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

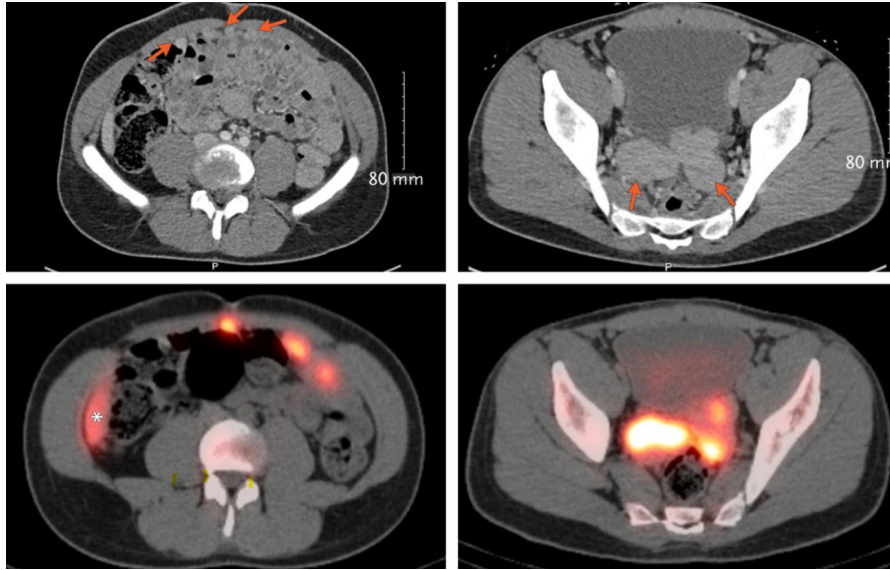
Usually every Wednesday 17:00 - 18:00



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!](#)



CT scans revealed multiple enhancing soft-tissue deposits in the omentum and perirectal space. The technetium-99m-labeled heat-damaged red-cell scan — a nuclear medicine study that identifies splenic tissue by showing where splenic macrophages clear partially lysed red cells — showed intense radiotracer uptake in the omental lesions and perirectal lesions, findings that are consistent with splenosis. Splenosis is the presence of ectopic splenic tissue resulting from intraperitoneal spillage of splenic cells during splenectomy or trauma.

A 19-year-old man who had undergone splenectomy at 5 years of age for hereditary spherocytosis presented to the emergency department with a 1-day history of sharp pain in the right wall of the chest. Physical examination was unremarkable. Serum laboratory studies showed compensated chronic hemolysis. A peripheral-blood smear showed sporadic Howell–Jolly bodies and spherocytes. Computed tomography of the abdomen and pelvis and a technetium-99m-labeled heat-damaged red-cell scan are shown. Which of the following is the most likely diagnosis?

Accessory spleens

Extramedullary hematopoiesis

Lymphoma

Peritoneal carcinomatosis

Splenosis

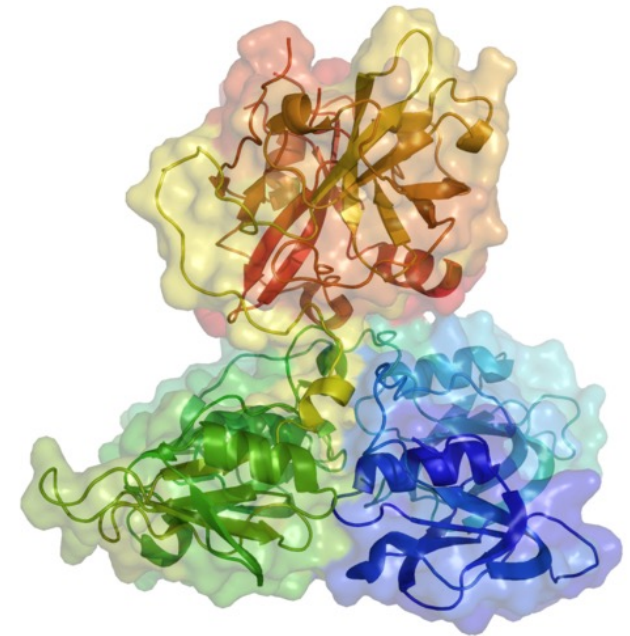
Faktor XI (auch bekannt als **Plasma Thromboplastin Antecedent**, abgekürzt **PTA** oder **Rosenthal-Faktor**) ist ein lebenswichtiges Eiweiß im menschlichen Blut, das eine zentrale Rolle bei der Blutgerinnung (Hämostase) spielt. Als sogenannte Serinprotease (ein Enzym) sorgt er im Zusammenspiel mit anderen Faktoren dafür, dass Wunden verschlossen werden und Blutungen stoppen.

Übersicht zu Funktion, Normalwerten, Mangelerscheinungen und aktuellen medizinischen Entwicklungen:

Funktion im Gerinnungssystem

Faktor XI gehört zum sogenannten **intrinsischen System** der plasmatischen Blutgerinnung.

- **Aktivierung:** Er zirkuliert als inaktive Vorstufe im Blutplasma und wird bei einer Verletzung entweder durch den aktivierten Faktor XII (FXIIa) oder direkt durch Thrombin aktiviert.
- **Kaskade:** Der aktivierte Faktor XIa aktiviert wiederum den **Faktor IX**, wodurch die Gerinnungskaskade weiterläuft und letztendlich ein stabiles Fibringerinnsel entsteht, welches die Wunde verschließt.
- **Bildung:** Produziert wird das Protein hauptsächlich in der **Leber**. Seine Halbwertszeit im Körper beträgt etwa **52 Stunden**

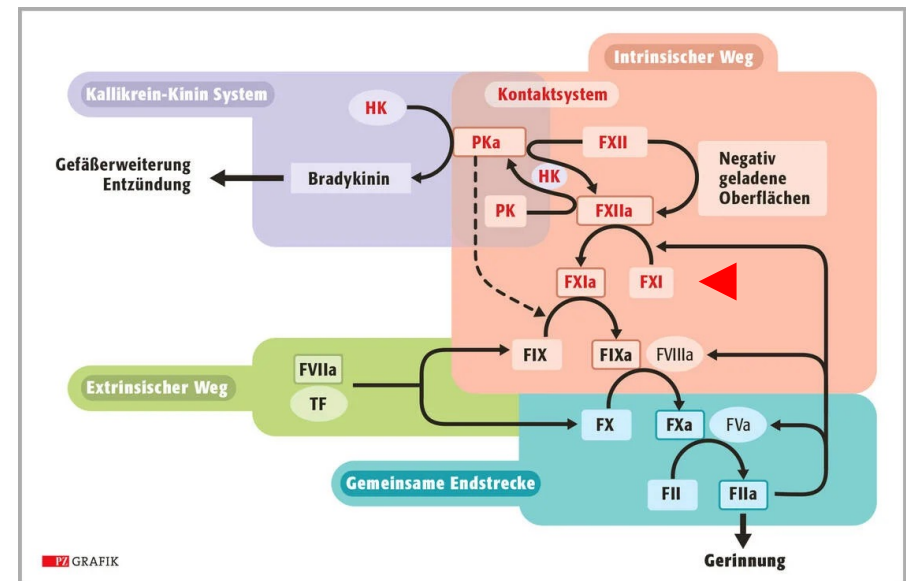


Bänder-/Oberflächenmodell

Faktor-XI-Inhibitoren (oft als „DOAK 2.0“ bezeichnet) und **MACE** (Major Adverse Cardiac Events, also schwerwiegende kardiovaskuläre Ereignisse wie Herzinfarkt, Schlaganfall oder kardiovaskulärer Tod) hängen in der modernen Kardiologie und Hämostaseologie eng zusammen: Das Ziel von Faktor-XI-Hemmern ist es, MACE oder Thromboembolien (z. B. bei Vorhofflimmern) zu verhindern, ohne dabei das unter klassischen Gerinnungshemmern erhöhte Blutungsrisiko zu steigern.

Hintergrund: Faktor XI als neues Therapieziel

- **Wirkungsweise:** Faktor XI ist ein Protein der intrinsischen Gerinnungskaskade. Seine gezielte Hemmung soll die Bildung von Thromben (Blutgerinnseln) stoppen, während die primäre Blutstillung bei Verletzungen (Hämostase) weitgehend erhalten bleibt.
- **Potenzial bezüglich MACE:** Durch diesen Mechanismus erhofft man sich einen effektiven Schutz vor Schlaganfällen und MACE – insbesondere für Patienten, bei denen herkömmliche Gerinnungshemmer (wie direkte orale Antikoagulanzen / DOAKs) ein zu hohes Blutungsrisiko bergen.

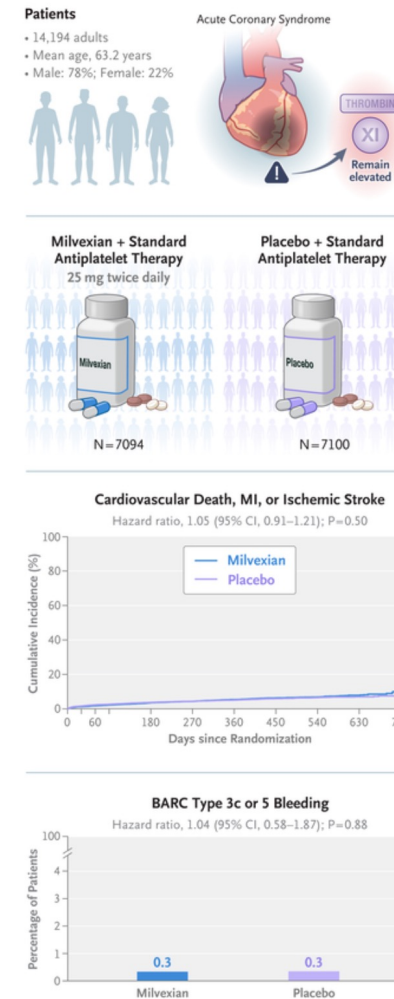


Der Faktor XI Inhibitor Milvexian

Milvexian with Antiplatelet Therapy after Acute Coronary Syndrome Event

Patients are at increased risk for recurrent ischemic events after an acute coronary syndrome event.

Milvexian, an oral factor XIa inhibitor, may reduce the risk of major adverse clinical events with minimal bleeding risk. In this phase 3, randomized, placebo-controlled trial, we evaluated the efficacy and safety of milvexian when added to standard antiplatelet therapy within 7 days after an acute coronary syndrome event. Patients were assigned in a 1:1 ratio to receive oral milvexian (25 mg twice daily) or matched placebo. The primary efficacy outcome was a composite of cardiovascular death, myocardial infarction, or ischemic stroke as evaluated in a time-to-event analysis. The principal safety outcome was Bleeding Academic Research Consortium (BARC) type 3c or 5 bleeding (intracranial or intraocular bleeding that compromises vision or fatal bleeding).



Among patients with myocardial infarction, the risk of recurrent events remains high despite modern pharmacotherapy, including dual antiplatelet therapy, high-dose statins, and the latest generation of drug-eluting stents. Although pharmacotherapy often focuses on platelets, thrombin generation and factor XI levels remain elevated for months after an acute coronary syndrome event, and persistently elevated levels of thrombin generation and factor XI are associated with an increased risk of major adverse cardiovascular events.

Factor XIa inhibition has been considered as an anticoagulant option with a reduced bleeding risk in patients receiving antiplatelet agents because although factor XI is involved in the intrinsic pathway of pathologic thrombus formation, it is not integral to physiologic hemostasis. Mendelian randomization studies have shown a lower risk of venous and arterial thrombosis in patients who have a low factor XI level than in those with a normal level, with little or no increased risk of spontaneous bleeding.

Milvexian (JNJ-70033093; BMS-986177) is an oral, reversible, high-affinity inhibitor of factor XIa, a serine protease involved in the intrinsic pathway of the coagulation cascade.

Patients

The patients who were eligible for enrollment included adults (≥ 18 years of age) who were evaluated within 7 days after an acute coronary syndrome event. The latter was defined as ST-segment elevation myocardial infarction [STEMI], type 1 non-ST-segment elevation myocardial infarction [NSTEMI], or unstable angina with cardiac biomarker positivity. All the patients had undergone cardiac catheterization with percutaneous coronary intervention (PCI) or were being treated conservatively with or without catheterization and had received **standard antiplatelet therapy**, as determined by the investigator. In addition, the patients needed to have at least two of the following risk-enhancing factors associated with an increase in the risk of recurrent ischemic events: an age of 65 years or older, diabetes mellitus, previous myocardial infarction, multivessel coronary artery disease, history of coronary-artery bypass grafting (CABG) before the index event.

Randomization and Treatment

The patients were randomly assigned in a **1:1 ratio to receive milvexian (25 mg twice daily) or matching placebo**.

Outcomes

The primary efficacy outcome was the first occurrence of a **composite of cardiovascular death, myocardial infarction, or ischemic stroke**, as evaluated in a time-to-event analysis. The first major secondary outcome was a composite of cardiovascular death, myocardial infarction, ischemic stroke, major adverse limb event, or symptomatic venous thromboembolism.

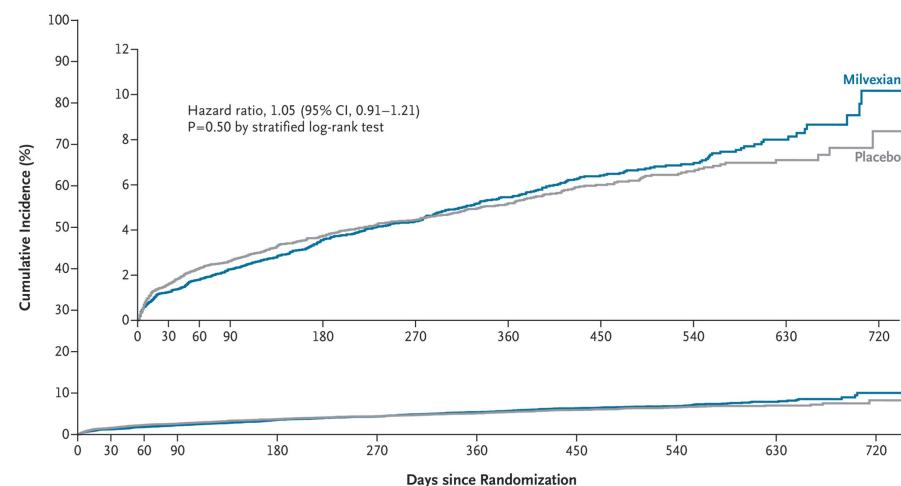
Characteristic	Milvexian (N = 7094)	Placebo (N = 7100)
Age		
Mean — yr	63.1±10.6	63.2±10.5
≥65 yr — no. (%)	3545 (50.0)	3559 (50.1)
Male sex — no. (%)	5542 (78.1)	5543 (78.1)
Geographic region — no. (%)		
Asia	1570 (22.1)	1572 (22.1)
Western Europe	1424 (20.1)	1419 (20.0)
Eastern Europe	1783 (25.1)	1785 (25.1)
North America	454 (6.4)	460 (6.5)
South America	1355 (19.1)	1354 (19.1)
Other	508 (7.2)	510 (7.2)
Medical history — no. (%)		
Diabetes	3014 (42.5)	3154 (44.4)
Previous myocardial infarction other than index event	1606 (22.6)	1569 (22.1)
Previous coronary revascularization	1808 (25.5)	1726 (24.3)
Hypertension	5181 (73.0)	5083 (71.6)
Type of index myocardial infarction — no. (%)		
STEMI	4085 (57.6)	4067 (57.3)
NSTEMI	2615 (36.9)	2644 (37.2)
Unstable angina with elevated cardiac biomarkers	393 (5.5)	389 (5.5)
PCI performed for index myocardial infarction — no. (%)	6516 (91.9)	6496 (91.5)
Medications — no. (%)		
Aspirin	6884 (97.0)	6893 (97.1)
P2Y12 inhibitor or other antiplatelet agent	6885 (97.1)	6880 (96.9)
Statin	6607 (93.1)	6628 (93.4)

Primary and Key Secondary Efficacy Outcomes.

Outcome	Milvexian (N = 7094)		Placebo (N = 7100)		Hazard Ratio (95% CI)
	<i>no. of patients with event (%)</i>	<i>no. of events per 100 person-yr (95% CI)</i>	<i>no. of patients with event (%)</i>	<i>no. of events per 100 person-yr (95% CI)</i>	
Primary outcome					
Cardiovascular death, myocardial infarction, or ischemic stroke	384 (5.4)	5.60 (5.06–6.19)	365 (5.1)	5.33 (4.81–5.90)	1.05 (0.91–1.21)*
Cardiovascular death	110 (1.6)	1.54 (1.28–1.86)	112 (1.6)	1.57 (1.30–1.89)	0.98 (0.75–1.28)
Myocardial infarction	249 (3.5)	3.61 (3.19–4.09)	236 (3.3)	3.43 (3.02–3.89)	1.05 (0.88–1.26)
Ischemic stroke	60 (0.8)	0.85 (0.66–1.10)	46 (0.6)	0.66 (0.49–0.88)	1.30 (0.89–1.91)
Key secondary outcomes					
Cardiovascular death, myocardial infarction, ischemic stroke, major adverse limb event, or symptomatic venous thromboembolism	402 (5.7)	5.87 (5.32–6.47)	386 (5.4)	5.65 (5.11–6.24)	1.04 (0.90–1.20)
Death from any cause, myocardial infarction, or ischemic stroke	430 (6.1)	6.27 (5.70–6.89)	408 (5.7)	5.95 (5.40–6.56)	1.05 (0.92–1.21)
Cardiovascular death	110 (1.6)	1.54 (1.28–1.86)	112 (1.6)	1.57 (1.30–1.89)	0.98 (0.75–1.28)
Death from any cause	158 (2.2)	2.21 (1.89–2.59)	164 (2.3)	2.30 (1.97–2.68)	0.96 (0.77–1.20)

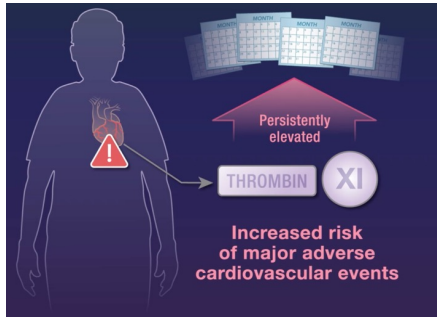
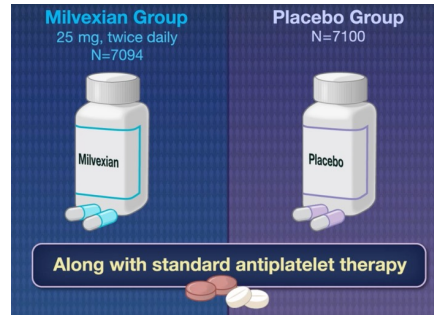
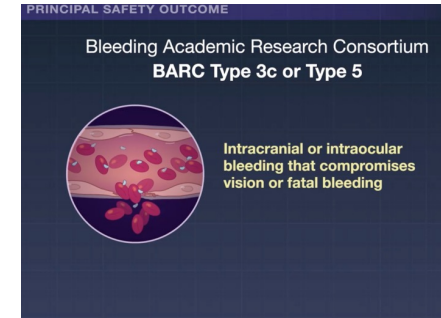
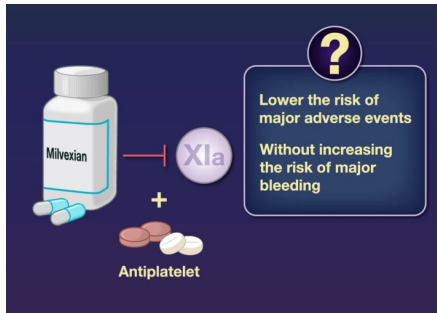
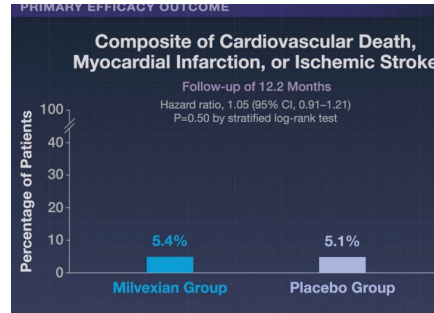
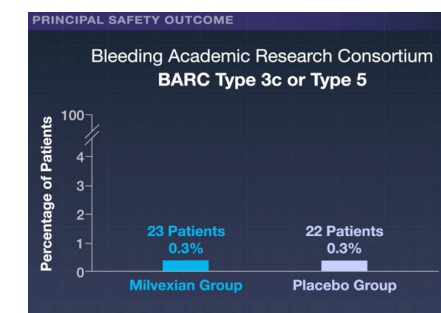
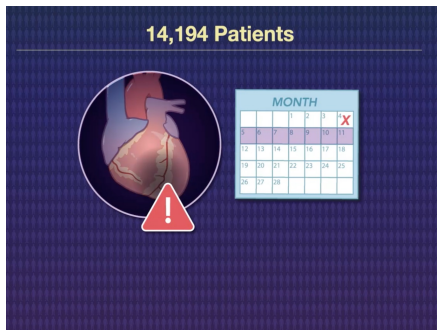
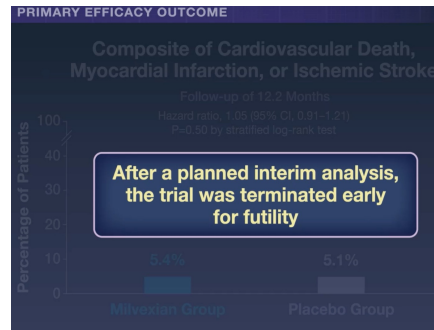
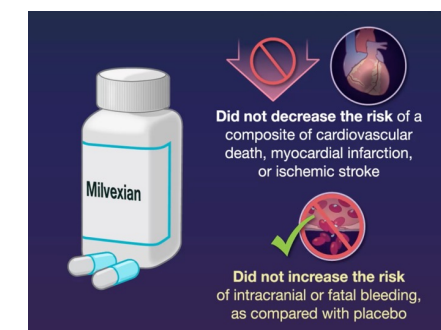
Safety

Outcome	Milvexian (N = 7008)		Placebo (N = 7027)		Hazard Ratio (95% CI)
	no. of patients with event (%)	no. of events per 100 person-yr (95% CI)	no. of patients with event (%)	no. of events per 100 person-yr (95% CI)	
Principal safety outcome†					
BARC type 3c or 5 bleeding	23 (0.3)	0.37 (0.25–0.56)	22 (0.3)	0.36 (0.24–0.54)	1.04 (0.58–1.87)‡
Key secondary safety outcomes					
BARC type 3b, 3c, or 5 bleeding	62 (0.9)	1.01 (0.79–1.29)	64 (0.9)	1.04 (0.82–1.33)	0.97 (0.68–1.37)
Type 3b	40 (0.6)	0.65 (0.48–0.89)	42 (0.6)	0.68 (0.51–0.93)	0.95 (0.62–1.47)
Type 3c	14 (0.2)	0.23 (0.13–0.38)	16 (0.2)	0.26 (0.16–0.43)	0.87 (0.43–1.79)
Type 5	9 (0.1)	0.15 (0.08–0.28)	6 (0.1)	0.10 (0.04–0.22)	1.50 (0.53–4.21)
GUSTO severe or life-threatening bleeding event	27 (0.4)	0.44 (0.30–0.64)	23 (0.3)	0.37 (0.25–0.56)	1.17 (0.67–2.04)
ISTH major bleeding	105 (1.5)	1.71 (1.41–2.07)	102 (1.5)	1.67 (1.37–2.02)	1.03 (0.78–1.35)
Non-CABG-related TIMI major bleeding	49 (0.7)	0.80 (0.60–1.05)	46 (0.7)	0.75 (0.56–1.00)	1.06 (0.71–1.59)
BARC type 2 bleeding	363 (5.2)	6.11 (5.51–6.77)	318 (4.5)	5.34 (4.79–5.96)	1.14 (0.98–1.33)
Adverse events					
Any adverse event	3656 (52.2)	—	3583 (51.0)	—	—
Adverse event leading to treatment discontinuation	318 (4.5)	—	333 (4.7)	—	—
Serious adverse event	819 (11.7)	—	790 (11.2)	—	—
Adverse event leading to death	71 (1.0)	—	73 (1.0)	—	—



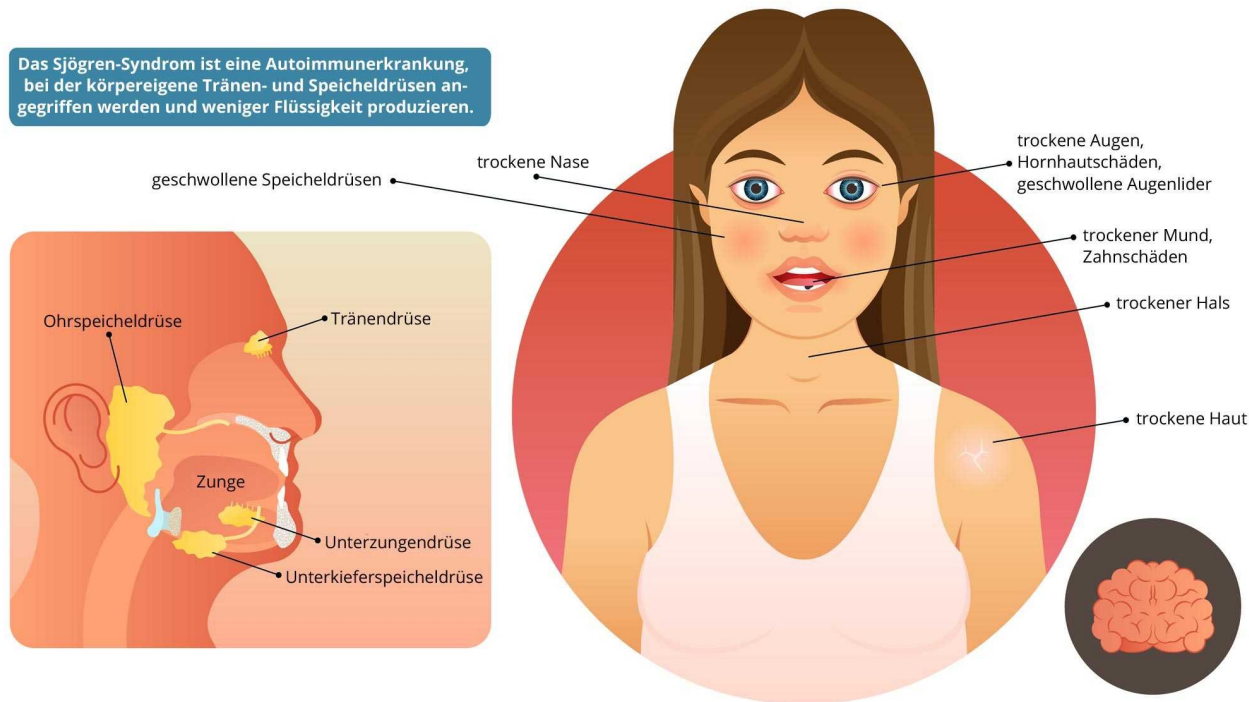
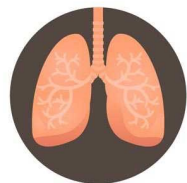
Primary Efficacy Outcome.

Shown is the cumulative incidence of the primary outcome (a composite of cardiovascular death, myocardial infarction, or ischemic stroke) in the milvexian group and the placebo group. After a planned interim analysis that was based on 556 adjudicated efficacy end points, the trial was terminated for futility.

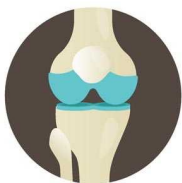


Sjögren-Syndrom

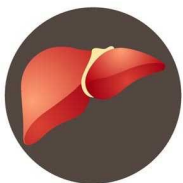
Das Sjögren-Syndrom ist eine Autoimmunerkrankung, bei der körpereigene Tränen- und Speicheldrüsen angegriffen werden und weniger Flüssigkeit produzieren.



Lungenentzündung



Gelenkschmerzen



Leberschäden



Verdauungsprobleme



Muskelschmerzen



Scheidentrockenheit



RTA

- **Anti-SS-A (auch Anti-Ro genannt):** Dies ist der **wichtigste und sensitivste Marker**. Er lässt sich bei etwa **50 % bis 70 %** der Patientinnen und Patienten nachweisen. (Hinweis: Die Antikörper richten sich oft gegen zwei Proteine, Ro52 und Ro60).
- **Anti-SS-B (auch Anti-La genannt):** Dieser Antikörper tritt meist zusammen mit Anti-SS-A auf. Er hat eine geringere Sensitivität, gilt aber mit über **90 % als hochspezifisch** für das Sjögren-Syndrom.

Das **Sjögren-Syndrom** ist eine chronisch-entzündliche Autoimmunerkrankung, bei der das Immunsystem vor allem die feuchtigkeitbildenden Drüsen (Tränen- und Speicheldrüsen) angreift und schädigt.

Häufigste Symptome (Sicca-Syndrom)

- **Augen:** Trockenheit, Brennen, Fremdkörpergefühl („wie Sand im Auge“) durch verringerte Tränenproduktion.
- **Mund:** Ausgeprägte Mundtrockenheit, Schluckbeschwerden, erhöhte Kariesanfälligkeit.
- **Weitere Schleimhäute:** Trockenheit in der Nase, den Atemwegen oder im Vaginalbereich.
- **Allgemeinbeschwerden:** Starke Erschöpfung (Fatigue), Gelenk- und Muskelschmerzen, geschwollene Speicheldrüsen oder ein Raynaud-Syndrom (weiße/blaue Finger bei Kälte).

Formen der Erkrankung

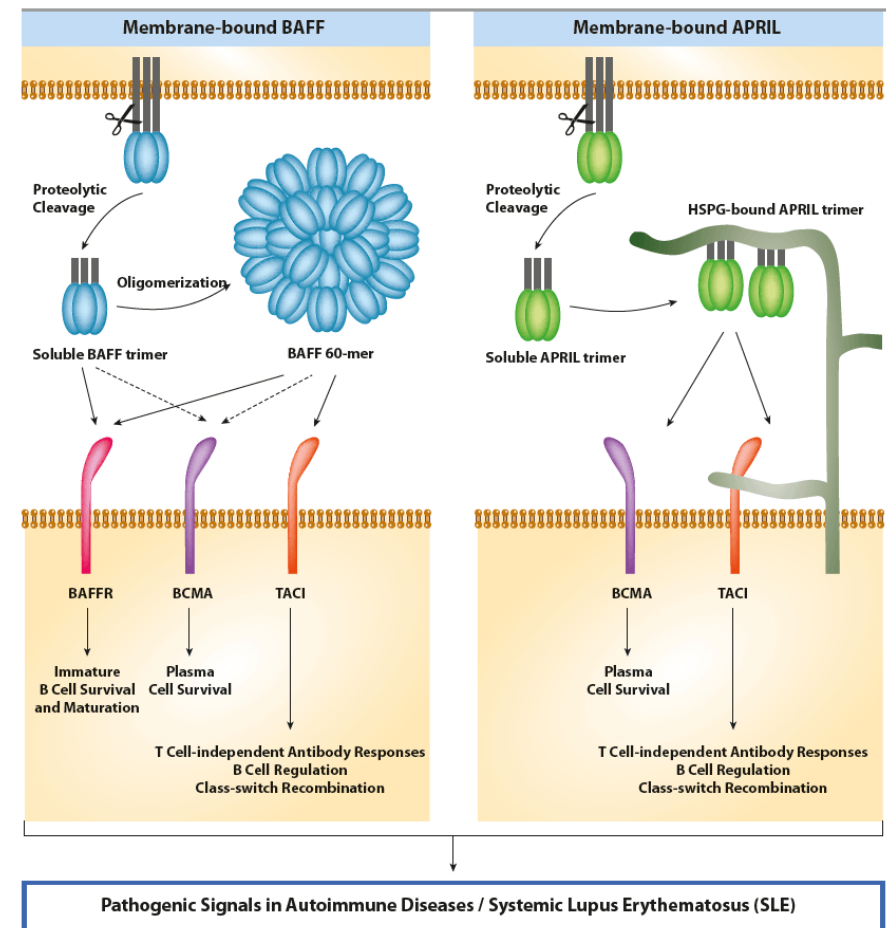
- **Primäres Sjögren-Syndrom:** Tritt eigenständig auf.
- **Sekundäres Sjögren-Syndrom:** Entwickelt sich im Begleitverlauf einer anderen rheumatischen Autoimmunerkrankung (z. B. rheumatoide Arthritis, Lupus erythematodes oder systemische Sklerose).
- **Geschlechterverteilung:** Etwa 9 von 10 Betroffenen sind Frauen.

BAFF steht für *B-cell activating factor* (B-Zell-aktivierender Faktor). Es handelt sich um ein körpereigenes Zytokin (ein Signalprotein des Immunsystems). Produziert wird es vor allem von Zellen des angeborenen Immunsystems wie Monozyten, Makrophagen und dendritischen Zellen.

Die Verbindung zu den Lymphozyten

Lymphozyten unterteilen sich im Wesentlichen in T-Zellen, B-Zellen und Natürliche Killerzellen. **BAFF steuert gezielt die B-Lymphozyten:**

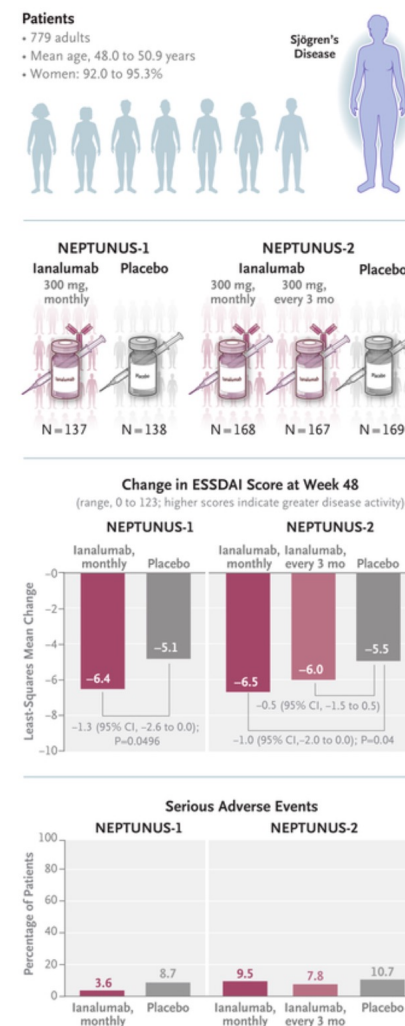
- **Reifung und Überleben:** B-Lymphozyten benötigen BAFF, um im Körper zu überleben und zu reifen. Ohne dieses Signal sterben unreife B-Zellen vorzeitig ab.
- **Andockstellen (Rezeptoren):** Auf ihrer Oberfläche besitzen B-Lymphozyten spezielle Rezeptoren (insbesondere den *BAFF-R*), an die das BAFF-Protein wie ein Schlüssel ins Schloss andockt, um das Überlebenssignal ins Zellinnere weiterzuleiten.
- **Antikörperproduktion:** BAFF regt die B-Zellen dazu an, sich zu Plasmazellen weiterzuentwickeln, welche wiederum Antikörper zur Krankheitsabwehr ausschütten.



Ianalumab for the Treatment of Patients with Sjögren's Disease

Sjögren's disease is a complex, systemic autoimmune disease with no approved targeted therapies. Ianalumab is an IgG1 monoclonal antibody with a dual mechanism of action, depleting B cells through antibody-dependent cellular cytotoxicity and inhibiting B-cell activation and survival through blockade of B-cell activating factor receptor.

We conducted two 52-week, double-blind, randomized, placebo-controlled trials involving patients with active Sjögren's disease. Patients in the NEPTUNUS-1 trial were assigned in a 1:1 ratio to receive subcutaneous ianalumab (300 mg monthly) or placebo; patients in the NEPTUNUS-2 trial were assigned in a 1:1:1 ratio to receive 300 mg of ianalumab monthly or every 3 months or placebo. The primary end point was the change from baseline in the score on the European Alliance of Associations for Rheumatology (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) at week 48 (scores range from 0 to 123, with higher scores indicating greater disease activity). The first key secondary end point in the hierarchical plan for the NEPTUNUS-1 trial was an ESSDAI response (≥ 5 -point reduction) at week 48; for the NEPTUNUS-2 trial, it was the change from baseline in the score on the Sjögren's Syndrome Symptom Diary (SSSD) or EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) at week 48.



Sjögren's disease is a systemic autoimmune disease characterized by lymphocytic infiltration of exocrine glands, leading to glandular dysfunction and serious complications. It is among the most prevalent rheumatic autoimmune diseases, affecting women more frequently than men (by a ratio of 9:1). Sjögren's disease manifests with a wide range of symptoms, including the cardinal features of dryness, fatigue, and joint pain. In addition, reports suggest that 30 to 40% of patients also have systemic manifestations that further increase disease burden and impair quality of life. The risk of B-cell lymphoma is 15 to 20 times as high among persons with Sjögren's disease as in the general population.

Currently, there are no approved targeted therapies available for the treatment of Sjögren's disease. B-cell depletion through antibody-dependent cellular cytotoxicity or BAFF inhibition alone with rituximab or belimumab, respectively, has shown inconsistent efficacy. In contrast, combination therapy (rituximab plus belimumab), which counteracts post-rituximab BAFF up-regulation, enhances B-cell depletion in salivary glands as compared with monotherapy, findings that support a synergistic effect.

Ianalumab is an afucosylated, fully human IgG1 monoclonal antibody targeting B cells through a dual mechanism of action, combining enhanced depletion of B cells through antibody-dependent cellular cytotoxicity and inhibition of B-cell activation and survival thorough BAFF receptor (BAFF-R) blockade.

Trial Design and Oversight

We conducted two phase 3, multicenter, double-blind, randomized, placebo-controlled trials to evaluate the efficacy and safety of ivalumab in patients with Sjögren's disease.

Patients

Patients 18 years of age or older who fulfilled the American College of Rheumatology (ACR)–EULAR 2016 classification criteria for Sjögren's disease and who had received a diagnosis within the past 7.5 years were eligible. Patients had to have active Sjögren's disease, as defined by an ESSDAI score of 5 or more at screening (scores range from 0 to 123, with higher scores indicating greater disease activity). Although activity in any ESSDAI domain was permitted, a score of 5 or more within eight domains (constitutional, lymphadenopathy, glandular, articular, cutaneous, renal, hematologic, and biologic) was required for inclusion.

End Points

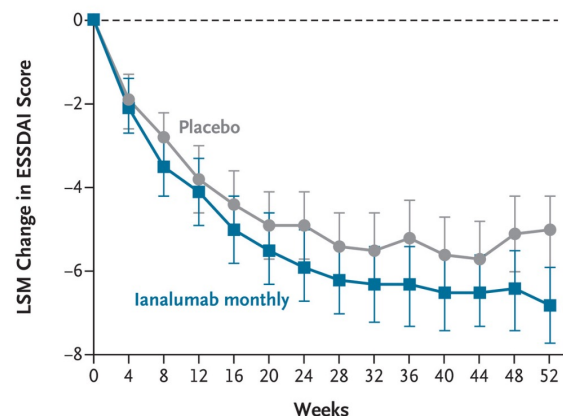
The primary objective of both trials was to **show the superiority of ivalumab over placebo** on the basis of the change from baseline in the ESSDAI score at week 48. Although ESSDAI scores have a theoretical range of 0 to 123, they rarely exceed 40, with scores greater than 13 indicating high disease activity.

Safety during the 52-Week Treatment Period (Safety Analysis Population).

Characteristic	NEPTUNUS-1 Trial		NEPTUNUS-2 Trial		
	Ianalumab Monthly (N=137)	Placebo (N=138)	Ianalumab Monthly (N=168)	Ianalumab Every 3 Mo (N=167)	Placebo (N=169)
Age — yr	48.8±11.7	48.0±13.8	49.6±11.4	50.4±12.7	50.9±12.8
Female sex — no. (%)	127 (92.7)	127 (92.0)	158 (94.0)	159 (95.2)	161 (95.3)
Race or ethnic group — no. (%)†					
White	77 (56.2)	78 (56.5)	98 (58.3)	109 (65.3)	96 (56.8)
Black	7 (5.1)	5 (3.6)	11 (6.5)	7 (4.2)	7 (4.1)
Asian	15 (10.9)	25 (18.1)	42 (25.0)	36 (21.6)	38 (22.5)
American Indian or Alaskan Native	10 (7.3)	16 (11.6)	9 (5.4)	8 (4.8)	22 (13.0)
Native Hawaiian or other Pacific Islander	1 (0.7)	0	0	1 (0.6)	0
Other	27 (19.7)	14 (10.1)	8 (4.8)	6 (3.6)	6 (3.6)
Time since diagnosis of Sjögren's disease — yr	3.0±2.3	2.4±2.1	2.7±2.3	3.3±2.4	2.9±2.2
ESSDAI total score‡					
Mean	12.7±6.8	12.6±6.7	11.7±5.8	11.5±6.2	12.1±5.7
>13 — no. (%)	51 (37.2)	48 (34.8)	52 (31.0)	41 (24.6)	47 (27.8)
ESSPRI total score§	6.4±2.0	6.0±2.2	6.3±2.1	6.2±2.2	6.3±2.2
SSSD score¶	6.2±1.9	5.7±2.2	6.1±1.9	6.1±2.1	6.2±2.0
Salivary flow — ml/min					
Stimulated	0.62±0.58	0.65±0.49	0.62±0.59	0.56±0.68	0.70±0.69
Unstimulated	0.15±0.19	0.16±0.19	0.13±0.17	0.14±0.34	0.15±0.20
Positive anti-ro (SSA) status — no. (%)	125 (91.2)	132 (95.7)	160 (95.2)	161 (96.4)	158 (93.5)
Positive rheumatoid factor status — no. (%)	86 (62.8)	85 (61.6)	87 (51.8)	95 (56.9)	102 (60.4)
Glandular-predominant phenotype — no. (%)**	60 (43.8)	43 (31.2)	73 (43.5)	82 (49.1)	80 (47.3)
Use of disease-modifying antirheumatic drugs — no. (%)					
Any	85 (62.0)	94 (68.1)	109 (64.9)	100 (59.9)	117 (69.2)
Hydroxychloroquine	65 (47.4)	78 (56.5)	95 (56.5)	82 (49.1)	103 (60.9)
Methotrexate	29 (21.2)	22 (15.9)	22 (13.1)	21 (12.6)	26 (15.4)
Azathioprine	4 (2.9)	14 (10.1)	9 (5.4)	14 (8.4)	10 (5.9)
Use of systemic glucocorticoid — no. (%)	43 (31.4)	47 (34.1)	43 (25.6)	42 (25.1)	44 (26.0)
≥5 mg/day	35 (25.5)	40 (29.0)	40 (23.8)	39 (23.4)	33 (19.5)
Background immunosuppressive therapy — no. (%)††	95 (69.3)	101 (73.2)	118 (70.2)	108 (64.7)	127 (75.1)
Any associated autoimmune rheumatic disease — no. (%)‡‡	16 (11.7)	15 (10.9)	18 (10.7)	16 (9.6)	24 (14.2)

Category†	NEPTUNUS-1 Trial		NEPTUNUS-2 Trial		
	Ianalumab Monthly (N=137)	Placebo (N=138)	Ianalumab Monthly (N=168)	Ianalumab Every 3 Mo (N=167)	Placebo (N=169)
Median duration of exposure to Ianalumab or placebo (IQR) — wk	52.1 (52.0–52.3)	52.1 (51.9–52.3)	52.1 (51.9–52.4)	52.1 (52.0–52.4)	52.1 (52.0–52.4)
≥1 Adverse event — no. (%)	116 (84.7)	111 (80.4)	146 (86.9)	145 (86.8)	145 (85.8)
Mild	54 (39.4)	46 (33.3)	72 (42.9)	78 (46.7)	57 (33.7)
Moderate	57 (41.6)	57 (41.3)	65 (38.7)	58 (34.7)	78 (46.2)
Severe	5 (3.6)	8 (5.8)	9 (5.4)	9 (5.4)	10 (5.9)
Serious adverse event — no. (%)	5 (3.6)	12 (8.7)	16 (9.5)	13 (7.8)	18 (10.7)
Death — no. (%)	0	1 (0.7)	0	0	0
Adverse event considered to be related to trial regimen — no. (%)‡	62 (45.3)	48 (34.8)	90 (53.6)	82 (49.1)	69 (40.8)
Adverse event leading to discontinuation of trial regimen — no. (%)	5 (3.6)	5 (3.6)	14 (8.3)	11 (6.6)	6 (3.6)
Serious adverse event leading to discontinuation of trial regimen — no. (%)	1 (0.7)	3 (2.2)	5 (3.0)	2 (1.2)	0
Infection or infestation — no. (%)	78 (56.9)	81 (58.7)	92 (54.8)	98 (58.7)	113 (66.9)
Serious adverse event involving infection	3 (2.2)	1 (0.7)	5 (3.0)	5 (3.0)	8 (4.7)
Opportunistic infection§	0	0	1 (0.6)	1 (0.6)	1 (0.6)
Lymphopenia — no. (%)	6 (4.4)	4 (2.9)	1 (0.6)	1 (0.6)	2 (1.2)
Decrease in IgG or IgM level — no./total no. (%)					
IgG level <LLN for ≥12 wk	5/134 (3.7)	0/138	0/165	2/165 (1.2)	0/167
IgM level <LLN for ≥12 wk	15/132 (11.4)	1/133 (0.8)	29/162 (17.9)	14/159 (8.8)	1/161 (0.6)
IgG level <LLN at any given visit	7/137 (5.1)	1/138 (0.7)	5/168 (3.0)	10/167 (6.0)	2/169 (1.2)
Cancer — no. (%)	0	1 (0.7)	1 (0.6)	3 (1.8)	0
Adverse events affecting ≥10% of patients in any group — no. (%)¶					
Local injection-site reaction	37 (27.0)	4 (2.9)	50 (29.8)	39 (23.4)	6 (3.6)
Upper respiratory tract infection	23 (16.8)	23 (16.7)	36 (21.4)	34 (20.4)	30 (17.8)
Nasopharyngitis	21 (15.3)	20 (14.5)	20 (11.9)	14 (8.4)	28 (16.6)
Systemic injection-related reaction**	19 (13.9)	1 (0.7)	25 (14.9)	22 (13.2)	14 (8.3)
Urinary tract infection	11 (8.0)	13 (9.4)	16 (9.5)	18 (10.8)	18 (10.7)
Headache	6 (4.4)	14 (10.1)	15 (8.9)	8 (4.8)	11 (6.5)
Covid-19	6 (4.4)	12 (8.7)	8 (4.8)	16 (9.6)	16 (9.5)

A NEPTUNUS-1 Trial

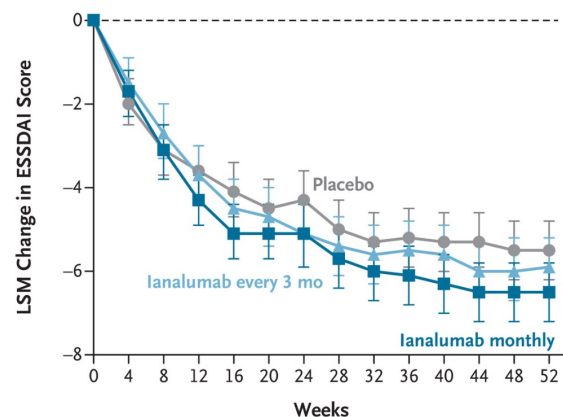


No. at Risk

Placebo	138	137	137	131	134	132	131	126	126	128	119	118	123	115
Ianalumab monthly	137	131	131	127	123	121	120	117	115	119	118	116	120	116

	Ianalumab Monthly (N=137)	Placebo (N=138)
LSM Change at Wk 48 (95% CI)	-6.4±0.5 (-7.4 to -5.5)	-5.1±0.5 (-6.0 to -4.2)
Difference in LSM Change (95% CI)	-1.3±0.7 (-2.6 to 0.0)	
P value	0.0496	

B NEPTUNUS-2 Trial

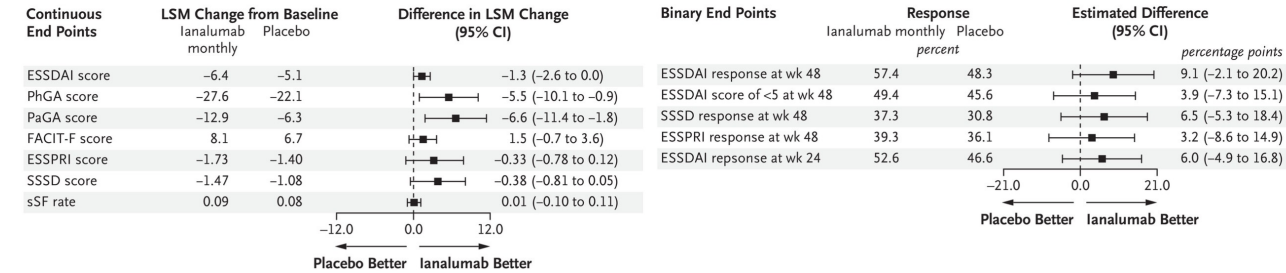


	Ianalumab Monthly (N=168)	Ianalumab Every 3 mo (N=167)	Placebo (N=169)
LSM Change at Wk 48 (95% CI)	-6.5±0.4 (-7.2 to -5.8)	-6.0±0.4 (-6.7 to -5.2)	-5.5±0.4 (-6.2 to -4.8)
Difference in LSM Change vs. Placebo (95% CI)	-1.0±0.5 (-2.0 to 0.0)	-0.5±0.5 (-1.5 to 0.5)	
P value	0.04		

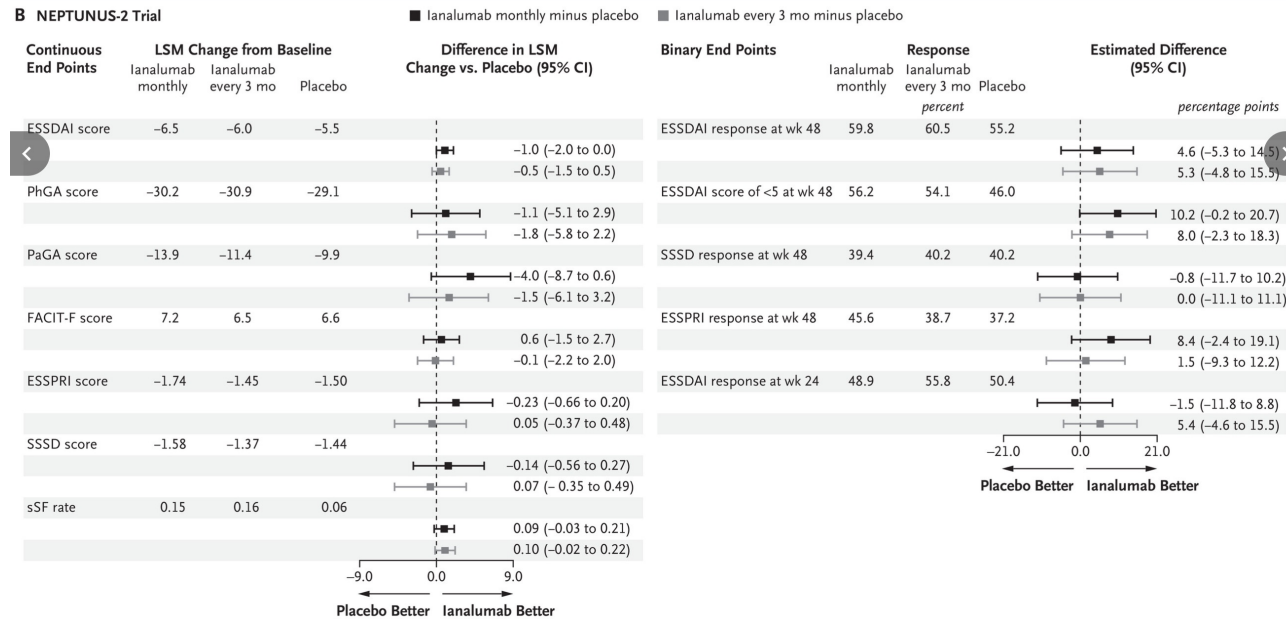
Change in ESSDAI Score over Time (Full Analysis Population).

The primary end point of both the NEPTUNUS-1 trial (Panel A) and the NEPTUNUS-2 trial (Panel B) was the change from baseline in the score on the European Alliance of Associations for Rheumatology (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) at week 48 (scores range from 0 to 123, with higher scores indicating greater disease activity). The full analysis population included all the patients who underwent randomization and received any dose of Ianalumab or placebo. Data are presented as least-squares means (LSMs) and 95% confidence intervals. Least-squares means and P values are derived from an analysis-of-covariance model, with trial-group assignment, ESSDAI stratum at baseline, and geographic region as factors and baseline score as a covariate. No multiplicity adjustments were conducted for estimates and 95% confidence intervals; confidence intervals should not be used in place of hypothesis testing. Plus-minus values are means ±SE. I bars indicate 95% confidence intervals.

A NEPTUNUS-1 Trial



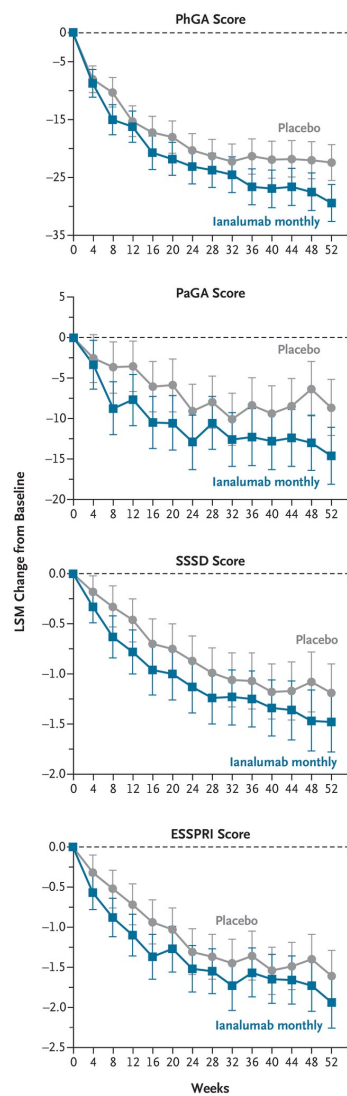
B NEPTUNUS-2 Trial



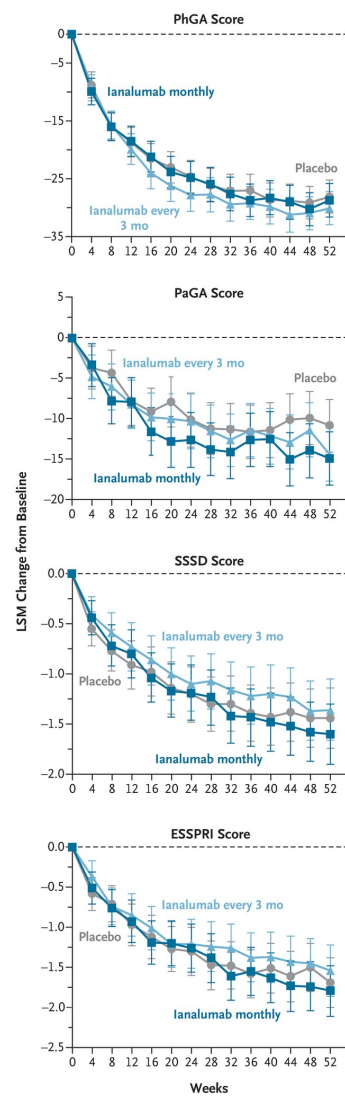
Forest Plot of Primary and Key Secondary Efficacy End Points (Full Analysis Population).

Scores on the Physician's Global Assessment (PhGA) and Patient's Global Assessment (PaGA) were assessed on a visual-analogue scale from 0 to 100, with higher scores indicating greater disease activity. Sjögren's Syndrome Symptom Diary (SSSD) scores and EULAR Sjögren's Syndrome Patient-Reported Index (ESSPRI) scores range from 0 to 10, with higher scores indicating worse symptoms. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores range from 0 to 52, with higher scores indicating less fatigue. For the purposes of presentation, the line segments showing least-squares mean differences and 95% confidence intervals for the continuous end points are transformed in the following ways: multiplied by -1 for ESSDAI, PhGA, and PaGA scores; multiplied by 10 for stimulated salivary flow (sSF) rate; and multiplied by -10 for ESSPRI and SSSD scores. With respect to binary end points, an ESSDAI response is defined as a reduction from baseline of at least 5 points, an SSSD response as a reduction of at least 2.0 points in patients with a baseline SSSD score of 3 or higher, and an ESSPRI response as a reduction of at least 2.3 points in patients with a baseline ESSPRI score of 3 or higher. No multiplicity adjustments were conducted for estimates and 95% confidence intervals; confidence intervals should not be used in place of hypothesis testing.

A NEPTUNUS-1 Trial



B NEPTUNUS-2 Trial



Physician- and Patient-Reported Outcomes (Full Analysis Population).

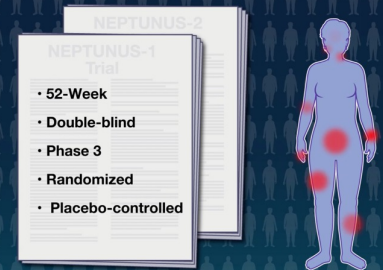
Data are presented as least-squares means and 95% confidence intervals. Least-squares means are derived from an analysis-of-covariance model, with trial-group assignment, ESSDAI stratum at baseline, and geographic region as factors and respective baseline score as the covariate. No multiplicity adjustments were conducted for estimates and 95% confidence intervals; confidence intervals should not be used in place of hypothesis testing.



Sjögren's Disease

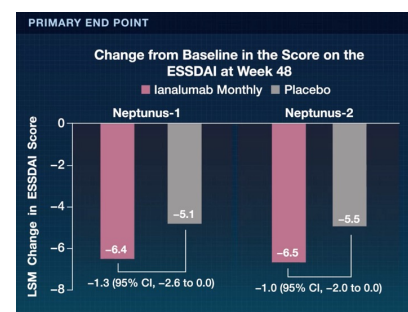
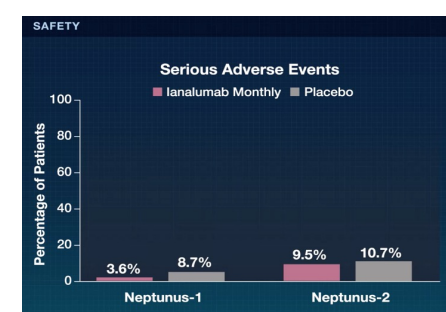
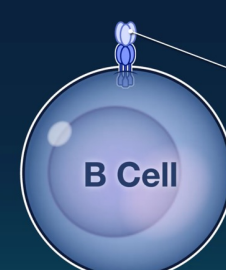
Systemic autoimmune disease characterized by lymphocytic infiltration of exocrine glands

- Glandular dysfunction
- Serious complications



NEPTUNUS-1 Trial

- 52-Week
- Double-blind
- Phase 3
- Randomized
- Placebo-controlled

B-Cell Activating Factor (BAFF)

Central to the pathogenesis of Sjögren's disease

B Cell

NEPTUNUS-1

lanalumab
300 mg

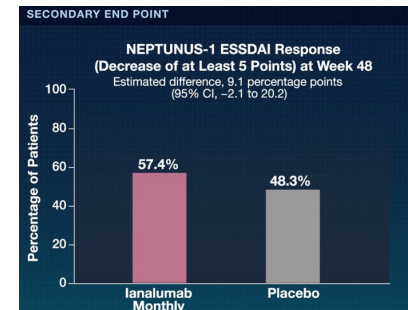
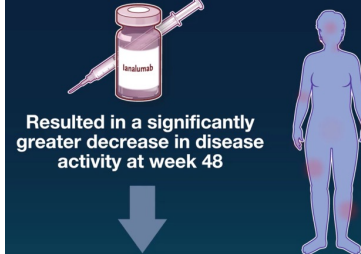


N=137

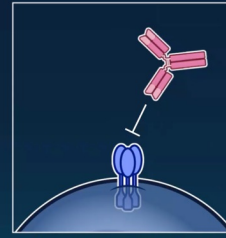
Placebo



N=138

Resulted in a significantly greater decrease in disease activity at week 48



IgG1 Monoclonal Antibody

B-Cell Activating Factor Receptor (BAFF-R)

NEPTUNUS-2

lanalumab
300 mg Monthly



N=168

lanalumab
300 mg Every 3 Months

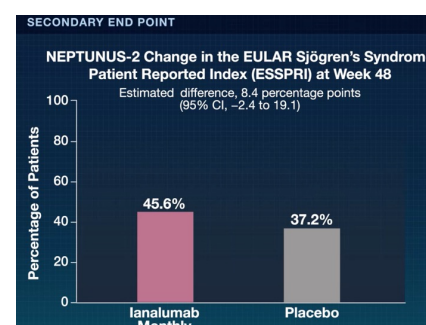


N=167

Placebo
Monthly



N=169



lanalumab has moved the field beyond biologic plausibility to a concordant, albeit modest, effect on systemic disease activity.

Infective endocarditis

An infection of the endocardial surface of the heart. Intractable congestive heart failure may result. If left untreated it is generally fatal.

Subacute endocarditis — symptoms are subtle and non-specific (in blue)

Roth spots

(retinal haemorrhages with small clear centres — these are rare)

Flu-like syndrome
Low grade/intermittent fever

Intra-cerebral pathology

Embolic stroke
Multiple cerebral microabscesses
Intracerebral haemorrhage
Delerium

Conjunctival haemorrhage

Stiff neck

Pallor

Pericardial rub
Pleural friction rub

Arrhythmias
Heart murmurs

Splenomegaly

Janeway lesions
(non-tender macules on the palms and soles)

Anorexia and weight loss

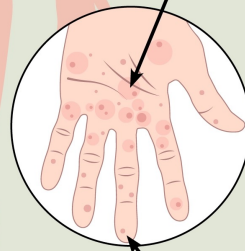
Pleuritic pain

Abdominal symptoms
(right upper quadrant pain, vomiting, appendicitis-like pain)

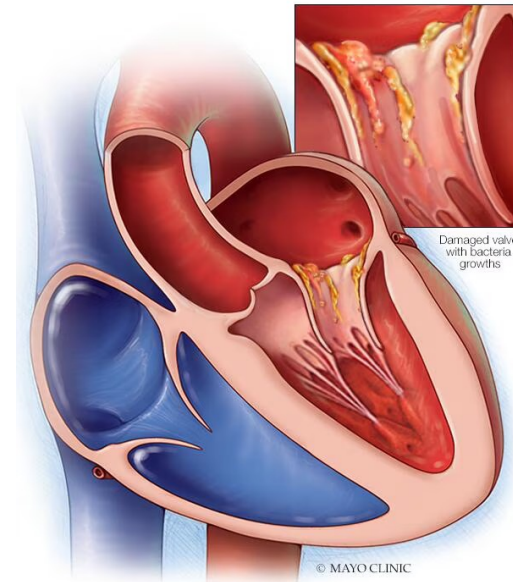


Subungual (splinter) haemorrhages
(dark red linear lesions in the nail bed)

Petechiae



Osler nodes
(tender subcutaneous nodules in the pulps of the fingers)



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Diagnosis of Infective Endocarditis Modified Duke's Criteria

Major Criteria

1. Bacteraemia by typical organism^a
2. Positive echo OR new regurgitant murmur

Minor Criteria

1. Predisposition: abnormal valve^b or IVDU
2. Fever
3. Vascular phenomenon^c
4. Immune phenomena^d
5. Bacteraemia from atypical organism

Definite Diagnosis = 2 major / 1 major + 3 minor / 5 minor

Die therapeutischen Säulen gliedern sich wie folgt:

Antibiotische Therapie (Medikamentös)

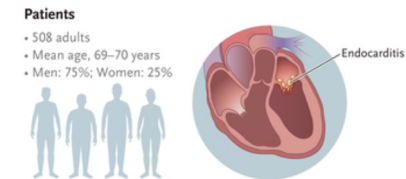
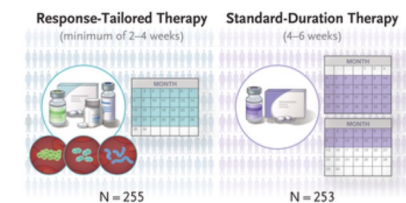
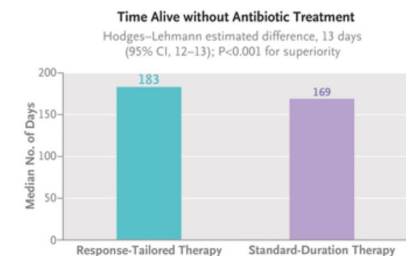
Die medikamentöse Bekämpfung der Erreger (meist Staphylokokken, Streptokokken oder Enterokokken) bildet das Fundament der Behandlung.

- **Kalkulierter (empirischer) Start:** Unmittelbar nach der Abnahme von Blutkulturen zur Erregerbestimmung wird eine sofortige, breite intravenöse Antibiotikakombination (z. B. Vancomycin und Ceftriaxon) begonnen, um keine Zeit zu verlieren.
- **Gezielte Therapie:** Sobald der genaue Erreger und dessen Resistenzen feststehen, wird auf ein spezifisch wirksames Antibiotikum (z. B. gezielte Penicilline oder Aminoglykoside) umgestellt.
- **Dauer der Behandlung:** Die intravenöse Gabe erstreckt sich standardmäßig über **4 bis 6 Wochen**. Bei körpereigenen Herzklappen (Nativklappen) reichen manchmal 4 Wochen; bei infizierten künstlichen Herzklappen (Klappenprothesen) oder bestimmten Erregern wie Enterokokken sind mindestens 6 Wochen zwingend vorgeschrieben

Response-Tailored or Standard-Duration Antibiotic Treatment for Infective Endocarditis

In patients with infective endocarditis on the left side of the heart, the current recommendation of up to 6 weeks of antibiotic therapy is based largely on expert consensus opinion. Whether a clinical response–tailored antibiotic management strategy can shorten treatment duration without compromising safety is unclear.

In this international, open-label, randomized trial, we assigned adults in stable condition with infective endocarditis caused by *Staphylococcus aureus*, *Enterococcus faecalis*, or streptococcus species to receive either response-tailored or standard-duration antibiotic therapy. Before randomization, all the patients received at least the prespecified 2 to 4 weeks of therapy and met criteria for clinical stabilization. After randomization, patients in the tailored-therapy group discontinued antibiotics and those in the standard-therapy group continued standard treatment (total duration, 4 to 6 weeks). The primary efficacy end point was days alive without antibiotic treatment for infective endocarditis or bacteremia within 6 months after randomization (tested for superiority). The primary safety end point was a composite of death from any cause, unplanned cardiac surgery, or symptomatic embolic events within 6 months after randomization (tested for noninferiority; margin, 7.5 percentage points). Relapse of bacteremia or infective endocarditis was a key secondary end point.



The management of infective endocarditis usually includes high-dose antibiotic treatment for up to 6 weeks. Current recommendations regarding the duration of antibiotic therapy are largely based on expert opinion and historical observations rather than randomized trials. For several infectious diseases, shorter antibiotic regimens have been shown to be effective, with several advantages over longer regimens, including fewer side effects, fewer health care–associated infections, a lower risk of antimicrobial resistance, decreased costs, and improved patient recovery and mental health. In principle, the optimal duration of antibiotic therapy is the time it takes for complete eradication of the causative pathogen, but for patients with infective endocarditis, no single marker reliably indicates when bacterial clearance has been achieved. In the Partial Oral Treatment of Endocarditis (POET) trial, which involved patients with infective endocarditis on the left side of the heart, a combination of clinical, biochemical, and imaging criteria (“POET criteria” [based on the clinical stabilization criteria that were required to be met before randomization in the trial]) was used to determine the timing of the shift from intravenous to oral step-down therapy. The switch to oral step-down antibiotic therapy resulted in 16 fewer days of intravenous antibiotic treatment than usual care, was shown to be noninferior to usual care after 6 months, and was associated with improved survival after 5 years of follow-up. On the basis of these results, we hypothesized that response-tailored treatment based on the POET criteria for clinical stabilization would result in 2 to 3 fewer weeks of intravenous or oral step-down antibiotic treatment than the standard duration of therapy in patients with infective endocarditis without compromising safety.

Patients

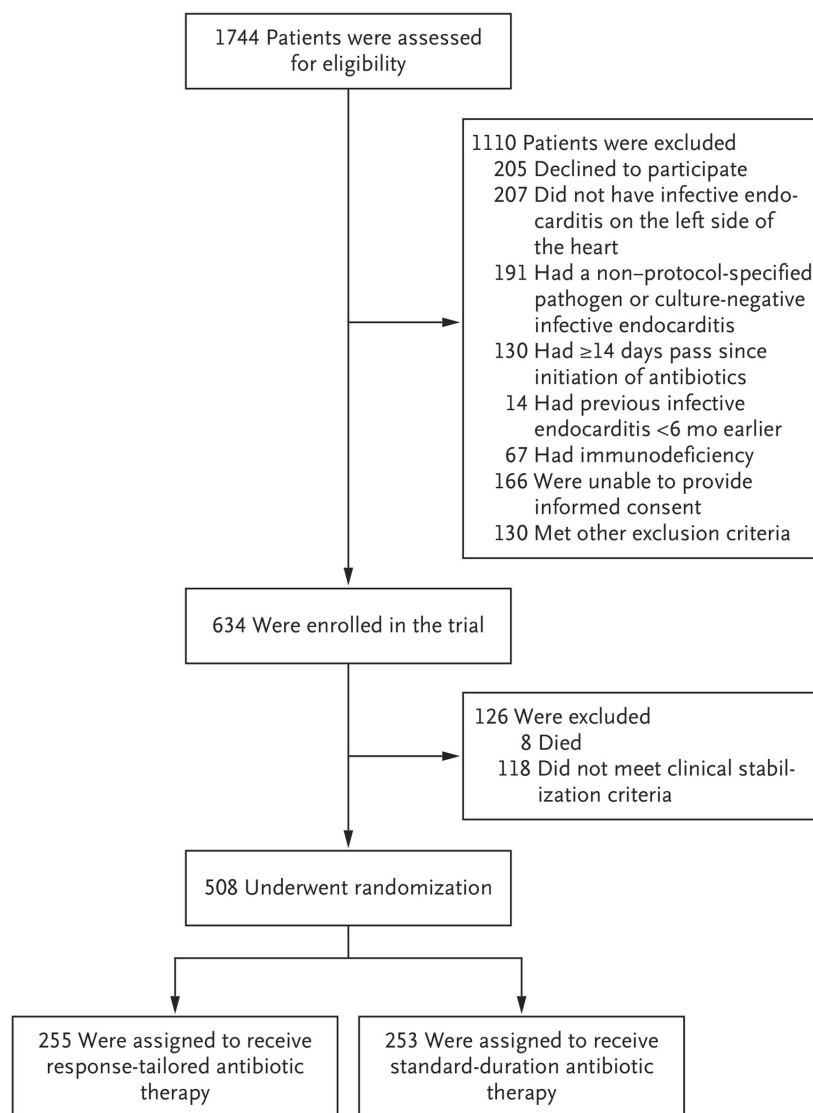
Adults 18 years of age or older were eligible for enrollment in the trial if they had infective endocarditis of native or prosthetic valves on the left side of the heart, according to modified Duke criteria, that was caused by *Staphylococcus aureus*, *Enterococcus faecalis*, or streptococcus species. Patients with previous infective endocarditis that had been caused by the same microorganism within 6 months before randomization and patients with known or presumed immunodeficiency were not eligible.

Randomization and Treatment

Patients were randomly assigned in a 1:1 ratio to receive antibiotic therapy according to a response-tailored strategy involving a shortened course of therapy (tailored-therapy group) or in a standard-duration regimen (standard-therapy group). Before randomization, all the patients received antibiotic therapy for at least the prespecified minimum duration of 2 to 4 weeks and met the POET criteria for clinical stabilization. Immediately after randomization, patients in the tailored-therapy group discontinued antibiotic therapy, whereas those in the standard-therapy group continued standard treatment until completion of the applicable total treatment duration of 4 to 6 weeks.

End Points

The primary efficacy end point was the number of days alive without antibiotic treatment for infective endocarditis or bacteremia within 6 months after randomization. The primary safety end point was a composite of death from any cause, unplanned cardiac surgery, or symptomatic embolic events as confirmed by imaging within 6 months after randomization.

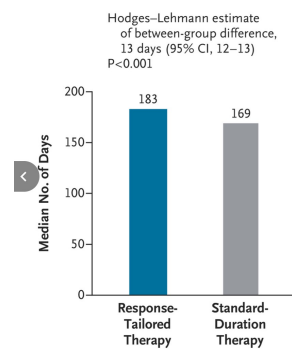


Characteristic	Response-Tailored Therapy (N = 255)	Standard-Duration Therapy (N = 253)
Age — yr	68.9 $\pm$ 13.7	70.2 $\pm$ 13.2
Male sex — no. (%)	193 (75.7)	190 (75.1)
Median duration of antibiotic treatment at randomization (IQR) — days	24 (17–30)	23 (15–29)
Coexisting condition or risk factor — no. (%)		
Diabetes	37 (14.5)	53 (20.9)
Renal failure†	28 (11.0)	31 (12.3)
Dialysis	6 (2.4)	8 (3.2)
Chronic obstructive pulmonary disease	20 (7.8)	24 (9.5)
Liver disease	11 (4.3)	8 (3.2)
Active cancer	17 (6.7)	16 (6.3)
Intravenous substance use disorder	5 (2.0)	0
Bacterial pathogen — no. (%)		
<i>Staphylococcus aureus</i>	61 (23.9)	62 (24.5)
<i>Enterococcus faecalis</i>	52 (20.4)	42 (16.6)
Streptococcus species	142 (55.7)	149 (58.9)
Median laboratory value at randomization (IQR)‡		
Hemoglobin — mmol/liter	6.7 (6.0–7.5)	6.8 (6.1–7.7)
Leukocyte count — $\times 10^9$ /liter	6.6 (5.2–7.8)	6.6 (5.6–7.8)
C-reactive protein — mg/liter	14.0 (5.1–26.0)	13.0 (4.3–26.0)
Procalcitonin — μ g/liter	0.10 (0.06–0.12)	0.10 (0.06–0.11)
Creatinine — μ mol/liter	77.0 (64.0–102.5)	83.0 (66.5–110.0)
Body temperature at randomization — °C	36.8 $\pm$ 0.4	36.7 $\pm$ 0.4
Preexisting prosthesis, implant, or cardiac disease — no. (%)		
Prosthetic heart valve	68 (26.7)	66 (26.1)
Pacemaker or implantable cardioverter-defibrillator	18 (7.1)	20 (7.9)
Congenital heart disease	15 (5.9)	13 (5.1)
Cardiac involvement — no. (%)		
Mitral-valve infective endocarditis	127 (49.8)	116 (45.8)
Aortic-valve infective endocarditis	160 (62.7)	161 (63.6)
Vegetation size >9 mm	17 (6.7)	18 (7.1)
Moderate-to-severe valve insufficiency	47 (18.4)	49 (19.4)
Valve surgery during current disease course	84 (32.9)	84 (33.2)

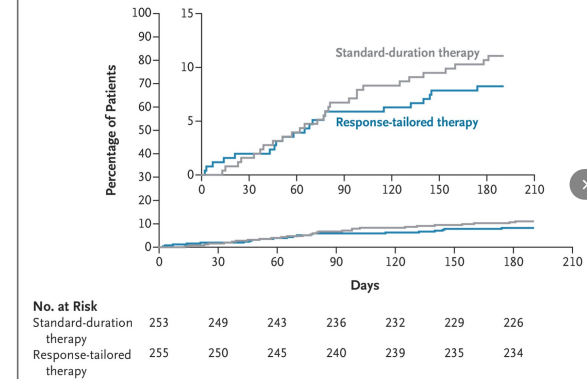
Safety

End Point	Response-Tailored Therapy (N=255)	Standard-Duration Therapy (N=253)	Hodges-Lehmann Estimate of Difference or Absolute Difference (95% CI) ^a	Mean Difference or Hazard Ratio (95% CI) [†]
Primary efficacy end point				
Median no. of days alive without antibiotic therapy for infective endocarditis or bacteremia within 6 months after randomization (IQR)	183 (181 to 183)	169 (166 to 171)	13 (12 to 13)	9.7 (5.2 to 14.2)
Safety end points				
Primary safety end point				
Death from any cause, unplanned cardiac surgery, or symptomatic embolic events within 6 months after randomization — no. (%)	21 (8.2)	27 (10.7)	-2.4 (-7.7 to 2.7)	0.77 (0.43 to 1.36)
Other safety end points				
Death from any cause — no. (%)	13 (5.1)	11 (4.3)	0.8 (-3.1 to 4.7)	1.18 (0.53 to 2.63)
Unplanned cardiac surgery — no. (%)	5 (2.0)	10 (4.0)	-2.0 (-5.4 to 1.1)	0.49 (0.17 to 1.45)
Symptomatic embolic events — no. (%)	6 (2.4)	8 (3.2)	-0.8 (-4.1 to 2.3)	0.75 (0.26 to 2.15)
Other key end point				
Relapse of bacteremia or infective endocarditis with primary pathogen — no. (%)	13 (5.1)	4 (1.6)	3.5 (0.4 to 7.1)	3.29 (1.07 to 10.11)

A Alive without Antibiotic Therapy

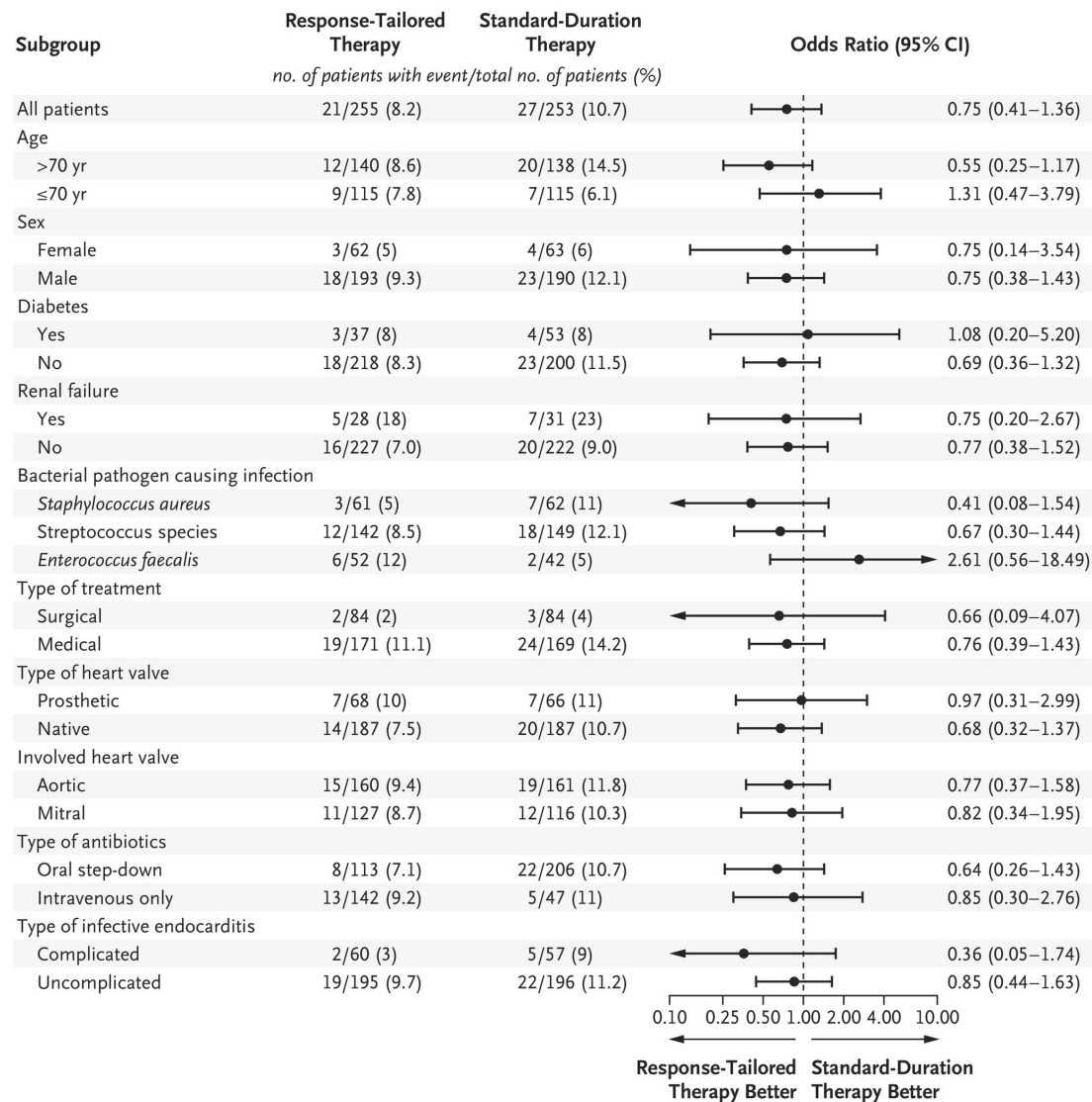


B Probability of a Primary Safety End-Point Event



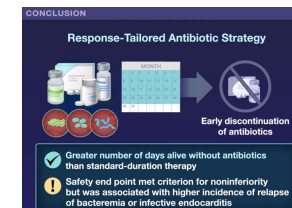
Primary Efficacy and Safety End Points.

Panel A shows the median number of days alive without antibiotic therapy for infective endocarditis or bacteremia within 6 months after randomization (the primary efficacy end point) among patients in the tailored-therapy and standard-therapy groups. Panel B shows the Kaplan–Meier estimates of the probability of a composite of death from any cause, unplanned cardiac surgery, or symptomatic embolic events within 6 months after randomization (the primary safety end point). The inset shows the same data on an enlarged y axis.

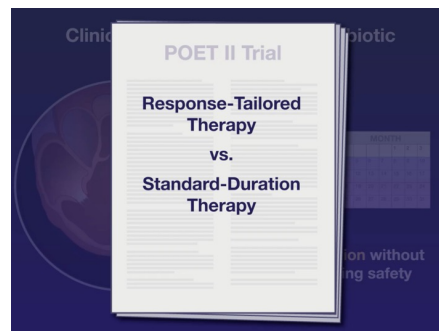
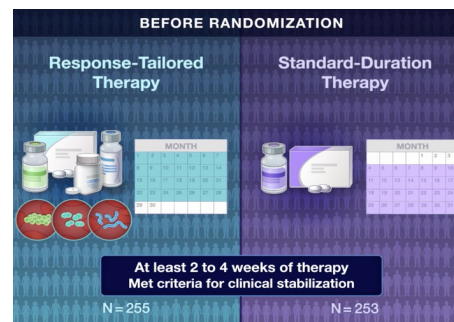
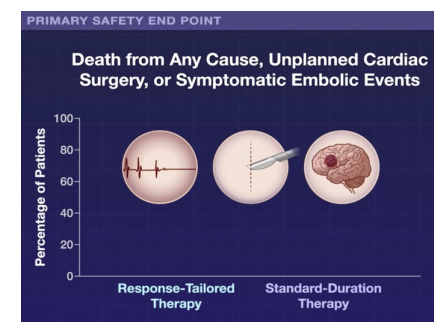
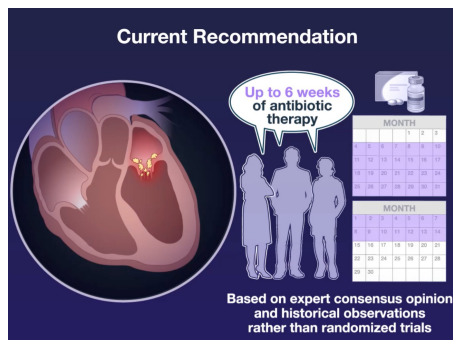
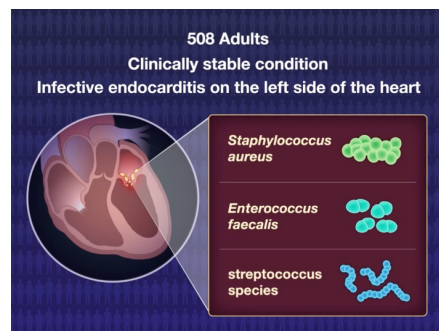
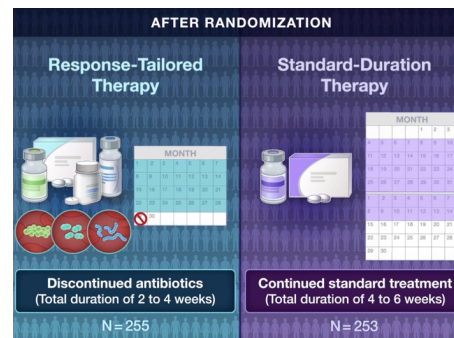
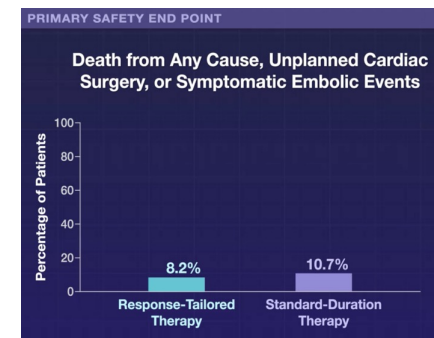
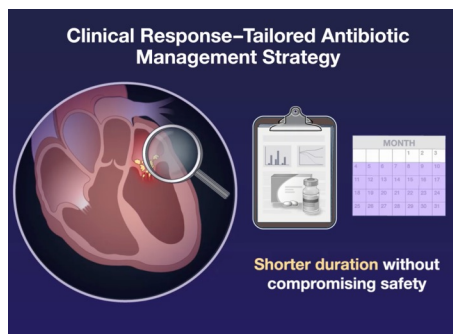
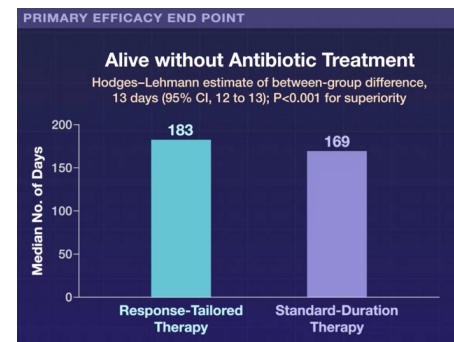
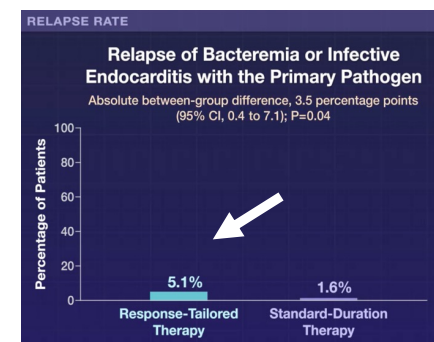


Primary Safety End Point in Prespecified Subgroups.

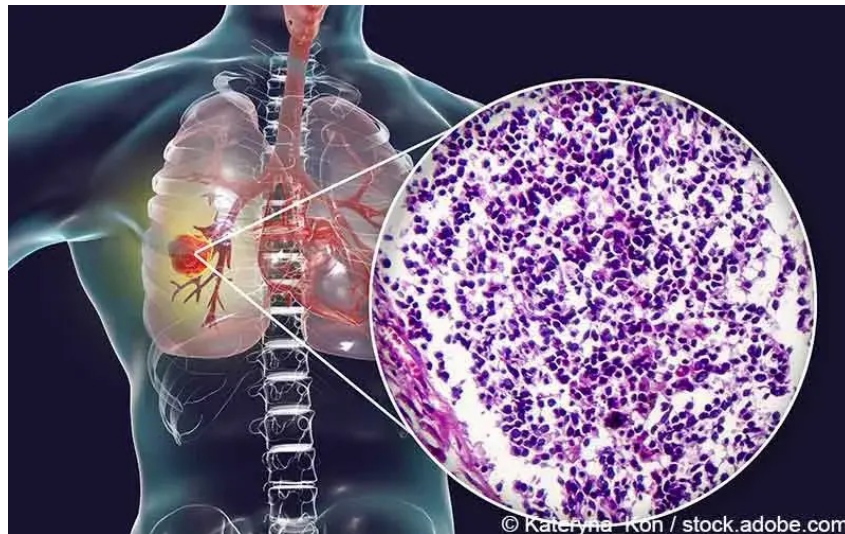
With respect to the presence of renal failure, chronic kidney disease had been diagnosed previously or was diagnosed during the current disease course by the treating physician. Patients could have had infective endocarditis that involved both the aortic valve and the mitral valve. Arrows on the confidence interval bars indicate that the upper or lower boundary of the confidence interval is off the scale. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer treatment effects.



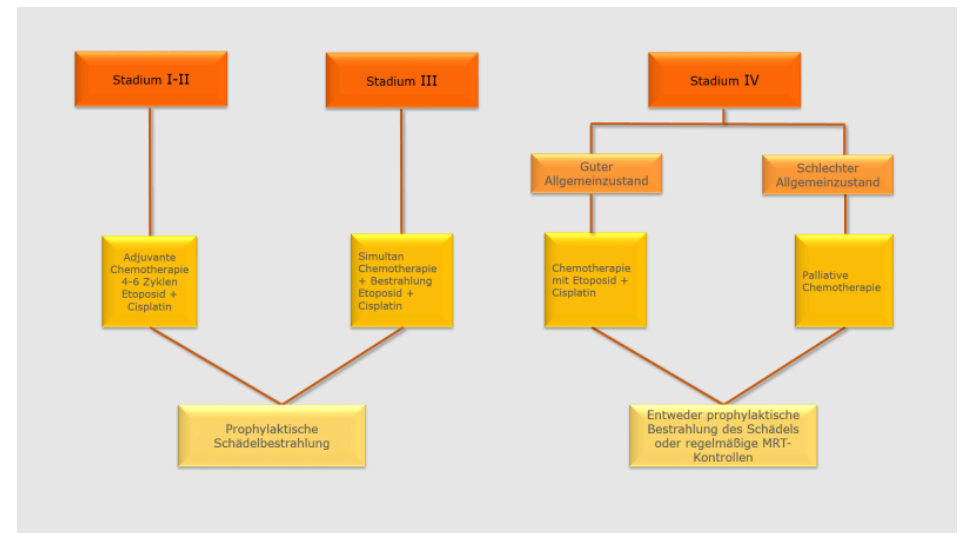
The next challenge is to define that response with enough confidence to know when treatment can safely stop without compromising microbiologic cure.



Kleinzelliger Lungenkarzinom



Jetzige Therapie

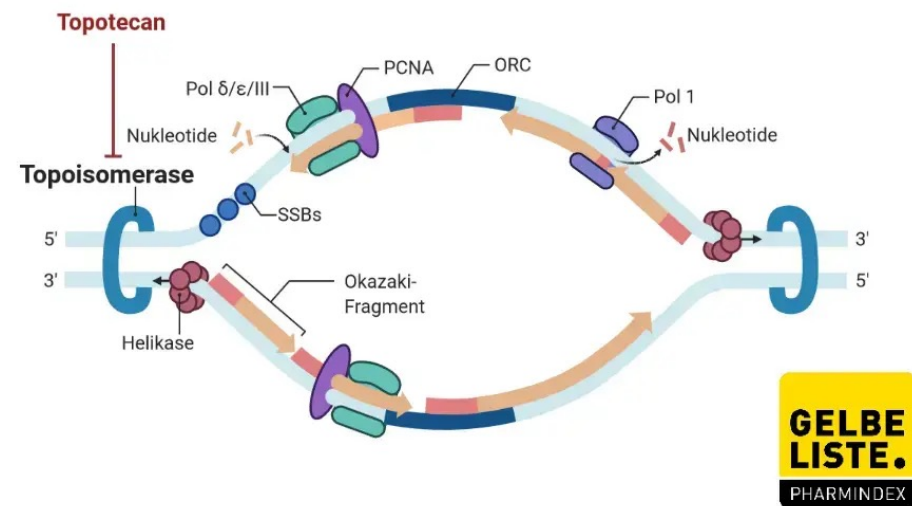


Topotecan ist ein Zytostatikum (Chemotherapeutikum) aus der Gruppe der Topoisomerase-I-Inhibitor. Es handelt sich um ein halbsynthetisches, wasserlösliches Derivat des pflanzlichen Alkaloids Camptothecin, das aus dem Baum *Camptotheca acuminata* gewonnen wird. Im Handel ist es vor allem unter dem Markennamen **Hycamtin®** sowie als Generika bekannt.

Wirkungsmechanismus

Während der Zellteilung muss die DNA-Doppelhelix entschräubt werden. Das Enzym Topoisomerase I schneidet dafür kontrolliert einen der DNA-Stränge. Topotecan bindet stabil an diesen Enzym-DNA-Komplex und blockiert den Prozess. Wenn die Replikationsgabel der Zelle auf dieses Hindernis trifft, kommt es zu irreparablen **DNA-Doppelstrangbrüchen**. Dies arretiert den Zellzyklus in der S-Phase und leitet den programmierten Zelltod (**Apoptose**) der Krebszelle ein.

DNA-ELONGATIONS-KOMPLEX



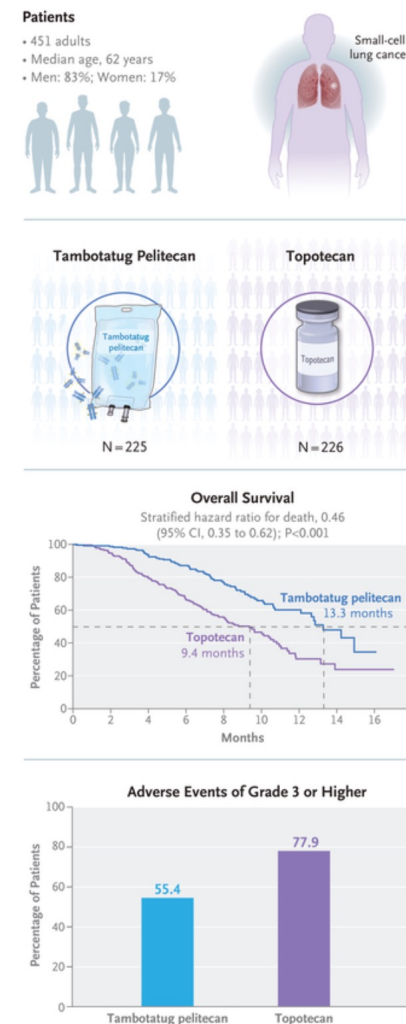
Tamotatug-Pelitecan (auch bekannt als **Tam-Peli** oder **YL201**) ist ein vielversprechendes, neues Medikament zur Behandlung von Krebs, das als Antikörper-Wirkstoff-Konjugat (Antibody-Drug Conjugate, ADC) funktioniert.

Der Wirkstoff richtet sich gezielt gegen das Protein **B7-H3**, einen Immun-Checkpoint-Marker, der auf der Oberfläche vieler verschiedener Krebszellen stark überaktiviert (exprimiert) ist, auf gesundem Gewebe hingegen kaum vorkommt



Tambotatug Pelitecan in Small-Cell Lung Cancer after Platinum-Based Therapy

Tambotatug pelitecan (**known as Tam-Peli**, a new antibody–drug conjugate that targets the immune-checkpoint molecule B7-H3) showed promising clinical efficacy in patients with relapsed extensive-stage small-cell lung cancer in early-phase trials. In this phase 3, multicenter, open-label, randomized trial, we assigned eligible patients with small-cell lung cancer that had progressed after first-line platinum-based therapy in a 1:1 ratio to receive **tambotatug pelitecan or topotecan**. The primary end point was overall survival. The key secondary end points were **progression-free survival** and objective response as assessed by investigators. Here, we report the results from the prespecified interim analysis.



Small-cell lung cancer accounts for approximately 15% of all lung cancers and remains one of the most aggressive and lethal cancers worldwide. Treatment with platinum–etoposide chemotherapy in combination with immune-checkpoint inhibitors targeting programmed death ligand 1 (PD-L1) or programmed cell death protein 1 (PD-1) has improved overall survival and become a standard first-line approach in extensive-stage small-cell lung cancer. However, the magnitude of benefit remains modest, and most patients ultimately have disease progression. B7 homologue 3 protein (B7-H3, also known as CD276), an immune-regulatory molecule in the B7 family that is up-regulated in various malignant tumors and has limited expression in normal tissues, has recently emerged as an attractive therapeutic target in solid tumors.

Tamotatug pelitecan (known as **Tam-Peli** and formerly known as YL201) is a B7-H3–targeting antibody–drug conjugate composed of a recombinant human IgG1 anti–B7-H3 monoclonal antibody linked to YL0010014 (a **topoisomerase I inhibitor** payload derived from camptothecin) through a new tripeptide-based linker.

Trial Design and Patients

We conducted this phase 3, open-label, randomized, controlled, superiority trial at 85 clinical sites in China. Eligible patients were 18 to 75 years of age and had histologically or cytologically confirmed small-cell lung cancer that had progressed or relapsed during or after first-line platinum-based therapy.

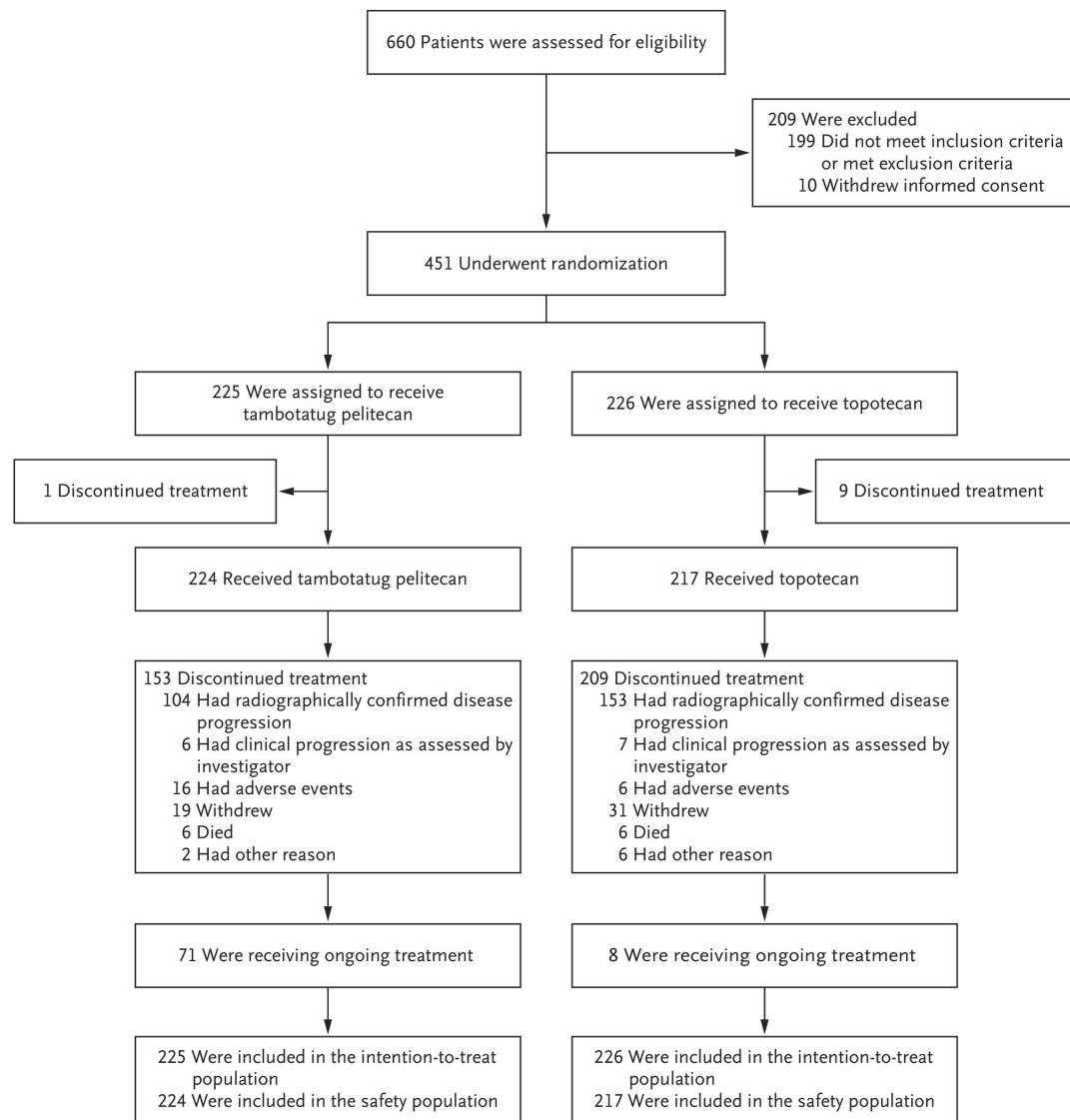
Randomization and Treatment

Eligible patients were randomly assigned in a 1:1 ratio to receive tambotatug pelitecan or topotecan through a centralized interactive Web-response system with the use of blocks stratified according to disease stage at enrollment (local disease or systemic disease), a history or presence of brain metastases (yes or no), and the chemotherapy-free interval, defined as the interval from the last dose of platinum-based therapy to documented progression or relapse (<90 days or ≥90 days).

Tambotatug pelitecan was administered intravenously at a dose of 2.0 mg per kilogram on day 1 of each 3-week cycle (with a maximum dose of 200 mg per cycle), and topotecan was administered intravenously at a dose of 1.2 mg per m² of body-surface area on days 1 through 5 of each 3-week cycle according to the approved prescribing information in China (Aosaikang Pharma).

End Points and Assessments

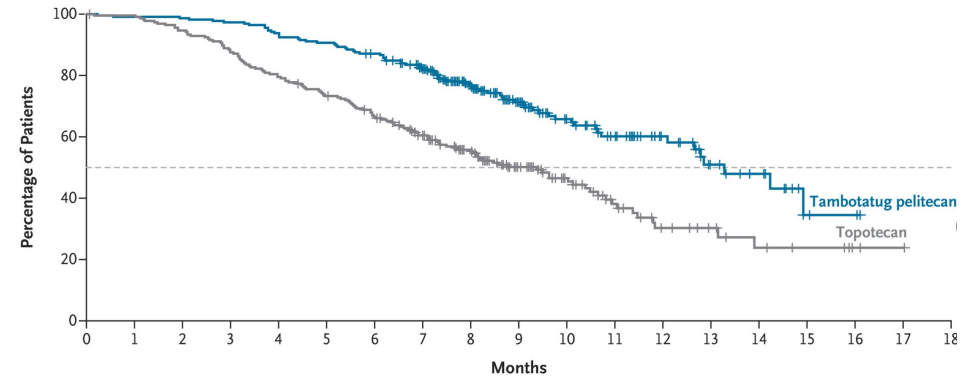
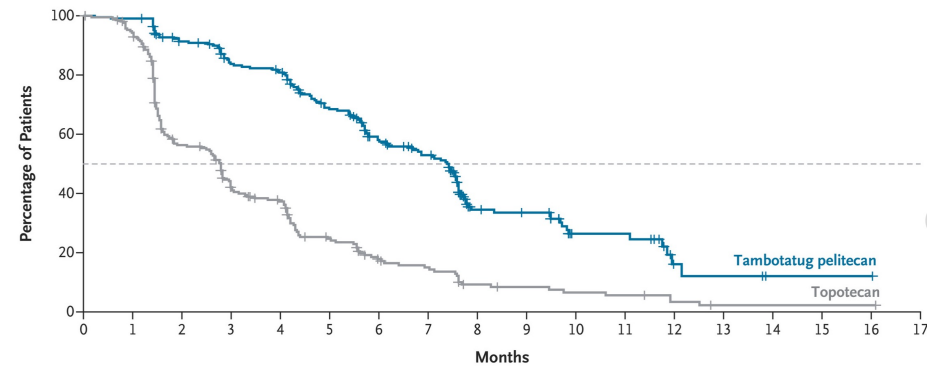
The primary end point was overall survival, defined as the time from randomization to death from any cause. The key secondary end points were progression-free survival and objective response, both assessed by the investigators.

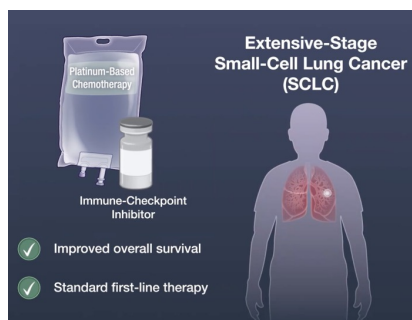
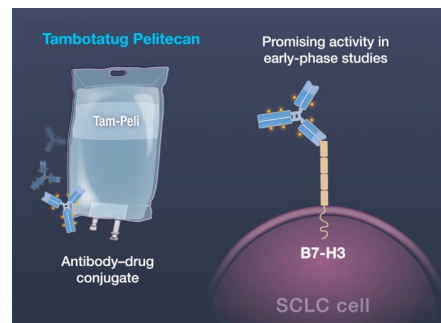
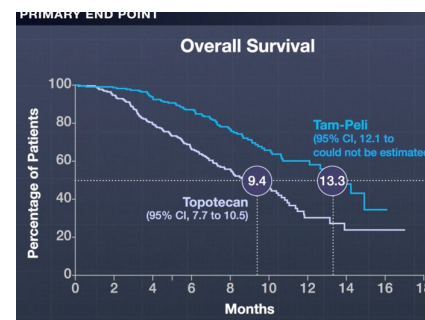
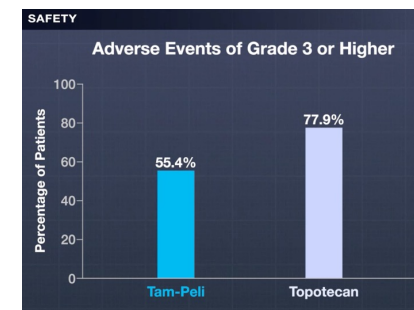
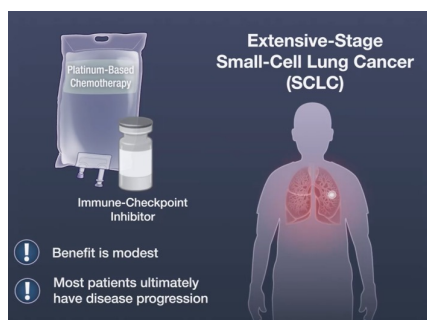
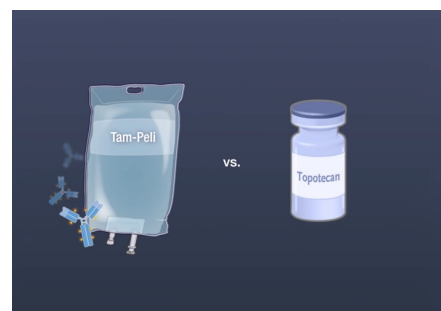
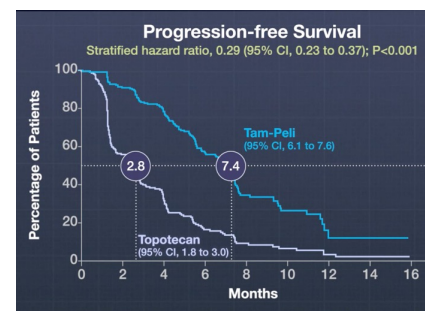
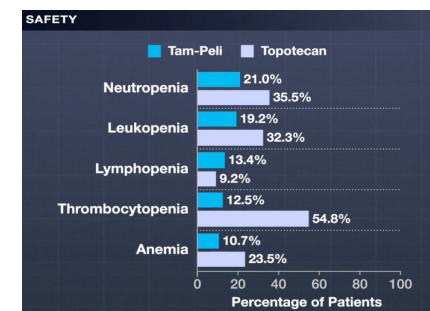
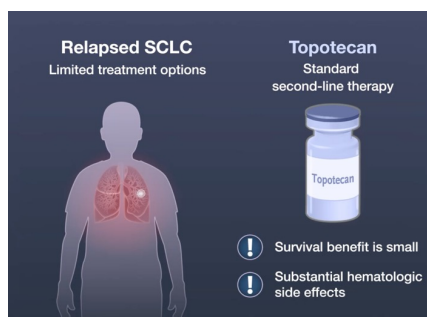
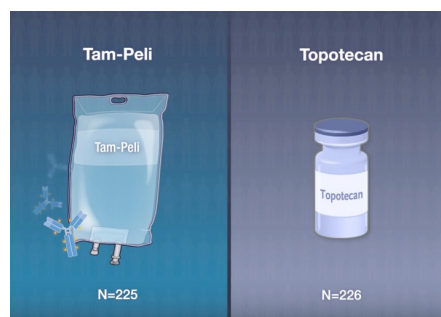
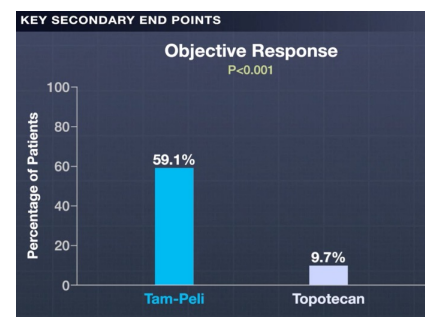


Characteristic	Tambotatug Pelitecan (N = 225)	Topotecan (N = 226)
Age		
Median (range) — yr	62 (28–74)	62 (18–75)
Distribution — no. (%)		
<65 yr	137 (60.9)	149 (65.9)
≥65 yr	88 (39.1)	77 (34.1)
Sex — no. (%)		
Male	183 (81.3)	191 (84.5)
Female	42 (18.7)	35 (15.5)
ECOG performance-status score — no. (%) †		
0	39 (17.3)	27 (11.9)
1	186 (82.7)	199 (88.1)
Smoking status — no. (%)		
Never smoked	63 (28.0)	68 (30.1)
Current smoker	22 (9.8)	24 (10.6)
Former smoker	140 (62.2)	134 (59.3)
Disease stage — no. (%)		
Local disease‡	7 (3.1)	10 (4.4)
Systemic disease	218 (96.9)	216 (95.6)
Previous anti-PD-1 or anti-PD-L1 therapy — no. (%)		
Yes	194 (86.2)	199 (88.1)
No	31 (13.8)	27 (11.9)
Chemotherapy-free interval — no. (%)		
<90 days	110 (48.9)	110 (48.7)
≥90 days	115 (51.1)	116 (51.3)
History or presence of brain metastases — no. (%)		
Yes	78 (34.7)	77 (34.1)
No	147 (65.3)	149 (65.9)
Liver metastases — no. (%)		
Yes	72 (32.0)	80 (35.4)
No	153 (68.0)	146 (64.6)

Safety

Event	Tambotatug Pelitecan (N = 224)		Topotecan (N = 217)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	<i>number of patients with event (percentage)</i>			
Any adverse event	223 (99.6)	124 (55.4)	216 (99.5)	169 (77.9)
Serious	87 (38.8)	—	94 (43.3)	—
Leading to dose reduction	63 (28.1)	—	81 (37.3)	—
Leading to dose interruption	112 (50.0)	—	95 (43.8)	—
Leading to discontinuation of assigned treatment	16 (7.1)	—	8 (3.7)	—
Leading to death	9 (4.0)	—	6 (2.8)	—
Any treatment-related adverse event	221 (98.7)	104 (46.4)	216 (99.5)	162 (74.7)
Serious	58 (25.9)	—	79 (36.4)	—
Leading to dose reduction	58 (25.9)	—	80 (36.9)	—
Leading to dose interruption	78 (34.8)	—	80 (36.9)	—
Leading to permanent discontinuation of assigned treatment	13 (5.8)	—	6 (2.8)	—
Leading to death	0	—	1 (0.5)	—
Treatment-related adverse events†				
Anemia‡	167 (74.6)	24 (10.7)	197 (90.8)	51 (23.5)
Leukopenia‡	131 (58.5)	43 (19.2)	144 (66.4)	70 (32.3)
Neutropenia‡	116 (51.8)	47 (21.0)	131 (60.4)	77 (35.5)
Fatigue‡	99 (44.2)	7 (3.1)	50 (23.0)	2 (0.9)
Thrombocytopenia‡	90 (40.2)	28 (12.5)	200 (92.2)	119 (54.8)
Decreased appetite	90 (40.2)	2 (0.9)	42 (19.4)	0
Transaminases increased‡	74 (33.0)	5 (2.2)	55 (25.3)	1 (0.5)
Hyperlipidemia‡	72 (32.1)	3 (1.3)	45 (20.7)	3 (1.4)
Nausea	71 (31.7)	0	47 (21.7)	0
Lymphopenia‡	65 (29.0)	30 (13.4)	54 (24.9)	20 (9.2)
Hypoproteinemia‡	60 (26.8)	0	53 (24.4)	0
Diarrhea	60 (26.8)	5 (2.2)	23 (10.6)	0
Constipation‡	52 (23.2)	0	68 (31.3)	0
Hyponatremia‡	48 (21.4)	12 (5.4)	42 (19.4)	5 (2.3)
Weight decreased	46 (20.5)	1 (0.4)	23 (10.6)	0
γ-Glutamyltransferase increased	44 (19.6)	4 (1.8)	27 (12.4)	2 (0.9)
Blood alkaline phosphatase increased	38 (17.0)	1 (0.4)	12 (5.5)	1 (0.5)
Dizziness	35 (15.6)	0	9 (4.1)	0
Hyperuricemia‡	34 (15.2)	0	23 (10.6)	0
Pneumonia‡	17 (7.6)	9 (4.0)	17 (7.8)	6 (2.8)
Febrile neutropenia	6 (2.7)	6 (2.7)	2 (0.9)	2 (0.9)

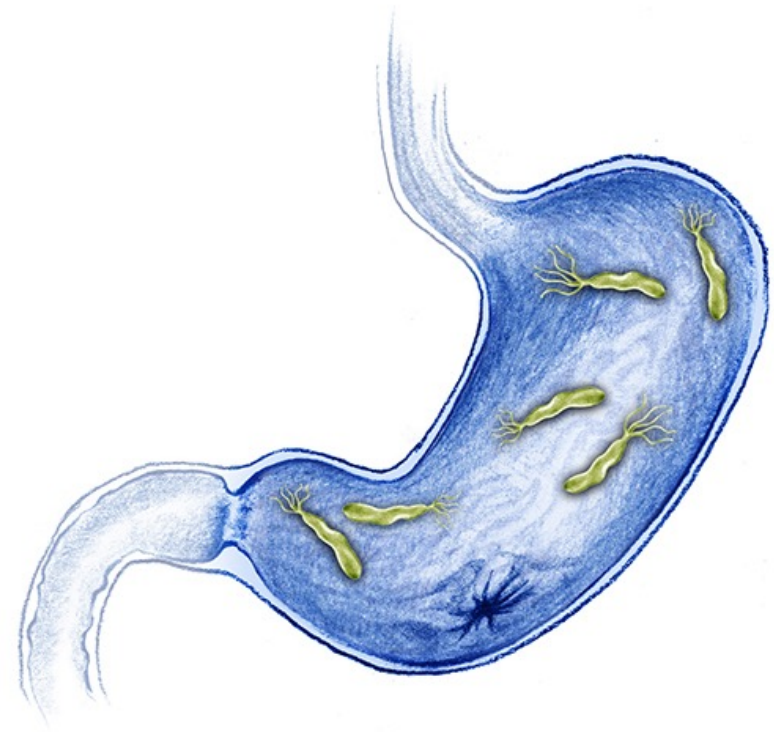




Helicobacter pylori (*H. pylori*) ist ein spiralförmiges Bakterium, das sich in der Magenschleimhaut des Menschen ansiedelt.

Wesentliche Fakten

- **Verbreitung:** Etwa 30 % bis 40 % der Menschen in Deutschland und bis zu 50 % weltweit sind infiziert. Die Ansteckung passiert meist bereits im Kindesalter.
- **Übertragung:** Von Mensch zu Mensch, entweder fäkal-oral oder oral-oral (über Speichel, Besteck oder mangelnde Handhygiene).
- **Symptome:** Viele Betroffene haben keine Beschwerden. Traten Symptome auf, sind es oft Völlegefühl, Sodbrennen, Oberbauchschmerzen, Übelkeit oder ein brennender Schmerz im Magen.
- **Folgeerkrankungen:** Eine chronische Infektion führt zu Magenschleimhautentzündungen (Gastritis), erhöht das Risiko für Magen- oder Zwölffingerdarmgeschwüre und gilt als Hauptrisikofaktor für Magenkrebs.



[Barry J. Marshall](#) und [J. Robin Warren](#) erhielten 2005 den **Nobelpreis für Physiologie oder Medizin**.

Wichtigste Details zur Entdeckung:

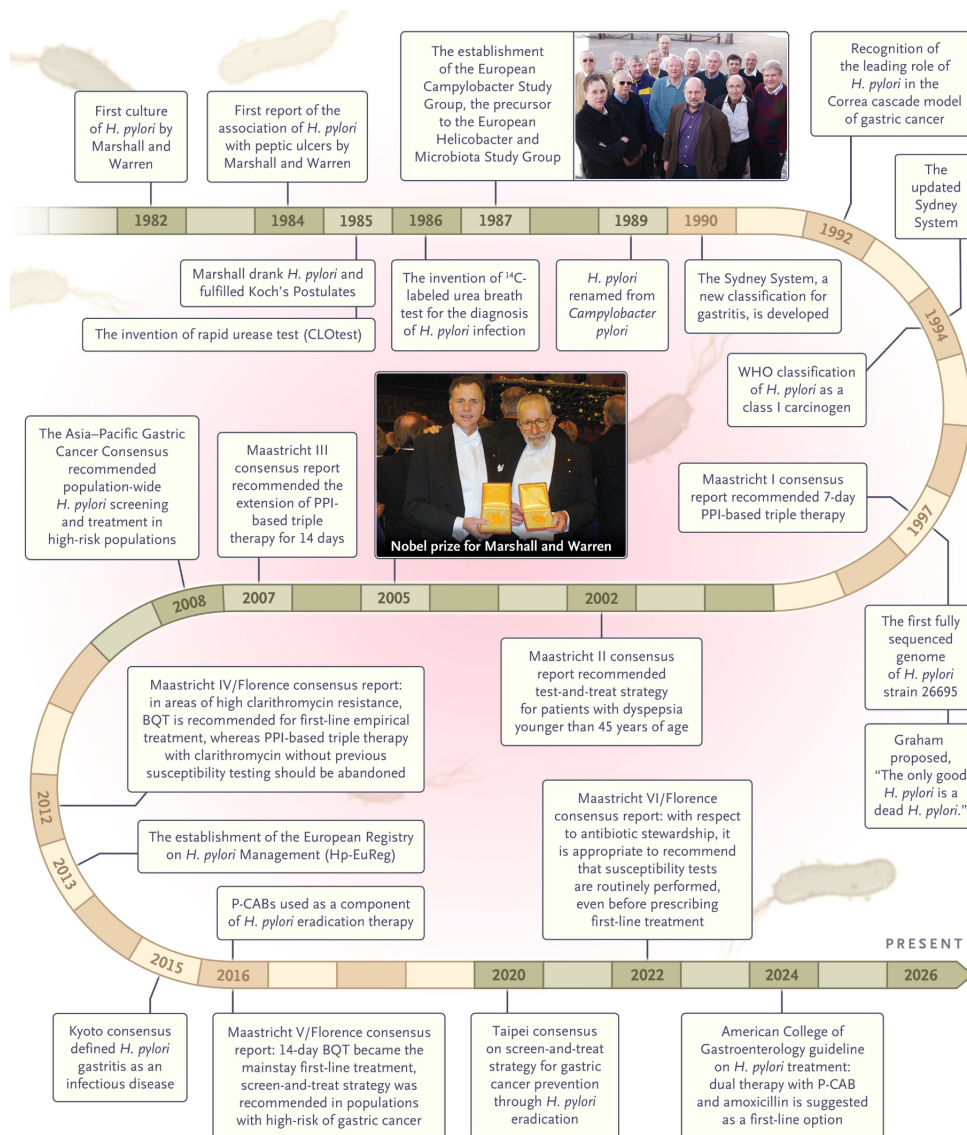
- **Die Preisträger:** Barry J. Marshall und J. Robin Warren (Australien).
- **Die Entdeckung:** Sie wiesen nach, dass Magenschleimhautentzündungen (Gastritis) und Magengeschwüre (Peptische Ulkusstatus) durch das Bakterium *Helicobacter pylori* verursacht werden – und nicht durch Stress oder scharfes Essen, wie zuvor angenommen.
- **Der Selbstversuch:** Barry Marshall trank 1984 eine Kultur des Bakteriums, erkrankte daraufhin an einer akuten Magenschleimhautentzündung und bewies damit den kausalen Zusammenhang.
- **Die medizinische Bedeutung:** Dank dieser Erkenntnis lassen sich Magen- und Zwölffingerdarmgeschwüre heute dauerhaft und unkompliziert mit **Antibiotika** und Säurehemmern heilen.



***Helicobacter pylori* Infection — Advances, Challenges, and the Road Ahead**

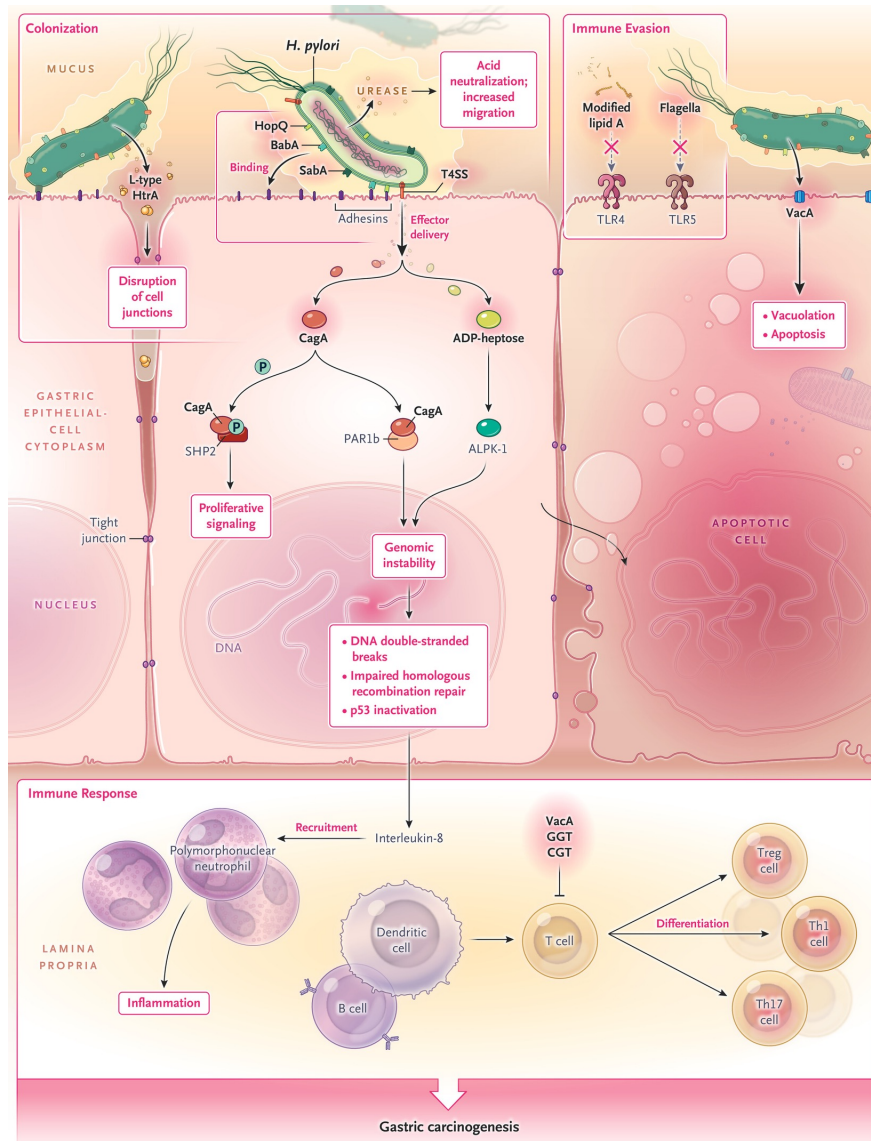
Summary

The discovery of *Helicobacter pylori* has revolutionized the prevention and treatment of gastritis, peptic ulcers, and, most important, gastric cancer. In the past 40 years, enormous progress has been achieved in the clinical and basic research on *H. pylori* infection. However, challenges in preventing and treating *H. pylori* infection exist owing to the lack of an *H. pylori* vaccine and the ever-increasing resistance to antibiotics worldwide. This review summarizes the history of and key milestones in *H. pylori* research, provides an update on the understanding of the pathogenesis and global burden of *H. pylori* infection and the screening strategy for the primary prevention of gastric cancer, and focuses on the emerging trends in the management of *H. pylori* infection.



Timeline of Key Events in *Helicobacter pylori* Research (1982 to 2024).

The successful culture of *H. pylori* in 1982 and the discovery of the link between *H. pylori* and peptic ulcers in 1984 revolutionized the prevention and treatment of gastric diseases. This timeline traces the major advances in the understanding and management of *H. pylori* infection.¹⁻²⁴ BQT denotes bismuth-based quadruple therapy, P-CAB potassium-competitive acid blocker, PPI proton-pump inhibitor, and WHO World Health Organization.



Pathogenesis of *H. pylori* Infection.

H. pylori pathogenesis is multifaceted, involving colonization factors and virulence factors that contribute to gastric inflammation and gastric carcinogenesis. Colonization is facilitated by urease activity, flagellar motility, and adhesins. Key virulence factors, including vacuolating cytotoxin A (VacA), cytotoxin-associated gene A (CagA), ADP-heptose, and *H. pylori* high-temperature requirement A (HtrA), exert diverse effects on host cells. HtrA and VacA are secreted virulence factors, whereas CagA and ADP-heptose are delivered into epithelial cells through the type IV secretion system (T4SS). HtrA, particularly the S171L type, cleaves junction proteins, which facilitates bacterial translocation and CagA delivery. Immune evasion is achieved through mechanisms such as lipid A modification to evade Toll-like receptor 4 (TLR4) recognition and flagellin modification to escape TLR5 detection. Virulence factors including VacA, cholesterol- α -glucosyltransferase (CGT), and γ -glutamyltransferase (GGT) modulate the immune response by skewing T-cell differentiation toward regulatory T cells (T_{reg} cells) while suppressing differentiation of type 1 helper T cells (Th1) and type 17 helper T cells (Th17). Hep denotes heptose.

KEY POINTS

***Helicobacter pylori* Infection — Advances, Challenges, and the Road Ahead**

- *Helicobacter pylori* infection is a transmissible infectious disease and the primary risk factor for gastric cancer; therefore, eradication therapy should be administered in infected persons unless it is contraindicated.
- Population-wide *H. pylori* screening and treatment is appropriate in regions with a high prevalence of *H. pylori* infection and a high incidence of gastric cancer but may not be practical. A family-based strategy targeting household members of infected persons offers a more feasible alternative.
- Treatment of *H. pylori* infection should adhere to antimicrobial stewardship principles and be guided by antimicrobial-susceptibility testing. Improvement in and standardization of high-throughput methods are needed to establish antimicrobial-susceptibility testing as routine clinical practice.
- Bismuth-based quadruple therapy and high-dose dual therapy are appropriate as empirical regimens for both first-line and rescue treatment; a weight-based dose of amoxicillin is suggested for high-dose dual therapy.
- New therapies for *H. pylori* infection are needed, including the development of new antimicrobials and effective vaccines.

Components

Gastric-acid inhibitors

PPI* or potassium-competitive acid blocker (vonoprazan)

Bismuth salts

Bismuth subcitrate, bismuth subsalicylate, or bismuth pectin

Antimicrobials (prevalence of primary resistance)

Amoxicillin (6%)^{73†}

Clarithromycin (30%)^{73†}

Metronidazole (61%)^{73†}

Levofloxacin (35%)^{73†}

Tetracycline (4%)^{73†} or minocycline‡

Furazolidone (0%)^{77§}

Rifabutin (0.07%)⁷⁸

Regimens

Regimens that can be used empirically

10-Day or 14-day bismuth-based quadruple therapy: PPI (standard dose, 2 times daily) plus bismuth (standard-dose, 4 times daily) plus tetracycline (500 mg, 4 times daily) plus metronidazole (500 mg, 3 or 4 times daily)

14-Day high-dose dual therapy: PPI (double dose [e.g., esomeprazole 40 mg 2 times daily]) or vonoprazan (20 mg, 2 times daily) plus amoxicillin¶

14-Day rifabutin-based triple therapy||: PPI (standard dose, 2 times daily) plus rifabutin (150 mg, 2 times daily) plus amoxicillin¶

Regimens effective only for susceptible infections confirmed by susceptibility testing

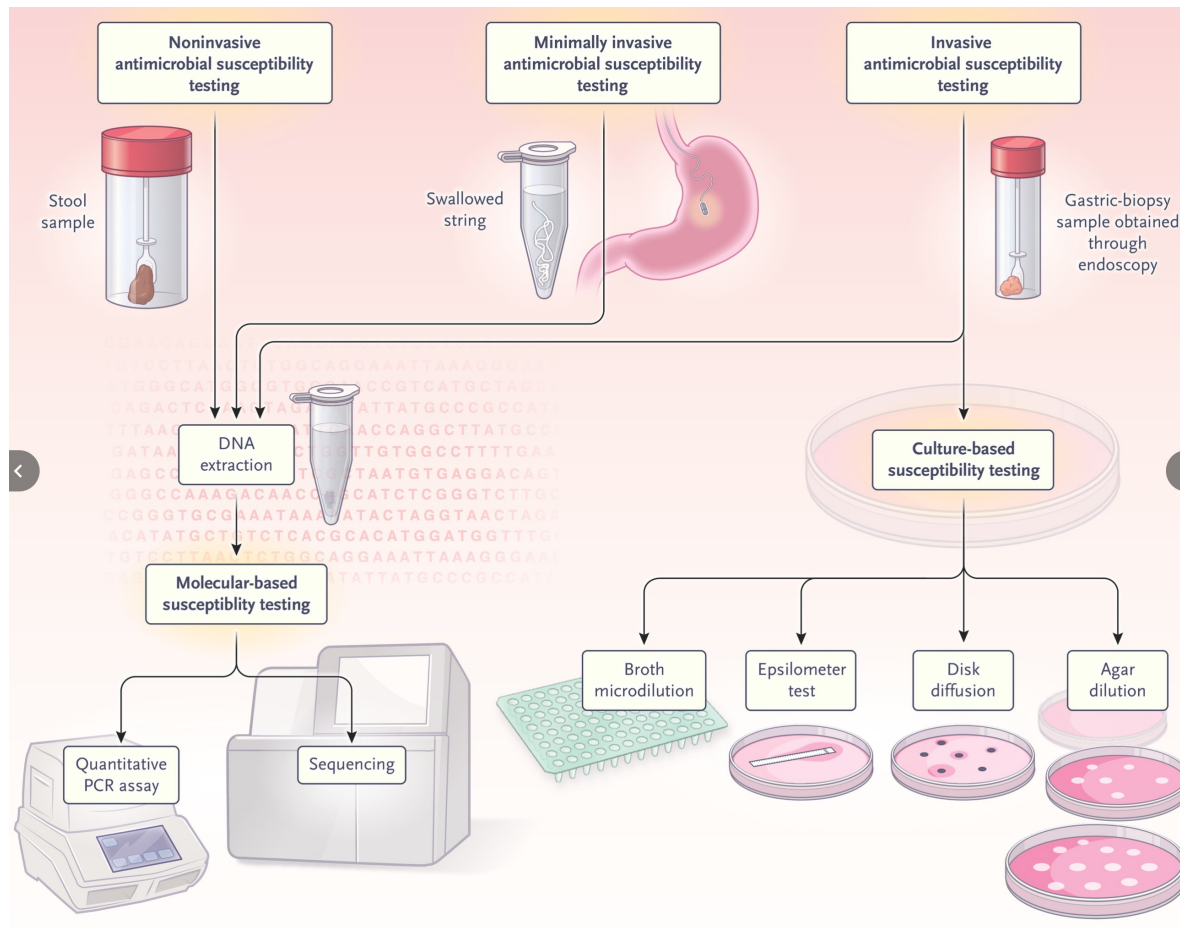
14-Day clarithromycin-based triple therapy: PPI (standard dose, 2 times daily) plus clarithromycin (500 mg, 2 times daily) plus amoxicillin¶

14-Day metronidazole-based triple therapy: PPI (standard dose, 2 times daily) plus metronidazole (500 mg, 2 times daily) plus amoxicillin¶

14-Day levofloxacin-based triple therapy: PPI (standard dose, 2 times daily) plus levofloxacin (500 mg, 1 time daily) plus amoxicillin¶

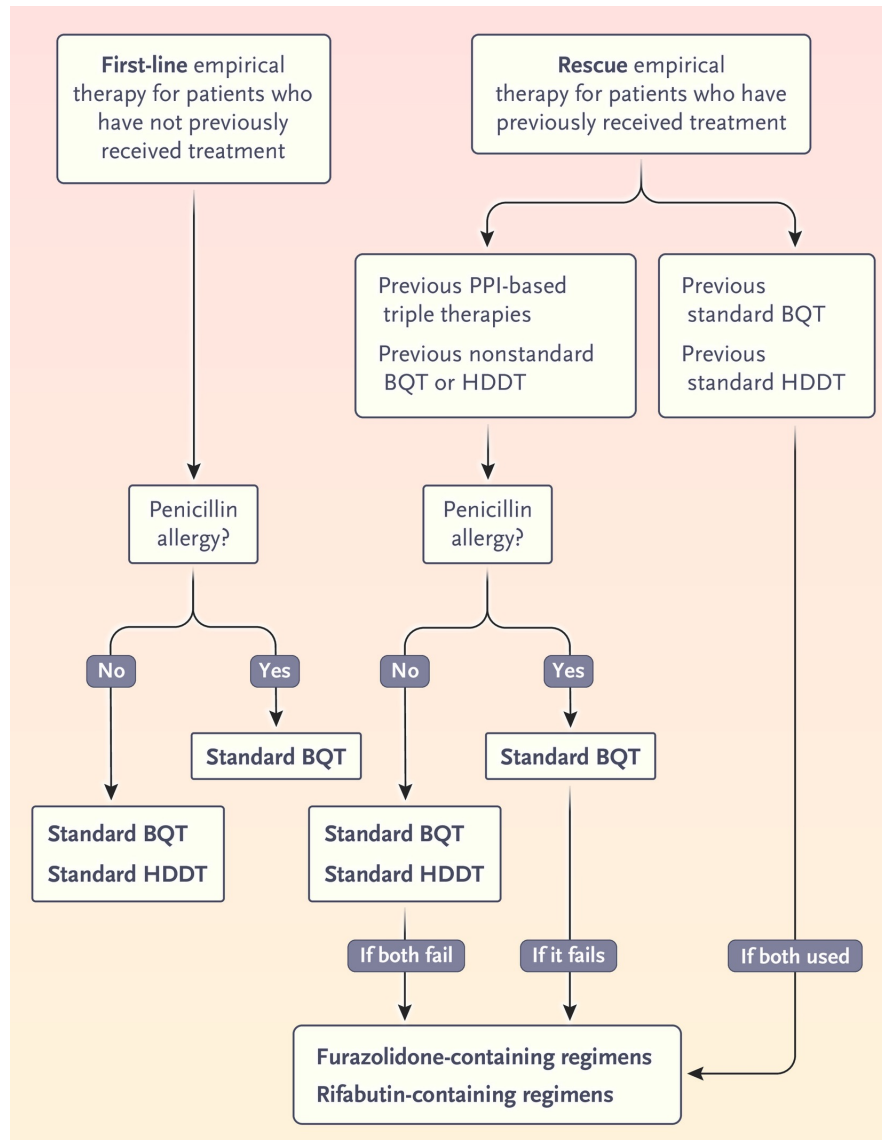
Therapy Guided by Antimicrobial-Susceptibility Testing

H. pylori infection is an infectious disease, and treatment regimens should ideally be guided by antimicrobial-susceptibility testing whenever possible. The 2022 Maastricht VI/Florence consensus report emphasizes the importance of routine antimicrobial-susceptibility testing, even before first-line treatment, to improve adherence to antimicrobial stewardship. This approach ensures targeted therapy and maximizes eradication success while minimizing antibiotic misuse and the risk of resistance development. Moreover, the approach facilitates ongoing surveillance of antimicrobial resistance, which enables timely adjustments to treatment strategies as needed.



Culture-Based and Molecular-Based Antimicrobial-Susceptibility Testing for *H. pylori*.

Culture-based antimicrobial-susceptibility testing requires isolating *H. pylori* from an endoscopic-biopsy sample or from gastric fluid obtained from a swallowed string. Subsequent susceptibility testing can be performed with agar dilution, an Epsilon meter test, disk diffusion, or broth microdilution. In contrast, molecular-based antimicrobial-susceptibility testing uses techniques such as quantitative polymerase-chain-reaction (PCR) assay or sequencing to directly detect resistance-conferring mutations in DNA extracted from clinical specimens, including gastric-biopsy samples, gastric fluid, or stool samples.



Algorithm for Empirical *H. pylori* Treatment.

Rifabutin-based triple therapy has been suggested as a first-line treatment option in the United States¹³; however, it is generally reserved as a third-line rescue therapy.¹² HDDT denotes high-dose dual therapy.

Bismuth quadruple therapy (BQT)

How Bismuth Works Against *H. pylori*

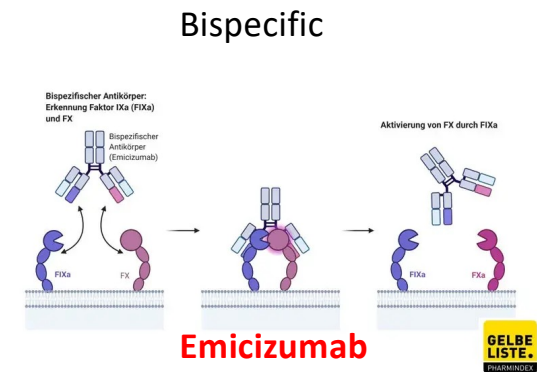
- **Direct Bactericidal Action:** Bismuth attacks the bacteria directly by forming complexes in the cell wall and periplasmic space, disrupting enzyme activity, blocking ATP (energy) synthesis, and stopping the bacteria from sticking to the stomach wall.
- **Synergism with Antibiotics:** It boosts the effectiveness of co-administered antibiotics and can even help re-sensitize strains of *H. pylori* that have grown resistant to drugs like metronidazole or clarithromycin.
- **Prevents Resistance:** *H. pylori* does not easily build resistance to bismuth, making it a reliable component in treatment regimens.

Vaccines against *H. pylori* Infection

An effective vaccine to prevent or clear *H. pylori* infection remains the ideal strategy for controlling this pathogen and preventing gastric cancer. **However, despite decades of research, no clinically validated vaccine has been developed.** A critical lesson from previous failures is that *H. pylori* has remarkable immune-evasion strategies to persist in the human stomach. Consequently, future vaccine development must incorporate strategies designed to counteract these immune-evasion mechanisms. Among the identified immune-evasion factors, the constitutively modified lipopolysaccharide structure has a crucial role. Therefore, developing an effective **lipopolysaccharide-based glycoconjugate vaccine** against *H. pylori* represents a promising direction for future investigation.

Reengineering Coagulation with a Bispecific Antibody

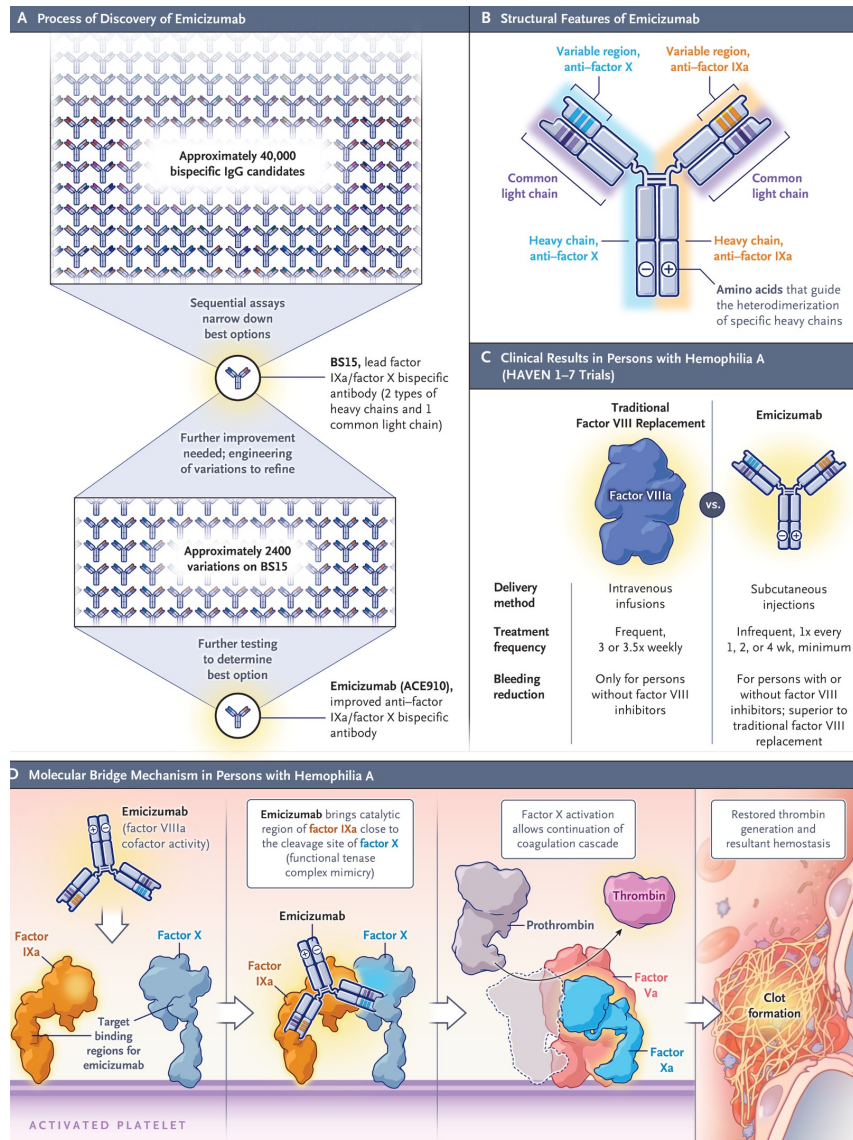
For decades, the treatment of hemophilia A rested on a single principle: replacing [factor VIII](#), the missing clotting factor. Plasma-derived and recombinant factor VIII concentrates transformed a once-fatal disease into a manageable chronic condition through prophylaxis and treatment. But factor VIII has a relatively short half-life and thus is administered through frequent intravenous infusions, and neutralizing anti-factor VIII antibodies (inhibitors) that render replacement therapy ineffective develop in up to one third of patients with severe hemophilia A. By showing that the coagulation cascade could be activated in the absence of factor VIII, **Kunihiro Hattori, Tomoyuki Igawa, and Takehisa Kitazawa** (of Chugai Pharmaceutical) overcame these limitations. They developed a [bispecific antibody](#) that mimics blood coagulation factor VIII, an achievement recognized by the 2026 Lasker–DeBakey Clinical Medical Research Award.



(not to be confused with Eculizumab)

In 2000, it had been established that activated factor VIII (factor VIIIa) binds both activated factor IX (factor IXa) and factor X and thereby accelerates prothrombinase complex formation and [thrombin](#) generation, presumably by modulating the catalytic activity of factor IXa and bringing factor IXa and factor X into close proximity. Hattori, who was working on therapeutic antibodies at Chugai, reasoned that an antibody that simultaneously binds factor IXa and factor X and positions them appropriately might reproduce the cofactor activity of factor VIIIa despite factor VIIIa having an entirely different molecular structure. His idea was also built on the earlier observation that a cofactor, protein S, can regulate the action of an enzyme toward its substrate by controlling their spatial positioning.

The concept was bold. Conventional antibodies recognize a single target through two identical antigen-binding arms. Hattori envisaged a molecule that could bind two different coagulation factors simultaneously while reproducing the highly dynamic spatial organization of the [intrinsic tenase complex](#) made up of factor VIIIa and factor IXa and assembled on the plasma membrane of platelets. Moreover, factor VIIIa accelerates coagulation through multiple molecular interactions, many of which were poorly understood at the time. Reproducing this function with an antibody that recognizes only a single epitope on each target seemed improbable



The Engineering of Emicizumab.

Panels A, B, and C summarize the key features of the nonclinical discovery research and clinical use of emicizumab, a humanized bispecific monoclonal antibody. After its engineering and improvement, emicizumab (originally called ACE910) was developed for subcutaneous prophylaxis with dose administration every week, every 2 weeks, or every 4 weeks. The phase 3 HAVEN clinical trials showed substantially lower annualized bleeding rates among participants who received emicizumab prophylaxis than among those who did not receive prophylaxis,⁷ which supports the use of emicizumab as routine prophylaxis in persons with hemophilia A. Panel D illustrates the mechanism of action of emicizumab, which simultaneously binds activated factor IX (factor IXa) and factor X, functionally replacing the cofactor activity of factor VIIIa. By bridging factor IXa and factor X, emicizumab promotes activation of factor X, which results in thrombin generation and restoration of effective hemostasis.

Clinical studies validated the strategy. In patients with hemophilia A, with or without inhibitors, **emicizumab dramatically reduces bleeding** and allows the replacement of frequent intravenous infusions with convenient subcutaneous administration ([Figure 1C](#)). The pivotal HAVEN 1 trial established the efficacy of emicizumab in patients with factor VIII inhibitors but also identified an important safety signal. Five thrombotic adverse events, including thrombotic microangiopathy and thrombosis, occurred in patients who received repeated high doses of activated prothrombin complex concentrate while receiving emicizumab prophylaxis. These observations led to recommendations to avoid prolonged use of high-dose activated prothrombin complex concentrate during emicizumab treatment, which were incorporated into a warning in the prescribing information. **Emicizumab was approved in the United States in 2017** and subsequently in Europe, Japan, and many other countries. It was initially approved for patients with factor VIII inhibitors and later expanded to prophylaxis for all patients with hemophilia A.

Hattori, Kitazawa, and Igawa established functional replacement as a new approach in coagulation medicine ([Figure 1D](#)). In so doing, they engineered a therapy that has transformed the lives of patients worldwide. **The 2026 Lasker–DeBakey Clinical Medical Research Award** recognizes not only the success of emicizumab but also the principle that biologic functions can be rationally engineered into therapeutic solutions.

Factor VIII

A large glycoprotein synthesized in liver sinusoidal and vascular endothelial cells that participates in the coagulation cascade. The active form of factor VIII (factor VIIIa), generated by the action of thrombin (activated factor II), is a cofactor for the serine protease factor IXa within the intrinsic tenase complex. The intrinsic tenase complex is essential for the generation of thrombin, the final enzyme of the coagulation cascade necessary for clot formation (so thrombin is activated by factor VIIIa; in an amplification reaction, it also activates factor VIII). In the circulation, the large majority of factor VIII molecules are bound to von Willebrand factor, which is necessary for its stability. Membrane-dependent assembly of the intrinsic tenase complex requires release of factor VIII from von Willebrand factor. Abnormalities of the factor VIII gene (located on the X chromosome) cause hemophilia A, a bleeding disorder. Conversely, factor VIII levels can double, triple, or quadruple during acute-phase responses and pregnancy, increasing the risk of thrombosis.

Bispecific antibody

An antibody with two binding sites directed at two different antigens or two different epitopes on the same antigen. Its effects are determined by its targets and structure. Bispecific antibodies may be full-length IgG or antibody fragments. Full-length bispecific antibodies are made with the use of strategies that ensure correct pairing of two different heavy and two different light chains, each with its own variable binding domain. Bispecific antibodies in clinical use include blinatumomab (for acute lymphoblastic leukemia), emicizumab (for hemophilia A), and faricimab (for neovascular age-related macular degeneration).

Thrombin

An enzyme that converts fibrinogen to fibrin to create a blood clot. It is generated from circulating prothrombin (factor II) by the action of factor Xa (activated factor X). A burst of thrombin generation is a critical step for stable clot formation. The activation of factors VIII and IX drives a robust burst of thrombin; genetic deficiency of factor VIII or factor IX causes hemophilia.

Intrinsic tenase complex

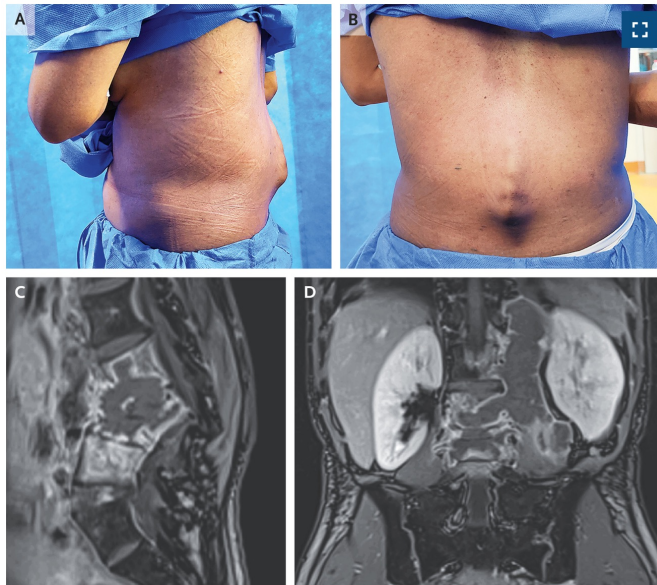
an enzymatic complex of the coagulation cascade composed of activated factor VIII (factor VIIIa) and activated factor IX (factor IXa). The intrinsic tenase complex assembles on the phosphatidylserine-exposing membrane of activated platelets in the presence of Ca^{2+} . Once assembled, the complex activates factor X: through a docking process scaffolded by factor VIII, factor IXa and factor X are brought together and positioned in a way that permits factor IXa to activate factor X. Thus, factor VIIIa accelerates factor X activation and thrombin generation. In hemophilia A, factor VIII is absent or dysfunctional, which impairs hemostasis.

FEIBA (Factor VIII Inhibitor Bypassing Activity) is not a single human protein, but rather a plasma-derived mixture of multiple human blood-clotting proteins and factors.

- **What it is made of:** It is manufactured from pooled human plasma and contains a mix of clotting zymogens and factors, primarily non-activated Factors II, IX, and X, along with activated Factor VII and trace amounts of others.
- **What it does:** It acts as an anti-inhibitor coagulant complex to help blood clot in patients with hemophilia A or B who have developed antibodies (inhibitors) against standard clotting factors.

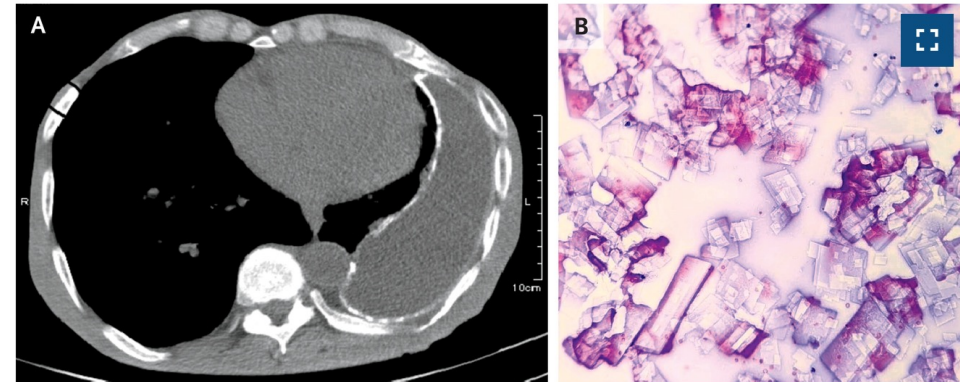
Spinal Tuberculosis

Morbus
Pott



A 36-year-old woman presented to the internal medicine clinic with a 6-year history of gradually worsening low back pain and intermittent night sweats. She had no fever, weight loss, or neurologic symptoms. She had recently emigrated from Angola, where she had faced barriers to access for health care. On physical examination, she had a sharp, kyphotic angulation of the lower spine — also known as a gibbus deformity (Panels A and B). She had limited forward flexion of the spine but no neurologic deficits and no tenderness to palpation. Magnetic resonance imaging of the spine showed L2–L4 segmental spondylitis complicated by abscess formation centered at L3–L4, with partial osseous destruction of the vertebral bodies, as well as L3 wedging and retropulsion that resulted in acute angulated kyphosis (Panel C, sagittal view). The abscess extended into the left paravertebral region from T11 to L4 and involved the psoas muscle (Panel D, coronal view). Mycobacterial culture and molecular testing of an aspirate from the paravertebral abscess identified *Mycobacterium tuberculosis*. Testing for human immunodeficiency virus was negative. A diagnosis of spinal tuberculosis — also known as Pott's disease — associated with cold abscesses (collections of pus without the typical signs of inflammation) was made. Spinal surgery was performed, and treatment with antituberculous agents was initiated. Fifteen months after the initiation of treatment, she had recovered fully and returned to work.

Tuberculous Empyema Resulting in



A 60-year-old man presented to the internal medicine clinic with a 3-month history of cough, dyspnea, and fatigue. On physical examination, decreased breath sounds over the left hemithorax were noted. Computed tomography of the chest showed a large pleural effusion associated with thickening and enhancement of both the parietal and the visceral pleura — a finding known as split pleura sign — and a partially calcified pleural rind (Panel A). Pleural fluid analysis was consistent with empyema. Additional pleural studies identified an adenosine deaminase level of 40 U per liter (reference value, <35), a triglyceride level of 21 mg per deciliter (0.2 mmol per liter; reference range, 40 to 200 mg per deciliter [0.5 to 2.3 mmol per liter]), and a cholesterol level of 272 mg per deciliter (7.0 mmol per liter; reference value, <45 mg per deciliter [<1.2 mmol per liter]). Microscopic examination of the fluid showed numerous polyhedral cholesterol crystals (Panel B). Mycobacterial culture and a polymerase-chain-reaction assay of the fluid were positive for *Mycobacterium tuberculosis*. Testing for human immunodeficiency virus was negative. A diagnosis of a tuberculous empyema resulting in pseudochylothorax was made. Tuberculous pleural effusions are a leading cause of pseudochylothorax. Pseudochylous effusions are associated with elevated cholesterol levels, in contrast to chylous effusions, which are associated with elevated triglyceride levels. A chest tube was temporarily inserted, and antituberculous therapy was started. Thereafter, the patient was lost to follow-up.



Case 30-2026: A 52-Year-Old Man with Vision Loss in the Left Eye

A 52-year-old man was evaluated in the ophthalmology clinic affiliated with this hospital because of **vision loss in the left eye**.

Twenty-seven months before the current presentation, **small-cell lung cancer metastatic to the liver was diagnosed at another hospital**. Treatment with carboplatin and etoposide was started, and 1 month later, atezolizumab was added to the regimen. Four months later, positron-emission tomography–computed tomography (PET-CT) showed evidence of a treatment response; treatment with carboplatin and etoposide was stopped, and atezolizumab was continued.

Twenty-one months before the current presentation, **PET-CT revealed a new left hypermetabolic adrenal nodule**, measuring 14 mm in the greatest dimension, that was suggestive of metastatic disease. Two months later, and 19 months before the current presentation, stereotactic body radiotherapy to the left adrenal gland was administered at a second hospital. One month later, and 18 months before the current presentation, **magnetic resonance imaging (MRI) of the head revealed new multifocal hemorrhagic cerebral lesions that were consistent with metastases**, and whole-brain radiation therapy was administered. PET-CT revealed evidence of disease in the neck involving lymph nodes along the internal jugular vein; during the next month, treatment with atezolizumab was stopped, and lurbinectedin was started. Subsequent MRI of the head and PET-CT showed evidence of a treatment response.

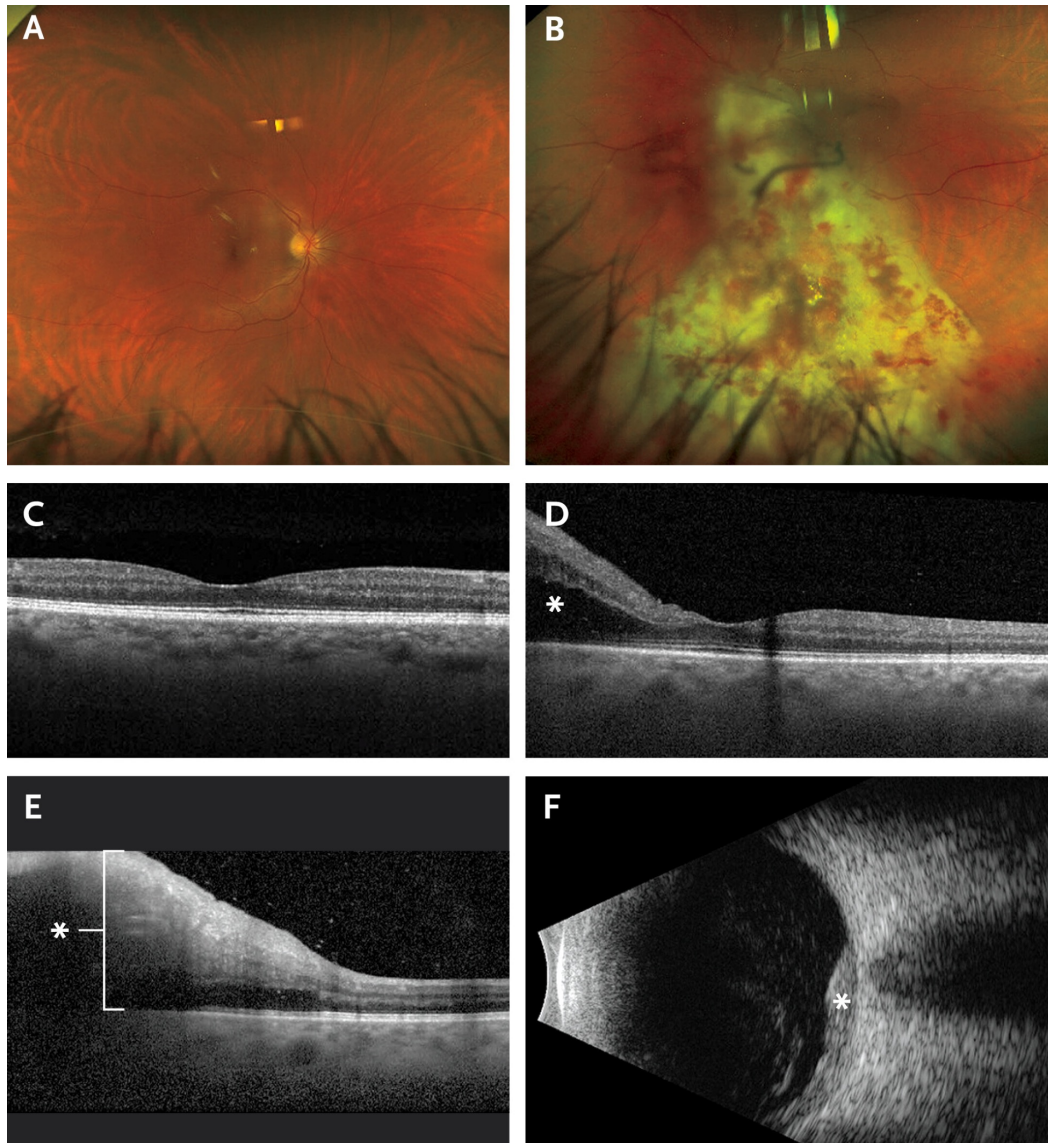
Eight months before the current presentation, blurred vision and intermittent pain developed in the left eye. Six months before the current presentation, seizure developed, along with aphasia and weakness involving the right side of the body. MRI of the head revealed evidence of progression of the supratentorial lesions that was consistent with metastatic disease. Treatment with levetiracetam and oral glucocorticoids was started. One month later, stereotactic radiotherapy was administered. Treatment with lurbnectin was stopped, and irinotecan was started. Subsequent MRI of the head and PET-CT showed evidence of a treatment response.

Three weeks before the current presentation, the blurred vision in the left eye began to worsen. The patient had floaters, intermittent pain, and new decreased vision in the temporal periphery in the left eye. He was evaluated in the ophthalmology clinic affiliated with this hospital.

In the ophthalmology clinic, additional history was obtained. The patient reported that he had had 1 week of sore throat and fatigue 2 months before the current presentation and that both had resolved spontaneously. He had no history of fever, chills, night sweats, odynophagia, or diarrhea. Other medical history included atrial fibrillation, diabetes mellitus, thoracic compression fractures, and depression. Medications included levetiracetam, pantoprazole, low-dose dexamethasone every other day for nausea (and higher-dose dexamethasone daily for 3 days after the administration of chemotherapy), and sulfamethoxazole–trimethoprim for prophylaxis against *Pneumocystis jirovecii* pneumonia.

He had no known adverse reactions to medications. The patient was born in Egypt and lived in northern Africa and the Middle East for most of his life. He moved to New England 5 years before the current presentation. He was retired and lived with his wife, adult children, and grandchildren. He had smoked one pack of cigarettes daily for the past 38 years and did not use alcohol or illicit drugs. A paternal uncle had had prostate cancer, and a paternal aunt had had stomach cancer.

On examination, the visual acuity was 20/100 in the right eye and 20/80 in the left eye. The pupils were symmetric and reactive to light. The intraocular pressure was normal in both eyes. A partial deficiency was noted in the outer inferior visual field of the left eye. Extraocular movements were normal. Slit-lamp examination revealed cataracts in both eyes; the anterior segments were otherwise normal. A dilated fundus examination ([Figure 1A and 1B](#)) revealed 2+ vitreous cells and a large, wedge-shaped lesion in the left eye; the lesion, which was characterized by retinal whitening associated with hemorrhages and some hard exudates, emanated from the inferior rim of the optic nerve head and extended to the inferior temporal aspect of the peripheral retina. No abnormalities were noted in the right eye on the dilated fundus examination.



Retinitis, sieht aus wie CMV

Multimodal Ophthalmic Imaging Studies.

Color fundus photographs show that the right eye is normal (Panel A) and the left eye has a retinal lesion (Panel B). Optical coherence tomographic images show the normal right eye (Panel C) and the lesion in the left eye (Panels D and E); intraretinal fluid (Panel D, asterisk) is seen in the nasal macula of the left eye, along with extensive intraretinal thickening (Panel E, asterisk) at the border between the normal retina and the lesion. An ultrasound image of the left eye shows the marked thickness of the lesion (Panel F, asterisk).

After a discussion with the patient regarding the risks and benefits of the procedure, a 30-gauge needle was inserted into the anterior chamber through the temporal cornea of the left eye, and approximately 100 µl of aqueous fluid was obtained. Nucleic acid amplification testing (NAAT) for CMV, herpes simplex virus (HSV), and varicella–zoster virus (VZV) DNA was performed. The patient received intravitreal foscarnet and oral valganciclovir for a presumed diagnosis of CMV retinitis. Two days later, additional laboratory test results became available. The CD4+ T-cell count was 239 per microliter (reference range, 295 to 1471), and the blood CMV DNA viral load was 348 IU per milliliter (reference value, not detected). A second dose of intravitreal foscarnet was administered, and the patient continued to receive two doses per week for the next 2 weeks. He reported resolution of the floaters in his left eye. The area of retinal whitening remained unchanged. Ten days later, the blood CMV DNA viral load had decreased to 47 IU per milliliter; testing for CMV IgM was nonreactive, and testing for CMV IgG was positive. CMV, HSV, and VZV DNA were not detected in the aqueous fluid.

Differential Diagnosis

This 52-year-old man with metastatic small-cell lung cancer presented with vision loss in the left eye. Ophthalmologic examination showed vitritis and a large area of retinal infiltration, and ultrasonography of the eye revealed retinal thickening at the site of the lesion. In light of the patient's immunocompromise owing to both chemotherapy and glucocorticoid therapy, I will begin by considering infectious causes of retinitis.

CMV Retinitis

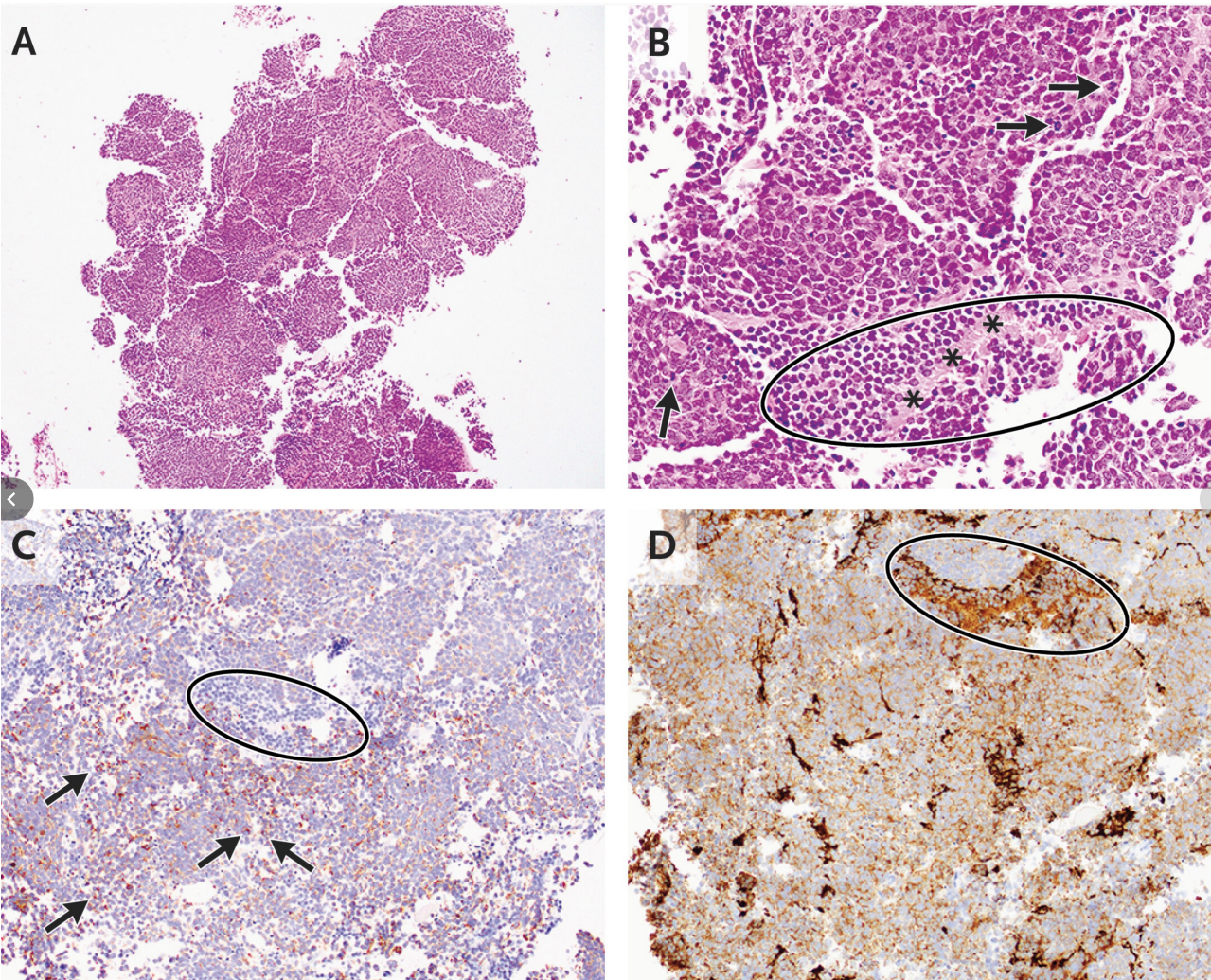
The patient received empirical treatment with intravitreal foscarnet and oral valganciclovir for a presumed diagnosis of CMV retinitis, which was based on the appearance of the retinal lesion and the history of immunosuppression. Two days after he began treatment, low-level CMV viremia was detected, which supported the diagnosis of CMV retinitis. However, a repeat examination performed after 2 weeks of treatment showed no improvement in the appearance of the lesion. In addition to the lack of response to therapy, several other aspects of the patient's presentation are not consistent with a diagnosis of CMV retinitis. First, CMV DNA was not detected in the aqueous fluid.

Cancer

Metastasis to the retina occurs on rare occasion in patients with small-cell lung cancer. Metastasis to the choroid is more common. In general, intraocular metastases are most common in patients who also have brain metastases, which were seen in this patient. The degree of retinal thickening seen on OCT and ultrasonography of the eye in this patient is more consistent with cancer than with infection or an adverse reaction to cancer treatment.

Next Steps

Given the range of possible diagnoses, each with a very different corresponding treatment, the next step in determining the diagnosis in this patient is a biopsy. In most patients with retinitis, the diagnostic approach begins with a vitrectomy (vitreous biopsy), which involves less risk than a retinal or chorioretinal biopsy. A vitrectomy provides only cytologic information but, in many cases, leads to a definitive diagnosis.



Retinal-Biopsy Specimen Obtained from the Left Eye.

Hematoxylin and eosin staining (Panel A) shows primitive-appearing, undifferentiated round blue tumor cells. At higher magnification (Panel B), the tumor cells are pleomorphic, with minimal eosinophilic cytoplasm and finely stippled (salt-and-pepper appearance) nuclear chromatin; admixed karyorrhectic debris is present, and mitotic activity is conspicuous (arrows). A small portion of background outer retina is present (oval), with the outer nuclear layer composed of monomorphic round cells adjacent to the eosinophilic photoreceptor outer segments (rods and cones; asterisks). Immunohistochemical staining for pancytokeratin (AE1/AE3/CAM5.2) (Panel C) shows varying amounts of staining in the tumor cells, often in a perinuclear dot or ringlike pattern (arrows), without staining of the retina (oval). Immunohistochemical staining for synaptophysin (Panel D) is positive, a finding that confirms the neuroendocrine nature of the tumor; normal bandlike staining within the retina is also present (oval).

Pathological Diagnosis

Retinal metastasis of small-cell lung cancer.

Discussion of Management

The patient was referred to the ocular oncology service for further evaluation and treatment. On examination of the left eye, there was no light perception, and the intraocular pressure was 28 mm Hg. The anterior chamber contained clinically significant cells that were suggestive of a disseminated intraocular tumor. The gradual decline in the patient's vision to no light perception suggested the possibility of optic-nerve infiltration of the tumor.

The patient and his family were informed of the poor visual prognosis. The possible management options were discussed, including observation, systemic chemotherapy, local radiation therapy, and enucleation. The patient opted for palliative ocular radiation therapy, with the goal of comfort and globe salvage. He was referred to the radiation oncology service, and generalized irradiation of the left globe was recommended to increase the likelihood of local disease control.

The patient was scheduled for follow-up in the ocular oncology clinic 6 weeks later.

However, he returned to his home country during this time and later died from complications of progressive small-cell lung cancer.

Final Diagnosis

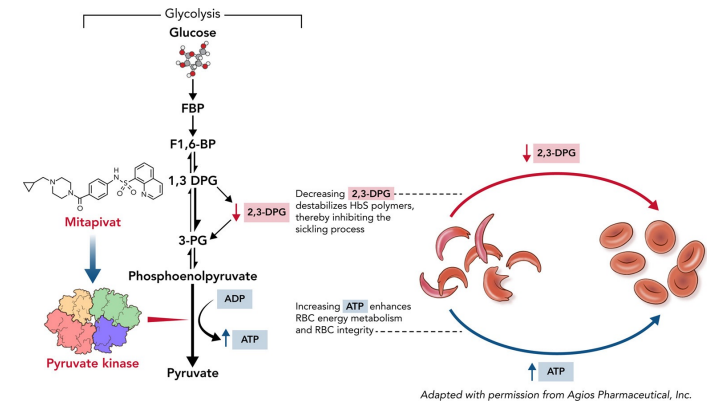
Retinal metastasis of small-cell lung cancer.

THE LANCET

Mitapivat (Handelsname: *Pyrukynd*) ist ein First-in-class-Arzneistoff zur Behandlung bestimmter Formen von seltener genetisch bedingter Blutarmut (hämolytische Anämie). Es ist der erste zugelassene **Aktivator der Pyruvatkinase**.

Wirkmechanismus

Rote Blutkörperchen (Erythrozyten) besitzen keine Mitochondrien und sind zur Energiegewinnung rein auf die anaerobe Glykolyse angewiesen. Ein zentrales Enzym in diesem Prozess ist die Pyruvatkinase (PK). Mitapivat bindet allosterisch an das Enzym und **aktiviert die Pyruvatkinase**. Dadurch steigt die Produktion von Adenosintriphosphat (ATP) in den Zellen. Die verbesserte Energieversorgung stabilisiert die Zellmembran der roten Blutkörperchen, verlängert ihre Lebensdauer und senkt die Rate des vorzeitigen Blutzerfalls (Hämolyse).



Mitapivat binds to the enzyme and **stabilizes the active tetrameric conformation**, shifting the equilibrium away from the inactive states. Because of this, it is effective against both normal (wild-type) and many mutant forms of the enzyme.

Efficacy and safety of mitapivat in patients with sickle cell disease (RISE UP): a phase 3, double-blind, global, randomised, placebo-controlled trial

Mitapivat works in Thalassemia; does it work in sickle cell disease?

Add this to hydroxyurea and save lots of “gene therapy”

Summary

Background Persistent haemolytic anaemia and recurrent vaso-occlusion drive complications and accelerate mortality in sickle cell disease. Mitapivat, an oral allosteric activator of pyruvate kinase, increases ATP and decreases 2,3-DPG with the potential to improve haemolytic anaemia and reduce sickling. We aimed to evaluate the efficacy and safety of mitapivat in patients with sickle cell disease.

Methods We report results from RISE UP, a phase 3, double-blind, global, randomised, placebo-controlled trial from 69 sites across 15 countries. Patients older than 16 years with anaemia and recurrent sickle cell pain crises were randomly assigned (2:1) to either mitapivat 100 mg or placebo twice a day using permuted-block randomisation. Primary endpoints, assessed in all randomly assigned patients, were haemoglobin response (≥ 1.0 g/dL increase in average haemoglobin concentration from week 24 to week 52 compared with baseline) and annualised rate of sickle cell pain crises. This study is registered with ClinicalTrials.gov, NCT05031780, and the open-label extension is ongoing.

Findings A total of 207 patients were randomly assigned to mitapivat (138 [67%]) or placebo (69 [33%]). 56 (41%) of 138 patients in the mitapivat group had a haemoglobin response, compared with two (3%) of 69 patients on placebo (adjusted difference 38%, 95% CI 29–47; two-sided $p < 0.0001$). The annualised rate (95% CI) of sickle cell pain crises was 2.6 (2.3–3.0) for mitapivat and 3.1 (2.6–3.6) for placebo (two-sided $p = 0.1213$). Serious adverse events were reported in 28 (20%) patients on mitapivat and 20 (29%) patients on placebo; one (1%) patient and 0 patients, respectively, were deemed treatment related.

Interpretation Mitapivat, an oral pyruvate kinase activator, with a novel mechanism that ameliorates haemolytic anaemia, has the potential to be an effective and convenient disease-modifying treatment for people with sickle cell disease.

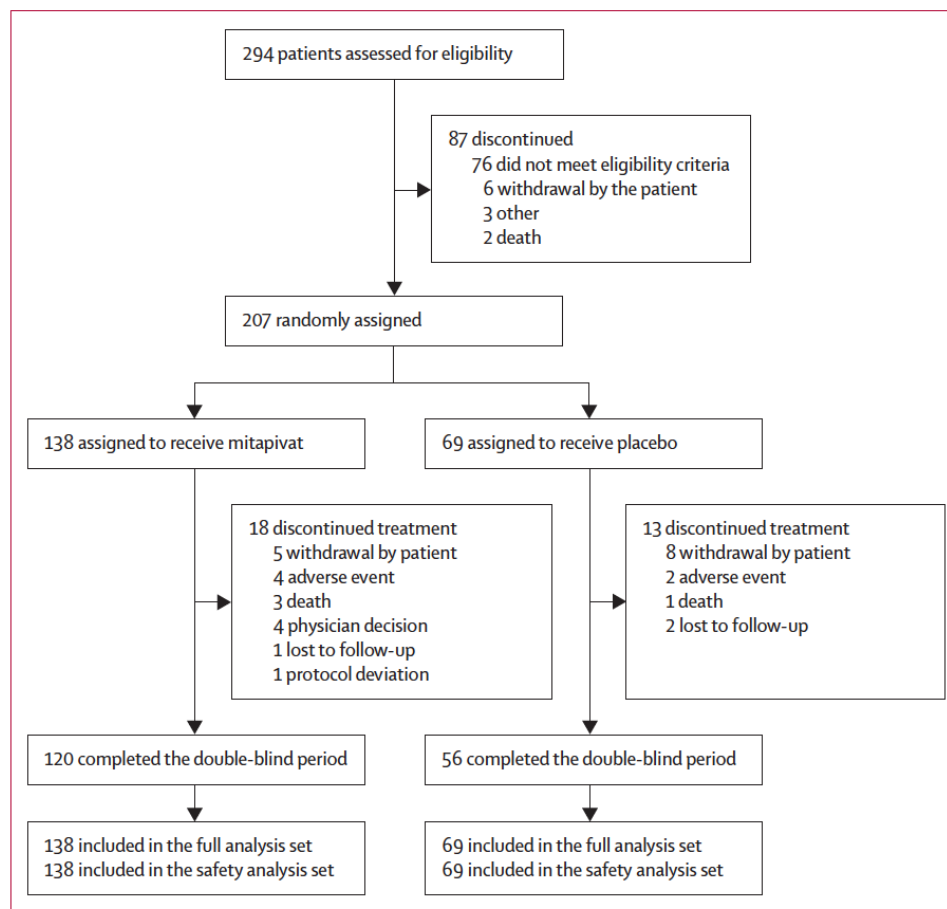


Figure 1: Trial profile

	Mitapivat 100 mg twice a day (n=138)	Placebo twice a day (n=69)
Median age, years	25.0 (20.0–34.0)	27.0 (22.0–37.0)
Sex		
Male	62 (45%)	26 (38%)
Female	76 (55%)	43 (62%)
Race		
Black or African American	103 (75%)	53 (77%)
White	20 (15%)	8 (12%)
Asian	1 (1%)	1 (1%)
Unknown	3 (2%)	2 (3%)
Not reported	11 (8%)	5 (7%)
Haemoglobin, g/dL	8.6 (1.1)	8.5 (1.2)
Indirect bilirubin, µmol/L	32.9 (28.9)	30.1 (25.8)
Lactate dehydrogenase, U/L	434.4 (178.2)	449.7 (199.9)
Reticulocyte count, ×10 ⁹ /L	267.5 (125.2)	248.3 (130.8)
Reticulocytes, %	10.0 (5.1)	9.4 (6.1)
Erythropoietin, IU/L	115.6 (130.4)	187.4 (498.7)
Sickle cell disease genotyping		
HbSS	119 (86%)	57 (83%)
HbSC	4 (3%)	2 (3%)
HbS/β ⁰ -thalassaemia	4 (3%)	5 (7%)
HbS/β ⁺ -thalassaemia	4 (3%)	3 (4%)
Other sickle cell syndrome variants*	3 (2%)	1 (1%)
Missing†	4 (3%)	1 (1%)
Number of sickle cell pain crises per year‡	3.4 (1.6)	3.4 (1.7)
Transfusion burden (number of red blood cell units)§		
0	89 (65%)	43 (62%)
1–2	30 (22%)	12 (17%)
3–5	13 (9%)	8 (12%)
>5	6 (4%)	6 (9%)
Previous disease-modifying, sickle cell disease-related therapies¶	104 (75%)	53 (77%)
Hydroxyurea use		
Yes	103 (75%)	51 (74%)
No	35 (25%)	18 (26%)

Data are n (%), median (IQR), or mean (SD). Baseline is defined as the average of all assessments during the screening period up to the randomisation date. Assessments within 8 weeks after a red blood cell transfusion are excluded from the baseline derivation. HbSS=sickle cell anaemia. HbSC=sickle cell disease from HbS and haemoglobin C. HbS=haemoglobin S. HbSD=sickle cell disease from HbS and haemoglobin D. HbO=haemoglobin O. *Compound heterozygous genotypes other than HbSS, HbSC, HbS/β⁰-thalassaemia, and HbS/β⁺-thalassaemia (eg, HbSD-Punjab, HbO). †Patients for whom the central genotype confirmation is not available and in which sickle cell disease diagnosis was established locally at the investigative site per eligibility criteria. ‡Sickle cell pain crises (pain or acute chest syndrome that resulted in an encounter with a health-care provider, hepatic sequestration, splenic sequestration, or priapism requiring a visit to a medical centre) within 12 months before informed consent and during screening. §In the 52 weeks before informed consent. ¶Previous disease-modifying, sickle cell disease-related therapies could include hydroxyurea (also includes patients on hydroxyurea at study entry), crizanlizumab, L-glutamine, and voxelotor. ||Assessed at study enrolment.

Table 1: Baseline characteristics of the full analysis set

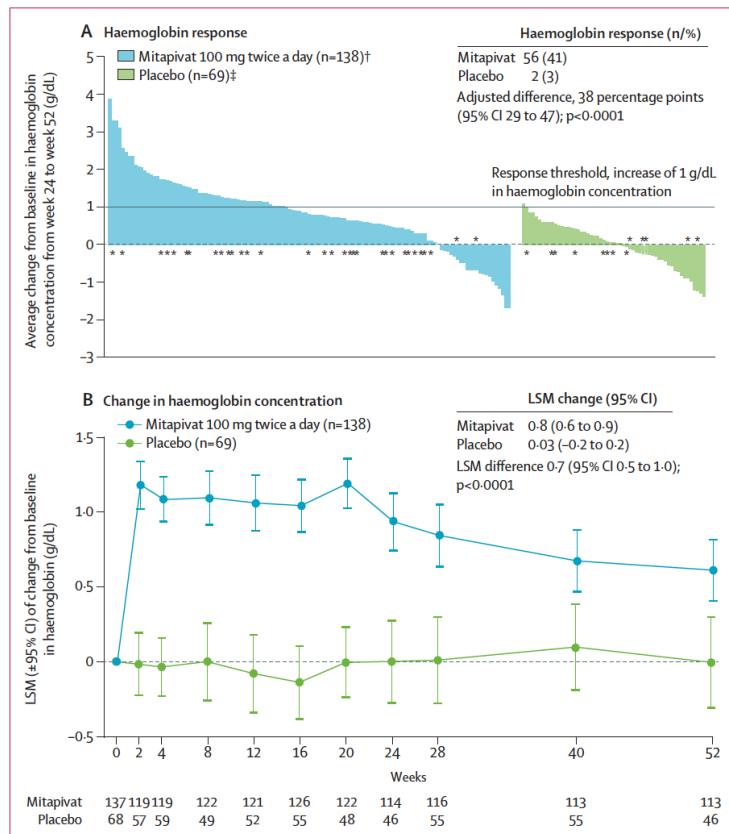


Figure 2: Changes from baseline in the haemoglobin concentration
Baseline was defined as the average of all assessments during the screening period up to the randomisation date. LSM=least-squares mean. *Indicates participants with no hydroxyurea use at randomisation. †Includes 13 patients with missing baseline or with fewer than two assessments from week 24 to week 52, not depicted. ‡Includes 12 patients with missing baseline or with fewer than two assessments from week 24 to week 52, not depicted.

	Mitapivat 100 mg twice a day (n=138)	Placebo twice a day (n=69)	Difference or rate reduction
Key secondary endpoints			
Haemoglobin, g/dL			
Average of week 24 to week 52 change from baseline	0.77 (0.6 to 0.9)	0.03 (-0.2 to 0.3)	..
Mitapivat/placebo	..	..	0.7 (0.5 to 1.0); p<0.0001
Indirect bilirubin, µmol/L			
Average of week 24 to week 52 change from baseline	-16.0 (-18.8 to -13.3)	0.9 (-2.8 to 4.6)	..
Mitapivat/placebo	..	..	-16.9 (-21.0 to -12.8); p<0.0001
PROMIS Fatigue 13a Short Form T-scores			
Average of week 24 to week 52 change from baseline	-2.7 (-4.5 to -0.9)	-2.3 (-4.6 to 0.1)	..
Mitapivat/placebo, LSM (95% CI)	..	..	-0.5 (-3.0 to 2.0); p=0.7112
Annualised frequency of hospitalisations for SCPC (95% CI)	1.6 (1.3 to 1.9)	1.8 (1.4 to 2.3)	..
Rate reduction*	14% (-10.8 to 32.7)	..	..
Rate ratio (95% CI)†; mitapivat/placebo‡	..	..	0.9 (0.7 to 1.1); p=0.2498
Reticulocytes			
Average of week 24 to week 52 change from baseline	-2.4% (-3.1 to -1.6)	-0.1% (-1.1 to 0.9)	..
Mitapivat/placebo‡	..	..	-2.2 (-3.3 to -1.1); p=0.0001
Additional secondary endpoints			
Lactate dehydrogenase, U/L			
Average of week 24 to week 52 change from baseline	-60.2 (-81.6 to -38.7)	10.6 (-19.1 to 40.2)	..
Mitapivat/placebo	..	..	-70.7 (-103.5 to -38.0)
Reticulocyte count ×10⁷/L			
Average of week 24 to week 52 change from baseline	-34.3 (-52.5 to -16.1)	-0.43 (-25.3 to 24.4)	..
Mitapivat/placebo	..	..	-33.9 (-62.1 to -5.6)
Erythropoietin, IU/L			
Average of week 24 to week 52 change from baseline	-38.0 (-54.8 to -21.1)	-42.1 (-65.6 to -18.5)	..
Mitapivat/placebo	..	..	4.1 (-21.6 to 29.8)
Time to sickle cell pain crises, weeks			
Time to first sickle cell pain crises	23.6 (15.9 to 30.4)	17.3 (12.1 to 32.0)	..
Time to second sickle cell pain crises	52.4 (41.3 to not estimable)§	40.3 (21.1 to not estimable)§	..
Annualised rate of emergency department visits for sickle cell pain crises	1.8 (1.5 to 2.1)	2.3 (1.8 to 2.8)	..
Rate reduction*; mitapivat/placebo	..	..	21% (0.0 to 36.9)
Rate ratio†; mitapivat/placebo	..	..	0.8 (0.6 to 1.0)

(Table 2 continues on next page)

	Mitapivat 100 mg twice a day (n=138)	Placebo twice a day (n=69)	Difference or rate reduction
(Continued from previous page)			
Ad-hoc analysis			
On-study red blood cell transfusions	33 (23.9%)	28 (40.6%)	..
Relative reduction*; mitapivat/placebo	..	..	41.1%
Total number of red blood cell units transfused	97	110	..
Average red blood cell units transfused per patient	0.7	1.6	..
Relative reduction*; mitapivat/placebo	..	..	55.9%

Data are least-squares mean (95% CI), % (95 CI), or n (%). Baseline is defined as the average of all assessments during the screening period up to the randomisation date, unless otherwise stated. For PROMIS Fatigue 13a Short Form T-score results, baseline is defined as the last assessment before randomisation for patients randomly assigned and not dosed or before the start of study treatment for patients randomly assigned and dosed. Assessments within 8 weeks after a red blood cell transfusion are excluded from the derivations and analysis, except for sickle cell pain crises-related endpoints. Sickle cell pain crises events that occur within 7 days from a previous sickle cell pain crises event onset are not counted as a separate event. Haemoglobin response is defined as a ≥1.0 g/dL increase in average haemoglobin concentrations from week 24 to week 52 compared with baseline. Patients who do not have at least two on-treatment haemoglobin assessments from week 24 to week 52 were considered non-responders. LSM=least-squares mean. PROMIS=Patient-Reported Outcomes Measurement Information System. SCPC=sickle cell pain crises.
*Rate reduction=100% × (1 - rate ratio). †Relative reduction (mitapivat vs placebo)=100% × (1 - proportion of patients transfused in mitapivat group/proportion of patients transfused in placebo group) or 100% × (1 - average red blood cell units transfused per patient in the mitapivat group/average red blood cell units transfused per patient in the placebo group). Missing transfusion data after treatment dropout were not imputed. ‡Due to the implementation of a hierarchical statistical testing strategy to control multiplicity in the overall study for type I error, statistical significance cannot be inferred for these additional endpoints. The statistical values provided are included to facilitate interpretation within the broader context but should not be considered to indicate statistical significance. §The primary reason for non-evaluable upper bounds is insufficient event data at later timepoints due to censoring.

Table 2: Secondary and ad-hoc endpoints

	Mitapivat 100 mg twice a day (n=138)	Placebo twice a day (n=69)
Any adverse events	134 (97%)	68 (99%)
Treatment-related adverse events	42 (30%)	20 (29%)
Grade ≥3 adverse events	46 (33%)	28 (41%)
Grade ≥3 treatment-related adverse events*	7 (5%)	2 (3%)
Serious adverse events	28 (20%)	20 (29%)
Serious treatment-related adverse events†	1 (1%)	0
Adverse events leading to discontinuation of study drug‡	6 (4%)	2 (3%)
Adverse events leading to dose reduction§	7 (5%)	0
Adverse events leading to interruption of study drug¶	5 (4%)	1 (1%)
Adverse events leading to death	2 (1%)	1 (1%)
Treatment-related adverse events leading to death	0	0
Most common adverse events**		
All events		
Any grade	134 (97%)	68 (99%)
Grade ≥3	46 (33%)	28 (41%)
Arthralgia		
Any grade	41 (30%)	13 (19%)
Grade ≥3	3 (2%)	1 (1%)
Pain in extremity		
Any grade	38 (28%)	16 (23%)
Grade ≥3	1 (1%)	0
Headache		
Any grade	34 (25%)	14 (20%)
Grade ≥3	1 (1%)	0
Back pain		
Any grade	30 (22%)	18 (26%)
Grade ≥3	0	0
Fatigue		
Any grade	24 (17%)	9 (13%)
Grade ≥3	2 (1%)	0
Malaria		
Any grade	23 (17%)	9 (13%)
Grade ≥3	3 (2%)	4 (6%)
Upper respiratory tract infection		
Any grade	20 (15%)	5 (7%)
Grade ≥3	0	1 (1%)
Nausea		
Any grade	19 (14%)	8 (12%)
Grade ≥3	0	0
Pneumonia		
Any grade	14 (10%)	11 (16%)
Grade ≥3	11 (8%)	5 (7%)
Pain		
Any grade	14 (10%)	9 (13%)
Grade ≥3	0	0

(Table 3 continues in next column)

	Mitapivat 100 mg twice a day (n=138)	Placebo twice a day (n=69)
(Continued from previous column)		
Pyrexia		
Any grade	14 (10%)	6 (9%)
Grade ≥3	2 (1%)	1 (1%)
Constipation		
Any grade	14 (10%)	5 (7%)
Grade ≥3	0	0
Influenza-like illness		
Any grade	10 (7%)	10 (15%)
Grade ≥3	0	0
Vomiting		
Any grade	8 (6%)	7 (10%)
Grade ≥3	0	0
Anaemia		
Any grade	6 (4%)	8 (12%)
Grade ≥3	6 (4%)	6 (9%)
Abdominal pain		
Any grade	5 (4%)	10 (15%)
Grade ≥3	0	0
Haemolysis		
Any grade	1 (1%)	4 (6%)
Grade ≥3	0	4 (6%)

Data are n (%). Adverse events were collected throughout the study and classified using Common Terminology Criteria for Adverse Events (version 4.03). *12 preferred terms were reported in seven patients treated with mitapivat, which were insomnia, middle insomnia, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased, arthralgia, pain in extremity, fatigue, hot flushes, gingivitis, pneumonia, and haemolytic anaemia; and two preferred terms were reported in two placebo patients, which were haemolysis and gamma-glutamyl transferase increased. †Haemolytic anaemia reported in one patient treated with mitapivat. ‡Mitapivat group: one patient had non-serious related adverse events of grade 3 fatigue, gingivitis, hot flushes, and middle insomnia that led to discontinuation; one patient had a non-serious related grade 3 adverse event of aspartate aminotransferase increased and a non-serious unrelated grade 2 adverse event of blood bilirubin increased that led to discontinuation; one patient had an unrelated serious adverse event of grade 4 hepatic enzyme increased (secondary to severe sickle cell pain crisis and multi-organ failure) that led to discontinuation; one patient had a non-serious related grade 2 adverse event of hepatic cytolysis, non-serious related grade 1 adverse event of flank pain, and non-serious related grade 2 adverse event of pruritus that led to discontinuation; and one patient had an unrelated non-serious adverse event of grade 2 transaminases increased (secondary to acute Epstein-Barr virus infection) that led to discontinuation. Placebo group: one patient had an unrelated serious adverse event of grade 4 dengue fever that led to discontinuation, and one patient had an unrelated serious adverse event of grade 3 haemolysis that led to discontinuation. §Fatigue, alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased, depressed mood, middle insomnia, hot flushes, retinopathy proliferative, hepatic cytolysis, gingivitis, joint swelling, and headache. ¶Mitapivat group: hepatitis A, pulmonary sepsis, sepsis, anaemia, diarrhoea, alanine aminotransferase increased, hyperkalaemia, neuromyopathy, and pulmonary hypertension. Placebo group: dengue fever, hepatitis viral, and pneumonia. ||Mitapivat group: aspiration and pulmonary hypertension. Placebo group: septic shock. **Any grade in at least 10% of patients or grade 3 and greater in at least 5% of patients in any treatment group.

Table 3: Adverse events

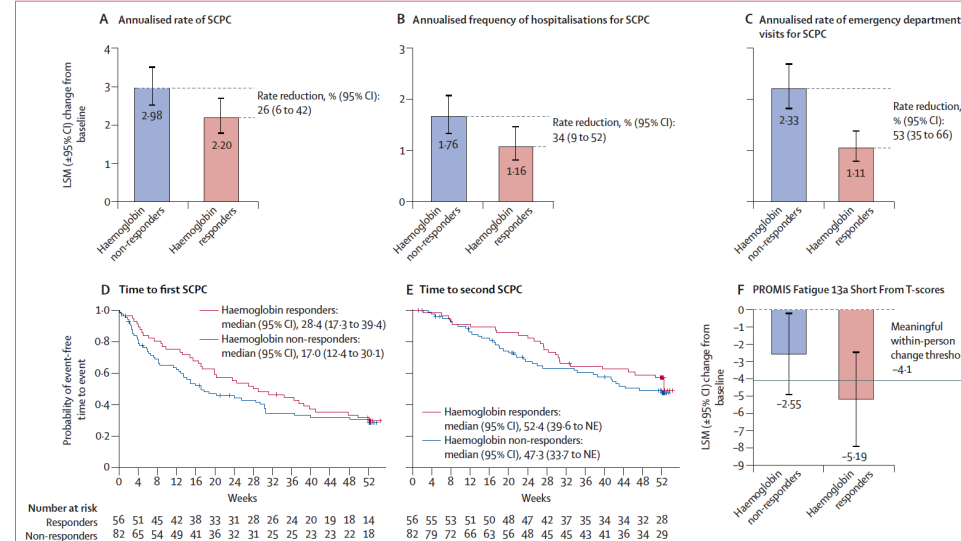


Figure 3: Post-hoc analysis of haemoglobin responders versus non-responders in the mitapivat group
Rate reduction=100% × (1 - rate ratio). LSM=least-squares mean. NE=not estimable. PROMIS=Patient-Reported Outcomes Measurement Information System. SSCP=sickle cell pain crises.

Implications of all the available evidence

Mitapivat is an oral pyruvate kinase activator that drives a haemoglobin response and improves haemolysis in patients with sickle cell disease. Combined with previous evidence from early-phase clinical trials of mitapivat in patients with sickle cell disease, evidence in this phase 3 study continues to support that mitapivat has the potential to minimise complications, improve quality of life, and provide clinical benefit by improving haemolytic anaemia in sickle cell disease. Ongoing extension trials continue to assess the long-term efficacy, safety, and tolerability of mitapivat in sickle cell disease.

Ein **Angioödem** (auch bekannt als **Quincke-Ödem**) ist eine plötzliche, tief sitzende Schwellung der Unterhaut (Subkutis) oder der Schleimhäute. Sie entsteht durch eine kurzfristig erhöhte Durchlässigkeit der Blutgefäße, wodurch Flüssigkeit ins Gewebe austritt. Besonders häufig betroffen sind das **Gesicht (Lippen, Augenlider)**, die Zunge, der Rachen sowie die Extremitäten oder der Magen-Darm-Trakt.

Histamin-vermittelt (Mastzell-vermittelt):

Merkmale: Tritt meist sehr schnell (Minuten bis Stunden) auf und geht fast immer mit **Juckreiz und Quaddeln (Nesselsucht/Urtikaria)** einher.

Auslöser: Allergische Reaktionen (z. B. auf Nahrungsmittel, Insektenstiche, Medikamente) oder Infekte und Stress.

Therapie: Reagiert gut auf klassische Notfallmedikamente wie **Antihistaminika, Kortison** und bei schweren Verläufen Adrenalin.

Bradykinin-vermittelt:

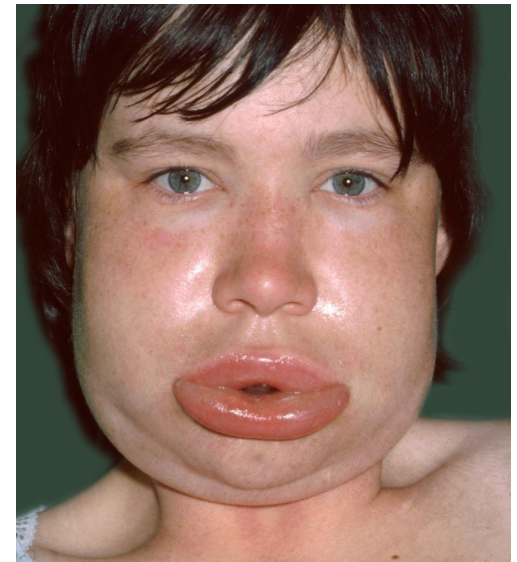
Merkmale: Die Schwellungen entwickeln sich oft langsamer (über Stunden) und halten tagelang an. Es gibt hierbei **keinen Juckreiz** und keine Quaddeln.

Auslöser:

Häufig als Nebenwirkung von Blutdrucksenkern wie **ACE-Hemmern** oder Sartanen.

Als seltene, genetisch bedingte Erkrankung: das **Hereditäre Angioödem (HAE)**, bei dem ein Mangel des Proteins C1-Inhibitor vorliegt.

Therapie: Herkömmliche Allergiemedikamente wie Kortison oder Antihistaminika sind hier **wirkungslos**. Behandelt wird stattdessen mit spezifischen Medikamenten (z. B. C1-Inhibitor-Konzentraten oder dem Wirkstoff Icatibant)

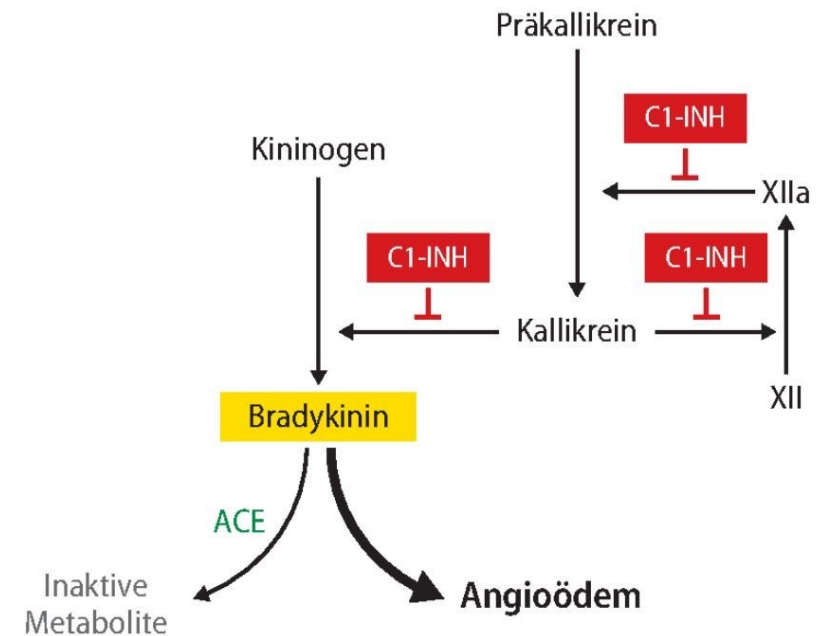


HAE wird meist **autosomal-dominant vererbt** (50 % Weitergabewahrscheinlichkeit an Nachkommen), wobei rund 20 % der Fälle auf spontane Neumutationen zurückgehen. Ursächlich ist meist ein Fehler im *SERPING1*-Gen auf Chromosom 11, welcher zu einem Mangel oder einer Fehlfunktion des **C1-Esterase-Inhibitors (C1-INH)** führt.

Durch diesen Mangel fehlt dem Komplement- und Kontaktsystem ein wichtiger Bremsmechanismus. In der Folge kommt es zu einer unkontrollierten **Überproduktion des Gewebehormons Bradykinin**, welches die Blutgefäße erweitert, sie durchlässig macht und so Flüssigkeit ins Gewebe austreten lässt.

Formen der Erkrankung

- **HAE Typ I (ca. 85 %):** Die Konzentration des C1-Inhibitors im Blut ist deutlich erniedrigt.
- **HAE Typ II (ca. 15 %):** Die Konzentration ist normal oder erhöht, aber das Protein ist funktionsunfähig.
- **HAE Typ III (sehr selten):** Normale C1-INH-Werte; oft liegen Mutationen in anderen Genen (z. B. Faktor XII) vor. Betrifft fast ausschließlich Frauen und wird stark durch Östrogene beeinflusst

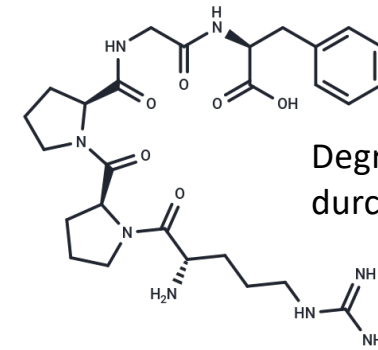


Bradykinin entsteht im Blutplasma und im Gewebe durch die enzymatische Abspaltung aus einem Vorläuferprotein, dem hochmolekularen Kininogen (HMWK). Dieser Prozess wird durch das Enzym **Kallikrein** katalysiert. Der Abbau im Körper erfolgt primär durch das *Angiotensin-Converting-Enzyme* (ACE) sowie andere Kininasen.

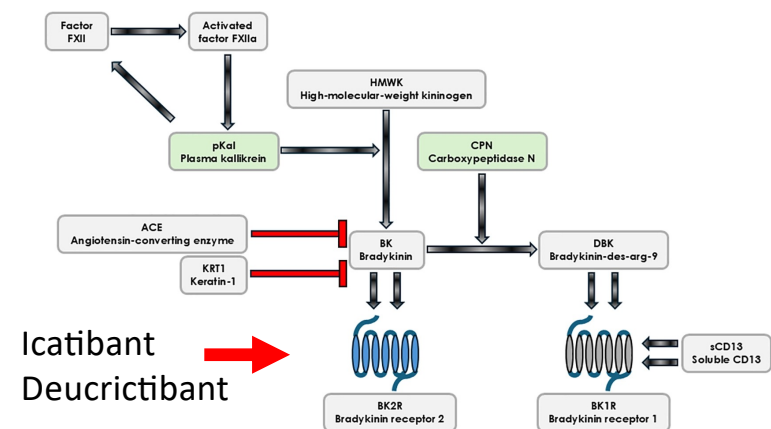
Hauptwirkungen im Organismus

Bradykinin entfaltet seine Wirkung über die Bindung an spezifische G-Protein-gekoppelte Rezeptoren (hauptsächlich B1 und B2) auf Zelloberflächen:

- **Gefäßerweiterung (Vasodilation):** Es entspannt die glatte Muskulatur der Blutgefäße, was zu einer deutlichen Senkung des Blutdrucks führt.
- **Erhöhte Gefäßdurchlässigkeit (Permeabilität):** Die Wände kleiner Blutgefäße werden durchlässiger, wodurch Flüssigkeit in das umliegende Gewebe austreten kann (Schwellung/Ödem).
- **Schmerzauslösung:** Bradykinin reizt direkt die freien Nervenenden (Nozizeptoren) und steigert die Schmerzempfindlichkeit an verletzten oder entzündeten Stellen



Degradiert
durch ACE



Oral deucricitbant for on-demand treatment of hereditary angioedema attacks: a phase 3, multicentre, randomised, double-blind, placebo-controlled crossover trial

Summary

Background In hereditary angioedema, a rare bradykinin-mediated condition, oral on-demand treatments facilitating prompt administration and providing rapid, sustained relief and attack resolution remain scant. We investigated the efficacy and safety of deucricitbant, an oral bradykinin B2 receptor antagonist, for on-demand treatment of hereditary angioedema attacks.

Methods RAPIDe-3 was a phase 3, double-blind, 2×2 crossover trial in adolescent and adult participants (aged ≥12 to <18 years and aged ≥18 to ≤75 years, respectively) with hereditary angioedema, at 59 sites across 24 countries on six continents. Eligible participants had hereditary angioedema, including those with normal C1 inhibitor associated with a documented genetic variant, at least two attacks within the last 3 months before screening, and experience with effectively using conventional on-demand therapies for hereditary angioedema attacks. Participants were randomly allocated in a 1:1 ratio to one of two double-blind crossover sequences to treat two attacks with a 20 mg oral deucricitbant immediate-release capsule or placebo as either deucricitbant–placebo or placebo–deucricitbant, stratified by age and use of long-term prophylaxis. The primary endpoint was time to onset of symptom relief, defined as Patient Global Impression of Change rating of at least a little better. Safety was assessed in all participants who received any dose of study drug. RAPIDe-3 is registered with ClinicalTrials.gov (NCT06343779) and is complete.

Findings Between April 4, 2024, and Sept 1, 2025, 149 people were assessed for eligibility, and 134 eligible participants (ten [7%] adolescents and 124 [93%] adults) were randomly allocated. 58 (43%) were male and 76 (57%) were female, and the median age was 38·0 years (IQR 27·0–50·0). 113 participants treated 201 attacks. The primary efficacy analysis included 88 participants with paired treated attacks. Of these, 47 (53%) participants were female and 41 (47%) were male, and 60 (68%), 16 (18%), 4 (5%), and 1 (1%) were White, Asian, Black, and American Indian or Alaska Native, respectively. Onset of symptom relief occurred significantly faster with deucricitbant than placebo, with median times of 1·28 h (95% CI 1·05 to 1·52) and more than 12 h (5·82 to >12), respectively ($p<0·0001$). Fatigue was the only adverse event reported more than once within 3 days post-treatment: a single event was reported by two participants, one of which was deemed unrelated to treatment. Across the study, no treatment-related adverse events were assessed as severe or serious, and no adverse events led to treatment discontinuation.

Interpretation Oral deucricitbant provided faster times to symptom relief than placebo and was generally well tolerated. These results support the use of deucricitbant as potentially the first orally administered bradykinin B2 receptor antagonist for the treatment of attacks of bradykinin-mediated angioedema, including hereditary angioedema, and may address an unmet need for options that are effective and well tolerated, with convenient administration.

Blocking B2
receptor is cheaper
than gene therapy.

A „pill-in-pocket“
cross-over trial

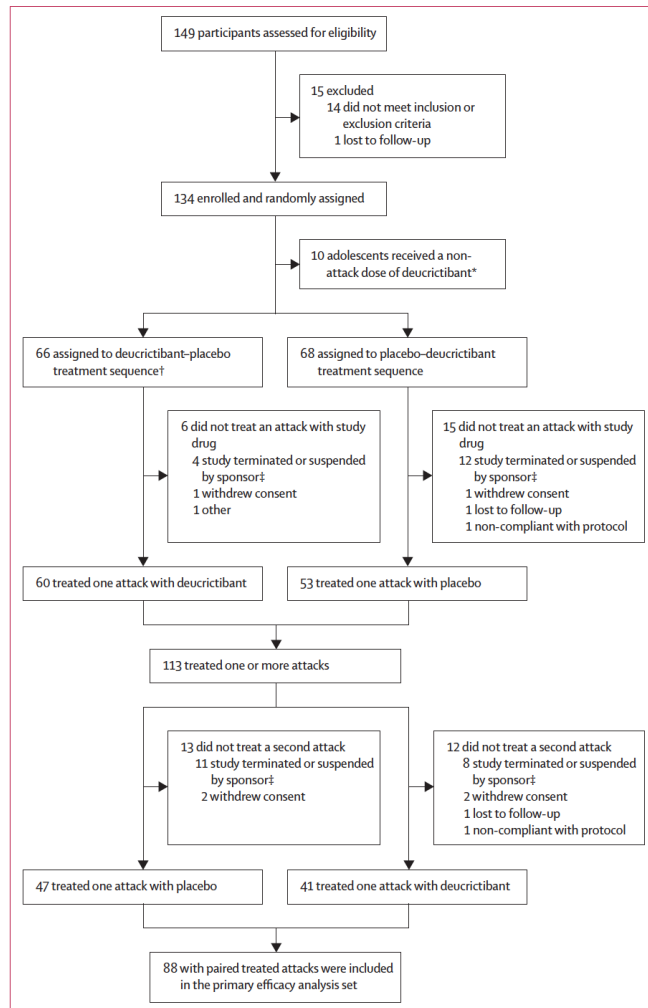


Figure 1: Trial profile
 *Dose given for pharmacokinetic sampling. †One participant who treated one attack was randomly allocated to receive deucricitibant first in the sequence but instead received placebo. ‡The sponsor ended the trial after the prespecified number of participants with treated attacks was met, and then participants were allowed to transition to the open-label extension before all participants completed treatment of two attacks.

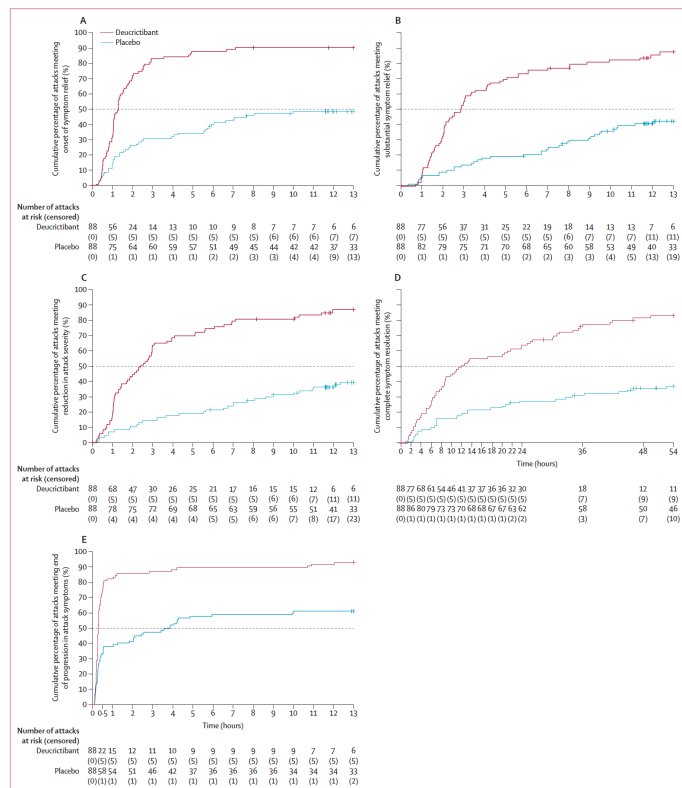
	Deucricitibant (n=101)*	Placebo (n=100)*	Overall patients (n=113)†
Age, years			
Median (IQR)	36.0 (27.0–49.0)	36.5 (28.0–50.0)	36.0 (27.0–50.0)
Sex‡			
Male	46 (46%)	46 (46%)	51 (45%)
Female	55 (54%)	54 (54%)	62 (55%)
Race§			
White	70 (69%)	70 (70%)	80 (71%)
American Indian or Alaska Native	1 (1%)	1 (1%)	1 (1%)
Asian	17 (17%)	16 (16%)	17 (15%)
Black or African American	4 (4%)	6 (6%)	6 (5%)
Other	5 (5%)	3 (3%)	5 (4%)
Not reported	4 (4%)	4 (4%)	4 (4%)
Geographical region¶			
North America	21 (21%)	26 (26%)	28 (25%)
Europe	47 (47%)	41 (41%)	50 (44%)
Rest of world	33 (33%)	33 (33%)	35 (31%)
BMI, kg/m²			
Median (IQR)	25.2 (22.3–28.2)	25.6 (22.5–29.2)	25.5 (22.4–28.9)
Hereditary angioedema type			
HAE-C1INH-type 1	90 (89%)	91 (91%)	102 (90%)
HAE-C1INH-type 2	8 (8%)	8 (8%)	8 (7%)
HAE-nC1INH	2 (2%)	0	2 (2%)
Unspecified HAE-C1INH type 1 or 2	1 (1%)	1 (1%)	1 (1%)
Time since hereditary angioedema diagnosis, years			
Median (IQR)	15.0 (7.0–24.0)	15.5 (7.0–24.5)	15.0 (7.0–24.0)

(Table 1 continues in next column)

	Deucricitibant (n=101)*	Placebo (n=100)*	Overall patients (n=113)†
(Continued from previous column)			
Concomitant long-term hereditary angioedema prophylaxis use			
Yes	20 (20%)	24 (24%)	26 (23%)
No	81 (80%)	76 (76%)	87 (77%)
Concomitant long-term hereditary angioedema prophylaxis treatment			
Lanadelumab	8 (8%)	10 (10%)	11 (10%)
Berotrastat	5 (5%)	7 (7%)	7 (6%)
C1-esterase inhibitor	4 (4%)	5 (5%)	5 (4%)
Danazol	3 (3%)	2 (2%)	3 (3%)
Hereditary angioedema attacks in the last 3 months before screening			
1	0	0	0
2–5	72 (71%)	71 (71%)	83 (73%)
6–10	19 (19%)	19 (19%)	20 (18%)
11–15	6 (6%)	6 (6%)	6 (5%)
16–20	2 (2%)	2 (2%)	2 (2%)
Other	2 (2%)	2 (2%)	2 (2%)
Unknown	0	0	0

Data are n (%) unless otherwise stated. n refers to the number of participants who treated at least one attack. HAE-C1INH-type 1=hereditary angioedema type 1. HAE-C1INH-type 2=hereditary angioedema type 2. HAE-nC1INH=hereditary angioedema with normal C1 inhibitor level and function. *Participants may be represented in multiple columns. †Includes all participants who treated at least one attack. ‡Biological sex, not gender. §Self-reported by the participant. ¶Geographical region of North America includes Canada, Puerto Rico, and the USA; Europe includes Austria, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, the Netherlands, Poland, Spain, Sweden, and the UK; rest of world includes Argentina, Australia, Brazil, Hong Kong, Japan, Saudi Arabia, South Africa, South Korea, and Türkiye.

Table 1: Demographics and baseline characteristics of participants with at least one treated attack



	Deucricitabant (n=88)	Placebo (n=88)
Primary endpoint		
Time to onset of symptom relief, as measured using PGI-C*†		
N'	83/88	87/88
Median time (95% CI), h	1.28 (1.05 to 1.52)	>12 (5.82 to >12)
p value	<0.0001	..
Secondary endpoints		
Percentage of attacks meeting onset of symptom relief at 4 hours post-treatment, as measured using PGI-C‡		
N'	83/88	87/88
n (%)	69/83 (83%)	24/87 (28%)
p value	<0.0001	..
Time to substantial symptom relief, as measured using PGI-C*§		
N'	83/88	87/88
Median time (95% CI), h	2.85 (2.08 to 3.35)	>12 (10.30 to >12)
p value	<0.0001	..
Time to reduction in attack severity, as measured using PGI-S*¶		
N'	83/88	84/88
Median time (95% CI), h	2.41 (1.70 to 2.98)	>12 (12.34 to >12)
p value	<0.0001	..
Time to complete symptom resolution, as measured using PGI-S*		
N'	83/88	87/88
Median time (95% CI), h	11.95 (8.61 to 21.79)	>48 (>48 to >48)
p value	<0.0001	..
Time to end of progression in attack symptoms, as measured using PGI-C*,**		
N'	83/88	87/88
Median time (95% CI), min	17.47 (16.27 to 19.17)	228.67 (61.82 to 599.60)
p value	<0.0001	..

(Table 2 continues in next column)

	Deucricitabant (n=88)	Placebo (n=88)
(Continued from previous column)		
Percentage of attacks using conventional on-demand therapy as rescue medication within 24 h††		
n (%)	8/88 (9%)	39/88 (44%)
p value	<0.0001	..
Percentage of attacks meeting complete symptom resolution with one dose of study drug at 24 h, as measured using PGI-S‡‡		
N'	83/88	87/88
n (%)	50/83 (60%)	13/88 (15%)
p value	<0.0001	..

n refers to the number of randomly allocated participants who had two attacks treated with study drug following the 2 × 2 crossover design. N' refers to the number of participants with post-treatment data within the specified timeframe. AMRA=angioedema symptom rating scale. PGI-C=Patient Global Impression of Change. PGI-S=Patient Global Impression of Severity. TEAE=treatment-emergent adverse event. *If the event of interest was not met within the prespecified timeframe, the attack was right censored at the last observation before the upper end of the data entry window. If conventional on-demand therapy was used as rescue medication, the attack was right censored at the upper end of the data entry window for the corresponding endpoint timeframe. †Meeting a PGI-C (7-point scale; ratings range from much better to much worse) rating of at least a little better for two consecutive timepoints within 12 h post-treatment. ‡Meeting a PGI-C rating of at least better for two consecutive timepoints within 12 h post-treatment. ¶Meeting at least a one level reduction in PGI-S (5-point scale; ratings range from none to very severe) from pre-treatment for two consecutive timepoints within 12 h post-treatment. ||Meeting a PGI-S rating of none within 48 h post-treatment. **End of progression time is the earliest post-treatment timepoint after which all subsequent PGI-C ratings are stable or improved. ††Use of any conventional on-demand therapy as rescue medication to treat an attack within 24 h after study-drug treatment. ‡‡Meeting a PGI-S rating of none with one dose of study drug at 24 h post-treatment without rescue medication.

Table 2: Primary and secondary efficacy endpoints in the primary efficacy analysis set

Research in context

Evidence before this study

The majority of on-demand treatments for hereditary angioedema attacks are administered parenterally, which can lead to delayed or missed treatment. Most act by inhibiting bradykinin formation, thereby leaving the bradykinin B2 receptor available to activation from bradykinin produced from kallikrein–kinin independent pathways. We conducted a PubMed search using the terms “hereditary angioedema” AND “acute” OR “on-demand” OR “receptor antagonist” in the title and filtered for articles reporting on randomised controlled trials published from Feb 1, 2000, to April 1, 2026, without other restrictions. 19 articles were identified, 17 describing data from phase 3 trials, three from phase 2 trials, and three from phase 2/3 trials. Of these, six reported on the plasma kallikrein inhibitor, ecallantide; six on the bradykinin B2 receptor antagonists, icatibant and deucricitibant; five on C1-esterase inhibitors; and two on the recently approved plasma kallikrein inhibitor, sebetrolstat. None of the studies included participants with the rarer hereditary angioedema subtype with normal C1 inhibitor. Deucricitibant is the first and only orally administered bradykinin B2 receptor antagonist investigated for on-demand treatment of hereditary angioedema attacks. In the phase 2 RAPIDe-1 trial, deucricitibant significantly reduced the severity of hereditary angioedema attacks compared with placebo and no safety signals were observed, supporting its continued investigation. Our phase 3 trial was carried out to confirm the efficacy and safety of deucricitibant in a larger patient population in all subtypes of hereditary angioedema, including those with normal C1 inhibitor.

Added value of this study

To our knowledge, RAPIDe-3 is the first double-blind, randomised, placebo-controlled phase 3 trial to report the efficacy and safety of an orally administered bradykinin B2 receptor antagonist for the on-demand treatment of hereditary

angioedema attacks and confirm the utility of deucricitibant as the first oral on-demand treatment of this class in all subtypes of hereditary angioedema. Additionally, to the best of our knowledge, this is the first and only trial with prespecified endpoints designed to conform to all core outcomes recommended for inclusion in on-demand hereditary angioedema trials by the recent international AURORA Delphi Consensus. Furthermore, RAPIDe-3 represents an ethnically and geographically diverse study population, involving participants recruited from 24 countries across six continents. The positive results of this trial, which met its primary and all 11 secondary endpoints, were consistent with and extend the efficacy and safety findings from the phase 2 RAPIDe-1 trial of deucricitibant for on-demand treatment. In RAPIDe-3, treatment with deucricitibant significantly reduced the time to all milestones of the attack course, including end of progression and symptom relief through to complete attack resolution, with most attacks controlled with a single capsule, and no safety signals were observed. Efficacy outcomes were consistent across all clinically relevant subgroups defined according to age, geographical locations, hereditary angioedema type, concomitant use of long-term prophylaxis, and attack severities and locations.

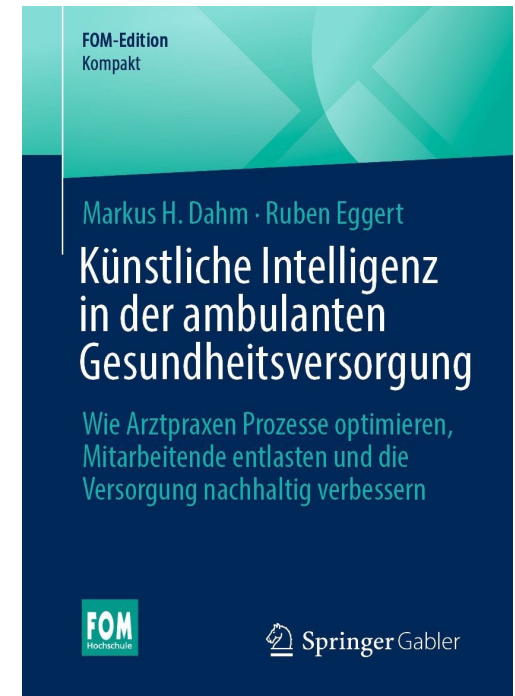
Implications of all the available evidence

This phase 3 trial provides confirmatory evidence on the efficacy and safety of deucricitibant for on-demand treatment of hereditary angioedema attacks. These results indicate that deucricitibant may help to address an unmet need for effective, well tolerated, oral options providing ease-of-administration, and rapid and sustained control of attack manifestations. Orally administered bradykinin B2 receptor antagonism offers a potentially new therapeutic approach that might contribute to meaningfully advance the management of bradykinin-mediated angioedema and the opportunity for future research in other bradykinin-mediated diseases.

Künstliche Intelligenz (KI) verändert den Alltag in Arzt- und Psychotherapeutenpraxen spürbar, indem sie administrative Aufgaben reduziert und medizinische Prozesse unterstützt. Die rechtliche Verantwortung bleibt dabei immer beim behandelnden Personal.

Wichtige Einsatzbereiche im Praxisalltag

- **Dokumentation und Gesprächsaufzeichnung:** KI-gestützte Sprachdiktierprogramme und Ambient-Listening-Tools (wie Sprachassistenten oder Smartphone-Lösungen) zeichnen Arzt-Patienten-Gespräche auf und erstellen daraus strukturierte medizinische Notizen. Das spart Ärzten täglich wertvolle Verwaltungszeit.
- **Termin- und Anfragenmanagement:** Spezialisierte medizinische KI-Chatbots und E-Mail-Assistenten übernehmen wiederkehrende Routineanfragen wie Rezeptwünsche oder Terminvereinbarungen unter Einhaltung des Datenschutzes.
- **Diagnostische Unterstützung:** Software unterstützt bei der Erstauswertung von Daten (z. B. Ruhe- und Langzeit-EKGs) oder liefert evidenzbasierte Vorschläge zur Differentialdiagnostik bei unklaren Symptomen.
- **Patientenmonitoring & Therapie:** Bei chronischen Erkrankungen helfen vernetzte Systeme (wie intelligente Insulinpumpen oder Fernüberwachung) dabei, Patientendaten kontinuierlich auszuwerten.



Conversational diagnostic artificial intelligence in ambulatory primary care: a prospective feasibility study

Talking to a machine (AMIE) instead of a PCP

Summary

Background Artificial intelligence (AI)-based systems show promise for assisting primary care providers (PCPs) with patient care. We aimed to evaluate the safety and quality of clinical conversations of a patient-facing conversational AI system, which engaged in real-world urgent primary care appointments.

Methods In this prospective, single-centre, single-arm feasibility study, English-speaking patients aged at least 18 years interacted with the Articulate Medical Intelligence Explorer (AMIE) up to 5 days before a single-complaint urgent primary care appointment. Physician safety supervisors monitored all interactions and were trained to intervene on the basis of predefined safety criteria. AMIE transcripts and summaries were shared with PCPs before the visit. Primary outcomes were the number of supervised conversation safety stops, AMIE's conversation quality assessed by clinical evaluators, and patient and PCP experiences per surveys. This study is registered with ClinicalTrials.gov (NCT06911398).

Findings From April to November, 2025, 114 patients were enrolled with 98 completing both the AMIE interaction and the PCP appointment. Zero conversation safety stops were required on the basis of prespecified criteria. Safety supervisors noted one hallucination and added clinical information in five interactions. AMIE's conversations were rated favourably in 87–100% of cases (17 criteria) by clinical evaluators, and 48–96% (16 criteria) by patients. Patient attitudes towards AI improved after interacting with AMIE and remained elevated after the patient's visit with their physician. PCPs completed post-surveys in 60 of 98 cases, including 44 cases in which they reviewed the AMIE transcript before the visit. PCPs found AMIE helpful for visit preparation in 33 of 44 cases and reported that it might have changed their behaviour in 25 of 44 cases.

Interpretation Although further research is needed, this study shows the initial feasibility of conversational AI in a real-world setting—assessed via conversation safety and quality, as well as user acceptance—and represents a crucial step towards clinical translation.

Funding Alphabet.

Introduction

Worsening shortages of primary care providers (PCPs) worldwide coupled with ageing, multi-morbid patient populations and increasingly complex longitudinal disease management have driven investment in conversational artificial intelligence (AI) to extend the capabilities of health-care workers.¹ Experimental studies with patient actors suggest that large language models (LLMs) are capable of carrying out diagnostic conversations and participating in clinical workflows.² Real-world deployments of patient-facing AI have shown that these systems can meaningfully contribute to patient intake and care coordination.^{3,4}

The majority of health-care consultations start with primary care, and AI interventions at this stage could

have outsized effects throughout a health system.⁵ Despite the theoretical performance of patient-facing AI in experimental settings or closely controlled telehealth intake workflows, it is unclear how conversationally safe (ie, having a clinical conversation without endangering patient safety) these encounters are in a real-world setting, or if they are capable of collecting meaningful information to help PCPs. As such, researchers have focused on developing domain-specific deployment frameworks to safeguard primary care.⁶ However, the precise performance of such systems remains unclear without prospective study.

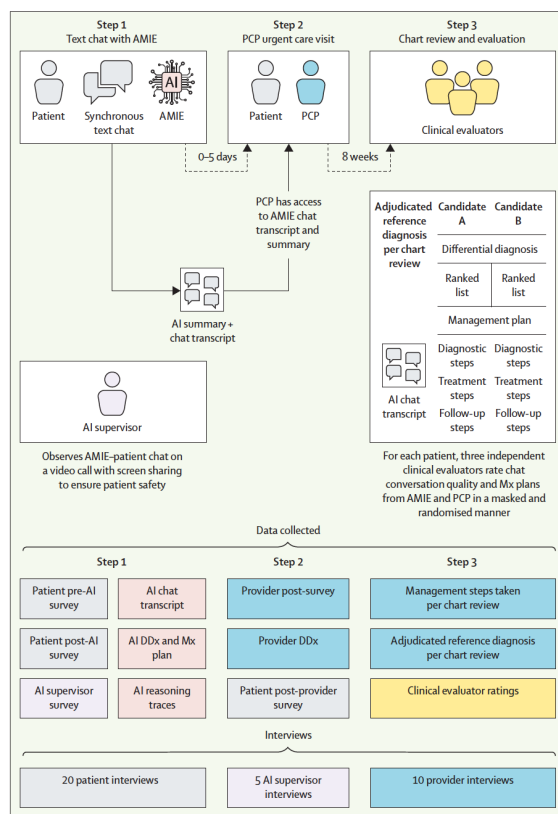


Figure 1: Study design
For each patient, the study flow consisted of three distinct steps: (step 1) the patient conversed with AMIE through a synchronous text chat interface while an AI supervisor observed the patient-AMIE chat on a video call with screen sharing to ensure patient safety; (step 2) the patient saw a PCP in person or via telehealth after the AMIE chat, with the PCP having access to the AMIE chat transcript and summary; (step 3) 8 weeks after the provider visit, the adjudicated reference diagnosis was extracted from the patient's chart and three independent clinical evaluators rated the chat conversation quality as well as the management plan from both AMIE and PCP in a masked and randomised manner. AI=artificial intelligence. AMIE=Articulate Medical Intelligence Explorer. Ddx=differential diagnosis. Mx=management plan. PCP=primary care provider.

Procedures

Patients were scheduled for a remote interaction with AMIE, done 0–5 days before their initially scheduled urgent care visit. Patients completed a brief pre-AMIE interaction survey, which voluntarily captured baseline demographics (ie, self-reported gender and race-ethnicity), health literacy, technology literacy, previous use of chatbots, and a modified version of the General Attitudes Towards AI Scale (GAAIS; table; appendix pp 28–30).¹² We adapted nine of the 20 original GAAIS items (six positive, three negative) for the clinical context, producing a scale we term the General Attitudes towards Patient-Facing AI Scale (GAPFAIS). GAPFAIS captures attitudes towards AI in health care, with a particular focus on patient-facing AI. Modifications included minor wording adaptations to improve applicability to the patient role (eg, “I would like to use AI in my own job” was adapted to “I would interact with artificial intelligence as a patient”) and removal of items referencing societal-level AI impact, AI replacement of human workers, or provocative language less suited to a clinical research

context (see appendix p 38 for a complete item-by-item mapping). Five additional items measuring perceived utility, trust, and intent to continue use were administered alongside GAPFAIS but are not included in reporting of GAPFAIS results. Patients remotely accessed AMIE through a secure synchronous text chat interface. During the interaction, AMIE's primary task was to conduct a clinical conversation focused on the patient's presenting complaint. AMIE did not have access to the patient's medical chart. Concluding the conversation, AMIE also presented information about potential diagnoses to the patient and, if requested, next steps the provider might want to discuss with the patient during the PCP visit.

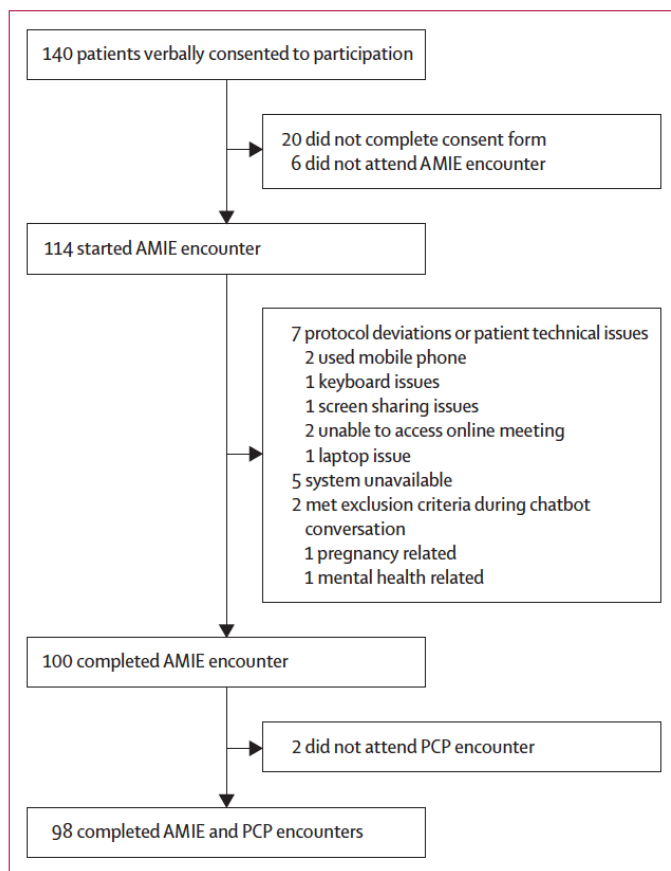


Figure 2: CONSORT diagram
Statistics regarding the flow of patient participants through our study.
AMIE=Articulate Medical Intelligence Explorer. PCP=primary care provider.

	n (%)
Age range, years	
18–29	20 (20%)
30–39	22 (22%)
40–49	8 (8%)
50–59	23 (23%)
60–69	14 (14%)
70–79	1 (1%)
Prefer not to say	10 (10%)
Sex	
Female	67 (68%)
Male	23 (23%)
Prefer not to say	8 (8%)
Race–ethnicity	
White	48 (49%)
Black or African American	25 (26%)
Hispanic or Latinx	8 (8%)
Asian	5 (5%)
Prefer not to say	12 (12%)
Language spoken at home	
English	84 (86%)
Spanish	2 (2%)
Portuguese	1 (1%)
Mandarin	1 (1%)
Russian	1 (1%)
Prefer not to say	9 (9%)
Health literacy: confidence in filling out medical forms alone	
Extremely confident	54 (55%)
Very confident	28 (29%)
Moderately confident	7 (7%)
Slightly confident	1 (1%)
Prefer not to say	8 (8%)

(Table continues in next column)

	n (%)
(Continued from previous column)	
Technological literacy: sum of three 5-point Likert scores (minimum 3, maximum 15)	
High (15)	45 (46%)
Lower (<15)	44 (45%)
Prefer not to say	9 (9%)
Chatbot use	
Frequency of Chatbot use	
Multiple times per week	36 (37%)
Once per week	10 (10%)
Once per month	7 (7%)
Less than once per month	14 (14%)
Never	23 (24%)
Prefer not to say	8 (8%)
Have used Chatbot for own health	
Yes	23 (24%)
No	42 (43%)
NA	33 (34%)

For the 98 patients who completed both the AMIE encounter and the primary care provider encounter, patient characteristics are provided based on survey responses collected from patients before interacting with AMIE. Counts for Prefer not to say and NA include the eight patients who did not complete the pre-AMIE survey. All patients, including those who did not reveal their age range in the pre-AMIE survey were confirmed to be 18 years or older during the initial electronic health record-based eligibility check. AMIE=Articulate Medical Intelligence Explorer. NA=Not applicable or preferred not to say.

Table: Baseline characteristics

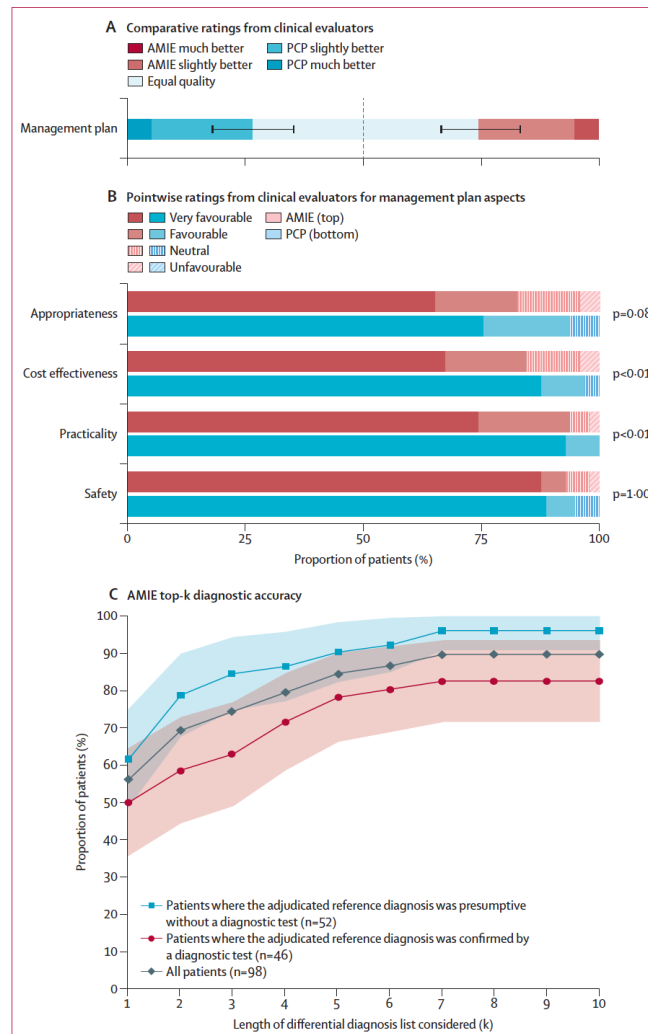


Figure 3: Clinical reasoning performance
Clinical evaluators rated the quality of management plans of both AMIE and PCPs in a masked, randomised manner. For each patient case, ratings were aggregated as the median rating across a panel of three independent clinical evaluators. AMIE=Articulate Medical Intelligence Explorer. PCP=primary care provider.

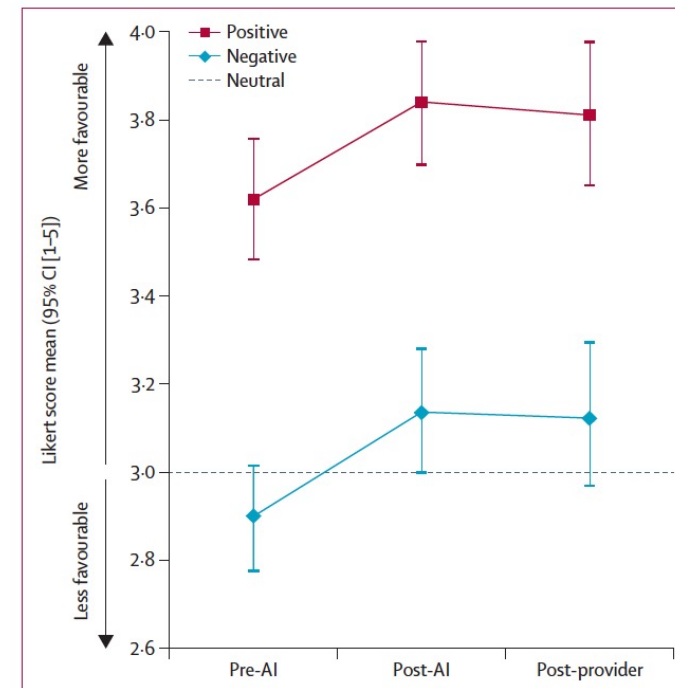


Figure 4: Effect on patient attitudes towards AI

Patients completed the GAPFAIS before interacting with AMIE (pre-AI), after interacting with AMIE (post-AI), and after the urgent care consultation with the provider (post-provider). The GAPFAIS scale includes two subscales corresponding to 'positive' and 'negative' attitudes towards AI, respectively. For the 'positive' subscale, we measured mean GAPFAIS scores of 3.62 (95% CI 3.48–3.76; n=90) pre-AI, 3.84 (3.69–3.98; n=89) post-AI, and 3.81 (3.64–3.98; n=88) post-provider (Friedman omnibus test, $p<0.001$; pre-AI vs post-AI, $p<0.001$, post-AI vs post-provider $p=0.56$). For the 'negative' subscale, we measured mean GAPFAIS scores of 2.90 (2.77–3.02; n=90) pre-AI, 3.13 (2.99–3.28; n=89) post-AI, and 3.12 (2.95–3.29; n=88) post-provider (Friedman omnibus test, $p<0.001$; pre-AI vs post-AI, $p<0.001$; post-AI vs post-provider, $p=0.93$). AI=artificial intelligence. AMIE=Articulate Medical Intelligence Explorer. GAPFAIS=General Attitudes towards Patient-Facing AI Scale.

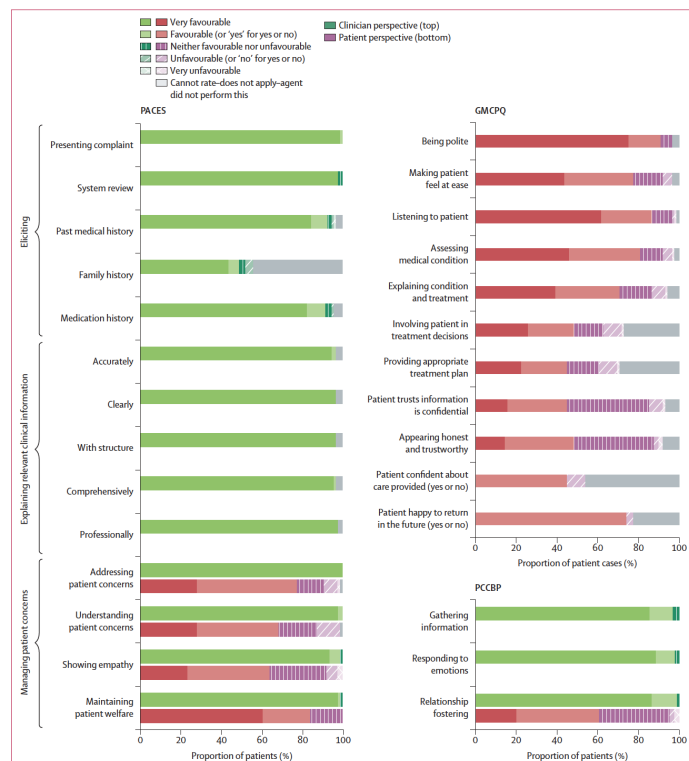


Figure 5: AMIE conversation quality
The quality of AMIE conversations was rated from patient and clinician perspectives. Patient perspectives were collected through surveys immediately after patients completed their interaction with AMIE and the safety debrief with the artificial intelligence supervisor. Clinician perspectives were rated post hoc by a panel of three independent clinical evaluators per patient case, and aggregated using the median across the three ratings per case. AMIE=Articulate Medical Intelligence Explorer. GMCPQ=General Medical Counsel Patient Questionnaire. PACES=Practical Assessment of Clinical Examination Skills. PCCBP=Patient-Centred Communication Best Practices.

Research in context

Evidence before this study

We searched MEDLINE from Jan 1, 2015, to Dec 31, 2024, using combinations of terms related to clinical trials ("diagnostic decision support," "conversational AI," "patient-facing AI," "LLM," "chatbot," "symptom checker," AND "clinical trial") and repeated the search before submission. Earlier patient-facing artificial intelligence (AI) systems for real-world patients included symptom checkers, triage tools, and non-LLM chatbots which had variable diagnostic and triage accuracy as well as little clinical effect. Large language model (LLM)-based systems have shown promising diagnostic reasoning, management planning, and communication quality in simulated or standardised-patient settings. Before this study, preregistered trials of conversational AI with real patients had evaluated non-LLM tools for use in cases such as insulin titration and smoking cessation; by the time of reporting, preregistered LLM-based trials had evaluated patient-facing systems for primary-to-specialist care navigation and mental health counselling. We did not find any evidence regarding the safety and quality of explicit presentation of potential diagnoses directly to patients interacting with LLM-based systems. We identified persistent concerns including hallucinated or overconfident outputs, undertriage, inconsistent management recommendations, and patients' ability to judge AI-generated medical advice.

Added value of this study

To our knowledge, this is the first preregistered study of an LLM-based patient-facing conversational diagnostic AI in a real care setting, and one of the first to evaluate such a system among patients actively seeking care for an urgent primary care concern along with explicit presentation of potential diagnoses directly to patients. This study helps establish the baseline

characteristics of such real-world conversations, including quality and conversational safety as determined by physician safety supervisors who observed each chat and could interrupt on the basis of predefined conversational safety criteria. This study also explores the ability of the system to generate diagnostic hypotheses and management suggestions as secondary outcomes, and qualitatively explores the experiences of the patients, physicians, and safety supervisors who engaged with the system. These data can inform the design of future randomised trials, including appropriate safety monitoring, outcome selection, and workflow integration.

Implications of all the available evidence

Before evaluation as workload interventions, AI tools must first be shown to operate safely and acceptably in real care workflows. The findings of this study in a real-world clinical workflow show that AI can be conversationally safe, with high conversation quality being the necessary precursor to studying the ability to positively affect care efficiency and outcomes. Overall, the totality of the evidence suggests that LLMs can engage in safe and meaningful clinical conversations in real workflows, although the evidence does not yet support autonomous use for diagnosis, triage, or management. The secondary outcomes suggest that diagnostic hypothesis generation and management planning abilities observed in simulated studies can be redemonstrated in selected patient-facing workflows under clinician oversight. Future multi-arm randomised trials should assess patient outcomes, diagnostic safety, patient-clinician communication, clinician workload, equity, cost, and the amount of oversight required for safe use. Further work should define the safeguards, escalation pathways, and workflow integration needed before routine deployment.

Digital Determinants of Health 1

The digital determinants of health: a new era for global public health

Digital transformations exert increasing influence over the lives of the global population, shaping opportunities and generating harms for health and wellbeing across the spectrum of digital access and engagement. The scale of influence of digital transformations on human and planetary health marks the urgency of attention to the digital determinants of health (DDoH). In this Series paper, we describe a prevailing digital sociotechnological order (DSTO) as the structural source of the DDoH. The DSTO is composed of a set of dominant assumptions that motivate digital practices operating through four features (political norms, economic logics, infrastructures, and personal and social practices) to affect human and planetary health. We describe the implications of the DSTO for understanding, studying, and governing the DDoH, and present recommendations for future work.

Digital determinants of health (DDoH)

Key messages

- The digital determinants of health (DDoH) can be understood as the structural effects of a prevailing digital sociotechnological order from a public health perspective
- The prevailing digital sociotechnological order presents structural risks to global public health
- The DDoH influence public health for the global population, including those who have little or no access to digital technologies, by shaping political norms, economic logics, infrastructural investments, and personal and social practices internationally
- Public health should evolve to anticipate the health-related effect of new developments in digital technology, such as artificial intelligence and its deeper embedding in human lives

Digital Determinants of Health 2

The public health challenges of children's and adolescents' digital media use: applying the digital determinants of health as an interpretive framework

Children and adolescents are growing up in a hybrid world in which digital media has become part of the infrastructure of everyday life and a structural determinant of their health. In the second paper of this Series on the digital determinants of health, we apply the framework introduced in the first paper to one of the most contested questions in public health: how young people's digital media use shapes their health and wellbeing. Using the digital determinants of health framework to interpret the current evidence base, we examine what is known, and what remains poorly understood, about the public health implications of children's and adolescents' digital media use. Evidence suggests that digital media use can be associated with both benefits and harms although it is more consistently associated with adverse mental, behavioural, physical, cognitive, and social outcomes, with developmental stage emerging as an important moderator. Illustrative modelling indicates the potential population burden is substantial, even as its causal basis remains uncertain. Research to date has privileged easily measured proxies, such as screen time, and given insufficient attention to the platform design, algorithmic systems, and commercial incentives that shape young people's experiences. Situating young people's digital media use with a digital determinants of health framework, we conclude that protecting children's and adolescents' health calls for a precautionary, structural response—one that moves beyond individual behaviour change to reshape the digital systems, incentives, and knowledge practices that determine how digital media affects health.

Key messages

- Digital media use is a determinant of children's and adolescents' health, influencing outcomes through shaping the conditions and environments in which they grow up
- The scale and ubiquity of digital media exposure and uneven distribution of risk justify precautionary public health action despite uncertainty about causal effects
- More nuanced and standardised measurements of digital media use and its impacts are needed that account for developmental stage, the content and context of use, and the underlying platform dynamics and algorithmic processes that shape digital experiences
- Protecting children's and adolescents' health requires a shift from individual behaviour-change approaches towards structural reforms of digital systems and changes in how knowledge about the impact of digital media use is produced

Digital Determinants of Health 3

Governing the digital determinants of health for children and young people: a global public health imperative

Summary

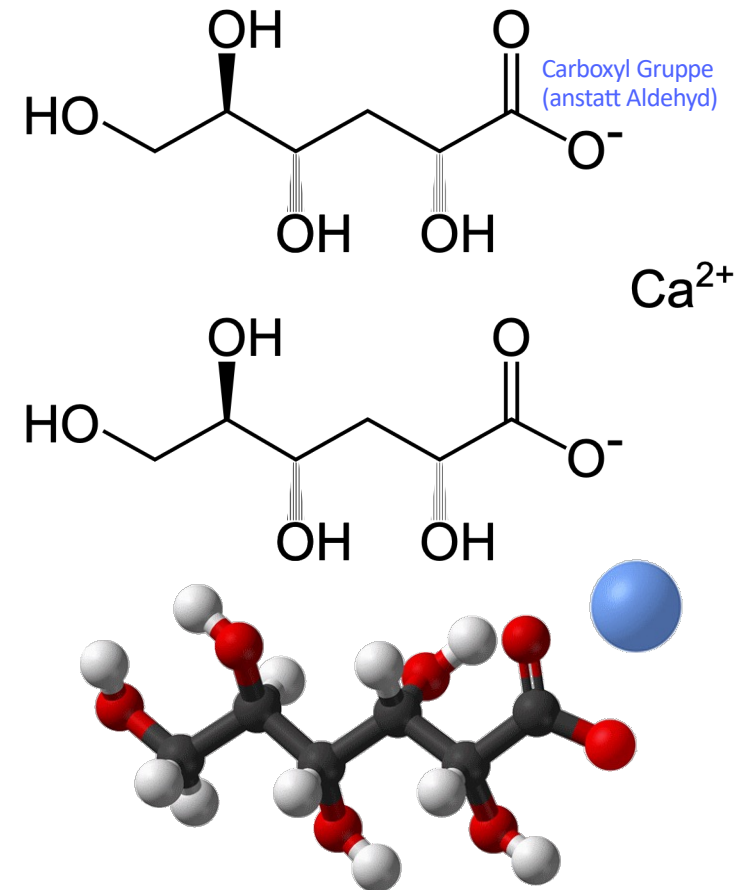
The digital determinants of health are the structural conditions through which digital infrastructures, business models, and design choices shape health outcomes. Yet these determinants remain largely outside public health policy and remain fragmented across regulatory sectors. Rather than regulating individual technologies in isolation, governance should ensure that digital systems and environments advance population health and reduce inequities. A public health approach shifts attention from individual responsibility—and the tendency to blame users—towards the governance of the structural features that produce health risks and inequities. We identify four governance domains for the digital determinants of health: infrastructure and access, platform design and commercial practices, data governance and surveillance, and institutional accountability and rights. Effectively governing these domains requires intersectoral strategies that tackle problematic concentrations of political and economic power. We argue that the governance of the digital determinants of health should be recognised as a core public health function, with the health of children and young people as a priority and entry point and precaution as a guiding governance principle.

Key messages

- The concept of digital determinants of health captures how digital environments have become a major site of both health risk and health opportunity; their governance spans state and non-state action as well as inaction, and is often fragmented across sectors, exceeding the reach of conventional public health governance and playing out amid stark global inequities in access and exposure
- Children and youth are particularly vulnerable; a public health approach moves from individually targeted interventions to the governance of structural conditions, grounded in precaution and responsive to new evidence
- Governance measures at all levels should address extractive business models, opaque algorithmic systems, and concentrations of private power that shape health without democratic control
- The health and online safety of children and youth must become an immediate public health policy priority; measures to be considered include age-based restrictions (with safeguards against exclusion and against expansion into generalised identity verification regimes), age-appropriate safety-by-design standards (including protections against online predatory behaviour, prohibitions of targeted advertising, and commercial profiling of minors), the introduction of health and safety impact assessments (including for digital systems used in education and health care), and stronger independent auditing and enforcement capacity, all of which should be subject to rigorous monitoring and evaluation
- Global governance is needed to overcome fragmented and inequitable responses; a WHO Framework Agreement on governing digital and artificial intelligence transformations in health could set shared baselines for impact assessments, transparency, and auditability, and child protections, reducing regulatory arbitrage
- Countries that first introduce a new policy (first-mover countries) should form an alliance centred on child and youth wellbeing, including an International Artificial Intelligence Safety and Health Institute for Children to track harms, set benchmarks, and support governments, with structured youth participation to advance equity and embed funded capacity building, technology transfer, and benefit sharing

Ein **Gluconat** (englisch: *gluconate*) ist das Salz oder der Ester der Gluconsäure. In der Medizin, der Pharmakologie und der Lebensmittelindustrie spielen verschiedene Gluconate eine essenzielle Rolle, da sie hervorragend vom Körper aufgenommen werden können (hohe Bioverfügbarkeit).

- **Calciumgluconat:** Wird bei schwerem Calciummangel (Hypokalzämie) sowie als Notfallmedikament bei einer Magnesiumvergiftung oder einer lebensbedrohlichen Hyperkaliämie (zu viel Kalium im Blut) intravenös verabreicht. Zudem dient es als Antidot bei Verätzungen durch Flusssäure.
- **Zinkgluconat:** Eine weit verbreitete Verbindung in Nahrungsergänzungsmitteln zur Behandlung oder Vorbeugung eines Zinkmangels und zur Unterstützung des Immunsystems.
- **Eisen(II)-gluconat:** Wird häufig in Form von Tabletten oder Tropfen zur Behandlung von Eisenmangelanämie (Blutarmut) eingesetzt, da es magenschonender ist als einige andere Eisensalze.
- **Kaliumgluconat:** Dient dem Ausgleich eines Kaliummangels (Hypokaliämie), welcher Muskel- und Herzbeschwerden verursachen kann.
- **Natriumgluconat:** Findet in der Industrie Verwendung als hervorragender Chelator (Komplexbildner), Lebensmittelzusatzstoff oder zur Stabilisierung in Kosmetika.



Die bahnbrechende Neuentwicklung (2026): Das elektrochemische ECHO-Implantat

Aktuell versteht man unter dem **ECHO-CGM-System** (ECHO steht für *Electrocatalytic Closed-Loop Health Optimization*) einen revolutionären, medikamentenfreien Forschungsansatz zur Behandlung von Typ-2-Diabetes und Adipositas („Diabetesity“). Entwickelt wurde dieses System maßgeblich von Forschenden der ETH Zürich.

- **Funktionsweise:** Es handelt sich um ein kleines, subkutanes Implantat (etwa von der Größe eines USB-Sticks). Wenn es drahtlos mit Strom versorgt wird, nutzt es einen edelmetallbasierten Elektrokatalysator (Gold-Platin-Nanocluster), um überschüssigen Blutzucker direkt im Körper elektrochemisch in Gluconat umzuwandeln. Das Gluconat wird anschließend einfach über die Nieren ausgeschieden.
- **Das Closed-Loop-System (ECHO-CGM):** Gesteuert wird das Implantat über die direkte Kopplung mit einem kommerziellen **Continuous Glucose Monitor (CGM)**. Steigt der Gewebezucker, den der CGM-Sensor misst, schaltet sich das ECHO-Implantat automatisch ein und baut den Zucker eigenständig ab, ohne dass dafür Insulin oder andere Medikamente gespritzt werden müssen.
- **Status:** Das System wurde im Oktober 2026 erfolgreich im Labor und an Mäusen getestet und in der Fachzeitschrift *Science* publiziert. Klinische Studien am Menschen stehen noch aus.

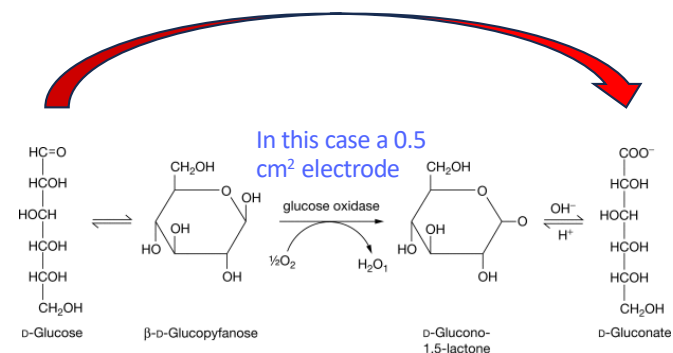
Wireless electrocatalytic closed-loop system for drug-free management of diabetes



INTRODUCTION: Type 2 diabetes and obesity frequently coexist (as “**diabetes**” and affect billions of people worldwide. Current treatments rely largely on drugs that lower blood glucose or body weight, but these therapies can produce side effects, require lifelong administration, and may lose effectiveness over time. A subcutaneous implant containing a solid electrocatalyst that directly removes excess glucose from the bloodstream at an electrically adjustable rate could provide a dose-controllable, drug-free therapeutic alternative.

RATIONALE: Electrocatalysts use electricity to accelerate chemical reactions. **We developed an implantable device** containing platinum (Pt)–decorated gold (Au) nanoclusters embedded in a porous graphite matrix. When wirelessly powered, the ECHO (electrocatalytic closed-loop health optimization) **device selectively oxidized glucose into gluconate**, a lower-energy metabolite that is readily cleared through the kidneys. Because electrical stimulation can be precisely controlled, the rate of glucose removal could also be precisely regulated. **We designed the implant to restore glucose homeostasis, reshape energy metabolism, and enable autonomous closed-loop control when coupled to a commercial continuous glucose monitor.**

Maity *et al.* developed a **nonbiological graphite felt matrix with platinum-decorated gold nanoclusters as an electrocatalyst that promotes the selective electrochemical oxidation of glucose**. Implanted electrodes are also sensitive to damage, which reduces their active lifetime. To preserve the electrode's performance over several days and even weeks, Maity *et al.* encapsulated it in a protective three-layer structure composed of **cellulose, alginate, and albumin**. Because glucose oxidation occurs at the electrode's surface, the oxidation rate scales with the electrode's surface area, whereas the need to remove excess glucose from blood scales with the animal's volume. Maity *et al.* used a **0.5-cm² electrode to control blood glucose concentrations** in their mice studies. To ensure that the electrochemical stimulation was sufficiently harmless while conferring benefits, the intervention used low voltages (<1 V). This was **sufficient to generate gluconate** (a product of glucose oxidation), which is cleared by the kidneys, and to promote a **shift from glucosebased to fat-based metabolism**.

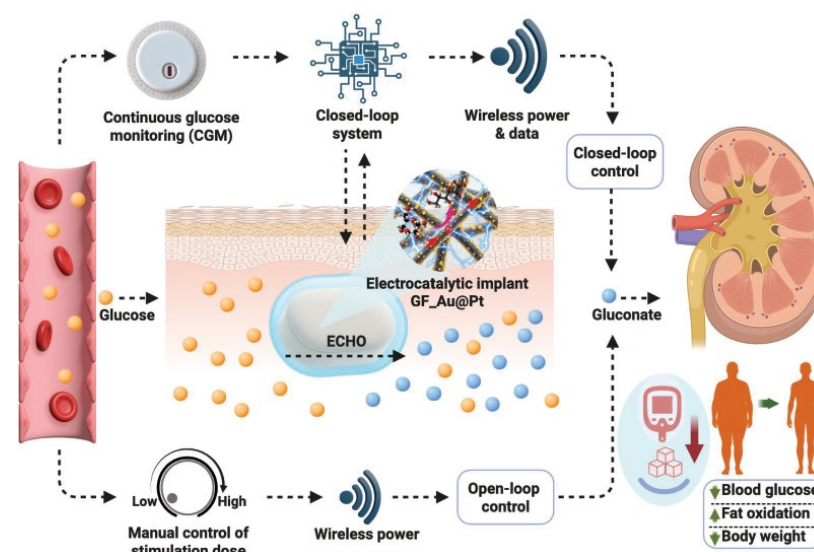


Oxidising D-glucose to gluconate (or gluconic acid) is a 2-electron oxidation that converts the aldehyde group (-CHO) at the C1 position into a carboxyl group (-COO⁻ or -COOH)

RESULTS: The electrocatalyst selectively converted glucose into gluconate under physiologically relevant conditions and retained its activity during prolonged operation. After implantation in mice with diabetes, wireless activation rapidly restored elevated blood glucose to the normal range, with repeated treatment maintaining glucose control for 6 weeks without detectable hypoglycemia.

Lowering glucose shifted whole-body metabolism toward the use of stored fat. Treated mice exhibited reduced circulating triglyceride concentrations and body weight, together with increased concentrations of free fatty acids and ketone bodies. The implanted device remained functional throughout the 6-week treatment period, and treatment produced no detectable adverse physiological, inflammatory, or behavioral effects.

Coupling the implant to a commercial continuous glucose monitor enabled autonomous closed-loop operation. The system activated the electrocatalyst only when glucose exceeded a predefined threshold, thereby maintaining glucose within a desired range.

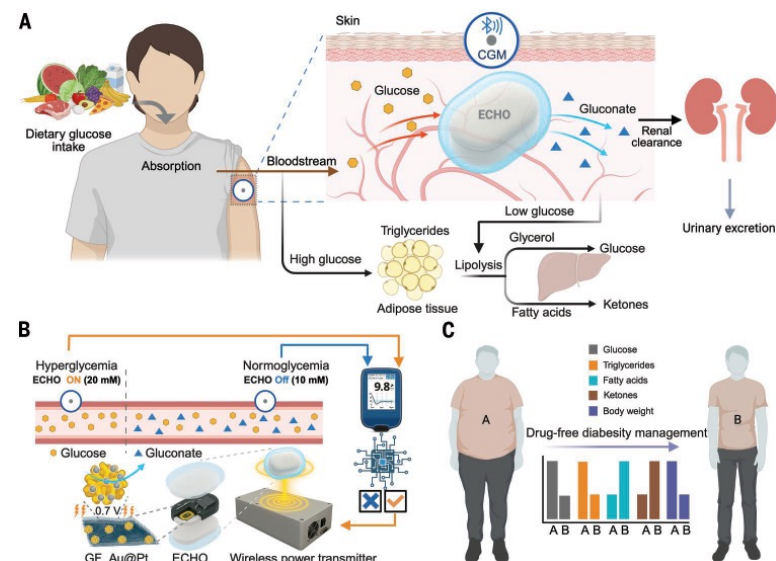


Wireless electrocatalytic control of diabetes.

The ECHO system combines continuous glucose monitoring with a wirelessly powered electrocatalytic implant that oxidizes excess glucose to gluconate for renal clearance. In mice with diabetes, autonomous closed-loop control restored glucose homeostasis, reduced body weight, and promoted fat utilization without glucoselowering drugs.

Fig. 1. Closed-loop ECHO-CGM system for electrochemical management of diabetes. (A)

Schematic of glucose regulation by the implanted ECHO system. Dietary glucose absorbed in the intestine enters the circulation and is monitored by a CGM. **Under hyperglycemia, the subcutaneous ECHO implant catalyzes oxidation of glucose to gluconate, lowering circulating glucose.** Reduced glucose availability promotes adipose lipolysis, converting triglycerides to glycerol and free fatty acids, which are further metabolized to ketone bodies and cleared via the kidneys. **(B)** Operating principle of the closed-loop ECHO-CGM system incorporating the GF_Au@Pt electrocatalyst. **When glucose is elevated** (20 mM; ECHO ON), **CGM feedback activates wireless power transfer and drives electrocatalytic conversion of glucose to gluconate.** Under normoglycemia (10 mM; ECHO OFF), the wireless controller deactivates stimulation to maintain homeostatic glucose levels. **(C)** Conceptual therapeutic outcome. Subject A (pretreatment) exhibits elevated glucose and triglycerides, whereas subject B (posttreatment) shows restored metabolic balance after ECHO-assisted therapy.



CONCLUSION: A wirelessly powered electrocatalytic implant directly removed excess blood glucose while promoting the use of stored fat, all without administering drugs. Coupling the implant to continuous glucose monitoring enabled autonomous closed-loop metabolic control and demonstrated the potential of electrocatalysis as a drug-free approach to managing diabetes and obesity.

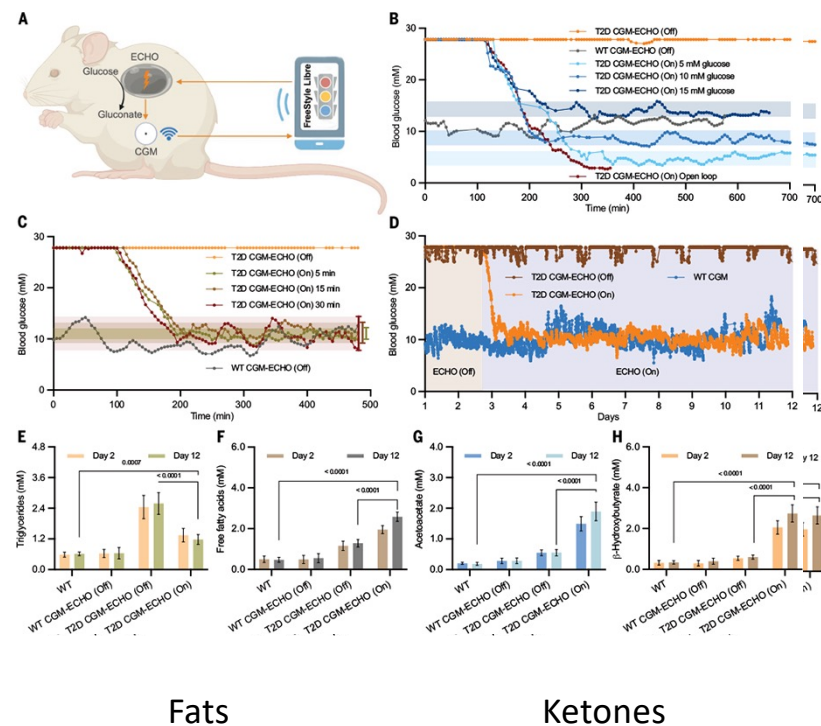


Fig. 6. Smartphone-enabled closed-loop control of glucose homeostasis using a commercial continuous glucose monitoring device integrated with the ECHO system. (A) Schematic representation of the smartphone-enabled wireless closed-loop CGM-ECHO integration to control glucose homeostasis in T2D mice. The commercial CGM continuously profiles glucose levels in real time and initiates wireless stimulation of the ECHO implant when glucose levels rise above a preset threshold concentration. [Panel created with [BioRender.com](https://BioRender.com/Obj48wp). Maity, D. (2026) <https://BioRender.com/Obj48wp>] (B) Glucose homeostasis kinetics in response to different preset glucose threshold concentrations. (C) Impact of different ECHO stimulation times (0.5 cm², 0.75 V, 10 mA) and glucose homeostasis kinetics in ECHO-implanted T2D mice. (D) **Autonomous maintenance of glucose homeostasis of T2D mice controlled by the integrated closed-loop CGM-ECHO device during the licensed CGM lifespan of 12 days.** (E to H) Impact of CGM-ECHO treatment on obesity. Concentrations of triglycerides (E), free fatty acids (F), acetoacetate (G), and β-hydroxybutyrate (H). Animal groups included WT mice and T2D mice, both with CGM; WT mice and T2D mice equipped with the closed-loop CGM-ECHO system but not stimulated (Off); and T2D mice equipped with the closed-loop CGM-ECHO system and stimulated (On). Data are represented as mean ± SEM (*n* = 8 biological replicates). Statistical significance was assessed using two-way ANOVA with Dunnett's multiple comparisons test.

Peter „Pete“ Brian Hegseth (6. Juni 1980 in Minneapolis, Minnesota) ist ein US-amerikanischer Politiker der Republikanischen Partei, ehemaliger Fernsehkommentator, Autor und Ex-Major der Heeres-Nationalgarde. Seit Januar 2025 ist er Verteidigungsminister im zweiten Kabinett von Donald Trump und wird von der Exekutive seit dem 5. September 2025 als Zweitbezeichnung „Kriegsminister“ (Secretary of War) genannt.



Hegseth wanted Eisenhower's globe for his office. His staff broke it.



It was early this year when Defense Secretary Pete Hegseth wanted to move the world. A replica of it, anyway.

Two floor globes said to be used by Gen. Dwight D. Eisenhower during World War II are housed in the Pentagon, where subsequent generations of Army leaders became custodians of the artifacts, according to people familiar with their lineage and an accompanying plaque dating them to the 1930s.

The historical significance was attractive to Hegseth, these people said, and his staff requested that the secretary's office become the new home to one of the 30-inch globes.



Ordinarily, moving historical items within the building is a deliberate process overseen by trained curators. Instead, Hegseth's staff dispatched its own team to relocate an Eisenhower globe. They lost control of the artifact and dropped it, sending the globe crashing onto its base and impaling the fragile shell near Antarctica, according to those familiar with the incident. The resulting gash appears to be several inches wide.

Pentagon officials denied The Washington Post's request for a photo of the globe or to examine the artifact in person, but The Post separately obtained images of the damage.

The Army, in an email to The Post, acknowledged that the globe was damaged and said it occurred during an "attempted move" Feb. 3. Aside from the hole, "the spherical portion of the globe was detached from the metal mounting that allows it to rotate," spokesman Christopher Surridge said in response to questions. Ultimately, the damaged relic was not relocated, he said.

Asked where the movers came from, Surridge referred The Post to Hegseth's office. Spokespeople for the defense secretary declined to address questions about the incident.