

<https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club>

The weekly Clinical Journal Club by Dr. Friedrich C. Luft

Usually every Wednesday 17:00 - 18:00



Klinische Forschung

Experimental and Clinical Research Center (ECRC) von MDC und Charité

Als gemeinsame Einrichtung von MDC und Charité fördert das Experimental and Clinical Research Center die Zusammenarbeit zwischen Grundlagenwissenschaftlern und klinischen Forschern. Hier werden neue Ansätze für Diagnose, Prävention und Therapie von Herz-Kreislauf- und Stoffwechselerkrankungen, Krebs sowie neurologischen Erkrankungen entwickelt und zeitnah am Patienten eingesetzt. Sie sind eingeladen, uns beizutreten. [Bewerben Sie sich!](#)



A diagnosis of Koebner phenomenon from wet cupping therapy was made. The Koebner phenomenon — also known as the isomorphic response — is **the appearance of new skin lesions of a preexisting dermatosis (such as psoriasis, vitiligo, or lichen planus) at sites of previously uninvolved skin owing to cutaneous trauma**. The phenomenon may occur even in patients with good control of their skin condition.

A 35-year-old man with a history of **moderate-to-severe plaque psoriasis** presented to the dermatology clinic with new skin lesions. His psoriasis had been in remission for the past 18 months while on risankizumab. Two weeks before presentation, the patient had **undergone his first ever session of wet cupping therapy** to treat low back pain. During the treatment, clusters of small incisions had been made at different sites across his back, after which glass cups had been applied with negative pressure to draw out small amounts of blood. What is the most likely diagnosis?

Impetigo

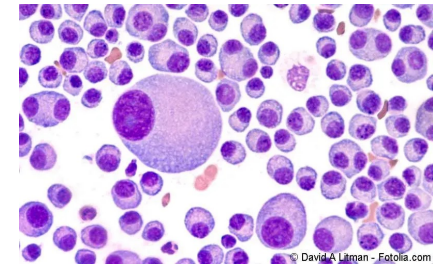
Isotopic response

☒ Koebner phenomenon (isomorphic response)

Pathergy

Relapse of psoriasis

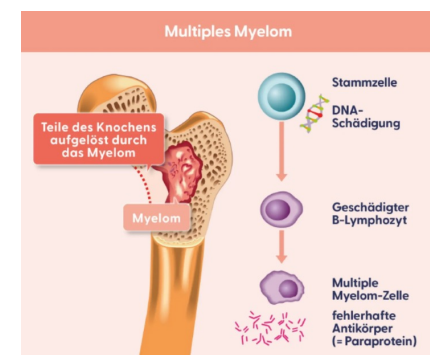
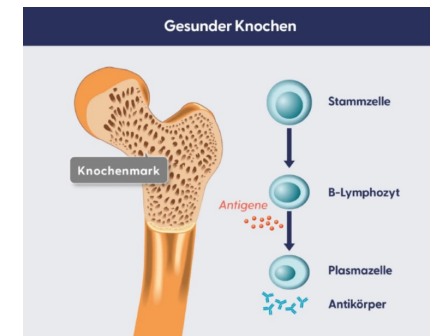
Das **Multiple Myelom** ist eine **bösartige Krebserkrankung des Knochenmarks**, die zu den Non-Hodgkin-Lymphomen zählt. Dabei vermehren sich entartete Plasmazellen (bestimmte weiße Blutkörperchen) unkontrolliert und verdrängen die gesunde Blutbildung. Die Erkrankung gilt nach wie vor als unheilbar, ist jedoch durch moderne Krebstherapien heutzutage **sehr gut behandelbar und kontrollierbar**, wodurch Betroffene oft viele Jahre bei guter Lebensqualität leben.



Typische Symptome (Die CRAB-Kriterien)

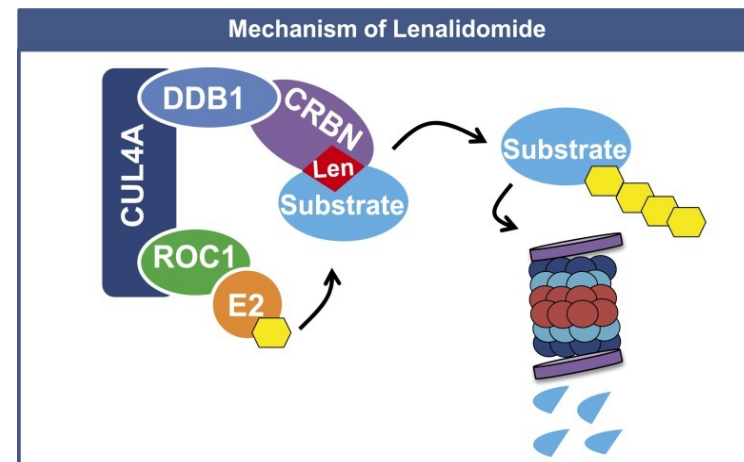
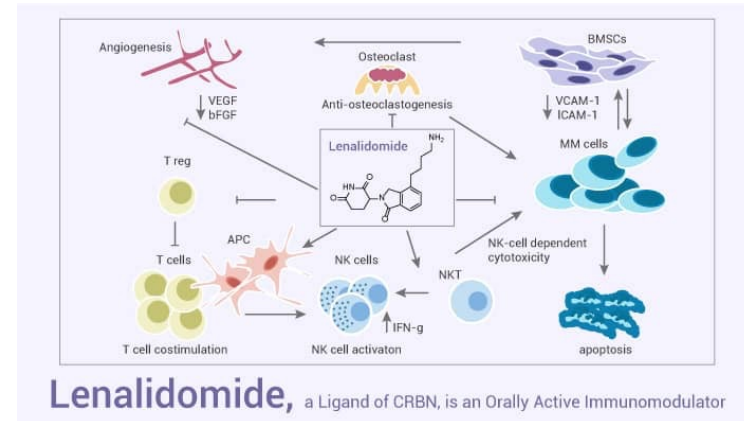
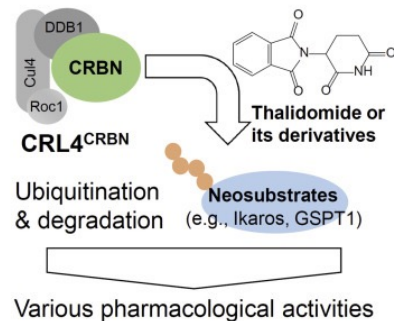
Die Beschwerden entwickeln sich meist schleichend. In der Medizin werden die Hauptsymptome oft über das "CRAB"-Akronym definiert:

- C (Calcium)**: Erhöhter Kalziumspiegel im Blut (Hyperkalzämie) führt zu Übelkeit, Verstopfung und Verwirrtheit.
- R (Renal)**: Nierenschäden oder Nierenversagen, oft erkennbar an schäumendem Urin.
- A (Anemia)**: Blutarmut (Anämie) verursacht starke Müdigkeit, Abgeschlagenheit und Atemnot bei Belastung.
- B (Bone)**: Knochenschmerzen (besonders im Rücken und den Rippen) sowie ein erhöhtes Risiko für Knochenbrüche.



Lenalidomid ist ein Arzneistoff aus der Gruppe der Immunmodulatoren. Es wird vorwiegend zur Behandlung von Blutkrebsarten wie dem multiplen Myelom (Knochenmarkkrebs), bestimmten Formen des myelodysplastischen Syndroms (MDS) und Lymphomen eingesetzt.

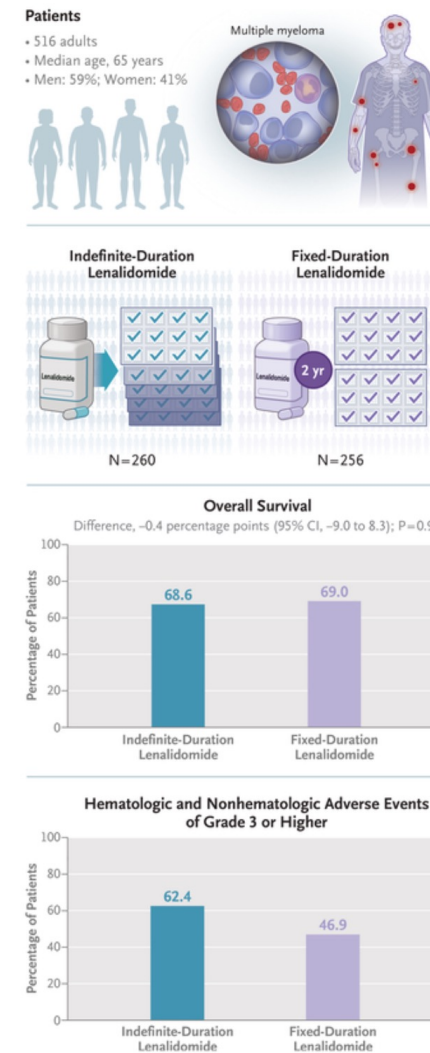
Lenalidomid beeinflusst das körpereigene Immunsystem aktiv, indem es die Aktivität bestimmter weißer Blutkörperchen (T-Zellen und natürliche Killerzellen) verstärkt. Zudem hemmt es das Wachstum von Tumorzellen, stört die Blutversorgung des Tumors und fördert den Zelltod der Krebszellen. Es wird sowohl als Erhaltungstherapie (oft nach Stammzelltransplantationen) als auch in Kombination mit anderen Medikamenten (wie Dexamethason oder Bortezomib) angewendet.



Continuous or Fixed-Duration Maintenance Therapy in Multiple Myeloma

Current treatment of newly diagnosed multiple myeloma involves lenalidomide maintenance therapy given until disease progression. The **appropriate duration of maintenance therapy with lenalidomide** has been unclear.

In this phase 3 trial, we enrolled patients with standard-risk newly diagnosed multiple myeloma who were not undergoing up-front autologous stem-cell transplantation. After induction treatment with a proteasome inhibitor–lenalidomide combination, patients were randomly assigned to receive **indefinite-duration (continuous) lenalidomide or fixed-duration lenalidomide (for 2 years)**. The primary end point was overall survival; the trial had **80% power to detect a 50% increase in median survival (from 5 years to 7.5 years)**, with a two-sided alpha level of 5%, 395 patients undergoing randomization, and 204 deaths occurring during 9 years of follow-up.



We designed this phase 3 trial to evaluate whether indefinite maintenance therapy would improve outcomes in patients with newly diagnosed multiple myeloma as compared with a predetermined treatment interval of 2 years. This is an important question in the context of multiple myeloma, given that trials have suggested that a higher-dose or longer-duration treatment strategy may not always be an appropriate approach. For example, longer survival was observed with dexamethasone given once weekly than with a more-intense regimen, and in another trial, a planned dose reduction of lenalidomide and the discontinuation of glucocorticoid therapy improved outcomes as compared with continued intense administration.

In brief, adult patients with newly diagnosed multiple myeloma who were considered to be ineligible for or were not planning to receive an up-front autologous stem-cell transplant were enrolled. Patients with high-risk multiple myeloma were excluded, given another ongoing trial involving patients with high-risk disease. High-risk multiple myeloma was defined as one or more of the following: t(14;16), t(14;20), or del17p on fluorescence in situ hybridization (FISH); a serum lactate dehydrogenase level of more than 2 times the upper limit of the normal range; at least 20% circulating plasma cells on peripheral-blood smear or 2000 plasma cells per microliter in peripheral blood; or a high-risk gene expression signature (GEP70) if tested. Patients who received KRd for at least four cycles or VRd for at least six cycles as induction therapy and had completed induction without having disease progression or starting nonprotocol therapy (alternative therapy before documented progressive disease) were eligible to enroll in the step 2 (maintenance) phase, provided that any adverse event that had been deemed by the investigators as being related to a therapy received during the step 1 phase was resolved to a severity of grade 2 or less.

End Points and Assessments

The primary end point for the step 2 (maintenance) phase of the trial was overall survival, which was defined as the time from the second randomization until death due to any cause or follow-up with data censored at the date on which the patient was last known to be alive. An additional planned analysis of overall survival used data that were censored for patients at the initiation of nonprotocol therapy.

A key secondary end point was progression-free survival, which was defined as the time from the second randomization until progressive disease or death due to any cause, whichever occurred earlier.

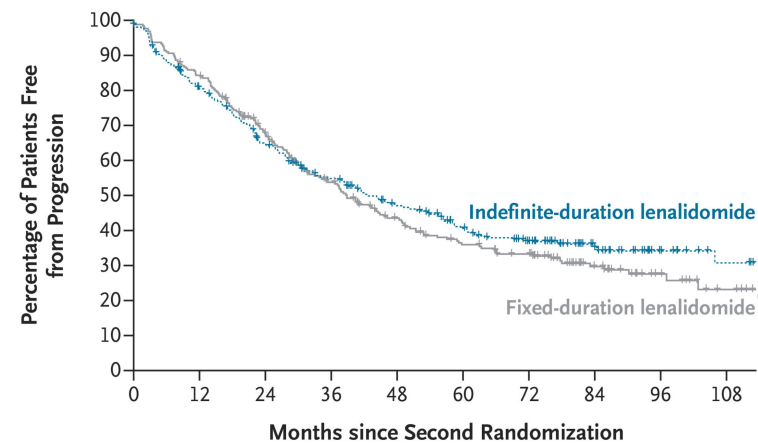
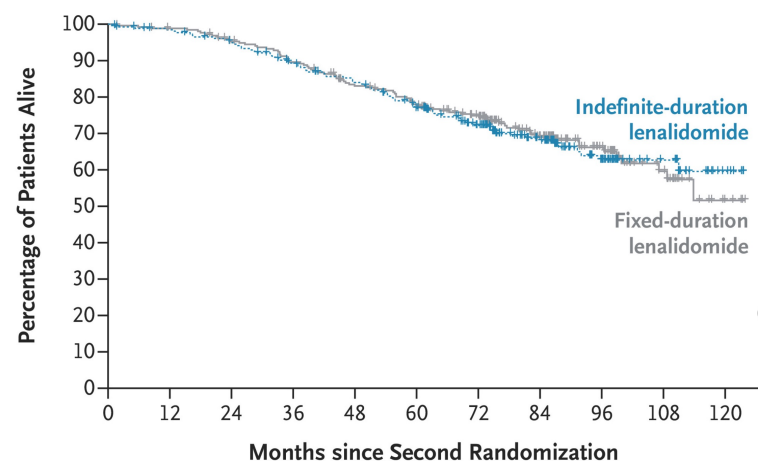
Characteristic	Indefinite-Duration Lenalidomide (N = 260)	Fixed-Duration Lenalidomide (N = 256)
Age		
Median (IQR) — yr	65 (59–71)	65 (59–72)
≥70 yr — no. (%)	79 (30.4)	87 (34.0)
Male sex — no. (%)	151 (58.1)	153 (59.8)
Race — no. (%) [†]		
White	216 (83.1)	211 (82.4)
Black	29 (11.2)	27 (10.5)
Other	8 (3.1)	7 (2.7)
Missing data	7 (2.7)	11 (4.3)
Hispanic ethnic group — no. (%) [†]		
No	235 (90.4)	239 (93.4)
Yes	16 (6.2)	15 (5.9)
Missing data	9 (3.5)	2 (0.8)
ISS stage — no. (%)		
I	102 (39.2)	100 (39.1)
II	98 (37.7)	91 (35.5)
III	58 (22.3)	62 (24.2)
Missing data	2 (0.8)	3 (1.2)
ECOG performance-status score — no. (%) [‡]		
0	128 (49.2)	118 (46.1)
1	122 (46.9)	128 (50.0)
2	7 (2.7)	9 (3.5)
3	0	1 (0.4)
Missing data	3 (1.2)	0
No intent to receive ASCT at progressive disease — no. (%)	63 (24.2)	78 (30.5)
Induction therapy — no. (%)		
VRd	110 (42.3)	108 (42.2)
KRd	150 (57.7)	148 (57.8)
Any high-risk cytogenetic abnormality — no. (%) [§]		
Absent	68 (26.2)	79 (30.9)
Present	90 (34.6)	91 (35.5)
Missing data	102 (39.2)	86 (33.6)
IMWG-IMS high-risk status — no. (%) [¶]		
No	159 (61.2)	167 (65.2)
Yes	34 (13.1)	27 (10.5)
Missing data	67 (25.8)	62 (24.2)
Lactate dehydrogenase ≥ULN — no. (%)	34 (13.1)	32 (12.5)
Median creatinine clearance (IQR) — ml/min	90 (64–114)	87 (66–110)
Median bone marrow plasma cells (IQR) — %	3 (1–5)	3 (1–5)

Response Status at the End of Induction Therapy

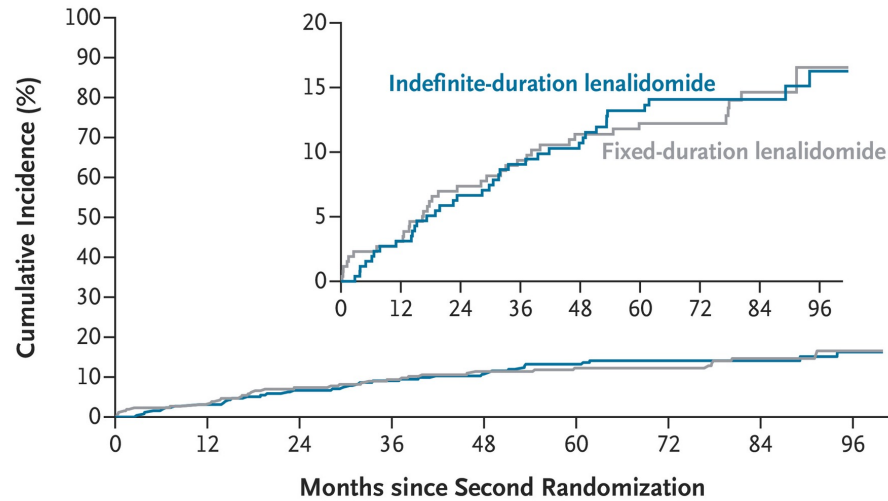
Variable	Response at End of Induction		Best Response during Maintenance	
	Indefinite-Duration Lenalidomide (N = 255)	Fixed-Duration Lenalidomide (N = 254)	Indefinite-Duration Lenalidomide (N = 255)	Fixed-Duration Lenalidomide (N = 254)
Response — no. (%)				
Stringent complete response	36 (14.1)	37 (14.6)	59 (23.1)	60 (23.6)
Complete response	52 (20.4)	53 (20.9)	60 (23.5)	65 (25.6)
Very good partial response	108 (42.4)	121 (47.6)	94 (36.9)	98 (38.6)
Partial response	30 (11.8)	23 (9.1)	23 (9.0)	16 (6.3)
Stable disease	8 (3.1)	2 (0.8)	6 (2.4)	4 (1.6)
Progressive disease	0	0	0	0
Could not be evaluated or insufficient data	21 (8.2)	18 (7.1)	13 (5.1)	11 (4.3)
Complete response or better				
No. of patients with response	88	90	119	125
Percent of patients (95% CI)	34.5 (28.7–40.7)	35.4 (29.5–41.6)	46.7 (40.4–53.0)	49.2 (42.9–55.6)
Very good partial response or better				
No. of patients with response	196	211	213	223
Percent of patients (95% CI)	76.9 (71.2–81.9)	83.1 (77.9–87.5)	83.5 (78.4–87.9)	87.8 (83.1–91.6)
Partial response or better				
No. of patients with response	226	234	236	239
Percent of patients (95% CI)	88.6 (84.1–92.3)	92.1 (88.1–95.1)	92.6 (88.6–95.5)	94.1 (90.4–96.7)

Solicited Adverse Events, According to Grade.

Event	Indefinite-Duration Lenalidomide (N = 255)		Fixed-Duration Lenalidomide (N = 254)	
	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4
	<i>number of patients (percent)</i>			
Anemia	126 (49.4)	7 (2.7)	109 (42.9)	9 (3.5)
Diarrhea	109 (42.7)	14 (5.5)	90 (35.4)	5 (2.0)
Dyspnea	57 (22.4)	4 (1.6)	50 (19.7)	1 (0.4)
Edema in the limbs	80 (31.4)	1 (0.4)	64 (25.2)	1 (0.4)
Fatigue	146 (57.3)	15 (5.9)	120 (47.2)	6 (2.4)
Fever	18 (7.1)	1 (0.4)	19 (7.5)	0
Hyperglycemia	93 (36.5)	6 (2.4)	73 (28.7)	3 (1.2)
Insomnia	69 (27.1)	1 (0.4)	46 (18.1)	1 (0.4)
Irritability	10 (3.9)	0	15 (5.9)	0
Lymphocyte count decreased	91 (35.7)	22 (8.6)	77 (30.3)	15 (5.9)
Muscle weakness in the trunk	20 (7.8)	2 (0.8)	22 (8.7)	1 (0.4)
Nausea	58 (22.7)	3 (1.2)	45 (17.7)	2 (0.8)
Neutrophil count decreased	68 (26.7)	72 (28.2)	71 (28.0)	45 (17.7)
Peripheral motor neuropathy	40 (15.7)	0	23 (9.1)	1 (0.4)
Peripheral sensory neuropathy	121 (47.5)	2 (0.8)	101 (39.8)	4 (1.6)
Platelet count decreased	97 (38.0)	7 (2.7)	75 (29.5)	5 (2.0)
Rash, acneiform	26 (10.2)	3 (1.2)	27 (10.6)	3 (1.2)
Vomiting	20 (7.8)	2 (0.8)	20 (7.9)	2 (0.8)



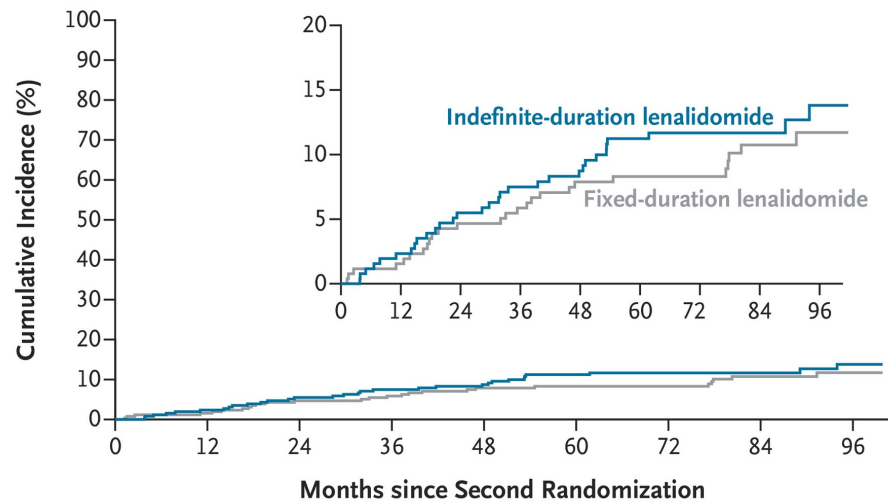
A All Second Primary Cancers



Cumulative Incidence of Second Primary Cancer (Treated Population).

Shown is the cumulative incidence of all second primary cancers (Panel A) and of all second primary cancers with the exclusion of nonmelanoma skin cancer (Panel B). The treated population included all the patients who received at least one dose of the assigned treatment. In both panels, insets show the same data on an expanded y axis.

B All Second Primary Cancers Excluding Nonmelanoma Skin Cancer



Newly Diagnosed Multiple Myeloma



- Lenalidomide maintenance therapy
- Until disease progression occurs

Indefinite-Duration Lenalidomide (continuous)

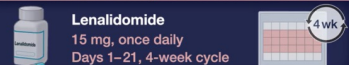


N=260

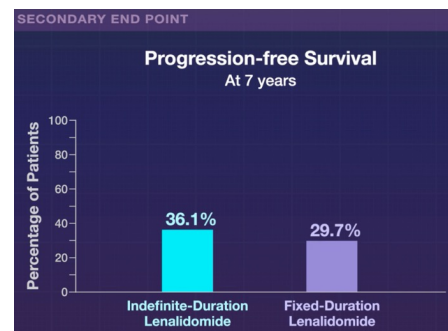
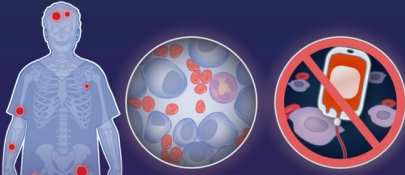
Fixed-Duration Lenalidomide (2 years)



N=256



Lenalidomide
15 mg, once daily
Days 1–21, 4-week cycle

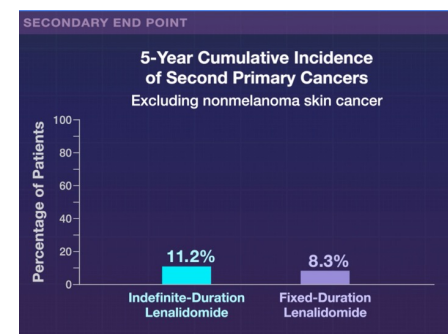
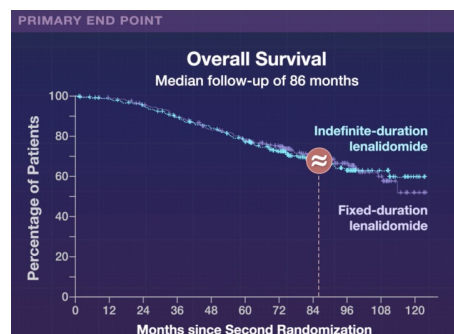
Standard-risk newly diagnosed multiple myeloma

No up-front autologous stem-cell transplantation

Newly Diagnosed Multiple Myeloma



- Lenalidomide maintenance therapy
- Until disease progression occurs



Indefinite-Duration Lenalidomide



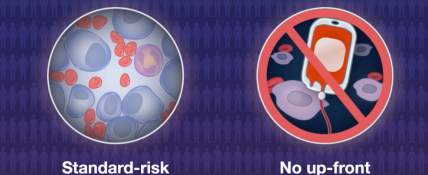
Fixed-Duration Lenalidomide



VS.

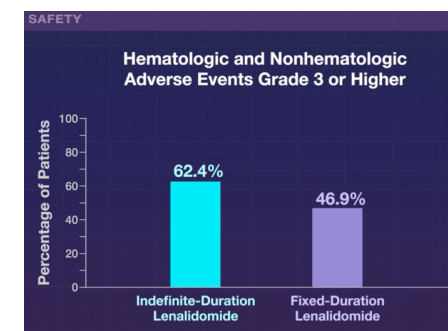
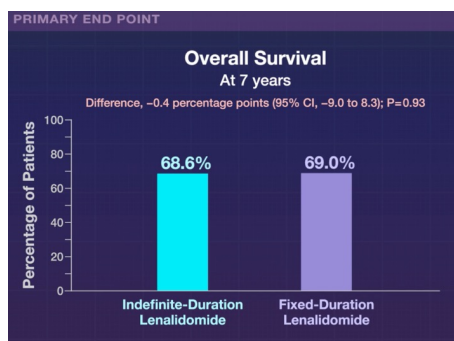
Did not result in significantly longer overall survival

516 Patients



Standard-risk newly diagnosed multiple myeloma

No up-front autologous stem-cell transplantation

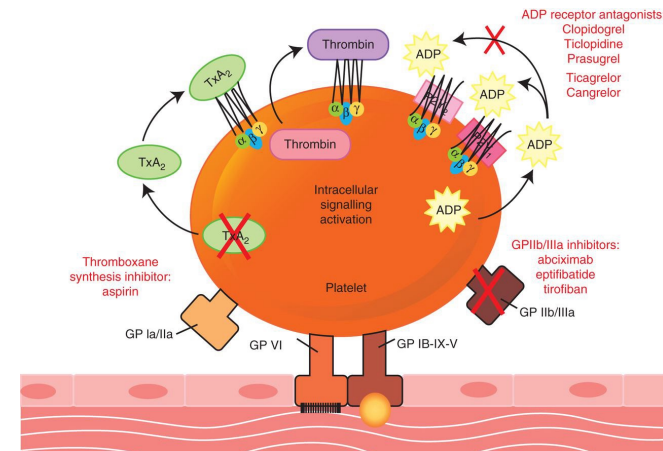


Dual Antiplatelet Therapy (DAPT) ist eine medizinische Behandlung, bei der **zwei verschiedene Thrombozytenaggregationshemmer gleichzeitig** eingenommen werden, um die Bildung von Blutgerinnseln in den Arterien zu verhindern. Diese Therapie kombiniert in der Regel **Aspirin (Acetylsalicylsäure)** mit einem sogenannten **P2Y12-Inhibitor**. DAPT kommt primär nach schweren kardiovaskulären Ereignissen wie einem **Herzinfarkt** oder nach dem Einsatz eines **Stents** zum Einsatz, um lebensbedrohliche Gefäßverschlüsse zu stoppen

Die beiden Wirkstoffklassen greifen an unterschiedlichen Stellen der Thrombozyten (Blutplättchen) an, um deren Verkleben maximal zu hemmen: **Basis-Medikament (Immer gesetzt):**

Aspirin (ASA / ASS): Hemmt das Enzym Cyclooxygenase-1 (COX-1) dauerhaft und verhindert so die Aktivierung der Plättchen.
Zweites Medikament (P2Y12-Inhibitoren):

- [Clopidogrel](#): Der Standardwirkstoff, häufig genutzt bei stabiler Herzkrankheit oder hohem Blutungsrisiko.
- **Ticagrelor (Brilinta)**: Ein potenterer, moderner Wirkstoff, der primär nach akuten Herzinfarkten eingesetzt wird.



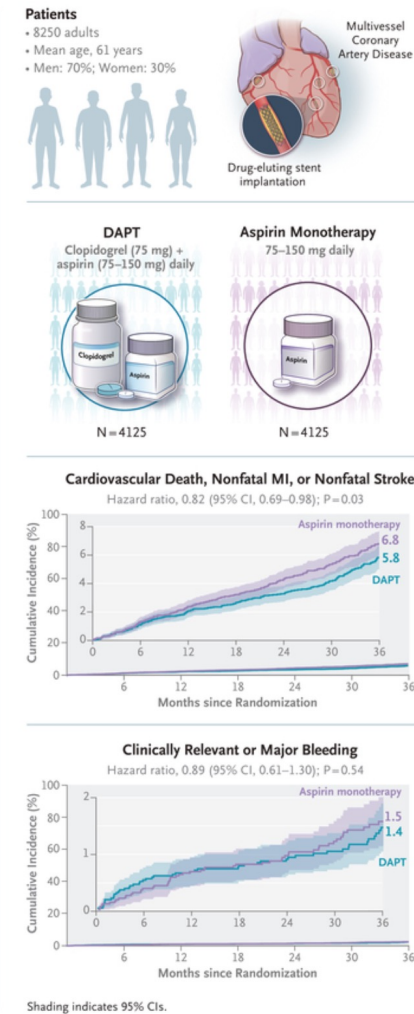
Plättchen Hemmung:
COX-1, P2Y12, oder Gpiib/iiia.

ASS und ein „Grel“ ist die DPT.

Extended Dual Antiplatelet Therapy for Multivessel Coronary Artery Disease

Patients with multivessel coronary artery disease often receive 12 months of dual antiplatelet therapy (DAPT) after stenting to reduce the risk of ischemic events. Whether extending DAPT beyond 12 months in event-free patients with multivessel disease provides a benefit is uncertain.

We conducted an open-label, randomized trial at 97 centers in China. Patients 18 to 75 years of age with multivessel coronary artery disease who had no major ischemic or bleeding events while receiving DAPT for 12 months after implantation of a drug-eluting stent were randomly assigned in a 1:1 ratio to receive an additional 12 months of DAPT (clopidogrel plus aspirin) or aspirin monotherapy. The primary efficacy end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary safety end point was clinically relevant or major bleeding (i.e., a bleeding event of Bleeding Academic Research Consortium [BARC] type ≥ 2 ; BARC types range from 0 to 5, with higher values indicating greater severity of bleeding).



Patients with multivessel disease at low risk for bleeding, especially those with acute coronary syndromes, routinely receive 12 months of dual antiplatelet therapy (DAPT) after implantation of a drug-eluting stent to reduce the risk of ischemic events. Whether the potential benefits of further extending the duration of DAPT in these patients outweigh the risk of bleeding is uncertain. Although guidelines provide a class Ia recommendation for extended DAPT in selected patients at high ischemic risk, evidence from previous trials is difficult to generalize to high-risk patients with multivessel disease.

To address this uncertainty, we designed the Dual Antiplatelet Therapy in Patients with Coronary Multivessel Disease (DAPT-MVD) trial. We aimed to determine the efficacy and safety of extending DAPT with clopidogrel plus aspirin, as compared with aspirin monotherapy, for an additional 12 months in patients with multivessel disease who remained event-free 12 months after implantation of a drug-eluting stent.

Trial Population

Eligible patients were 18 to 75 years of age, had multivessel coronary artery disease, and had remained in stable condition for 12 months after implantation of a drug-eluting stent without major ischemic or bleeding events. Multivessel disease was defined as two or more major epicardial coronary arteries with a diameter stenosis of at least 50%, with up to 30% diameter stenosis in the left main coronary artery.

End Points

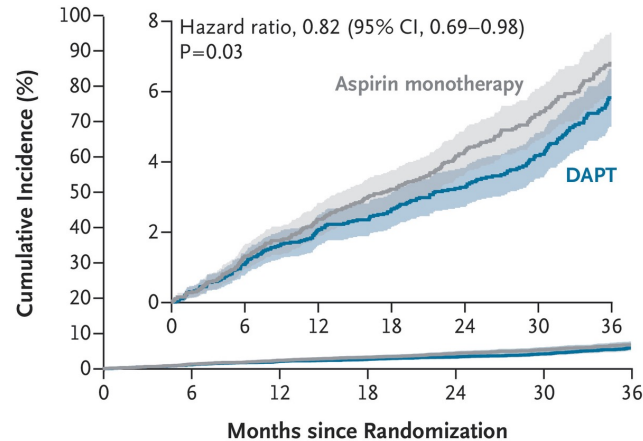
The primary efficacy end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke and was assessed in a time-to-event analysis, according to the first event that occurred between randomization and the latest follow-up visit, which was determined in relation to the time the last enrolled patient completed 1 year of follow-up. Secondary efficacy end points included death from any cause, death from cardiovascular causes, nonfatal stroke, nonfatal myocardial infarction, a net adverse clinical event (a composite of ischemic events or a bleeding event).

Characteristic	DAPT (N=4125)	Aspirin Monotherapy (N=4125)
Age — yr	60.5±8.8	60.5±8.9
Female sex — no. of patients (%)	1223 (29.6)	1274 (30.9)
Body-mass index†	25.3±2.9	25.3±2.9
Diabetes mellitus — no. of patients (%)	1187 (28.8)	1136 (27.5)
Hypercholesterolemia — no. of patients (%)	1534 (37.2)	1540 (37.3)
Hypertension — no. of patients (%)	2244 (54.4)	2170 (52.6)
Cigarette smoker within the past year — no. of patients (%)	1434 (34.8)	1355 (32.8)
Indication for index PCI — no. of patients (%)		
STEMI	946 (22.9)	994 (24.1)
NSTEMI	417 (10.1)	449 (10.9)
Unstable angina	2695 (65.3)	2608 (63.2)
Stable angina	67 (1.6)	74 (1.8)
Medication use before enrollment — no. of patients (%)		
Aspirin plus clopidogrel	2773 (67.2)	2761 (66.9)
Aspirin plus ticagrelor	1352 (32.8)	1364 (33.1)
No. of diseased vessels — no. of patients (%)‡		
Two-vessel disease§	1849 (44.8)	1938 (47.0)
Three-vessel disease	2273 (55.1)	2186 (53.0)
Location of diseased vessels — no. of patients (%)¶		
Left anterior descending artery	3846 (93.2)	3782 (91.7)
Left circumflex artery	3192 (77.4)	3112 (75.4)
Right coronary artery	3475 (84.2)	3534 (85.7)
Time from the index PCI to randomization — days	378.8±19.9	378.4±19.6

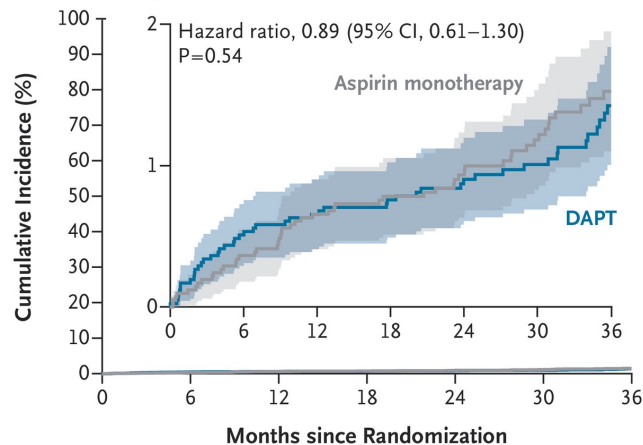
Major Adverse Cardiovascular, Cerebrovascular, and Bleeding Events (Intention-to-Treat Population).

End Point	DAPT (N=4125)	Aspirin Monotherapy (N=4125)	Hazard Ratio (95% CI)	P Value
<i>no. of patients with event (estimated %)*</i>				
Efficacy end points				
Primary efficacy end point: death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke†	222 (5.8)	266 (6.8)	0.82 (0.69–0.98)	0.03
Secondary efficacy end points‡				
Death from any cause	120 (3.1)	116 (3.0)	1.02 (0.79–1.32)	—
Death from cardiovascular causes	73 (2.0)	75 (1.9)	0.96 (0.70–1.33)	—
Nonfatal stroke	97 (2.5)	120 (3.1)	0.80 (0.61–1.04)	—
Nonfatal myocardial infarction	67 (1.8)	97 (2.5)	0.68 (0.50–0.93)	—
Safety end points§				
BARC type 2–5 bleeding	51 (1.4)	57 (1.5)	0.89 (0.61–1.30)	0.54
BARC type 3–5 bleeding	29 (0.8)	33 (0.9)	0.87 (0.53–1.43)	0.59

A Major Adverse Cardiovascular and Cerebrovascular Events

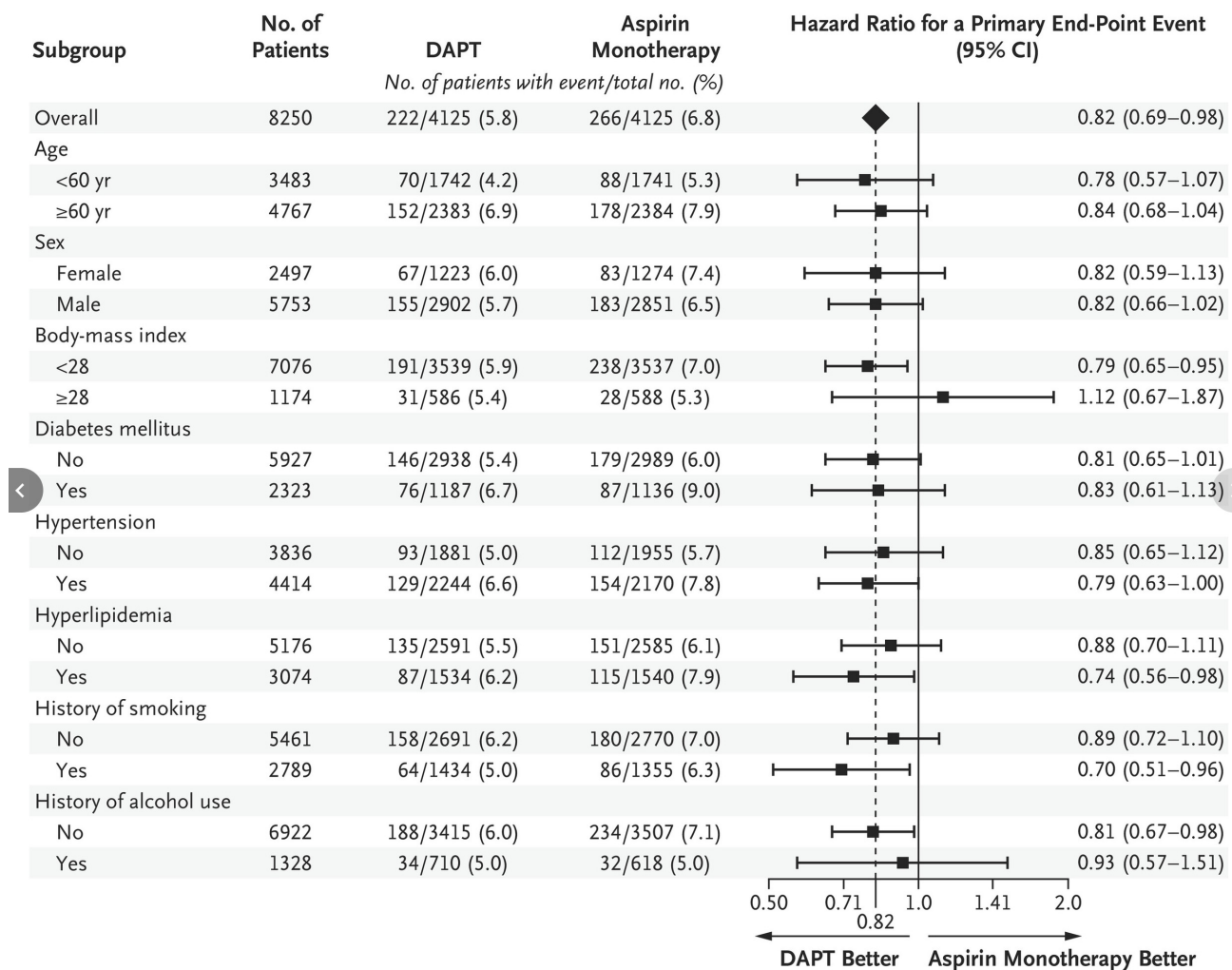


B Clinically Relevant Bleeding Events



Cumulative Incidence of Primary Efficacy and Safety End-Point Events (Intention-to-Treat Population).

Time-to-first-event curves are shown for the primary efficacy end point in Panel A and the primary safety end point in Panel B. The primary efficacy end point was a composite of death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction. The primary safety end point was clinically relevant or major bleeding, defined as a bleeding event of Bleeding Academic Research Consortium (BARC) type 2 to 5. BARC types include 0 (no bleeding), 1 (mild bleeding that is not medically actionable), 2 (nonmajor bleeding that is medically actionable), 3 (major bleeding), 4 (bypass surgery–related bleeding), and 5 (fatal bleeding). The blue and gray shaded areas indicate the 95% confidence intervals for the Kaplan–Meier curves for the DAPT group and the aspirin monotherapy group, respectively. The insets show the same data on an expanded y axis.



Prespecified Subgroup Analysis of the Primary Efficacy End Point.

Unadjusted hazard ratios for the primary efficacy end point (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) are shown with 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. The body-mass index is the weight in kilograms divided by the square of the height in meters.

Multivessel Coronary Artery Disease



12 Months of dual antiplatelet therapy (DAPT)

Clopidogrel
(75 mg daily)
+ Aspirin
(75 to 150 mg daily)

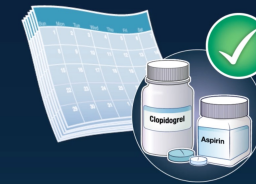


N=4125

Aspirin
(75 to 150 mg daily)



N=4125

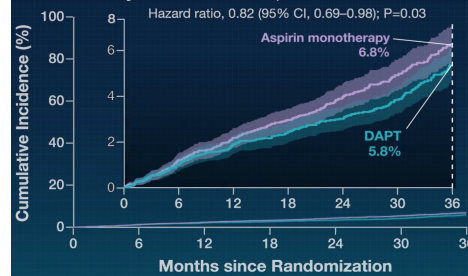


Additional 12 months of DAPT led to a lower risk of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke than aspirin monotherapy



PRIMARY EFFICACY END POINT

Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Nonfatal Stroke



DAPT-MVD

- Randomized
- Open-label
- Multicenter

• 8250 Adults

• No major ischemic or bleeding events while receiving DAPT for 12 months after stent implantation

SAFETY

BARC (Bleeding Academic Research Consortium) Type 2 to 5 Bleeding



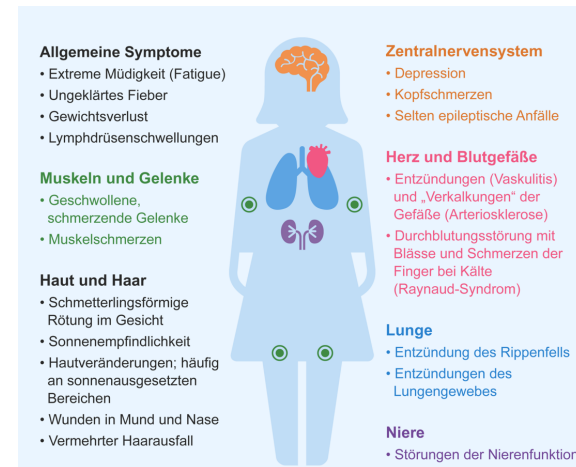
Der Systemische Lupus erythematodes (SLE) ist eine chronisch-entzündliche Autoimmunerkrankung, bei der sich das Immunsystem gegen körpereigenes Gewebe richtet. Betroffen sind meist junge Frauen zwischen 20 und 40 Jahren. Typisch sind ein schubweiser Verlauf, ausgeprägte Müdigkeit (Fatigue), Gelenkschmerzen, Hautausschläge (z.B. Schmetterlingserythem) und oft eine unbemerkte Beteiligung der Nieren.

Diagnose

Die Diagnose stützt sich auf die typischen Beschwerden, Blutuntersuchungen auf spezifische Autoantikörper (z.B. ANA, Anti-dsDNA) sowie Urin- und Organuntersuchungen. Ohne Therapie kann die Krankheit zu irreversiblen Organschäden führen

Basistherapie: Fast alle Patienten erhalten das Malaria-Medikament Hydroxychloroquin, welches das Immunsystem moduliert und Schübe vorbeugt.

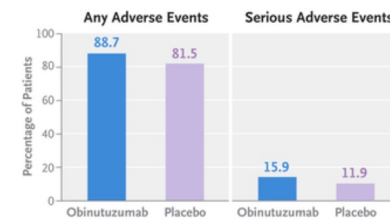
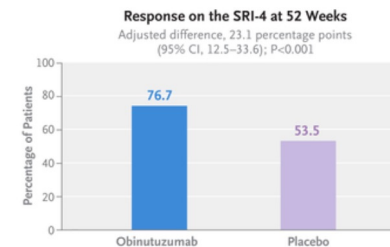
Schubtherapie: Bei akuten Entzündungen und Organbefall kommen entzündungshemmendes Kortison sowie Immunsuppressiva (wie Mycophenolatmofetil oder Belimumab) zum Einsatz.



Efficacy and Safety of Obinutuzumab in Active Systemic Lupus Erythematosus

Obinutuzumab, a glycoengineered type II anti-CD20 monoclonal antibody, induces potent B-cell depletion and is approved for the treatment of active lupus nephritis. Its efficacy and safety in patients with active systemic lupus erythematosus (SLE) are yet to be determined.

We conducted a phase 3, multicenter, double-blind, placebo-controlled trial involving adults with active SLE but without proliferative or membranous lupus nephritis who were receiving standard therapy. Patients were randomly assigned in a 1:1 ratio to receive obinutuzumab (1000 mg) or placebo on day 1 and weeks 2, 24, and 26. In the prespecified analysis, the primary end point at week 52 was a response on the SLE Responder Index 4 (SRI-4), defined by a reduction from baseline of at least 4 points in the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score, no worsening of disease as assessed by the British Isles Lupus Assessment Group (BILAG) 2004 index and Physician's Global Assessment, and no intercurrent events (i.e., major concomitant-therapy violation, receipt of rescue medication, or early discontinuation of trial participation due to death, lack of efficacy, or adverse events).



Therapies for systemic lupus erythematosus (SLE) that have been approved in the past several years represent important advances, and their early initiation is recommended by the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR). However, many patients still have persistent disease activity, progressive organ damage, treatment-limiting side effects, or premature death, underscoring ongoing needs for new therapies. Obinutuzumab is a humanized glycoengineered type II anti-CD20 antibody approved for adults with active lupus nephritis. Relative to type I anti-CD20 monoclonal antibodies, obinutuzumab induces more potent B-cell depletion owing to enhanced FcγRIIIa binding and greater direct cell death, antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis and less reliance on complement-dependent cytotoxicity. We conducted the current trial (ALLEGORY) to evaluate the efficacy and safety of obinutuzumab, as compared with placebo, when added to standard therapy in adults with active SLE.

Entry Criteria

Adults 18 to 75 years of age were eligible if they had SLE that met the 2019 EULAR–ACR classification criteria at least 12 weeks before screening. Eligible patients had Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) scores of 8 or higher, excluding points for alopecia, headache, or fever. SLEDAI-2K, a 24-item instrument, assigns 1 to 8 points for each clinical or laboratory abnormality attributed to active SLE, with scores of 6 to 12 representing moderate activity and more than 12 representing severe activity. Seropositivity for antinuclear antibodies (titer of $\geq 1:80$) or anti–double-stranded DNA (anti-dsDNA; ≥ 100 IU per milliliter) or anti-Smith antibodies (≥ 100 AU per milliliter), along with low C3, C4, or CH50 complement levels, was required. Patients were receiving stable doses of at least one of the following classes of standard therapy: antimalarial agents, nonglucocorticoid immunosuppressants, or glucocorticoids.

End Points

The primary end point at week 52 was a response on the SLE Responder Index 4 (SRI-4), a dichotomous composite end point defined by a reduction from baseline of at least 4 points in the SLEDAI-2K score, no worsening of BILAG-2004 and PGA scores, and no intercurrent events.

Characteristic	Obinutuzumab (N = 151)	Placebo (N = 152)
Age — yr	41.1±12.3	41.4±12.6
Female sex — no. (%)	139 (92.1)	135 (88.8)
Race or ethnic group — no. (%)†		
American Indian or Alaska Native	44 (29.1)	42 (27.6)
Asian	4 (2.6)	2 (1.3)
Black	22 (14.6)	25 (16.4)
Native Hawaiian or other Pacific Islander	0	1 (0.7)
White	64 (42.4)	62 (40.8)
Multiple	7 (4.6)	11 (7.2)
Unknown or not reported	10 (6.6)	9 (5.9)
Hispanic or Latino ethnic group — no. (%)†	75 (49.7)	86 (56.6)
SLEDAI-2K‡		
Mean global score	13.1±4.4	13.2±4.0
Score of ≥12 — no. (%)§	98 (64.9)	99 (65.1)
BILAG-2004 domain A or B score — no. (%)¶		
Constitutional	4 (2.6)	4 (2.6)
Mucocutaneous	135 (89.4)	145 (95.4)
Neuropsychiatric	2 (1.3)	1 (0.7)
Musculoskeletal	139 (92.1)	144 (94.7)
Cardiorespiratory	7 (4.6)	7 (4.6)
Gastrointestinal	2 (1.3)	0
Ophthalmic	0	0
Renal	16 (10.6)	22 (14.5)
Hematologic	0	2 (1.3)
PGA score	1.9±0.4	1.9±0.4
Baseline treatment for SLE		
Antimalarial: hydroxychloroquine, chloroquine, or quinacrine — no. (%)	121 (80.1)	124 (81.6)
Conventional immunosuppressant — no. (%)	107 (70.9)	102 (67.1)
Azathioprine — no./total no. (%)	40/107 (37.4)	26/102 (25.5)
Methotrexate — no./total no. (%)	32/107 (29.9)	28/102 (27.5)
Mycophenolate mofetil or mycophenolic acid — no./total no. (%)	34/107 (31.8)	44/102 (43.1)
Prednisone (or equivalent) dose of ≥10 mg/day — no. (%)	86 (57.0)	85 (55.9)

Results for Primary and Secondary Efficacy End Points

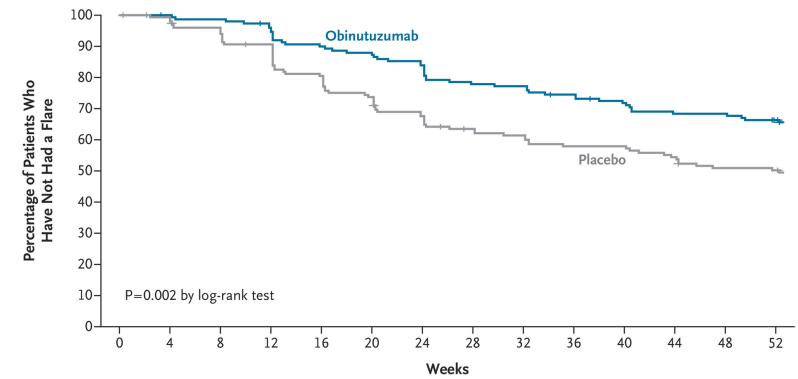
End Point	Obinutuzumab (N = 151)*	Placebo (N = 152)*	Adjusted Difference or Hazard Ratio (95% CI)*	P Value†
Primary end point: SRI-4 response at wk 52 (95% CI) — %‡§	76.7 (69.8–83.5)	53.5 (45.3–61.6)	23.1 (12.5–33.6)	<0.001
Supplementary treatment policy analysis¶	85.4 (79.6–91.2)	68.5 (60.7–76.3)	16.8 (7.1–26.4)	<0.001
Key secondary end points‡				
BICLA response at wk 52 (95% CI) — %	62.0 (54.2–69.8)	40.1 (32.1–48.1)	21.9 (10.8–32.9)	<0.001
Reduction in glucocorticoid dose to ≤7.5 mg/day, sustained from wk 40 to wk 52 (95% CI) — %**	80.0 (71.5–88.5)	54.1 (43.5–64.7)	26.1 (12.7–39.5)	<0.001
SRI-4 response at wk 40, sustained to wk 52 (95% CI) — %††	72.0 (64.6–79.3)	46.4 (38.3–54.6)	25.4 (14.6–36.2)	<0.001
SRI-6 response at wk 52 (95% CI) — %‡‡	68.9 (61.4–76.5)	38.9 (31.0–46.9)	30.0 (19.2–40.7)	<0.001
Median time to first BILAG flare through wk 52 — wk§§	Could not be estimated	52.3	0.58 (0.40–0.82)	0.002
Additional secondary end points¶¶				
DORIS response at wk 52 — %	33.8	13.8	19.9 (10.6–29.2)	
LLDAS at wk 52 — %***	57.6	25.0	32.6 (22.3–43.0)	

Flares over Time and Disease Activity.

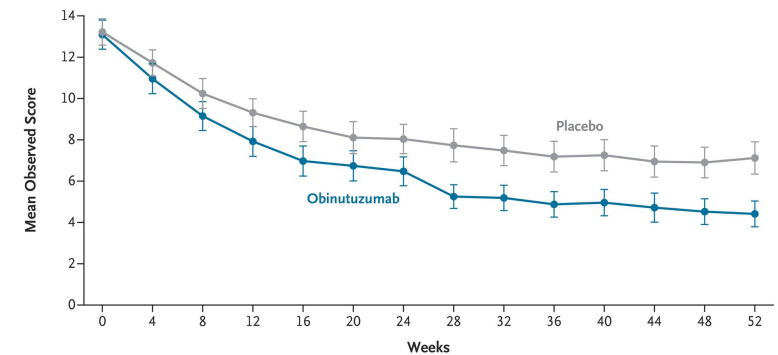
Adverse Events through Week 52

Event	Obinutuzumab (N=151)	Placebo (N=151)
Any adverse event — no. (%)	134 (88.7)	123 (81.5)
Total no. of adverse events	568	468
Any serious adverse event — no. (%)	24 (15.9)	18 (11.9)
Deaths — no. (%)	1 (0.7)	3 (2.0)
Adverse event leading to withdrawal from trial — no. (%)	1 (0.7)	2 (1.3)
Adverse event of grade 3 or higher — no. (%)	25 (16.6)	21 (13.9)
Infection — no. (%)	103 (68.2)	82 (54.3)
Infection as a serious adverse event — no. (%)	13 (8.6)	7 (4.6)
Adverse event with fatal outcome — no. (%)†	1 (0.7)	5 (3.3)
Adverse event leading to discontinuation of obinutuzumab or placebo — no. (%)	6 (4.0)	6 (4.0)
Serious adverse event leading to discontinuation of obinutuzumab or placebo — no. (%)	3 (2.0)	3 (2.0)
Infusion-related reaction — no. (%)	18 (11.9)	5 (3.3)
Infection of grade 3 or higher — no. (%)	11 (7.3)	7 (4.6)
Any hepatitis B reactivation or progressive multifocal leukoencephalopathy — no. (%)	0	0
Drug-related neutropenia — no. (%)	7 (4.6)	3 (2.0)
Drug-related thrombocytopenia — no. (%)	0	0
Gastrointestinal perforation — no. (%)	0	1 (0.7)
Worsening of preexisting cardiac condition — no. (%)	0	0
Potential drug-induced liver failure meeting Hy's law criteria — no. (%)	0	1 (0.7)
Suspected transmission of an infectious agent by obinutuzumab or placebo — no. (%)	0	0

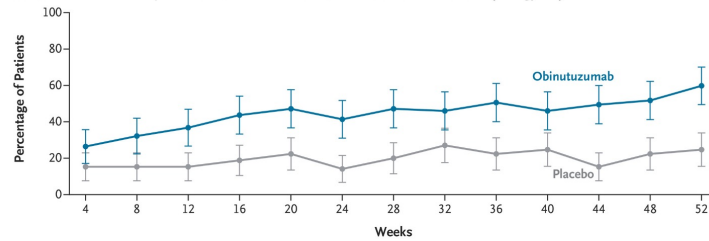
A Time to First BILAG Flare



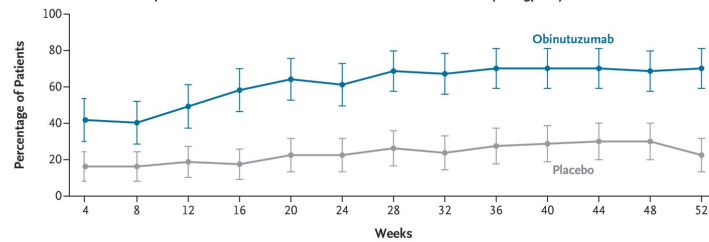
B SLEDAI-2K Score



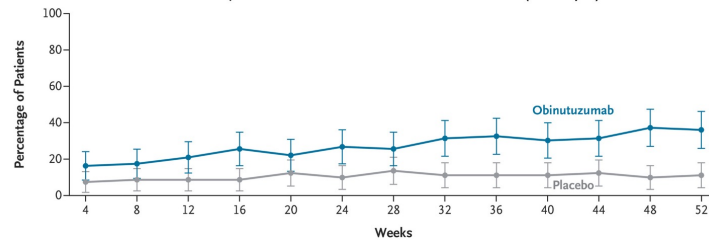
A Normalization of C3 Complement Levels in Patients with Abnormal Baseline Values (<0.9 g/liter)



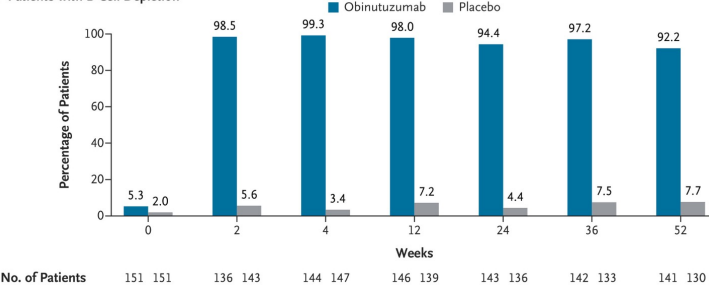
B Normalization of C4 Complement Levels in Patients with Abnormal Baseline Values (<0.1 g/liter)



C Normalization of Anti-dsDNA Antibody Levels in Patients with Abnormal Baseline Values (≥ 100 IU/ml)



D Patients with B-Cell Depletion



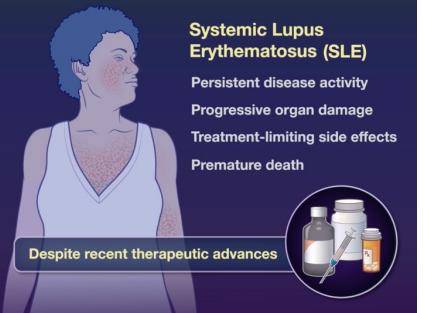
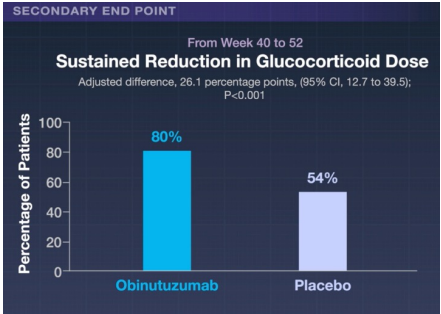
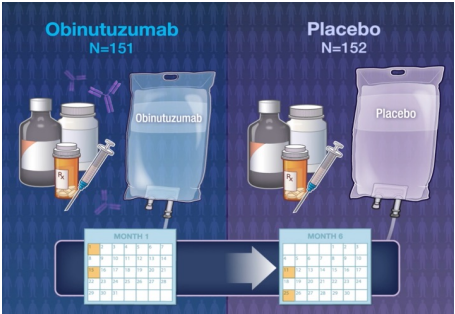
Serologic and Pharmacodynamic Analyses over Time.

Panels A and B show the percentage of patients with normal C3 complement levels (≥ 0.9 g per liter) and normal C4 complement levels (≥ 0.1 g per liter), respectively, per visit, from baseline through week 52, among patients with abnormal baseline levels (for C3 levels, 87 patients in the obinutuzumab group and 85 patients in the placebo group; for C4 levels, 67 patients in the obinutuzumab group and 80 patients in the placebo group). Panel C shows the percentage of patients with normal anti-double-stranded DNA antibody levels (<100 IU per milliliter) per visit, from baseline through week 52, among patients with abnormal baseline levels (86 patients in the obinutuzumab group and 81 patients in the placebo group). For Panels A, B, and C, I bars indicate Wald 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, and the intervals may not be used in place of hypothesis testing. Percentages are calculated as the number of patients with normal levels at each visit among those with abnormal baseline levels. Panel D shows the percentage of patients with B-cell depletion per visit, from baseline through week 52, in the obinutuzumab and placebo groups. B-cell depletion was defined by an absolute CD19-positive B-cell count of fewer than 10 cells per microliter, determined with the use of a flow cytometric assay of T, B, and natural killer cells.

Systemic Lupus Erythematosus (SLE)

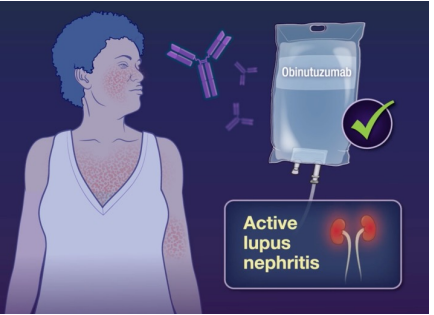
- Persistent disease activity
- Progressive organ damage
- Treatment-limiting side effects
- Premature death

Despite recent therapeutic advances

Obinutuzumab

Active lupus nephritis



PRIMARY END POINT

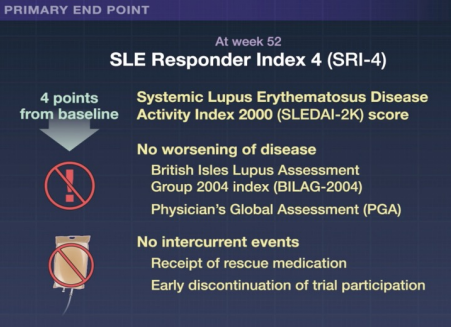
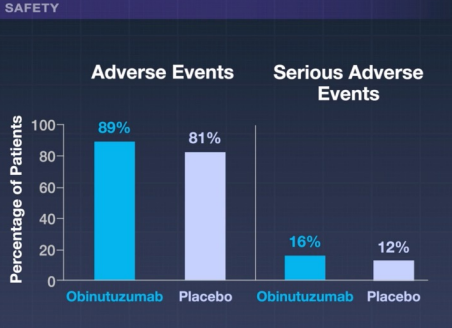
At week 52

SLE Responder Index 4 (SRI-4)

4 points from baseline

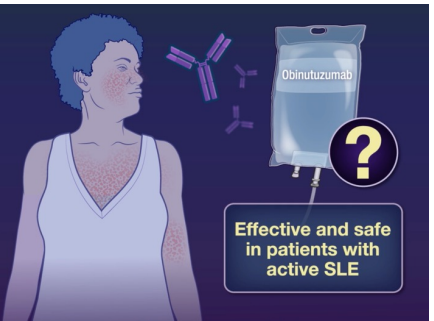
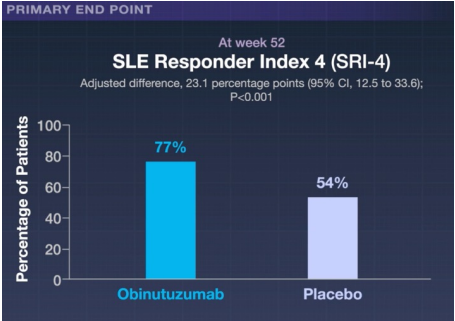
Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score

- No worsening of disease
 - British Isles Lupus Assessment Group 2004 index (BILAG-2004)
 - Physician's Global Assessment (PGA)
- No intercurrent events
 - Receipt of rescue medication
 - Early discontinuation of trial participation

Obinutuzumab

Effective and safe in patients with active SLE

Obinutuzumab

Achieving an SRI-4 response at week 52



"Health care associated infections" (HAI) werden im Deutschen als **nosokomiale Infektionen** oder **Gesundheitssystem-assoziierte Infektionen** bezeichnet. Umgangssprachlich sind sie oft als **Krankenhausinfektionen** bekannt

Ursachen

Die Erreger können entweder aus der eigenen Keimbesiedlung des Patienten stammen (*endogen*, z.B. wenn Darmbakterien in die Wunde gelangen) oder von außen übertragen werden (*exogen*, z.B. über das medizinische Personal oder kontaminierte Oberflächen).

Händedesinfektion: Die wichtigste Maßnahme zum Schutz vor Keimübertragung.

Isolierung: Patienten mit multiresistenten Erregern (MRE) werden isoliert.

Surveillance: Krankenhäuser in Deutschland sind gesetzlich verpflichtet, Infektionen zu erfassen und zu melden.

Healthcare-associated infections – a threat to patient safety in Europe

In 2016 and 2017, ECDC coordinated point prevalence surveys to collect data on healthcare-associated infections (HAIs) in hospitals and long-term care facilities in EU/EEA countries. Although some HAIs can be treated easily, others may more seriously affect a patient's health, increasing their stay in the hospital and hospital costs. HAIs in hospitals alone cause more deaths in Europe than any other infectious disease under surveillance at ECDC.

On any given day:



Hospitals

1 / 15
hospital patients have
at least one HAI.

98 000
patients have at least
one HAI.



Long-term
care facilities

1 / 26
long-term care facilities
residents have at least
one HAI.

130 000
residents have at least
one HAI.

Facts

A total of 8.9 million HAIs were estimated to occur each year in European hospitals and long-term care facilities combined.

8.9 million HAIs occur



Hospitals Long-term
care facilities

HAIs in hospitals (for example pneumonia, surgical site infections and bloodstream infections, are usually more severe than HAIs in long-term care facilities (for example respiratory infections other than pneumonia, urinary tract infections and skin and soft tissue infections).

More than half of certain HAIs are considered preventable.



Microbiological samples

HAIs are frequently treated without taking microbiological samples or samples remain negative.



Microorganisms

The responsible microorganism was identified in 53% of HAIs in hospitals and only in 19% of HAIs in long-term care facilities.



Resistance to
antibiotics

1 in 3 bacteria associated with HAIs, both in hospitals and in long-term care facilities, was resistant to antibiotics.

Measures to prevent healthcare-associated infections:



Infection prevention and control, including hand hygiene as well as screening for carriage of infection with multidrug-resistant bacteria and isolation of carriers/infected patients.



Training for all healthcare staff.



Surveillance of HAIs at local and national level.



Antimicrobial stewardship programmes.



Improved information for patients, residents and their relatives about what they can themselves do to prevent HAIs and to use antibiotics prudently.



Improved microbiological laboratory support in hospitals and especially in long-term care facilities.



ecdc.europa.eu
antibiotic.ecdc.europa.eu

#KeepAntibioticsWorking
#EAAD

Health Care–Associated Infections in U.S. Hospitals, 2023 versus 2015

Background

Prevalence surveys in U.S. hospitals showed that on any given day, 1 of 25 patients had a health care–associated infection in 2011, as compared with 1 of 31 patients in 2015. We repeated the survey in 2023 to assess changes in the prevalence of such infections.

Methods

Using established methods, 10 Emerging Infections Program (EIP) sites recruited up to 25 hospitals each. Hospitals selected a survey day between May 1 and September 30, 2023. EIP staff reviewed medical records of randomly selected patients to identify health care–associated infections using National Healthcare Safety Network definitions. We described patient and hospital characteristics, compared the prevalence of health care–associated infections in 2023 and 2015, and estimated the national burden of health care–associated infections in 2023.

Conclusions

The prevalence of health care–associated infections was lower in 2023 than in 2015, with 1 of 38 patients on any given day having such an infection; however, the burden of health care–associated infections in U.S. hospitals continued to be high. A majority of the health care–associated infections that were identified were not associated with a device or procedure. (Funded by the Emerging Infections Program cooperative agreement from the Centers for Disease Control and Prevention.)

Prevention of health care–associated infections is a long-standing priority of U.S. public health and health care systems. Before the coronavirus disease 2019 (Covid-19) pandemic, hospitals had reduced the occurrence of health care–associated infections monitored by the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN), including central catheter–associated bloodstream infections, catheter-associated urinary tract infections, and hospital-onset *Clostridioides difficile* infections. However, the pandemic reversed many of these improvements, possibly because of altered patient care and infection prevention and control practices and increased illness severity in hospitalized patients. Some rates of health care–associated infections began to decline again in 2022; in 2023, some had fallen below prepandemic levels.

Methods

Hospitals and Patients

We used the hospital and patient selection methods that were used in the 2015 hospital point-prevalence survey. Emerging Infections Program (EIP) sites in California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee recruited up to 25 hospitals each: hospitals that had participated in the 2015 survey were prioritized.

Demographic and Clinical Characteristics of Patients in the 2015 and 2023 Hospital Point-Prevalence Surveys.

Characteristic	2015 Survey (N=12,299)	2023 Survey (N=13,653)
Location of patient in hospital on survey day — no. (%)†		
Ward, excluding nursery	9,174 (74.6)	10,039 (73.5)
Critical care unit	1,834 (14.9)	2,018 (14.8)
Step-down unit	547 (4.4)	803 (5.9)
Newborn or special care nursery	456 (3.7)	397 (2.9)
Unit housing patients receiving different levels of acute care	228 (1.9)	349 (2.6)
Specialty care area	60 (0.5)	47 (0.3)
Age — no. (%)		
<1 yr	1,339 (10.9)	1,119 (8.2)
1–17 yr	527 (4.3)	426 (3.1)
18–24 yr	457 (3.7)	386 (2.8)
25–44 yr	1,951 (15.9)	1,948 (14.3)
45–64 yr	3,211 (26.1)	3,364 (24.6)
65–84 yr	3,756 (30.5)	5,102 (37.4)
≥85 yr	1,058 (8.6)	1,307 (9.6)
Missing	0	1 (<0.1)
Urinary catheter in place on survey day — no. (%)		
Yes	2,299 (18.7)	2,216 (16.2)
No	9,959 (81.0)	11,378 (83.3)
Missing	41 (0.3)	59 (0.4)
Ventilator in place on survey day — no. (%)		
Yes	586 (4.8)	671 (4.9)
No	11,683 (95.0)	12,946 (94.8)
Missing	30 (0.2)	36 (0.3)
Central catheter in place on survey day — no. (%)		
Yes	2,081 (16.9)	2,054 (15.0)
No	10,175 (82.7)	11,553 (84.6)
Missing	43 (0.3)	46 (0.3)
Median hospital length of stay (IQR) — days‡	5 (3–11)	6 (3–14)

Demographic and Clinical Characteristics of Patients with and without Health Care–Associated Infections, 2023 Survey

Characteristic	All Patients (N=13,653)	Patients without Health Care– Associated Infection (N=13,298)	Patients with Health Care– Associated Infection (N=355)
Hospital size — no. (%)†			
Small	4,309 (31.6)	4,243 (31.9)	66 (18.6)
Medium	6,448 (47.2)	6,273 (47.2)	175 (49.3)
Large	2,896 (21.2)	2,782 (20.9)	114 (32.1)
Location of patient in hospital on survey day — no. (%)‡			
Ward, excluding nursery	10,039 (73.5)	9,832 (73.9)	207 (58.3)
Critical care unit	2,018 (14.8)	1,906 (14.3)	112 (31.5)
Step-down unit	803 (5.9)	777 (5.8)	26 (7.3)
Newborn or special care nursery	397 (2.9)	397 (3.0)	0
Unit housing patients receiving different levels of acute care	349 (2.6)	343 (2.6)	6 (1.7)
Specialty care area	47 (0.3)	43 (0.3)	4 (1.1)
Race or ethnic group — no. (%)§			
Hispanic or Latino, any race	1,343 (9.8)	1,311 (9.9)	32 (9.0)
Not known to be Hispanic or Latino			
White	8,571 (62.8)	8,350 (62.8)	221 (62.3)
Black	2,158 (15.8)	2,090 (15.7)	68 (19.2)
Asian	391 (2.9)	386 (2.9)	5 (1.4)
Multiple races	87 (0.6)	87 (0.7)	0
Other¶	510 (3.7)	498 (3.7)	12 (3.4)
Unknown race	593 (4.3)	576 (4.3)	17 (4.8)
Ventilator in place on survey day — no. (%)			
Yes	671 (4.9)	595 (4.5)	76 (21.4)
No	12,946 (94.8)	12,667 (95.3)	279 (78.6)
Missing	36 (0.3)	36 (0.3)	0
Central catheter in place on survey day — no. (%)			
Any	2,054 (15.0)	1,899 (14.3)	155 (43.7)
None	11,553 (84.6)	11,353 (85.4)	200 (56.3)
Missing	46 (0.3)	46 (0.3)	0
Median hospital length of stay (IQR) — days	6 (3–14)	6 (3–13)	23 (14–42)

Prevalence of Health Care–Associated Infections among All Patients, 2015 vs. 2023 Surveys.

Type of Infection	2015 Survey			2023 Survey			Risk Difference (95% CI) [†]
	No. of Patients with Infection	No. of Infections	Percentage of Patients with Infection	No. of Patients with Infection	No. of Infections	Percentage of Patients with Infection	
Pneumonia	110	110	0.89	102	102	0.75	−0.15 (−0.37 to 0.07)
Ventilator-associated pneumonia	39	39	0.32	35	35	0.26	−0.06 (−0.19 to 0.07)
Other pneumonia	71	71	0.58	67	67	0.49	−0.09 (−0.26 to 0.09)
Gastrointestinal infection	91	91	0.74	56	56	0.41	−0.33 (−0.52 to −0.14)
<i>Clostridioides difficile</i> infection	66	66	0.54	30	30	0.22	−0.32 (−0.47 to −0.17)
Other gastrointestinal infection	25	25	0.20	26	26	0.19	−0.01 (−0.12 to 0.10)
Surgical-site infection [‡]	69	69	0.56	81	82	0.59	0.03 (−0.15 to 0.22)
Deep incisional or organ-space infection	54	54	0.44	66	67	0.48	0.04 (−0.12 to 0.21)
Superficial incisional infection	15	15	0.12	15	15	0.11	−0.01 (−0.10 to 0.07)
Bloodstream infection	51	52	0.41	47	47	0.34	−0.07 (−0.22 to 0.08)
Central catheter–associated bloodstream infection	37	38	0.30	22	22	0.16	−0.14 (−0.26 to −0.02)
Other primary bloodstream infection	14	14	0.11	25	25	0.18	0.07 (−0.02 to 0.16)
Urinary tract infection	39	39	0.32	35	35	0.26	−0.06 (−0.19 to 0.07)
Catheter-associated urinary tract infection	24	24	0.20	12	12	0.09	−0.11 (−0.20 to −0.01)
Other urinary tract infection	15	15	0.12	23	23	0.17	0.05 (−0.05 to 0.14)
Other infection [§]	61	66	0.50	62	68	0.45	−0.04 (−0.21 to 0.13)
Any infection	394	427	3.20	355	390	2.60	−0.60 (−1.01 to −0.19)

Multivariable Log-Binomial Regression Model to Evaluate Changes in Prevalence of Health Care–Associated Infections among 19,597 Patients from 151 Hospitals Participating in Both the 2015 and 2023 Surveys.

Variable [†]	Total No. of Patients	No. of Patients with Health Care–Associated Infection	Adjusted Risk Ratio (95% CI)
Survey year			
2015	9,822	322	Reference
2023	9,775	274	0.73 (0.63–0.85)
Central catheter in place on the survey day			
No	16,455	306	Reference
Yes	3,142	290	1.74 (1.47–2.06)
Ventilator in place on the survey day			
No	18,635	464	Reference
Yes	962	132	1.81 (1.50–2.19)
Hospital length of stay — days			
<6	9,453	25	Reference
6 or 7	2,181	36	5.57 (3.35–9.27)
8–12	2,864	78	8.77 (5.58–13.76)
13–24	2,591	184	20.40 (13.38–31.10)
≥25	2,508	273	31.40 (20.67–47.71)
Age — yr			
<23	3,210	75	Reference
23–45	3,317	68	1.56 (1.14–2.15)
46–68	6,241	267	2.15 (1.68–2.76)
≥69	6,829	186	1.76 (1.35–2.29)

Pathogens Reported for Health Care–Associated Infections, 2023 Survey.

Pathogen	All Infections (N=390)	Pneumonia (N=102)†	Gastrointestinal Infection (N=56)‡	Surgical-Site Infection (N=82)	Bloodstream Infection (N=47)§	Urinary Tract Infection (N=35)¶	Other Infection (N=68)‖
number of infections (percent)							
<i>Staphylococcus aureus</i>	54 (14)	13 (13)	2 (4)	12 (15)	10 (21)	3 (9)	14 (21)
<i>Escherichia coli</i>	49 (13)	3 (3)	8 (14)	15 (18)	6 (13)	12 (34)	5 (7)
<i>Clostridioides difficile</i>	30 (8)	0	30 (54)	0	0	0	0
<i>Enterococcus faecalis</i>	26 (7)	0	5 (9)	10 (12)	4 (9)	3 (9)	4 (6)
<i>Pseudomonas aeruginosa</i>	26 (7)	4 (4)	2 (4)	7 (9)	6 (13)	4 (11)	3 (4)
<i>Klebsiella aerogenes</i> , <i>K. oxytoca</i> , or <i>K. pneumoniae</i>	25 (6)	7 (7)	1 (2)	5 (6)	3 (6)	8 (23)	1 (1)
<i>Candida</i> species	22 (6)	1 (1)	5 (9)	6 (7)	6 (13)	0	4 (6)
<i>Staphylococcus epidermidis</i>	15 (4)	0	0	8 (10)	4 (9)	0	3 (4)
<i>Streptococcus</i> species	14 (4)	1 (1)	5 (9)	4 (5)	1 (2)	0	3 (4)
Other gram-negative bacterium**	12 (3)	2 (2)	3 (5)	3 (4)	2 (4)	0	2 (3)
<i>Enterobacter cloacae</i> or <i>E. cloacae</i> complex	11 (3)	1 (1)	1 (2)	8 (10)	1 (2)	0	0
<i>Proteus mirabilis</i>	10 (3)	1 (1)	1 (2)	3 (4)	1 (2)	2 (6)	2 (3)
Other gram-positive bacterium††	9 (2)	1 (1)	0	4 (5)	2 (4)	0	2 (3)
<i>Enterococcus faecium</i>	7 (2)	0	0	3 (4)	0	4 (11)	0
<i>Serratia marcescens</i>	7 (2)	3 (3)	1 (2)	1 (1)	2 (4)	0	0
Other enterococcus species	5 (1)	0	0	3 (4)	1 (2)	1 (3)	0
<i>Corynebacterium</i> species	4 (1)	2 (2)	0	1 (1)	1 (2)	0	0
Other enterobacterales	4 (1)	1 (1)	0	1 (1)	0	2 (6)	0
Other staphylococcus species	4 (1)	0	0	2 (2)	2 (4)	0	0
Yeast, not otherwise specified	4 (1)	1 (1)	0	2 (2)	0	0	1 (1)
Virus‡‡	3 (1)	0	1 (2)	0	1 (2)	0	1 (1)
<i>Acinetobacter</i> species§§	3 (1)	2 (2)	0	0	0	0	1 (1)
Gram-negative bacterium	2 (1)	0	0	2 (2)	0	0	0
<i>Proteus vulgaris</i>	1 (<1)	0	0	1 (1)	0	0	0
Other pathogen	5 (1)	1 (1)	0	3 (4)	0	0	1 (1)
No pathogen reported	129 (33)	69 (68)	8 (14)	18 (22)	0	0	34 (50)
Any pathogen reported	261 (67)	33 (32)	48 (86)	64 (78)	47 (100)	35 (100)	34 (50)
Total no. of pathogens	357	45	66	104	55	39	48

Discussion

The prevalence of health care–associated infections was lower in 2023 than in 2015, with an estimated 1 of 38 patients on any given day having at least one health care–associated infection. Patients in the 2023-23 survey were 27% less likely to have a health care–associated infection than in the 2015-11 survey, although the estimated national burden still exceeded 500,000 infections. The narrower confidence intervals of the national burden estimates in the 2023 survey than in the 2015 survey can be attributed to fewer stratification levels among patients, which led to larger sample sizes within individual strata and, in turn, increased precision in the point estimates.

We found that the prevalence of health care–associated infections in hospitals in 2023 was lower than in 2015, with reductions in *C. difficile* infection, central catheter–associated bloodstream infection, and catheter-associated urinary tract infection. However, we estimate that there were still more than half a million health care–associated infections affecting U.S. hospital patients in 2023. Although the reduction in prevalence provides evidence of continued success of prevention strategies, additional interventions focusing on prevention of surgical-site infections and health care–associated infections that are not associated with devices or procedures are recommended to further reduce the risk of health care–associated infections in hospitals.

Fibromyalgia

A 43-year-old man presents with a 3-year history of chronic low back pain that has been unresponsive to muscle relaxants, nonsteroidal antiinflammatory drugs (NSAIDs), epidural glucocorticoid injections, and physical therapy. A recent diagnostic workup revealed a normal erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, thyroid-stimulating hormone (TSH) level, and complete blood count and normal results of liver-function tests. Magnetic resonance imaging of the lumbar spine showed mild degenerative changes and a protruding disk (at L5 or S1). At intake, he used a body map (i.e., a paper and pencil mannequin) to indicate sites of pain in his back, head, shoulders, and legs. He reports a long history of tension headache and noncardiac chest pain and a previous diagnosis of chronic prostatitis. He reports long-term insomnia, fatigue, and sensitivity to bright lights and multiple drug allergies. The physical examination is generally unremarkable except for tenderness in many regions but otherwise normal strength and sensation throughout and negative findings on provocative maneuvers of the lower back and sacroiliac joint. He is frustrated and wondering whether he should have lumbar surgery to relieve his pain or whether opioids would be helpful. How would you treat this patient?

Fibromyalgia

- Fibromyalgia is associated with widespread pain plus other centrally mediated symptoms, such as poor sleep, fatigue, impaired cognition, depressed mood, and general sensory sensitivity.
- Fibromyalgia is common and can manifest as the primary problem (i.e., primary pain) or be superimposed on other conditions (e.g., autoimmune disorders or osteoarthritis).
- The workup of fibromyalgia depends on the context. Persons who have widespread pain that developed during childhood and evolved slowly over time need very little workup, and those who have acute or subacute onset of symptoms need a more extensive workup.
- The treatment of fibromyalgia begins with education and self-care activities such as physical activity, resilience training, and improvement of sleep. Nonpharmacologic integrative approaches, including cognitive behavioral therapy, movement-promoting therapies (e.g., yoga and tai chi), and stress-reduction therapies (e.g., meditation and mindfulness), are the most effective treatments.
- Classes of drugs that can be helpful include tricyclic drugs, gabapentinoid agents, and serotonin–norepinephrine reuptake inhibitors. Nonsteroidal antiinflammatory drugs and opioid agents are not useful, and opioids may be harmful.

ACR Diagnostic Criteria

WPI

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19

SSS

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19

ACR Diagnostic Criteria

The 2016 ACR diagnostic criteria for fibromyalgia combine data from the Widespread Pain Index with those from the Symptom Severity Scale to obtain the Fibromyalgia Severity score. A diagnosis of fibromyalgia is presumed if pain is indicated in at least four of five regions on the Widespread Pain Index body map and the Fibromyalgia Severity score is greater than 13.

PROMIS-29+2

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100

PROMIS-29+2

The PROMIS-29+2 tool is used to assess the following fibromyalgia symptoms:

- physical function
- anxiety
- depression
- fatigue
- sleep disturbance
- pain
- pain interference
- ability to participate in social roles and activities
- cognitive function

Scores on the PROMIS-29+2 are converted to T scores with a mean of 50 and standard deviation of 10 for comparison with population means.

COPC-S

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100

COPC-S

The COPC-S is used by the patient to assess the following conditions on the basis of standardized diagnostic criteria: fibromyalgia, temporomandibular disorder, irritable bowel syndrome, chronic tension headache, chronic migraine headache, chronic urologic pelvic pain, chronic low back pain, painful endometriosis, vulvodynia, and myalgic encephalomyelitis (also known as chronic fatigue syndrome). This assessment tool can be administered in less than 10 to 15 minutes.

Diagnosis and Assessment of Fibromyalgia.

Shown are clinician resources for diagnosing fibromyalgia, monitoring symptoms, and identifying chronic overlapping pain conditions. The 2016 revisions to the 2010/2011 fibromyalgia diagnostic criteria⁹ include several tools to diagnose the condition: the Widespread Pain Index (WPI) is used to assess chronic pain at 19 sites on a body map, the Symptom Severity Scale (SSS) is used to record nonpain symptoms, and the Fibromyalgia Severity score is a continuous measure of the burden of fibromyalgia symptoms and can serve as a proxy measure of the degree of nociplasticity. The Patient-Reported Outcomes Measurement Information System (PROMIS)–29+2 tool,¹⁰ developed by the National Institutes of Health, is used to assess the effects of fibromyalgia symptoms on physical and mental health during a 7-day recall period. The Chronic Overlapping Pain Conditions– Screener (COPC-S)¹¹ is used to help identify chronic overlapping pain conditions that may be present in patients with fibromyalgia. ACR denotes American College of Rheumatology.

Pain education

Pain education aims to clarify the known scientific underpinnings of fibromyalgia (e.g., central sensitization and nociceptive mechanisms), assure patients about the legitimacy and prognosis of the condition, and engage patients in taking an active role in care. This foundation helps provide a rational framework for understanding why specific medications, nonpharmacologic treatments, and self-care approaches can provide benefit.

Physical activity

Physical activity approaches integrate physical activities with education about the benefits of regular activity for maintaining health and reducing pain. Physical activity can include expansion of regular lifestyle activities (e.g., climbing stairs at work and pushing a loaded grocery cart) or starting a walking program. The intensity of activities should be low initially and progress according to the patient's tolerance.

Sleep hygiene and behavioral sleep strategies

Sleep habit formation is key to maintaining consistent sleep-wake schedules, developing relaxing bedtime routines, being observant of items consumed before bedtime (e.g., alcohol, caffeine, and nicotine), and maintaining an environment conducive to sleep.

Pleasant activity scheduling

Pleasant activity scheduling is a structured method of incorporating something pleasant for a brief time each day in order to improve mood and increase function. Activities can be low cost and as simple as calling a friend or watching a show, but they must be scheduled in advance and completed.

Activity pacing

Pacing is used to conserve energy and prevent flare-ups by strategically breaking down large tasks into smaller tasks, with rest periods in between, or by alternating fixed periods of activity with fixed periods of rest.

Resilience training

Resilience training combines a number of skills that promote positive thinking and emotions. Skills include savoring (taking time to appreciate subtle sensory experiences), expressing gratitude (noticing the positive events in the day and acknowledging them), and identifying and using unique positive personal attributes (signature strengths).

Stress management

Stress management combines a number of coping skills to achieve physiological and mental calmness. Skills include relaxation techniques (e.g., progressive muscle relaxation and visual imagery), mindfulness practices, time management skills, and cognitive reappraisal or reframing (structured reevaluation of negative thinking and emotions).

Dietary modifications

Health-promoting balanced diets and antiinflammatory Mediterranean diets, plus adequate hydration and identification of dietary triggers, are beneficial to overall health and weight management in patients with fibromyalgia. Weight management is important because overweight and obesity can exacerbate pain and reduce function.

Social support

Support for living with fibromyalgia can come from interactions with others, including family, friends, workplace colleagues, and health care providers. Effective management of these relationships can be challenging but is key to successful self-care.

Environmental modifications

Optimizing one's environment can reduce symptom triggers and improve function. Activities include workplace adjustments to improve ergonomics and home modifications to enhance safety and sleep.

Self-Care Approaches for Fibromyalgia.

Shown are selected evidence-based self-care activities for pain that provide a foundation for the long-term management of fibromyalgia.¹⁹

Nonpharmacologic Treatments with the Strongest Support.

Treatment and Outcome Measure	Standardized Mean Difference (95% CI)†	Effect Size‡
Physical activity ²⁴		
Exercise		
Pain	-1.11 (-1.52 to -0.71)	Large
Fibromyalgia symptoms	-0.67 (-0.89 to -0.45)	Medium
HRQOL-physical health	0.77 (0.47 to 1.08)§	Medium
HRQOL-mental health	0.39 (0.27 to 0.52)§	Small
Depression	-0.40 (-0.55 to -0.24)	Small
Aerobic exercise		
Pain	-1.05 (-1.78 to -0.33)	Large
Fibromyalgia symptoms	-0.65 (-1.14 to -0.16)	Medium
Depression	-0.39 (-0.77 to -0.01)	Small
Muscle strengthening		
Pain	-1.39 (-2.16 to -0.62)	Large
Fibromyalgia symptoms	-0.84 (-1.23 to -0.45)	Large
HRQOL-physical health	0.72 (0.23 to 1.21)§	Medium
HRQOL-mental health	0.44 (0.17 to 0.71)§	Small
Depression	-0.37 (-0.61 to -0.13)	Small
Stretching		
HRQOL-physical health	1.15 (0.61 to 1.69)§	Large
HRQOL-mental health	0.57 (0.06 to 1.08)§	Medium
Depression	-0.36 (-0.72 to 0.00)	Small
Psychological and behavioral therapies		
Cognitive behavioral therapy ²⁵		
Pain	-0.45 (-0.80 to -0.10)	Medium
Acceptance and commitment therapy ²¹		
Fibromyalgia symptoms	-1.43 (-2.17 to -0.69)	Large
Depression	-0.81 (-1.31 to -0.31)	Large
Anxiety	-0.94 (-1.29 to -0.59)	Large
Mindfulness ²⁵		
Fatigue	-0.49 (-0.91 to -0.07)	Medium
Depression	-0.46 (-0.75 to -0.17)	Medium
Multidisciplinary treatment ²⁵		
Pain	-1.33 (-2.16 to -0.49)	Large
Sleep	-1.15 (-2.11 to -0.18)	Large
Depression	-1.26 (-2.06 to -0.45)	Large
Complementary and integrative therapies ²⁶		
Electroacupuncture		
Pain	-0.63 (-1.02 to -0.23)	Medium
Sleep	-0.40 (-0.01 to -0.79)	Small
HRQOL	-0.65 (-1.05 to -0.26)	Medium
Qigong		
Pain	-0.69 (-1.25 to -0.12)	Medium
Sleep	-0.67 (-1.01 to -0.34)	Medium
Fatigue	-0.56 (-1.07 to -0.34)	Medium
Tai chi		
Sleep	-0.71 (-1.28 to -0.13)	Medium
Yoga		
Pain	-0.54 (-0.96 to -0.11)	Medium
HRQOL	-0.72 (-1.32 to -0.12)	Medium

Medications for Fibromyalgia with the Strongest Support.

Drug and Outcome Measure	Standardized Mean Difference (95% CI or 95% Credible Interval)†	Effect Size‡
Tricyclic agents		
Amitriptyline ³²		
Sleep	-0.97 (-1.10 to -0.83)	Large
Fatigue	-0.64 (-0.75 to -0.53)	Medium
HRQOL	-0.80 (-0.94 to -0.65)	Large
Cyclobenzaprine ³³		
Pain	-0.25 (-0.34 to -0.16)	Small
Sleep	-0.21 (-0.32 to -0.11)	Small
Function	-0.18 (-0.35 to -0.02)	Negligible
Fibromyalgia symptoms	-0.23 (-0.33 to -0.13)	Small
SNRIs		
Duloxetine ³²		
Pain	-0.33 (-0.36 to -0.30)	Small
Sleep	-0.21 (-0.30 to -0.13)	Small
Depression	-0.25 (-0.32 to -0.17)	Small
Fatigue	-0.12 (-0.16 to -0.08)	Small
HRQOL	-0.39 (-0.55 to -0.23)	Small
Milnacipran ³²		
Pain	-0.17 (-0.20 to -0.15)	Negligible
Depression	-0.10 (-0.12 to -0.07)	Negligible
Fatigue	-0.10 (-0.14 to -0.05)	Negligible
Gabapentinoid agent		
Pregabalin ³²		
Pain	-0.30 (-0.32 to -0.27)	Small
Sleep	-0.60 (-0.67 to -0.54)	Medium
Depression	-0.22 (-0.26 to -0.19)	Small
Fatigue	-0.27 (-0.29 to -0.24)	Small
HRQOL	-0.18 (-0.29 to -0.06)	Negligible

Conclusions and Recommendations

The case vignette intentionally described a male patient, since providers often consider fibromyalgia only in female patients. He reports pain in many body regions (i.e., chronic overlapping pain conditions) and is sensitive to touch and other nonpainful sensory stimuli. This man has a classic presentation for fibromyalgia and, like most patients with fibromyalgia, does not need a referral to subspecialty care or further workup. For patients with fibromyalgia who may have an underlying autoimmune disorder, neuropathy, or radiculopathy, referral to the appropriate subspecialist for a one-time consultation might be helpful. Often, however, fibromyalgia can be treated in primary care. We would reassure this patient that he does not need surgery and would prescribe a low nighttime dose of a tricyclic agent (e.g., cyclobenzaprine or nortriptyline), in combination with a graduated physical activity and exercise plan (e.g., a yoga or walking program). If he does not have a response to these treatments, we would consider trying other classes of centrally acting nonopioid analgesics (e.g., SNRIs or gabapentinoids), as well as a wide range of integrative nonpharmacologic therapies (e.g., various forms of CBT, movement therapy, and neurostimulation therapy) that can be helpful in persons with fibromyalgia.

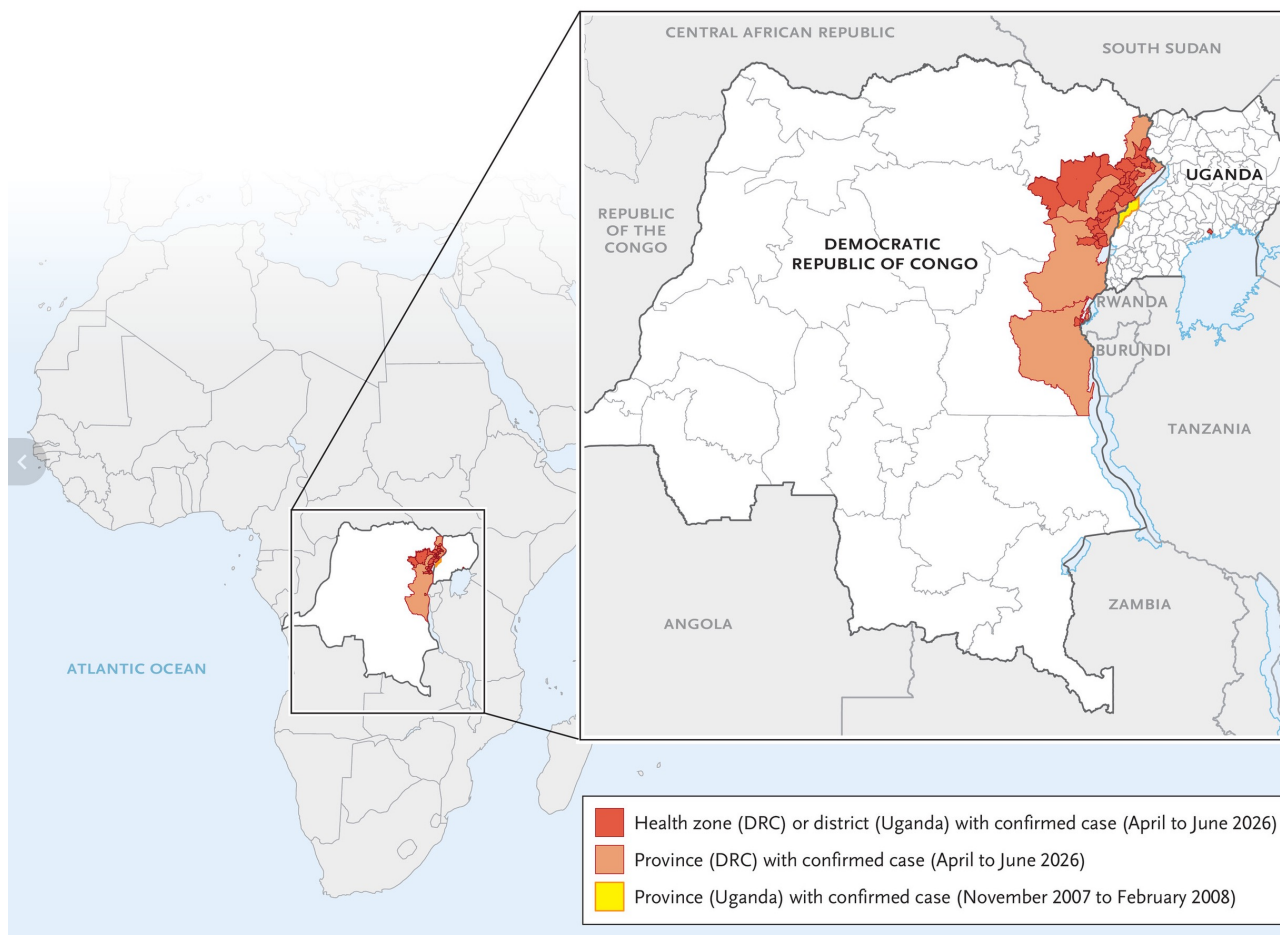
Bundibugyo Virus Disease in 2026 — Clinical and Public Health Responses

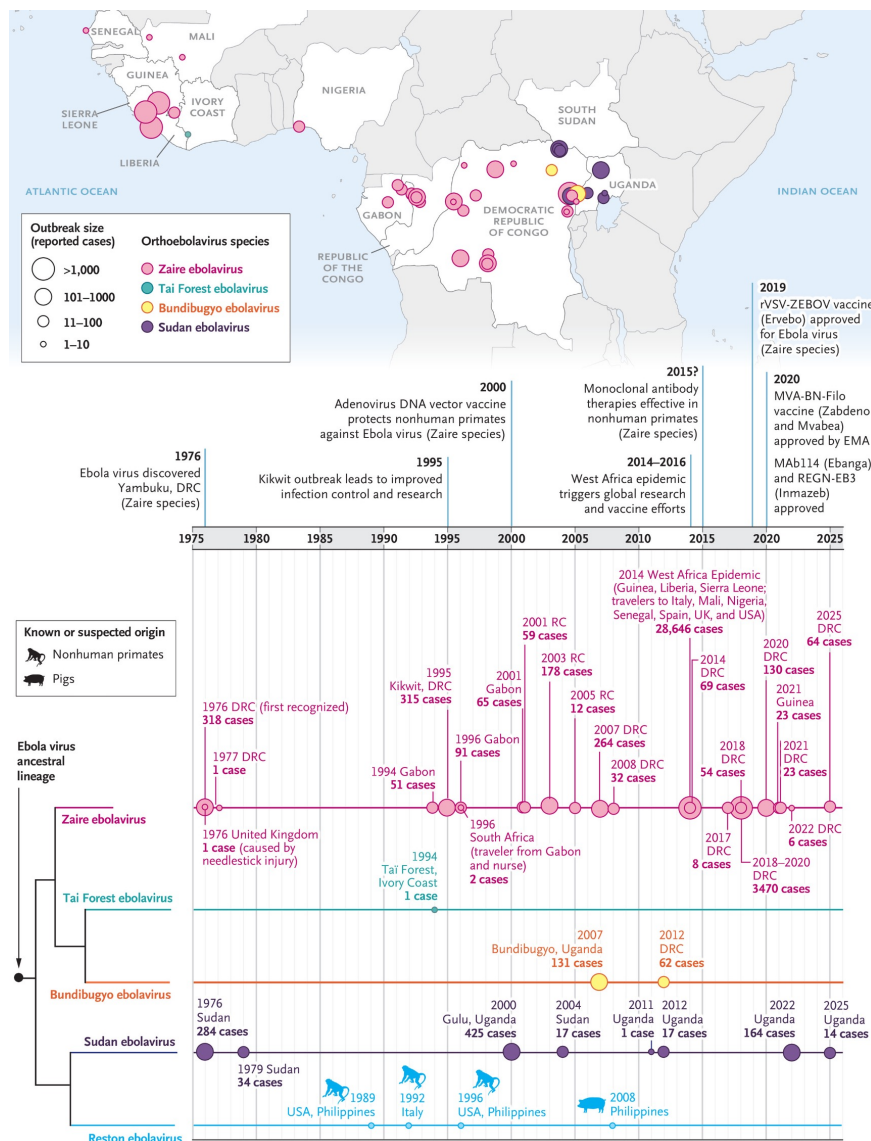
Summary

Bundibugyo virus is a relatively rare orthoebolavirus that has caused only two previously recognized disease outbreaks but remains capable of producing severe epidemic disease with substantial mortality. The 2026 outbreak of Bundibugyo virus disease in the Democratic Republic of Congo has highlighted persistent challenges in the detection of filovirus disease outbreaks, as well as in diagnosis, clinical management, and the public health response, particularly in resource-limited settings. As with other filovirus infections, effective control of the Bundibugyo virus disease outbreak depends on rapid identification of cases, laboratory confirmation of infection, isolation of cases, contact tracing, infection-prevention measures, protection of health care workers, and community engagement. Although no licensed vaccines or approved therapeutics specific to Bundibugyo virus disease are currently available, advances in supportive care have improved outcomes during recent filovirus disease outbreaks. Experimental evidence from studies involving nonhuman primates, serologic investigations with human samples, and monoclonal antibody research suggests that vaccines and therapeutics developed against Ebola virus may provide cross-protective activity against Bundibugyo virus. These observations support prototype-pathogen approaches to preparedness while underscoring the need for continued development of pathogen-specific countermeasures. The current outbreak reinforces the principle that a successful response to filovirus disease requires integration of medical countermeasures, clinical care, surveillance, diagnostics, and coordinated multinational public health operations.

Bundibugyo Virus Disease in 2026

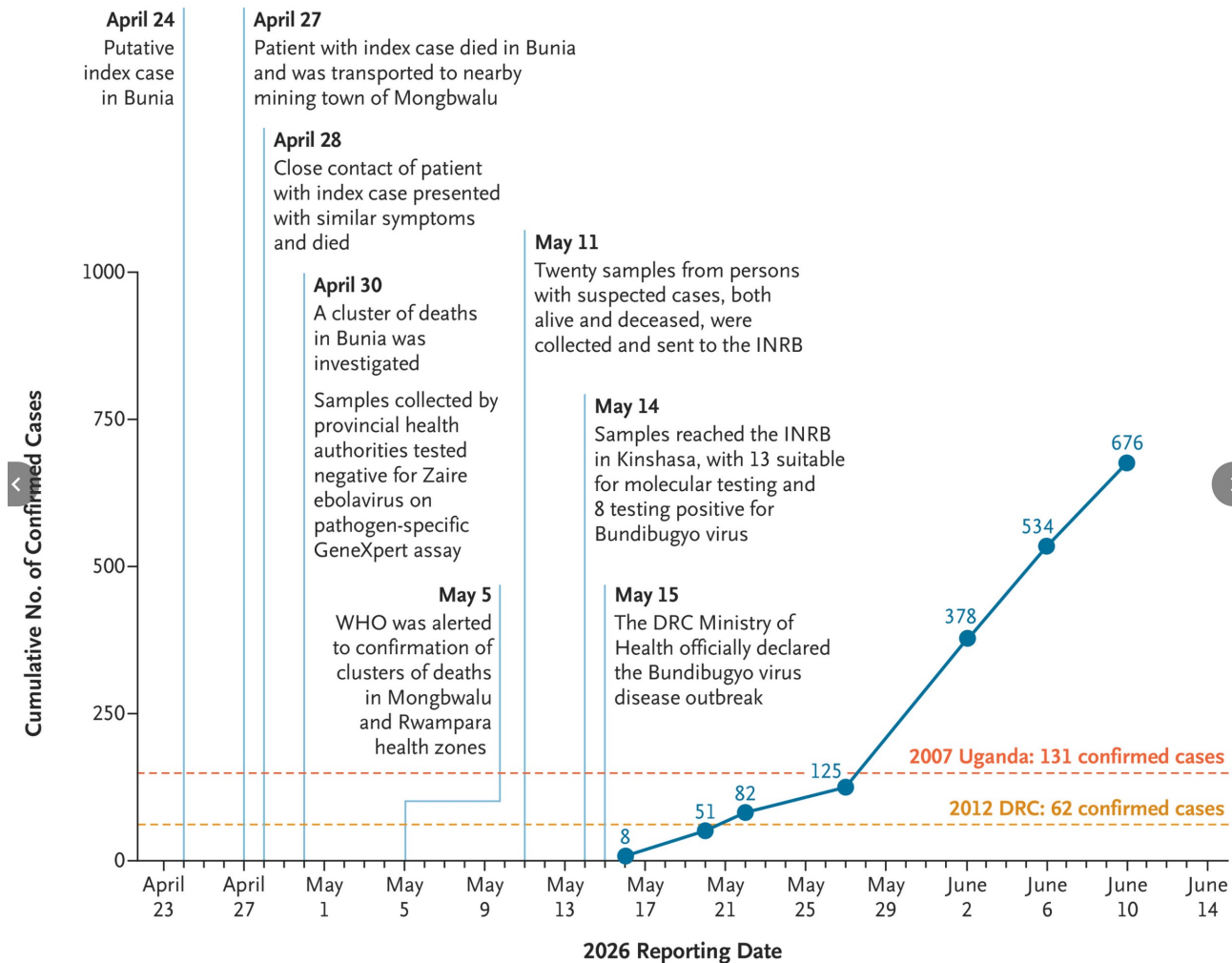
- Bundibugyo virus is a member of the family Filoviridae. Although capable of causing severe hemorrhagic fever in humans, Bundibugyo virus has caused only two previously documented outbreaks, in Uganda in 2007 and in the Democratic Republic of Congo (DRC) in 2012.
- Bundibugyo virus disease was identified in the DRC in April 2026, and an outbreak was officially declared in May 2026. The current outbreak has already exceeded previous outbreaks in trajectory and scale.
- In all outbreaks of filovirus disease, rapid identification and isolation of cases, contact tracing, infection-control measures, and supportive clinical care are essential features of the public health response. Effective surveillance systems that facilitate the rapid interruption of transmission are a cornerstone of outbreak control. Previous outbreaks of filovirus disease have also shown the importance of protecting health care workers (who are often disproportionately affected) and building public trust through community engagement.
- In resource-limited settings, outbreak control depends on operational support from a variety of governmental, nongovernmental, and international organizations. Advances in supportive care have improved outcomes in recent filovirus disease outbreaks.
- Currently, no licensed vaccines or approved therapeutics that are specific to Bundibugyo virus are available. However, studies involving nonhuman primates and human serum have shown the potential for cross-protection from vaccines developed for Ebola virus. Data from these studies support a prototype-pathogen approach to vaccine development, with pathogen-specific medical countermeasures advanced rapidly in parallel.
- The current outbreak has exposed persistent vulnerabilities in preparedness strategies, diagnostics, health care delivery, and deployment of medical countermeasures, particularly in resource-limited settings. Strengthening laboratory networks, improving access to advanced clinical care, protecting health care workers, and expanding capacity for rapid implementation of clinical trials remain essential priorities.





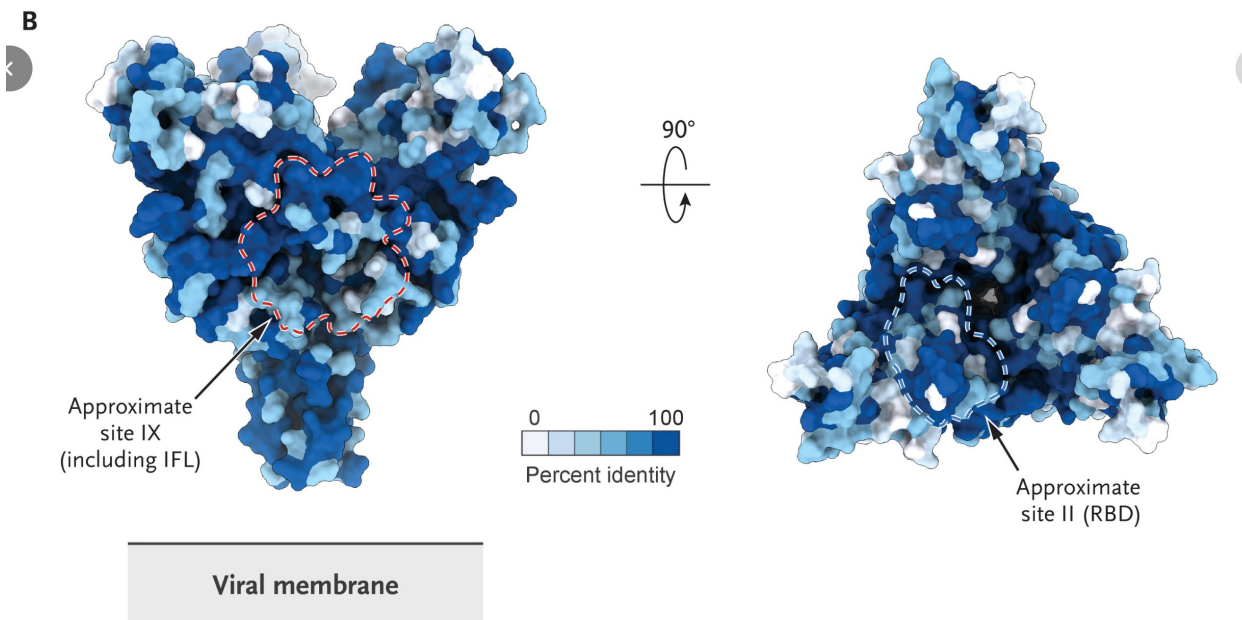
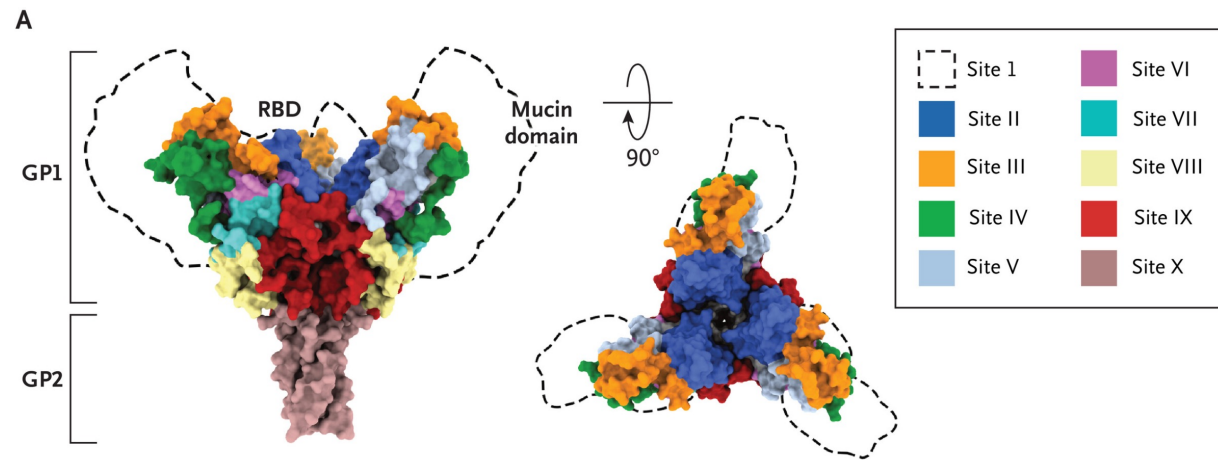
Outbreaks of Orthoebolavirus Disease over Time.

The map shows the geographic distribution of major orthoebolavirus disease outbreaks, with identification of the countries in which outbreaks have occurred. The timeline below shows key milestones in Ebola virus research and the development of medical countermeasures, including virus discovery, major outbreaks, the use of monoclonal antibody therapies, and vaccine licensure. Also shown are the history of outbreaks caused by various orthoebolaviruses from 1976 to 2026 and the genetic relatedness of orthoebolaviruses (branch lengths do not represent actual genetic distance or divergence times).^{3,4} Colored branches represent Ebola virus (also known as Zaire ebolavirus), Tai Forest ebolavirus, Bundibugyo ebolavirus, Sudan ebolavirus, and Reston ebolavirus. The circles indicate the sizes of individual outbreaks and are scaled according to the total number of reported cases. Animal hosts are indicated by corresponding symbols. EMA denotes European Medicines Agency, RC Republic of the Congo, and UK United Kingdom.



Timeline of Recognition and Progression of the 2026 Bundibugyo Virus Disease Outbreak in the Democratic Republic of Congo.

Shown is a timeline of key events that led to the detection and official declaration of the Bundibugyo virus disease outbreak.^{13,15–20} The index case was identified in Bunia in the DRC on April 24, 2026, after which additional deaths occurred in Bunia and Mongbwalu. The samples collected by the health authorities tested negative on the Zaire ebolavirus–specific GeneXpert polymerase-chain-reaction assay. After the notification of the World Health Organization (WHO) and the shipment of clinical specimens to the Institut National de Recherche Biomédicale (INRB) in Kinshasa, laboratory testing confirmed Bundibugyo virus infection on May 14, 2026. The DRC Ministry of Health officially declared the Bundibugyo virus disease outbreak on May 15, 2026. The y axis indicates the cumulative number of laboratory-confirmed cases of Bundibugyo virus disease reported during the outbreak. The steep increase in the number of cases reported coincides with increased diagnostic capacity and batch processing of samples that had been backlogged owing to a lack of reagents. Horizontal dashed lines indicate the total number of confirmed cases reported during the 2007 Uganda Bundibugyo virus disease outbreak (131 cases) and the 2012 DRC outbreak (62 cases), to provide historical data for comparison.



Virus Glycoprotein Antigenic Sites and Sequence Conservation across Orthoebolaviruses.

Panel A shows antigenic sites on Ebola virus glycoprotein superimposed onto a space-filling model from the crystal structure of Ebola virus glycoprotein with mucin deletion (Protein Data Bank number, [5JQ3](#)) fit into the cryoelectron microscopy density of mucin-containing glycoprotein (Electron Microscopy Data Bank number, [EMD-8630](#)) with the use of rigid-body fitting. The surface glycoprotein (GP1) and the covalently linked transmembrane anchoring protein (GP2) are shown, along with the receptor-binding domain (RBD). The mucin domain is modeled with a dashed line.

Antigenic sites were determined by monoclonal antibody competition binding. Sites are numbered and color-coded according to unique antibody binding footprints. Side and top views are shown. Adapted from Misasi and Sullivan.⁵⁷ In Panel B, Bundibugyo virus glycoprotein lacking the mucin domain (Protein Data Bank number, [6DZM](#)) is shown as molecular surfaces, which are colored according to the percentage of amino acid identity across five orthoebolaviruses. The level of GP amino acid identity between Ebola virus and the two other major orthoebolavirus pathogens, Bundibugyo virus and Sudan virus, is 65.3% and 54.7%, respectively. Protein sequences from the following orthoebolaviruses (with UniProt accession codes listed in parentheses) were aligned with ChimeraX, version 12.5: Reston ebolavirus (Q91DD8), Sudan ebolavirus (Q7T9D9), Zaire ebolavirus (Q05320), Cote d'Ivoire ebolavirus (Q66810), and Bundibugyo virus (B8XCNO). Dashed lines indicate the approximate locations of Ebola virus antigenic site IX (red), which encompasses the internal fusion loop (IFL), and site II (blue), which comprises the RBD, on the Bundibugyo virus glycoprotein according to the sites defined in Panel A.

Conclusions

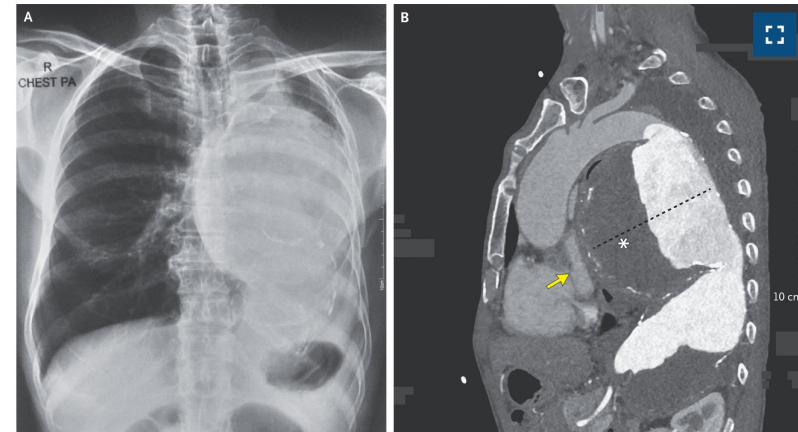
The 2026 outbreak of Bundibugyo virus disease illustrates the progress achieved in pandemic preparedness of medical countermeasures, but challenges remain for responses to filovirus disease outbreaks. Effective outbreak control requires the integration of surveillance, diagnostics, clinical management, infection prevention, community engagement, and medical countermeasures within a coordinated public health framework. Evidence supporting cross-protective vaccines and antibodies suggests that prototype-pathogen approaches may provide actionable options during outbreaks caused by rare or previously neglected pathogens.

Lead Lines in Severe Lead Poisoning



A 6-month-old baby boy was transferred to a quaternary children's hospital for the evaluation and management of seizures. One week earlier, he had had decreased oral intake, vomiting, and irritability. On physical examination, the baby was awake, alert, and no longer in a postictal state. Laboratory testing showed hypocalcemia, hypophosphatemia, and microcytic anemia. Radiography of the left hand and wrist was performed to evaluate the hypocalcemia. The radiograph showed dense, transverse bands of metaphyseal sclerosis in the radius, ulna, metacarpals, and phalanges (arrows). In the context of acute encephalopathy and seizures, these bands were suspected to represent "lead lines" as seen in severe lead poisoning. Although radiographs are not recommended in the diagnostic workup of lead poisoning, the presence of lead lines may help the clinician make a delayed diagnosis. The blood lead level was 97 μg per deciliter (4.66 μmol per liter; reference value, <3.5 μg per deciliter [0.17 μmol per liter]), a finding that confirmed the diagnosis. On further history taking, the source of lead exposure was found to be an Ayurvedic medication that had been given to the baby since early infancy to treat colic. Chelation therapy with oral succimer was initiated. After a 1-month hospital stay, the baby was discharged with a plan for ongoing outpatient chelation therapy and monitoring of the blood lead level.

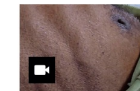
Descending Thoracic Aortic Aneurysm



A 54-year-old man with no known medical history presented to the emergency department with chest heaviness that had persisted for 2 months and a 2-week history of shortness of breath. His heart rate was 93 beats per minute and his blood pressure was 140/93 mm Hg. On physical examination, there were visible pulsations

in the fourth through seventh intercostal spaces on the left side ([Video 1A](#)). Elevated jugular venous pressure and decreased breath sounds on the left side of the chest were noted. A radiograph of the chest showed a large, rounded opacity occupying the left hemithorax (Panel A). Point-of-care ultrasonography of the heart showed a rounded structure with both anechoic and echogenic components that was compressing the left atrium ([Video 1B](#), asterisk). Computed tomographic angiography of the chest showed a large, fusiform aneurysm in the descending thoracic aorta (Panel B, dashed line; sagittal view). The aneurysm contained an eccentric thrombus (asterisk) and compressed the left atrium (arrow). Emergency open surgical repair of the aneurysm was performed. However, the patient died on postoperative day 3. An autopsy was not performed. The histopathological report was recorded on paper and was not available for retrospective review; therefore, the cause of the aneurysm is unknown.

VIDEOS



Descending Thoracic Aortic Aneurysm 0m 26s

Case 20-2026: A 38-Year-Old Man with Abdominal Pain

The patient had been in his usual state of good health until 6 weeks before the current presentation, when watery diarrhea (up to 20 episodes per day), accompanied by fever, chills, nausea, and vomiting, developed during a 3-week trip to rural Madagascar for work. Episodes of diarrhea started approximately 1 week after he arrived in Madagascar and lasted for 3 days, during which time he had limited food intake. The symptoms then gradually resolved, and he reported feeling well for 3 days afterward; however, the diarrhea then recurred. He received a single oral dose of levofloxacin, and the diarrhea resolved after 2 days. He returned to Massachusetts and then took a brief trip to Texas. Two weeks after returning from Madagascar, the patient began to have episodes of postprandial nausea, abdominal cramping and pain, bloating, and gas. The episodes resolved spontaneously within approximately 5 to 7 hours. No diarrhea was associated with these episodes. His symptoms did not worsen after ingestion of dairy, grains, fruits, or vegetables, but he recalled that an episode of cramping pain and bloating occurred after he had eaten a hamburger.

The patient's medical history included two episodes of malaria, for which he had been treated with mefloquine and atovaquone–proguanil, respectively. Six years before the current admission, a screening test for human immunodeficiency virus (HIV) types 1 and 2 was negative. Medications included a multivitamin and melatonin as needed for sleep; he had taken atovaquone–proguanil for malaria prophylaxis during his recent trip to Madagascar. He had no known adverse reactions to medications. The patient had received vaccines against coronavirus disease 2019, hepatitis A and B, Japanese encephalitis, measles, mumps, polio, rabies, rubella, tetanus, typhoid fever, varicella, and yellow fever, as well as the bacillus Calmette–Guérin vaccine. The patient resided in Massachusetts and was employed as an ornithologist, which often involved fieldwork in southern and coastal Africa, East Asia, South America, and the South Pacific. The family history was unremarkable. He did not use alcohol, tobacco, or illicit substances. The patient noted that he had had previous tick exposures, including one tick that had attached to his body in eastern Massachusetts 5 months before the trip to Madagascar, as well as possible tick exposures in South America 1 month before the trip.

On examination, the temporal temperature was 36.6°C, the heart rate 68 beats per minute, the blood pressure 121/72 mm Hg, and the oxygen saturation 95% while the patient was breathing ambient air. The weight was 86.0 kg. He appeared well, and no lymphadenopathy was present. The abdomen was soft and nontender, with normal bowel sounds and without organomegaly. He had no rashes.

The blood levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, albumin, globulin, and total protein were normal. The white-cell count was 7690 per microliter (reference range, 4500 to 11,000), and the **eosinophil count was 1700 per microliter (reference range, <1000)**. Other laboratory test results are shown. Specimens of blood and stool were obtained for further testing.

Over the course of the following week, the patient had episodic abdominal pain and increased frequency of bowel movements. During this time, an examination of a stool specimen revealed **no ova or parasites, including cyclospora and cystoisospora**. **In addition, tests for antibodies to schistosoma and strongyloides and stool antigen tests for giardia and rotavirus were negative.**

Diagnostic test results were received.

Variable	Reference Range, Adults*	On Current Presentation
Hemoglobin (g/dl)	13.5–17.5	14.9
Hematocrit (%)	41.0–53.0	43.3
White-cell count (per μ l)	4500–11,000	7690
Differential count (per μ l)		
Neutrophils	1800–7700	3100
Lymphocytes	1000–4800	2100
Monocytes	200–1200	660
Eosinophils	0–900	1700
Basophils	0–300	110
Platelet count (per μ l)	150,000–400,000	240,000

Differential Diagnosis

A limited acute diarrheal syndrome developed in this 38-year-old ornithologist during a recent work trip to Madagascar, and the patient now presents with recurrent postprandial abdominal pain and peripheral eosinophilia. He has a background of residence in Massachusetts and frequent global travel, including trips to Africa, Asia, and the South Pacific. The patient is presumed to be immunocompetent; he is not known to have HIV infection and does not take any immunosuppressive medications. I will approach this case by considering infectious causes of the patient's presentation, his immune status, the timeline of symptoms relative to his travel history, and the relevant epidemiologic factors and exposures before, during, and after travel to Madagascar.

Initial Diarrheal Illness

The patient's first gastrointestinal symptoms began approximately 1 week after his arrival in Madagascar and included watery diarrhea, nausea, and vomiting, accompanied by fever and chills. Did this patient have traveler's diarrhea? Diarrhea is the most common illness in travelers visiting resource-limited countries, and it occurs in 30 to 70% of persons after 2 weeks of travel.

Helminthic Infections

Eosinophilia was a notable finding in this patient's laboratory evaluation. It is observed in 8 to 10% of travelers returning from resource-limited countries, and helminths are implicated in 14 to 64% of those cases. Several helminthic infections that are associated with gastrointestinal symptoms and are common across Africa, including Madagascar, may provide a unifying diagnosis in this patient.

Other Causes of Eosinophilia

Several viral, bacterial, mycobacterial, and fungal infections can cause eosinophilia. I would perform testing for HIV, but other infectious causes of eosinophilia would be unlikely to explain the patient's postprandial abdominal pain. Similarly, noninfectious causes of eosinophilia, such as allergic diseases, cancer, or drug reactions, would be unlikely to account for his gastrointestinal symptoms.

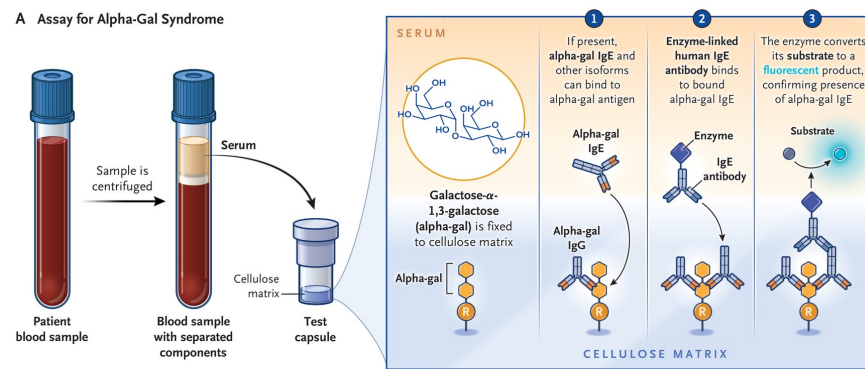
Pretravel Exposures

When evaluating a returning traveler, it is important to consider epidemiologic factors and exposures unrelated to travel. This patient's pretravel exposures included living in Massachusetts, where he had had one reported tick bite 5 months before he traveled to Madagascar. This tick exposure in the northeastern United States puts him at risk for alpha-gal syndrome, a disease that could explain postprandial abdominal pain, bloating, and eosinophilia.

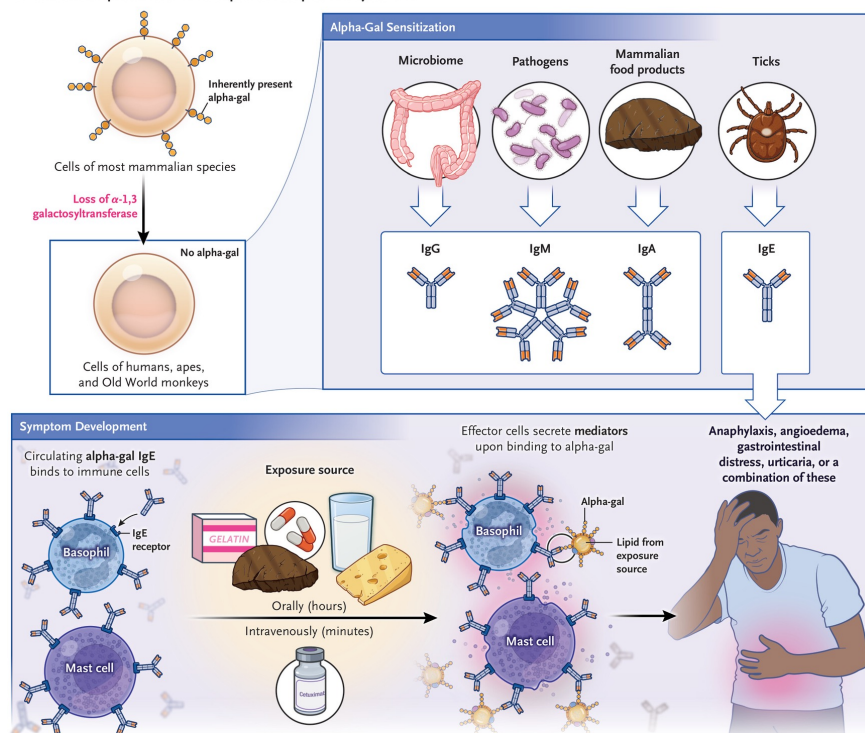
Alpha-Gal Syndrome

Alpha-gal syndrome is an IgE-mediated delayed hypersensitivity to **galactose- α -1,3-galactose (alpha-gal)**, a carbohydrate found in mammalian meat but absent from human tissue. The condition is initiated by exposure to alpha-gal through tick bites, particularly those from the lone star tick (*Amblyomma americanum*), which can lead to sensitization. Patients with alpha-gal syndrome can present with a broad spectrum of clinical features that ranges from isolated gastrointestinal symptoms to cutaneous manifestations (e.g., urticaria, pruritus, and angioedema) and severe systemic reactions, including anaphylaxis and, in rare cases, death from cardiovascular collapse. Delayed onset of symptoms (3 to 8 hours) after consumption of mammalian meat products is a notable distinction from other foodborne allergens. Alpha-gal syndrome can develop several weeks after the initial tick exposure, and *A. americanum* has become more common in the northeastern United States during the past decade — a factor that increased recognition of the alpha-gal syndrome, expansion of diagnostic testing, and the geographic expansion of tick vectors. **The Centers for Disease Control and Prevention has estimated that alpha-gal syndrome might have developed in 96,000 to 450,000 persons in the United States since 2010.**

A Assay for Alpha-Gal Syndrome



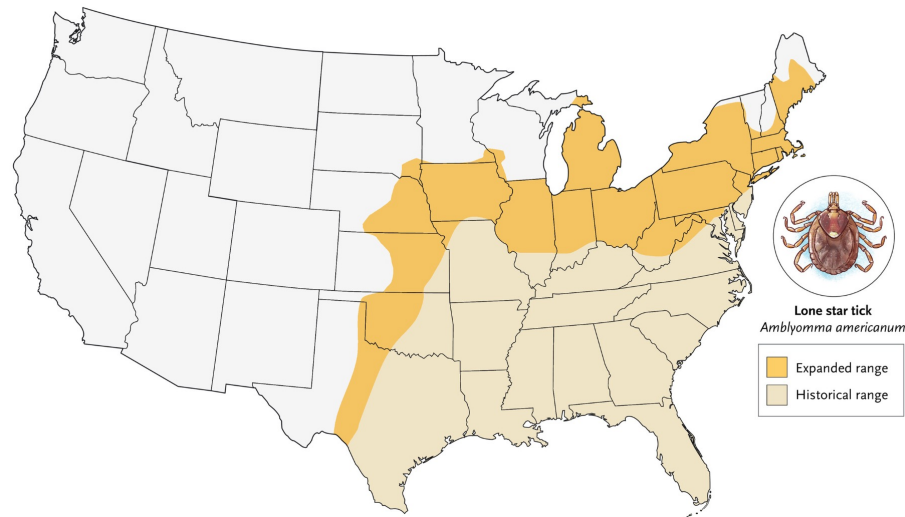
B Human Acquisition and Development of Alpha-Gal Syndrome



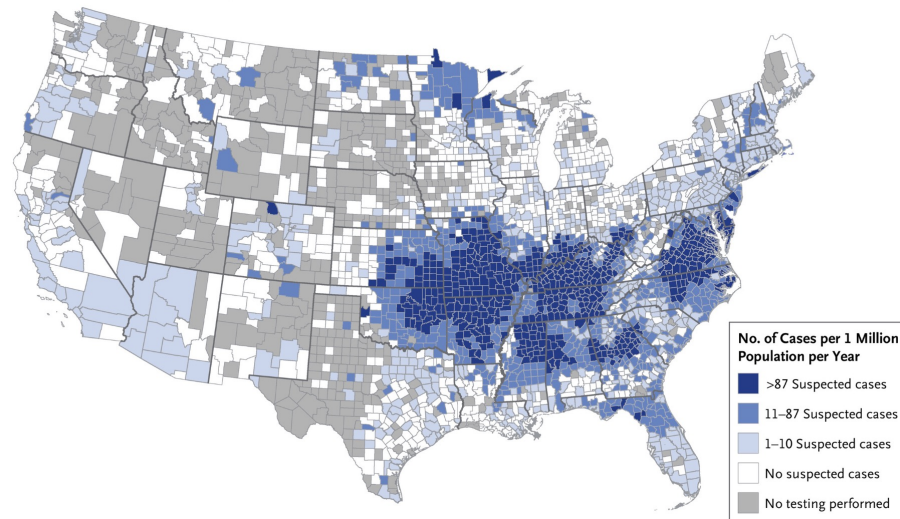
Alpha-Gal Syndrome Testing and Pathogenesis.

In the assay for IgE specific to galactose- α -1,3-galactose (alpha-gal) (Panel A), a sample of the patient's blood is centrifuged to separate out the serum component. Serum is then applied to a test capsule containing a cellulose matrix bound to the carbohydrate antigen alpha-gal. Alpha-gal-specific antibodies in the patient's serum bind to the alpha-gal on the matrix while the remainder of the serum contents are washed away. An enzyme-linked reagent antibody specific for human IgE is then added and binds to captured alpha-gal IgE. Finally, the enzyme converts its substrate into a fluorescent product. The resulting fluorescence is measured and converted to an alpha-gal IgE concentration with a calibration curve. The cells of most mammalian species display alpha-gal on their surface (Panel B). Owing to the loss of one of the enzymes required for its synthesis, humans, apes, and Old World monkeys do not produce alpha-gal and are thus able to produce antibodies against it. In these species, alpha-gal IgG, IgM, and IgA are naturally occurring owing to exposure to alpha-gal from the gut microbiome, pathogens, and consumption of mammalian food products. Alpha-gal IgE is produced only after sensitization through the bite from a tick of certain species. The saliva of these ticks contains alpha-gal along with immunomodulatory molecules that combine with host factors to promote alpha-gal IgE production. Once produced, alpha-gal IgE attaches to IgE receptors on the surfaces of basophils and mast cells. When the sensitized individual encounters alpha-gal again, these cells can mediate the development of symptoms, which can range from gastrointestinal distress to anaphylaxis. Symptoms typically develop hours after oral ingestion of alpha-gal and minutes after intravenous exposure. Alpha-gal is found in food products derived from mammalian species (e.g., meats, dairy products, and gelatin). Some biologic therapies (e.g., cetuximab) also contain alpha-gal moieties. R denotes rest of the molecule.

A Geographic Distribution of the Lone Star Tick, 1945 to 2015

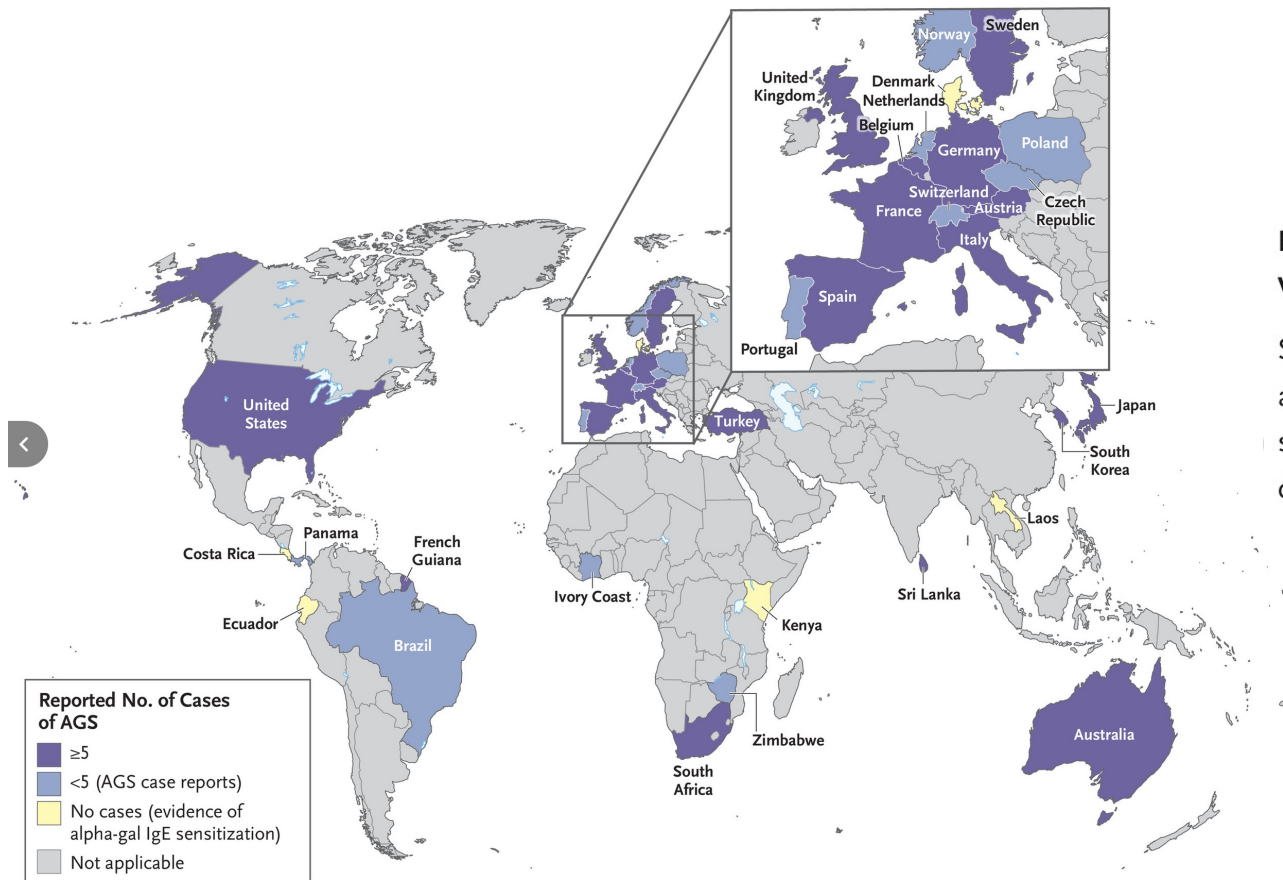


B Suspected Cases of Alpha-Gal Syndrome, 2017 to 2022



Geographic Distribution of the Lone Star Tick and Suspected Cases of Alpha-Gal Syndrome.

Panel A, adapted from Monzón et al.,¹⁴ shows the geographic range of the lone star tick (*Amblyomma americanum*) in the continental United States over time. The expanded range includes data from 2013, 2014, and 2015, and the historical range includes data from 1945. Panel B shows the geographic distribution of suspected cases of alpha-gal syndrome (2017 to 2022).⁷



Patient Perspective

The Patient: I do remember being bitten by a tick in Massachusetts sometime in late May. It was a small tick, possibly a lone star tick, that bit me, so it is possible the tick exposure occurred as many as 5 months before I started to develop symptoms, if that was in fact the tick that caused this. **Also noteworthy is that I ate red meat in Texas**, probably 3 weeks before the diagnosis of alpha-gal syndrome. In the past, I had eaten red meat with no issues, and then I very suddenly started to get abdominal symptoms after eating red meat. In my discussions with Dr. Heller, what tipped us off to this was the clear association between the symptoms and eating pork or beef. **I would eat something, and there would be a delay of maybe 1 to 3 hours, then I would have really severe abdominal pain without diarrhea or rash.** The pain would subside maybe 5 to 7 hours later, and I would generally feel very exhausted, sort of like having the flu but without the other flu symptoms. After eating dairy, I did not have abdominal pain but just a general feeling of exhaustion.

Since the diagnosis, **I have cut out all red meat, dairy, gelatin — any sort of exposure I can find.** I have not had feelings of exhaustion or recurrence of the abdominal pain. I'm grateful to have a diagnosis, and hopefully, this is a condition that resolves.

Final Diagnosis

Alpha-gal syndrome.

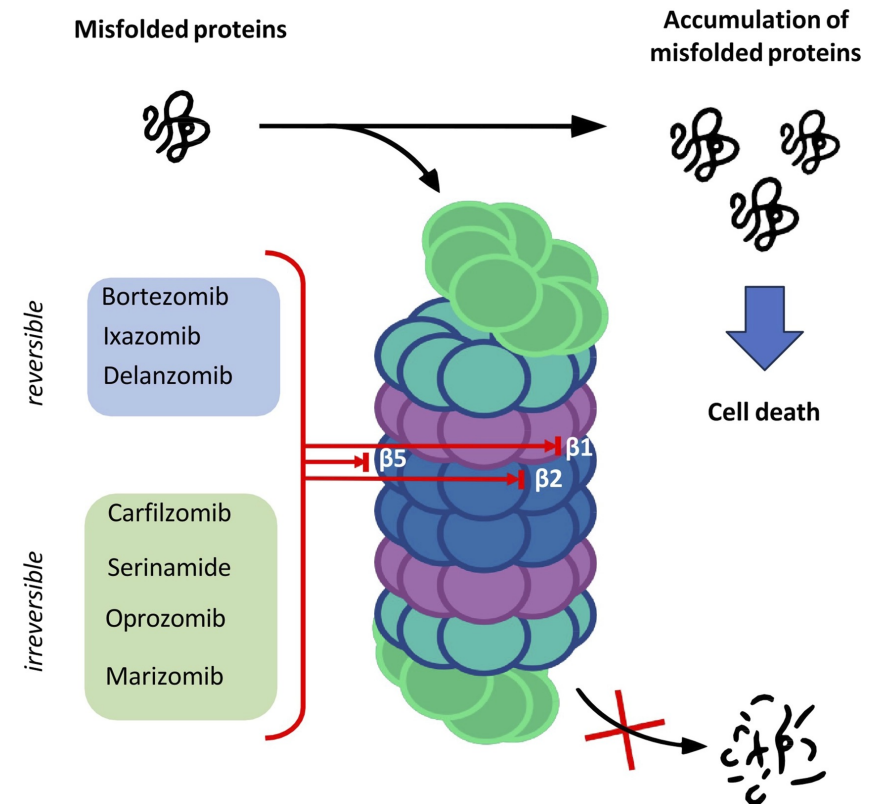
Proteasom-Inhibitoren sind beim Multiplen Myelom genau deshalb so erfolgreich, weil diese Krebszellen massive Mengen an Proteinen produzieren. Myelomzellen sind bösartige Plasmazellen, deren Hauptaufgabe in der exzessiven Herstellung von [fehlerhaften monoklonalen Immunglobulinen \(Paraproteinen\)](#) liegt. Diese extreme Produktionslast macht sie im Vergleich zu gesunden Zellen extrem anfällig für Störungen im zellulären Müllentsorgungssystem.

Das zelluläre Müllsystem: Das Proteasom fungiert als Recyclinganlage der Zelle. Es baut alte, überschüssige oder [fehlgefaltete Proteine ab](#).

Der kritische Proteinstau: Proteasom-Inhibitoren (wie Bortezomib oder Carfilzomib) [blockieren diesen Abbauprozess](#). Da Myelomzellen ununterbrochen Proteine anstauen, kollabiert ihr System durch den rasanten [Zuwachs an zellulärem Abfall](#)

Endoplasmatischer Retikulum-Stress (ER-Stress): Die Proteine stauen sich im Endoplasmatischen Retikulum. Dies löst eine irreversible Stressreaktion aus (die sogenannte *Unfolded Protein Response* / UPR).

THE LANCET



THE LANCET

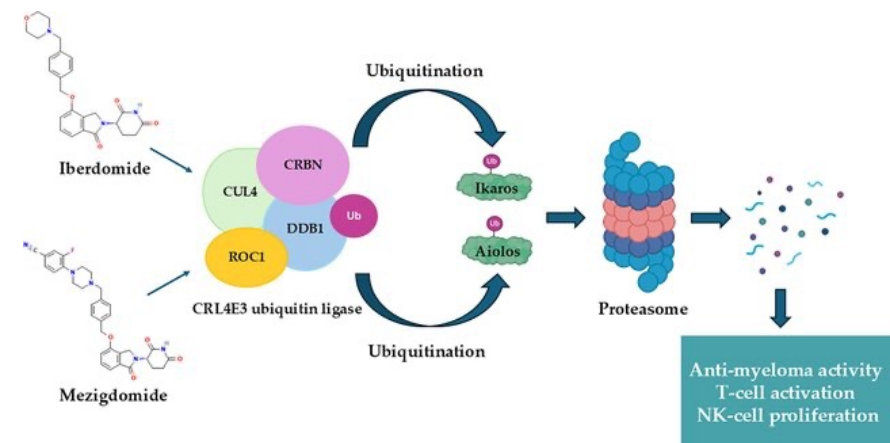
Mezigdomid (Forschungsname: *BMS-986348* oder *CC-92480*) ist ein neuartiges, orales Medikament, das zur Behandlung von Patienten mit rezidiertem oder refraktärem Multiplem Myelom (RRMM) – einer besonderen Form von Blutkrebs – entwickelt wird.

CELMoD-Klasse: Mezigdomid gehört zur Wirkstoffklasse der Cereblon-E3-Ligase-Modulatoren.

Proteinabbau: Es wirkt als "molekularer Klebstoff", der spezifische Proteine in den Krebszellen (genauer: die Transkriptionsfaktoren *Ikaros* und *Aiolos*) für den natürlichen Recycling-Prozess der Zelle markiert, was zu deren schnellem Abbau und Tod führt.

Immunstimulation: Gleichzeitig stimuliert es das körpereigene Immunsystem (T-Zellen und natürliche Killerzellen), die Tumorzellen anzugreifen.

Lenalidomide/thalidomide successors



Mezigdomide, carfilzomib, and dexamethasone versus carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma (SUCCESSOR-2): a phase 3, open-label, randomised controlled trial

New Rx for
multiple
myeloma

Summary

Background A growing number of patients with multiple myeloma are anti-CD38 antibody-exposed and lenalidomide-exposed at first relapse, subsequently limiting their treatment options. Mezigdomide, a potent cereblon E3 ligase modulator, induces maximal, rapid Ikaros and Aiolos degradation, resulting in enhanced myeloma cell cytotoxicity and immune stimulation versus immunomodulatory drugs. The SUCCESSOR-2 trial evaluates the efficacy and safety of mezigdomide in combination with carfilzomib and dexamethasone versus carfilzomib plus dexamethasone.

Methods This phase 3, open-label, randomised controlled trial was conducted at 160 hospital-based sites in 26 countries using a two-stage, inferentially seamless design. Eligible adult patients had measurable multiple myeloma, had received at least one previous regimen (including anti-CD38 antibodies and lenalidomide) on which they had achieved minimal response or better, and documented disease progression during or after their most recent treatment. Interactive response technology was used to randomly assign patients, stratified by age (≤ 70 years or > 70 years), number of previous lines of therapy (≤ 2 or > 2), and International Staging System stage (I, II, or III). Patients received oral mezigdomide (days 1–21 of each 28-day cycle) plus intravenous carfilzomib (56 mg/m² weekly) and oral or intravenous dexamethasone (40 mg weekly) or carfilzomib (56 mg/m² twice weekly or 70 mg/m² weekly) and dexamethasone (20 mg twice weekly or 40 mg weekly). In stage 1, mezigdomide dosing across three levels was optimised. In stage 2, patients were randomly assigned to the selected mezigdomide dose (1·0 mg) plus carfilzomib and dexamethasone or carfilzomib–dexamethasone alone. The primary endpoint was progression-free survival (PFS) evaluated in patients who received 1·0 mg mezigdomide plus carfilzomib and dexamethasone or carfilzomib–dexamethasone alone across both study stages. No imputation was planned for missing efficacy endpoint values or missing safety evaluations. The trial is registered with ClinicalTrials.gov (NCT05552976) and EUClinicalTrials.eu (EUCT number 2022–500861–29–00). The trial is active but not recruiting.

Findings Between Feb 3, 2023, and Nov 28, 2025, 762 patients were assessed for eligibility, of which 606 patients were enrolled and 479 were included in the analyses (288 patients in the mezigdomide–carfilzomib–dexamethasone group and 191 patients in the carfilzomib–dexamethasone group). 252 (53%) patients were male, 411 (86%) were anti-CD38 antibody-refractory, and 363 (76%) were lenalidomide-refractory, with a median of two previous lines of therapy (IQR 2–4). At 10·6 months median follow-up, mezigdomide–carfilzomib–dexamethasone significantly improved PFS compared with carfilzomib–dexamethasone (median 18·0 months *vs* 8·3 months; hazard ratio 0·48 [95% CI 0·36–0·63]; $p < 0·0001$). Grade 3 or 4 adverse events were observed in 241 (84%) patients receiving mezigdomide–carfilzomib–dexamethasone versus 105 (56%) patients receiving carfilzomib–dexamethasone, including neutropenia (176 [61%] *vs* 17 [9%]) and infections (98 [34%] *vs* 29 [16%]). Eight (3%; 95% CI 1–5) and one (1%; 95% CI 0–3) treatment-related grade 5 adverse events were reported with mezigdomide–carfilzomib–dexamethasone and with carfilzomib–dexamethasone, respectively (rate difference 2%; 95% CI –1 to 5). Deaths occurred in 62 (22%) patients in the mezigdomide–carfilzomib–dexamethasone group and 51 (27%) patients in the carfilzomib–dexamethasone group, mainly due to disease progression.

Interpretation Mezigdomide–carfilzomib–dexamethasone provided a significant PFS benefit compared with carfilzomib–dexamethasone alone, with higher rates of grade 3 or 4 adverse events, including infections, which were mostly manageable with standard clinical practice and supportive care. These findings support mezigdomide–carfilzomib–dexamethasone as a clinically meaningful treatment option as early as first relapse in predominantly triple-class-exposed, anti-CD38 antibody-refractory and lenalidomide-refractory patients, a growing population with substantial unmet need.

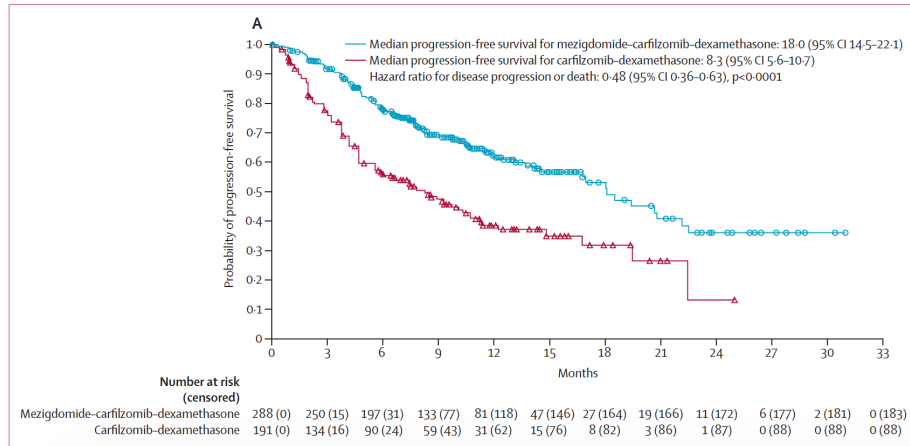
	Mezigdomide– carfilzomib– dexamethasone (n=288)	Carfilzomib– dexamethasone (n=191)	All patients (N=479)
Age, years	68 (61–75)	67 (61–74)	68 (61–75)
Age group, years			
<65	102 (35%)	79 (41%)	181 (38%)
65 to <75	111 (39%)	67 (35%)	178 (37%)
≥75	75 (26%)	45 (24%)	120 (25%)
Sex*			
Male	146 (51%)	106 (55%)	252 (53%)
Female	142 (49%)	85 (45%)	227 (47%)
Race			
American Indian or Alaska Native	10 (3%)	3 (2%)	13 (3%)
Asian	90 (31%)	57 (30%)	147 (31%)
Black or African American	11 (4%)	13 (7%)	24 (5%)
Native Hawaiian or Other Pacific Islander	0	0	0
White	162 (56%)	114 (60%)	276 (58%)
Not collected, unknown, or missing	15 (5%)	4 (2%)	19 (4%)
Region			
Asia	88 (31%)	56 (29%)	144 (30%)
Europe	109 (38%)	72 (38%)	181 (38%)
USA	27 (9%)	26 (14%)	53 (11%)
Rest of world	64 (22%)	37 (19%)	101 (21%)
Time since initial diagnosis, years	4.6 (2.5–7.1)	4.5 (2.6–7.5)	4.5 (2.5–7.3)
ECOG performance status score			
0	116 (40%)	74 (39%)	190 (40%)
1	154 (53%)	103 (54%)	257 (54%)
2	16 (6%)	14 (7%)	30 (6%)
3	2 (1%)†	0	2 (<1%)†
Derived International Staging System stage at study entry			
I	149 (52%)	96 (50%)	245 (51%)
II	87 (30%)	59 (31%)	146 (30%)
III	52 (18%)	36 (19%)	88 (18%)
Presence of soft-tissue plasmacytomas			
Extramedullary	25 (9%)	20 (10%)	45 (9%)
Paraskeletal	51 (18%)	34 (18%)	85 (18%)
Cytogenetic abnormality‡			
High risk	74 (26%)	62 (32%)	136 (28%)
Standard risk	178 (62%)	102 (53%)	280 (58%)
Not evaluable or data missing	36 (13%)	27 (14%)	63 (13%)
Number of previous lines of antimyeloma therapy, range; IQR	2.0 (1–9); 2.0–3.5	2.0 (1–8); 2.0–4.0	2.0 (1–9); 2.0–4.0
One previous line	43 (15%)	33 (17%)	76 (16%)
Two previous lines	109 (38%)	68 (36%)	177 (37%)
Three previous lines	64 (22%)	35 (18%)	99 (21%)
Four or more previous lines	72 (25%)	55 (29%)	127 (27%)
Therapy exposure			
Anti-CD38 antibody	288 (100%)	191 (100%)	479 (100%)
Immunomodulatory drug	288 (100%)	191 (100%)	479 (100%)
Lenalidomide	288 (100%)	191 (100%)	479 (100%)
Pomalidomide	114 (40%)	64 (34%)	178 (37%)

(Table 1 continues on next page)

	Mezigdomide– carfilzomib– dexamethasone (n=288)	Carfilzomib– dexamethasone (n=191)	All patients (N=479)
(Continued from previous page)			
Proteasome inhibitor (triple-class exposed)	265 (92%)	176 (92%)	441 (92%)
BCMA-targeted therapy§	23 (8%)	12 (6%)	35 (7%)
T-cell engager	12 (4%)	9 (5%)	21 (4%)
CART cell therapy	9 (3%)	3 (2%)	12 (3%)
Antibody-drug conjugate	5 (2%)	3 (2%)	8 (2%)
T-cell-redirecting therapy	28 (10%)	12 (6%)	40 (8%)
Refractory status¶			
Anti-CD38 antibody	248 (86%)	163 (85%)	411 (86%)
Immunomodulatory agent	247 (86%)	154 (81%)	401 (84%)
Lenalidomide	220 (76%)	143 (75%)	363 (76%)
Pomalidomide	99 (34%)	56 (29%)	155 (32%)
Proteasome inhibitor	138 (48%)	102 (53%)	240 (50%)
Triple-class refractory	111 (39%)	75 (39%)	186 (39%)
Refractory to last line of therapy	264 (92%)	181 (95%)	445 (93%)

Data are median (IQR) or n (%), unless indicated otherwise. Percentages might not total 100% due to rounding. In the confirmatory analysis group, defined as all patients from stages 1 and 2 randomly assigned to 1.0 mg mezigdomide plus carfilzomib and dexamethasone or carfilzomib–dexamethasone alone. BCMA=B-cell maturation antigen. CAR=chimeric antigen receptor. ECOG=Eastern Cooperative Oncology Group. *Sex was self-reported by patients. †Eligibility required an ECOG performance status score of 0–2 at screening; these two patients had an ECOG performance status score of 1 during screening and an ECOG performance status score of 3 at baseline, the timepoint shown in this table. ‡High risk is defined as presence of del(17p), and/or translocation t(4;14), and/or translocation t(14;16); standard risk is defined as absence of del(17p), translocation t(4;14), and translocation t(14;16). §Some patients might have received more than one BCMA-targeted therapy before being randomly assigned in SUCCESSOR-2. ¶Refractory is defined as disease that is non-responsive on therapy (did not reach minimal response or development of progressive disease while on therapy) or progresses within 60 days of the last dose. ||Triple-class refractory is defined as refractory to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody.

Table 1: Demographic and disease characteristics of patients at baseline

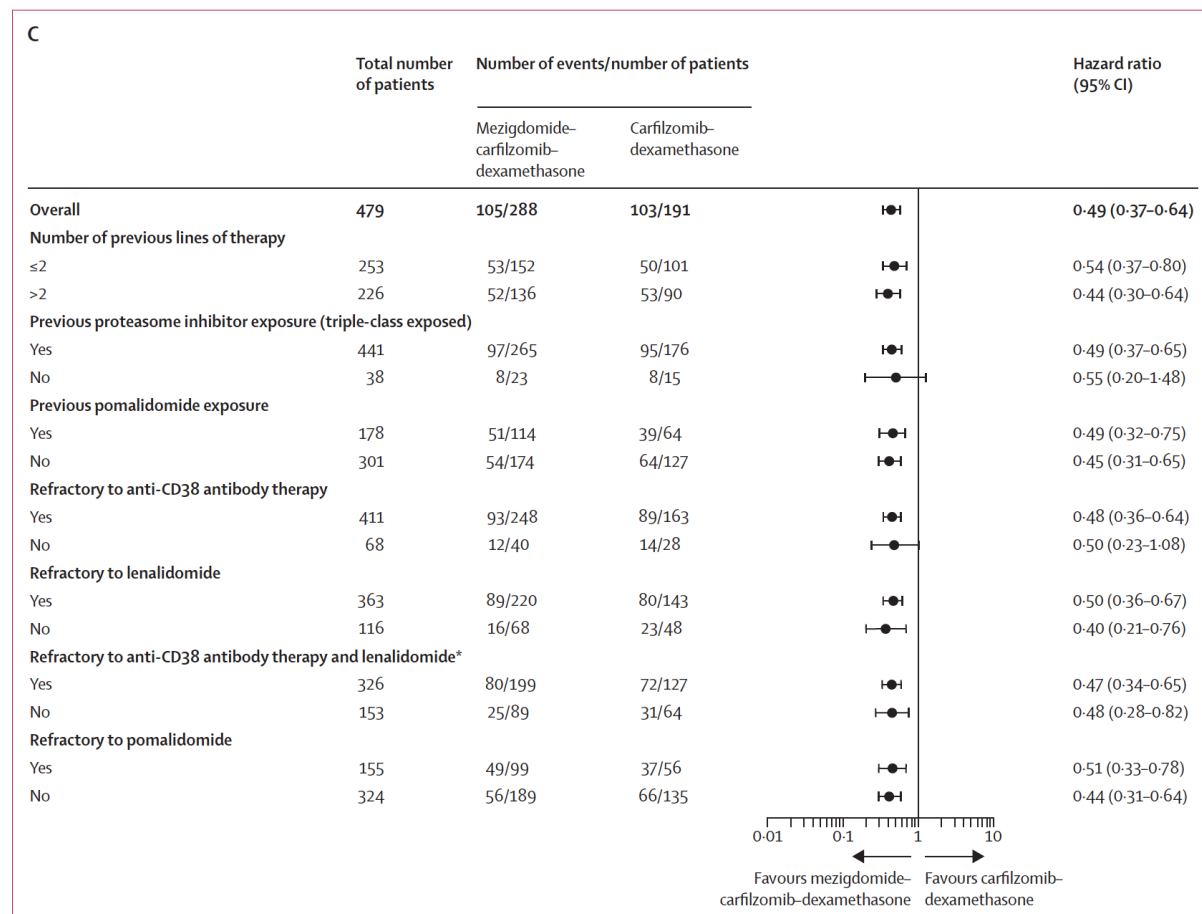


B

	Total number of patients	Number of events/number of patients			Hazard ratio (95% CI)
		Mezigdomide-carfilzomib-dexamethasone	Carfilzomib-dexamethasone		
Overall	479	105/288	103/191	0.49	0.49 (0.37-0.64)
Age, years					
<65	181	40/102	44/79	0.52	0.52 (0.34-0.80)
65 to <75	178	41/111	38/67	0.43	0.43 (0.27-0.67)
≥75	120	24/75	21/45	0.52	0.52-0.29-0.94)
Sex					
Female	227	50/142	44/85	0.48	0.48 (0.32-0.73)
Male	252	55/146	59/106	0.48	0.48 (0.33-0.70)
Race					
Asian	147	36/90	28/57	0.61	0.61 (0.37-1.00)
Black or African American	24	3/11	6/13	0.50	0.50 (0.13-2.01)
White	276	58/162	67/114	0.44	0.44 (0.31-0.63)
Other, not collected, or unknown	31	8/25	2/6	0.45	0.45 (0.09-2.26)
Missing	1	0/0	0/1		
Region					
USA	53	3/27	9/26	0.28	0.28 (0.08-1.05)
Europe	181	39/109	42/72	0.49	0.49 (0.32-0.76)
Asia	144	34/88	28/56	0.58	0.58 (0.35-0.96)
Rest of the world	101	29/64	24/37	0.40	0.40 (0.23-0.70)
Renal function					
<45 mL/min	64	18/36	16/28	0.56	0.56 (0.28-1.12)
45 to <60 mL/min	83	25/49	23/34	0.36	0.36 (0.20-0.66)
60 to <90 mL/min	208	38/128	41/80	0.46	0.46 (0.30-0.72)
≥90 mL/min	124	24/75	23/49	0.52	0.52 (0.29-0.92)
ISS staging at study entry					
Stage I	245	45/149	50/96	0.42	0.42 (0.28-0.64)
Stage II	146	32/87	31/59	0.51	0.51 (0.31-0.84)
Stage III	88	28/52	22/36	0.60	0.60 (0.34-1.05)
Cytogenetic risk					
High risk	136	32/74	36/62	0.49	0.49 (0.30-0.80)
Standard risk	280	58/178	50/102	0.51	0.51 (0.35-0.74)
Not evaluable or data missing	63	15/36	17/27	0.44	0.44 (0.22-0.90)
Functional high-risk disease*					
Yes	166	32/98	38/68	0.36	0.36 (0.22-0.58)
No	313	73/190	65/123	0.57	0.57 (0.41-0.80)
Presence of soft-tissue plasmacytomas					
Yes	118	32/66	42/52	0.34	0.34 (0.21-0.54)
No	361	73/222	61/139	0.58	0.58 (0.42-0.82)
Presence of extramedullary plasmacytomas*					
Yes	45	14/25	18/20	0.33	0.33 (0.16-0.67)
No	434	91/263	85/171	0.51	0.51 (0.38-0.69)

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Favours mezigdomide-carfilzomib-dexamethasone Favours carfilzomib-dexamethasone



	Mezigdomide-carfilzomib-dexamethasone (n=288)	Carfilzomib-dexamethasone (n=191)	Difference*
Overall response†	231	102	..
Rate	80% (75-85)	53% (46-61)	27% (18-35)
Best response			
Stringent complete response	72 (25%)	16 (8%)	..
Complete response	5 (2%)	1 (1%)	..
Very good partial response	96 (33%)	42 (22%)	..
Partial response	58 (20%)	43 (23%)	..
Minimal response	6 (2%)	5 (3%)	..
Stable disease	38 (13%)	62 (32%)	..
Progressive disease	3 (1%)	14 (7%)	..
Not evaluable	2 (1%)	0	..
Missing	8 (3%)	8 (4%)	..
Complete response or better	77	17	..
Rate	27% (22-32)	9% (5-14)	18% (11-24)
Very good partial response or better	173	59	..
Rate	60% (54-66)	31% (24-38)	29% (20-37)
Time to response, months‡	1.1 (1.0-1.9)	1.1 (1.0-1.9)	..

Data are n, n (%), % (95% CI), or median (IQR). Percentages might not total 100% due to rounding. In the confirmatory analysis group, defined as all patients from stages 1 and 2 randomly assigned to 1.0 mg mezigdomide plus carfilzomib and dexamethasone or carfilzomib-dexamethasone alone. Best overall response was evaluated by an independent review committee. *Proportion difference with two-sided 95% CI. †Patients who had a partial response or better. ‡Time to response is defined as the time from randomisation to the first documentation of response (partial response or better).

Table 2: Treatment response

Figure: Progression-free survival

(A) Kaplan-Meier estimates of progression-free survival among patients in the confirmatory analysis group, defined as all patients from stages 1 and 2 randomly assigned to 1.0 mg mezigdomide plus carfilzomib and dexamethasone or carfilzomib-dexamethasone alone. (B) Subgroup analysis by demographics and disease characteristics of progression-free survival in patients in the confirmatory analysis group. (C) Subgroup analysis by previous therapy and refractoriness of progression-free survival in patients in the confirmatory analysis group. (B) and (C) A hazard ratio of less than 1.0 indicates an advantage for mezigdomide-carfilzomib-dexamethasone versus carfilzomib-dexamethasone; hazard ratios are unstratified. Higher stages of the ISS indicate more severe disease. High-risk cytogenetics is defined as presence of del(17p), and/or translocation t(4;14), and/or translocation t(14;16); standard risk is defined as absence of del(17p), translocation t(4;14), and translocation t(14;16). ISS=International Staging System. *Subgroup analyses were prespecified unless indicated as exploratory.

	Mezigdomide- carfilzomib- dexamethasone (n=288)	Carfilzomib- dexamethasone (n=191)	Difference*
Overall response†	231	102	..
Rate	80% (75–85)	53% (46–61)	27% (18–35)
Best response			
Stringent complete response	72 (25%)	16 (8%)	..
Complete response	5 (2%)	1 (1%)	..
Very good partial response	96 (33%)	42 (22%)	..
Partial response	58 (20%)	43 (23%)	..
Minimal response	6 (2%)	5 (3%)	..
Stable disease	38 (13%)	62 (32%)	..
Progressive disease	3 (1%)	14 (7%)	..
Not evaluable	2 (1%)	0	..
Missing	8 (3%)	8 (4%)	..
Complete response or better	77	17	..
Rate	27% (22–32)	9% (5–14)	18% (11–24)
Very good partial response or better	173	59	..
Rate	60% (54–66)	31% (24–38)	29% (20–37)
Time to response, months‡	1.1 (1.0–1.9)	1.1 (1.0–1.9)	..
Data are n, n (%), % (95% CI), or median (IQR). Percentages might not total 100% due to rounding. In the confirmatory analysis group, defined as all patients from stages 1 and 2 randomly assigned to 1.0 mg mezigdomide plus carfilzomib and dexamethasone or carfilzomib–dexamethasone alone. Best overall response was evaluated by an independent review committee. *Proportion difference with two-sided 95% CI. †Patients who had a partial response or better. ‡Time to response is defined as the time from randomisation to the first documentation of response (partial response or better).			
Table 2: Treatment response			

	Mezigdomide–carfilzomib– dexamethasone (n=288)		Carfilzomib– dexamethasone (n=186)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Patients with an adverse event	286 (99%)	241 (84%)	178 (96%)	105 (56%)
Haematological				
Neutropenia*	199 (69%)	176 (61%)	32 (17%)	17 (9%)
Thrombocytopenia†	174 (60%)	113 (39%)	77 (41%)	42 (23%)
Anaemia	149 (52%)	75 (26%)	66 (35%)	28 (15%)
White blood cell count decrease	67 (23%)	54 (19%)	23 (12%)	7 (4%)
Non-haematological				
Diarrhoea	112 (39%)	10 (3%)	33 (18%)	1 (1%)
Upper respiratory tract infection	79 (27%)	13 (5%)	31 (17%)	3 (2%)
Fatigue	67 (23%)	9 (3%)	39 (21%)	7 (4%)
Cough	66 (23%)	1 (<1%)	22 (12%)	0
Pneumonia	58 (20%)	45 (16%)	21 (11%)	11 (6%)
Dyspnoea	58 (20%)	11 (4%)	26 (14%)	5 (3%)
Hypertension	31 (11%)	11 (4%)	40 (22%)	17 (9%)
Patients with a serious adverse event	188 (65%)	157 (55%)	63 (34%)	52 (28%)
Pneumonia	44 (15%)	38 (13%)	12 (6%)	10 (5%)
Acute kidney injury	14 (5%)	13 (5%)	3 (2%)	3 (2%)
Thrombocytopenia†	13 (5%)	13 (5%)	3 (2%)	3 (2%)
Febrile neutropenia	13 (5%)	13 (5%)	0	0
Neutropenia*	11 (4%)	11 (4%)	0	0
Upper respiratory tract infection	11 (4%)	9 (3%)	0	0
Data are n (%). Reported here are the treatment-emergent adverse events of any grade that occurred in ≥20% of patients and grade 3 or 4 treatment-emergent adverse events that occurred in ≥10% of patients in either treatment group, and serious treatment-emergent adverse events (any grade) that occurred in ≥4% of patients in either treatment group in the confirmatory analysis group of the safety population, defined as all patients from stages 1 and 2 randomly assigned to 1.0 mg mezigdomide plus carfilzomib and dexamethasone or carfilzomib–dexamethasone alone who received at least one dose of study treatment. Adverse events were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. *Includes Medical Dictionary for Regulatory Activities preferred terms of neutropenia and neutrophil count decreased. †Includes preferred terms of thrombocytopenia and platelet count decreased.				
Table 3: Most common adverse events and serious adverse events				

Implications of all the available evidence

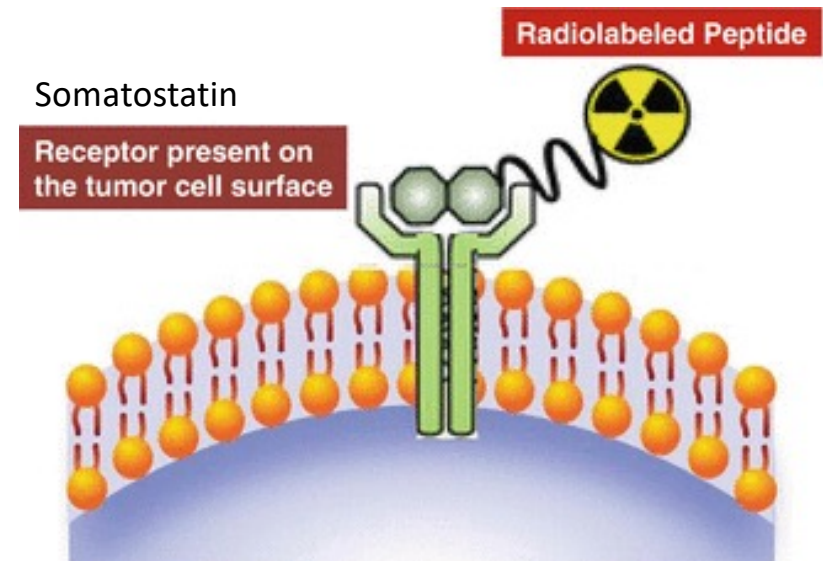
Taken together with previous real-world evidence and data from early-phase clinical trials, the results of SUCCESSOR-2 showed that mezigdomide–carfilzomib–dexamethasone substantially improves outcomes versus carfilzomib–dexamethasone in a growing and under-studied population of patients with relapsed or refractory multiple myeloma who are predominantly refractory to anti-CD38 antibodies and lenalidomide. These findings address a major evidence gap in early relapse and support mezigdomide–carfilzomib–dexamethasone as a potent, differentiated combination that addresses distinct clinical needs in the evolving relapsed or refractory multiple myeloma treatment paradigm at early relapse. Mezigdomide is under active investigation across additional combinations and multiple myeloma populations.

Peptide-Receptor-Radionuklid-Therapie (PRRT) ist eine hochpräzise, zielgerichtete molekulare Krebstherapie, die hauptsächlich zur Behandlung von fortgeschrittenen, inoperablen oder metastasierten **neuroendokrinen Tumoren (NETs)** eingesetzt wird. Dabei transportiert ein biologisches Eiweiß (Peptid) eine radioaktive Substanz direkt zu den Krebszellen, um diese gezielt von innen heraus zu zerstören.

Zielgerichtete Erkennung: Neuroendokrine Tumorzellen besitzen auf ihrer Oberfläche eine extrem hohe Anzahl an Andockstellen, den sogenannten **Somatostatin-Rezeptoren**.
Das Träger-Schloss-Prinzip: Dem Patienten wird eine Infusion verabreicht, die aus einem künstlichen Peptid (z. B. *Octreotat* oder *Octreotid*) besteht, das exakt auf diese Rezeptoren passt.
Die radioaktive Ladung: An dieses Peptid ist ein therapeutisches Radionuklid gekoppelt – in der klinischen Praxis meist **Lutetium-177 (^{177}Lu)** oder seltener **Yttrium-90 (^{90}Y)**.

Präzise Zerstörung: Das Peptid dockt an die Tumorzelle an und wird von ihr aufgenommen. Die abgegebene Strahlung verursacht irreversible DNA-Schäden in den Krebszellen, während das umliegende gesunde Gewebe weitgehend geschont wird.

Um GEP-NETS zu bekämpfen



[¹⁷⁷Lu]Lu-edotreotide versus everolimus for gastroenteropancreatic neuroendocrine tumours (COMPETE): a phase 3, multicentre, randomised, open-label, superiority trial

Summary

PRRT for GEP NETs **Background** Peptide receptor radionuclide and targeted therapy are both approved treatment options for patients with metastatic gastroenteropancreatic neuroendocrine tumours (GEP NETs), but clinical evidence for preferred sequencing is scarce. The COMPETE trial evaluated the efficacy and harms of peptide receptor radionuclide therapy ([¹⁷⁷Lu]Lu-edotreotide) versus targeted molecular therapy (everolimus) in patients with advanced, progressive, somatostatin receptor-positive GEP NETs.

Methods This phase 3, open-label, superiority trial included patients aged 18 years or older with treatment-naïve or previously treated unresectable or metastatic (or both) grade 1–2 GEP NETs. Patients were enrolled from 49 specialist neuroendocrine tumour treatment centres across 14 countries in Africa, Europe, North America, and Oceania and randomised (2:1) to intravenous [¹⁷⁷Lu]Lu-edotreotide (7.5 ± 0.7 GBq every 3 months, maximum four cycles) or oral everolimus (10 mg/day) for up to 30 months. Random assignment was via a central, web-based randomisation system (block size of 6) and stratified by primary tumour origin and previous therapy. The primary endpoint was progression-free survival, assessed via blinded independent central review in all randomly assigned patients at 30 months. Harms were assessed in all enrolled patients who received at least one dose of a study drug. This study was registered with ClinicalTrials.gov (NCT03049189) and is no longer recruiting.

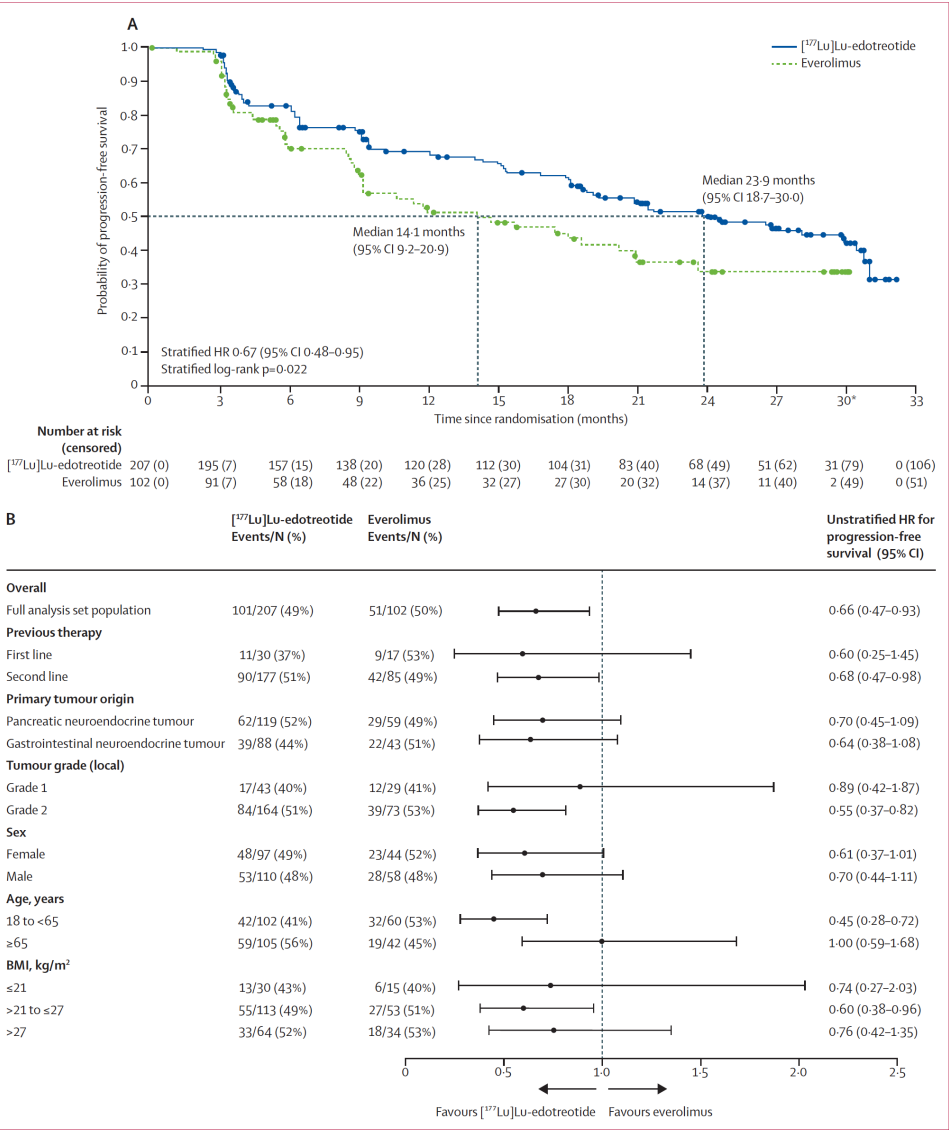
Findings Between April 13, 2017, and June 20, 2022, 324 patients were enrolled and 309 patients (including 168 [54%] male patients and 141 [46%] female patients) were randomly assigned to treatment: 207 to the [¹⁷⁷Lu]Lu-edotreotide group and 102 to the everolimus group. The median follow-up for progression-free survival was 27·5 months (IQR 19·6–30·4) for the [¹⁷⁷Lu]Lu-edotreotide group and 21·2 months (8·9–29·4) for the everolimus group. Median progression-free survival was significantly longer with [¹⁷⁷Lu]Lu-edotreotide versus everolimus (23·9 months [95% CI 18·7–30·0] vs 14·1 months [9·2–20·9]; stratified hazard ratio 0·67 [95% CI 0·48–0·95]; p=0·022). Treatment-related adverse events occurred in 178 (82%) of 217 patients in the [¹⁷⁷Lu]Lu-edotreotide group and 96 (97%) of 99 patients in the everolimus group. 40 (18%) patients in the [¹⁷⁷Lu]Lu-edotreotide group and 40 (40%) in the everolimus group had at least one treatment-related grade 3–4 adverse event. The most common treatment-related adverse events in the [¹⁷⁷Lu]Lu-edotreotide group were diarrhoea and nausea (both 79 [36%] patients) and asthenia (66 [33%] patients), whereas those in the everolimus group were diarrhoea (45 [45%] patients), asthenia (36 [36%] patients), and anaemia (27 [27%] patients). No treatment-related deaths occurred in either study group.

Interpretation [¹⁷⁷Lu]Lu-edotreotide led to statistically significant and clinically meaningful improvements in progression-free survival. Efficacy and harms results support the use of [¹⁷⁷Lu]Lu-edotreotide in early lines of therapy in patients with advanced, progressive GEP NETs.

	[¹⁷⁷ Lu]Lu- edotreotide (n=207)	Everolimus (n=102)
Sex		
Male	110 (53%)	58 (57%)
Female	97 (47%)	44 (43%)
Age, years	65.0 (54.0–72.0)	61.0 (52.0–69.0)
Race		
White	177 (86%)	84 (82%)
Black or African American	4 (2%)	4 (4%)
Not reported or mixed race	26 (13%)	14 (14%)
BMI, kg/m ²	25.2 (22.3–27.9)	24.6 (21.9–28.4)
Primary tumour site		
Pancreas	119 (57%)	59 (58%)
Ileum	35 (17%)	17 (17%)
Colorectum	18 (9%)	9 (9%)
Jejunum	9 (4%)	7 (7%)
Duodenum	7 (3%)	2 (2%)
Stomach	2 (1%)	0
Other ^a	17 (8%)	8 (8%)
Tumour grade (local) [†]		
Grade 1	43 (21%)	29 (28%)
Grade 2	164 (79%)	73 (72%)
Gastroenteropancreatic neuroendocrine tumour type [‡]		
Non-functional gastrointestinal	88 (43%)	43 (42%)
Non-functional pancreatic	99 (48%)	51 (50%)
Functional pancreatic	20 (10%)	8 (8%)
Received previous line of therapy (second-line population) [‡]	177 (86%)	85 (83%)
Treatment-naïve	30 (14%)	17 (17%)
Received previous surgery to primary tumour	151 (73%)	63 (62%)
Time from disease progression at prebaseline to baseline imaging [§] , months		
First-line population	7.9 (5.1–14.6)	12.2 (6.0–14.3)
Second-line population	9.8 (6.0–15.8)	9.9 (6.2–17.7)
Prestudy treatments		
Somatostatin analogue	182 (88%)	85 (83%)
Chemotherapy	36 (17%)	30 (29%)
Embolisation	13 (6%)	7 (7%)
Other antineoplastic agent	22 (11%)	15 (15%)
Tyrosine kinase inhibitor	15 (7%)	13 (13%)
Sensitisers during photodynamic radiation therapy	4 (2%)	4 (4%)
Angiogenesis inhibitor	2 (1%)	0
Other [¶]	4 (2%)	0
Ki-67	5% (3–10)	5% (2–10)

Data are n (%) or median (IQR). ^aFor patients in the [¹⁷⁷Lu]Lu-edotreotide group, other primary tumour sites were the small bowel (n=12), appendix (n=1), gastrointestinal tract (n=1), ileocaecum (n=1), liver (n=1), and mesentery (n=1); for everolimus, other primary tumour sites were the small bowel (n=6), mesentery (n=1), and unspecified digestive origin (n=1). [†]WHO classification, local assessment. [‡]Stratification factors: primary tumour origin (gastrointestinal vs pancreatic neuroendocrine tumour) and previous therapy (first line vs second line). [§]Calculated for patients with both prebaseline and baseline imaging. Five (17%) of 30 patients receiving first-line [¹⁷⁷Lu]Lu-edotreotide, six (35%) of 17 patients receiving first-line everolimus, 30 (17%) of 177 patients receiving second-line [¹⁷⁷Lu]Lu-edotreotide, and 14 (16%) of 85 patients receiving second-line everolimus had no prebaseline imaging. [¶]For patients in the [¹⁷⁷Lu]Lu-edotreotide group, other antineoplastic agents were an immune checkpoint inhibitor (n=1), interferon alfa-2b (n=1), other immunostimulant (n=1), other therapeutic product (n=1), and microwave ablation to the liver (n=1).

Table 1: Demographic and clinical characteristics of the patients at baseline (full analysis set)



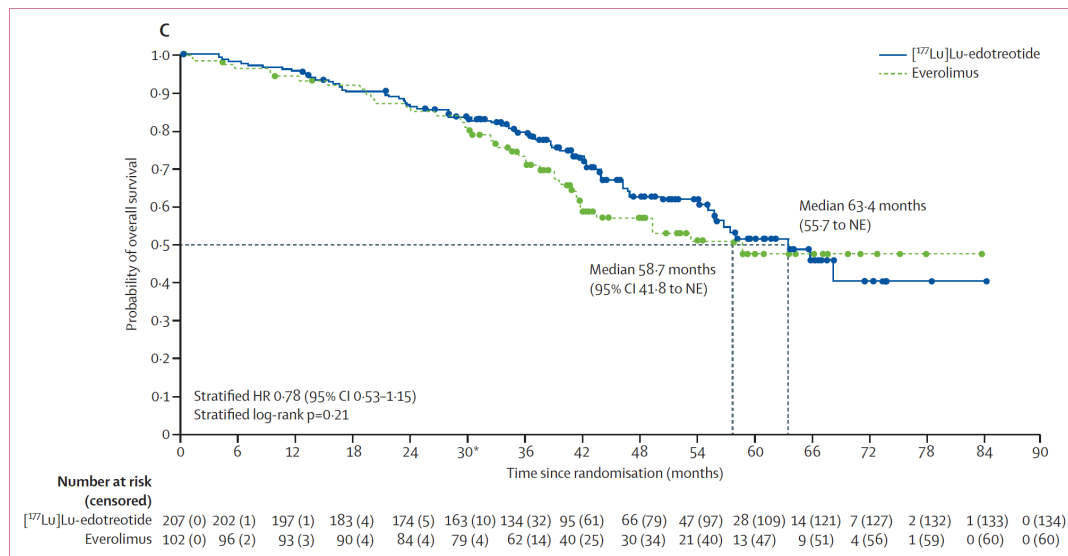


Figure 2: Progression-free survival, subgroup analyses of progression-free survival, and overall survival in the full analysis set
 (A) Kaplan-Meier plot of progression-free survival. (B) Forest plot for subgroup analyses of progression-free survival. (C) Kaplan-Meier plot of overall survival. In A and C, the log-rank p value was derived from a two-sided test between the two groups; stratification factors were primary tumour origin (gastrointestinal vs pancreatic neuroendocrine tumour) and previous therapy (first line vs second line). HR=hazard ratio. NE=not evaluable. *End of study.

	[¹⁷⁷ Lu]Lu-edotreotide (n=207)	Everolimus (n=102)	p value
Key secondary endpoint			
Objective response rate*	44 (22%; 16.2 to 27.6)	4 (4%; 0.2 to 8.2)	<0.0001
Best overall response			
Complete response	4 (2%)	0	..
Partial response	40 (19%)	4 (4%)	..
Stable disease	123 (59%)	74 (73%)	..
Progressive disease	34 (16%)	17 (17%)	..
Not evaluable	0	0	..
No post-baseline CT scan data available	6 (3%)	7 (7%)	..
Other secondary endpoints			
Disease control rate	167 (83%; 77.9 to 88.3)	78 (82%; 74.4 to 89.8)	0.87
Median duration of disease control (IQR), months	27.3 (14.7 to NR)	17.2 (6.0 to NR)	..

Data are n (%; 95% CI) or n (%) unless otherwise indicated. NR=not reached.
 *Patients with no available post-baseline CT scan data were excluded from the objective response rate analysis. 201 patients in the [¹⁷⁷Lu]Lu-edotreotide group and 95 patients in the everolimus group were included in the objective response rate analysis.

Table 2: Selected secondary efficacy endpoints in the full analysis set

	[¹⁷⁷ Lu]Lu-edotreotide (n=217)	Everolimus (n=99)	p value*
Patients with ≥1 TEAE	211 (97%)	99 (100%)	0.18
Patients with ≥1 TEAE related to study treatment	178 (82%)	96 (97%)	0.0001
Patients with ≥1 SAE	66 (30%)	44 (44%)	0.022
Patients with ≥1 SAE related to study treatment	7 (3%)	15 (15%)	0.0004
Patients with ≥1 TEAE leading to study discontinuation	14 (6%)	23 (23%)	<0.0001
Patients with ≥1 TEAE related to study treatment leading to study discontinuation	4 (2%)	15 (15%)	<0.0001
Patients with ≥1 TEAE leading to action on study treatment (drug interrupted, withdrawn, or dose reduced)	23 (11%)	67 (68%)	<0.0001
Patients with ≥1 TEAE related to study treatment leading to action on study treatment (drug interrupted, withdrawn, or dose reduced)	8 (4%)	52 (53%)	<0.0001
TEAEs leading to death	14 (6%)	7 (7%)	0.81

Data are n (%). SAE=serious adverse event. TEAE=treatment-emergent adverse event. *Calculated using Fisher's exact test.

Table 3: Overview of TEAEs in the safety analysis set

	[¹⁷⁷ Lu]Lu-edotreotide (n=217)		Everolimus (n=99)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Gastrointestinal disorders				
Diarrhoea	79 (36%)	4 (2%)	45 (45%)	6 (6%)
Nausea	79 (36%)	1 (<1%)	22 (22%)	0
Abdominal pain	51 (24%)	4 (2%)	20 (20%)	0
Abdominal pain upper	31 (14%)	2 (1%)	12 (12%)	0
Constipation	31 (14%)	1 (<1%)	9 (9%)	0
Vomiting	30 (14%)	1 (<1%)	19 (19%)	0
Stomatitis	3 (1%)	0	25 (25%)	6 (6%)
Mouth ulceration	1 (<1%)	0	12 (12%)	0
General disorders and administration site conditions				
Asthenia	66 (30%)	4 (2%)	36 (36%)	6 (6%)
Fatigue	53 (24%)	2 (1%)	17 (17%)	0
Pyrexia	19 (9%)	0	18 (18%)	1 (1%)
Oedema peripheral	13 (6%)	1 (<1%)	29 (29%)	2 (2%)
Mucosal inflammation	2 (1%)	0	29 (29%)	1 (1%)
Metabolism and nutrition disorders				
Hyperkalaemia	38 (18%)	8 (4%)	0	0
Decreased appetite	22 (10%)	0	22 (22%)	1 (1%)
Hyperglycaemia	13 (6%)	4 (2%)	25 (25%)	6 (6%)
Hypokalaemia	8 (4%)	1 (<1%)	11 (11%)	3 (3%)
Hypertriglyceridaemia	0	0	10 (10%)	3 (3%)
Blood and lymphatic system disorders				
Lymphopenia	38 (18%)	13 (6%)	1 (1%)	1 (1%)
Anaemia	35 (16%)	10 (5%)	27 (27%)	2 (2%)
Thrombocytopenia	33 (15%)	3 (1%)	13 (13%)	1 (1%)
Neutropenia	16 (7%)	4 (2%)	10 (10%)	2 (2%)
Infections and infestations				
COVID-19	32 (15%)	0	9 (9%)	1 (1%)

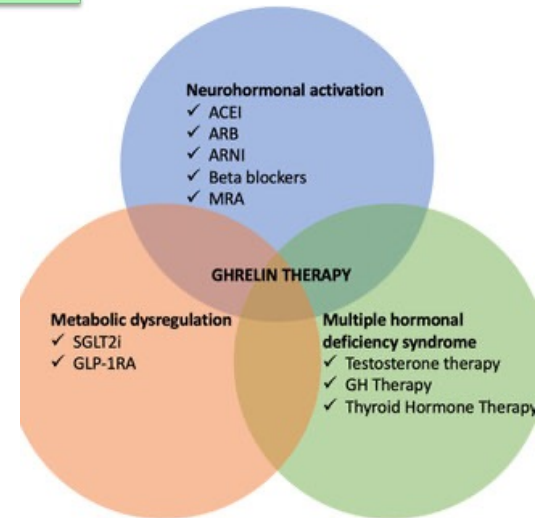
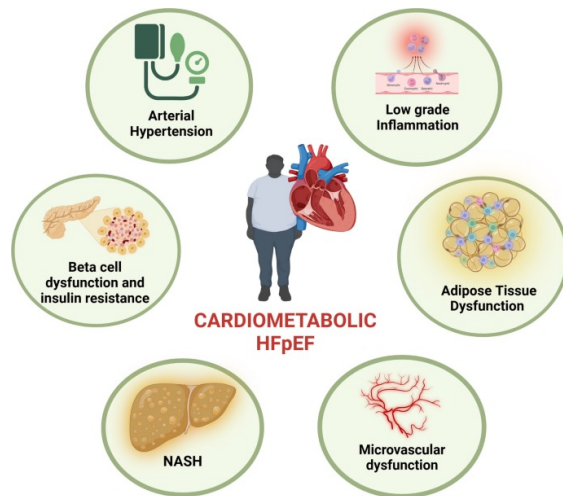
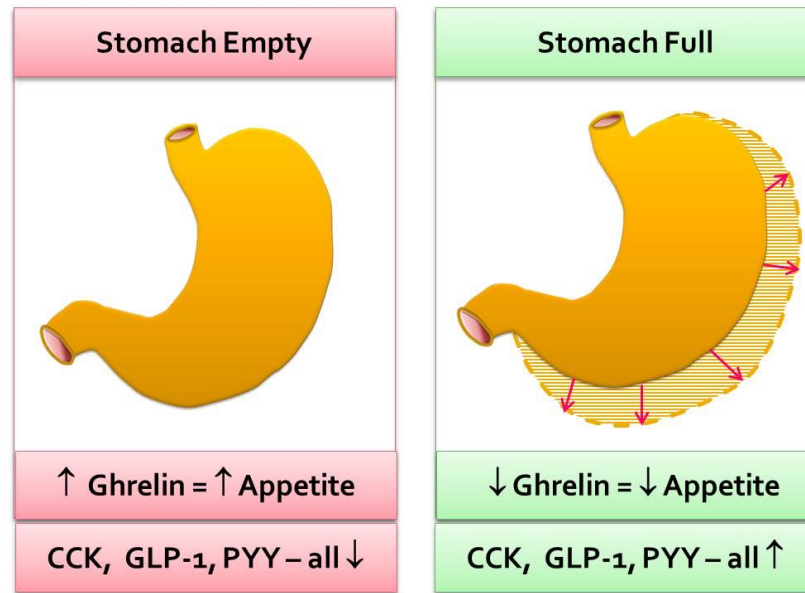
(Table 4 continues on next column)

	[¹⁷⁷ Lu]Lu-edotreotide (n=217)		Everolimus (n=99)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
(Continued from previous column)				
Musculoskeletal and connective tissue disorders				
Arthralgia	30 (14%)	1 (<1%)	15 (15%)	1 (1%)
Back pain	26 (12%)	1 (<1%)	11 (11%)	0
(Continued from previous column)				
Skin and subcutaneous tissue disorders				
Dry skin	17 (8%)	0	14 (14%)	0
Pruritus	13 (6%)	0	15 (15%)	0
Rash	9 (4%)	0	24 (24%)	0
Nervous system disorders				
Headache	26 (12%)	0	19 (19%)	0
Dysgeusia	4 (2%)	0	16 (16%)	0
Investigations				
Weight decreased	17 (8%)	0	18 (18%)	0
AST increased	18 (8%)	1 (<1%)	10 (10%)	3 (3%)
ALT increased	15 (7%)	1 (<1%)	13 (13%)	4 (4%)
Vascular disorders				
Hypertension	32 (15%)	15 (7%)	8 (8%)	3 (3%)
Respiratory, thoracic, and mediastinal disorders				
Cough	11 (5%)	0	12 (12%)	0
Dyspnoea	10 (5%)	0	12 (12%)	1 (1%)
Epistaxis	3 (1%)	0	14 (14%)	0
Data are n (%). Shown are any events occurring in ≥10% of patients in either group and grade 3 or 4 events occurring in ≥5% of patients in either group. All treatment-emergent adverse events are reported in appendix 1 (p 13). ALT=alanine aminotransferase. AST=aspartate aminotransferase.				
Table 4: Most frequent treatment-emergent adverse events in the safety analysis set				

Implications of all the available evidence

On the basis of current clinical evidence, PRRT should be considered the established treatment choice in patients with advanced, progressive GEP NETs, particularly in the second-line setting following progression under somatostatin analogue therapy. Future research should evaluate the optimal positioning of PRRT in the treatment of patients with advanced GEP NETs and assess the optimal number of PRRT cycles needed for maximum treatment benefit, while maintaining an acceptable safety profile.

Ghrelin



Ghrelin-Rezeptor-Agonisten sind Wirkstoffe, die an den gleichen Rezeptoren (GHS-1a) wie das körpereigene Hormon Ghrelin andocken. Sie entfalten dadurch ähnliche Wirkungen wie das sogenannte „Hungerhormon“.

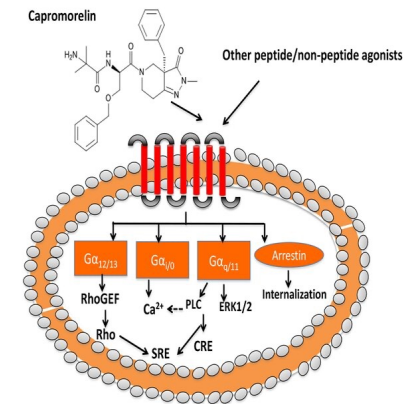
Wirkungsweise und Einsatzgebiete

Ghrelin wird natürlicherweise im Magen produziert und reguliert unter anderem den Appetit und die Magenentleerung. Entsprechende Agonisten (wie beispielsweise Relamorelin) haben spezifische Anwendungsbereiche:

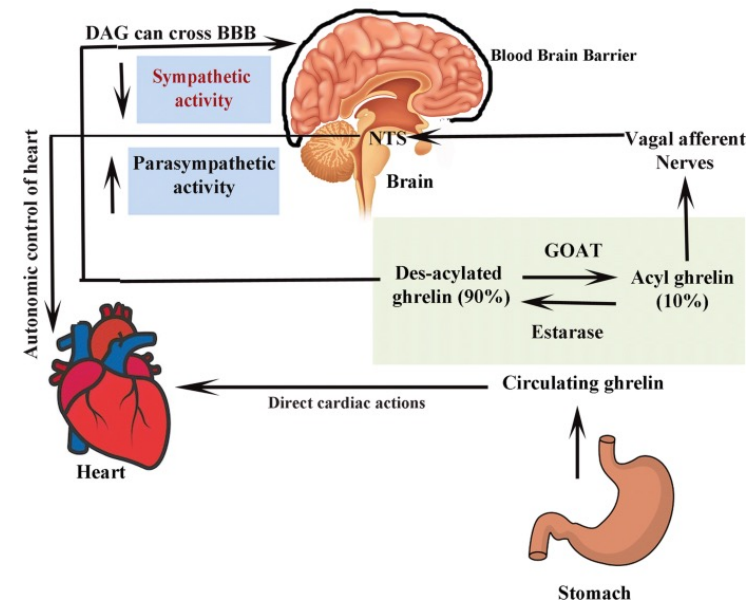
Magen-Darm-Erkrankungen (Gastroparese): Hier liegt oft eine verzögerte Magenentleerung vor. Ghrelin-Rezeptor-Agonisten regen die Darmmotilität an und beschleunigen die Magenentleerung. Dies kann Symptome wie Erbrechen und Übelkeit lindern

Appetitstimulation: In der Tiermedizin (z.B. bei Katzen und Hunden) werden Ghrelin-Agonisten wie Capromorelin zur Steigerung der Nahrungsaufnahme bei chronischen Erkrankungen eingesetzt.

Wachstumshormon-Stimulation: Sie stimulieren die Freisetzung von Wachstumshormonen und IGF-1, was unter anderem zum Aufbau von Muskelmasse führen kann.



Autonomic nervous control of heart by ghrelin



Ghrelin zeigt vielversprechende Ansätze zur Behandlung von HFpEF (Herzinsuffizienz mit erhaltener Ejektionsfraktion), befindet sich klinisch jedoch noch in der Erforschung. Während die meisten Studien zu Ghrelin historisch bei HFrEF (reduzierte Ejektionsfraktion) durchgeführt wurden, rückt der Einsatz bei HFpEF zunehmend in den Fokus der Wissenschaft.

Ghrelin greift an zentralen pathophysiologischen Stellschrauben von HFpEF an:

Reduktion von Fibrose: Ghrelin hemmt die Kollagensynthese und mindert die Gewebeversteifung im Herzmuskel.

Verbesserung der Entspannung (Dastole): Es optimiert die Funktion der Calcium-Pumpe SERCA2a in den Herzzellen, was die kardiale Erschlaffung erleichtert.

Steigerung der Kontraktilität: Klinische Daten zeigen, dass intravenöses Ghrelin das Schlagvolumen und das Herzzeitvolumen lastunabhängig verbessern kann (z. B. über Calcium-Sensitierung).

Entzündungshemmung: Es dämpft den systemischen proinflammatorischen Status, der als Haupttreiber von HFpEF gilt.

Autonome Balance: Ghrelin senkt den schädlichen Sympathikustonus und stärkt die vagale (parasympathische) Aktivität.

Safety, pharmacokinetics, and exploratory efficacy of the oral ghrelin receptor agonist AC01 in heart failure with reduced ejection fraction (GOAL-HF1): a randomised,

Ghrelin and
HFpEF

Summary

Background The central problem in heart failure with reduced ejection fraction (HFrEF) is reduced contractility. Existing inotropes are associated with adverse effects. In this exploratory study, we aimed to assess the safety and tolerability of AC01, a novel oral calcium-sensitising inotrope and ghrelin receptor agonist, in patients with HFrEF.

Methods In this phase 1b/2a, randomised, double-blind, placebo-controlled study, adults aged 18–80 years with heart failure for at least 6 months and an ejection fraction of 40% or lower were enrolled at 14 sites in the Netherlands, the UK, Sweden, and Italy. All patients had a transvenous implantable cardioverter defibrillator for primary prevention, with back-up pacing to protect against excessive bradycardia. Other eligibility criteria included sinus rhythm or permanent, persistent, or paroxysmal atrial fibrillation or flutter (only allowed in phase 2a), with a mean resting heart rate of 55–90 beats per min. Randomisation used permuted blocks, with block sizes of four for phase 1b and three for phase 2a. In phase 1b, patients were enrolled in four sequential dose cohorts and randomly assigned 3:1 to ascending doses of AC01 (0·1 mg, 0·3 mg, 1·0 mg, or 3·0 mg) or placebo twice daily for 7 days. In phase 2a, patients were randomly assigned 1:1:1 to parallel groups receiving 1·0 mg AC01, 3·0 mg AC01 (1·0 mg AC01 on days 1 and 2 and 3·0 mg thereafter), or placebo orally twice daily for 28 days. Patients, study personnel, outcomes assessors, those analysing the data, and the sponsor were masked to treatment assignment. The primary outcome was safety and tolerability. Safety was monitored by physical examination, vital signs, safety laboratory assessments, and 12-lead electrocardiograms (ECGs) periodically during the treatment period and until the end-of-study visit (day 12 in phase 1b and day 42 in phase 2a), and cardiac rhythm was continuously monitored remotely using a patch device until day 9 in phase 1b and until day 4 in phase 2a. Adverse or unexpected events, signs, or symptoms were recorded. This study is registered with ClinicalTrials.gov, NCT05642507, and has been completed.

Findings Between Feb 23, 2023, and Aug 28, 2025, 58 patients (53 [91%] male and five [9%] female patients with a median age of 66·0 years [IQR 60·3–72·0]) were randomly assigned: 32 in phase 1b and 26 in phase 2a. In phase 1b, four cohorts of eight patients were enrolled; in each cohort, six patients were allocated to AC01 and two to placebo, with AC01 dose cohorts of 0·1 mg, 0·3 mg, 1·0 mg, and 3·0 mg. In phase 2a, nine patients were allocated to 1·0 mg AC01, eight to 3·0 mg AC01, and nine to placebo. There were 12 AC01-related adverse events in phase 1b and 18 in phase 2a. There were no AC01-related serious adverse events; one treatment-related serious adverse event of increased high-sensitivity cardiac troponin I concentration occurred in a patient receiving placebo in phase 1b. Mild or moderate treatment-emergent adverse events were reported in 33 (80%) of 41 patients receiving AC01 and 12 (71%) of 17 patients receiving placebo. The most common treatment-emergent adverse events were hypotension, non-sustained ventricular tachycardia, dyspnoea, hyperglycaemia, dizziness or vertigo, and headache. ECG data showed no apparent signs of tachycardia, new-onset tachyarrhythmias, myocardial ischaemia, or morphological or conduction abnormalities. No case of symptomatic hypotension was reported, and there were no apparent effects of AC01 on high-sensitivity cardiac troponin I or NT-proBNP. There were no deaths during the study.

Interpretation In patients with HFrEF, AC01 over 28 days appeared safe and well tolerated, and no major harms were identified in this early-phase study. These findings support further investigations of AC01 in larger studies.

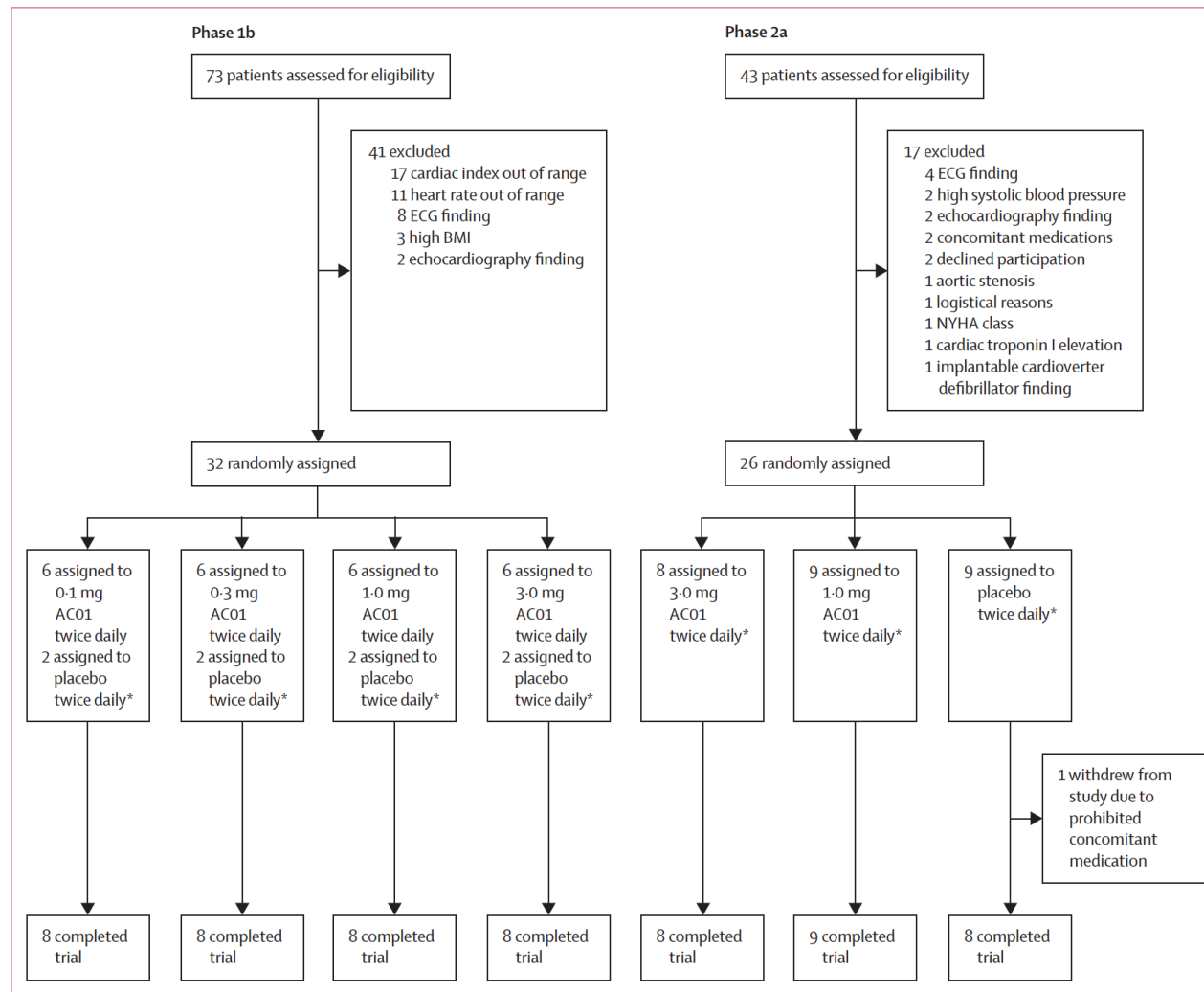


Figure 1: Study profile

ECG=electrocardiogram. NYHA=New York Heart Association. *Included in the safety analysis set.

	Phase 1b					Phase 2a		
	AC01 0·1 mg (n=6)	AC01 0·3 mg (n=6)	AC01 1·0 mg (n=6)	AC01 3·0 mg (n=6)	Placebo (n=8)	AC01 1·0 mg (n=9)	AC01 3·0 mg* (n=8)	Placebo (n=9)
Demographics								
Age, years	67·0 (62·0–72·8)	70·5 (68·3–72·0)	69·0 (65·0–71·5)	60·5 (57·2–67·5)	61·5 (58·8–62·8)	64·0 (60·0–69·0)	67·0 (62·2–70·5)	69·0 (67·0–77·0)
Sex								
Male	6 (100%)	5 (83%)	5 (83%)	6 (100%)	8 (100%)	8 (89%)	8 (100%)	7 (78%)
Female	0	1 (17%)	1 (17%)	0	0	1 (11%)	0	2 (22%)
Race or ethnicity								
White	6 (100%)	5 (83%)	6 (100%)	6 (100%)	7 (88%)	8 (89%)	8 (100%)	9 (100%)
Black or African American	0	1 (17%)	0	0	0	0	0	0
Asian	0	0	0	0	1 (13%)	1 (11%)	0	0
BMI, kg/m²	25·8 (23·2–29·7)	27·1 (26·1–27·4)	29·3 (24·9–30·0)	28·5 (25·0–30·5)	30·0 (29·0–30·9)	27·4 (23·2–29·7)	28·4 (24·6–31·3)	26·7 (25·4–28·0)
Laboratory variables								
NT-proBNP, pg/mL	552 (291–680)	930 (492–1209)	540 (174–627)	328 (80–613)	372 (223–901)	993 (573–2165)	545 (201–644)	551 (373–953)
Estimated glomerular filtration rate, mL/min per 1·73 m²	72·0 (18·4)	56·0 (5·9)	65·8 (13·5)	89·2 (19·8)	70·0 (20·7)	62·6 (22·1)	79·9 (20·4)	65·0 (21·2)
Haemoglobin, g/dL	15·9 (1·6)	14·0 (1·1)	15·3 (1·2)	15·8 (2·1)	16·2 (0·9)	15·6 (1·8)	14·7 (0·8)	15·4 (2·2)
Vital signs								
Heart rate, beats per min	70·8 (6·4)	66·7 (8·5)	71·8 (6·7)	68·3 (5·5)	68·5 (5·2)	67·4 (9·2)	68·6 (8·2)	62·1 (6·9)
Systolic blood pressure, mm Hg	108·8 (9·5)	119·9 (18·9)	109·0 (9·0)	104·2 (8·3)	119·3 (9·8)	109·9 (13·3)	110·9 (6·1)	113·0 (13·0)
Clinical presentation								
Sinus rhythm	6 (100%)	6 (100%)	6 (100%)	6 (100%)	8 (100%)	8 (89%)	8 (100%)	9 (100%)
Atrial fibrillation or flutter	0	0	0	0	0	1 (11%)	0	0
Heart failure characteristics								
NYHA class								
II	2 (33%)	4 (67%)	6 (100%)	4 (67%)	6 (75%)	8 (89%)	6 (75%)	8 (89%)
III	4 (67%)	2 (33%)	0	2 (33%)	2 (25%)	1 (11%)	2 (25%)	1 (11%)
Left ventricular ejection fraction, %	30·2% (6·2)	28·8% (6·7)	34·2% (6·7)	34·0% (5·5)	31·0% (7·5)	28·6% (6·8)	32·1% (5·7)	33·0% (5·8)
Duration of heart failure, years	5·3 (2·5)	8·0 (9·0)	6·2 (4·9)	5·7 (7·1)	13·5 (9·7)	8·7 (8·2)	5·9 (3·0)	12·8 (8·0)
Primary aetiology of heart failure								
Ischaemic	5 (83%)	6 (100%)	4 (67%)	4 (67%)	8 (100%)	8 (89%)	6 (75%)	7 (78%)
Non-ischaemic	1 (17%)	0	2 (33%)	2 (33%)	0	1 (11%)	2 (25%)	2 (22%)

HZV

Schlag-
volumen

EF %

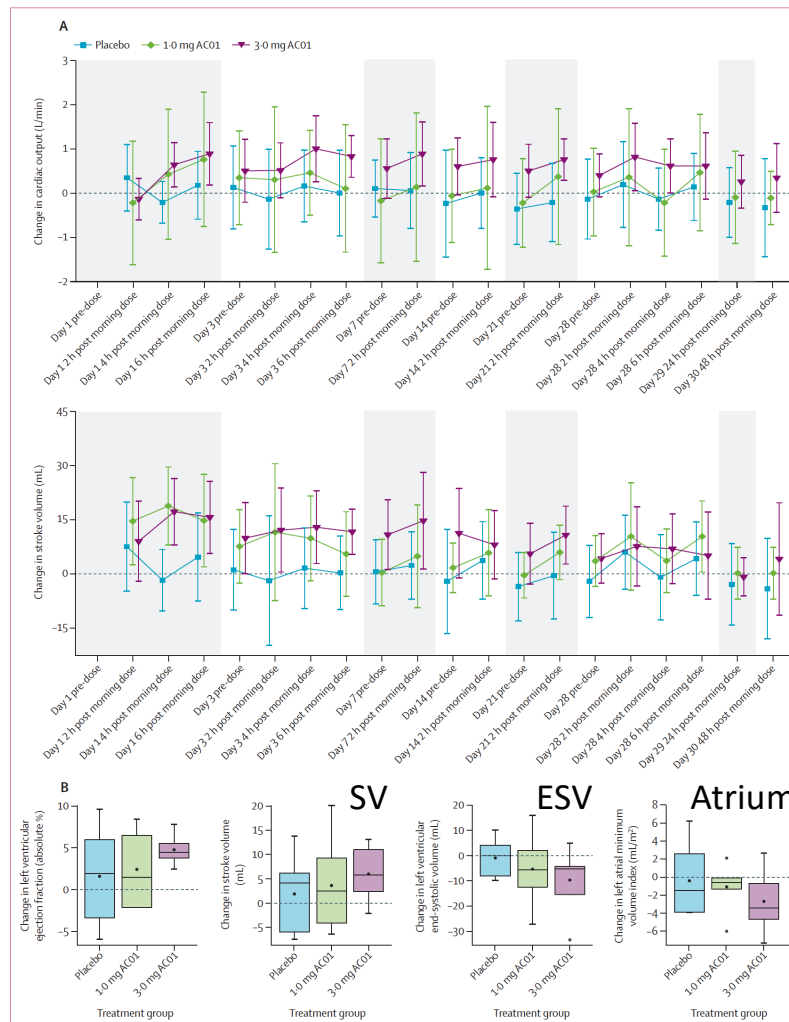


Figure 2: Exploratory haemodynamic (A) and echocardiography (B) outcomes in phase 2a
 (A) Mean changes from baseline in cardiac output (upper plot) and stroke volume (lower plot) by treatment group; whiskers indicate SD. The group assigned to 3.0 mg AC01 received 1.0 mg AC01 twice daily on days 1 and 2 and 3.0 mg twice daily from day 3 onwards. (B) Changes from baseline to day 28 (assessments at 2–4 h after dosing) in left ventricular ejection fraction, stroke volume, left ventricular end-systolic volume, and left atrial minimum volume index by treatment group. Box plots show medians (horizontal lines) and IQRs (box limits); filled points represent means, and hollow points represent outliers. Echocardiography data were interpreted by the central core laboratory.

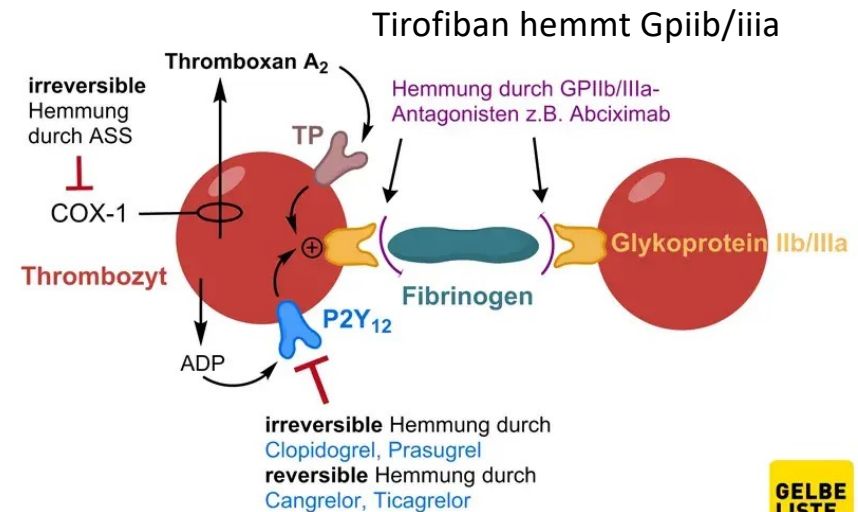
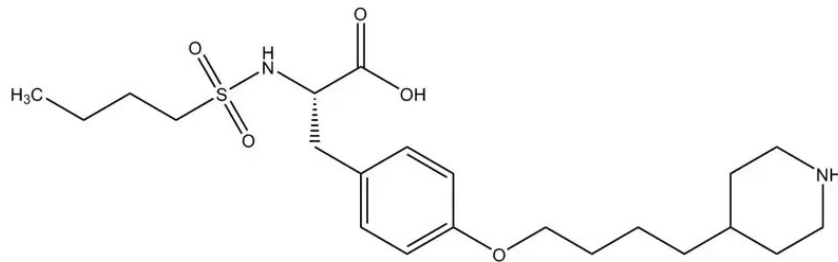
Added value of this study

GOAL-HF1 is the first clinical study of AC01 in patients with HFrEF. These results provide early clinical evidence on the short-term safety, tolerability, and pharmacokinetics of AC01 and prespecified exploratory haemodynamic and echocardiographic observations to inform the design of larger trials.

Implications of all the available evidence

These findings support further evaluation of AC01 in larger, adequately powered studies designed to assess dose selection, longer-term safety, and clinical efficacy in patients with HFrEF.

Tirofiban ist ein intravenös verabreichter Thrombozytenaggregationshemmer aus der Gruppe der Glykoprotein-IIb/IIIa-Rezeptorantagonisten. Der Wirkstoff blockiert die Bindung von Fibrinogen an Blutplättchen und verhindert so effektiv die Bildung neuer Blutgerinnsel.



Efficacy and safety of tirofiban after successful endovascular reperfusion in acute ischaemic stroke (ATTRACTION) in China: a multicentre, double-blind, randomised controlled trial

Tirofiban
after
stroke?

Summary

Background Successful reperfusion after endovascular thrombectomy does not consistently result in functional independence in acute ischaemic stroke. We aimed to assess the efficacy and safety of tirofiban, a glycoprotein IIb/IIIa receptor antagonist, given to patients with acute ischaemic stroke who had had a successful endovascular reperfusion.

Methods This multicentre, double-blind, randomised controlled trial at 82 hospitals in China included patients with acute ischaemic stroke due to anterior-circulation large-vessel occlusion who had had a successful reperfusion after thrombectomy. Eligible patients were randomly assigned (1:1) to receive either tirofiban (intra-arterial bolus 5 µg/kg followed by intravenous infusion 0.1 µg/kg per min for 24 h) or placebo (administered with the same volume and according to the same bolus and infusion procedures as tirofiban), using computer-generated randomisation with fixed blocks stratified by study site. Patients, treating clinicians, investigators, and outcome assessors were masked to group assignments. The primary efficacy outcome was functional independence at 90 days (with a modified Rankin Scale score of 0–2), assessed in all randomly assigned participants (intention-to-treat population). Safety outcomes were symptomatic intracranial haemorrhage within 48 h, any evidence of intracranial haemorrhage on imaging within 48 h, and death within 90 days, and they were assessed in patients having received the study treatment with at least one safety evaluation. The Adjunct Tirofiban Treatment after Successful Endovascular Thrombectomy Recanalisation in Acute Anterior Circulation Ischaemic Stroke (ATTRACTION) trial is registered with ClinicalTrials.gov, NCT06265051 and is now completed.

Findings Of 1686 patients assessed, 1380 were randomly assigned to either the tirofiban group (689 patients) or the placebo group (691 patients) between April 9, 2024, and Sept 29, 2025. Median age was 71 years (IQR 62–77), 591 (43%) patients were female and 789 (57%) were male, and 1367 (99%) were of Han Chinese ethnicity. No patients were lost to follow-up at 90 days. Functional independence at 90 days was recorded in 340 (49%) of 689 patients in the tirofiban group and 299 (43%) of 691 patients in the placebo group (unadjusted absolute risk difference 6·1 percentage points, 95% CI 0·8–11·3, $p=0\cdot023$; adjusted risk ratio 1·15, 95% CI 1·03–1·27, $p=0\cdot0092$). There was no significant difference between study groups in the proportion of patients with symptomatic intracranial haemorrhage within 48 h (82 [12%] of 687 patients in the tirofiban group *vs* 65 [9%] of 691 patients in the placebo group), the proportion with any intracranial haemorrhage within 48 h (235 [34%] patients *vs* 219 [32%] patients), and 90-day mortality (126 [18%] patients *vs* 131 [19%] patients).

Interpretation In patients with acute ischaemic stroke due to anterior-circulation large-vessel occlusion achieving successful reperfusion, adjunctive tirofiban increased the likelihood of functional independence compared with placebo. Although symptomatic intracranial haemorrhage occurred numerically more often with tirofiban, the between-group difference was not significant, and this finding warrants caution when weighing potential benefit against bleeding risk.

	Tirofiban (n=689)	Placebo (n=691)
Age (years)	71 (63-77)	71 (62-77)
Sex		
Female	295 (43%)	296 (43%)
Male	394 (57%)	395 (57%)
Ethnicity		
Han Chinese ethnic group	682 (99%)	685 (99%)
Other ethnic groups (Tujia, Miao, Dong, and Daur)	7 (1%)	6 (1%)
Median NIHSS score*	15 (12-19)	15 (11-19)
Median ASPECTS†	8 (7-9)	8 (7-9)
Medical history		
Hypertension	411 (60%)	407 (59%)
Hyperlipidaemia	229 (33%)	217 (31%)
Coronary heart disease	150 (22%)	131 (19%)
Diabetes	128 (19%)	130 (19%)
Previous stroke or transient ischaemic attack	123 (18%)	133 (19%)
Atrial fibrillation	329 (48%)	345 (50%)
Smoking status		
Current smoker	148 (21%)	155 (22%)
Former smoker	49 (7%)	40 (6%)
Stroke aetiology‡		
Large-artery atherosclerosis	202 (29%)	203 (29%)
Cardioembolism	442 (64%)	443 (64%)
Unknown and others	45 (7%)	45 (7%)
Wake-up stroke	182 (26%)	189 (27%)
Modified Rankin Scale score before stroke		
0	638 (93%)	633 (92%)
1	50 (7%)	56 (8%)
2	1 (<1%)	2 (<1%)
Occlusion site		
Intracranial internal carotid artery	210 (30%)	203 (29%)
M1 middle cerebral artery segment	411 (60%)	423 (61%)
M2 middle cerebral artery segment	68 (10%)	65 (9%)
Intravenous thrombolysis therapy	240 (35%)	251 (36%)
mTICI§		
2b	219 (32%)	225 (33%)
3	470 (68%)	466 (67%)
Interval between time last known well and puncture time (min)	270 (190-437)	285 (188-444)
Interval between time last known well and time of reperfusion (min)	340 (245-507)	351 (243-510)
Interval between time last known well and time of randomisation (min)	357 (259-526)	366 (254-520)
Interval between time last known well and intra-arterial study agent infusion (min)	360 (265-531)	370 (260-524)
Data are n (%) and median (IQR). Percentages may not total 100 because of rounding. ASPECTS=Alberta stroke program early CT score. mTICI=modified thrombolysis in cerebral infarction. NIHSS=National Institutes of Health Stroke Scale. *Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficits. †ASPECTS is an imaging measure of the extent of ischaemic stroke; scores range from 0 to 10, with higher scores indicating a smaller infarct core. ‡The Trial of Org 10172 in Acute Stroke Treatment system classifies ischaemic stroke and transient ischaemic attack into five subtypes based on likely causes: large-artery atherosclerosis, cardioembolism, small-artery occlusion, other determined aetiology, and undetermined aetiology. §The mTICI scale measures reperfusion based on digital subtraction angiography (range from zero [no reperfusion] to three [complete reperfusion]).		
Table 1: Baseline characteristics of the intention-to-treat population		

	Tirofiban group (n=689)	Placebo group (n=691)	Effect measure	Adjusted effect value (95% CI)*	p value
Primary efficacy outcome					
mRS score of 0-2 at 90 days†	340 (49%)	299 (43%)	Risk ratio	1.15 (1.03-1.27)	0.0092
Secondary efficacy outcomes					
mRS score of 0-1 at 90 days	242 (35%)	205 (30%)	Risk ratio	1.20 (1.04-1.37)	0.012
mRS score of 0-3 at 90 days	436 (63%)	424 (61%)	Risk ratio	1.04 (0.96-1.12)	0.37
Ordinal distribution of mRS at 90 days‡	3 (1-5)	3 (1-5)	Common odds ratio	1.22 (1.01-1.48)	0.040
Early neurological improvement§	426 (62%)	427 (62%)	Risk ratio	1.01 (0.93-1.09)	0.89
EQ-5D-5L score at 90 days					
Median value (IQR)	0.59 (0.06-0.96)	0.65 (0.06-0.96)	..	..	..
Number of wins/total number of pairs¶	217 299/476 099 (45.6%)	212 222/476 099 (44.6%)	Win ratio¶	1.04 (0.91-1.18)	0.61
Safety outcomes					
Symptomatic intracranial haemorrhage within 48 h	82/687 (12%)	65/691 (9%)	Risk ratio	1.24 (0.91-1.68)	0.17
Any intracranial haemorrhage within 48 h	235/687 (34%)	219/691 (32%)	Risk ratio	1.07 (0.92-1.25)	0.35
All-cause mortality within 90 days	126 (18%)	131 (19%)	Hazard ratio	0.96 (0.75-1.22)	0.72
Data are n (%), number of wins/total number of pairs, or n/N (%), unless otherwise stated. ASPECTS=Alberta stroke program early CT score. mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. *Adjusted for age, baseline NIHSS score, baseline ASPECTS score, occlusion site, and time from last known well to randomisation, but were not adjusted for multiple comparisons. †The mRS of functional disability ranges from 0 (no symptoms) to 6 (death) . ‡mRS scores 5-6 were combined to avoid counting a shift from death (mRS score of 6) to severe disability requiring constant nursing care (mRS score of 5) as a treatment success. §Early neurological improvement was defined as an NIHSS score of 0 to 1 or a reduction of at least 4 points at 36 h (±12 h) from baseline. ¶ For the win ratio analysis, a win was defined as a better health status across the five EQ-5D dimensions, compared hierarchically. If patients were tied on one dimension, subsequent dimensions were compared sequentially. A win ratio greater than 1 indicates a favourable outcome in the tirofiban group. Two patients in the tirofiban group were not evaluable for intracranial haemorrhage due to absence of post-procedural imaging.					
Table 2: Primary and secondary outcomes					

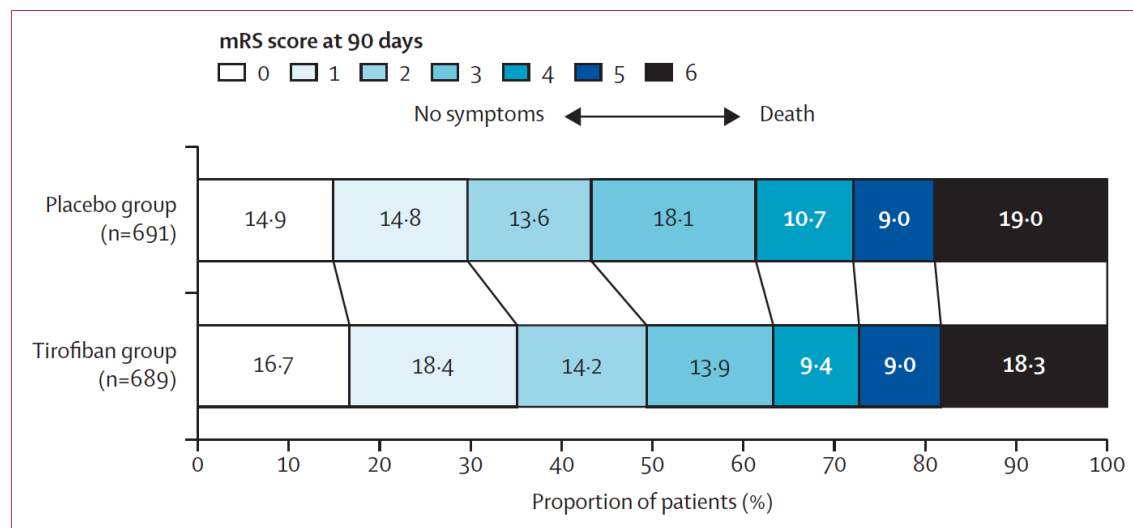


Figure 2: Distribution of mRS scores at 90 days in the intention-to-treat population

Distribution of scores on the mRS among patients in the tirofiban group and the placebo group. The mRS is a 7-point ordinal scale of functional disability. Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. No patients were lost to follow-up at 90 days. Percentages might not total 100 because of rounding. mRS=modified Rankin Scale.

	Tirofiban (n=689)	Placebo (n=691)
Overall*	275 (40%)	280 (41%)
Blood and lymphatic system disorders	13 (2%)	7 (1%)
Cardiac disorders	43 (6%)	60 (9%)
Gastrointestinal disorders	12 (2%)	9 (1%)
General disorders and administration site conditions	2 (<1%)	1 (<1%)
Hepatobiliary disorders	4 (1%)	1 (<1%)
Infections and infestations	152 (22%)	176 (25%)
Metabolism and nutrition disorders	6 (1%)	11 (2%)
Musculoskeletal and connective tissue disorders	0	1 (<1%)
Neoplasms (benign, malignant, and unspecified)	3 (<1%)	3 (<1%)
Nervous system disorders	121 (18%)	105 (15%)
Renal and urinary disorders	3 (<1%)	2 (<1%)
Respiratory, thoracic, and mediastinal disorders	26 (4%)	25 (4%)
Skin and subcutaneous tissue disorders	1 (<1%)	1 (<1%)
Surgical and medical procedures	6 (1%)	4 (1%)
Vascular disorders	16 (2%)	13 (2%)
Endocrine disorders	1 (<1%)	0

Data are n (%). Serious adverse events were classified using the fifth edition of the Common Terminology Criteria for Adverse Events of the USA. *Overall indicates the number of patients with at least one serious adverse event. For each system organ class, patients with multiple events of one type were counted once. Patients could have serious adverse events in more than one system organ class; therefore, the numbers across system organ classes should not be summed.

Table 3: Serious adverse events

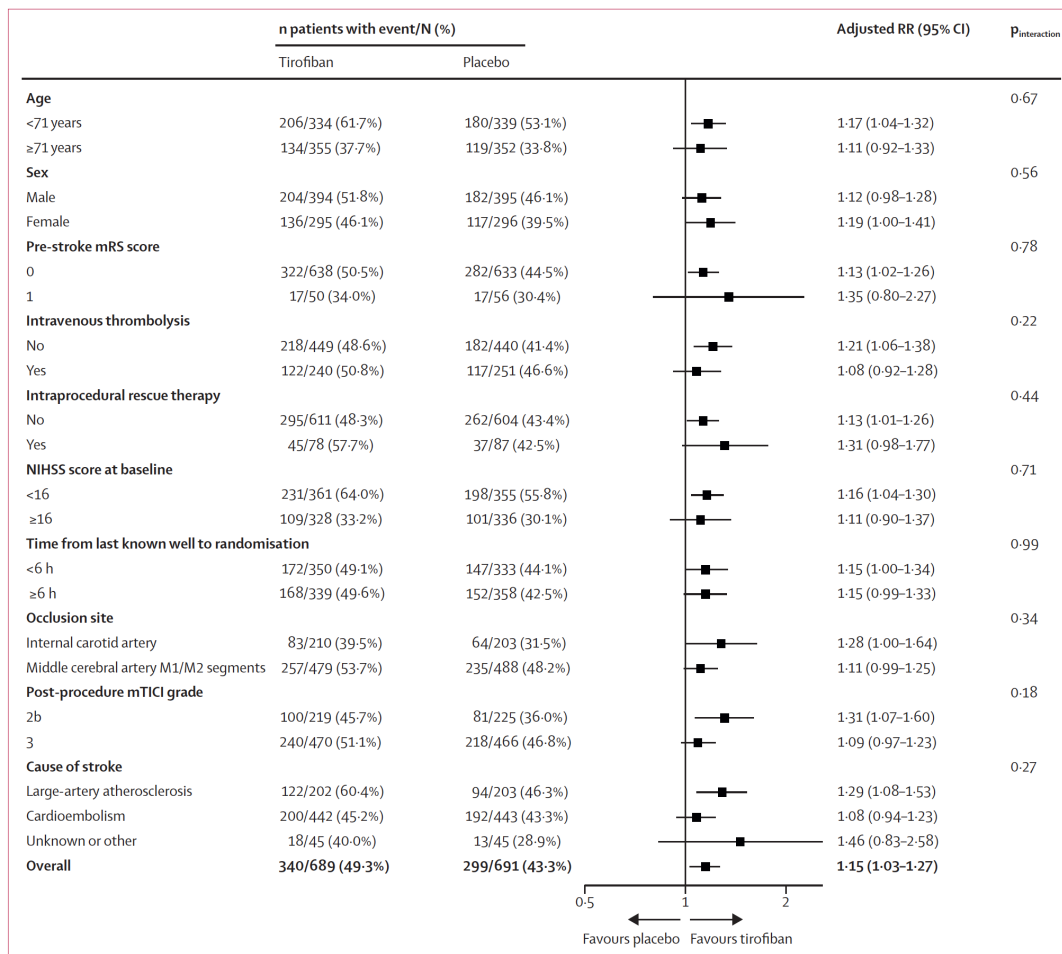


Figure 3: Subgroup analyses of the primary outcome in the intention-to-treat population

Forest plot comparing the tirofiban group with the placebo group according to subgroup with respect to the finding of a score of 0 to 2 on the mRS at 90 days (the primary outcome). The trial was not powered and had no prespecified correction for multiple comparisons for a definitive analysis of subgroups. The RR was adjusted for age, baseline NIHSS score, baseline ASPECTS, occlusion site, and time from last known well to randomisation. The median age of the patients was 71 years. Subgroups are defined as younger than 71 years and as age 71 years or older. Scores on the NIHSS range from 0 to 42, with higher scores indicating greater neurological deficits; a score of 16 or higher on this scale indicates a severe stroke. ASPECTS=Alberta stroke program early CT score. mRS=modified Rankin Scale. mTICI=modified thrombolysis in cerebral infarction. NIHSS=National Institutes of Health Stroke Scale. RR=risk ratio.

Implications of all the available evidence

The ATTRACTION trial supports further consideration of tirofiban as a potentially useful adjunct after successful endovascular reperfusion, while highlighting the need for caution regarding bleeding risk. The trial also suggests the potential importance of early, targeted platelet inhibition in the immediate post-reperfusion period and invites continued investigation into early antiplatelet approaches after successful endovascular reperfusion aimed at improving microvascular reperfusion and neurological recovery.

Safety and efficacy of mRNA vaccines: a mechanistic and public health perspective

mRNA vaccines represent a transformative advance in vaccinology, combining rapid development timelines, scalable manufacturing, and strong immunogenicity with a favourable safety profile. Global deployment of mRNA vaccines during the COVID-19 pandemic provided an unprecedented real-world evaluation of this platform, with billions of doses administered across diverse populations. In this Review, we critically examine the safety and efficacy of mRNA vaccines from mechanistic, preclinical, clinical, and public health perspectives. We outline the biological basis of mRNA vaccines, including their transient cytoplasmic expression, lack of genomic integration, and rapid clearance, distinguishing them clearly from other gene therapies. We synthesise evidence on vaccine components, manufacturing quality controls, and regulatory standards that underpin safety, alongside data from randomised trials, post-authorisation surveillance, and active pharmacovigilance systems. We also review real-world effectiveness across age groups, pregnancy, and populations that are immunocompromised, along with the effects on transmission. Last, we address public perception and vaccine confidence, and discuss implications for next-generation mRNA vaccines, including strategies to reduce reactogenicity, improve breadth and durability of immunity, enhance global access, and support sustainable public trust. Together, the accumulated evidence affirms mRNA vaccines as a safe, effective, and adaptable platform with enduring relevance for future infectious disease prevention and public health preparedness, and for the treatment of cancer and autoimmunity.

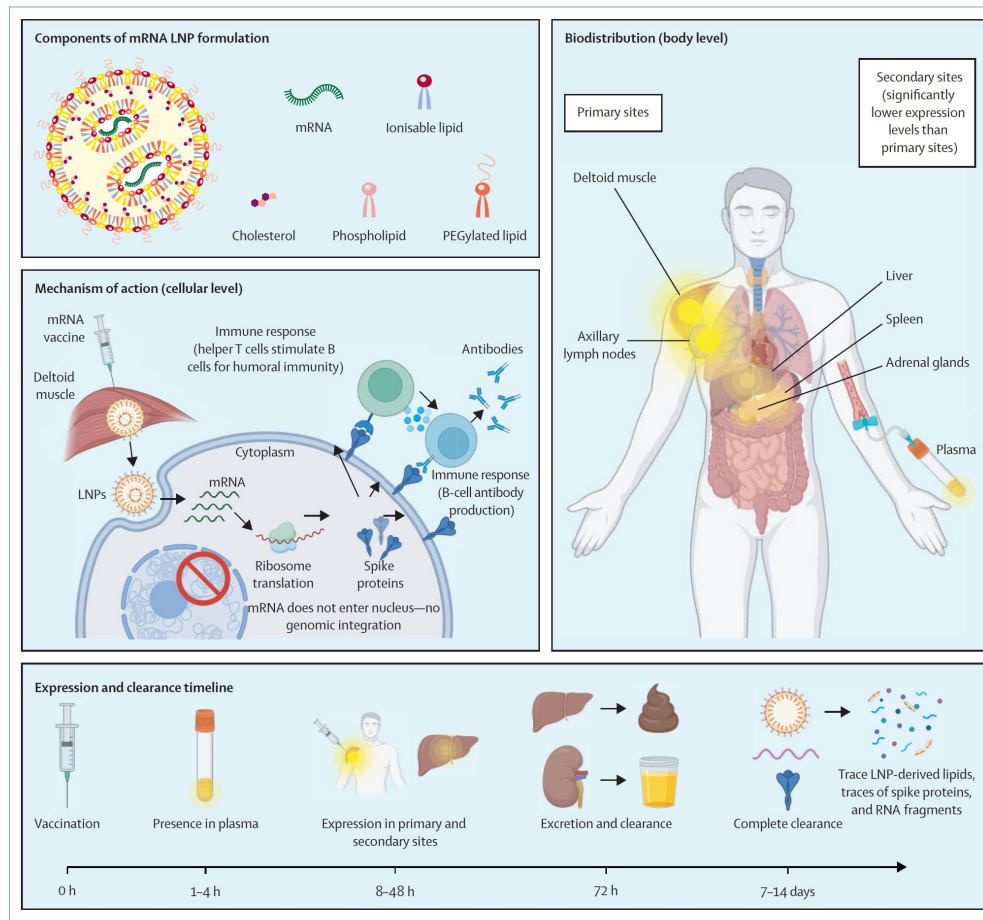
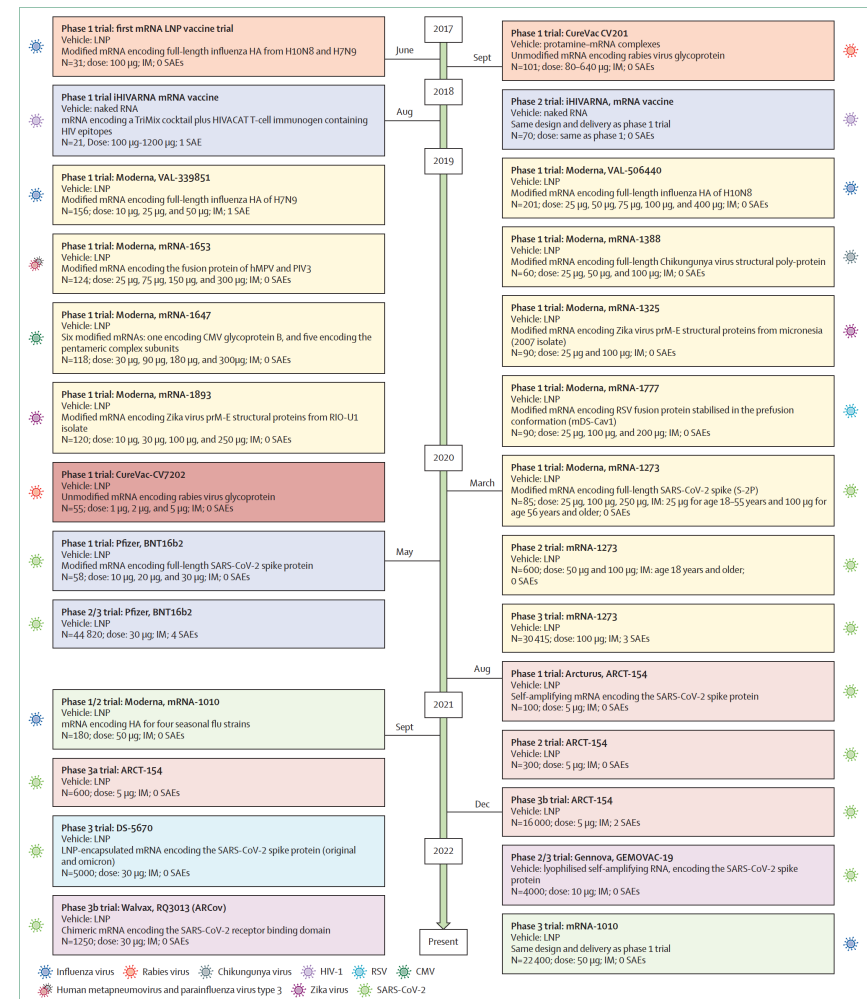


Figure 1: Schematic of mRNA lipid nanoparticle components, mechanism of action, biodistribution, and expression and clearance timeline for mRNA vaccines
LNP=lipid nanoparticle. PEG=polyethylene glycol.



	Vaccine	Common reactogenicity*	Serious adverse events
mRNA	Pfizer–BioNTech (BNT162b2) ^{3,90–92}	Pain at injection site (~75%); fatigue (~48%); headache (~40%); muscle pain (~25%)	Myocarditis and pericarditis: risk—12·6 cases per million (second dose); highest in males age 18–29 years. Anaphylaxis: risk—4·7 cases per million doses.
mRNA	Moderna (mRNA-1273) ^{89,91,92}	Pain (~80%); fatigue (~70%); headache (~65%); muscle pain (~61%)	Myocarditis and pericarditis: risk—35·6 cases per million (second dose). Anaphylaxis: risk—2·5 cases per million doses.
Self-amplifying RNA	Arcturus (ARCT-154) ^{93,94}	Pain (~70%); fatigue (~55%); headache (~38%); muscle pain (70%)	Myocarditis and pericarditis: risk—0 cases per 17 000 participants (note, trial n=<20 000; larger surveillance required to confirm rare risks).
Protein	Novavax (NVX-CoV2373) ^{95,96}	Pain (~35%); fatigue (~35%); headache (~40%); muscle pain (~40%)	Myocarditis and pericarditis: risk—1 case in 15 187 participants (note, likely viral myocarditis rather than vaccine-related).
Viral vector	AstraZeneca (ChAdOx1 nCoV-19) ^{97–100}	Pain (~25%); fatigue (~13·7%); headache (~8%); swelling (~4·7%)	Myocarditis and pericarditis: risk—0 reported. TTS: risk—5 cases in 130 000 vaccinated participants. GBS: 38 cases in 10 million people.
Viral vector	Johnson & Johnson–Janssen (Ad26.COV2.S) ^{101–104}	Pain (~45%); fatigue (~35%); headache (~35%); swelling (~15%)	Myocarditis and pericarditis: risk—68 cases from 1·33 million doses. TTS: risk—60 cases from 17 million doses. GBS: 12 cases from 7 million doses.
TTS=thrombosis and thrombocytopenia. GBS=Guillain–Barré syndrome. *Including age 16–55 years and 55 year and older groups.			
Table: Comparison of reactogenicity and serious adverse events between COVID-19 vaccination platforms			

Conclusions and future directions

The cumulative evidence from mechanistic studies, randomised trials, and extensive post-authorisation surveillance shows that mRNA vaccines are both safe and highly effective. mRNA vaccine mechanism of action and transient cytoplasmic mRNA translation without genomic integration, coupled with rapid clearance of both RNA and lipid components, underpins a favourable safety profile that is distinct from gene therapy and persistent viral vector platforms. Across billions of administered doses, serious adverse events have been rare, well characterised, and consistently outweighed by the substantial protection conferred against severe disease, hospitalisation, and death. Effectiveness has been shown across age groups, in pregnancy, and in populations that are immunocompromised, establishing mRNA vaccines as a clinically validated and adaptable platform.

The COVID-19 pandemic underscored the crucial role of science-driven public health policy. Rapid vaccine development and deployment were made possible by decades of foundational research, robust regulatory

frameworks, and coordinated global surveillance systems. Where transparent communication and evidence-based decision making were prioritised, public health benefits were maximised. Conversely, misinformation and erosion of trust highlight the fragility of vaccine confidence and the necessity of sustained investment in scientific literacy, regulatory credibility, and pharmacovigilance.

Looking forward, continued vigilance is essential. Ongoing safety monitoring, long-term follow-up of rare adverse events, and iterative improvements in vaccine design should remain priorities as mRNA technologies expand to new pathogens and indications. Equally important is clear, proactive communication of evidence to clinicians, policy makers, and the public. Strengthening global surveillance infrastructure, manufacturing capacity, and equitable access, particularly in LMICs, will be crucial to ensure that the full public health potential of mRNA vaccines is realised beyond pandemic settings.

The role of community-based blood pressure screening in improving hypertension care

In their recent Viewpoint, Frieden and colleagues argue that mass blood pressure screening diverts resources from improving hypertension care. We present a counterargument that community-based blood pressure screening can complement health-care services by increasing hypertension detection, particularly in populations with limited access to health care. Opportunistic community-based screening can be delivered at relatively low cost and reach individuals who might not otherwise engage with health-care systems. In settings where access to health-care facilities is constrained, such approaches provide an additional route to identifying raised blood pressure and initiating further assessment. When implemented using validated blood pressure devices and standardised protocols, community-based screening can support accurate measurement, although confirmatory diagnosis and long-term management require linkage to health-care facilities. In addition to case detection, screening initiatives contribute to improved awareness of hypertension through community engagement and public health messaging. Increasing detection of raised blood pressure will be essential to improving population-level control. Community-based screening, alongside strengthened primary care, could form part of a broader strategy to address the global burden of hypertension.

Screening for hypertension is highly worthwhile. Major health organizations, including the [U.S. Preventive Services Task Force \(USPSTF\)](#), give hypertension screening an "**A**" **recommendation** because it is a low-risk, highly effective way to prevent life-threatening cardiovascular events. Hypertension—commonly known as high blood pressure—is often called a "silent killer" because it rarely causes symptoms until significant damage has already occurred.

Regaining your voice

Speech is one of the most remarkable and essential human behaviors. We precisely control nearly 100 muscles to produce an exquisitely timed series of breaths and rapid articulator movements that vibrate air in just the right way so that another person can understand our verbalized thoughts. The loss of this ability owing to neurological injuries such as stroke or amyotrophic lateral sclerosis (ALS) is devastating. Yet our understanding of the neural basis of speech—and our efforts to restore this ability—have been limited because of the complexity of speaking and the lack of animal models.

Despite these challenges, neuroscientists have started to unravel the neural code for speech production thanks to opportunities to directly measure people's brain activity during medical procedures such as epilepsy treatment. Such studies revealed that computer algorithms could predict the content of speech from simultaneously recorded neural signals. These discoveries, when combined with 20 years of brain-computer interface (BCI) research showing that the brain still encodes movement intentions even after years of paralysis, suggested that it might be possible to build a speech neuroprosthesis: a device that directly translates brain activity into words, bypassing injured parts of the nervous system. By combining neuro science and artificial intelligence (AI), this effort has made swift progress in just a few years.

Regaining your voice

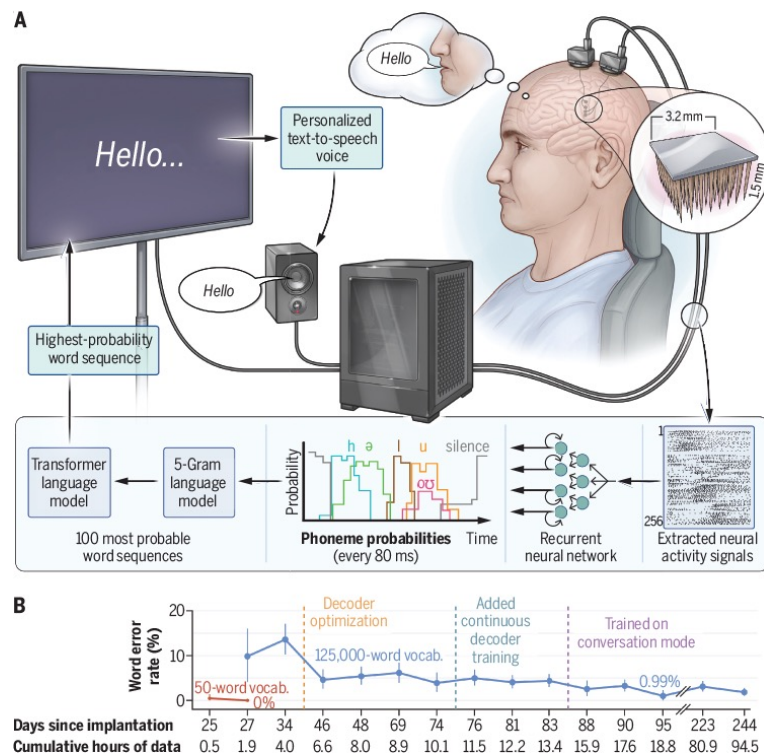
AI speech neuroprostheses can restore day-to-day communication after neurological injury



Our team recently demonstrated an AI-based speech neuroprosthesis capable of restoring day-to-day communication. We worked with a 45-year-old man who could no longer speak intelligibly because of ALS. He volunteered for our academic clinical trial and had **256 microelectrodes implanted across three speech-related regions of his brain (cortical areas 4, 6, and 55b)**. We found that across the population of measured neurons, **distinct spatiotemporal patterns of neural activity occurred for all 39 English phonemes**. This finding enabled us to train deep learning algorithms to predict what phoneme the participant was trying to say at any given moment. **Language models then strung these phoneme sequences together into words and sentences.**

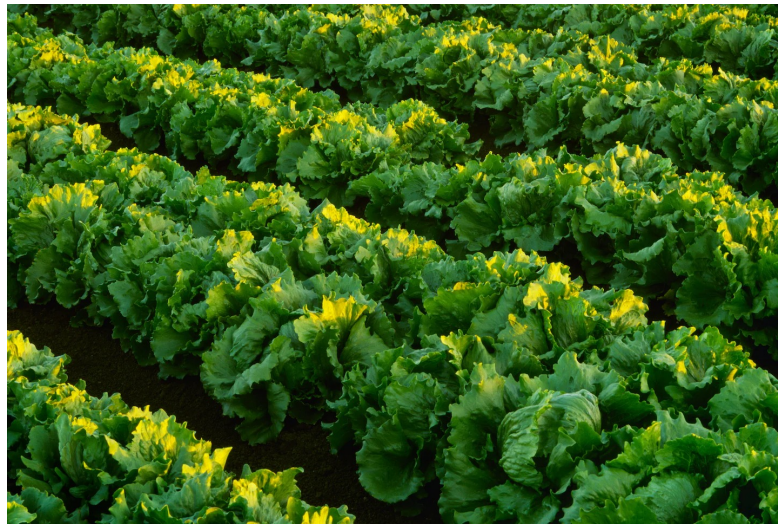
On the first day of its use, the neuroprosthesis achieved 99.6% accuracy with a limited 50-word vocabulary. Given the high signal-to-noise ratio of our intracortical sensors, which capture individual neuronal action potentials, the initial calibration required only 30 min of recording while the participant attempted to speak. On the second day, we expanded the available vocabulary to the whole English dictionary (125,000 words) with 90.2% accuracy. The participant's words appeared on-screen as soon as he tried to say them. When he finished a phrase, it was vocalized by text-to-speech software trained on old audio recordings to sound like his pre-ALS voice. That very day, the first thing he did was use the neuroprosthesis to speak to his 4-yearold daughter, who until then had no memories of being able to understand her dad.

Our speech neuroprosthesis provides a life-changing way to communicate, but it lacks the full range of human expression afforded by our voices. Even when the resulting text is read aloud by a computer, this approach does not capture the prosody that we use to convey emotional nuance. It also does not enable the quick back-and-forth of interactive conversation or the vocal flexibility needed for singing. Fortunately, these paralinguistic elements of voice can also be decoded from cortical activity. Thus, the next frontier for restoring speech is to develop a BCI that essentially acts as a digital vocal tract, transforming neural activity into sounds almost instantaneously.



A speech restoration neuroprosthesis. (A) As the participant tried to speak, neural activity was measured using four microelectrode arrays placed in speech production-related areas of his cortex. An initial AI model predicted the likelihood of each potential phoneme at every time step. Then a pair of language models converted those phoneme probability sequences into the most likely series of words. A computer read the final sentence out loud or sent it as text to his personal computer. **(B)** We quantified the system's accuracy by measuring what percentage of outputted words were incorrect (lower is better) when the participant tried to speak prompted sentences. Performance improved as we accumulated more training data and introduced improvements to the algorithms. Decoding remained consistently accurate for many months.

CDC, FDA link Taco Bell lettuce supplier to multistate cyclosporiasis outbreak



Federal health officials said Thursday that a multistate outbreak of cyclosporiasis that has sickened thousands of people has been linked to shredded iceberg lettuce served at Taco Bell restaurants in five states, confirming key findings first reported by The Washington Post.

The Centers for Disease Control and Prevention and the Food and Drug Administration said traceback investigators identified a single supplier of iceberg lettuce from Mexico used at Taco Bell restaurants in Indiana, Kentucky, Michigan, Ohio and West Virginia. In updates posted to the [CDC webpage](#) and [FDA webpage](#) late Thursday, officials urged consumers not to eat shredded iceberg lettuce from Taco Bell restaurants in those states while the investigation continues.

Taco Bell Corp. added: “While no official advisory has been issued, we believe public health is a shared responsibility among restaurants, their suppliers, and authorities, and we are proud to have consistently acted quickly and proactively to protect our guests. Taco Bell has taken precautionary action, and we encourage all relevant restaurants, retailers, and foodservice operators to do the same.”

Cyclosporiasis ist eine durch den mikroskopisch kleinen, einzelligen Darmparasiten **Cyclospora cayetanensis** verursachte Infektionskrankheit, die zu heftigen, teils langanhaltenden Magen-Darm-Beschwerden führt. Die Infektion tritt weltweit auf – besonders in den Tropen und Subtropen –, sorgt jedoch durch importierte Lebensmittel oder kontaminiertes Wasser regelmäßig für Infektionswellen in Industrienationen.

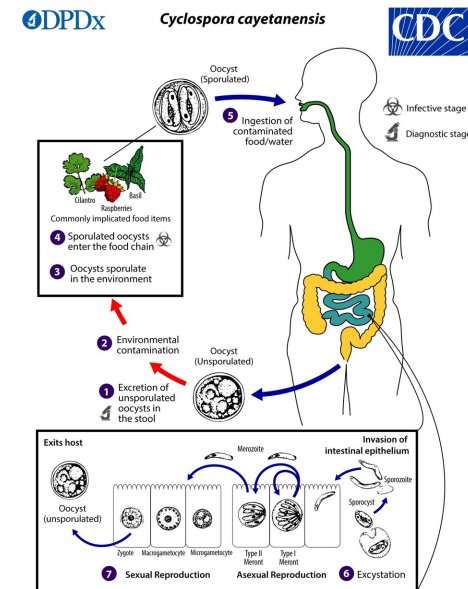
Der Parasit wird fäkal-oral übertragen. Da die vom Wirt ausgeschiedenen Sporen (Oozysten) erst nach Tagen bis Wochen in der Umwelt infektiös werden, ist eine direkte Übertragung von Mensch zu Mensch extrem unwahrscheinlich.

Blattsalate (insbesondere fertige Salatmischungen aus Plastikbeuteln)

Frische Kräuter (wie Koriander und Basilikum)

Beeren (wie Himbeeren, Erdbeeren und Brombeeren)

Zuckererbsen und Zuckerschoten



Diagnose: Die Erkrankung lässt sich über eine laborchemische Untersuchung von Stuhlproben (Nachweis der Oozysten oder mittels PCR-Test) feststellen.

Medikation: Zur gezielten Behandlung wird in der Regel das Antibiotikum **Trimethoprim/Sulfamethoxazole (Cotrimoxazol)** eingesetzt, welches die Krankheitsdauer erheblich verkürzt.