sicherheit von allogenen MSCs bei Erwachsenen mit CD-bedingten perianalen Fisteln zu aktualisieren.

Update des Berichts von 2018

Die systematische Literatursuche nach randomisierten kontrollierten Studien (RCTs) und nicht vergleichenden Studien wurde in fünf Datenbanken (Cochrane, CRD, Embase, Medline, INAHTA-Database) durchgeführt. Sie wurde auf einen Zeitraum von Dezember 2018 bis Dezember 2022 beschränkt.

Systematische Literatursuche in 5 Datenbanken

Die Studienauswahl, die Datenextraktion und die Bewertung der methodischen Qualität der Studien wurden von zwei unabhängigen Wissenschaftler*innen (VH, GG) durchgeführt. Darüber hinaus wurde mit Hilfe des Grading of Recommendations, Assessment, Development and Evaluation (GRADE)-Schemas die verfügbare Evidenz qualitativ zusammengefasst.

Studienauswahl, Extraktion und Qualitätsbeurteilung: durchgeführt von 2 Forscher*innen

Die folgenden entscheidungsrelevanten Endpunkte wurden für eine Empfehlung herangezogen:

entscheidungsrelevante Endpunkte für:

- **Wirksamkeit:** kombinierte Remission (definiert als eine Kombination aus Verschluss der behandelten Fistel ohne Sezernierung bei Kompression und dem Fehlen von Flüssigkeitsansammlungen, die ≥ 2 cm sind und durch eine Magnetfeld-Resonanz-Therapie (MRT) bestimmt wurden), Reaktion (Verschluss der äußeren Öffnungen), Lebensqualität,

Wirksamkeit und

- **Sicherheit:** alle unerwünschten Nebenwirkungen und schwerwiegenden unerwünschten Nebenwirkungen.

Sicherheit

Ergebnisse

Verfügbare Evidenz

Aus dem Bericht 2018 wurden zwei RCTs (n=233) in denen allogene MSCs mit Placebo verglichen wurden – die ADMIRE-CD-Studie und eine Dosiseskalationsstudie – sowie eine einarmige Studie (n=24) eingeschlossen. Zu diesen beiden RCTs wurden Publikationen mit Langzeitergebnissen (bis zu 4 Jahre Follow-up) identifiziert. Zusätzlich wurden, eine einarmige Studie (n=22) und eine Fallserie (n=11) publiziert. Die Studienpopulationen umfassten Patient*innen mit CD-assoziierten komplexen perianalen Fisteln.

verfügbare Evidenz für Wirksamkeit und Sicherheit: 2 RCTs mit Follow-up (f/u) Veröffentlichungen, 3 nicht vergleichende Studien

Das Verzerrungsrisiko (RoB) der beiden RCTs (f/u bis 24 Wochen) wurde mit einem moderaten Risiko für die ADMIRE-CD-Studie und einem hohen Risiko für die Dosiseskalationsstudie eingestuft. Die einarmige Studie, die bereits im vorangegangenen Bericht enthalten war, wurde mit einem hohen Risiko bewertet, und die neu eingeschlossene Fallserie bzw. einarmige Studie wurden mit einem moderaten bzw. geringen Risiko für Verzerrungen eingestuft.

Risiko für Verzerrungen der eingeschlossenen Studien: niedrig bis hoch

Klinische Wirksamkeit

Die ADMIRE-CD-Studie zeigte eine statistisch signifikante Verbesserung des patientenrelevanten Endpunkts der kombinierten Remission. Nach 24 Wochen erreichten 50 % der Patient*innen der Interventionsgruppe, verglichen mit 34 % der Patient*innen der Kontrollgruppe (p=0,024) eine kombinierte Remission. Zum Zeitpunkt der 52-wöchigen Nachbeobachtung konnte bei 56 % der mit MSCs behandelten Patient*innen, im Vergleich zu 39 % der

statistisch signifikante (s.s.) Verbesserung der kombinierten Remission;

kein Unterschied bei Endpunkt „Reaktion“

Patient*innen, die das Placebo erhielten, eine kombinierte Remission nachgewiesen werden (p=0,021). Hinsichtlich der Reaktion waren keine signifikanten Veränderungen zu beobachten.

keine Verbesserungen der Lebensqualität

Die Lebensqualität wurde in den verfügbaren Studien anhand verschiedener Fragebögen als sekundärer Endpunkt erhoben. Es wurden keine statistisch signifikanten Unterschiede festgestellt, mit Ausnahme einiger Teilergebnisse in der Dosiseskalationsstudie.

Sicherheit

mehrere schwere, unerwünschte Nebenwirkungen

Mehrere schwere unerwünschte Nebenwirkungen wurden in einem RCT und zwei einarmigen Studien registriert. Bis zwei Jahre nach Behandlung traten schwere Analabszesse/Fisteln häufiger in der MSC-Gruppe als in der Kontrollgruppe des RCTs auf. Im Gegensatz dazu wurden nur in der Kontrollgruppe schwere Fälle von Morbus Crohn, Proktalgie, analen Entzündungen und Leberabszessen dokumentiert. In den einarmigen Studien traten je ein Fall von Pyrexie, perianalem Abszess, Darmverschluss, Komplikation der Darmanastomose, Harnstein, Morbus Crohn und tubulo-interstitieller Nephritis als schwerwiegende Nebenwirkung auf.

häufigste unerwünschte Nebenwirkungen: (peri)anale Abszesse

Unerwünschte Nebenwirkungen wurden von allen Studien berichtet, wobei (peri)anale Abszesse/Fisteln, Proktalgie und Nasopharyngitis in den Interventionsgruppen und Analabszesse/Fisteln, Proktalgie und Bauchschmerzen in den Kontrollgruppen der RCTs am häufigsten auftraten. Die ADMIRE-CD Studie berichtete, dass jeweils 9 % der Patient*innen beider Untersuchungsgruppen bis Woche 52 aufgrund von Nebenwirkungen vorzeitig aus der Studie ausschieden. Außerdem erkrankte ein Patient der Dosiseskalationsstudie an einem Adenokarzinom und verstarb zwei Jahre nach dem Eingriff; diese unerwünschte Nebenwirkung war jedoch nicht auf die Therapie zurückzuführen. Die häufigsten berichteten unerwünschten Nebenwirkungen in den nicht-vergleichenden Studien waren: (peri)anale Abszesse und Proktalgie.

Laufende Studien

5 laufende Studien

Insgesamt wurden fünf laufende RCTs identifiziert, in denen Stammzellen aus vier unterschiedlichen Quellen untersucht werden. Der RCT (ADMIRE-CD-II) mit der größten Studienpopulation (554 Patient*innen), der neue Informationen über die Wirksamkeit und Sicherheit von allogenen MSCs im Vergleich zu Placebo liefert, wird voraussichtlich im Juli 2023 abgeschlossen. Darüber hinaus wird in einem RCT (IRCT20210830052332N1) mit einer sehr kleinen Studienpopulation (24 Patient*innen) die Wirksamkeit und Sicherheit von allogenen MSCs in Kombination mit der Standardbehandlung im Vergleich zu anderen Komparatoren aus der klinischen Praxis (z. B. chirurgischer Eingriff) untersucht. Ein voraussichtliches Studienende ist allerdings noch nicht bekannt.

Diskussion

nur Placebo als Komparator

Beide eingeschlossenen RCTs verglichen MSCs mit einem Placebo. Ausgehend von der klinischen Praxis können z. B. Fistelpfropfen oder Fibrinkleber, als weiterer Komparator verwendet werden. Gegenwärtig gibt es allerdings keine Evidenz, die allogene MSCs im Vergleich zu anderen Behandlungen als Placebo untersucht.

wenig Daten zu Langzeiteffekten (> 52 Wochen)

Zu den Langzeiteffekten (> als 52 Wochen) liegen nur sehr wenige Daten aus zwei RCTs vor. Für eine Nachbeobachtung von 104 Wochen standen in einem RCT nur beschränkte Daten für 25 Patient*innen der Interventionsgruppe und 15 Patient*innen der Placebogruppe zur Verfügung (loss to follow-up > 80 %). Für das zweite RCT lagen für das Follow-up von 4 Jahren keine Vergleichsdaten zur Kontrollgruppe vor. Eine selektive Berichterstattung der beiden RCTs hinsichtlich der Langzeitwirkung von MSCs kann daher nicht ausgeschlossen werden. Die geringe Anzahl von Patient*innen in den Nachbeobachtungsstudien könnte zudem das Auftreten von (schwerwiegenden und seltenen) unerwünschten Nebenwirkungen beeinflusst haben.

Vertrauenswürdigkeit der Evidenz der entscheidungsrelevanten Endpunkte: sehr gering bis gering

Die Vertrauenswürdigkeit der Evidenz für die entscheidungsrelevanten Endpunkte für den Vergleich mit Placebo wurde als sehr gering bis gering eingeschätzt, da sich Limitationen aufgrund von fehlender Präzision (die meisten Studien hatten zu wenig Teilnehmer*innen, um einen statistisch signifikanten Unterschied festzustellen, oder hatten ein breites Konfidenzintervall) und des hohen RoB einiger eingeschlossener Studien ergaben.

MSCs derzeit nicht im Leistungskatalog in Österreich

Derzeit sind allogene MSCs für perianale Fisteln nicht im Leistungskatalog der leistungsorientierten Krankenanstaltenfinanzierung (LKF) enthalten und somit keine voll erstattungsfähige Leistung im österreichischen Gesundheitssystem.

Zusammenfassung und Empfehlung

positive klinische Ergebnisse nur zu 1 von 3 relevanten Endpunkten

keine Daten zu langfristigem Nutzen

Die derzeitige Evidenz zu allogenen mesenchymalen Stammzellen bei Morbus Crohn-assoziierten komplexen perianalen Fisteln deutet auf einen Nutzen für die kombinierte Remission im Vergleich zu Placebo hin: statistisch signifikante Unterschiede zugunsten von MSCs konnten nach 24 Wochen (geringe Vertrauenswürdigkeit der Evidenz) und 52 Wochen (sehr geringe Vertrauenswürdigkeit der Evidenz) beobachtet werden. Bei der Reaktion und Lebensqualität (gemessen als sekundäre Endpunkte) konnten keine statistisch signifikanten Gruppenunterschiede gefunden werden. Darüber hinaus besteht aufgrund der wenigen Daten Unsicherheit zum langfristigen Nutzen. Was die Sicherheit betrifft, so war das Auftreten unerwünschter Nebenwirkungen in der Behandlungs- und der Kontrollgruppe (Placebo) ähnlich. Eine Aufnahme in den Krankenhausleistungskatalog von allogenen MSCs für die Behandlung von perianalen Fisteln bei Morbus Crohn sollte auf erwachsene Patient*innen mit nicht aktivem/schwach aktivem luminalen Morbus Crohn, deren Fisteln auf mindestens eine konventionelle oder biologische Therapie unzureichend angesprochen haben, beschränkt werden. Weiters sollte die Aufnahme zeitlich – bis Daten zu anhaltenden Effekte vorliegen – und auf spezialisierte Zentren limitiert werden.

Aufnahme von MSCs in den Krankenhausleistungskatalog zeitlich beschränkt und nur für ausgewählte Pat. & spezialisierte Zentren

neue Studienergebnisse könnten mehr Evidenz liefern

Für weitere randomisierte Evidenz zur klinischen Wirksamkeit und Sicherheit verschiedener allogener MSCs im Vergleich zu Placebo und Standardbehandlung sind die Ergebnisse laufender RCTs abzuwarten. Neue Studienergebnisse aus der ADMIRE-CD-II-Studie könnten die Einschätzung der Wirksamkeit beeinflussen. Eine Neubewertung wird deshalb frühestens 2025 empfohlen.

Updated background and summary of the clinical evidence from 2018

Zusammenfassung des Berichtes von 2018

This chapter summarizes the results of the previous assessment published in 2018. The reader is referred to this report for a nuanced description of the health problem, current use, and technological characteristics. Information was checked for accuracy and updated in case changes occurred within the past years (e.g. for clinical guidelines).

Health problem and characteristics of the technology (updated)

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

Patient*innen mit komplexen perianalen Fisteln, verursacht durch Morbus Crohn

The scope of this report includes complex perianal fistulas caused by Crohn's disease (CD) that are refractory to conventional and/or biologic agents or in patients intolerant to such treatments.[2] CD is a chronic inflammatory condition characterised by transmural inflammation and skip lesions. The natural course of CD is deemed to be both relapsing and remitting. CD may lead to fibrosis and strictures or result in sinus tracts giving rise to micro-perforations and fistulas [1]. Fistulas usually occur when a fissure penetrates the gut wall surrounded by granulation tissue with acute and chronic inflammation [2]. In the case of perianal fistulas, an abnormal connection occurs between the anorectum and the perianal epithelium [3].[3,4]

geschätzte Inzidenzrate in Österreich: 11,5 pro 100.000 Einwohner*innen

Fisteleinteilung gemäß AGA Definition in einfache und komplexe Fisteln

The highest number of CD patients is reported in the United States of America, Canada, and Europe, with prevalence rates above 300 per 100,000 inhabitants [1]. In Austria, incidence rates of 11.5 per 100,000 inhabitants were estimated, with 9.5 and 14.6 in the rural and urban areas, respectively [4]. Perianal fistula disease affects about five to 40 percent of patients during their Crohn's disease [5]. The cumulative incidence of CD-associated perianal fistulas is 12% after one year and doubles 20 years after diagnosis [6]. The American Gastroenterological Association (AGA) distinguishes between simple and complex perianal fistulas. Complex fistulas are high and involve more than two-thirds of external sphincter, of high inter-sphincteric, high trans-sphincteric, extra-sphincteric or supra-sphincteric origin. Complex perianal fistulas may have multiple external openings and are possibly associated with present perianal abscesses, rectovaginal fistulas, anorectal strictures, or active rectal disease at endoscopy [7]. [5,6]

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[1] **A0001 –** For which health conditions, and for what purposes are allogeneic mesenchymal stem cells used?

[2] **A0007 –** What is the target population in this assessment?

[3] **A0002 –** What are Crohn's disease-associated complex perianal fistulas in the scope of this assessment?

[4] **A0004 –** What is the natural course of Crohn's disease-associated complex perianal fistulas?

[5] **A0006 –** What are the consequences of Crohn's disease-associated perianal fistulas for the society?

[6] **A0023 –** How many people belong to the target population?

komplexe, perianale Fisteln zeigen verschiedene Krankheitsbilder und wirken sich negative auf die Lebensqualität (LQ) aus

Complex perianal fistulas negatively impact patients' quality of life (QoL), particularly through anal pain on defecation and associated swelling. Other symptoms may include perianal itching, bleeding and/or discharge of pus or stool from cutaneous fistula openings, and fecal incontinence in some cases [2, 8, 9]. Besides, additional problems induced by perianal fistulas, such as secondary infections, abscess formations, organ system function impairment, and high disability rates, can occur [10]. About one-third of the patients with CD-associated perianal fistulas are non-responders to standard medical treatments, complicating the treatment of perianal fistulas [9]. [7,8]

Current clinical practice[9]

Erstlinientherapie: Anti-TNF-Therapie in Kombination mit weiteren Antibiotika und/oder Immunsuppressiva

In the first step, the diagnosis of CD-associated perianal fistulas should be followed by immediate damage control policies, including treatment of local infection, usually by antibiotics. In addition, perianal abscesses should be drained with non-cutting seton placements to control infections, as setons allow a continuous draining of the fistula tract [8, 11]. The choice of medical treatments depends on the location of the disease, its severity, and the response to earlier therapies [12]. Generally, the standard medical therapy consists of first-line anti-TNF therapy in combination with further antibiotics and/or immunosuppressants. For medication, the European Crohn's and Colitis Organisation (ECCO) guideline 2019 [13] recommends:

ECCO 2019 Leitlinien …

- Infliximab (strong recommendation; low quality of evidence) and maybe Adalimumab (weak recommendation, very low-quality evidence) for the induction and maintenance of remission in complex perianal fistulas in Crohn's disease.
- The use of antibiotics alone (weak recommendation, low-quality evidence) or thiopurine monotherapy (azathioprine, mercaptopurine) (weak recommendation, very low-quality evidence) for fistula closure in patients with Crohn's disease and complex perianal fistulas is not suggested.

… und AWMF S3-Leitlinie 2022

A current updated S3 guideline on the Diagnosis and Therapy of Crohn's Disease by the German Society for Gastroenterology, Digestive and Metabolic Diseases [14] recommends the following drug therapy for fistulas:

- The TNF-α antibody infliximab should be used as a primary therapy for complex perianal fistulas after abscess exclusion or drainage (evidence level 1, recommendation grade B, strong consensus).
- The TNF-α antibody adalimumab can be used as a secondary therapy (evidence level 2, recommendation grade 0, strong consensus).
- Antibiotics can be used for short-term improvement of acute clinical symptoms (evidence level 4, recommendation grade 0, strong consensus).

[7] **A0005 –** What is the burden of disease for patients with Crohn's disease-associated complex perianal fistulas?

[8] **A0003 –** What are the known risk factors for Crohn's disease-associated complex perianal fistulas?

[9] **A0025 –** How are Crohn's disease-associated complex perianal fistulas currently managed according to published guidelines and in practice?

bei fehlenden Ansprechen auf medikamentöse Therapie → Therapiewechsel

In the case of no clinical response to medical treatments, other treatment options apply: a change in biologics, e.g. a new anti-TNF agent, re-assessment and consideration of surgical options or local therapy such as mesenchymal stem cell (MSC) therapy [1, 9, 11].

vor jeder medizinischen oder chirurgischen Behandlung: lokale Infektionskontrolle

Surgical treatments are administered after imaging techniques and endoscopy have outlined the fistulas' anatomy [8]. Local infection control with an incision, drainage and/or seton placement is crucial before any definitive medical or surgical management. Once the perianal infection is controlled, management of the enterocutaneous tract can be planned utilising techniques such as a mucosal advancement flap, ligation of the inter-sphincteric fistula tract (LIFT), fistula plug or glue, diverting temporary stoma or proctectomy [2, 6, 14-18]. In complex perianal fistulas, combined surgical and medical management is more effective than either modality alone [2].

Features of the intervention[10]

MSC-Therapie als Add-on-Therapie zu medizinischen Standardtherapien

All surgical interventions have high recurrence rates in common and an increased risk of a permanent stoma. MSC therapy is recommended as an ultima ratio add-on therapy to standard medical therapies in patients refractory to anti-TNF agents (e.g. infliximab) as first-line therapy alone or combined with antibiotics and/or immunomodulators [19].[11] The MSC therapy claims to reduce the risk of repeated surgery and thus lead to lower morbidity (i.e. incontinence) and increased QoL [1, 9]. Also, MSC therapy may reduce the risk of removing parts of the colon and/or the need for a permanent stoma [18]. MSCs aim to be a less invasive therapy for sphincter-based fistulas, avoiding anal incontinence, recurrence of new fistulas, and reducing impairment caused by standard surgical treatment [20]. Another potential benefit of the therapy with MSCs is its local mode of action, meaning that the injection of MSCs might lead to fewer systemic complications, including infections, compared to systemic therapies [18].[12]

MSC-Administration in multidisziplinärem Setting und spezialisierten Krankenhäusern

MSCs are administered in a multidisciplinary setting consisting of a specialist surgeon, proctologist, gastroenterologist and radiologist [1, 9, 11, 21]. A magnetic resonance imaging (MRI) scan of the pelvis is required before surgery to guide the surgical procedure and assess for the presence of abscesses. At least two weeks before the investigational administration of MSCs, patients must undergo a fistula preparation visit, including an examination under general anaesthesia (EUA), fistula curettage and seton placement (if necessary). The actual interventional process is conducted under general anesthesia. For the preparations and the actual intervention, an operating room in a specialised hospital is needed [20].[11,13]

lokale Injektion in die Fisteln

During the interventional process, MSCs are injected locally and distributed into the patient's tissue adjacent to all fistula tracts and internal openings. Subsequently, the cells are distributed along the fistula tracks through external openings and openings of the fistula walls [22]. Therefore, a fine, long

[10] **B0001 –** What are the mesenchymal stem cells and what is/are its comparator(s)?

[11] **B0004 –** Who administers allogeneic mesenchymal stem cell transplantation and in what context and level of care are they provided?

[12] **B0002 –** What is the claimed benefit of allogeneic mesenchymal stem cells in relation to the comparators?

[13] **B0008 –** What kind of special premises are needed to use allogeneic mesenchymal stem cells?

needle is required. Repeated injections may be required for patients who did not achieve closure of their fistula tracts after the first administration [1].[14]

Alofisel®: ATMP EMA Zulassung seit 2018

Alofisel® (darvadstrocel) is an advanced therapy medicinal product[15] (ATMP) and was designated as an orphan medicinal product for the treatment of anal fistula by the European Medicines Agency (EMA) in 2009. In 2018, the European Union authorised Alofisel® to treat complex perianal fistulas. Patients must be adults with non-active/mildly active luminal Crohn's disease whose fistulas have responded inadequately to at least one conventional or biological therapy [24, 25].[16]

Österreich: keine Kostenübernahme

The Austrian hospital benefit catalogue does not include the administration of allogeneic MSCs (Cx601) for perianal fistulas. Therefore, it is not reimbursed by the Austrian health care system.[17] According to the submission materials, the expected annual utilisation of MSCs is 15 interventions per year in Austria. The expected annual utilisation of MSCs at the submitting hospital is four yearly interventions[18].

Results of the systematic review from 2018

Bericht 2018: 2 RCTs + 1 single-arm Studie (n=233 + 24 pts)

ØAlter: 37-41 Jahren

2 unterschiedliche Stammzelltypen und unterschiedliche Dosierungen in den 3 Studien

In the Ludwig Boltzmann Institute (LBI)-HTA report 2018 [16], effectiveness outcomes were addressed by two RCTs [26, 27] – the ADMIRE-CD trial and a dose-escalation trial – comparing allogeneic MSCs to placebo. One further single-arm study [22] was included for the safety outcomes. Both RCTs included in the initial trial included a total of 233 patients. The single-arm study included 24 patients. All studies included European patients. The mean age of all included patients was within a range of 37-41 years. The studies included patients based on different Crohn's Disease Activity Index (CDAI)-scores ranging from ≤200 to ≤250, indicating differences in the severity of the disease at baseline (study start). Two studies [26, 28] administered adipose-tissue-derived MSCs, while one study [27] assessed bone-marrow-derived stem cells. The dosages of the studies ranged from 10 million to 120 million cells. In one study [28], a second dose of cells was administered in case of lacking response to the first dose. Two studies [26, 28] were sponsored by the manufacturer TiGenix NV (which is part of the Takeda group since 2018), and one study [27] was funded by the DigestScience Foundation, which has possible ties to the manufacturer (Takeda Pharmaceutical Company Limited).

[14] **B0009 –** What supplies are needed to use allogeneic mesenchymal stem cells?

[15] These are medicines for human use that are based on genes, tissues or cells [23]

[16] **A0020 –** For which indications has the technology received marketing authorisation or CE marking?

[17] **A0021 –** What is the reimbursement status of allogeneic mesenchymal stem cells?

[18] **A0011 –** How much are allogeneic mesenchymal stem cells utilised?

Clinical effectiveness

Evidenz zu MSCs im Vergleich zu Placebo

Both RCTs [26, 27] reported improvements in combined remission –defined as the closure of all treated external openings draining at baseline despite gentle finger compression, the absence of discharge in all individual fistulas, and/or the absence of collections larger than 2 cm determined by MRI – in the interventional group compared to the placebo group, with significant improvements observed in the ADMIRE-CD trial [26]. Only ADMIRE-CD [26] reported on response rates. However, these results were not statistically significant. The two RCTs used similar scores to evaluate the patient's QoL/ severity of disease: the Irritable Bowel Disease Questionnaire (IBDQ) [26, 27], the Short-form 36 questionnaire (SF-36) [27], the Perianal Disease Activity Index (PDAI) [26, 27], the Crohn's Disease Activity Index (CDAI) [26, 27]. The main findings were that none of the studies showed a relevant improvement in QoL compared to the baseline or the control group, expect for some subscores of the dose-escalation trial.

statistisch signifikante Verbesserung der kombinierten Remission (1 RCT)

Safety

häufigste schwere, unerwünschte Nebenwirkungen (NW): Analabszesse

Several severe adverse events were reported in the included studies, with anal abscesses reported the most often. Across all studies, severe anal abscesses occurred more commonly in the MSC-groups than in the control groups. In contrast, severe cases of proctalgia, anal inflammation and liver abscesses were only reported in the control groups. The single-arm study [28] reported one case of pyrexia out of 24 patients. In the dose-escalation trial [27], one patient of the first MSC-group (10 million cell dose) developed an adenocarcinoma. However, the correlation between the administration of the MSC therapy and the occurrence of the adenocarcinoma remained unclear.

1 RCT:
1 Patient*in mit Adenokarzinom

Recommendation 2018

Evidenz unzureichend, um Wirksamkeit und Sicherheit von MSCs im Vergleich zu Placebo zu belegen; Re-Evaluierung 2022 vorgeschlagen

The current evidence is insufficient to prove that allogeneic MSCs in patients with complex perianal fistulas caused by CD, refractory to standard medical therapy, are more effective than placebo therapy. Additionally, it remains uncertain if MSCs are safer than placebo procedures. New study results will potentially influence the effectiveness and safety estimate considerably. The re-evaluation is recommended in 2022 when further ongoing studies will be finished, bringing additional evidence for long-term effectiveness and safety beyond 24 weeks.

UPDATE 2023

1 Objectives and Scope

1.1 PICO question

PIKO-Frage

Are adult human mesenchymal stem cells (MSCs) of allogeneic origin in comparison to placebo, fibrin glue or fistula plugs in patients with complex perianal fistulas without abscesses caused by non-active or mildly active luminal Crohn's disease (CD) more effective to increase the quality of life (QoL) and remission rates and safer concerning adverse events?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarized in Table 1-1.

Table 1-1: Inclusion criteria

Population	Adult (≥18 years old) patients with complex perianal fistulas without abscesses caused by non-active or mildly active luminal Crohn's disease. The presented fistulas are refractory to conventional and/or biologic agents for Crohn's disease, or in patients intolerant to such treatments. International classification of disease (ICD)-10-CM code: K50.1, Crohn's disease of the colon, K60.3 anal fistulas, K60.4 rectal fistulas, K60.5 anorectal fistulas Contraindications/exclusions: concomitant rectovaginal or abdominal fistulas MeSH Terms: Ileitis terminals, Enterocolitis regionalis, Enteritis regionalis colon/rectum, Morbus Crohn (MC), sklerosierende chronische Enteritis
Intervention	Adult human mesenchymal stem cells of allogeneic origin administered by a single local (intralesional) injection (as second line or add on therapy). ■ Alofisel® (Takeda Pharmaceutical Company Limited) MeSH Term: Mesenchymal stem cell, MSC, Cx601, Cx-601, darvadstrocel
Control	Placebo/Sham/No treatment Filling materials for the fistula tracts, i.e. fibrin glue, fistula seton
Outcomes	
Efficacy	■ Remission ■ Response ■ Quality of life ■ Fistula relapse-free survival
Safety	■ Serious adverse events ■ Adverse events
Study design	Time duration: 12.2017 – 12.2022
Efficacy	Randomised controlled trials Prospective non-randomised controlled trials
Safety	Randomised controlled trials Prospective non-randomised controlled trials Non-comparative observational studies ≥ 10 patients

2 Methods

2.1 Research questions

Assessment elements from the European Network for Health Technology Assessment (EUnetHTA) Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to the specific objectives of this assessment [29].

EUnetHTA Core Model® Version 4.2. für SR herangezogen

2.2 Clinical effectiveness and safety

2.2.1 Systematic literature search

The systematic literature search was conducted on 14.12.2022 in the following databases:

systematische Literatursuche in 5 Datenbanken

- Medline via Ovid
- Embase
- The Cochrane Library
- INAHTA database
- CRD (DARE, NHS-EED, HTA)

The systematic search was limited from 12.2017 to 12.2022, and articles published in English or German. After deduplication[19], overall 536 citations were included. The specific search strategy employed can be found in the Appendix.

Zeitraum: 2017-2022, deutsche und englische Literatur

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trial registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted in January 2023, resulting in 56 potential relevant hits.

Suche nach laufenden Studien

Manufacturers from the most common products (Alofisel®, Takeda Pharmaceutical Company Limited) submitted 13 publications after written contact, of which no new citations were identified.

insgesamt 536 Publikationen identifiziert

[19] Duplicates were removed with the automated deduplication tool "Deduklick" [30] and afterwards manually if some duplicates were not sorted out by the tool.

2.2.2 Flow chart of study selection

Literaturauswahl: 5 Studien (2 RCTs + 3 Beobachtungsstudien)

Overall, 536 hits were identified. Two independent researchers (VH, GG) screened the references, and in case of disagreement, a third researcher was involved to solve the differences. The selection process is displayed in Figure 2-1.

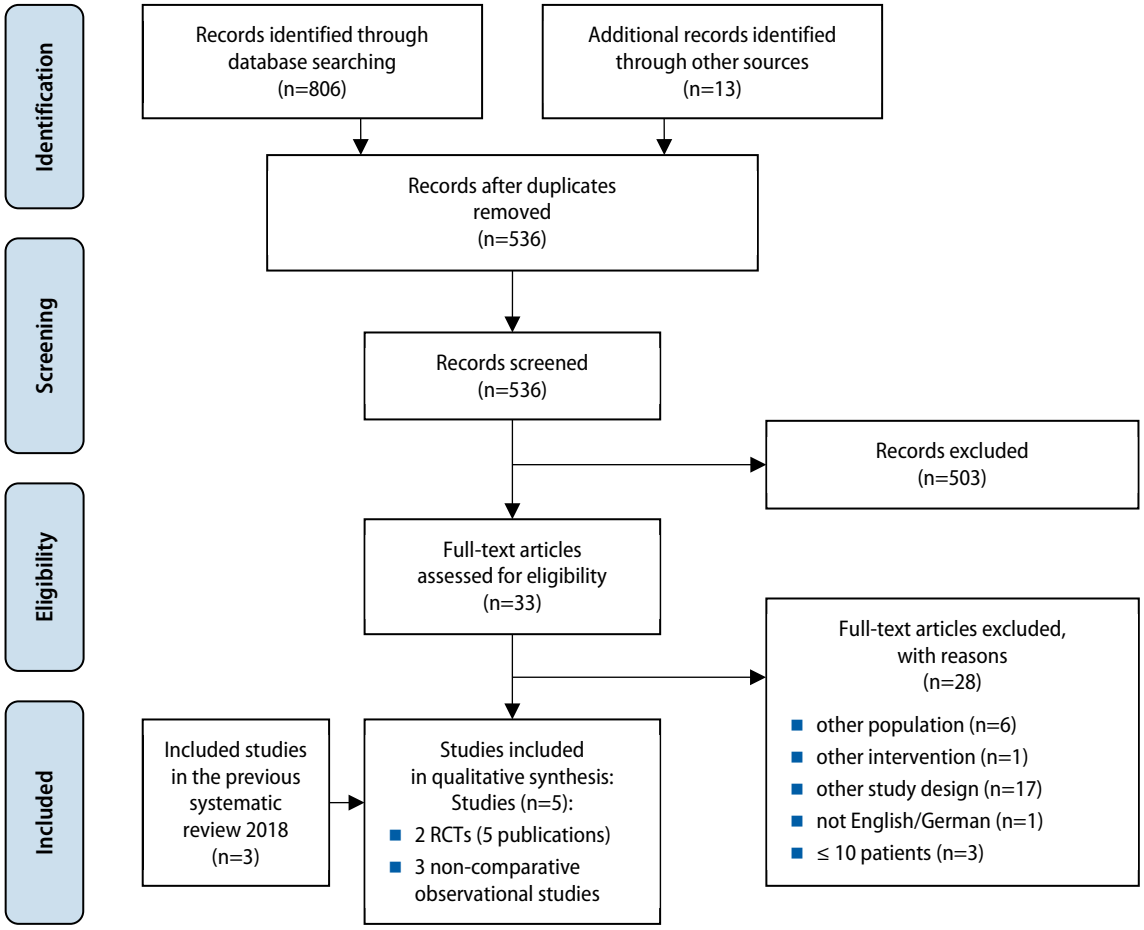

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

2.2.3 Analysis

Beurteilung der Studienqualität mit Cochrane RoB Tool (V.2) & IHE-20 Checkliste

Two independent researchers (VH, GG) critically appraised the included studies; differences were settled via consensus. The studies were systematically assessed for internal validity and risk of bias (RoB). The 'Cochrane Collaboration's tool' version 2 [31] was used for assessing the RoB for the RCTs and the 'Institute of Health Economics (IHE)-20 checklist' [32] was used for assessing the RoB of the non-comparative observational studies (see Appendix Table A-3 and Table A-4).

For the 'IHE-20 checklist', overall, the RoB was assessed using a predefined point score (range: 0-20, Table 2-1): Higher scores indicate a lower RoB, and lower scores indicate a high RoB. Detailed thresholds are presented in Table 2-2.

Table 2-1: Overall risk of bias point scores for risk of bias assessment of case-series

Answers to specific questions of the IHE checklist	Points
No	**0**
Partial	**0.5**
Unclear	**0.5**
Yes	**1**

Table 2-2: Cut-off criteria for the risk of bias assessment of overall risk of bias of case-series

Criteria	Points
Low risk	**> 18**
Moderate risk	**14.5 to 18**
High risk	**≤ 14**

Datenextraktion aus Studien

The data retrieved from the selected studies were systematically extracted into data-extraction-tables based on the data extraction tables from the 2018 report [16]. The tables were adjusted where necessary (see Table A-1 and Table A-2). No further data processing was applied. The data were extracted by one researcher (VH) and validated for accuracy by another researcher (GG).

2.2.4 Synthesis

qualitative Synthese der Evidenz

A qualitative synthesis of the evidence was performed. The research questions were answered in plain text format.

Zusammenfassung der Ergebnisse mit GRADE

Furthermore, the GRADE scheme was used to synthesise the identified evidence [33]. A GRADE summary of findings table and a GRADE evidence table were compiled (see Table 4-1 and Table A-5 in the Appendix). No inferential statistical analysis was conducted.

3 Results: Clinical effectiveness and Safety

3.1 Outcomes

3.1.1 Outcomes effectiveness

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

- Combined remission
- Response
- Quality of life (QoL) measured with Inflammatory Bowel Disease Questionnaire, Short-form-36 score and the two clinical scores: Perianal Disease Activity Index (CDAI) or Crohn's Disease Activity Index (PDAI).

wesentliche Endpunkte: Lebensqualität, kombinierte Remission, Reaktion

Combined remission is characterised as the closure of all treated external openings draining at baseline despite gentle finger compression, the absence of discharge in all individual fistulas, and/or the absence of collections larger than 2cm determined by MRI. In the literature, the combination of the last two criteria is also referred to as fistula healing of all individual fistulas [26, 27].

kombinierte Remission: Verschluss von allen nässelnden, behandelten Fisteln, keine Kollektionen >2 cm

Response is characterised as the closure of at least 50% of all treated external openings draining at baseline. The response definition was chosen from the biggest RCT available with 200 patients [16, 26].

Reaktion: Verschluss von zumindest 50 % der behandelten Fisteln

Inflammatory Bowel Disease Questionnaire (IBDQ) is a 32-item questionnaire filled in by patients, including four categories: bowel function, emotional status, systemic symptoms, and social functioning. It does not include a special category for perianal CD. The total score on this index ranges from 32 to 224, with higher scores indicating better QoL. The score of patients in remission is between 170 and 190 [34].

IBDQ: Fragebogen mit 4 Kategorien, höhere Punkte assoziiert mit besserer LQ

The Short-form-36 (SF-36) score is a multi-item generic health survey filled in by patients, including eight health domains: physical functioning, role physical functioning, bodily pain, general health, vitality, social functioning, emotional role, and mental health. The questionnaires are not specially formed for CD. The response scales for the SF-36 items vary across and within the scales with the number of response options ranging from 3 (for physical functioning) to 6 (for vitality and mental health). The scores are calculated by summing the responses across scale items and then transforming these raw scores to a 0–100 scale, with higher scores indicating better QoL [35].

SF-36: Fragebogen mit 8 Gesundheitszuständen, höhere Punkte assoziiert mit besserer LQ

The Perianal Disease Activity Index (PDAI) is a scoring system for clinicians to evaluate the severity of perianal CD, with lower scores indicating more severe disease. The score includes five items: discharge, pain, restriction of sexual activity, type of perianal disease, and degree of induration. Thus, it includes a special category for fistulising disease. Each item is graded on a 5- point Likert scale ranging from score 0 (no symptoms) to score 4 (severe symptoms) [34].

PDAI: Fragebogen mit 5 Kategorien, niedrigere Punkte assoziiert mit weniger schwerwiegender Krankheit

CDAI: Fragebogen mit 8 Kategorien, niedrigere Punkte assoziiert mit weniger schwerwiegender Krankheit

The Crohn's Disease Activity Index (CDAI) is a scoring system for clinicians to evaluate the severity of the disease, involving eight categories: the number of liquid stools, abdominal pain, general well-being, extraintestinal complications, antidiarrheal drugs, abdominal mass, and hematocrit body weight. A special category for fistulising disease is not included. The score ranges from 0 to 600, with lower scores indicating less experienced severe disease. The limit between active and very severe disease was defined as a cut-off value of 450 points. CDAI scores of 220-450 were labelled as moderately active disease and 150-219 as mildly active disease [34].

The following outcomes were considered to be also important:

wichtige Endpunkte: Klinische Remission: und …

Clinical remission is defined as the closure of all treated external openings draining at baseline despite gentle finger compression. The clinical remission definition was chosen from the biggest RCT available with 200 patients [26]. This endpoint was deemed important for this report but not critical to derive a recommendation.

… Fistel-rezidiv-freies-Überleben

Fistula relapse-free survival is the length of time patients survive without any signs or symptoms of returning and/or new fistulas after primary stem cell treatment for CD-associated perianal fistulas. According to expert opinions, a decisive benefit for patients results as of 13 weeks of fistula relapse-free survival [20]. This endpoint was deemed important, but not critical to derive a recommendation.

3.1.2 Outcomes safety

wesentliche Endpunkte: schwerwiegende unerwünschte NW und unerwünschte NW

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

- Serious adverse events (SAE) and
- Adverse events (AE)

NW definiert gemäß den EUnetHTA Leitlinien

In accordance with the EUnetHTA guidelines on safety outcomes, adverse events are defined as "any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device" [36]. Adverse events, which may occur during, shortly after the intervention or during follow-up, are the most common safety issues associated with the MSC-administration and the comparator interventions.

unerwünschte Ereignisse, die nach der Behandlung auftreten (S)TEAE & behandlungsbedingte unerwünschte Ereignisse (S)TRAE

These adverse events were classified as (severe) treatment-emergent adverse events (TEAE) or (severe) treatment-related adverse events (TRAE) by the included studies. Treatment-emergent adverse events are events that did not occur before medical treatment or are pre-existing events that worsen in intensity or frequency after treatment [37].

3.2 Included studies

3.2.1 Included studies effectiveness

To evaluate the effectiveness of allogeneic MSCs, we included two RCTs comparing allogeneic MSCs with placebo from the previous report – the ADMIRE-CD trial [26] and a dose-escalation trial [27]. In addition, to the primary analyses (both with a follow-up of 24 weeks), two follow-ups [38, 39], for the ADMIRE-CD trial [26] and one follow-up [40] for the dose-escalation trial [27] were new available.

2 RCTs aus vorherigem Bericht und 3 Nachbeobachtungen

Study characteristics

The ADMIRE-CD was conducted in Spain, Belgium, Austria, Canada, Germany, France, Italy, and Israel [20, 30, 31], and the dose-escalation trial in the Netherlands [27, 40]. The studies were sponsored by TiGenix NV (which is part of the Takeda group since 2018) and the Digest Science Foundation (which has possible ties to the manufacturer Takeda Pharmaceutical Company Limited), respectively. In both studies, the follow-up period for the primary analysis was 24 weeks, with extended follow-ups of two [26, 38, 39] and four years [27, 40], respectively. However, for some outcomes (e.g. the questionnaire survey for quality of life), there are missing outcome data after the 104-week follow-up and no comparative data on the control group after the 4-year follow-up.

Nachbeobachtung bis 2 Jahre (J.) (ADMIRE-CD) bzw. 4 J. (Dosiseskalationsstudie)

The overall RoB for the ADMIRE-CD trial with 107 patients in the intervention group and 105 in the control group (f/u 24 weeks) reached some concerns [26]. The RoB of the dose-escalation trial [27] with a total of 15 patients in the intervention groups and six patients in the control group (f/u 24 weeks) was judged to be high.

Risiko für Verzerrung: moderat bis hoch

The two RCTs investigated different types of MSCs, namely adipose-derived MSCs [26, 38, 39] and bone marrow (BM) derived MSCs [27, 40]. In ADMIRE-CD [26], 120 million cells were administered in the interventional group for a maximum of three fistula tracts and 24 mL saline solution (placebo) in the control group. In comparison, the dose-escalation trial study [27] investigated three different doses of BM-MSCs: (1) 10 million, (2) 30 million and (3) 90 million cells compared to placebo, defined as 0.9% NaCI/5% human albumin solution.

verschiedener Ursprung der MSCs: ADMIRE-CD: Fettgewebe, Dosisskalationsstudie: Knochenmark

Patient characteristics, follow-ups and outcomes

Overall, the RCTs enrolled 233 patients receiving different doses of allogeneic MCS (n=122) or standard care without allogeneic MCS (n=111). While ADMIRE-CD enrolled 212 patients (90 % of included patients in the RCTs) [26, 38, 39], the dose-escalation trial enrolled 21 patients (10 % of the included patients in the RCTs) [27, 40].

RCTs: insgesamt 233 Patient*innen

The loss to follow-up rate for the primary follow-up was 19.3% in the ADMIRE-CD trial (n=212) [26, 38, 39], while 0% of patients were lost to follow-up in the dose-escalation trial (n=21) [27, 40]. For long-term follow-up data, loss to follow-up was up to 38.2% after one year. In the intervention group, four patients did not participate in the 52-week follow-up and 14 patients discontinued treatment before week 52. Four patients experienced adverse events, seven patients had a significant worsening of clinical condition, one patient experienced a major protocol deviation, and two patients decided

(long term) loss to follow-up: 0 % bis 81 %

not to participate. In the control group, three participants did not enter the 52-week follow-up period and 19 participants dropped out of the study before week 52, three because of adverse events, seven because of significant clinical deterioration, six because of major protocol deviation, two decided not to participate and one because of another surgical procedure. After 104 weeks (two years) only 40 patients (18.9%, 25 in the intervention group and 15 in the control arm) opted to participate in an extended follow-up in ADMIRE-CD [26, 38, 39]. In the dose-escalation trial, 24% of patients in the intervention groups were lost to follow-up after four years; one patient died due to an adenocarcinoma in the caecum and one patient was lost to follow-up [27, 40].

Ø Alter: 38 Jahre, Ø Dauer von CD: 7 bis 17 Jahre

The mean age of the patients at the beginning of the trials was 38 years in both RCTs ranging from 33.4 to 40.8 years across the different treatment groups. The patients' mean CD duration ranged between 6.8 to 16.8 years. The mean fistula duration was reported by one study [27] and ranged from 3.6 to 9.0 years between the different treatment groups.

Frauenanteil: 44 % bis 80 %

The percentage of female patients in the intervention and control groups was 44% and 47% in ADMIRE-CD, respectively [26, 38, 39]. In the dose-escalation trial, the percentage of female patients was insufficiently reported for the control group and ranged from 0% to 80% in intervention groups, receiving different dosages of allogeneic MCS [27, 40].

unterschiedliche CDAI-Werte der Patient*innen in beiden Studien, sowie unterschiedliche Definition von komplexen, perianalen Fisteln

Both RCTs had the same inclusion criteria except for the categorisation of CDAI score and number of fistula tracts. In ADMIRE-CD [26], the included patients had a CDAI score ≤220 and complex perianal fistulas defined by the AGA guidelines. In comparison, the dose-escalation trial [27] included patients with a CDAI score ≤250 and actively draining perianal fistulas with one to two internal openings and one to three fistula tracts. For exclusion criteria, there was similarity, except for pregnancy and breastfeeding, renal or hepatic failure, change in concomitant medication, documented human immunodeficiency virus infection, active hepatitis B, C, or tuberculosis, malignancy within the past five years and a history of lymphoproliferative disease, which were only considered in the dose-escalation trial [26].

ADMIRE-CD: bis W. 52: (modifizierte) Intention-to-treat Analyse

primärer Endpunkt: kombinierte Remission (ADMIRE-CD) und Fistelheilung (Dosiseskalationsstudie)

For the evaluation of primary and secondary outcomes, the ADMIRE-CD study [26, 38, 39] used an intention to treat (ITT) or modified intention to treat (mITT) analysis up to week 52. Combined remission at week 24 was assessed as the primary outcome. This endpoint was assessed by clinical assessment of closure of external openings combined with the absence of collections >2 cm of treated perianal fistula (confirmed by masked central MRI). The dose-escalation trial used fistula healing, determined as the absence of discharge and <2 cm of fluid collection (measured by both physical examination and MRI) as a primary outcome [27, 40].

Study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table A-6.

3.2.2 Additional included studies safety

The two RCTs (incl. follow-ups) and three non-comparative observational studies (two single-arm studies [28, 41] and one case-series [42]) were included for the safety evaluation of allogeneic MSC for perianal fistulas. The two RCTs [26, 27] have already been described in the previous section (3.2.1).

2 RCTs und 3 Beobachtungsstudien für die Bewertung der Sicherheit

Study characteristics

The two single-arm studies were conducted in Spain [28] and Japan [41] and the case-series in Switzerland [42]. One study [28] was sponsored by the manufacturer TiGenix NV and one [41] by Takeda Pharmaceutical Company Limited. No sponsoring was declared for the third one [42]. The length of the reported follow-ups were 24 weeks [28] and 52 weeks [41, 42].

2 Studien industriefinanziert

The overall RoB reached high risk for one study [28] moderate for another study [42], and low for the third study [41].

Verzerrungsrisiko: niedrig bis hoch

The three studies [28, 41] assessed the safety and efficacy of allogeneic adipose-derived MSCs. In one study [28], 20 million cells were injected into one draining fistula tract during the first administration. If fistula closure was not complete at week 12, the second administration of 40 million cells was performed. In the second study [42], patients were treated with a local injection of 120 million allogeneic MSCs. In the Japanese study [41], patients received 24 mL (120×10^6 cells) of allogeneic MSCs as a single intralesional dose.

Ursprung der MSCs: Fettgewebe

Patient characteristics, follow-ups and outcomes

The studies enrolled 57 patients [28, 41, 42]. In one study [28], 24 patients with complex perianal fistulas caused by CD underwent the administration of allogeneic MSCs. Eight of the 24 patients (33%) withdrew from the study prematurely. Thus, 16 patients completed the study period of 24 weeks. The Switzerland study [36] included eleven patients with complex perianal fistulas with non-active or mildly active luminal disease. This studies aim was to examine the effect of commercially available drug "Darvadstrocel" outside a clinical trial setting. None of the patients was lost to follow-up. The third study [41] included 22 patients, of which two (9%) were lost to follow-up prematurely (between week 25 and 52) due to lack of efficacy.

insgesamt 57 Patient*innen

loss to follow-up (2 Studien): 2 und 8 Patient*innen

The mean age of the patients ranged from 36 to 38 years. The mean CD duration was reported by two studies [41, 42] and ranged between 11.3 to 13.9 years. The mean fistula duration was only reported by one study [42] and was 7.8 years.

Ø Alter: 36 – 38 Jahre
Ø Dauer von CD: 11 bis 14 Jahre

The percentage of female patients was 54.2% in one study [28], 27.3% in the second [42] and 36.4% in the third study [41].

Frauenanteil: 27 % bis 54 %

Two non-comparative studies, included patients with a CDAI score of ≤220 [26, 41, 42] and ≤250 [12] and one single-arm study [28] included patients with non-active luminal CD, defined by a CDAI ≤200. Regarding the classification of the fistulas, this study [28] reported the effect of allogeneic MSCs on complex perianal fistulas. However, the majority of the treated fistulas had solely one track (62.5%), one external opening (75.0%) and pictured transsphincteric tracks (70.8). The other two non-comparative studies [41, 42] used the same inclusion criteria as the AMIRE-CD trial. They included patients with refractory complex perianal fistulas with a maximum of two internal and three external openings. One study [42] expanded the criteria to

unterschiedliche CDAI-Werte, sowie unterschiedliche Definition von komplexen, perianalen Fisteln

patients with CD and ileoanal pouch following restorative proctocolectomy for ulcerative colitis as initial diagnosis in two patients who had already had a fistula surgery.

primäre Endpunkte: Häufigkeit von unerwünschten Ereignissen, die nach der Behandlung auftreten (1 Studie) und kombinierte Remission (1 Studie)

One single-arm study used the incidence of treatment-emergent adverse events as the primary endpoint [28], and the other the proportion of patients with combined remission at Week 24. [41]. In this study [41], primary and secondary endpoints were analysed in the intention-to-treat (ITT) population, which included all patients enrolled in the treatment period. No information about the primary endpoint was given for the case-series [42].

Study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table A-6.

3.3 Results

3.3.1 Clinical effectiveness outcomes

In the following, the effectiveness-related outcomes are presented. We searched for minimally clinically important differences (MCID) for the outcomes but could not find validated MCID.

Treatment effect on morbidity[20]

Combined remission

2 RCTs (n=233), ADMIRE-CD (n=212): s.s. Unterschied zugunsten MSCs nach 24 W. (n=212, 50 % vs. 34 %) und 52 W. (n=204, 56 % vs. 39 %) Dosiseskalations-RCT: n.s. Unterschiede

Combined remission was reported in the primary analyses of both RCTs [26, 27] and the 52-week follow-up of the ADMIRE-CD trial [38]. Statistically significant improvement in the interventional group compared to the placebo arm was observed in the ADMIRE-CD study [26, 38, 39]: combined remission after 24 weeks was achieved in 53 (50%) out of 107 patients vs. 36 (34%) out of 105 patients in the intervention and control group (mean difference 15.2%, p=0.024), respectively. At the 52-week follow-up [38], combined remission was observed in 61 (56.3%) out of 103 patients of the intervention group compared to 39 (38.6%) out of 101 placebo subjects (mean difference: 17.7%, p=0.021). In the dose-escalation trial, improvements were also observable after 12 weeks [27], but these were not statistically significant.

Response

1 RCT (n=212): ADMIRE-CD (n=204): keine s.s. Unterschiede im Ansprechen nach 24 und 52 W.

Response rates were reported in the ADMIRE-CD trial [26, 38, 39]. After 24 weeks, 71 (66%) out of 107 patients receiving MSCs responded to the treatment, compared to 56 (53%) out of 105 patients who received placebo, but the difference was not statistically significant (p=0.054). After 52 weeks [38], 68 (66%) out of 103 patients of the intervention group versus 56 (55.4%) out of 101 placebo patients responded to the treatment. However, no statistical significance could be observed (p=0.128).

[20] **D0006 –** How do allogeneic mesenchymal stem cells affect progression (or recurrence) of Crohn's disease-associated complex perianal fistulas?

Clinical remission

Clinical remission was reported in both RCTs at every measurement time point [26, 27, 38-40]. A significant improvement in clinical remission in the interventional group compared to the placebo arm was observed after the follow-up of 52 weeks in ADMIRE-CD [26, 38, 39]. In the intervention group, 61 (59.2%) out of 103 patients achieved clinical remission compared to 42 (41.6%) out of 101 patients in the placebo group (mean difference: 17.6%, p= 0.013) [38]. No statistically significant differences were reported at any other time point in this study [26, 38, 39] or in the dose-escalation trial [27, 40].

2 RCTs (n=233), ADMIRE-CD (n=204): 52 W: s.s. Unterschied zugunsten MSCs (59 vs. 42 %), n.s. zu anderen Zeitpunkten, Dosiseskalations-RCT: n.s. Unterschiede

Relapse-free survival

In ADMIRE-CD [26, 38, 39] at the 52 weeks follow-up 39 (75%) out of 52 of patients who received MSCs and had a combined remission at week 24, were relapse-free compared with 19 (56%) patients out of 34 from the placebo group (difference 19.1 percentage points (-1.3 to 39.5); p= 0.052) [38].

1 RCT (n=212): ADMIRE-CD keine s.s. Unterschiede bei Rückfällen

Health related quality of life[21,22,23]

Both RCTs reported on QoL using different validated measurement instruments.

Lebensqualität:

The RCTs used different versions of the *IBDQ questionnaire:* ADMIRE-CD [26, 38, 39] used the IBDQ and reported similar improvements in QoL-scores from baseline to week 52 in the treatment group (n=103) and control group (n=101). The dose-escalation trial (n=21) used the short-form IBDQ [27, 40]. No statistically significant differences between different doses of MSC and placebo were observable at week 24. At the 4-year follow-up, a significant improvement compared to baseline was observable in patients receiving MSCs (n=13; p=0.047) [40].

2 RCTs (n=225), IBDQ, 1 RCT (n=204): keine s.s. Unterschiede, sIBDQ, 1 RCT (n=13): s.s. Unterschied MSC vs. Basiswert nach 4 J.

Solely the dose-escalation RCT [27, 40] reported *SF-36* scores for week 0, week 24 (n=21) and the four-year follow-up (n=13). There were no statistically significant differences to baseline and between different doses of MSC and placebo in any of the domains observable at any time point.

SF-36: 1 RCT (n=21): keine s.s. Unterschiede

Clinical scores

PDAI-scores were reported form the primary analyses of the RCTs [26, 27] and their follow-ups of 52 weeks (ADMIRE-CD [38]) and four years (dose-escalation RCT [40]). At week 12 in both RCTs [26, 27] patients' disease was less severe compared to baseline, with better improvements in the interventional group [26, 27]. Significant PDAI decrease was observable in the dose-escalation trial at week 12 in patients of the second intervention group (n=5) compared with baseline (p=0.03) as well as with placebo treatment (n=6, p=0.04). No statistically significant effects were observed at any other time point in the studies [26, 27, 38, 40].

PDAI: 2 RCTs (n=225), 1 RCT (n=204): keine s.s. Unterschiede, 1 RCT (n=21): s.s. Unterschied MSC vs. Basiswert nach 12 W.

[21] **D0005 –** How do allogeneic mesenchymal stem cells affect progression (or recurrence) of Crohn's disease-associated complex perianal fistulas?

[22] **D0012 –** What is the effect of allogeneic mesenchymal stem cells on generic health-related quality of life?

[23] **D0013 –** What is the effect of allogeneic mesenchymal stem cells on disease-specific quality of life?

CDAI: 2 RCTs (n=225), 1 RCT (n=204): keine s.s. Unterschiede, 1 RCT (n=13): s.s Unterschied MSC vs. Basiswert nach 4 J.

Both primary analyses [26, 27] reported *CDAI scores*. Further data was available for the 52-week (ADMIRE-CD [38]) and 4-year follow-up (dose-escalation trial [40]). In the ADMIRE-CD trial, different categories were reported with an overall worse severe disease of the patients at week 24 [26] compared to baseline for both groups (n=204). However, there was less worsening for the control group (n=101). After 52 weeks [38], both groups still showed more severe disease in the patients compared to baseline, but at this time point, the deterioration was slightly greater in the control group. In the dose-escalation RCT [27, 40] less severe disease at week 24 compared to baseline was reported in all groups, except the third interventional group (n=5). After the 4-year follow-up, a significant improvement comparing baseline was observable in patients receiving MSCs (n=13; p=0.014).

Specific improvements or deteriorations in the scores are listed in the GRADE Table A-5. An overview of all results of the RCTs are displayed in Table A-1.

Function[24,25]

keine vergleichenden Daten zu Körperfunktion, Darstellung an Hand der erhobenen Fragebögen

None of the studies reported on comparative evidence concerning patient's body function. The effect of MSC therapies on patients' body functions was illustrated with different validated QoL scores. Both studies found slight within-group differences and compared to baseline, with few statistically significant differences in the dose-escalation trial: there might be minor improvements in the CDAI score, PDAI score and some subscores of the IBDQ and SF-36 sores, e.g. for physical functioning (i.e. the number of liquid stools), social functioning and mental health.

Patient satisfaction[26]

keine Daten zur Patient*innenzufriedenheit

None of the studies reported results on patient satisfaction.

3.3.2 Patient safety[27,28]

Sicherheit: Evidenz aus 2 RCTs und 3 Beobachtungsstudien

Safety outcomes were reported by the two included RCTs [26, 27, 38-40] and three non-comparative observational studies [28, 41, 42].

Serious adverse events

1 RCT und 2 Beobachtungsstudien zu STEAE und STRAE

Serious adverse events and if they were related to the treatment or not were reported by three studies (one RCT [26, 38, 39] and two single-arm studies [28, 41]).

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[24] **D0011 –** What is the effect of allogeneic mesenchymal stem cells on patients' body functions?

[25] **D0016 –** How does the use of allogeneic mesenchymal stem cells affect activities of daily living?

[26] **D0017 –** Was the use of allogeneic mesenchymal stem cells worthwhile?

[27] **C0008 –** How safe are allogeneic mesenchymal stem cells in comparison to placebo?

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

Serious treatment-emergent adverse events

Serious treatment-emergent adverse events were reported in two studies (one RCT [26, 38, 39] and one single-arm study [41]). In the primary analysis of ADMIRE-CD, 32 out of 205 patients experienced severe treatment-emergent adverse events (STEAE) after 24 weeks [26]: 18 (17%) and 14 (14%) STEAEs occurred in the intervention and control group, respectively. Most patients suffered from anal abscesses (n=9 vs. n=7). After 52 weeks [38], 25 (24.3%) out of 103 patients of the MSC and 21 (20.6%) out of 102 patients of the placebo group experienced STEAE, with anal abscesses/fistulas being the most common ones in both groups. Between weeks 52 and 104 [39], STEAE were reported from three (12%) out of 25 patients in the intervention group and one (6.7%) out of 15 patients in the control group. The reported events were fistula discharge in one patient from each group, as well as one anal fistula and one anal abscess in the intervention group. The single-arm study [41] (mean follow-up: 52 weeks) reported that four (18%, n=22) patients experienced STEAE after 52 weeks. The mentioned events were intestinal obstruction, intestinal anastomosis complication, urinary calculus and tubulointerstitial nephritis.

STEAE: 1 RCT (n=205) & 1 einarmige Studie (n=22)

ADMIRE-CD: 52 W. (n=205): 24 % vs. 21 %, 104 W. (n=40): 12 % vs. 7 %

häufigstes STEAE: Analabszess

einarmige Studie (n=22): 52 W.: 18 %

Serious treatment-related adverse events

Serious treatment-related adverse events (STRAE) were reported in three studies (one RCT [26, 38, 39] and two single-arm studies [28, 41]). In ADMIRE-CD [26, 38, 39], five patients (5%) of the allogeneic MSC (n=103) and seven (7%) of the placebo group (n=102) reported STRAEs up to 24 weeks [26]. The most reported STRAE were anal abscesses (n=5 vs. n=5), followed by proctalgia, anal inflammation and liver abscess in one patient each from the control group. By week 52, the follow-up study [38] reported seven patients per group who developed a serious treatment-related AE. STRAE were anal abscesses/fistula in both groups (n=7 vs. n=5), and proctalgia, anal inflammation and liver abscess in one patient each from the control group. No further STRAEs occurred from week 52 to week 104 (n=40) [39]. In the two single-arm studies [28, 41] (follow-up range 24 to 52 weeks, n=38), overall, three (8%) STRAEs occurred in patients receiving MSCs. One patient each experienced pyrexia (fever) and a perianal abscess during the follow-up of 24 weeks [28] and Crohn's disease during the follow-up of 52 weeks [41].

STRAE: 1 RCT (n=205), 2 einarmige Studien (n=38)

ADMIRE-CD (n=205): 52 W: 7 % vs. 7 %

einarmige Studien (n=38): 8 %

häufigstes STRAE: (peri)anale Abszesse

Adverse events

Adverse events were reported in all studies (two RCTs [26, 27, 38-40] and three non-comparative studies [28, 41, 42]). Two studies (one RCT [26, 38, 39] and one single-arm study [41]) provided information if patients experienced adverse events that were treatment-emergent or treatment-related. Further, two studies (one RCT [27, 40] and one single-arm trial [28]) made a distinction between adverse events and treatment-related adverse events. No information if any of the adverse events were treatment-related was provided by the case-series [42]. Due to the lack of clear distinction, the reported AEs are consequently described under the classification of adverse events and treatment-related AEs.

2 RCTs (n=226), 3 nicht-vergleichende Studien (n=49)

Adverse events

AE: 2 RCTs (n=226), 3 nicht-vergleichende Studien (n=49)

In the primary analysis of ADMIRE-CD [26] (24-week follow-up, n=204), TEAE led to study withdrawal in five (5%) patients of the intervention group and six (6%) of the control group. The most common TEAEs reported in the intervention group (n=103) at this time point were 13 cases of proctalgia, 12 cases of anal abscesses and ten cases of nasopharyngitis. In the control group (n=102), 13 cases of anal abscesses, 11 cases of proctalgia and six cases each of fistula and abdominal pain were the most reported TEAS.

2 RCTs (n=226): häufigste NW in beiden Gruppen: anale Abszesse/Fisteln, Proktalgie, Nasopharyngitis

ADMIRE-CD (n=205), 52 W: TEAEs, die zu Studienabbruch führten: 9 % vs. 9 % insg. 77 % vs. 73 % TEAE

Up to week 52 [38], nine (8.7%) patients from the MSC group and nine (8.8%) from the placebo group withdrew due to TEAEs. Overall, 79 patients (76.7%, n=203) in the intervention and 74 (72.5%, n=102) in the control group reported TEAE up to this follow-up. The three most common TEAEs were anal abscesses/fistulas (34 [33%] vs. 30 [29.4%]), proctalgia (15 [14.6%] vs. 12 [11.8%]) and nasopharyngitis (11 [10.7%] vs. 5 [4.9%]). Other TEAEs that occurred in more than 5% of patients were diarrhea, pyrexia, arthralgia, abdominal pain and Crohn's disease. From week 52 to week 104, no TEAEs were reported from patients in the ADMIRE-CD [39].

Dosiseskalationsstudie (n=23, bis 4 J. Nachbeobachtung): 1 Adenokarzinom, 1 Lymphoproliferative B-Zell-Krankheit

In the dose-escalation trial [27, 40], all adverse events were recorded during follow-up visits. Several AEs occurred, but none were judged to be related to MSC injection. However, there was a lack of information on the severity. In this study [27, 40], all patients (n=21) reported symptoms of postoperative anal pain and pus and/or blood discharge from the fistula or anus for approximately one week. Other most frequently reported AEs after 24 weeks were nasopharyngitis[29], abdominal pain[30], anal abscesses[31] and painful perianal swelling[32]. One patient experienced an adenocarcinoma of the cecum with peritoneal carcinomatosis more than 15 months after the injection of 10 million MSCs and died two years after intervention. In general, the lowest dose of MSCs resulted in more adverse events than the highest MSC dose and more adverse events than in the control group. The median dose of MSCs resulted in the lowest number of adverse events.[33] After the 4-year follow-up (n=13) [40], the most commonly reported adverse events were: seven infections in five patients, six perianal abscesses in four patients and three cases of CD activity in the past four years in three patients. Further, one patient each experienced gout, psoriasis, uveitis and a B-cell lymphoproliferative disease (LPD). However, after investigation, it was concluded that a relation between the Epstein-Barr virus (EBV)-associated LPD and the BM-MSC therapy was unlikely but rather was the result of prolonged immunosuppressive therapy.

[29] IG1: n=5 (100); IG2: n=2 (40); IG3: n=1 (20); CG: n=2 (33.3)

[30] IG1: n=1 (20); IG2: n=1 (20); IG3: n=3 (60); CG: n=0

[31] IG1: n=1 (20); IG2: n=1 (20); IG3: n=1 (20); CG: n=1 (16.7)

[32] IG1: n=1 (20); IG2: n=0; IG3: n=0; CG: n=3 (50)

[33] C0002 – Are the harms related to dosage or frequency of applying allogeneic mesenchymal stem cells?

The most frequent AEs reported from patients in the non-comparative studies [28, 41, 42] (follow-up range 24 weeks to 52 weeks, n=38) were eight cases each of (peri)anal abscesses and proctalgia, five cases of nasopharyngitis and four cases each of pyrexia and anal fistula. Other mentioned adverse events were three cases each of increased C reactive protein, anxiety and muscoskeletal and connective tissue disorders, two cases each of anal fistula infection, Crohn's disease, nausea, acrochordon and one case of flu-like symptoms and cytomegalovirus (CMV) viraemia. Further, in one study [42], one out of eleven patients experienced a testicular carcinoma more than 16 weeks after treatment. However, a connection to the treatment was deemed unlikely.

3 nicht-vergleichende Studien (n=49): häufigste NW: (pri)anale Abszesse, Proktalgie, Nasopharyngitis

1 Hodenkarzinom

Treatment-related adverse events

In ADMIRE-CD [26, 38, 39] TRAEs reported in more than 2% of patients up to week 52 were anal abscesses/fistulas [13 (12.6%) vs. 16 (15.7%)], proctalgia [5 (4.9%) vs. 8 (7.8%)], procedural pain [1 (1.0%) vs. 2 (2.0%)] and induration [0 (0%) vs. 2 (2.0%)]. No TEAEs occurred in weeks 52 to 104 after the study started [39]. In the two single-arm studies (follow-up range 24 weeks to 52 weeks, n=38), anal abscesses (n=3), and pyrexia, uterine leiomyoma, diarrhea and blood bilirubin increase in one patient each were reported as treatment-related adverse events [28, 41].

TRAE: 1 RCT (n=205), 2 einarmige Studien (n=38)

häufigste behandlungsbedingte NW: Analabszesse

4 Certainty of evidence

RCTs: einige Bedenken bis hohes Verzerrungsrisiko

For this update report, no new RCTs were identified. This evidence synthesis newly included long-term follow-up publications of available RCTs and two non-comparative observational studies. The risk of bias for the RCTs was assessed with the Cochrane Risk of Bias 2 tool [31]. The RoB of the ADMIRE-CD trial [26] was assessed to have some concerns, mainly due to the unclear blinding of the patients. The dose-escalation RCT [27] was ranked as having a high risk of bias. The main reasons for the high RoB in the mentioned RCT was due to the missing information about the allocation method and the missing information about an appropriate analysis used to estimate the effect of assignment to intervention.

nicht-vergleichende Beobachtungsstudien: niedriges bis hohes Verzerrungsrisiko

In the three non-comparative observational studies, the RoB was assessed with the IHE-20 checklist [32]. The study [28] included in the previous report was judged to have a high risk, and the new non-comparative studies were assessed to have a moderate [42] and low risk of bias [41]. The main reasons for the RoB in the non-comparative studies were due to the unclear information if the study was conducted prospectively, the patients were recruited consecutively and if the outcome assessors were blinded to the intervention. Further, in one single-arm study, the missing comparison of effects before and after the intervention and that the results did not support the conclusion led to a higher risk of bias (see Appendix Table A-3 to Table A-4).

Vertrauenswürdigkeit der Evidenz zu Effektivität und Sicherheit von MSCs vs. Placebo …

Overall, the level of certainty for the effectiveness and safety of allogeneic MSCs compared to placebo ranged between very low and low. No evidence is available for comparing the MSCs to fistula plugs or fibrin glue.

… LQ (2 RCTs): sehr gering,

kombinierte Remission (2 RCTs): sehr gering – gering,

Reaktion (1 RCT): sehr gering – gering,

Sicherheit (2 RCTs): sehr gering – gering,

Sicherheit (3 nicht-vergleichende Studien): sehr gering

The level of certainty for QoL based on two RCTs was rated as very low due to RoB, downgraded by two levels to very serious (studies with bias due to deviations from the planned interventions, bias due to the randomisation process, missing data and loss to f/u and subjective outcome measures for the assessment of quality of life) and indirectness (heterogeneity of the intervention and different inclusion criteria) and imprecision (optimal information size not reached), both downgraded by one level to serious. The level of certainty on combined remission and response for a follow-up of 24 weeks, based on two and one RCT respectively, was judged to be low due to imprecision, which was downgraded by two levels to very serious (small study population and wide confidence intervals). The level of certainty regarding combined remission and response for 52 weeks of follow-up, both based on one RCT, was rated very low due to RoB, downgraded by one level (high losses to follow-up for long-term analysis), and imprecision, downgraded by two levels to very serious (optimal information size not reached and wide confidence intervals). The level of certainty for safety up to week 24, based on two RCTs, was rated low due to imprecision (small sample size) being downgraded by two levels to very serious. The level of certainty for safety up to 4 years, based on two RCTs, was rated as very low due to the downgrades of RoB by one level to serious (high loss to follow-up for the long-term analysis) and imprecision by two levels to very serious (optimal information size not reached). The level of certainty for safety from the non-comparative studies was judged to be very low, due to RoB (studies with unclear study design, intervention and co-intervention, outcome measures, results and conclusions) and imprecision (optimal information size not reached), both downgraded by one level to serious.

Vertrauenswürdigkeit der Evidenz nach GRADE

The level of certainty was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) Scheme [33] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement, a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [33].

Unterscheidung zwischen hoher, moderater, niedriger oder sehr niedriger Vertrauenswürdigkeit der Evidenz

GRADE uses four categories to rank the level of certainty:

- 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 and in the evidence profile in Appendix Table A-5.

Table 4-1: Summary of findings table of allogeneic MSCs for Crohn's disease-associated complex perianal fistulas

Outcome	Anticipated effects (Risk with placebo/Risk with allogneneic MSCs)	N of analysed participants (studies)	Certainty	Comments
Quality of life (IBDQ, PDAI, CDAI, SF-36)	Long-term within-group differences were found for IBDQ and CDAI scores at 4 years f/u. For between-group differences, none of the RCTs except for the PDAI score at week 12 detected a significant difference between one treatment group and the control group.	225 (2 RCTs)	⨁◯◯◯[a,b,c] very low	Patient-reported outcome
Combined remission follow-up: mean 24 weeks	W 24: mean combined remission was 15% more in the IG (n=107 vs. n=105; p=0.024)	233 (2 RCTs)	⨁⨁◯◯[d,e] low	Evidence is mainly applicable to adipose-tissue-derived MSCs
Combined remission follow-up: mean 52 weeks	W 52: mean combined remission was 17.7% more in the IG (n=102 vs. n=101; p=0.010)	204 (1 RCT)	⨁◯◯◯[e,f] very low	High loss to follow-up for the long-term analysis.
Response follow-up: mean 24 weeks	W 24: mean response was 13% more in the IG (n=107 vs. n=105; p=0.054)	204 (1 RCT)	⨁⨁◯◯[e] low	Optimal information size not reached
Response follow-up: mean 52 weeks	W 52: mean response was 10.6 % more in the IG (n=102 vs. n=101; p=0.128)	204 (1 RCT)	⨁◯◯◯[e,f] very low	High loss to follow-up for the long-term analysis.
(Serious) adverse events (RCT evidence: up to 24 w f/u)	STRAE up to w 24 (n=205): 5 (5 %) vs. 7 (7 %) Other less severe AEs and SAE included a variety of complications as pyrexia, diarrhea, proctalgia, fistula discharge. The reader is referred to Table A-1 for a nuanced description of these AEs.	226 (2 RCTs)	⨁⨁◯◯[c] low	Optimal information size not reached.
(Serious) adverse events (RCT evidence: up to 4 yr f/u)	STRAE up to w 52 (n=205): 7 (6.8 %) vs. 7 (7.1 %) One patient died in the DE study due to an adenocarcinoma (n=15) Other less severe AEs and SAE included a variety of complications as arthralgia, abdominal pain, proctalgia, fistula discharge (up to 4 yr f/u). The reader is referred to Table A-1 for a nuanced description of these AEs.	220 (2 RCTs)	⨁◯◯◯[c,f] very low	High loss to follow-up for the long-term analysis.
(Serious) adverse events (observational evidence: up to 52 w f/u)	7 cases of SAE (up to 52 w f/u) Other less severe AEs included a variety of complications as nausea, proctalgia, and abscesses (up to 52 w f/u).	49 (3 non-comparative observational studies)	⨁◯◯◯[c,g] very low	Optimal information size not reached

Abbreviations: AE(s) – (serious) adverse events; CDAI – Crohn's Disease Activity Index; CG – control group; f/u – follow-up; IBDQ – Irritable Bowel Disease Questionnaire; IG – interventional group; MRI – Magnetic Resonance Imaging; MSC – mesenchymal stem cells; p – p-value; PDAI – Perianal Disease Activity Index; RCT – randomized controlled trail; SAE(s) – serious adverse events; SF-36 – Short-form 36; STRAE – serious treatment-related adverse events; w – week; yr – year.

Explanations

[a] *Risk of Bias was downgraded by two levels to very serious, due to bias due to deviations from intended interventions, bias arising from the randomization process as well as missing data and a high loss to f/u and as studies used subjective outcome measures (questionnaires) for the assessment of quality of life.*

[b] *Indirectness was downgraded by one level to serious as there were some heterogeneity in the interventions (allogeneic MSCs from bone-marrow vs. adipose derived tissue) and inclusion criteria (definition of complex fistula + CDAI score).*

[c] *Imprecision was downgraded by two levels to very serious, as the optimal information size was not reached.*

[d] *No indicators detected but evidence is mostly applicable to adipose-derived MSC.*

[e] *Imprecision was downgraded by two levels to very serious, as the optimal information size was not reached and wide confidence intervals were reported in the study.*

[f] *Risk of Bias was downgraded by one level to serious due to high loss to follow-up for the long-term analysis.*

[g] *Bias was downgraded by one level to serious due bias of included studies in study design, intervention and co-intervention, outcome measures, results and conclusion.*

5 Discussion

Complex perianal fistulas caused by Crohn's disease (CD) occur when a fissure penetrates the gut wall, surrounded by granulation tissue with acute and chronic inflammation [2]. The main symptoms of perianal fistulas are anal pain with defecation and associated swelling, perianal itching, bleeding, and/or discharge of pus or stool from cutaneous fistula openings [2, 8, 9]. Perianal fistula disease affects about five to 40 percent of patients during their Crohn's disease [5]. In 2018, the European Union authorised Alofisel® as an ATMP to treat complex perianal fistulas [24, 25].

komplexe perianale Fisteln als Folge von MC

The update report identified new long-term follow-up results of previously available RCTs and two new non-comparative studies. The current evidence consists of two RCTs [26, 27, 38-40] and three non-comparative studies (two single-arm studies [28, 41] and one case-series [42]).

Update-Report: 2 RCTs und 3 nicht-vergleichende Studien

Summary of the main findings

The two included RCT (n=233) investigated the use of allogeneic MSC compared to placebo in patients with Crohn's disease-associated perianal fistulas. The additional three non-comparative studies (n=57) also investigated allogeneic MSCs. Out of five studies, four were sponsored by the manufacturer of Alofisel (TiGEnix NV [26, 28] and Takeda Pharmaceutical Company Limited [41]) or by the associated DigestScience Foundation [27]. Only one study [42] was investigator-initiated. The ADMIRE-CD trial [26, 38, 39] investigated the safety and efficacy of allogeneic adipose-derived stem cells and enrolled 212 patients at the beginning of the study. After the follow-up of 52 weeks, data were available on 205 patients. After the follow-up of 104 weeks, data were available on only 40 patients (19% of originally enrolled patients), whereby not all outcomes were recorded at this time point either. In the second RCT [27, 40], allogeneic expanded bone-marrow-derived MSCs were administrated in a dose-escalating manner in three intervention groups compared to one control group. Follow-up data were mainly available for the intervention groups in an accumulated form (n=13, 57% of enrolled patients). In the non-comparative studies, an overall of 57 patients were included, and there was a loss to follow-up of 10 (18%) enrolled patients. The range of the follow-up of the non-comparative studies was 24 to 52 weeks.

2 RCTs: ADMIRE-CD (n=212, Nachbeobachtung bis W. 104), Dosiseskalationsstudie (n=21, Nachbeobachtung bis 4 J.)

3 nicht-vergleichende Studien (n=57, Nachbeobachtungszeitraum 24 W. bis 52 W.)

Clinical effectiveness and safety

Statistically significant improvements in the MSC group compared to placebo were observed only for the endpoint combined remission in the ADMIRE-CD trial [26, 38, 39] after 24 and 52 weeks: 50% (n=107) vs. 34% (n=105) (mean difference 15.2%, CI 0.2-30.3, p=0.024) and 56% compared to 39% (mean difference: 17.7%, p=0.021), respectively. No statistically significant improvement was observed in the dose-escalation RCT [27, 40]. No statistically significant differences were observed concerning response in both studies. Both RCTs assessed the quality of life via different questionnaires as secondary endpoints. They failed to show statistically significant differences favouring allogeneic MCS, except for some subscores in the dose-escalation trial [26, 27, 38-40].

Effektivität: s.s. Verbesserungen in kombinierter Remission, aber keine s.s. Unterschiede in Reaktion und LQ

Sicherheit: (peri)anale Abszesse häufigste (schwerwiegende) NW

weitere häufige NW: Proktalgie, Nasopharyngitis

One RCT [26, 38, 39] and two single-arm studies [28, 41] reported several severe treatment-emergent and treatment-related adverse events. Up to week 52 severe treatment-emergent and treatment-related anal abscesses/fistulas were reported more commonly in the MSC-groups than in the control groups of the RCT. In contrast, only the control group reported severe treatment-related cases of proctalgia, anal inflammation, and liver abscesses [26, 38, 39]. In the single-arm studies (n=38) [28, 41], seven patients reported SAE, with three (pyrexia, perianal abscess and Crohn's disease) reported as treatment-related. In ADMIRE-CD [26, 38, 39] overall nine (8.7%) patients in the MSC group and nine (8.8%) in the placebo group withdrew due to AE by week 52. Adverse events [26-28, 38-42] were reported in all studies, with peri(anal) abscesses/fistulas, proctalgia and nasopharyngitis being the most common ones in the intervention groups and anal abscesses/fistulas, proctalgia and abdominal pain in the control groups of the RCTs [26, 38, 39]. As treatment-related adverse events anal abscesses/fistulas, proctalgia, procedural pain and induration were reported in the ADMIRE-CD trial [26, 38, 39]. The most common adverse events in the non-comparative studies [28, 41, 42] were: (peri)anal abscesses and proctalgia. Treatment-related adverse events reported in two single-arm studies [28, 41] were three (peri)anal abscesses and one case each of pyrexia, uterine leiomyoma, diarrhea and blood bilirubin increase.

1 Adenokarzinom, 1 Lymphoproliferative B-Zell-Krankheit, 1 Hodenkarzinom

In the dose-escalation RCT [27, 40] one patient of the first MSC-group (10 million cell dose) developed an adenocarcinoma (>15 months after the surgical intervention) and died two years after intervention and one patient of the second intervention group (30 million cell dose) was diagnosed with B-cell lymphoproliferative disease (LPD) during the 4 year follow-up. Further, in a case-series [42], one patient experienced a testicular carcinoma 16 weeks after treatment. However, none of them were reported as not related to the treatment.

Vertrauenswürdigkeit der Evidenz: sehr niedrig bis moderat

The certainty of evidence was very low to low for effectiveness and safety outcomes.

Interpretation of the findings

ADMIRE-CD zeigt Nutzen für MSC, aber Effekt ist nicht groß + unklarer Langzeiteffekt

Very low to low certainty evidence was found indicating that allogeneic MCS improves the patient-relevant endpoint combined remission, which is defined as the closure of all treated external openings draining at baseline despite gentle finger compression, the absence of discharge in all individual fistulas, and/or the absence of collections larger than 2 cm determined by MRI. However, the evidence is mainly applicable to adipose-tissue-derived MSCs. Overall, ADMIRE-CD shows a benefit of darvadstrocel compared with placebo, but the effect is not large, and there are uncertainties about how long the benefit will be maintained.

fehlende Nachweise für Unterschiede in gesundheitsbezogener LQ

Very low evidence was found for quality of life, measured by different questionnaires. The main findings are that none of the studies was able to detect a relevant improvement in QoL compared to the baseline or the control group, expect for some subscores in the dose-escalation trial. However, QoL data via the IBDQ and SF-36 questionnaires involve subjectiveness, as data are assessed through questionnaires handed out to patients.

unterschiedliche Berichterstattung von NW

Overall very low to low certainty of evidence, consisting of two RCTs and three non-comparative studies, was found concerning safety. In most studies, adverse events were counted based on the number and percentage of patients,

except in one follow-up publication, the total number of adverse events per patient was reported. However, there was a varying presentation of the adverse events (e.g. the distinction between treatment-emergent and treatment-related) and a lack of information on severity across the five included studies.

weitere Forschung nötig ob MSCs zu schweren, lebensbedrohlichen Zuständen führt

The effect of MSCs on the immune system is not sufficiently addressed in current evidence. Overall, two cases of cancer (adenocarcinoma in the dose-escalation trial and testicular carcinoma in a case-series) and one case of B-cell lymphoproliferative disease (LPD) (in the dose-escalation trial) occurred. None of the three cases were reported as severe, and an association with therapy was deemed "unlikely." However, evidence reported that there could be unwarranted differentiation of the transplanted MSCs with the potential to suppress anti-tumour immune response and generate new blood vessels, which consequently can promote tumour growth and metastasis development [43, 44]. As CD patients often already receive immune suppressive treatments, an additional MSC therapy may lead to patients being more receptive to infections. Therefore, further research is crucial if the therapy leads to severe, life-threatening patient conditions.

kleine Patient*innenpopulation für Nachbeobachtung > 52 W.

Concerning the long-term effects, very little data is available. In the ADMIRE-CD, patients could volunteer for a longer follow-up than 52 weeks, which resulted in data availability for only 25 patients of the intervention group and 15 patients of the placebo group. At this time point not all outcomes assessed in the previous publications were reported for this follow-up. Furthermore, no comparative data to the control group were available in the follow-up for the dose-escalation trial, which already had a very small patient population. A selective reporting of both RCTs regarding effectiveness can therefore not be ruled-out. For the long-term evaluation of safety (more than 52 weeks), the small number of patients in the follow-up across the studies could have influenced the perception of a lack of (serious and rare) adverse events.

verschiedene CDAI-Werte zu Beginn der Studien

unterschiedliche Interpretation von perianalen Fisteln

unterschiedliche Anzahl an Fisteln

auch Einschluss von Patient*innen, die nicht in die AGA Definition von komplexen Fisteln fallen

The included studies were not consistent regarding the severity of the disease of the participants at the study start. In ADMIRE-CD [26] and two non-comparative studies [41, 42], the included patients had a CDAI score ≤220, indicating non-active or mildly active luminal CD. In comparison, the dose-escalation RCT [27] included patients with a CDAI score ≤250 and single-arm study [28] included patients with non-active luminal CD, defined by a CDAI ≤200. The CDAI-scores, used as inclusion criteria, ranged from ≤200 to ≤250, indicating different disease severity at study start. In addition, the definitions of complex perianal fistulas varied across the studies. The ADMIRE-CD [26] and two non-comparative studies [41, 42] included patients with complex perianal fistulas, defined by the AGA guidelines[34]. In comparison the dose-escalation RCT [27] included patients with draining perianal fistulas with one to two internal openings and to three fistula tracks and in the third non-comparative study the majority of the treated fistulas had solely one track, one external opening and pictured trans-sphincteric tracks. These characteristics of the fistula tracks do not match the AGA definition of complex perianal fistulas. Thus, the complexity of the fistula tracks might not be the same for every study, even though the studies explicitly stated that they include patients with complex perianal fistulas.

[34] Defined as high fistulas involving more than two thirds of the external sphincter, of high inter-sphincteric, high trans-sphincteric, extra-sphincteric or supra-sphincteric origin and with possible multiple external openings.

unterschiedliche Dosierungen und Zelltypen

Furthermore, different allogeneic stem cell types and stem cell dosages were used in the included studies. The dose-escalation RCT [27, 40] showed that dosage differences might influence effectiveness and safety outcomes. However, there is no direct evidence on whether cell type or dosage affects different stages of the disease.

Evidenz übertragbar auf österreichische Population

In terms of external validity, the generalisability of the study results to the Austrian context can be assumed, as all included studies, except one [41], were conducted across several European countries (Switzerland, Spain, Netherlands, Germany, United Kingdom, Czech Republic, and Italy). Further aspects of the applicability of the included studies are summarised in the Appendix (see Table A-6).

Embedding into existing literature

2 systematische Übersichtsarbeiten zu Therapien mit Kombination von allogenen und autogenen MSCs

Comparing our results with systematic reviews and meta-analyses, no study could be identified comparing the effect of allogeneic MSCs on complex perianal fistulas caused by CD. However, two systematic reviews and meta-analyses [45, 46] were found, which compared allogeneic and autologous stem cells to a control group. In both reviews, the studies included in our assessment are included, however also many more studies with mixed interventions are included. One review [45] included 29 studies with a total of 1252 fistula patients enrolled. Only 12 of 29 studies were RCTs: comparing stem cells to control (placebo and un-CD fistulas). The remaining received stem cell therapy (SCT) with no control group. 18 studies used autologous stem cells, seven allogeneic stem cells, and both were used in two studies. Patients with Crohn's fistula in the stem cell group had a higher healing rate of 61.75% than the placebo group (40.46%) with significant statistical difference (p=0.01).

s.s. höhere Heilungsrate der Fisteln in den MSC-Gruppen im Vergleich zur KG ersichtlich

höhere Verschlussraten von Fisteln bei Patienten mit MSCs

Further, a systematic review of the Cochrane Collaboration group about "stem cell transplantation for induction of remission in medically refractory Crohn's disease" was identified [46]. This review also evaluated, among other things, the closure of fistulas from patients with perianal CD using autologous and allogeneic SCT compared to placebo or non-stem cell therapy. For the short-term outcome (eight and 24 weeks), more people had fistula closure with SCT than placebo/no SCT (RR 1.48, 95% CI [1.12 to 1.96], studies = 4; participants = 269; low certainty of evidence). For the long-term follow-ups (one to four years), more people had fistula closure in the SCT than with placebo/no SCT (RR 1.42, 95% CI [1.09 to 1.87], studies = 4; participants = 250; low certainty of evidence). Although the patients' characteristics in the intervention and control groups are not quite the same in these two systematic reviews as in our review, it is shown that stem cells improve fistula closure related to Crohn's disease.

retrospektive Analyse (n=86) von ADMIRE-CD Pts. zu Effektivität und Sicherheit

Effektivität (Nachbeobachtung bis 156 W/3 J): keine s.s. Gruppen-Unterschiede bei Rückfall

Based on the study population of ADMIRE-CD a further retrospective analysis (INSPECT [47]) was published (and excluded in our assessment because of the study design). INSPECT evaluated the long-term efficacy and safety of darvadstrocel, with eligible patients who completed at least 52 weeks in the ADMIRE-CD trial. Clinical remission and fistula relapse outcomes were collected retrospectively at 104 and 156 weeks after treatment. The adverse events with particular interest (tumorigenicity and ectopic tissue formation) were collected up to 208 weeks after treatment. For the intervention group, 43 patients and 46 patients for the control group were included in the analysis. At post-treatment weeks 52, 104 and 156, clinical remission was observed in 29 (67.4%), 23 (53.5%) and 23 (53.5%), respectively, of 43 patients treated

with darvadstrocel. In the control group, 24 (52.2%), 20 (43.5%), and 21 (45.7%) of 46 control patients, respectively, achieved clinical remission at the given time points. In patients with clinical remission at week 52, the remission was sustained at 104 and 156 weeks after treatment in 19 (65.5%) and 16 (55.2%) of 29 darvadstrocel-treated patients and 17 (70.8%) and 13 (54.2%) of 24 control patients, respectively. No significant differences between groups were observed for time to fistula relapse and incidence of fistula relapse or new fistula occurrence. Two adverse events of interest were reported between 156 and 208 weeks after treatment. One patient (2.2%) in the control group had a malignant epidermoid carcinoma from which the patient had not recovered until the end of the study period. Another patient (2.3%) in the intervention group experienced a benign fibroadenoma (uterine leiomyoma) which was considered unrelated to darvadstrocel. The patient recovered from this non-malignant event with sequelae.

Sicherheit (Nachbeobachtung bis 208 W/4 J) 1 Patient*in aus KG mit malignem Epidermoidkarzinom, 1 Patient*in aus IG mit gutartigem Fibroadenom (nicht therapie-bedingt)

There are slightly different interpretations of the available evidence between different systematic reviews and HTA reports regarding Alofisel® in different countries. The countries derive at different conclusions dependent on national policies on ATMP and on the inclusion of cost-effectiveness analysis.

Unterschiedliche Interpretationen der Evidenz auf Basis von HTAs zu Alofisel® in Europa:

- In **France**, an HTA from the Haute Autroité De Santé (HAS) concluded that Alofisel® shows a *"high clinical benefit in the treatment of complex perianal fistulas in Crohn's disease in combination with a biologic therapy, when fistulas have shown an inadequate response to at least one biologic therapy, and minor clinical added value in the therapeutic strategy"*[35] [48].

HAS: hoher klinischer Nutzen

- In **Germany**, a dossier on the benefit assessment of Alofisel® demonstrated considerable additional benefits for two endpoints only (remission and relapse), but overall it was rated as having low additional benefits [49]. However, according to the German § 35a para. 1 sentence 11 SGB V, the additional benefit of an orphan drug is considered to be proven by the marketing authorisation [50]. In 2018, Alofisel® approval was granted by the Federal Joint Committee (G-BA) for *"the treatment of complex perianal fistulas in adult patients with non-active/low-activity luminal Crohn's disease when the fistulas have responded inadequately to at least one conventional or biologic therapy"* [51].

IQWIG: erheblicher Zusatznutzen bei Remission und Wiederauftreten, aber insgesamt geringer Zusatznutzen

- In **Spain**, the product is included in Valtermed (a registry system designed to collect real-world clinical data through a web-based tool to reduce the uncertainty associated with new therapies and the benefit observed in clinical practice) [52] with a payment by results agreement. The therapeutic positioning report (IPT) of Alofisel® included restrictions for reimbursement in the patient population [53].

AEMPS: Outcome-based Rückerstattung

- In **Ireland**, *"the National Centre for Phamacoeconomics recommends that darvadostrocel (*Alofisel®*) **not** be considered for reimbursement. Cost effectiveness of darvadstrocel (*Alofisel®* for the treatment of complex perianal fistulae in adult patients with non-active/mildly active luminal Crohn's disease, when fistulae have shown an inadequate response to at least one conventional or biologic therapy has not been demonstrated, and therefore is not recommended for reimbursement"* [54].

NCPE: nicht-kosteneffektiv

[35] ALOFISEL provides minor clinical added value (CAV IV) in the treatment of complex, uncomplicated perianal fistulas in adult patients with non-active/mildly active Crohn's disease, in combination with biologic therapy, when fistulas have shown an inadequate response to at least one biologic therapy.

NICE: nicht empfohlen

- in England the NICE Guidance 2019 for for "Darvadstrocel for treating complex perianal fistulas in Crohn's disease" [55] states, "*darvadstrocel is not recommended, within its marketing authorisation, for previously treated complex perianal fistulas in adults with non-active or mildly active luminal Crohn's disease.*" A new review was scheduled for 2022, but the result has not been published yet.

nationale sehr unterschiedliche Erstattungsentscheidungen

Accordingly the differences in the HTA reports resulted in different reimbursement decisions.

Gaps in the Evidence and ongoing studies

meiste Evidenz für aus Fettgewebe stammende MSCs, in Zukunft weitere Quellen für MSCs

Most of the evidence on allogeneic MSC for perianal fistulas was on the treatment of allogeneic adipose-derived MSCs, as the study population of the trial with bone-marrow-derived MSCs was very small. Different origins can probably be considered for the future, as there is also research on stem cells derived from the human expanded umbilical cord and Wharton jelly (see ongoing studies).

nur Vergleiche zu Placebo

Both included RCTs had a placebo as the comparator. Based on clinical practice, fistula track filling material, such as fistula plugs, may be used as another comparator [56]. Currently, no evidence that investigates allogeneic MSCs compared to treatments other than placebo is available.

Studien zu autogenen Stammzellen

In addition to allogeneic stem cell therapies, therapy for perianal fistulas with autologous stem cells are also being investigated [22]. The cell samples are taken from the patient's body, so the likelihood of triggering an immunological reaction is very low. Autologous MSCs may survive better in the body than donor-derived material [57], as allogeneic MSCs are more likely to be rejected by immunocompetent patients [58]. No study that directly compares allogeneic with autologous stem cells has been identified, so it is unclear which of the two stem cell therapies is more effective or safer.

5 laufende RCTs, 4 versch. Quellen der MSCs, Patient*innenanzahl: 10 bis 554

The systematic search and the search in clinical trial registries yielded five ongoing RCTs, in which, however, four different origins of the stem cells (bone marrow (1), adipose tissue (2), Wharton jelly (1), human-expanded umbilical cord (1)) are evaluated. The comparator for these studies encompass placebo in three studies, secretome and MSC-secreted extracellular vesicles in one study and platelet-rich fibrin along with conventional surgery, allogeneic mesenchymal stem cells with platelet-rich fibrin along with conventional surgery and conventional surgery in one study. The study sizes ranged from 10 to 554 patients. One study should already be completed in November 2022, however in January 2023 the study was still recruiting participants, and two other studies should be completed in July and August 2023. No information on the expected end of the study is available for two studies (see Appendix Table A-7 for a more detailed information for the ongoing studies).

Limitations

Beobachtungsstudien für Sicherheits-Endpunkte eingeschlossen

This report should be seen in light of its limitations. Some methodologists may consider it a weakness that we included observational studies (if > 10 patiens enrolled) next to randomised trials within the evidence synthesis. To mitigate concerns, we have selected these studies based on the number of patients (small case-series ≤10 enrolled patients), and believe we better understood safety by including observational studies in our report.

Studien mit gemischten Populationen ausgeschlossen

Another limitation is that we excluded studies with a mixed population (e.g. combination of perianal and rectovaginal fistulas) and studies with autologous stem cells. However, it is in line with the EMA approval for Alofisel (darvadstrocel), which is indicated for the treatment of complex perianal fistulas in adult patients with non-active/mildly active lumbar Crohn's disease when the fistulas have responded inadequately to at least one conventional or biological therapy [24].

Evidenz hauptsächlich aus einem RCT

The main limitation of the evidence is that the evidence for combined remission mainly comes from the results of one RCT. Further evidence is only applicable to adults and not to children or youth.

Conclusion

Effektivität teilweise mit positiven Ergebnissen, jedoch mehr Langzeitforschung nötig

The current evidence of allogeneic mesenchymal stem cells for Crohn's Disease-associated complex perianal fistulas indicates modest benefit for combined remission over placebo: statistically significant differences favouring MSCs could be observed after 24 weeks (low certainty of evidence) and 52 weeks (very low certainty of evidence). However, in the outcomes of response and QoL the evidence showed no statistically differences between the groups. Additional there is uncertainty on the long term benefits (more than 52 weeks) due to few data. In terms of safety, the occurrence of adverse events were similar in the treatment and the control group (placebo). No knowledge is available on the active comparison with treatments as used in clinical practice: e.g. fistula plugs or fibrin glue.

6 Recommendation

In Table 6-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 6-1: Evidence based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
X	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
	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 of allogeneic mesenchymal stem cells for Crohn's Disease-associated complex perianal indicates modest benefit for clinical remission over placebo. Long-term benefit of darvadstrocel is still uncertain. In terms of safety, the occurrence of adverse events were similar in the treatment and the control group. Thus, MSC therapy is meant to be as safe as, but not safer, as the placebo procedure. No evidence was available for comparing MSC therapy to treatments other than placebo, i.e. fibrin glue or fistula plugs.

allogene MSCs gleich sicher und geringer Zusatznutzen gegenüber Placebo

Based on these results, we recommend the inclusion of allogeneic MSCs in the hospital benefit catalogue restricted to adult patients with non-active/ mildly active luminal Crohn's disease whose fistulas have responded inadequately to at least one conventional or biological therapy. Furthermore, the inclusion should be limited in time – until data on long-lasting effects are available – and to specialised centres.

Aufnahme von MSCs in Krankenhausleistungskatalog zeitlich beschränkt und nur für ausgewählte Pat. & spezialisierte Zentren

Further ongoing RCTs will shed more light on the efficacy and safety of different allogeneic MSCs compared to placebo and standard treatment. The results from the upcoming ADMIRE CD-II trial will potentially influence the effect estimate considerably. Re-evaluation is recommended 2025 (when long-term evaluation will be available of ADMIRE CD-II).

neue Studienergebnisse könnten mehr Evidenz liefern

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Allogeneic MSCs for Crohn's Disease-associated complex perianal fistulas: Results from randomised controlled trials

Author, year	Molendijk et al., 2015 [27] Barnhoorn, 2020 (4-year follow-up) [40]	Panés et al., 2016 [26], Panés et al., 2018 (52-week follow-up) [38], Garcia-Olmo, 2022 (104-week follow-up) [39]
Country	The Netherlands	Spain, Belgium, Austria, Canada, Germany, France, Italy, Israel
Sponsor	DigestScience Foundation	TiGenix NV
Intervention/Product	Allogeneic expanded bone-marrow-derived MSCs: **IG1:** 1 x 107 (10 million cells) (n=5) **IG2:** 3 x 107 (30 million cells) ((n=5) **IG3:** 9 x 107 (90 million cells) (n=5) 4 year f/u: IG1: n=4; IG2: n=4; IG3: n=5	Allogeneic expanded adipose-derived MSCs (Davardstrocel, Cx601) **IG:** 120 million cells for a maximum of 3 fistulas (n=107) Week 52[36]: n=84 Week 104: n=25
Comparator	Placebo, namely 0.9% NaCl/5% human albumin solution with no cells (n=6) 4-year f/u: n=3[37]	Placebo, namely 24 mL saline solution (n=105) Week 52: n=80 Week 104: n=15
Study design	Randomised, double-blind, placebo-controlled study (NCT01144962)	Randomised, double-blind, parallel-group, placebo-controlled study (NCT01541579)
Number of pts	21 in the initial trial 4 year f/u: 16 pts	212[38] 164 pts entered the 52-week f/u; 40 were included in the extended f/u
Inclusion criteria	■ ≥18 years of age ■ CDAI score of <250 at screening and baseline ■ Actively draining perianal fistulas ■ Refractory to conventional therapies, namely anti-TNF agents, antibiotics, steroids, thiopurines, methotrexate, surgery or a combination thereof ■ 1-2 internal openings and 1-3 fistula tracts ■ Diagnosis of CD at least 3 months before enrollment ■ Stable dose of current drugs (mesalamine and steroids ≥4 weeks; immunosuppressive drugs ≥8 weeks; anti-TNF agents ≥8 weeks)	■ ≥18 years of age ■ CDAI score of ≤220: no ■ mercaptopurine, or methotrexate or induction or maintenance of anti-TNF agents

[36] Completed the 52 week follow-up

[37] Six patients received placebo in the initial study, of whom two patients received open-label bmMSC therapy in our centre 2 years after the initial study, and one patient was treated with Cx60110 2 years later. These three patients had draining fistula[s] at the time of these treatments. The other three placebo-treated patients were consulted by phone for evaluation of fistula drainage.

[38] The number of patients was not clearly defined. In clinicaltrials.gov the number of patients included was 278. In the study 289 patients were assessed for eligibility and 212 patients were randomly assigned.

Author, year	Molendijk et al., 2015 [27] Barnhoorn, 2020 (4-year follow-up) [40]	Panés et al., 2016 [26], Panés et al., 2018 (52-week follow-up) [38], Garcia-Olmo, 2022 (104-week follow-up) [39]
Exclusion criteria	■ Rectovaginal fistulas ■ Active luminal disease ■ Anal or rectal stricture ■ Acute perianal infection ■ Need for immediate surgery ■ Complex perianal fistulas with >2 internal openings ■ Opportunistic infection within 6 months before screening or serious infection in previous 3 months ■ Infection and need for antibiotic treatment ■ Use of antibiotics after trial inclusion ■ Use of any investigational drug within 1 month before screening or within 5 half-lives of the investigational agent ■ Change in concomitant medication ■ Not able or willing to undergo MRI ■ Renal or hepatic failure ■ Documented human immunodeficiency virus infection, active hepatitis B, C, or tuberculosis ■ Malignancy within past 5 years ■ History of lymphoproliferative disease ■ Pregnancy, breastfeeding or no adequate contraception	■ Rectovaginal fistulas ■ Active severe proctitis ■ Rectal or anal stenosis ■ Abscess ■ Previous fistula surgery other than drainage or seton placement ■ Diverting stomas ■ Collections >2 cm if not properly drained during preparation visit ■ No previous treatment for perianal fistulizing CD, including antibiotics ■ Treatment with corticosteroids within 4 weeks before study start
The mean age of patients (years)	40.4 (4.6[39]) vs. 40.8 (1.7) vs. 33.4 (5.2) vs. 37.3 (3.6) Age at f/u: 43 vs. 46 vs. 38 vs. NR	39.0 (13.1) vs. 37.6 (13.1) Age at 52-week f/u: NR; 104 weeks: 38.6 (14.4) vs. 42.7 (14.8)
Crohn's disease duration, years mean (SD)	7.6 (1.1)[39] vs. 16.8 (4.0) vs. 13.2 (4.1) vs. 6.8 (2.9) f/u 4 years: NR	12.1 (10.0) vs. 11.3 (8.9) F/u 52-week: NR, 104 weeks: 9.9 (7.9) vs. 10.7 (7.5)
Fistula duration, years mean (SEM)	3.6 (0.7) vs. 5.4 (2.5) vs. 9.0 (3.2) vs. 4.2 (1.1) F/u 4 years: NR	NR
Sex, female (%)	1 (20) vs. 1 (20) vs. 4 (80) vs. 3 (50) 4 year f/u: 1 (25) vs. 0 (0) v. 4 (80) vs. NR	47 (44) vs. 49 (47) F/u: 52 weeks: NR; 104 weeks: 11 (44) vs. 7 (47)
Follow-up (weeks)	After intervention: ■ 12 weeks ■ 24 weeks ■ 4 years	After intervention[40]: ■ 12 weeks ■ 24 weeks ■ 52 weeks ■ 104 weeks

[39] For Molendijk 2015 not the standard deviation (SD) but the standard error (SEM) is given.

[40] In week 12 efficacy data were assessed. In week 24, 52 and 104 both, efficacy and safety data were assessed.

Author, year	Molendijk et al., 2015 [27] Barnhoorn, 2020 (4-year follow-up) [40]		Panés et al., 2016 [26], Panés et al., 2018 (52-week follow-up) [38], Garcia-Olmo, 2022 (104-week follow-up) [39]	
Loss to follow-up, n (%)	0 (0) 4 years f/u: 1 (20) vs. 1 (20) vs. 0 (0) vs. 3 (50)		19 (17.8) vs. 22 (21) f/u: 52 weeks[41]: 37 (34.6) vs. 43 (41.9) 104 weeks[42]: 45 (NR) vs. 46 (NR)	
Outcomes				
Efficacy				
	Primary analysis	**Long term follow-up**	**Primary analysis**	**Long term follow-up**
QoL: **(1) s(IBDQ) (high is better)** **(2) SF-36 (high is better)** **(3) PDAI (low is better)** **(4) CDAI (lower is better)**	**(1) sIBDQ scores (week 0 to 24):** 61.0 to 60.0 vs. 48.8 to 51.7 vs. 52.8 to 50.5 vs. 55.3 to 59.3 **(2) SF-36 scores (week 0 to 24)** *Physical functioning:* 96.0 to 97.0 vs. 75.0 to 87.5 vs. 92.0 to 92.0 vs. 85.0 to 86.7 *Physical role functioning:* 80.0 to 73.8 vs. 53.8 to 51.6 vs. 75.0 to 71.3 vs. 69.8 to 70.8 *Bodily pain:* 91.6 to 81.3 vs. 71.6 to 67.5 vs. 74.6 to 77.8 vs. 62.2 to 74.2 *General health perceptions:* 68.0 to 61.6 vs. 33.4 to 30.5 vs. 64.6 to 60.2 vs. 58.2 to 51.8 *Vitality:* 73.8 to 70.0 vs. 38.8 to 39.1 vs. 62.5 to 50.0 vs. 64.0 to 63.5 *Social functioning:* 90.0 to 82.5 vs. 57.5 to 62.5 vs. 77.5 to 80.0 vs. 87.5 to 87.5 *Emotional role functioning:* 85.0 to 80.0 vs. 51.7 to 62.5 vs. 68.3 to 71.7 vs. 80.6 to 79.2 *Mental health:* 81.0 to 85.0 vs. 51.0 to 53.8 vs. 70.0 to 66.0 vs. 79.2 to 80.0 **(3) PDAI scores (estimation based on graphical representation[43])** week 0 to 12: 4.4 to 3.2 vs. 3.8 to 1.0[44] (significant, **p=0.03**) vs. 5.0 to 3.9 vs. 5.2 to 5.3	4 years f/u (n=13[45]): **(1) sIBDQ scores (week 0 to 4 years):** 54.8 to 60.1 (significant, **p = 0.047**) **(2) SF-36 (week 0 to 4 years)** *Mental health:* 42.8 to 48.1 *Physical component score:* 52.2 to 52.8 **(3) PDAI (week 0 to 4 years)** 4.3 vs 3.8 **(4) CDAI (week 0 to 4 years), n=13** 101.5 to 46.2; (significant, **p=0.014**)	**1) IBDQ scores (week 0 to 24)[46]:** *Total:* 173.5 to 178.3 vs. 169.4 to 174.7 *Bowel function:* 57.1 to 57.2 vs. 56.8 to 56.4 *Emotional status:* 63.2 to 64.7 vs. 61.5 to 63.9 *Systemic symptoms:* 25.9 to 26.2 vs. 25.0 to 25.6 *Social function:* 27.7 to 29.5 vs. 26.5 to 28.4 **(2) SF-36: NR** **(3) PDAI scores:** Week 0 to 12: 6.7 to 3.9 vs. 6.5 to 4.9 Week 0 to 24: 6.7 to 4.4 vs. 6.5 to 5.1 **(4) CDAI scores (week 0 to 24):** *Total:* 87.8 to 92.5 vs. 93.3 to 94.1 *Number of liquid stools*: 9.8 to 9.5 vs. 9.3 to 10.0 *Abdominal pain:* 1.6 to 2.7 vs. 2.0 to 3.0 *General well being:* 2.7 to 3.1 vs. 3.2 to 3.3	**(1) IBDQ scores (week 0 to 52[47])** *Total:* 173.5 to 176.1 vs. 169.4 to 172.7 *Bowel function:* 57.1 to 56.3 vs. 56.8 to 55.7 *Emotional status:* 63.2 to 64.4 vs. 61.5 to 63.1 *Systemic symptoms:* 25.9 to 25.9 vs. 25.0 to 25.3 *Social function:* 27.7 to 29.1 vs. 26.5 to 28.4 Week 104:NR **(2) SF-36: NR** **(3) PDAI scores (week 0 to 52):** Week 0 to 52: 6.7 to 4.4 vs. 6.5 to 5.0 Week 104: NR **(4) CDAI scores (week 0 to 52):** *Total:* 87.8 to 97.4 vs. 93.3 to 99.2 *Number of liquid stools:* 9.8 to 11.0 vs. 9.3 to 10.9 *Abdominal pain:* 1.6 to 2.6 vs. 2.0 to 3.1 *General well-being:* 2.7 to 3.4 vs. 3.2 to 3.7 Week 104: NR

41 Lost to follow-up of the 212 randomised patients at the beginning of the study.

42 Lost to follow-up from the patients finished the 52-week follow-up.

43 Figure 3 of Molendijk et al. [27]

44 In group 2, PDAI decrease was most prominent and significantly lower at week 12 compared with baseline (p=**0.03**) as well as with placebo treatment (**p=0.04**) at week 12.

45 Evaluations of QoL are only available for the total number of patients who received bmMSC therapy.

46 All QoL scores in Panés et al. 2016 were reported for the modified intention-to-treat population (204 pts not the total intention-to-treat population of 212).

47 All QoL scores in Panés et al. 2018 were reported for the modified intention-to-treat population (204 pts not the total intention-to-treat population of 212).

Author, year	Molendijk et al., 2015 [27] Barnhoorn, 2020 (4-year follow-up) [40]		Panés et al., 2016 [26], Panés et al., 2018 (52-week follow-up) [38], Garcia-Olmo, 2022 (104-week follow-up) [39]	
QoL: (1)-(4) *(continuation)*	Week 0 to 24: 4.4 to 1.8 vs. 3.8 to 1.5 vs. 5.0 to 4.3 vs. 5.2 to 3.9 **(4) CDAI scores (week 0 to 24):** 80.2 to 64.8 vs. 203.3 to 171.3 vs. 57.3 to 80.8 vs. 75.8 to 58.0			
Fistula relapse-free survival	NR	NR	NR	Week 52 (n=86[48]): 39 (75) vs. 19 (55.9) Week 104: NR
Combined remission, n (%)	Week 12[49]: 2 (40.0) vs. 4 (80.0) vs. 1 (20.0) vs. 2 (33.3) (difference IG2 vs. CG: p=0.06)	NR	Week 24[50]: 53 (50) vs. 36 (34) (significant difference: 15.2%, 97.5% CI 0.2-30.3; **p=0.024**)	Week 52 (n=204): 58 (56.3) vs. 39 (38.6) (significant difference: 17.7%, 97.5% CI 2.9 – 32.5; **p=0.010**) Week 104: NR
Clinical remission, n (%)	Week 6[51]:3 (60.0) vs. 4 (80.0) vs. 1 (20.0) vs.1 (16.7) Week 24: 4 (80.0) vs. 4 (80.0) vs. 1 (20.0) vs.1 (16.7)	4-year f/u: 3 (75.0) vs. 4 (100.0) vs. 1 (20.0) vs. 0 (0.0)	Week 24: 57 (53) vs. 43 (41)	Week 52 (n=204): 61 (59.2) vs. 42 (41.6) (significant difference: 17.6%, 95% CI 4.1 to 31.1; **p=0.013**) Week 104 (n=40): 14 (56) vs. 6 (40)
Response, n (%)	NR	NR	Week 24[52]: 71 (66) vs. 56 (53)	Week 52 (n=204): 68 (66) vs. 56 (55.4) Week 104: NR
Safety				
SAE, n (%)	NR	NR	**Total number of patients with serious TEAEs reported up to 24 weeks:** 18 (17) vs. 14 (14) *Serious TEAEs in ≥2·0% of pts:* *Anal abscess:* 9 (9) vs. 7 (7) **Total number of patients with serious treatment-related AEs reported up to 24 weeks:** 5 (5) vs. 7 (7)	**Total number of patients with serious TEAEs reported up to week 52:** 25 (24.3) vs. 21 (20.6) *Serious TEAEs in ≥2.0% patients:* *Anal abscess/fistula:* 16 (15.5) vs. 10 (9.8) *Crohn's disease:* 0 (0) vs. 3 (2.9) **Patients with STEAEs week 52 up to 104:** 3 (12) vs. 1 (6.7) *Anal fistula: 1 (4) vs. 0 (0)*

48 Of the patients in the mITT population who achieved combined remission at week 24

49 MRI assessment was done only at week 12, thus, combined remission could only be measured in accordance with the definition with 12 weeks of follow-up; n presents the number of all individual fistulas demonstrate the absence of discharge and of collections ≥2 cm; percentages present the proportion of completely healed fistulas of the total number of all individual fistulas

50 n presents the number of patients who achieved closure of all treated external openings and had an absence of collections ≥2 cm; Percentages present the proportion of patients with combined remission of the total number of patients per treatment group

51 Determined by absence of discharge at physical examination and absence of ≥2 cm collections on MRI

52 n presents the number of patients who achieved closure of at least 50% of all treated external openings; percentages present the proportion of patients with a respond of the total patients per treatment group.

Author, year	Molendijk et al., 2015 [27] Barnhoorn, 2020 (4-year follow-up) [40]		Panés et al., 2016 [26], Panés et al., 2018 (52-week follow-up) [38], Garcia-Olmo, 2022 (104-week follow-up) [39]	
SAE, n (%) *(continuation)*			*Anal abscess:* 5 (5) vs. 5 (5) *Proctalgia (cramps in the anal region):* 0 (0) vs. 1 (1) *Anal inflammation:* 0 (0) vs. 1 (1) *Liver abscess:* 0 (0) vs. 1 (1) No deaths occurred	*Anal abscess: 1 (4) vs. 0 (0)* *Fistula discharge: 1 (4) vs. 1 (6.7)* No deaths occurred **Total number of patients with serious treatment-related AEs reported up to week 52:** 7 (6.8) vs. 7 (6.9) *Anal abscess/fistula:* 7 (6.8) vs. 5 (4.9) *Proctalgia:* 0 (0) vs. 1 (1.0) *Anal inflammation: 0 (*0) vs. 1 (1.0) *Liver abscess:* 0 vs. 1 (1.0) **Patients with STRAEs from week 52 up to 104:** None occurred
AE, n (%)	One patient experienced an adenocarcinoma[53] **Total number of AEs per treatment group[54,55]:** All patients reported for approximately 1 week symptoms of postoperative anal pain and pus and/or blood discharge from the fistula or anus **IG1:** 17 (340); **IG2:** 9 (180); **IG3:** 10 (200); **CG:** 14 (233) *Anal abscess:* **IG1:** 1 (20); **IG2:** 1 (20); **IG3:** 1 (20); **CG:** 1 (16.7) *Diarrhea:* **IG1:** 1 (20); **CG:** 1 (16.7) *Abdominal pain:* **IG1:** 1 (20); **IG2:** 1 (20); **IG3:** 3 (60) *Painful perianal swelling:* **IG1:** 1 (20); **CG:** 3 (50) *Not painful perianal swelling:* **IG1:** 1 (20); **CG:** 1 (16.7)	**Total number of AEs (in n of pts)[56],:** *Perianal abscess:* **IG1:** 2 (1); **IG3:** 4 (3) *CD activity in the past 4 years:* **IG1:** 1 (1); **IG2:** 1 (1); **IG3:** 1 (1) *Infections:* **IG1:** 4 (2); **IG2:** 1 (1); **IG3:** 2 (2) *Gout:* **IG1:** 1 (1) *Psoriasis guttae:* **IG1:**1 (1) *Uveitis:* **IG2:** 2 (1) *B-cell lymphoproliferative disease [LPD]:* **IG2:1** (1)	**TEAEs leading to study withdrawal up to week 24:** 5 (5) vs. 6 (6) **Patients with TEAEs up to week 24:** *TEAEs in ≥5·0% of patients* *Anal abscess:* 12 (12) vs. 13 (13) *Diarrhoea:* 7 (7) vs. 3 (3) *Abdominal pain:* 4 (4) vs. 6 (6) *Proctalgia (cramps in the anal region):* 13 (13) vs. 11 (11) *Nasopharyngitis (common cold):* 10 (10) vs. 5 (5) *Fistula:* 3 (3) vs. 6 (6) **Total number of patients with treatment-related AEs reported up to 24 weeks:** 18 (17) vs. 30 (29) *Treatment-related AEs in ≥2.0% patients:* *Anal abscess:* 6 (6) vs. 9 (9) *Proctalgia (cramps in the anal region):* 5 (5) vs. 9 (9)	**Patients with TEAEs up to week 52:** 79 (76.7) vs. 74 (72.5) **TEAEs leading to study withdrawal:** 9 (8.7) vs. 9 (8.8) *TEAEs in ≥5.0% patients:* *Anal abscess/fistula:* 34 (33) vs. 30 (29.4) *Proctalgia:* 15 (14.6) vs. 12 (11.8) *Nasopharyngitis.* 11 (10.7) vs. 5 (4.9) *Diarrhea:* 9 (8.7) vs. 3 (2.9) *Pyrexia:* 6 (5.8) vs**.**5 (4.9) *Arthralgia:* 6 (5.8) vs. 4 (3.9) *Abdominal pain:* 5 (4.9) vs. 7 (6.9) *Crohn's disease:* 4 (3.9) vs. 8 (7.8) **Patients with TEAEs from week 52 up to 104:** None occurred

[53] One patient treated with 10 million MSCs developed an adenocarcinoma of the cecum with peritoneal carcinomatosis. The correlation between the intervention and the occurrence of an adenocarcinoma was unclear. The patient died two years after intervention.

[54] If a treatment group is not mentioned for a specific AE, this AE did not occur in any patient of that treatment group.

[55] No information on the severity of the AE was given in the study.

[56] Of bmMSC-treated patients included in the long-term follow-up. If a treatment group is not mentioned for a specific AE, this AE did not occur in any patient of that treatment group.

Author, year	Molendijk et al., 2015 [27] Barnhoorn, 2020 (4-year follow-up) [40]		Panés et al., 2016 [26], Panés et al., 2018 (52-week follow-up) [38], Garcia-Olmo, 2022 (104-week follow-up) [39]	
AE, n (%) *(continuation)*	*Nasopharyngitis (common cold):* **IG1:** 5 (100); **IG2:** 2 (40); **IG3:** 1 (20); **CG:** 2 (33.3) *Pyrexia (fever (29.7°C)):* **IG2:** 1 (20) *Blood from fistula:* **IG1:** 1 (20) *Painful anal sphincters:* ■ Fissura ani: **IG1:** 1 (20) ■ Anal blood: **CG: 1** (16.7) ■ Anal pus: **IG2:** 1 (20) ■ Thrombosed haemorrhoid: **CG:** 1 (16.7) ■ Pimples buttocks: **IG3:** 1 (20); **CG:** 1 (16.7) ■ Pimples abdomen: **CG:** 1 (16.7) ■ Mild activity CD: **IG1:** 1 (20); **CG:** 1 (16.7) ■ Exacerbated activity CD: **IG1:** 1 (20) ■ Flatulence: **CG:** 1 (16.7) ■ Nausea: **IG3: 1** (20) ■ Vomiting: **IG3:** 1 (20) ■ Lack of appetite: **IG1:** 1 (20) ■ Pneumonia: **IG2:** 1 (20) ■ Otitis: **IG2:** 1 (20) ■ Headache: **IG2:** 2 (40) ■ Back pain: **IG3:** 1 (20) ■ Rosacea: **IG1:** 1 (20) Cold sore: **IG1:** 1 (20)		*Procedural pain:* 1 (1) vs. 2 (2) *Fistula discharge:* 1 (1) vs. 2 (2) *Induration:* 0 (0) vs. 2 (2)	**Total number of patients with treatment-related AEs reported up to week 52:** 21 (20.4) vs. 27 (26.5) *Treatment-related TEAEs in ≥2.0% patients:* *Anal abscess/fistula:* 13 (12.6) vs. 16 (15.7) *Proctalgia:* 5 (4.9) vs. 8 (7.8) *Procedural pain:* 1 (1.0) vs. 2 (2.0) *Induration:* 0 (0) vs. 2 (2.0) **Patients with TRAEs from week 52 up to 104:** None occured

Abbreviations: AEs – adverse events, CD – Crohn's disease, CDAI – Crohn's Disease Activity Index, CG – control group, CI – confidence interval, f/u – follow-up, IG – interventional group, MRI – Magnetic Resonance Imaging, MSC – mesenchymal stem cellsn – number, NA – not applicable, NR – not reported, p – p-value, PDAI – Perianal Disease Activity Index, pts – patients, QoL – quality of life, SD – standard deviation,(s)IBDQ – (short-form) Irritable Bowel Disease Questionnaire, STEAE – severe treatment-emergent adverse event, STRAE – severe treatment-related adverse event, TEAE – treatment-emergent adverse event, TNF – tumour necrosis factor, TRAE – treatment-related adverse event.

Explanation: *Newly identified evidence marked gray.*

Table A-2: Allogeneic MSCs for Crohn's Disease-associated complex perianal fistulas: Results from non-comparative observational studies

Author, year	de la Portilla et al., 2013 [28]	Cabalzar-Wondberg, 2020 [42]	Furukawa, 2022 [41]
Country	Spain	Switzerland	Japan
Sponsor	TiGenix NV	-	Takeda Pharmaceutical Company Limited
Intervention/Product	Allogeneic expanded adipose-derived MSCs: 20 million cells/draining fistula tract additional 40 million cells/ draining fistula tract if fistula closer was incomplete at week 12	120 million stem cells (darvadstrocel, Alofisel®) were injected into each patient	Allogeneic expanded adipose-derived MSCs (Davardstrocel, Cx601)
Comparator	None	None	None
Study design	Open-label, single-arm clinical trial (NCT01372969)	Case series	Phase 3, open-label, multicentre single-arm study
Number of pts	24	11	22
Inclusion criteria	■ ≥18 years of age ■ CDAI score ≤200: non-active luminal CD ■ Diagnosis of CD at least 12 months before enrolment ■ Presence of persistent and active complex perianal fistula with <3 fistulous tracts and/or external openings ■ Good general state of health	■ ≥18 years of age ■ Non-active or mildly active CD with complex fistula ■ Maximum of 2 internal and 3 external fistulas ■ Refractory to standard medical treatment for fistula ■ Patients with CD and ileoanal pouch following restorative proctocolectomy for ulcerative colitis as initial diagnosis in two patients who had already had a fistula surgery	■ ≥18 years of age ■ Non-active or mildly active CD for at least 6 months (CDAI score ≤ 220) ■ Active complex perianal fistulas defined one as the following: [1] a fistula with a high location, including inter-sphincteric, trans-sphincteric, extra-sphincteric, or supra-sphincteric fistulas; [2] at least two external openings; [3] associated fuid collections ■ Refractory fistulas had to have a maximum of 2 internal and 3 external openings and had to have been draining for at least 6 weeks prior study begin
Exclusion criteria	■ Rectovaginal, anal, or non-perianal enterocutaneous fistulas ■ Any abscess before start of treatment ■ Presence of setons unless removed prior to treatment ■ Rectal and/or anal stenosis ■ Severe proctitis or dominant active luminal disease requiring immediate therapy ■ Treatment with anti-TNF agent in previous 8 weeks or tacrolimus or cyclosporine in previous 4 weeks ■ Congenital or acquired immunodeficiency and allergy to anaesthetics or MRI contrast	■ Patients with a previous surgery for the fistula, except for abscess incision and loose seton placement	■ Rectovaginal, rectourethral, bladder fistulas, anorectal stenosis, active proctitis diverting stomas ■ Abscess or collection >2 cm diameter ■ Malignant tumour [including patients who had a history of any type of malignant tumour] ■ Active luminal lesion in the lower part of the rectum ■ Patients who had not received previous treatment for perianal fistulising CD or who underwent previous surgery other than drainage or seton placement for the active fistula ■ Patients received systemic steriods within the previous 4 weeks
Age of patients, mean years (SD)	36.0 (9.0)	38.3 (range 25-82 years)	36.4 (10.4)
Crohn's disease duration, years mean (SD)	NR	13.9 (range 2–38 years)	11.3 (6.6)
Fistula duration, years mean	NR	7.8 (range 1–17 years)	NR

Author, year	de la Portilla et al., 2013 [28]	Cabalzar-Wondberg, 2020 [42]	Furukawa, 2022 [41]
Sex, female n (%)	13 (54.2)	3 (27.3)	8 (36.4)
Follow-up (months)	After intervention: ■ 12 weeks ■ 24 weeks	After intervention: ■ 52 weeks	After intervention: ■ 24 weeks ■ 52 weeks
Loss to follow-up, n (%)	8[57]	0 (0)	2[58]
Outcomes			
Efficacy			
QoL: **(1) s(IBDQ) (high is better)** **(2) SF-36 (high is better)** **(3) PDAI (low is better)** **(4) CDAI (lower is better)**	**(1) (s)IBDQ:** NR **(2) SF-36 scores:** NR **(3) PDAI scores (estimations[59]):** Week 0: 6.2; Week 12: 5.2; Week 24: 3.9 (significantly decreased at week 24 of more than 37% compared to baseline mean value; p=0.0076) **(4) CDAI scores (estimations):** Week 0: 80; Week 12:91; Week 24:80	NR	**(1) (s)IBDQ:** NR **(2) SF-36 scores:** NR **(3) PDAI score** change from baseline (SD): Week 0: 4.8 (2.2); Week 24: -2.4 (2.2); Week 52: -2.8 (2.6) **(4) CDAI score** Week 0: 94.3 (60.0); Week 24: -5.2 (47.5); Week 52: -20.9 (51.3)
Fistula-relapse free survival	NR	NR	Relapsed[60] patients: Week 24 [61]: NR (25.0) of 16 patients Week 52[62]: 3 (23.1) of 13 patients
Combined remission, n (%)	Week 12: 6 (30) of 24 patients Week 24: NA	NR	Week 24: 13 (59.1) of 22 patients [95% CI, 38.5-79.6] Week 52: 15 (68.2) of 22 patients [95% CI, 48.7-87.6]
Clinical remission, n (%)	Week 12: 8 (38.1) of 24 patients Week 24: 9 (56.3) of 24 patients	Complete clinical fistula healing: 8 (73) Week 4: 3 (NR) Week 6: 5 (NR)	Week 24: NR (59.1) of 22 patients [95% CI, 38.5-79.6] Week 52: 16 (72.2) of 22 patients [95% CI, 54.1–91.3]
Response, n (%)	NR	NR	Week 24: NR (81.8) of 22 patients [95% CI, 65.7–97.9] Week 52: 20 (90.9) of 22 patients [95% CI, 78.9–100.0]

[57] Of 24 treated patients, 16 patients completed the study period and 8 were prematurely withdrawn for various reasons.

[58] Loss to follow-up due to lack of efficacy

[59] Data of PDAI- and CDAI-scores were estimated from Figure 2 of de la Portilla et al [28].

[60] Defined as the clinically confirmed reopening of any of the treated external openings with active drainage, or the development of a collection >2 cm in the treated fistulas confirmed by central magnetic resonance imaging [MRI] assessment

[61] In patients with clinical remission at previous visit; darvadstrocel [n=16].

[62] In patients with combined remission at Week 24; darvadstrocel [n=13].

Author, year	de la Portilla et al., 2013 [28]	Cabalzar-Wondberg, 2020 [42]	Furukawa, 2022 [41]
Safety			
SAE, n (%)	**Serious treatment-related AE:** *Pyrexia (fever):* 1 (4.2) *Perianal abscess:* 1 (4.2)	NR	**Serious TEAEs:** ■ 4 (18.2) ■ intestinal obstruction ■ intestinal anastomosis complication ■ urinary calculus ■ tubulointerstitial nephritis **Serious treatment-ralated AE** *Crohn's disease:* 1 (4.5)
AE, n (%)	**Adverse events n = 24[63]:** *Proctalgia (cramps in the anal region):* 2 (8.3) *Pyrexia (fever):* 4 (16.7) *Anal abscess:* 4 (16.7) *Anal fistula infection:* 2 (8.3) *Increase in C reactive protein:* 3 (12.5) *Musculoskeletal and connective tissue disorders:* 3 (12.5) *Anxiety:* 3 (12.5) **Treatment-related AE:** *Anal abscess:* 3 (12.5) *Pyrexia (fever):* 1 (4.2) *Uterine leiomyoma:* 1 (4.2)	**Total number of AEs (n=11)[64]:** *Perianal abscess:* 4 (36.4) *Flu-like symptoms and cytomegalovirus (CMV) viraemia*: 1 (NR) *Testicular carcinoma:* 1 (NR)	**Total number of treatment-emergent AEs reported up to 52 weeks (n=22):** 20 (90.1) Leading to study discontinuation: 0 *Most commonly TEAEs (in ≥ 5% of patients):* ■ Proctalgia: 6 (27.3) ■ Nasopharyngitis: 5 (22.7) ■ Anal fistula: 4 (18.2) ■ Crohn's disease: 2 (9.1) ■ Nausea: 2 (9.1) ■ Acrochordon: 2 (9.1) **Total number of treatment-related AEs per treatment group reported up to 52 weeks (n=22):** 2 (9.1) *diarrhoea ['worsening of diarrhoea' was originally reported by an investigator as a non-MedDRA term] and CD ['worsening of CD' was also originally reported, but the date of onset was different from 'worsening of diarrhoea']:* 1 (4.5) *blood bilirubin increase:* 1 (4.5) No deaths occurred

Abbreviations: CD – Crohn's disease, CDAI – Crohn's Disease Activity Index, MRI – Magnetic Resonance Imaging, MSC – mesenchymal stem cells, MSS – Magnetic Resonance Imaging Score of Severity, NA – not applicable, NR – not reported, p – p-value, PDAI – Perianal Disease Activity Index, pts – patients, SD – standard deviation,(s)IBDQ – (short-form) Irritable Bowel Disease Questionnaire, STEAE – severe treatment-emergent adverse event, STRAE – severe treatment-related ad-verse event, TEAE – treatment-emergent adverse event, TNF – Tumour necrosis factor, TRAE – treatment-related adverse event.

Explanation: Newly identified evidence marked gray.

[63] Presented are TEAEs and TRAEs that have been occurred in >1 patient of the full analysis population (24 patients).

[64] No information on the severity of the AE was given in the study.

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the AIHTA [59] and in the Guidelines of EUnetHTA [29].

Table A-3: Risk of bias – study level (randomised studies), see [31]

Trial	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
ADMIRE-CD, Panés et al., 2016 [26] NCT01541579	Low[65]	Some concerns[66]	Low	Low	Low	Some concerns[67,]
Molendijk et al., 2015 [27] NCT01144962	Some concerns[68]	High[69]	Low	Low	Low[,]	High[70,]

Table A-4: Risk of bias – study level (case series), see [32]

Study reference/ID	de la Portilla, 2013 [28]	Cabalzar-Wondberg, 2021 [42]	Furukawa, 2022 [41]
Study objective			
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes
Study design			
2. Was the study conducted prospectively?	Unclear	Unclear	Yes
3. Were the cases collected in more than one centre?	Yes	No	Yes
4. Were patients recruited consecutively?	Unclear	Unclear	Unclear

[65] There are some differences in baseline characteristics, but the study reports no significance values.

[66] Unclear blinding of the patients.

[67] Due to the lack of blinding of the patients the study is judged with “some concerns”.

[68] The method of allocation was not stated.

[69] No information about an appropriate analysis used to estimate the effect of assignment to intervention.

[70] Due to the unclear allocation process the study is judged with “some concerns”.

Study reference/ID	de la Portilla, 2013 [28]	Cabalzar-Wondberg, 2021 [42]	Furukawa, 2022 [41]
Study population			
5. Were the characteristics of the patients included in the study described?	Partial[71]	Yes	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	Yes	Yes
7. Did patients enter the study at a similar point in the disease?	Yes	Yes	Yes
Intervention and co-intervention			
8. Was the intervention of interest clearly described?	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Partial[72]	No[73]	Yes
Outcome measures			
10. Were relevant outcome measures established a priori?	Yes	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	Yes	Unclear	Unclear
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	No	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	No[74]	Yes	Yes
Statistical Analysis			
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Unclear[75]	Yes
Results and Conclusions			
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	Yes
16. Were losses to follow-up reported?	No	Yes	Yes
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Partial	No	Yes
18. Were the adverse events reported?	Yes	Yes	Yes
19. Were the conclusions of the study supported by results?	No[76]	Yes	Yes
Competing interests and sources of support			
20. Were both competing interests and sources of support for the study reported?	Yes	Yes	Yes
Points	**14**	**15.5**	**19.5**
Overall Risk of bias	**High**	**Moderate**	**Low**

Explanation: Newly identified evidence marked gray.

[71] Not all relevant patient characteristics were reported.

[72] It can be assumed that there might be concomitant therapies like in other bigger studies.

[73] Althogh not reported, it may be assumed that patients received concomitant therapies.

[74] Outcome measures were made 12 and 24 weeks after the interventional process.

[75] No information about statistical analysis

[76] The intervention was reported as safe, even if two patients left the study, due two severe adverse events (i.e. anal abscess and pyrexia).

Table A-5: Evidence profile: efficacy and safety of allogeneic mesenchymal stem cells in patients with perianal fistulas

Certainty assessment							Summary of findings			
N of studies	Study design	RoB	Inconsistency	Indirectness	Imprecision	Other	N of patients* AMCS	N of patients* Placebo	Effect	Certainty
EFFICACY (RCT evidence)										
Quality of life (assessed with: IBDQ, PDAI, CDAI, SF-36)										
2	1 RCT, 4-arm RCT (DE)	very serious[a]	not serious	serious[b]	very serious[c]	none	118	107	Long-term within-group differences were found for IBDQ and CDAI scores at 4 years f/u. For between-group differences, none of the RCTs except for the PDAI score at week 12 detected a significant difference between one treatment group and the control group. IBDQ: W 24 in 2 RCTs (n=225): +4.8 vs. +5.3// -1.0 vs.+2.9 vs. -2.3 vs. +4.0; W 52 in 1 RCT(n=204): + 2.6 vs. + 3.3; Yr 4 in 1 RCT (n=13): +5.3 (IG only, s. s. from baseline) PDAI: W 12 in 1 RCT (n=21): -1.2. vs. -2.8 vs. -1.1 vs. -0.1 (s. diff: IG2 vs. CG); W 24 in 2 RCTs (n=225): -2.3 vs -1.4 // -2.6 vs. -2.3 vs. -0.7 vs. -1.3; W 52 in 1 RCT (n=204): -2.6 vs. -2.3 vs. -0.7 vs. -1.3; Yr 4 year in 1 RCT (n=13): -0.5 (IG only) CDAI: W 24 in 2 RCTs (n=225): + 4,7 vs. +0.8 points // -15.2 vs. 32 vs. +23.5 vs. -17.8; W 52 in 1 RCT (n=204): + 9.6 vs. + 5.9; Yr 4 in 1 RCT (n=13): + 55.3 (IG only, s. diff. in change from baseline) SF-36: W 24 in 1 RCT (n=21): n.s. diff. between IGs and CG in any of the 8 health states[h]; Yr 4 in 1 RCT (n=13): n.s. diff. from baseline in 2 health states (IG only)[h]	⊕◯◯◯ very low
Combined remission: allogeneic MSCs (short-term: up to 24 weeks; assessed with: clinical and MRI assessment)										
2	RCT	not serious	not serious	not serious[d]	very serious[e]	none	122	111	W 12 in 1 RCT (n=21): 40% vs. 80% vs. 20% vs. 33.3% (diff. IG2 vs. CG: p=0.06) W 24 in 1 RCT (n=212): 50% vs. 34%; mean 15.2% more (97.5 % CI 0.2-30.2, p=0.024)	⊕⊕◯◯ low
Combined remission: adipose-tissue-derived MSCs (long-term: 52 weeks; assessed with: clinical and MRI assessment)										
1	RCT	serious[f]	not serious	not serious	very serious[e]	none	103	101	W 52 in 1 RCT (n=204): 56% vs. 39%; mean 17.7% more (97.5% CI 2.9-32.5, p=0.010)	⊕◯◯◯ very low
Response to 120 million adipose-tissue-derived MSCs (short-term: mean 24 weeks; assessed with: closure of at least 50% of all treated external openings)										
1	RCT	not serious	not serious	not serious	very serious[e]	none	103	101	W 24 (n=204): 66% vs. 53%; mean 13% more (95% CI -0.1 to 26.1, p=0.054)	⊕⊕◯◯ low
Response to 120 million adipose-tissue-derived MSCs (long-term: mean 52 weeks; assessed with: closure of at least 50% of all treated external openings)										
1	RCT	serious[f]	not serious	not serious	very serious[e]	none	103	101	W 52 (n=204): 66% vs. 55.4%; mean 10.6 % (95% CI -2.8 to 23.9; p=0.128)	⊕◯◯◯ very low

Certainty assessment							Summary of findings			
N of studies	Study design	RoB	Inconsistency	Indirectness	Imprecision	Other	N of patients*		Effect	Certainty
							AMCS	Placebo		
SAFETY										
RCT evidence: Adverse events/Serious adverse events (up to 24 weeks follow-up)										
2	1 RCT, 4-arm RCT (DE)	not serious	not serious	not serious	very serious[c]	none	118	107	1 RCT: STRAE up to w 24 (n=205): 5 (5 %) vs. 7 (7 %) Other less severe AEs and SAE included a variety of complications as pyrexia, diarrhea, proctalgia, fistula discharge. The reader is referred to Table A-1 for a nuanced description of these AEs.	⊕⊕◯◯ low
RCT evidence: Adverse events/Serious adverse events (up to 4 years follow-up)										
2	1 RCT, 4-arm RCT (DE)	serious[f]	not serious	not serious	very serious[c]	none	118	102	1 RCT: STRAE up to w 52 (n=205): 7 (6.8 %) vs. 7 (7.1 %) STRAE from w 52 to w 104 (n=40): 0 (0 %) vs. 0 (0 %) One patient died in the DE study due to an adenocarcinoma (n=15) Other less severe AEs and SAE included a variety of complications as arthralgia, abdominal pain, proctalgia, fistula discharge. The reader is referred to Table A-1 for a nuanced description of these AEs	⊕◯◯◯ very low
Observational evidence: Adverse events/Serious adverse events (up to 52 week follow-up)										
3	non-comparative observational studies	serious[g]	not serious	not serious	serious[c]	none	49	-	7 patients reported SAE Other less severe AEs included a variety of complications as nausea, proctalgia, abscesses. The reader is referred to Table A-2 for a nuanced description of these AEs	⊕◯◯◯ very low

Abbreviations: AE(s) – adverse event(s); CADI – Crohn's Activity Index; DE – dose-escalating; diff. – difference; f/u – follow-up; IBDQ – Inflammatory Bowel Disease Questionnaire; MSCs – mesenchymal stem cells; PDAI – Pemphigus Disease Area Index; RCT – randomized controlled trail; s.- significant; SAE(s) – severe adverse events.

Explanations:

**Number of analysed patients.*

[a] *Risk of Bias was downgraded by two levels to very serious, due to bias due to deviations from intended interventions, bias arising from the randomization process as well as missing data and a high loss to f/u and as studies used subjective outcome measures (questionnaires) for the assessment of quality of life.*

[b] *Indirectness was downgraded by one level to serious as there were some heterogeneity in the interventions (allogeneic MSCs from bone-marrow vs. adipose derived tissue) and inclusion criteria (definition of complex fistula + CDAI score).*

[c] *Imprecision was downgraded by two levels to very serious, as the optimal information size was not reached.*

[d] *No indicators detected but evidence is mostly applicable to adipose-derived MSC.*

[e] *Imprecision was downgraded by two levels to very serious, as the optimal information size was not reached and wide confidence intervals were reported in the study.*

[f] *Risk of Bias was downgraded by one level to serious due to high loss to follow-up for the long-term analysis.*

[g] *Bias was downgraded by one level to serious due to bias of included studies in study design, intervention and co-intervention, outcome measures, results and conclusions.*

[h] *Full data can be taken from the data extraction tables.*

Applicability table

Table A-6: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The study population of the included studies differed with regard to the CDAI score. In the five studies, the CDAI scores for inclusion in the study ranged from ≤200 to ≤250, indicating different severity of the disease at study start. In addition, in one study the inclusion criteria was expanded to patients with CD and ileoanal pouch following restorative proctocolectomy for ulcerative colitis as initial diagnosis in two patients who had already had a fistula surgery. Further, in two studies the definition of complex perianal fistulas differed from the definition of the American Gastroenterological Association. Thus, the complexity of the fistula tracks might not be the same for every study, even though the studies explicitly stated that they include patients with complex perianal fistulas. The mean age of participants was consistent across the studies (range: 36-41 years) and was reflective for the usual time of diagnosing perianal fistulas. Four studies delivered evidence from European populations and one from a Japanese population.
Intervention	The interventions differed in allogeneic stem cell type and dosage. Four studies administered adipose-derived mesenchymal stem cells, while the third study was a dose-escalation trial which assessed bone-marrow-derived stem cells. Currently, there are no direct comparisons of these two cell types. The dosages of the studies ranged from 10 million to 120 million cells (for a maximum of three fistula tracks). In one study, the second dose of cells was administered in case of lacking response to the first dose. Based on the dose-escalation RCT, a higher dosage is not necessarily associated with better effects on patients' outcomes.
Comparators	In both RCTs, placebo was used as the comparator. In ADMIRE-CD, placebo was defined as saline solution, while in the dose-escalation RCT, it was defined as human albumin solution. There are suggestions that fistula track filling material, such as fistula plug could be used as a comparator treatment. However, there is no evidence of MSC therapy compared to other treatments than placebo.
Outcomes	Not all critical efficacy endpoints were reported by all included studies. With regard to combined remission, ADMIRE-CD reported it for 24 weeks and 52 weeks, while the other study assessed it for 12 weeks. Furthermore, response to treatment was only reported by ADMIRE-CD. There were differences in the reported safety outcomes, and measurements were not clearly described. For two studies the severity of the AEs was not applicable.
Setting	ADMIRE-CD was conducted in various hospitals in Spain, Belgium, Austria, Germany, France, Italy, Canada, and Israel. The dose-escalation trial was conducted at the Leiden University Medical Center in the Netherlands. One single-arm was conducted in the Virgen del Rocio University Hospital in Spain and one in nine sites in Japan. The case-series conducted in a tertiary hospital in Switzerland. Two out of the three studies were sponsored by TiGenix NV (which is part of the Takeda group since 2018). The ADMIRE-CD and the Spanish single-arm study was sponsored by TiGenix NV, the dose-escalatig study was funded by the DigestScience Foundation, which is also sponsored by one manufacturer (Takeda Pharmaceutical Company Limited) and the Japanese study was founded by Takeda Pharmaceutical Company Limited.

Abbreviations: CD – Crohn's Disease; CDAI – Crohn's Disease Activity Index; MSC – mesenchymal stem cell; RCT – randomised controlled trial.

List of ongoing randomised controlled trials

Table A-7: List of ongoing RCTs of allogeneic MSCs for CD-associated complex perianal fistulas

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT04519671	n=40 Pat. with 18-75 years of age with a diagnosis of Crohn's disease for at least six months duration. With single and multitract perianal fistula, with or without previous failed surgical repair. Have no contraindications to MR evaluations: e.g. pacemaker or magnetically active metal fragments, claustrophobia. Ability to comply with protocol. Competent and able to provide written informed consent. Concurrent Crohn's-related therapies with stable doses (>2 months) corticosteroids, 5- ASA drugs, immunomodulators, anti-TNF therapy, anti-integrin and anti-interleukin therapies are permitted	Allogeneic bone marrow-derived mesenchymal stem cells	Placebo (normal saline)	Treatment-related adverse events	November 2022	Amy Lightner
NCT03279081	N=554 Pts with signed informed consent, with 18 to 75 years of age, presence of complex perianal fistula(s) with max. 2 internal and max. 3 external openings, clinically controlled, nonactive or mildly active CD, inadequate response to other treatment (medicaments)	Cx601 eASCs 120 million cells intralesional injection	Placebo – Cx601 placebo-matching eASCs cells	Percentage of Participants with Combined Remission at Week 24	July 2023	Tigenix S.A.U.
NCT05677672	N= 84 Pts with signed informed consent, aged between 18 and 70 years, subject clinically diagnosed with complex anal fistula (criteria by the 2016 American Association of Colorectal Surgeons Guidelines for the Treatment of Perianal Abscess, Anal Fistula and Recto-vaginal Fistula) and received conventional treatment, not planning to have a child from screening to the end of the trial	Human TH-SC01 Cell Injection (allogeneic Umbilical Cord-derived Mesenchymal Stem Cells)	Placebo (saline solution)	Severity and incidence of study drug-related adverse-events, ose-limiting toxicity, maximum tolerated dose, percentage of effectiveness	August 2023	Jiangsu Topcel-KH Pharmaceutical Co., Ltd.

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
IRCT20200809048342N2	n=10 Adults between 18-75 years old with a clinically confirmed diagnosis of Crohn's disease, medical therapy resistant perianal fistula, mild to moderate Crohn's disease activity index	Warton jelly Mesenchymal Stem Cells	CG1: Placebo or CG2: secretome and MSC-secreted extracellular vesicles (Exosome)	Total number of soft/liquid stools in the last 7 days, flatus, IL-10, TNFα, liquid secretion, solid secretion, pad, life style, abdominal pain, generall wellbeing, anti-diarrhea drug use, abdominal mass, hematocrit, arthritis/arthralgiaslritis/ uveitis, erythema nodosum, pyoderma gangrenosum, or aphthous stomatitis, anal fissure, fistula, or abscess, fever	NI	Shahid Beheshti University of Medical Sciences
IRCT20210830052332N1	n= 24 Pts with complex anal fistula (recurrent fistula, High Trans Sphincteric fistula, Supra Sphincteric fistula, Extra Sphincteric fistula, and Horse Shoe fistula), over 18 years old, who are able to give informed consent	Allogeneic MSCs with conventional surgery	CG1: platelet-rich fibrin along with conventional surgery CG2: allogeneic mesenchymal stem cells with platelet-rich fibrin along with conventional surgery CG3: conventional surgical method	Efficacy and Safety allogeneic adipose derived mesenchymal stem cells along with platelet-rich fibrin for perianal fistula	NI	NI

Abbreviations: CD – Crohn's Disease; CG: control group; eASCs – expanded allogeneic adipose-derived stem cells; n – number; NI – no information; MSC – mesenchymal stem cell; RCT – randomised controlled trial.

Literature search strategies

Search strategy for Cochrane

Search Name: Mesenchymal Stem Cells for Crohn's Fistula_Update 2023	
Search date: 14.12.2022	
ID	Search
#1	MeSH descriptor: [Rectal Fistula] explode all trees
#2	(anal or anus or ano* or peri*an* or rect*) near fistul* (Word variations have been searched)
#3	MeSH descriptor: [Crohn Disease] explode all trees
#4	Crohn* (Word variations have been searched)
#5	#1 or #2 or #3 or #4
#6	MeSH descriptor: [Mesenchymal Stem Cells] explode all trees
#7	MeSH descriptor: [Mesenchymal Stem Cell Transplantation] explode all trees
#8	(mesenchymal or stroma*) near cell* (Word variations have been searched)
#9	MSC:ti,ab,kw
#10	#6 or #7 or #8 or #9
#11	#5 and #10
#12	(stem cell* near ((anal or anus or ano* or peri?an* or rect*) near (fistul* or Crohn*))) (Word variations have been searched)
#13	(Alofisel*) (Word variations have been searched)
#14	(Darvadstrocel*) (Word variations have been searched)
#15	(TiGenix*) (Word variations have been searched)
#16	"Living Medicines" (Word variations have been searched)
#17	(Cx*601*) (Word variations have been searched)
#18	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 (Word variations have been searched)
#19	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 with Cochrane Library publication date Between Dec 2017 and Dec 2022 (Word variations have been searched)
#20	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 with Publication Year from 2017 to 2022, in Trials (Word variations have been searched)
#21	#19 OR #20 (Word variations have been searched)
#22	(conference proceeding):pt
#23	(abstract):so
#24	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#25	#22 OR #23 OR #24
#26	#21 NOT #25
Total hits: 33	

Search strategy for Embase

Search Name: Mesenchymal Stem Cells for Crohn's Fistula (Update 2023)		
Search date: 14.12.2021		
No.	Query Results	Results
#1.	'anus fistula'/mj/exp	3,632
#2.	((anal OR anus OR ano* OR peri*an* OR rect*) NEAR/4 fistul*):ti,ab,kw,lnk,de	18,790
#3.	'crohn disease'/mj/exp	59,518
#4.	crohn*:ti,ab,kw,lnk,de	123,153
#5.	#1 OR #2 OR #3 OR #4	137,428
#6.	'mesenchymal stroma cell'/mj/exp	8,791

#7.	'mesenchymal stem cell transplantation'/mj/exp	9,270
#8.	((mesenchymal OR stroma*) NEAR/4 cell*):ti,ab,kw,lnk,de	230,506
#9.	#6 OR #7 OR #8	230,706
#10.	#5 AND #9	1,288
#11.	'stem cell*' NEAR/4 (anal OR anus OR ano* OR peri*an* OR rect*) NEAR/5 (fistul* OR crohn*)	88
#12.	alofisel*	43
#13.	'darvadstrocel'/exp	87
#14.	darvadstrocel*	95
#15.	cx601	24
#16.	'cx 601'	5
#17.	tigenix*:df,dn,mn,tn	45
#18.	'living medicines'	11
#19.	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	1,423
#20.	(#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18) AND [13-12-2017]/sd NOT [15-12-2022]/sd	705
#21.	(#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18) AND [13-12-2017]/sd NOT [15-12-2022]/sd AND ([english]/lim OR [german]/lim)	693
#22.	#21 AND 'Conference Abstract'/it	213
#23.	#21 NOT #22	480
Total hits: 480		

Search strategy for Medline via Ovid

Search Name: Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to December 13, 2022>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <2018 to December 13, 2022>	
Search date: 14.12.2021	
ID	Search
#1	exp Rectal Fistula/ (7469)
#2	((anal or anus or ano* or peri?an* or rect*) adj5 fistul*).mp. (14355)
#3	exp Crohn Disease/ (50904)
#4	Crohn*.mp. (81306)
#5	Crohn$2 fistul*.mp. (177)
#6	1 or 2 or 3 or 4 or 5 (92997)
#7	exp Mesenchymal Stromal Cells/ (68107)
#8	exp Mesenchymal Stem Cell Transplantation/ (19607)
#9	((mesenchymal or stroma*) adj5 cell*).mp. (221049)
#10	7 or 8 or 9 (221127)
#11	6 and 10 (825)
#12	(stem cell* adj5 ((anal or anus or ano or peri?an* or rect*) adj5 (fistul* or Crohn*))).mp. (119)
#13	Alofisel*.mp. (14)
#14	Darvadstrocel*.mp. (38)
#15	Cx?601.mp. (15)
#16	TiGenix.mp. (4)
#17	Living Medicines.mp. (11)
#18	11 or 12 or 13 or 15 or 16 or 17 (868)
#19	limit 18 to dt=20171213-20221214 (538)
#20	limit 18 to ed=20171213-20221214 (455)
#21	19 or 20 (565)
#22	limit 21 to (english or german) (553)
#23	remove duplicates from 22 (290)
Total hits: 290	

Search strategy for HTA-INATHTA

Search Mesenchymal Stem Cells for Crohn's Fistula (Update 2023)	
Search date: 14.12.2021	
ID	Search
1	"Rectal Fistula"[mhe],"5","2022-12-14T16:08:53.000000Z"
2	(anal OR anus OR ano* OR peri*an* OR rect*) NEAR fistul*) AND (fistul*),"0","2022-12-14T16:10:14.000000Z"
3	"Crohn Disease"[mhe],"54","2022-12-14T16:10:51.000000Z"
4	Crohn*,"84","2022-12-14T16:11:09.000000Z"
5	(Crohn*) OR ("Crohn Disease"[mhe]) OR ((anal OR anus OR ano* OR peri*an* OR rect*) NEAR fistul*) AND (fistul*)) OR ("Rectal Fistula"[mhe]),"90","2022-12-14T16:11:25.000000Z"
6	"Mesenchymal Stem Cells"[mhe],"0","2022-12-14T16:12:07.000000Z"
7	"Mesenchymal Stem Cell Transplantation"[mhe],"5","2022-12-14T16:13:04.000000Z"
8	(mesenchymal OR stroma*) AND (cell*),"9","2022-12-14T16:14:21.000000Z"
9	((mesenchymal OR stroma*) AND (cell*)) OR ("Mesenchymal Stem Cell Transplantation"[mhe]) OR ("Mesenchymal Stem Cells"[mhe]),"12","2022-12-14T16:14:40.000000Z"
10	(((mesenchymal OR stroma*) AND (cell*)) OR ("Mesenchymal Stem Cell Transplantation"[mhe]) OR ("Mesenchymal Stem Cells"[mhe])) AND ((Crohn*) OR ("Crohn Disease"[mhe]) OR ((anal OR anus OR ano* OR peri*an* OR rect*) NEAR fistul*) AND (fistul*)) OR ("Rectal Fistula"[mhe])),"7","2022-12-14T16:14:52.000000Z"
11	(stem cell*) AND (fistul* OR Crohn*),"2","2022-12-14T16:15:47.000000Z"
12	Alofisel*,"1","2022-12-14T16:16:43.000000Z"
13	Darvadstrocel*,"1","2022-12-14T16:16:57.000000Z"
14	cx601,"1","2022-12-14T16:17:14.000000Z"
15	cx-601,"2","2022-12-14T16:17:28.000000Z"
16	TiGenix*,"0","2022-12-14T16:17:48.000000Z"
17	Living Medicines,"9","2022-12-14T16:18:02.000000Z"
18	(Living Medicines) OR (TiGenix*) OR (cx-601) OR (cx601) OR (Darvadstrocel*) OR (Alofisel*) OR ((stem cell*) AND (fistul* OR Crohn*)) OR ((((mesenchymal OR stroma*) AND (cell*)) OR ("Mesenchymal Stem Cell Transplantation"[mhe]) OR ("Mesenchymal Stem Cells"[mhe])) AND ((Crohn*) OR ("Crohn Disease"[mhe]) OR ((anal OR anus OR ano* OR peri*an* OR rect*) NEAR fistul*) AND (fistul*)) OR ("Rectal Fistula"[mhe]))),"18","2022-12-14T16:18:39.000000Z"
19	((Living Medicines) OR (TiGenix*) OR (cx-601) OR (cx601) OR (Darvadstrocel*) OR (Alofisel*) OR ((stem cell*) AND (fistul* OR Crohn*)) OR ((((mesenchymal OR stroma*) AND (cell*)) OR ("Mesenchymal Stem Cell Transplantation"[mhe]) OR ("Mesenchymal Stem Cells"[mhe])) AND ((Crohn*) OR ("Crohn Disease"[mhe]) OR ((anal OR anus OR ano* OR peri*an* OR rect*) NEAR fistul*) AND (fistul*)) OR ("Rectal Fistula"[mhe]))))) AND ((Crohn*) OR ("Crohn Disease"[mhe]) OR ((anal OR anus OR ano* OR peri*an* OR rect*) NEAR fistul*) AND (fistul*)) OR ("Rectal Fistula"[mhe])),"7","2022-12-14T16:18:54.000000Z"
20	(((Living Medicines) OR (TiGenix*) OR (cx-601) OR (cx601) OR (Darvadstrocel*) OR (Alofisel*) OR ((stem cell*) AND (fistul* OR Crohn*)) OR ((((mesenchymal OR stroma*) AND (cell*)) OR ("Mesenchymal Stem Cell Transplantation"[mhe]) OR ("Mesenchymal Stem Cells"[mhe])) AND ((Crohn*) OR ("Crohn Disease"[mhe]) OR ((anal OR anus OR ano* OR peri*an* OR rect*) NEAR fistul*) AND (fistul*)) OR ("Rectal Fistula"[mhe]))))) AND ((Crohn*) OR ("Crohn Disease"[mhe]) OR ((anal OR anus OR ano* OR peri*an* OR rect*) NEAR fistul*) AND (fistul*)) OR ("Rectal Fistula"[mhe]))) FROM 2017 TO 2022,"3","2022-12-14T16:19:24.000000Z"
21	((((Living Medicines) OR (TiGenix*) OR (cx-601) OR (cx601) OR (Darvadstrocel*) OR (Alofisel*) OR ((stem cell*) AND (fistul* OR Crohn*)) OR ((((mesenchymal OR stroma*) AND (cell*)) OR ("Mesenchymal Stem Cell Transplantation"[mhe]) OR ("Mesenchymal Stem Cells"[mhe])) AND ((Crohn*) OR ("Crohn Disease"[mhe]) OR ((anal OR anus OR ano* OR peri*an* OR rect*) NEAR fistul*) AND (fistul*)) OR ("Rectal Fistula"[mhe]))))) AND ((Crohn*) OR ("Crohn Disease"[mhe]) OR ((anal OR anus OR ano* OR peri*an* OR rect*) NEAR fistul*) AND (fistul*)) OR ("Rectal Fistula"[mhe]))) FROM 2017 TO 2022) AND (English OR German)[Language],"3","2022-12-14T16:19:52.000000Z"
Total hits: 3	

Search strategy for CRD (DARE, NHS-EED, HTA)

Search Name: Stem Cell Therapy for Crohns Fistula (MEL-Update 2023)	
Search date: 14.12.2021	
ID	Search
1	MeSH DESCRIPTOR Rectal Fistula EXPLODE ALL TREES
2	((anal OR anus OR ano* OR peri*an* OR rect*) NEAR fistul*)
3	MeSH DESCRIPTOR Crohn Disease EXPLODE ALL TREES
4	(Crohn*)
5	(Crohn* NEAR Fistul*)
6	#1 OR #2 OR #3 OR #4 OR #5
7	MeSH DESCRIPTOR Mesenchymal Stromal Cells EXPLODE ALL TREES
8	MeSH DESCRIPTOR Mesenchymal Stem Cell Transplantation EXPLODE ALL TREES
9	((mesenchymal OR stroma*) NEAR cell*)
10	#7 OR #8 OR #9
11	#6 AND #10
12	(stem cell* NEAR (fistul* OR Crohn*))
13	(Alofisel)
14	(cx601)
15	(cx-601)
16	(TiGenix)
17	(Living Medicines)
18	(darvadstrocel*)
19	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
20	(#19) WHERE LPD FROM 13/12/2017 TO 14/12/2022
Total hits: 0	

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Health Technology Assessment
GmbH