

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

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

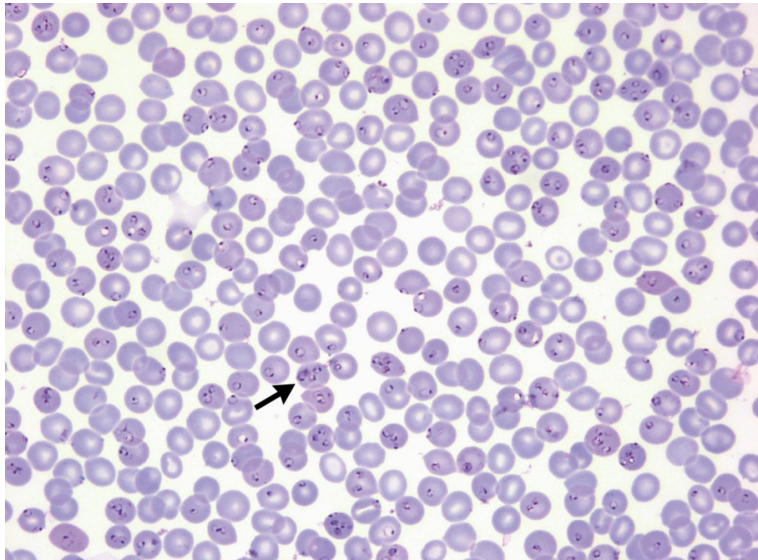
Usually every Wednesday 17:00 - 18:00



Klinische Forschung

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

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



The peripheral blood smear showed ring-form trophozoites within erythrocytes and an estimated parasitemia level of 50.7%. Some erythrocytes had multiple ring forms (arrow), a finding highly characteristic of infection with *Plasmodium falciparum*. This patient met criteria for severe malaria, including impaired consciousness, acidosis, renal impairment, and a parasitemia level of greater than 10%. Parenteral artesunate is indicated as initial treatment for severe malaria, regardless of infecting species.

An 82-year-old man presented after being “found down.” One week earlier, he had returned from a 1-month visit to Chad, his country of birth, and had started having weakness. His body temperature was 37.4°C, and his blood pressure was 88/47 mm Hg. The physical examination was notable for confusion. Laboratory studies showed a hemoglobin level of 12 g per deciliter (reference range, 13.5 to 17), an elevated lactate dehydrogenase level, thrombocytopenia, metabolic acidosis, and acute kidney injury. A peripheral-blood smear is shown. Which of the following is the most appropriate next step in management?

Chloroquine phosphate

Exchange transfusion

Oral artemether-lumefantrine

Oral atovaquone-proguanil

☒ Parenteral artesunate

The use of exchange transfusions: a potentially useful adjunct in the treatment of fulminant falciparum malaria

Abstract

Fulminant falciparum malaria with greater than 500,000/mm³ parasites in the peripheral blood portends a poor prognosis. We recently managed a patient who had greater than 1.2 million/mm³ parasitized erythrocytes in her peripheral blood, following initially inadequate antimalarial therapy, with exchange transfusion in addition to conventional chemotherapy. This patient recovered from her disease despite severe cerebral involvement and acute failure. We feel that exchange transfusion was a useful adjunct and should be considered in patients with life threatening falciparum malaria when conventional measures fail to control the disease.

Malaria-Erreger (Plasmodien) sitzen nicht nur außen auf der Zellmembran. Sie dringen aktiv in die Wirtszellen ein und leben **vollständig im Inneren** von Zellen (sie sind obligat intrazellulär).

Nielsen et al. Am J Med Sci 1979

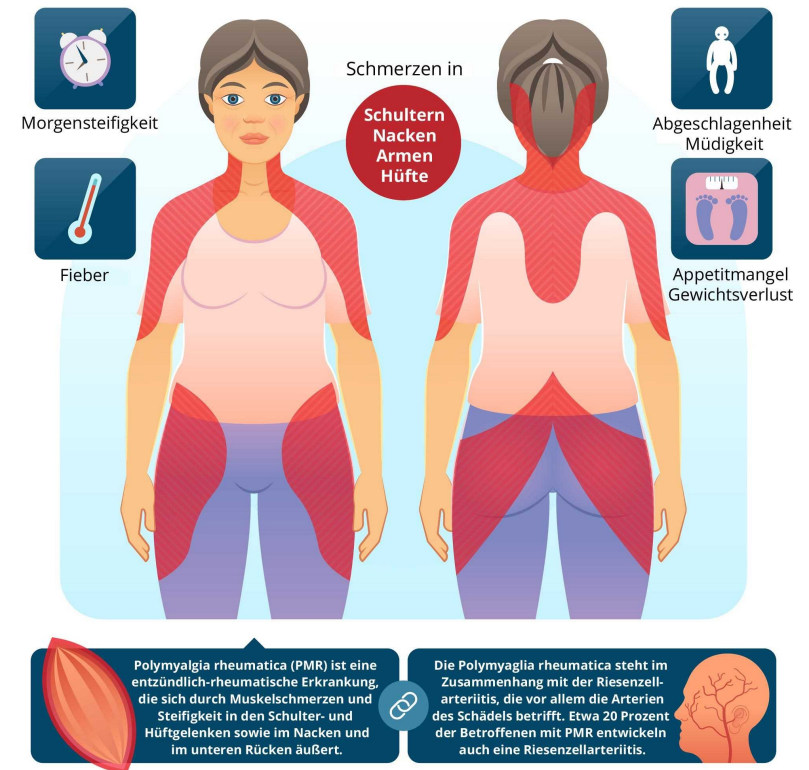
Artemisinin gab es noch nicht.
Quinin wurde von CDC nach Indy geflogen.
Am Anfang bekam sie Quinidin.

Die **Polymyalgia rheumatica (PMR)** und die **Riesenzellarteriitis (RZA)** gehören zum selben **Krankheitsspektrum**. Etwa 15 bis 30 Prozent der Menschen mit PMR entwickeln auch eine Riesenzellarteriitis, während umgekehrt etwa die Hälfte aller Patienten mit einer Riesenzellarteriitis typische polymyalgische Beschwerden aufweist. Beide Krankheiten treten fast nie bei Personen unter 50 Jahren auf.

Gemeinsamkeiten und Unterschiede

- **Gemeinsames Spektrum:** Beide Zustände sind entzündliche Autoimmunerkrankungen. Man vermutet, dass sie unterschiedliche Ausprägungen derselben Grunderkrankung sind.
- **Polymyalgia rheumatica (PMR):** Hier schmerzen und steif werden vor allem die Muskeln an Schultern und Becken.
- **Riesenzellarteriitis (RZA):** Dies ist eine Entzündung der großen und mittleren Blutgefäße, oft an den Schläfen (Arteriitis temporalis)

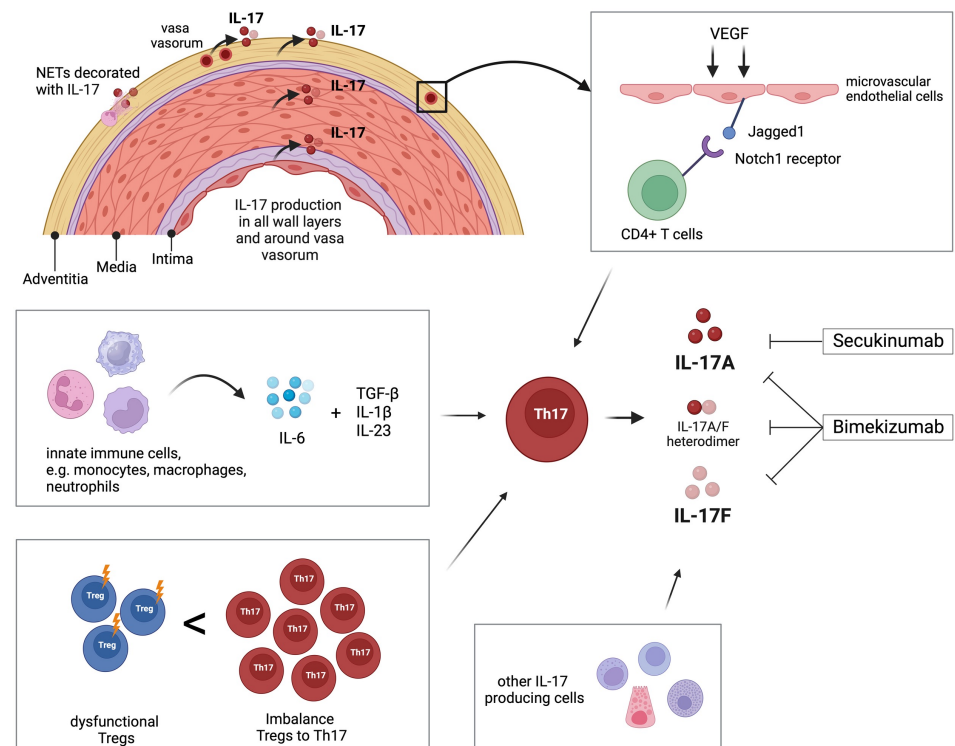
Polymyalgia rheumatica



Interleukin-17 (IL-17) ist ein Entzündungsbotenstoff im Immunsystem, der bei Polymyalgia rheumatica (PMR) im Blut erhöht ist und als neuer Ansatzpunkt für Therapien dient, um den Bedarf an Cortison zu senken.

Rolle von IL-17 bei Polymyalgie

- **Erhöhte Werte:** Bei Patienten mit Polymyalgie finden sich oft höhere Konzentrationen von IL-17A im Blut, was die typischen Entzündungsprozesse antreibt.
- **Therapieansatz:** Forscher untersuchen den Einsatz von **IL-17-Hemmern** (wie [Secukinumab](#)), um Entzündungen gezielt zu stoppen.
- **Cortison-Einsparung:** Ziel dieser neuerlichen Behandlungsstudien ist es, die langfristige Einnahme von schädlichen Glukokortikoiden (Cortison) zu verringern

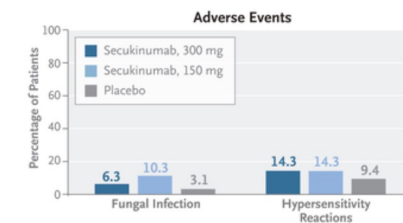
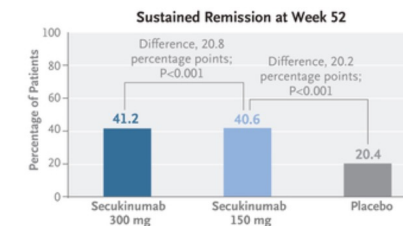
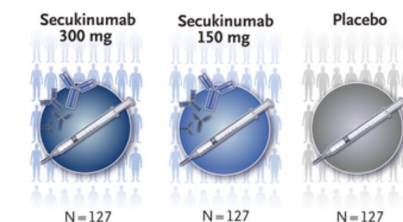
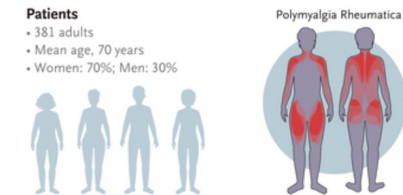


Interleukin-17 (IL-17) wird primär von einer spezialisierten Gruppe von T-Helferzellen, den **Th17-Zellen**, produziert. Neben diesen Hauptproduzenten wird das Zytokin jedoch auch von verschiedenen anderen Zellen des adaptiven und angeborenen Immunsystems ausgeschüttet.

Phase 3 Trial of Secukinumab in Polymyalgia Rheumatica

Polymyalgia rheumatica is a common inflammatory disease characterized by pain and stiffness in the shoulders and hips. Glucocorticoids are the first-line treatment, but relapses and glucocorticoid-related toxic effects are common, which underscores the need for effective alternatives. **Secukinumab is a fully human monoclonal antibody that selectively inhibits interleukin-17A.**

We enrolled patients with recently relapsed polymyalgia rheumatica and randomly assigned them, in a 1:1:1 ratio, to receive secukinumab at a dose of 300 mg (SEC-300 group), secukinumab at a dose of 150 mg (SEC-150 group), or placebo for 52 weeks. Patients in all the groups also received prednisone on a tapering schedule for 24 weeks. **The primary outcome was sustained remission at week 52**, defined as remission (the absence of signs or symptoms attributable to polymyalgia rheumatica and no new diagnosis of giant-cell arteritis that warranted escape or rescue treatment) that was sustained from week 12 until week 52. The annual cumulative glucocorticoid dose was a secondary outcome. Safety was also assessed.



Polymyalgia rheumatica is the second most common idiopathic inflammatory rheumatic disease after rheumatoid arthritis. Polymyalgia rheumatica occurs nearly exclusively in adults who are 50 years of age or older and is predominantly seen in women. It is characterized by bursitis and tendinitis that is associated with intense pain and stiffness in the neck, shoulders, and pelvic girdle, negatively affecting quality of life and physical function. Polymyalgia rheumatica is associated with giant-cell arteritis in approximately 16 to 21% of patients. Although the pathogenesis of polymyalgia rheumatica is not fully understood, elevated acute-phase reactants, increased interleukin-17A levels, and an imbalance between proinflammatory type 17 helper T (Th17) cells and regulatory T cells have been reported. Interleukin-17A contributes to articular and periarticular inflammation, which is typical of polymyalgia rheumatica. Glucocorticoids, an effective first-line treatment for polymyalgia rheumatica, are recommended by the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR). The REPLENISH trial was based on evidence of Th17 pathway activation in polymyalgia rheumatica, the efficacy of secukinumab in ankylosing spondylitis and psoriatic arthritis, and preliminary evidence of efficacy from a phase 2 trial in giant-cell arteritis

Patients

Eligible patients were 50 years of age or older, met the EULAR–ACR classification criteria for polymyalgia rheumatica, had a history of pain in both shoulders, and had an elevated C-reactive protein level (≥ 10 mg per liter) or an elevated erythrocyte sedimentation rate (≥ 30 mm per hour). Patients had to have had at least one polymyalgia rheumatica relapse while tapering prednisone or prednisone equivalent.

Trial Regimens

Patients were randomly assigned to receive secukinumab at a dose of 300 mg (SEC-300 group), secukinumab at a dose of 150 mg (SEC-150 group), or placebo for 52 weeks. Patients in the secukinumab groups received secukinumab subcutaneously once a week until week 4, and then every 4 weeks thereafter. The patients in all three groups received the same protocol-specified 24-week tapering course of prednisone, starting at either 15 mg per day or 10 mg per day.

Outcomes

Remission was defined as the absence of signs or symptoms attributable to polymyalgia rheumatica and no new diagnosis of giant-cell arteritis that warranted escape or rescue treatment.

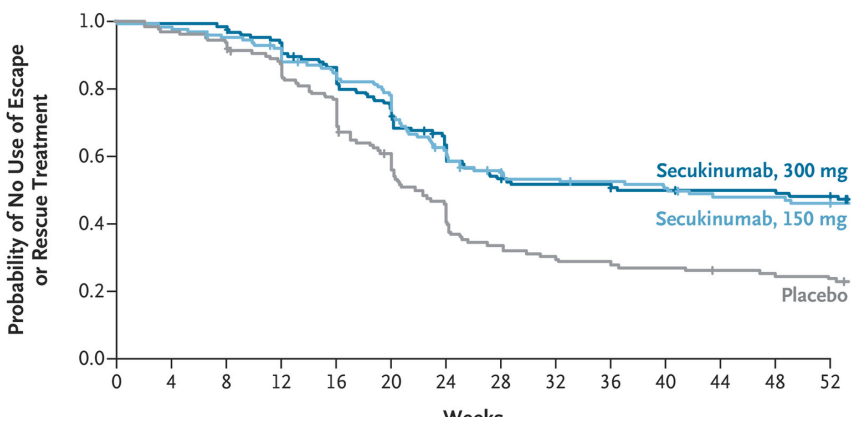
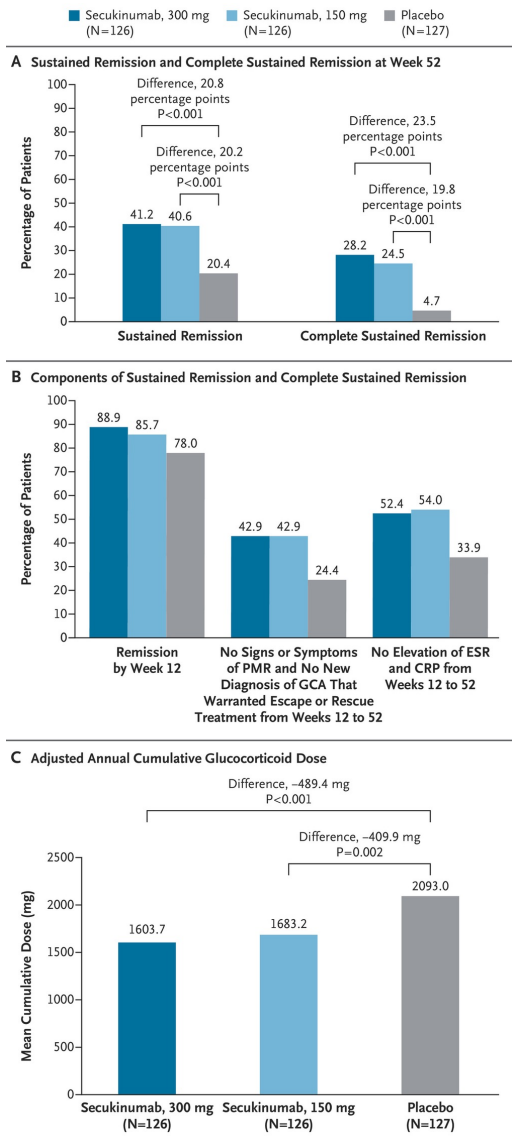
Characteristic	Secukinumab, 300 mg (N=127)	Secukinumab, 150 mg (N=127)	Placebo (N=127)
Age — yr	69.9±8.04	70.3±7.57	69.8±9.03
Female sex — no. (%)	96 (75.6)	86 (67.7)	86 (67.7)
Weight — kg	76.0±16.2	75.7±17.2	73.6±17.2
Body-mass index†	28.7±5.7	28.2±5.2	27.3±5.7
Race or ethnic group — no. (%)‡			
White	92 (72.4)	88 (69.3)	85 (66.9)
Asian	16 (12.6)	16 (12.6)	17 (13.4)
Other	19 (15.0)	23 (18.1)	25 (19.7)
Hispanic or Latino ethnic group — no. (%)‡			
Yes	18 (14.2)	16 (12.6)	19 (15.0)
No	90 (70.9)	98 (77.2)	87 (68.5)
Not reported or unknown	19 (15.0)	13 (10.2)	21 (16.5)
Signs and symptoms of active polymyalgia rheumatica — no. (%)	107 (84.3)	111 (87.4)	110 (86.6)
Previous polymyalgia rheumatica relapses — no. (%)			
1	64 (50.4)	51 (40.2)	54 (42.5)
>1	62 (48.8)	76 (59.8)	73 (57.5)
Missing data	1 (0.8)	0	0
Starting prednisone dose at baseline — no. (%)			
10 mg	88 (69.3)	87 (68.5)	92 (72.4)
15 mg	38 (29.9)	39 (30.7)	35 (27.6)
Missing data	1 (0.8)	1 (0.8)	0
High-sensitivity C-reactive protein level — mg/liter§	9.8±17.8	8.2±13.1	7.1±12.2
Erythrocyte sedimentation rate — mm/hr§	29.0±21.6	29.4±25.2	27.9±22.9

Adversity

Event	Secukinumab, 300 mg (N=126)	Secukinumab, 150 mg (N=126)	Placebo (N=127)
<i>number of patients (percent)</i>			
Any adverse event	115 (91.3)	111 (88.1)	114 (89.8)
Mild	49 (38.9)	49 (38.9)	46 (36.2)
Moderate	58 (46.0)	50 (39.7)	54 (42.5)
Severe	8 (6.3)	12 (9.5)	14 (11.0)
Adverse events reported in >10% of patients			
Nasopharyngitis	18 (14.3)	23 (18.3)	11 (8.7)
Urinary tract infection	14 (11.1)	14 (11.1)	7 (5.5)
Arthralgia	17 (13.5)	10 (7.9)	14 (11.0)
Diarrhea	12 (9.5)	7 (5.6)	13 (10.2)
Serious adverse event	17 (13.5)	20 (15.9)	18 (14.2)
Fatal serious adverse event	0	2 (1.6)	1 (0.8)
Adverse event leading to discontinuation of the trial regimen	4 (3.2)	4 (3.2)	8 (6.3)
Adverse event leading to interruption of the trial regimen	16 (12.7)	13 (10.3)	14 (11.0)
Adverse event of interest			
Infection or infestation†	73 (57.9)	77 (61.1)	68 (53.5)
Serious infection	4 (3.2)	3 (2.4)	4 (3.1)
Fungal infection	8 (6.3)	13 (10.3)	4 (3.1)
Hypersensitivity reaction‡	18 (14.3)	18 (14.3)	12 (9.4)

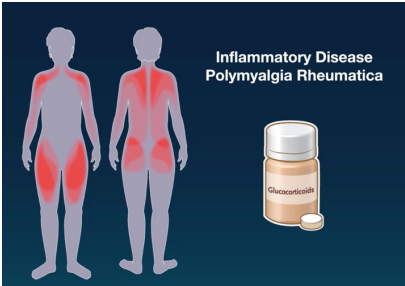
Remission and Cumulative Glucocorticoid Dose at Week 52.

Remission was defined as the absence of signs or symptoms attributable to polymyalgia rheumatica (PMR) and no new diagnosis of giant-cell arteritis (GCA) that warranted escape or rescue treatment. The primary outcome was sustained remission at week 52, defined as remission that occurred by week 12 and was sustained until week 52, without recurrence of PMR and with no new diagnosis of GCA that warranted treatment. Complete sustained remission was defined as remission by week 12 with no elevation in the erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (CRP) level at two consecutive visits from week 12 to week 52. The P values were adjusted for multiplicity. The adjusted mean annual cumulative glucocorticoid dose was calculated as the total cumulative glucocorticoid dose divided by the total number of days the patient participated in the trial up to the time of discontinuation or week 52 (whichever occurred first), multiplied by 365.25. The total cumulative glucocorticoid dose was calculated by combining the doses included in the prednisone taper, the escape or rescue glucocorticoid, and other glucocorticoid (converted to the prednisone-equivalent dose). Other glucocorticoid was a glucocorticoid other than the prednisone taper or the escape or rescue glucocorticoid.

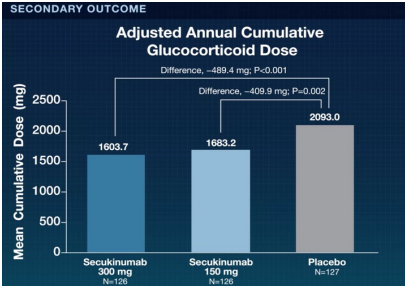


Time to First Use of Escape or Rescue Treatment through Week 52.

The results for the ESR and CRP level were concealed from the investigators, trial personnel, and the clinical trial team. Data for patients who discontinued the trial early or were lost to follow-up and had not received escape treatment, rescue treatment, or a prohibited medication were censored on the date of discontinuation or the date of the week 52 visit, whichever occurred earlier. One patient (in the placebo group) had a new diagnosis of GCA that warranted escape treatment. The tick marks indicate censored data.



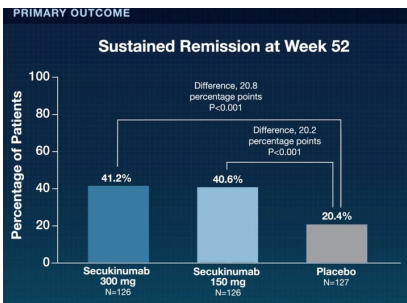
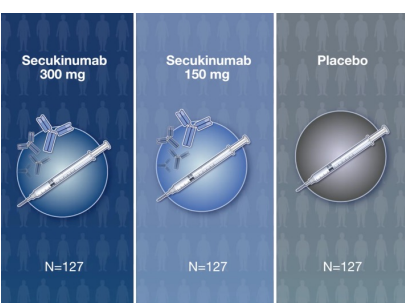
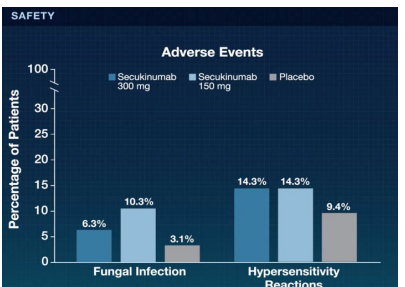
All patients received a 24-week tapering course of prednisone



PRIMARY OUTCOME

Sustained Remission

- Absence of signs or symptoms attributable to polymyalgia rheumatica
- No new diagnosis of giant-cell arteritis
- ...That required escape or rescue treatment

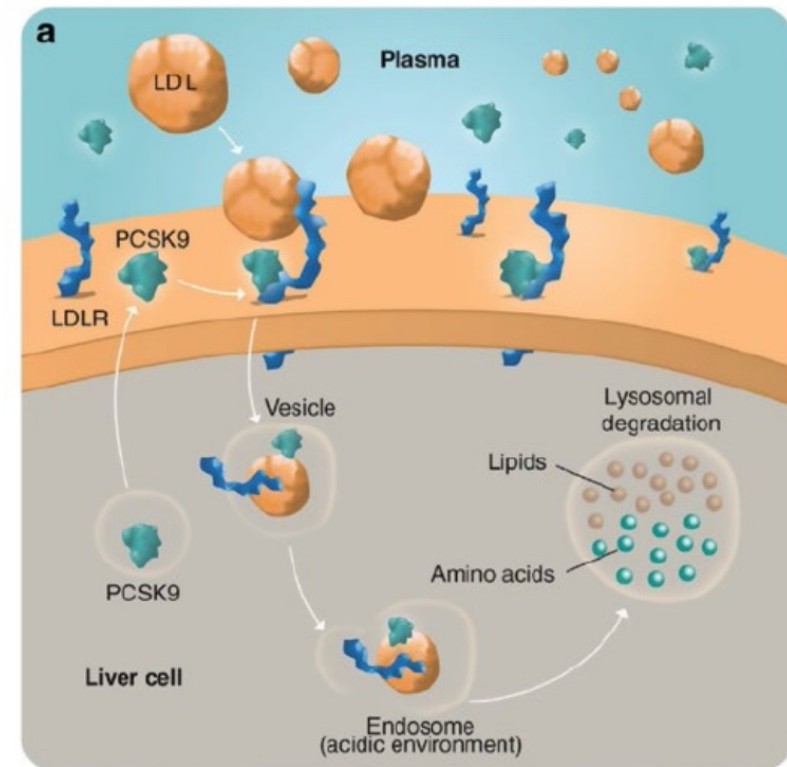


PCSK9 ist ein körpereigenes Protein, das den Abbau von LDL-Cholesterin-Rezeptoren in der Leber steuert. Blockiert man dieses Protein durch sogenannte PCSK9-Hemmer (wie [Evolocumab](#) oder [Alirocumab](#)), verbleiben mehr Rezeptoren auf den Zellen, was den "schlechten" LDL-Cholesterinspiegel im Blut um bis zu 60 Prozent senkt.

Funktion von PCSK9

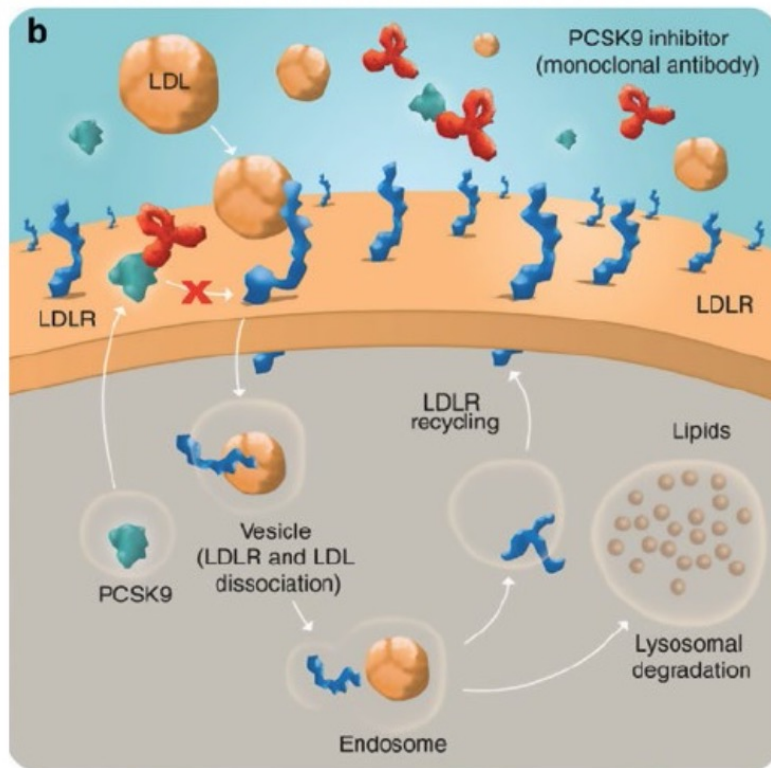
- **Regulierung:** Das Protein bindet an LDL-Rezeptoren der Leberzelle.
- **Abbau:** Der Rezeptor wird zusammen mit dem Cholesterin zerstört statt recycelt.
- **Folge:** Weniger Rezeptoren fangen LDL-Cholesterin ab, wodurch der Wert im Blut steigt.

How does PCSK9 work?



a) Secreted PCSK9 binds to LDLR on the liver cell surface and mediates the lysosomal degradation of the complex formed by PCSK9 - LDLR - LDL.

How does Inhibitors work?



b) In the presence of a monoclonal antibody that binds to PCSK9, the PCSK9-mediated degradation of LDLR is inhibited, resulting in an increased uptake of LDL-cholesterol by LDLR as more LDLR are recycled at the cell surface.

Medizinische Bedeutung (PCSK9-Hemmer)

- **Wirkung:** Sehr starke Senkung des LDL-Cholesterins (um ca. 60 %).
- **Anwendung:** Als Spritze unter die Haut (alle zwei bis vier Wochen) oder per RNA-Therapie.
- **Zielgruppe:** Hochrisikopatienten oder Menschen mit familiärer Hypercholesterinämie, bei denen Statine nicht ausreichen oder nicht vertragen werden.

In Vivo Base Editing of PCSK9 with VERVE-102 for Hypercholesterolemia

Persons carrying loss-of-function variants of proprotein convertase subtilisin–kexin type 9 (*PCSK9*) have reduced levels of low-density lipoprotein (LDL) cholesterol and fewer atherosclerotic cardiovascular disease events than persons without such variants. VERVE-102 is an investigational base-editing therapy designed to durably inactivate *PCSK9* in the liver.

In this phase 1, open-label, single-ascending-dose study, we administered one intravenous infusion of VERVE-102 at one of six doses (ranging from 0.3 to 1.0 mg of total RNA per kilogram of body weight [mg per kilogram]) to adults with heterozygous familial hypercholesterolemia or premature coronary artery disease. VERVE-102 consists of a messenger RNA encoding an adenine base-editor protein and a guide RNA targeting *PCSK9*, which are encapsulated in a lipid nanoparticle incorporating *N*-acetylgalactosamine. The objectives were to assess safety and changes in blood *PCSK9* protein and LDL cholesterol levels.

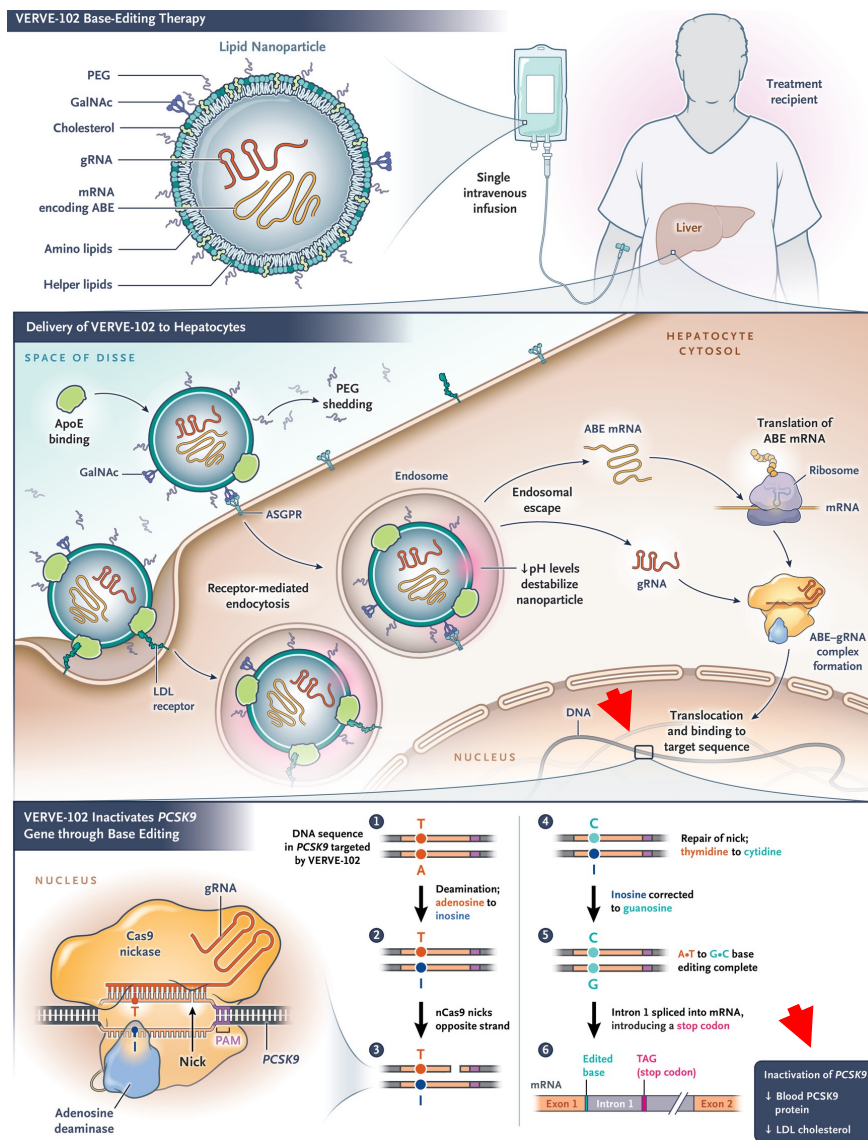
Conclusions

One dose of VERVE-102 led to dose-dependent, substantial, and sustained reductions in *PCSK9* and LDL cholesterol levels. (Funded by Verve Therapeutics; ClinicalTrials.gov number, [NCT06164730](https://clinicaltrials.gov/ct2/show/study/NCT06164730).)

Twenty years ago, seminal studies of human genetics showed that loss-of-function variants in the gene proprotein convertase subtilisin–kexin type 9 (*PCSK9*) confer lifelong low levels of blood *PCSK9* protein and low-density lipoprotein (LDL) cholesterol, without apparent adverse effects.

These biomarker changes were associated with a markedly reduced incidence of atherosclerotic cardiovascular disease events. Since its discovery, *PCSK9* has emerged as one of the most validated therapeutic targets in cardiovascular medicine. Multiple *PCSK9*-targeting therapies have been approved, and several cardiovascular-outcome studies have confirmed the safety and efficacy of *PCSK9* inhibition in patients with hypercholesterolemia.

To overcome the limitations of the current treatment model, we developed an in vivo base-editing medicine — *VERVE-102* — which was designed to mimic the effects of naturally occurring cardioprotective *PCSK9* variants and durably lower the LDL cholesterol level after a single infusion. *VERVE-102* consists of two drug substances — a messenger RNA (mRNA) encoding an adenine base-editor protein and a guide RNA targeting *PCSK9*. These two drug substances are encapsulated in a lipid nanoparticle delivery system that incorporates an *N*-acetylgalactosamine (GalNAc)–targeting ligand to enhance delivery to hepatocytes. The guide RNA targets a splice site at the 5′ end of intron 1 of *PCSK9*. Altering the splice site with a single DNA base-pair substitution enables read-through to a stop codon that prevents translation and expression of *PCSK9* protein in the liver.



In Vivo Gene Editing of Hepatocyte *PCSK9* with VERVE-102.

VERVE-102 consists of a messenger RNA (mRNA) encoding an adenine base-editor (ABE) protein and a guide RNA (gRNA) targeting *PCSK9*, which are encapsulated within an *N*-acetylgalactosamine (GalNAc)-lipid nanoparticle. VERVE-102 is administered by a single intravenous infusion with the dose based on milligrams of total RNA administered per kilogram of body weight. After infusion, the GalNAc-lipid nanoparticle binds to apolipoprotein E (ApoE) in the bloodstream. The ApoE-bound lipid nanoparticle then enters hepatocytes through low-density lipoprotein (LDL) receptor-mediated endocytosis or through GalNAc binding to asialoglycoprotein receptor (ASGPR). Inside the cell, pH changes in the endosome destabilize the GalNAc-lipid nanoparticle and the mRNA and guide RNA escape to the cytosol, where the mRNA is translated into the adenine base-editor protein that pairs with the guide RNA. The adenine base-editor complex then localizes to the nucleus and aligns with the target location at the 5' end of intron 1 of the gene *PCSK9* that is complementary to the unique guide RNA sequence. In this conformation, the adenosine deaminase domain chemically converts adenosine to inosine. The adenine base editor nicks the opposite strand of DNA to trigger the process of DNA repair. During the repair, which is based on the intact strand, the inosine is read as guanosine, which leads to placement of a cytidine on the repaired strand. Finally, endogenous DNA-repair mechanisms complete the A•T to G•C single base-pair substitution. Altering the splice site enables read-through to a stop codon that prevents translation and expression of *PCSK9* protein. PAM denotes protospacer adjacent motif, and PEG polyethylene glycol.

Putting a stop codon into the *PCSK9* gene

Participant Eligibility and Study Procedure

Adults 18 to 70 years of age were eligible for inclusion if they had a diagnosis of heterozygous familial hypercholesterolemia or premature coronary artery disease (defined as disease occurrence at ≤ 55 years of age in men or at ≤ 65 years of age in women).

Participants had to have a fasting LDL cholesterol level of at least 70 mg per deciliter (1.8 mmol per liter) while receiving the maximum tolerated dose of oral lipid-lowering therapy (a statin with or without ezetimibe).

Participants received a single intravenous infusion of VERVE-102 at one of six weight-based doses (0.3, 0.45, 0.6, 0.7, 0.8, or 1.0 mg of total RNA per kilogram of body weight [mg per kilogram]) over a period of up to approximately 4 hours. Premedication was administered to all the participants to reduce the risk of infusion-related reactions and consisted of dexamethasone on the day before VERVE-102 infusion and dexamethasone plus a histamine H₁–receptor antagonist and histamine H₂–receptor antagonist on the day of infusion.

Clinical-Outcome Assessments

The primary objective was to assess the safety of VERVE-102 in participants with heterozygous familial hypercholesterolemia or premature coronary artery disease. Adverse events were graded according to the Common Terminology Criteria for Adverse Events.

Characteristic	Participants (N=35)
Mean age (range) — yr	52 (27–66)
Male sex — no. (%)	24 (69)
Race — no. (%)†	
Asian	6 (17)
Black	1 (3)
White	30 (86)
Mean weight — kg	79±14
Mean body-mass index‡	27±4
Mean PCSK9 level — µg/liter	455±98
Mean LDL cholesterol level — mg/dl	129±42
Clinical status — no. (%)	
Heterozygous familial hypercholesterolemia only	20 (57)
Heterozygous familial hypercholesterolemia and pre-mature coronary artery disease	9 (26)
Premature coronary artery disease only	6 (17)
Concomitant statin use — no. (%)	
High intensity	25 (71)
Moderate or low intensity	7 (20)
None	3 (9)
Concomitant ezetimibe use — no. (%)	15 (43)

Adversity

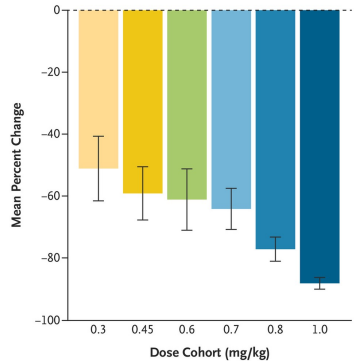
Event	Participants (N=35)
	no. (%)
Any adverse event	26 (74)
Any adverse event of grade 3 or higher*	1 (3)
Any serious adverse event*	1 (3)
Any treatment-related adverse event	11 (31)
Treatment-related adverse events occurring in >1 participant	
Infusion-related reaction	7 (20)
Fatigue	2 (6)

AST and ALT elevations

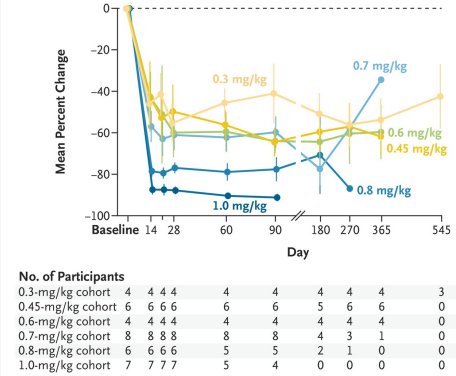
Changes in PCSK9 and LDL Cholesterol Levels According to VERVE-102 Dose Cohort.

Variable	0.3 mg/kg (N=4)	0.45 mg/kg (N=6)	0.6 mg/kg (N=4)	0.7 mg/kg (N=8)	0.8 mg/kg (N=6)	1.0 mg/kg (N=7)
Total RNA dose (range) — mg	20 (18 to 23)	37 (27 to 45)	51 (40 to 58)	55 (34 to 70)	62 (48 to 80)	80 (57 to 95)
Mean PCSK9 level (range) — µg/liter						
At baseline	448 (264 to 591)	482 (351 to 599)	451 (420 to 489)	474 (340 to 578)	421 (283 to 604)	447 (317 to 740)
At day 28	201 (82 to 288)	251 (45 to 535)	181 (57 to 273)	193 (32 to 416)	101 (56 to 202)	58 (30 to 118)
Time-averaged PCSK9 level during follow-up (range) — µg/liter	220 (97 to 316)	199 (39 to 306)	173 (71 to 260)	176 (34 to 317)	98 (49 to 204)	53 (28 to 99)
Mean percent change from baseline in time-averaged PCSK9 level (range) — %	-51 (-73 to -30)	-59 (-92 to -34)	-61 (-84 to -38)	-64 (-93 to -34)	-77 (-87 to -66)	-88 (-94 to -78)
Mean LDL cholesterol level (range) — mg/dl						
At baseline	154 (61 to 200)	140 (89 to 205)	124 (111 to 159)	105 (90 to 129)	139 (82 to 203)	128 (82 to 230)
At day 28	114 (47 to 147)	82 (46 to 124)	67 (53 to 102)	65 (20 to 94)	73 (26 to 156)	51 (20 to 127)
Time-averaged LDL cholesterol level during follow-up (range) — mg/dl	143 (50 to 234)	77 (55 to 107)	69 (51 to 105)	70 (32 to 95)	68 (26 to 171)	51 (20 to 118)
Mean change from baseline in LDL cholesterol level (range) — mg/dl	-11 (-51 to 48)	-64 (-97 to -34)	-55 (-60 to -49)	-35 (-74 to -15)	-71 (-163 to -31)	-78 (-117 to -54)
Mean percent change from baseline in time-averaged LDL cholesterol level (range) — %	-9 (-26 to 26)	-44 (-57 to -30)	-45 (-54 to -34)	-33 (-70 to -14)	-51 (-86 to -16)	-62 (-79 to -45)

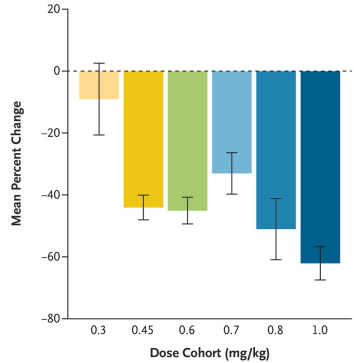
A Change in Time-Averaged PCSK9 Level from Baseline



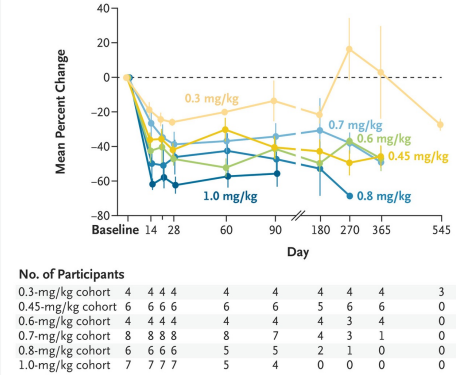
B Change in PCSK9 Level over Time



C Change in Time-Averaged LDL Cholesterol Level from Baseline



D Change in LDL Cholesterol Level over Time



Discussion

In this phase 1 study, a single infusion of VERVE-102 produced dose-dependent and sustained reductions in PCSK9 and LDL cholesterol levels, with a mean reduction of 88% and 62%, respectively, at the highest dose. Mild-to-moderate infusion-related reactions and transient elevations in alanine aminotransferase levels (<2.5 times the upper limit of normal) were observed.

Participants who received 1 mg per kilogram of VERVE-102 had a mean absolute reduction in LDL cholesterol level of 78 mg per deciliter (range, 54 to 117). A reduction of this magnitude, if maintained over 20 years, is predicted to reduce the risk of atherosclerotic cardiovascular disease by more than 50% for most patients with hypercholesterolemia, but larger and much longer studies are warranted to determine whether the decrease in LDL cholesterol levels observed in this study is durable over the course of decades.

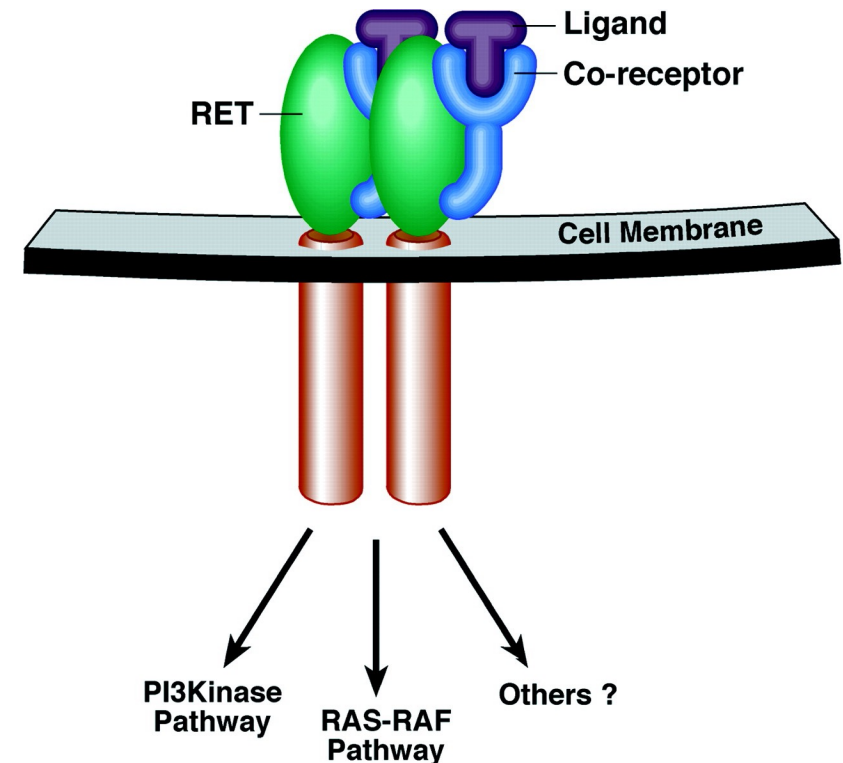
Treatment with VERVE-102 led to dose-dependent, substantial, and sustained reductions in PCSK9 and LDL cholesterol levels. Together with the safety data, these results support continued development of VERVE-102 as a treatment for hypercholesterolemia. Twenty years after the observation that lifelong inactivation of *PCSK9* protects against atherosclerotic cardiovascular disease, these data provide early clinical evidence that a single infusion of a base-editing therapy can mimic the LDL cholesterol-lowering effects of *PCSK9* cardioprotective variants.

Das **RET-Protoonkogen** (*abgekürzt für REarranged during Transfection*) ist ein Gen auf dem Chromosom 10, das den Bauplan für ein ganz bestimmtes Eiweiß liefert: die **Rezeptor-Tyrosinkinase RET**. Dieses Protein sitzt wie eine Antenne in der Zellmembran und hat die Aufgabe, **Wachstumssignale von außen in das Innere der Zelle weiterzuleiten**. Dadurch steuert es maßgeblich, wie Zellen wachsen, sich teilen und spezialisieren. In einem gesunden Körper erfüllt das Gen zwei Hauptaufgaben, bringt aber auch medizinische Risiken mit sich, wenn es mutiert.

Während der Embryonalentwicklung und auch im späteren Leben ist das intakte RET-Gen unentbehrlich für:

- **Das Nervensystem:** Es steuert die Entwicklung und Reifung bestimmter Nervenzellen. Besonders wichtig ist es für das sogenannte enterische Nervensystem – also das Nervengeflecht, das unseren Magen-Darm-Trakt steuert.
- **Die Organentwicklung:** Es reguliert das Wachstum und die feine Gewebestruktur der Nieren während der Schwangerschaft.

RET proto-oncogene encodes a receptor tyrosine kinase, which is a type of cell-surface transmembrane receptor.



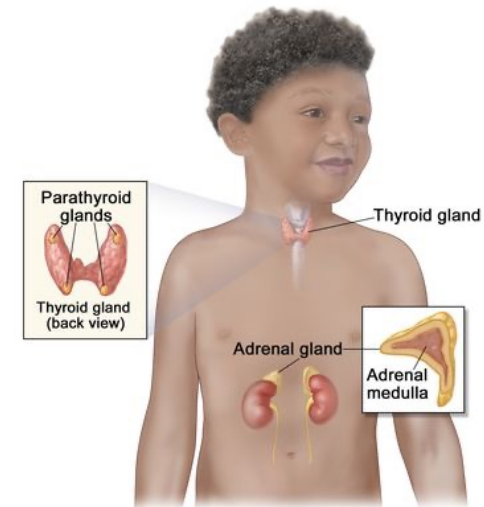
MEN2A (Sipple-Syndrom)

Diese Variante macht etwa **95 % aller MEN2-Fälle** aus. Neben dem medullären Schilddrüsenkarzinom (MTC) können zwei weitere Organsysteme betroffen sein:

- **Phäochromozytom:** Tritt bei ca. 50 % der Betroffenen auf (oft beidseitige Tumoren des Nebennierenmarks, die Adrenalin/Noradrenalin ausschütten und schweren Bluthochdruck verursachen).
- **Primärer Hyperparathyreoidismus (pHPT):** Tritt bei 20–30 % der Patienten durch eine gutartige Vergrößerung der Nebenschilddrüsen auf, was zu erhöhtem Kalzium im Blut führt.
- **Sonderformen: Das familiäre medulläre Schilddrüsenkarzinom (FMTC)** gilt heute als Variante von MEN2A, bei der über Generationen hinweg ausschließlich das MTC ohne andere Begleittumoren auftritt. Selten ist MEN2A mit Hautveränderungen (Lichen amyloidosus oder Morbus Hirschsprung) assoziiert.

Eine bekannte RET-Krankheit

Parts of the Body Affected by MEN2 Syndrome



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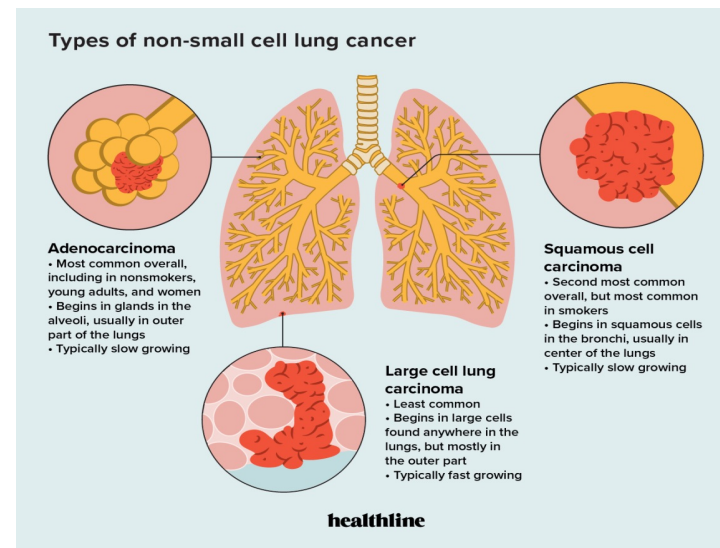
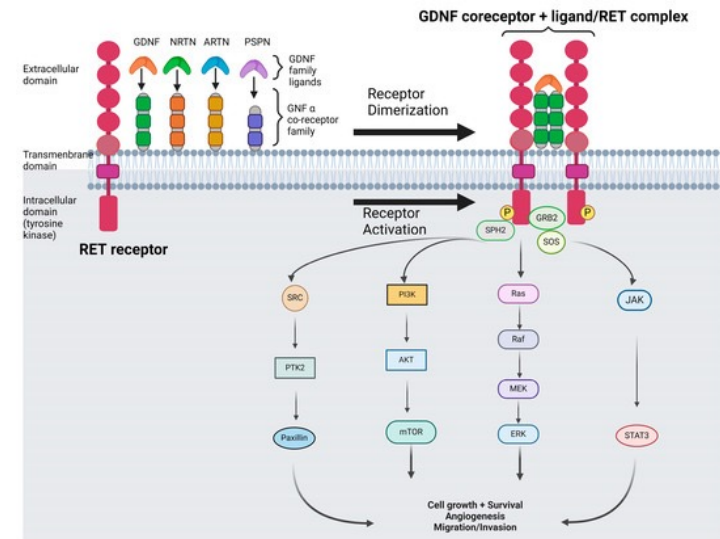
Die Multiple endokrine Neoplasie Typ 2 (MEN2) wird **autosomal-dominant** vererbt und beruht auf einer **Gain-of-Function-Mutation** (einer aktivierenden Genveränderung) im **RET**-Protoonkogen. Diese Mutation führt zu einer dauerhaften und unkontrollierten Aktivierung des RET-Rezeptors, was das Zellwachstum antreibt und zu Tumoren führt.

Somatic RET mutations within NSCLC

Das RET-Protoonkogen (REarranged during Transfection) ist bei etwa 1–2 % aller nicht-kleinzelligen Lungenkarzinome (NSCLC) durch Genfusionen verändert. Diese Veränderungen dienen als wichtige molekulare Treibermutationen für das Tumorstwachstum und ermöglichen den Einsatz hochwirksamer, zielgerichteter Therapien.

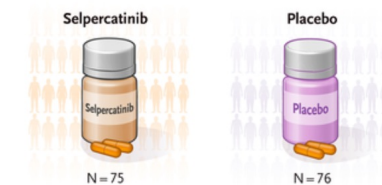
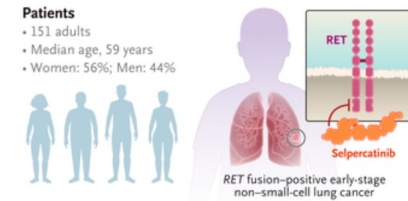
Häufigkeit und Merkmale

- **Vorkommen:** Betrifft ca. 1 bis 2 % der NSCLC-Fälle (hauptsächlich Adenokarzinome).
- **Patientengruppe:** Kommt oft bei jüngeren Patienten und Nichtrauchern vor.
- **Fusionspartner:** Häufigste Fusionspartner sind Gene wie *KIF5B* oder *CCDC6*, die zu einer dauerhaften **Aktivierung der RET-Tyrosinkinase führen (gain of function)**.

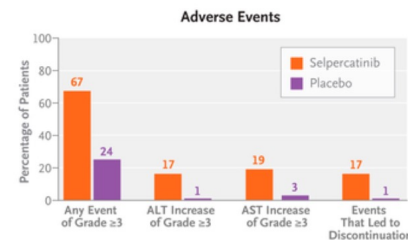
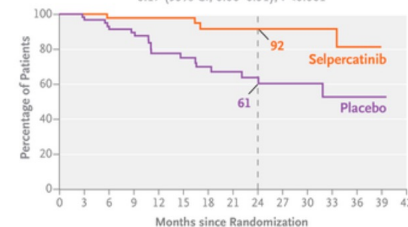


Selpercatinib in Early-Stage RET Fusion–Positive Non–Small-Cell Lung Cancer

Selpercatinib, a highly selective, potent, and central nervous system–penetrant RET inhibitor, is approved for *RET* fusion–positive advanced or metastatic non–small-cell lung cancer (NSCLC). The efficacy and safety of selpercatinib in early-stage NSCLC are unknown. We conducted a phase 3, double-blind trial involving patients with *RET* fusion–positive NSCLC who had received definitive therapy with curative intent (surgery or radiotherapy with adjuvant systemic anticancer therapy, if applicable). Patients were randomly assigned to receive adjuvant selpercatinib or placebo for up to 3 years. The primary end point was investigator-assessed event-free survival in patients with stage II or IIIA disease. Secondary end points were investigator-assessed event-free survival in patients with stage IB, II, or IIIA disease; event-free survival as assessed by blinded independent central review; overall survival; and safety.



Event-free Survival in Patients with Stage II or IIIA Disease
Hazard ratio for disease recurrence, progression, or death, 0.17 (95% CI, 0.06–0.51); $P < 0.001$



Approximately 30 to 40% of patients with non–small-cell lung cancer (NSCLC) present with early-stage disease (stage IB, II, or IIIA). Standard-care options for resectable early-stage NSCLC include surgery and neoadjuvant or perioperative chemoimmunotherapy. Unfortunately, despite these interventions, up to two thirds of patients have disease recurrence and may eventually die from metastatic disease. Rearranged during transfection (*RET*) fusions are actionable, oncogenic drivers identified in 1 to 2% of all patients with NSCLC. Selpercatinib, a highly selective, potent, and central nervous system–penetrant *RET* inhibitor, has been approved by the health authority in many countries for the treatment of patients with advanced *RET*-driven cancers. In advanced or metastatic *RET* fusion–positive NSCLC, selpercatinib results in a high percentage of patients with a response and durable disease control, as shown in the phase 1–2 LIBRETTO-001 trial and the phase 3, randomized LIBRETTO-431 trial. No adjuvant targeted therapy is approved for early-stage *RET* fusion–positive NSCLC.

Selpercatinib ist ein hochwirksamer, zielgerichteter Krebswirkstoff aus der Gruppe der Tyrosinkinase-Inhibitoren (RET-Inhibitoren).

Methods

Trial Design

We conducted a phase 3, multinational, double-blind, randomized, placebo-controlled trial. Patients were randomly assigned in a 1:1 ratio to receive **selpercatinib (160 mg twice daily for patients with a weight of ≥ 50 kg and 120 mg twice daily for patients with a weight of < 50 kg) or placebo in continuous 28-day cycles.**

Patients

Eligible patients were 18 years of age or older and had an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (score range, 0 to 5, with higher scores reflecting greater disability), adequate organ function, and histologically confirmed stage IB, II, or IIIA *RET* fusion–positive NSCLC according to the 8th edition of the staging system for lung cancer. *RET* status was determined through local testing with a polymerase-chain-reaction assay, comprehensive genomic profiling, or another molecular test approved by the sponsor.

End Points and Assessments

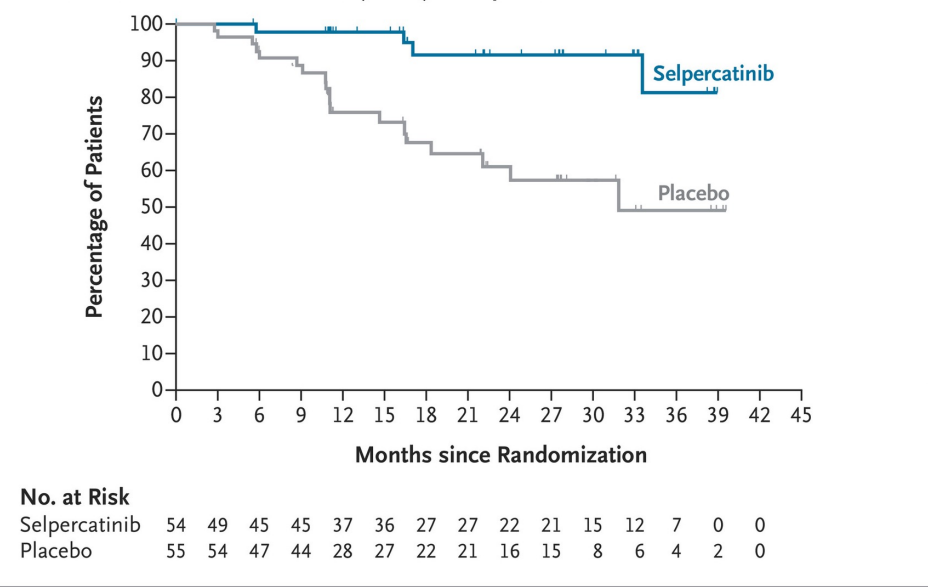
The primary end point was investigator-assessed event-free survival according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and was assessed in the primary analysis population (all the patients with stage II or IIIA NSCLC who had undergone randomization).

Characteristic	Primary Analysis Population (N=109)		Overall Population (N=151)	
	Selpercatinib (N=54)	Placebo (N=55)	Selpercatinib (N=75)	Placebo (N=76)
Sex — no. (%)				
Female	34 (63)	30 (55)	45 (60)	40 (53)
Male	20 (37)	25 (45)	30 (40)	36 (47)
Age — yr				
Median	59.5	61.0	59.0	59.0
Range	41.0–84.0	26.0–78.0	33.0–84.0	26.0–86.0
Age distribution — no. (%)				
<65 yr	39 (72)	34 (62)	54 (72)	48 (63)
≥65 yr	15 (28)	21 (38)	21 (28)	28 (37)
Smoking status — no. (%)				
Former or current smoker	17 (31)	17 (31)	22 (29)	23 (30)
Never smoked	37 (69)	38 (69)	53 (71)	53 (70)
Region — no. (%)				
East Asia	31 (57)	31 (56)	44 (59)	48 (63)
Europe	12 (22)	14 (25)	17 (23)	17 (22)
North America	6 (11)	7 (13)	8 (11)	8 (11)
Other	5 (9)	3 (5)	6 (8)	3 (4)
Race or ethnic group — no. (%)†				
Asian	33 (61)	32 (58)	47 (63)	49 (64)
White	21 (39)	21 (38)	27 (36)	24 (32)
Black	0	2 (4)	0	2 (3)
Native Hawaiian or other Pacific Islander	0	0	0	1 (1)
ECOG performance-status score — no. (%)‡				
0	30 (56)	36 (65)	45 (60)	52 (68)
1	24 (44)	18 (33)	30 (40)	22 (29)
Initial disease stage — no. (%)				
Stage IB	0	0	21 (28)	21 (28)
Stage II	23 (43)	24 (44)	23 (31)	24 (32)
Stage IIIA	31 (57)	31 (56)	31 (41)	31 (41)
NSCLC histologic type — no. (%)				
Adenocarcinoma	51 (94)	51 (93)	72 (96)	71 (93)
Other§	3 (6)	4 (7)	3 (4)	5 (7)
RET fusion — no. (%)				
KIF5B–RET	33 (61)	34 (62)	50 (67)	51 (67)
CCDC6–RET	14 (26)	11 (20)	18 (24)	13 (17)
Other¶	7 (13)	10 (18)	7 (9)	12 (16)
PD-L1 expression — no. (%)				
Negative	11 (20)	16 (29)	18 (24)	22 (29)
Positive	25 (46)	28 (51)	29 (39)	33 (43)
Tumor proportion score of 1–49%	13 (24)	14 (25)	15 (20)	16 (21)
Tumor proportion score of ≥50%	12 (22)	9 (16)	14 (19)	11 (14)
Tumor proportion score unknown	0	5 (9)	0	6 (8)
Other	1 (2)	0	1 (1)	0
Not assessed	17 (31)	11 (20)	27 (36)	21 (28)
Previous anticancer therapy — no. (%)				
Surgery	54 (100)	54 (98)**	75 (100)	75 (99)**
Radiotherapy	2 (4)	6 (11)	2 (3)	7 (9)
Adjuvant systemic chemotherapy††	50 (93)	50 (91)	56 (75)	55 (72)
Immunotherapy‡‡	2 (4)	1 (2)	3 (4)	1 (1)
Platinum chemotherapy	48 (89)	49 (89)	54 (72)	54 (71)

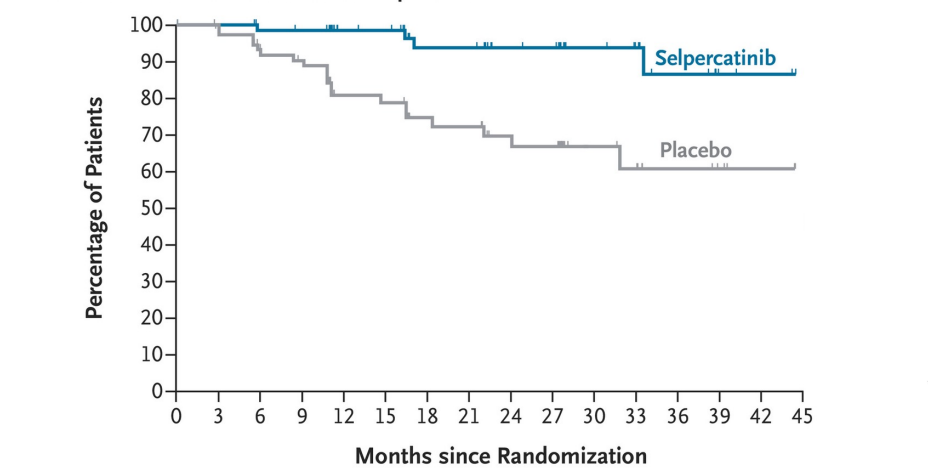
Adversity

Event	Selpercatinib (N=75)		Placebo (N=76)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	<i>number of patients (percent)</i>			
Any adverse event	75 (100)	50 (67)	74 (97)	18 (24)
ALT level increased	47 (63)	13 (17)	14 (18)	1 (1)
AST level increased	45 (60)	14 (19)	12 (16)	2 (3)
Diarrhea	29 (39)	3 (4)	13 (17)	0
Dry mouth	30 (40)	0	12 (16)	0
Cough	20 (27)	0	18 (24)	0
Blood bilirubin level increased	20 (27)	1 (1)	11 (14)	0
Hypertension	23 (31)	8 (11)	8 (11)	2 (3)
Constipation	17 (23)	0	10 (13)	0
Upper respiratory tract infection	12 (16)	1 (1)	13 (17)	0
Rash	14 (19)	1 (1)	10 (13)	0
Coronavirus disease 2019	12 (16)	0	11 (14)	0
Hyperuricemia	15 (20)	0	8 (11)	0
Nausea	12 (16)	0	11 (14)	0
Fatigue	11 (15)	0	11 (14)	0
Headache	14 (19)	0	7 (9)	0
Blood creatinine level increased	14 (19)	0	6 (8)	0
Dizziness	13 (17)	0	6 (8)	0
Peripheral edema	13 (17)	0	6 (8)	0
Neutrophil count decreased	8 (11)	0	10 (13)	3 (4)
Pyrexia	12 (16)	1 (1)	6 (8)	1 (1)
Abdominal pain	14 (19)	2 (3)	3 (4)	0
Dyspnea	10 (13)	0	6 (8)	0
White-cell count decreased	8 (11)	1 (1)	8 (11)	0

A Event-free Survival in the Primary Analysis Population



B Event-free Survival in the Overall Population

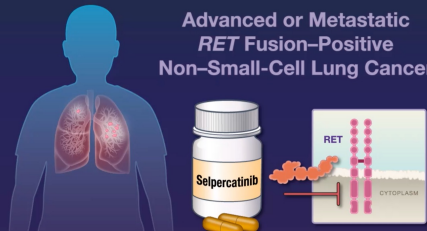


Subgroup	Total No. of Patients	Selpercatinib <i>no. of patients with event</i>	Placebo	Hazard Ratio for Disease Recurrence, Progression, or Death (95% CI)
Overall	109	4	19	0.18 (0.07, 0.46)
Sex				
Female	64	3	11	0.15 (0.05, 0.41)
Male	45	1	8	0.25 (0.04, 1.51)
Age				
≤65 yr	78	2	10	0.12 (0.03, 0.51)
>65 yr	31	2	9	0.28 (0.05, 1.51)
Geographic region				
North America or Europe	39	3	9	0.18 (0.06, 0.51)
Other	70	1	10	0.22 (0.04, 1.11)
Smoking status				
Never	75	1	12	0.18 (0.05, 0.61)
Former or current	34	3	7	0.22 (0.05, 0.91)
ECOG performance-status score				
0	66	1	10	0.18 (0.05, 0.61)
>0	42	3	9	0.25 (0.05, 1.11)
Disease stage				
Stage II	47	2	3	0.22 (0.05, 0.91)
Stage IIIA	62	2	16	0.18 (0.06, 0.51)
Previous chemotherapy				
Yes	100	3	17	0.18 (0.07, 0.46)
No	9	1	2	0.22 (0.04, 1.11)

0.001 0.01 0.1 1.0 10.0 100.0

Selpercatinib Better Placebo Better

**Advanced or Metastatic
RET Fusion-Positive
Non-Small-Cell Lung Cancer**

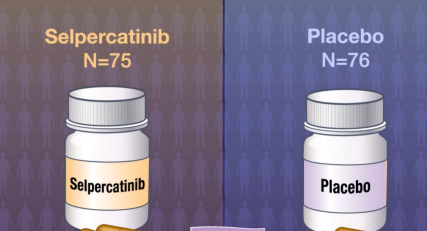


Selpercatinib

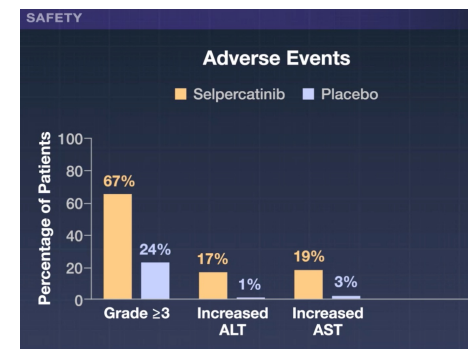
High percentage of patients with a response and durable disease control

**Selpercatinib
N=75**

**Placebo
N=76**



YEAR

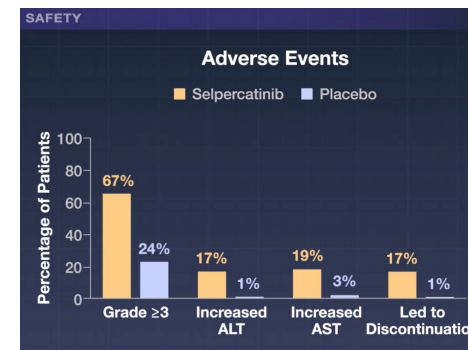
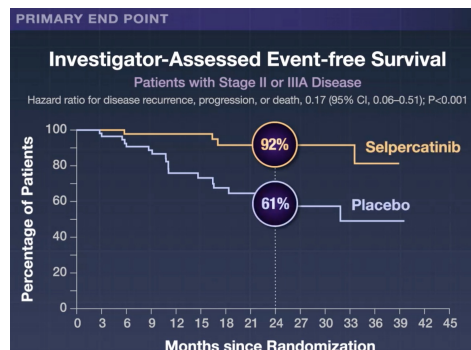


? Efficacy and Safety

TRIAL

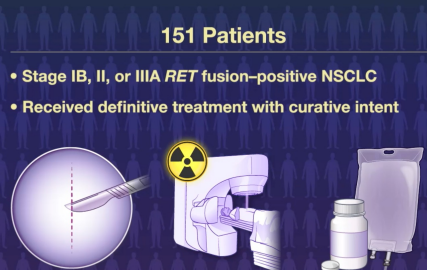
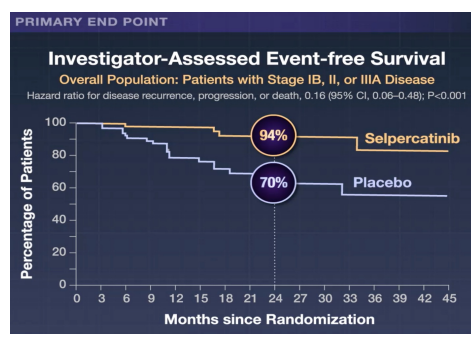


Early-stage non-small-cell lung cancer (NSCLC)



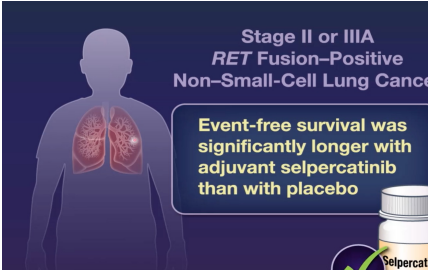
151 Patients

- Stage IB, II, or IIIA *RET* fusion-positive NSCLC
- Received definitive treatment with curative intent

**Stage II or IIIA
RET Fusion-Positive
Non-Small-Cell Lung Cancer**

Event-free survival was significantly longer with adjuvant selpercatinib than with placebo



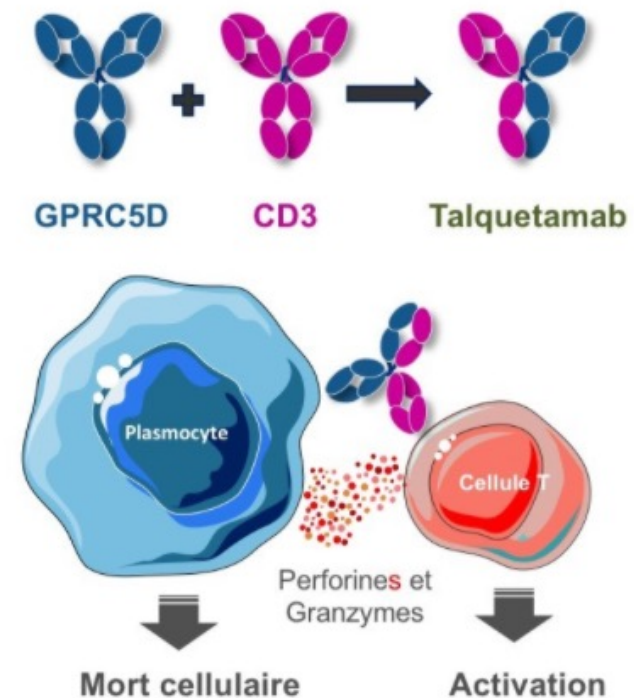
Selpercatinib

GPRC5D steht für „G protein-coupled receptor, family C, group 5, member D“. Es ist ein Protein (ein Transmembranrezeptor), das beim Menschen auf der Oberfläche bestimmter Zellen sitzt.

Bedeutung in der Medizin

- **Vorkommen:** GPRC5D kommt in gesundem Gewebe nur sehr selten vor, findet sich jedoch in großer Menge auf den Zellen des **Multiplen Myeloms** (einer Krebserkrankung des Knochenmarks).
- **Krebstherapie:** Weil das Protein so spezifisch auf den Tumorzellen sitzt, ist es ein wichtiger Angriffspunkt für moderne Immuntherapien gegen Blutkrebs.
- **Therapiearten:** Forscher nutzen GPRC5D, um Krebszellen mit speziellen **CAR-T-Zellen** oder **bispezifischen Antikörpern** gezielt zu erkennen und zu zerstören. Das hilft besonders Patienten, bei denen andere Therapien (wie solche gegen das Zielzelleiweiß BCMA) nicht mehr ausreichen oder der Krebs zurückgekehrt ist.

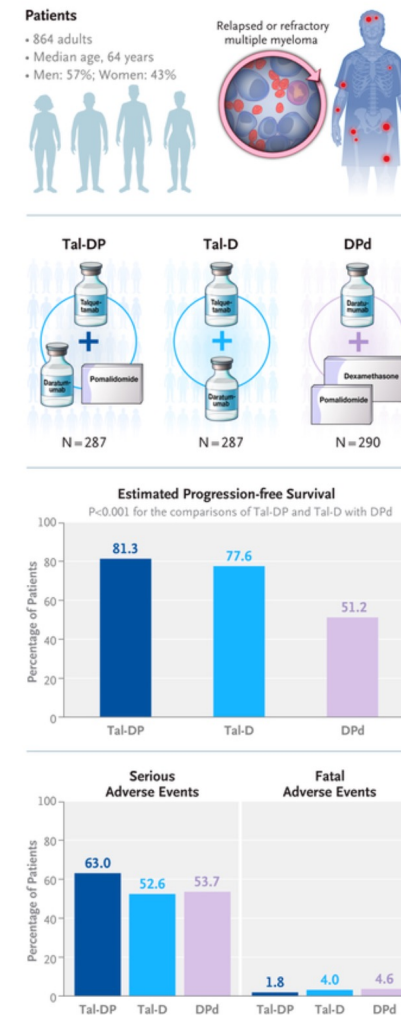
GPRC5D (G-protein coupled receptor family C group 5 member D) ist ein **Waisenrezeptor (Orphan-Rezeptor)** aus der Klasse der **G-Protein-gekoppelten Rezeptoren**, dessen genaue biologische Funktion und natürlicher Ligand in gesundem Gewebe noch weitgehend **unbekannt sind**.



Talquetamab–Daratumumab in Relapsed or Refractory Myeloma

Talquetamab, a bispecific antibody targeting GPRC5D and CD3, has led to durable responses in patients with heavily pretreated relapsed or refractory multiple myeloma in phase 1–2 trials, with a limited effect on normal B cells.

In a phase 3 trial, we randomly assigned patients with relapsed or refractory multiple myeloma who had previously received at least one line of therapy to receive talquetamab plus daratumumab and pomalidomide (Tal-DP), talquetamab plus daratumumab (Tal-D), or daratumumab plus pomalidomide and dexamethasone (DPd). **The primary end point was progression-free survival** as assessed by an independent review committee. Key secondary end points were overall response, complete response or better (complete or stringent complete response), measurable residual disease–negative complete response, and overall survival.



Talquetamab is a bispecific antibody targeting G protein–coupled receptor class C group 5 member D (GPRC5D) on myeloma cells and CD3 on T cells that has been approved for the treatment of patients with relapsed or refractory multiple myeloma who have previously received four or more lines of therapy. In the phase 1–2 MonumenTAL-1 study, 69.5% of the patients receiving talquetamab at a dose of 0.8 mg per kilogram of body weight had a response, and the 36-month overall survival estimate was 60.8% with extended follow-up. Talquetamab preferentially targets myeloma cells, with a limited effect on normal B cells. Talquetamab has been associated with a manageable infection profile and can be included in combination regimens. Daratumumab modulates the immune microenvironment by reducing immunosuppressive regulatory T cells and enhancing cytotoxic T-cell activity, creating synergistic effects with talquetamab-mediated eradication of myeloma cells.

We report results from the prespecified interim analysis of the phase 3 MonumenTAL-3 trial, which is investigating the efficacy and safety of talquetamab plus daratumumab and pomalidomide (Tal-DP) and talquetamab plus daratumumab (Tal-D) as compared with daratumumab plus pomalidomide and dexamethasone (DPd) in patients with relapsed or refractory multiple myeloma who have previously received at least one line of therapy.

Patients

Patients 18 years of age or older were eligible for enrollment in the trial if they had **relapsed or refractory multiple myeloma** with a measurable M-protein level in serum (≥ 0.5 g per deciliter) or urine (≥ 200 mg in a 24-hour urine collection) or light-chain multiple myeloma without a measurable M-protein level in serum or urine; **had previously received at least one line of therapy, including lenalidomide and a proteasome inhibitor**; and had an Eastern Cooperative Oncology Group performance-status score of 0, 1, or 2 (scores range from 0 to 5, with higher scores indicating greater disability).

Treatment

Patients were randomly assigned in a 1:1:1 ratio to receive Tal-DP, Tal-D, or DPd.

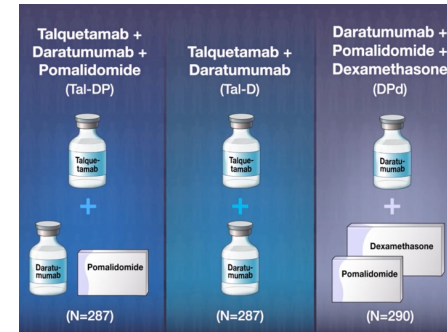
Randomization was stratified according to International Staging System stage at screening (I vs. II vs. III), previous exposure to daratumumab, and number of previous lines of therapy (1 vs. 2 or 3 vs. >3). In the **Tal-DP** and **Tal-D** groups, talquetamab and **daratumumab were administered in 28-day cycles.**

End Points and Assessments

The primary end point was progression-free survival as assessed by an independent review committee in an analysis of the time from randomization to the first documentation of disease progression or death from any cause, whichever was reported first.

Characteristic	Tal-DP (N = 287)	Tal-D (N = 287)	DPd (N = 290)	All Patients (N = 864)
Median age (range) — yr	64 (40–83)	64 (32–88)	63 (30–88)	64 (30–88)
Male sex — no. (%)	169 (58.9)	166 (57.8)	161 (55.5)	496 (57.4)
Race or ethnic group — no. (%)†				
White	185 (64.5)	179 (62.4)	193 (66.6)	557 (64.5)
Black	14 (4.9)	14 (4.9)	16 (5.5)	44 (5.1)
Asian	80 (27.9)	86 (30.0)	71 (24.5)	237 (27.4)
Other	8 (2.8)	8 (2.8)	10 (3.4)	26 (3.0)
≥60% Plasma cells in bone marrow — no./total no. (%)‡	27/283 (9.5)	30/282 (10.6)	31/290 (10.7)	88/855 (10.3)
≥1 Soft-tissue plasmacytoma — no. (%)§	37 (12.9)	51 (17.8)	42 (14.5)	130 (15.0)
True extramedullary plasmacytoma	12 (32.4)	19 (37.3)	17 (40.5)	48 (36.9)
Paraskeletal plasmacytoma	31 (83.8)	40 (78.4)	30 (71.4)	101 (77.7)
Cytogenetic risk — no. (%)¶				
Standard risk	129 (44.9)	115 (40.1)	131 (45.2)	375 (43.4)
High risk	88 (30.7)	97 (33.8)	82 (28.3)	267 (30.9)
Not evaluable	70 (24.4)	75 (26.1)	77 (26.6)	222 (25.7)
International Staging System stage — no. (%)				
I	190 (66.2)	187 (65.2)	192 (66.2)	569 (65.9)
II	68 (23.7)	69 (24.0)	67 (23.1)	204 (23.6)
III	29 (10.1)	31 (10.8)	31 (10.7)	91 (10.5)
ECOG performance-status score — no. (%)**				
0	148 (51.6)	154 (53.7)	147 (50.7)	449 (52.0)
1	126 (43.9)	124 (43.2)	129 (44.5)	379 (43.9)
2	13 (4.5)	9 (3.1)	14 (4.8)	36 (4.2)
Median time since diagnosis (range) — yr	3.5 (0.3–22.0)	3.7 (0.4–17.0)	4.1 (0.5–19.0)	3.8 (0.3–22.0)
Median no. of previous lines of therapy (range)	2 (1–8)	2 (1–7)	2 (1–8)	2 (1–8)
No. of previous lines of therapy — no. (%)				
1	111 (38.7)	106 (36.9)	114 (39.3)	331 (38.3)
2 or 3	150 (52.3)	153 (53.3)	148 (51.0)	451 (52.2)
>3	26 (9.1)	28 (9.8)	28 (9.7)	82 (9.5)
Previous stem-cell transplantation — no. (%)	207 (72.1)	192 (66.9)	196 (67.6)	595 (68.9)
Previous exposure — no. (%)				
Immunomodulatory drug	287 (100.0)	287 (100.0)	290 (100.0)	864 (100.0)
Proteasome inhibitor	287 (100.0)	287 (100.0)	288 (99.3)††	862 (99.8)
Anti-CD38 monoclonal antibody				
Daratumumab	33 (11.5)	34 (11.8)	33 (11.4)	100 (11.6)
Isatuximab	0	0	3 (1.0)	3 (0.3)
Anti-BCMA CAR T-cell therapy	2 (0.7)	1 (0.3)	2 (0.7)	5 (0.6)
Belantamab mafodotin	1 (0.3)	2 (0.7)	2 (0.7)	5 (0.6)
Refractory status — no. (%)				
Proteasome inhibitor	132 (46.0)	121 (42.2)	118 (40.7)	371 (42.9)
Immunomodulatory drug	253 (88.2)	250 (87.1)	250 (86.2)	753 (87.2)
Lenalidomide	244 (85.0)	248 (86.4)	243 (83.8)	735 (85.1)
Most recent therapy	267 (93.0)	269 (93.7)	271 (93.4)	807 (93.4)

The three groups: 2 Tal groups and 1 Dex group



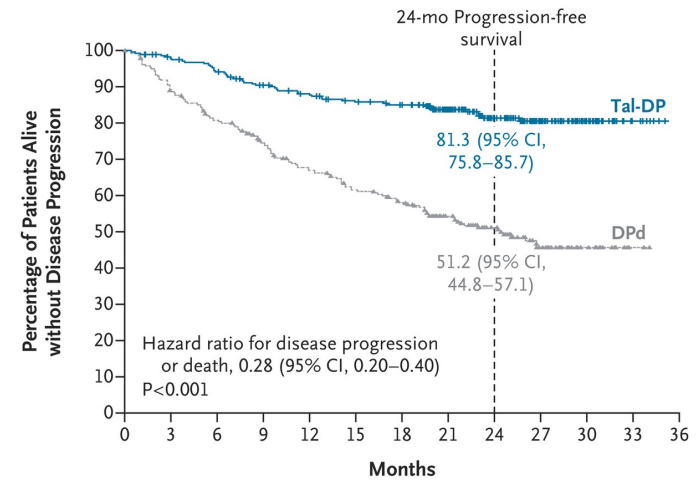
Treatment Response

Variable	Tal-DP (N = 287)	Tal-D (N = 287)	DPd (N = 290)	Risk Ratio (95% CI)†	
				Tal-DP vs. DPd	Tal-D vs. DPd
Overall response: partial response or better — no. (%)	253 (88.2)	254 (88.5)	225 (77.6)	1.14 (1.06–1.23)	1.14 (1.06–1.23)
Response or disease progression — no. (%)§					
Stringent complete response	154 (53.7)	131 (45.6)	72 (24.8)	—	—
Complete response	50 (17.4)	67 (23.3)	28 (9.7)	—	—
Very good partial response	40 (13.9)	40 (13.9)	67 (23.1)	—	—
Partial response	9 (3.1)	16 (5.6)	58 (20.0)	—	—
Minimal response	1 (0.3)	1 (0.3)	11 (3.8)	—	—
Stable disease	18 (6.3)	13 (4.5)	36 (12.4)	—	—
Progressive disease	1 (0.3)	2 (0.7)	6 (2.1)	—	—
Not evaluable	14 (4.9)	17 (5.9)	12 (4.1)	—	—
Complete response or better — no. (%)	204 (71.1)	198 (69.0)	100 (34.5)	2.07 (1.74–2.46)	2.01 (1.68–2.39)
Very good partial response or better — no. (%)	244 (85.0)	238 (82.9)	167 (57.6)	1.48 (1.33–1.65)	1.44 (1.29–1.61)
Response measures					
Median duration of response (95% CI) — mo	NE (NE–NE)	NE (NE–NE)	NE (24.8–NE)	—	—
Median time to first response (range) — mo	1.2 (0.5–11.0)	1.2 (0.7–17.1)	1.2 (0.9–15.3)	—	—
Median time to complete response or better (range) — mo	7.0 (1.1–18.6)	7.7 (1.1–25.1)	6.6 (1.1–20.5)	—	—
Measurable residual disease–negative complete response, assessed at a 10 ⁻⁵ threshold — no. (%)‡	150 (52.3)	133 (46.3)	46 (15.9)	3.31 (2.48–4.40)	2.92 (2.19–3.91)

Adversity

Event	Tal-DP (N=276)		Tal-D (N=274)		DPd (N=283)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	<i>number of patients (percent)</i>					
Any adverse event	276 (100.0)	267 (96.7)	274 (100.0)	216 (78.8)	283 (100.0)	271 (95.8)
Hematologic						
Neutropenia	232 (84.1)	211 (76.4)	112 (40.9)	80 (29.2)	255 (90.1)	244 (86.2)
Anemia	136 (49.3)	66 (23.9)	107 (39.1)	41 (15.0)	117 (41.3)	45 (15.9)
Thrombocytopenia	136 (49.3)	66 (23.9)	93 (33.9)	36 (13.1)	108 (38.2)	39 (13.8)
Lymphopenia	99 (35.9)	86 (31.2)	82 (29.9)	68 (24.8)	72 (25.4)	50 (17.7)
Leukopenia	94 (34.1)	63 (22.8)	53 (19.3)	26 (9.5)	79 (27.9)	60 (21.2)
Nonhematologic						
Infection	241 (87.3)	104 (37.7)	231 (84.3)	80 (29.2)	235 (83.0)	120 (42.4)
Taste change†	201 (72.8)	—	205 (74.8)	—	11 (3.9)	—
Nonrash skin adverse event‡	191 (69.2)	6 (2.2)	177 (64.6)	7 (2.6)	24 (8.5)	0
Cytokine release syndrome	187 (67.8)	2 (0.7)	160 (58.4)	2 (0.7)	—	—
Nail-related adverse event§	155 (56.2)	1 (0.4)	157 (57.3)	1 (0.4)	1 (0.4)	0
Pyrexia	127 (46.0)	8 (2.9)	112 (40.9)	3 (1.1)	35 (12.4)	2 (0.7)
Decreased weight	126 (45.7)	21 (7.6)	105 (38.3)	13 (4.7)	21 (7.4)	1 (0.4)
Rash-related adverse event¶	105 (38.0)	5 (1.8)	107 (39.1)	7 (2.6)	43 (15.2)	1 (0.4)
Diarrhea	104 (37.7)	7 (2.5)	81 (29.6)	2 (0.7)	79 (27.9)	13 (4.6)
Fatigue	83 (30.1)	14 (5.1)	60 (21.9)	8 (2.9)	69 (24.4)	9 (3.2)
Nausea	79 (28.6)	1 (0.4)	50 (18.2)	1 (0.4)	34 (12.0)	1 (0.4)
Dry mouth	77 (27.9)	1 (0.4)	73 (26.6)	0	3 (1.1)	0
Cough	74 (26.8)	2 (0.7)	70 (25.5)	0	50 (17.7)	1 (0.4)
Hypokalemia	68 (24.6)	17 (6.2)	55 (20.1)	10 (3.6)	45 (15.9)	9 (3.2)

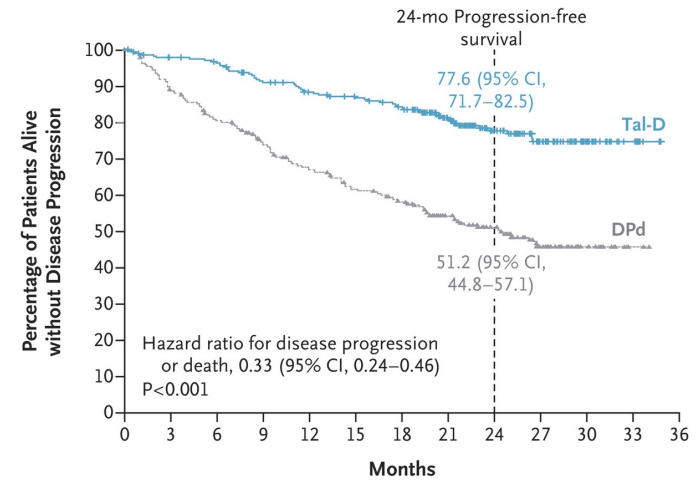
A Progression-free Survival, Tal-DP vs. DPd



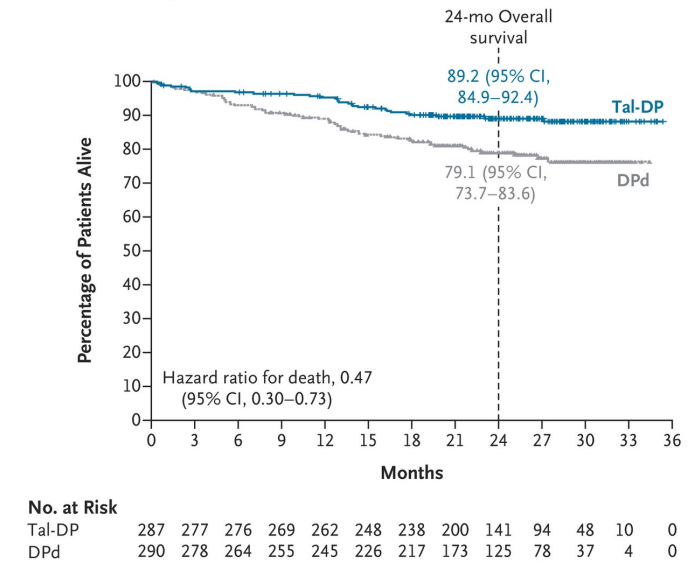
No. at Risk

Tal-DP	287	266	255	240	229	218	212	169	116	74	32	8	0
DPd	290	249	223	198	175	158	146	113	81	44	22	2	0

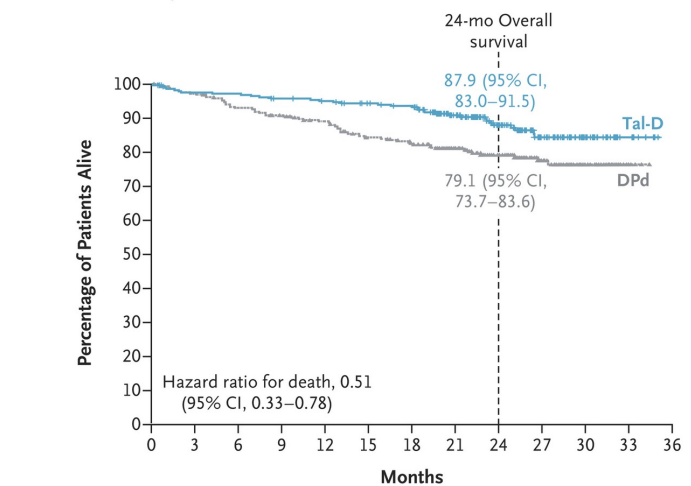
B Progression-free Survival, Tal-D vs. DPd



A Overall Survival, Tal-DP vs. DPd



B Overall Survival, Tal-D vs. DPd



Overall Survival (Intention-to-Treat Population).

Shown are Kaplan–Meier estimates of overall survival in the Tal-DP group as compared with the DPd group (Panel A) and in the Tal-D group as compared with the DPd group (Panel B). Tick marks indicate censored data. At a median follow-up of 24.6 months, the P values ($P=0.0006$ for Tal-DP; $P=0.0015$ for Tal-D) did not cross the prespecified stopping boundaries for superiority, given the nominal alpha level allocated for each comparison at the interim analysis (0.0001). At the clinical cutoff, death had occurred in 123 of 864 patients: 30 in the Tal-DP group, 34 in the Tal-D group, and 59 in the DPd group. The intention-to-treat population included all the patients who had undergone randomization.

Relapsed or Refractory Multiple Myeloma

Have a relapse or disease that is refractory to one or more agents

Talquetamab + Daratumumab + Pomalidomide (Tal-DP)

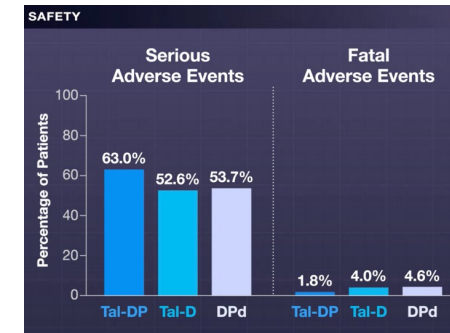
(N=287)

Talquetamab + Daratumumab (Tal-D)

(N=287)

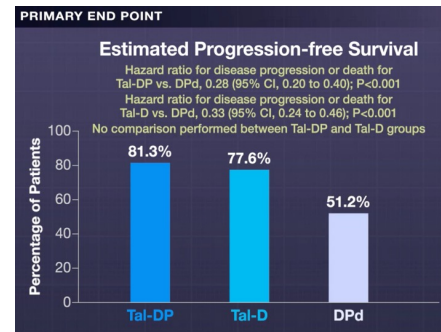
Daratumumab + Pomalidomide + Dexamethasone (DPd)

(N=290)



Talquetamab

- Bispecific antibody



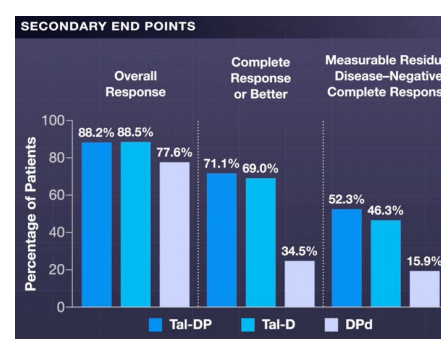
Led to significantly longer progression-free survival

864 Patients

MonumentAL-3 Trial

- Phase 3
- Open-label
- Randomized

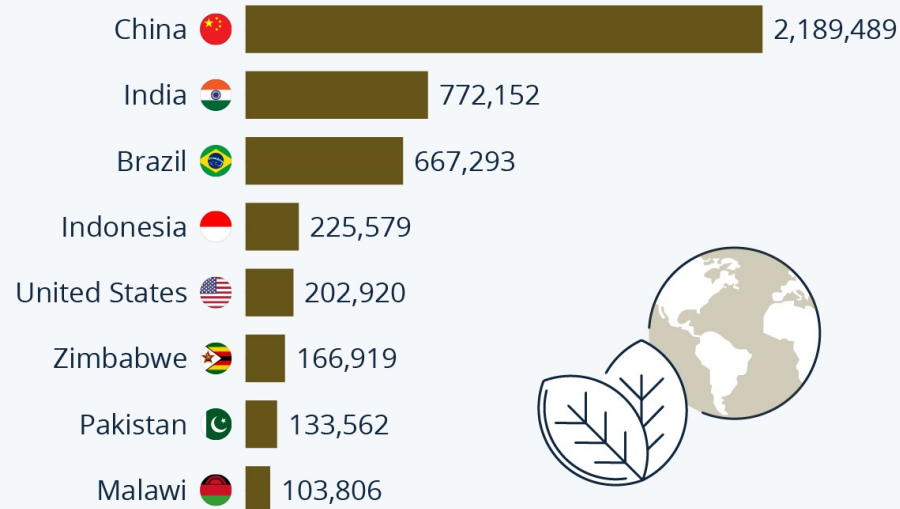
Had received at least one previous line of therapy



Do we really believe these people will cooperate to destroy their business?

The World's Largest Tobacco Producers

Unmanufactured tobacco production in 2022 (in metric tons)



Source: FAO



statista



Source: Companies Market Cap

(As of Market Cap)

Vorwürfe des Drogenbeauftragten Hendrik Streeck erklärte im Juli 2026, dass Vertreter der Tabakwirtschaft versuchen, ihn zu zermürben und zu diskreditieren. Als Auslöser gelten seine gesundheitspolitischen Vorstöße, darunter Forderungen nach höheren Tabaksteuern und strengeren Regeln zum Schutz vor Nikotinprodukten.

Genannte Methoden der Einflussnahme

- **Beobachtung und Ansprache:** Streeck schilderte, dass Lobbyisten ihn auf Veranstaltungen (wie Berliner Sommerfesten) gezielt beobachten, um im direkten Umfeld Gesprächspartner vorzuwarnen und seine Argumente als unsachlich darzustellen.
- **Öffentliche Diskreditierung:** In Online-Foren und im Netz werde versucht, ihn als wissenschaftlich unseriös darzustellen oder den Eindruck zu erwecken, er ignoriere andere Drogenprobleme zugunsten eines Angriffs auf die Wirtschaft.
- **Politischer Druck:** Kritisiert wurde von ihm zudem, dass über Lobbystrukturen und flankierende Verbände massiv Stimmung gegen Steuererhöhungen gemacht und politischer Druck auf Abgeordnete ausgeübt werde.



National German Drug-(abuse)
officer, Dr. med. Hendrik Streeck

He says he is mobbed and
stalked by the Tobacco crowd.

Evidence-Based Tobacco-Cessation Strategies for Low- and Middle-Income Countries

Summary

Tobacco use is the leading cause of preventable death globally, claiming more than 7 million lives each year. The burden of disease is highest in low- and middle-income countries, where more than 80% of the world's 1.3 billion tobacco users reside. The World Health Organization (WHO) defines six proven strategies to reduce tobacco use, referred to by the acronym MPOWER, with one of the strategies being to offer tobacco users help with quitting. Many low- and middle-income countries provide tobacco-cessation services; however, only 31 meet the WHO best practice, defined as providing both cost-covered behavioral interventions and pharmacotherapy. In this article, case studies from India and Vietnam illustrate how cross-country differences in tobacco-related sociocultural norms, tobacco-use patterns (e.g., smokeless tobacco or water pipes), the tobacco-control regulatory environment, industry influence, and health care system financing shape treatment access and uptake. These cases further show that cost-effective population-level strategies, including quitlines, digital interventions, and systemwide screening for tobacco use paired with clinician advice to quit, are essential for expanding treatment reach. Combining these interventions with pharmacotherapy products that are included on the WHO Model List of Essential Medicines (e.g., varenicline and nicotine-replacement therapy) further improves cessation outcomes. System-level models, such as the Ask–Advise–Connect model (ask about tobacco use, advise to quit, connect to cessation help), offer a feasible, low-burden pathway for integrating cessation care into routine practice. Ultimately, curbing the rising global burden of tobacco-related disease requires establishing comprehensive cessation support as a universal standard of care, which would ensure equitable access for those most affected.

80% of
smokers in
LMCs

Evidence-Based Tobacco-Cessation Strategies for Low- and Middle-Income Countries

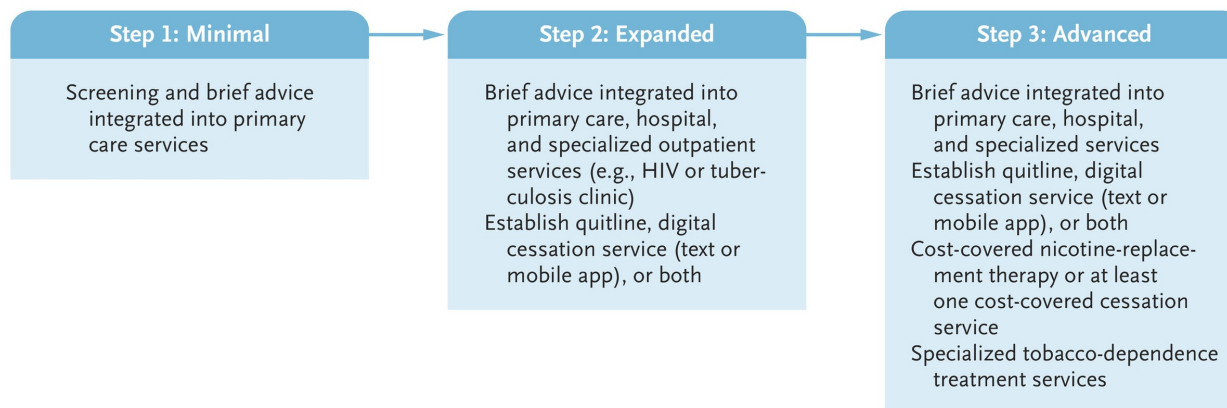
- More than 80% of the world's 1.3 billion tobacco users reside in low- and middle-income countries, yet only 31 of those countries meet the WHO best practice, defined as providing cost-covered behavioral interventions and pharmacotherapy.
- Population-level strategies, such as quitlines, digital cessation interventions, and systemwide routine screening for tobacco use paired with clinician advice to quit, are cost-effective and essential for expanding treatment reach.
- Prioritizing subsidized access to pharmacotherapies that are listed on the WHO Model List of Essential Medicines is vital for improving treatment access and clinical outcomes.
- System-level models, such as the Ask–Advise–Connect model (ask about tobacco use, advise to quit, and connect to cessation programs), offer a feasible approach for integrating cessation care across diverse clinical settings.
- Case studies from India and Vietnam show how contextual differences in tobacco-use patterns, sociocultural norms, tobacco regulation, and health care system financing facilitate or impede access to recommended treatment.
- Curbing the tobacco-related disease burden requires establishing equitable access to comprehensive cessation support as a universal standard of care.

Behavioral, Pharmacotherapeutic, Systemic, and Policy Interventions for Tobacco Cessation.

Intervention	Description
Behavioral interventions	
Population level	Brief advice: 30 seconds to 3 minutes, delivered by health care provider during routine visits
	Quitlines: national toll-free telephone counseling services
	mCessation: text-message interventions, mobile applications
Individual patient level	Counseling with a specialist: multiple sessions of individual or group counseling provide support and resources to develop skills and strategies for changing behavior
	Cessation clinic: available in some countries for intensive behavioral support
Pharmacotherapy	
Nicotine-replacement therapy†	Long-acting nicotine patch Short-acting nicotine gum, lozenge, inhaler, or spray
Non-nicotine pharmacotherapy‡	Varenicline, bupropion, and cytisine
System-level intervention and policy change	
Train all health care workers	Train health care workers (doctors, nurses, and community health workers) to provide brief advice, behavioral support, and medications Define roles and responsibilities
Implement screening and documentation system	Include tobacco-use status in medical records
Implement quitline referral system	Integrate proactive referral systems to link patients to quitline or other behavioral interventions
Monitor performance	Track adherence to treatment policy
Reduce or eliminate costs	Provide cost coverage Offer financial incentives, such as cash payments or vouchers

Ask–Advise–Connect Model.

Step	Approach	Suggested Talking Points
Ask	Ask every patient about tobacco use during clinic visits.	“Do you currently use any tobacco products, such as cigarettes, water pipe, hookah, or bidi cigarettes or smokeless forms such as chewing tobacco, snuff, snus, dip, or betel quid with tobacco?” “Do you use electronic cigarettes or a heated tobacco product?”
Advise	Deliver clear advice to stop using tobacco. Focus on the benefits of quitting and the support available. Personalize advice and tailor it to the patient's risk factors and patterns of tobacco use.	“Quitting is challenging, but it is the most important thing you can do to protect your health and live longer. Quitting will also protect the people around you from the dangers of secondhand smoke and will save you money. There are medications and programs that can help.” “Would you like to hear about treatment options to help you quit or make a plan to cut down on your tobacco use?”
Connect	For patients who are not ready to quit, offer reassurance that support is available should they reconsider. If a patient is ready to quit, provide information about pharmacotherapy and behavioral programs. Prescribe medication and connect the patient directly to behavioral therapy (e.g., with patient consent, connect them to the quitline during the visit).	If the patient is not ready to quit: “I understand that quitting can be hard, but I am here to support you. I will ask you about it again the next time I see you.” If the patient is ready to quit: “There are several medications that can help you quit by reducing cravings and withdrawal symptoms. Counseling can also help you create a plan.” Depending on available resources, prescribe or recommend over-the-counter medication, provide instructions on how to use the medication, and proactively refer the patient to national or local behavioral programs.



Minimal, Expanded, and Advanced Cessation Interventions.

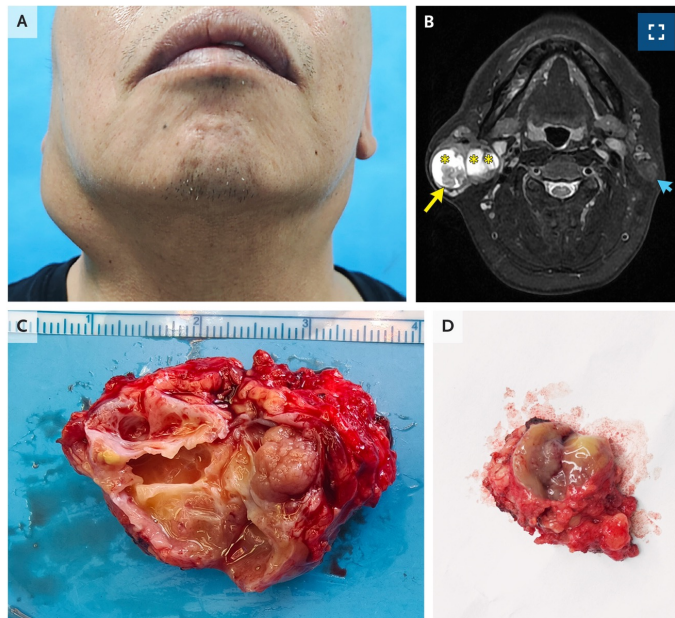
Adapted from the World Health Organization (WHO) Report on the Global Tobacco Epidemic 2019.⁹ HIV denotes human immunodeficiency virus.

Conclusion

Low- and middle-income countries are making meaningful progress in implementing population- and system-level cessation strategies that promote treatment engagement. However, regional disparities in tobacco-related outcomes persist. Curbing the growing tobacco-related disease burden requires establishing equitable access to comprehensive cessation support as a universal standard of care.

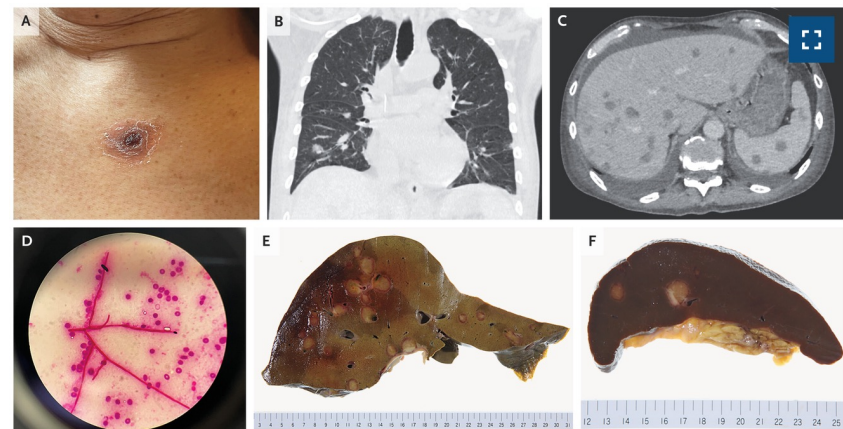
(Might have focused on the role of, and responsibility of, the tobacco industry)

Warthin Tumors



A 55-year-old man with a smoking history of 10 pack-years presented to the surgery clinic with a 2-year history of an enlarging, painless lump below his right ear. Physical examination showed a well-circumscribed, nontender mass below the right ear, as well as a smaller mass at the inferior pole of the left parotid gland, which the patient had not noticed (Panel A). No cervical lymphadenopathy or cranial nerve VII deficit was seen. Axial T2-weighted, fat-suppressed magnetic resonance imaging of the neck showed a lesion in the right parotid gland, with hyperintense areas representing cystic contents (Panel B, asterisks) and mural nodules in the outermost cyst (arrow), as well as a solid nodule in the left parotid gland (arrowhead). Biopsies, which are typically performed to evaluate salivary-gland masses, were not performed in this case. The masses were resected. When sectioned longitudinally, the mass from the right side (4.0 cm in the greatest dimension) had a multicystic architecture (Panel C), and the mass from the left side had solid morphologic features with focal microcysts (Panel D). Histopathological analysis of both tumors showed bilayered oncocytic epithelium with lymphoid stroma. A diagnosis of Warthin tumors — benign, slow-growing salivary-gland tumors that are strongly associated with smoking and that often occur on both sides — was made. The patient did well postoperatively. Smoking cessation was advised.

Disseminated Fusariosis



A 61-year-old man with prolonged neutropenia as a result of salvage chemotherapy for acute myeloid leukemia was evaluated on hospital day 37 for persistent fever despite treatment with broad-spectrum antimicrobial agents. Physical examination was notable for a macule with central necrosis on the chest (Panel A), as well as a nodule on the left palm. A serum 1,3- β -D-glucan level was elevated, and a test for galactomannan was negative. Computed tomography of the chest, abdomen, and pelvis that was performed after the administration of contrast material showed multiple pulmonary nodules (Panel B, coronal view) and hypoattenuating lesions in the liver, spleen (Panel C, axial view), and kidneys. Gram's staining of a blood culture revealed septate, hyaline hyphae (Panel D), which were subsequently identified as *Fusarium keratoplasticum* with the use of molecular sequencing. A diagnosis of disseminated fusariosis was made. In contrast to other invasive mold infections, fusarium species frequently cause fungemia in immunocompromised hosts. Treatment with voriconazole and liposomal amphotericin B was initiated, but the patient died of respiratory failure on hospital day 67. At autopsy, the leukemia was found to have been in morphologic remission. Gross examination of the liver (Panel E) and spleen (Panel F) showed multiple well-circumscribed yellow foci that were confirmed on histopathological analysis to be abscesses from disseminated fusariosis.



Case 23-2026: A 28-Year-Old Woman with Nausea, Dizziness, and Metabolic Acidosis

The patient had been in her usual state of generally good health until the night before this presentation, when epigastric pain and vomiting developed abruptly after the consumption of spicy food. Her partner had consumed the same food but did not have similar symptoms. The patient had persistent vomiting and lightheadedness and was unable to maintain adequate hydration; subsequently, she presented to the emergency department of this hospital, accompanied by her partner.

On presentation to the emergency department, the oral temperature was 36.0°C, the blood pressure 122/88 mm Hg, the respiratory rate 20 breaths per minute, the heart rate 88 beats per minute, and the oxygen saturation 100% while the patient was breathing ambient air. She reported ongoing epigastric pain and nausea, and several witnessed episodes of emesis occurred after her arrival at the emergency department, with vomitus that was nonbloody and nonbilious. The patient also reported ongoing dizziness, lightheadedness, and vertigo. A review of systems was negative for fever, chest pain, diarrhea, hematochezia, melena, anorexia, cough, dyspnea, headache, paresthesia, vision symptoms, and motor weakness. Her partner reported that the patient had presented to the emergency department with similar symptoms 2 months earlier; the symptoms had been self-limited and had been treated with antiemetic agents and antacids. The partner described the patient as having a “sensitive stomach” and noted that she often had similar symptoms after eating spicy foods.

Four hours after presentation to the emergency department, the oral temperature was 35.8°C, the blood pressure 139/93 mm Hg, the **heart rate 130 beats per minute**, the **respiratory rate 25 breaths per minute**, and the oxygen saturation 99% while the patient was breathing ambient air. The weight was 50 kg, and the body-mass index (the weight in kilograms divided by the square of the height in meters) was 18. The patient was upset and agitated. Tachycardia was present without murmur, and the lungs were clear on auscultation. The abdomen was mildly tender on deep palpation of the epigastrium; no masses or hepatosplenomegaly were noted. The neurologic examination showed end-gaze nystagmus on lateral gaze that resolved spontaneously; no other abnormalities were observed on pupillary or extraocular muscle testing. The gait was normal, and the patient had no motor or sensory deficits. Treatment with intravenous **lactated Ringer's solution, ondansetron, and famotidine was initiated**.

Laboratory test results were notable for a **blood bicarbonate level of 10 mmol per liter** (reference range, 23 to 32), with normal blood levels of sodium, chloride, and glucose. **The anion gap was 21 mmol per liter** (reference range, 3 to 17). **A venous blood gas analysis was notable for a pH of 7.23** (reference range, 7.30 to 7.40) and a **partial pressure of carbon dioxide of 26 mm Hg** (reference range, 30 to 50).

AG increased 9 mmol/L
HCO₃ decreased 14 mmol/L

Six hours after presentation to the emergency department, the patient reported increasing dizziness. She appeared to be more anxious and less engaged than she had appeared during the previous interview. Her partner, who was still present, was asked to leave the examination room in order to allow for assessment of the possibility of intimate partner violence contributing to the presentation. After the patient's partner left the room, the patient gradually became more activated and anxious, pacing the room and becoming distraught and tearful, and requested to leave the hospital. She reported no abuse by her partner and that she felt safe and would feel better if he accompanied her while she was in the hospital. The patient was intent on pursuing a self-directed discharge. However, in the context of emotional dysregulation, she did not show sufficient capacity to decide to leave the hospital and was placed under a psychiatric hold and clinical monitoring owing to concern about severe metabolic acidosis. A decision was made to admit the patient to the hospital.

Labs

Variable	Reference Range, Adults†	On Presentation, Emergency Department	6 Hr after Presentation, Emergency Department
Hemoglobin (g/dl)	12.0–16.0	14.9	—
Hematocrit (%)	41.0–53.0	45.2	—
White-cell count (per μ l)	4500–11,000	7400	—
Platelet count (per μ l)	150,000–400,000	206,000	—
Sodium (mmol/liter)	135–145	138	138
Potassium (mmol/liter)	3.4–5.0	4.4	4.5
Chloride (mmol/liter)	98–108	107	108
Carbon dioxide (mmol/liter)	23–32	10	9
Anion gap (mmol/liter)	3–17	21	—
Urea nitrogen (mg/dl)	8–25	8	5
Creatinine (mg/dl)	0.60–1.50	0.51	0.40
Calcium (mg/dl)	8.5–10.5	8.5	9.0
Glucose (mg/dl)	70–110	111	103
Aspartate aminotransferase (U/liter)	10–40	27	—
Alanine aminotransferase (U/liter)	10–55	28	—
Alkaline phosphatase (U/liter)	30–100	70	—
Total bilirubin (mg/dl)	0.0–1.2	0.9	—
Direct bilirubin (mg/dl)	0.0–0.3	0.3	—
Albumin (g/dl)	3.3–5.0	5.1	—
Globulin (g/dl)	1.9–4.1	3.2	—
Serum osmolality (mOsm/kg of water)	280–296	—	363
Lactic acid (mmol/liter)	0.5–2.0	—	0.9
β -Hydroxybutyric acid (mmol/liter)	<0.4	—	0.1
Prothrombin time (sec)	10.0–13.0	10.9	—
International normalized ratio	0.9–1.1	1.0	—
Venous blood gases			
pH	7.30–7.40	7.23	7.18
Partial pressure of carbon dioxide (mm Hg)	30–50	26	23
Partial pressure of oxygen (mm Hg)	35–50	77	60

Bicarbonate dropped by 14 and AG increased by 9 mmol/L.
When this was measured, her methanol concentration was 78 mmol/L

Regular laboratory testing performed 6 hours after presentation to the emergency department was notable for a blood bicarbonate level of 9 mmol per liter and a blood urea nitrogen level of 5 mg per deciliter (2 mmol per liter; reference range, 8 to 25 mg per deciliter [3 to 9 mmol per liter]). Blood levels of lactic acid and β -hydroxybutyric acid were within normal limits, and urinalysis results were unremarkable. Blood toxicology studies were negative for ethanol, salicylates, acetaminophen, and tricyclic antidepressant medications, and urine toxicology testing was negative for opioids, amphetamines, cocaine metabolites, and benzodiazepines. The serum osmolality was elevated, at 363 mOsm per kilogram of water (reference range, 280 to 296).

Psychiatric Considerations for Identifying the Cause of Toxic Substance Intoxication.

Intentional ingestion by the patient: think about the “why”

- Suicide attempt
- Nonsuicidal self-injury
- Intoxication

Intentional administration by a third party: think about the “why”

- Homicide
- Induction of illness
- Prank

Accidental ingestion: think about the “how”

- Contamination (e.g., poison accidentally mixed with food or drink)
- Substitution (e.g., drinking from the wrong container)
- Improper preparation (e.g., fermentation leading to an unanticipated by-product)

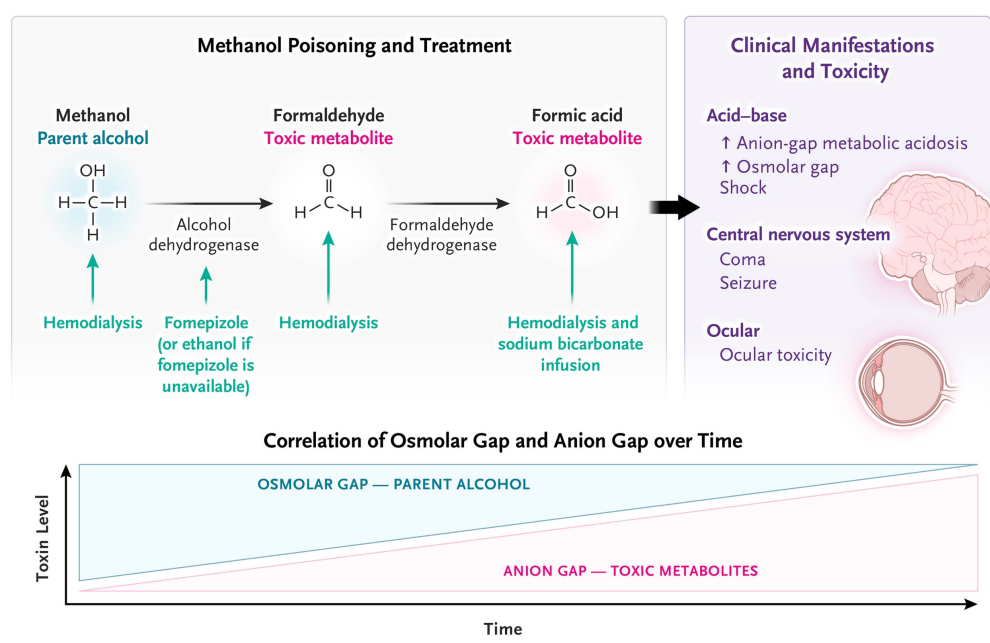
How about: „Think about the AG“?

Why did it take 6 h for anyone to act?

Fomepizole or ETOH?

Toxic Alcohol Ingestion

In the context of unexplained anion-gap acidosis, measurement of serum osmolality can provide important information by allowing for calculation of an osmolar gap, which may indicate whether unmeasured osmoles, such as toxic alcohols, are present in the blood. The patient's **calculated serum osmolality**, based on laboratory values obtained on presentation, **was 285 mOsm per kilogram of water** (on the basis of the formula of $[2 \times \text{sodium level}] + [\text{glucose level}/18] + [\text{urea nitrogen level}/2.8]$), and the **measured serum osmolality was 363 mOsm** per kilogram of water, which resulted in an osmolar gap of 78 mOsm per kilogram of water (reference value, <10). A high osmolar gap in the context of high anion-gap metabolic acidosis is highly suggestive of an unmeasured osmotically active substance and, in the context of this patient's clinical presentation, prompted immediate consideration of toxic alcohol ingestion. **It is important to note that the osmolar gap tends to be highest early after ingestion and can normalize as the parent compound is metabolized to its toxic organic acid metabolites, which subsequently expands the anion gap — meaning that a normal osmolar gap does not rule out toxicity and that timing of the assessment should be considered.**



Methanol Poisoning and Treatment.

Shown are the clinical manifestations and laboratory findings typically associated with methanol poisoning, along with the mechanisms of action of the various pharmacologic agents used in the treatment of methanol poisoning, denoted in green.

Treatment amid Uncertainty

Treatment for ingestion of toxic alcohols should not be delayed until a definitive diagnosis is confirmed. Fomepizole, an inhibitor of ADH, should be administered to block the conversion of methanol or ethylene glycol to their toxic metabolites. Because folate is required for the elimination of formic acid in persons with methanol toxicity, and because thiamine and pyridoxine support alternative metabolic pathways in persons with ethylene glycol toxicity, coadministration of B vitamins, including thiamine and leucovorin (also known as folinic acid), is a low-risk intervention. For this patient, the nephrology service was also consulted for consideration of hemodialysis.

Hospital Course

Once the methanol level was found to be markedly elevated, the decision was made to initiate emergency hemodialysis. Given the patient's ongoing anxiety and agitation, she was transferred to the medical intensive care unit, where a continuous infusion of dexmedetomidine (clonidine-like) was initiated for placement of a temporary hemodialysis catheter. On the basis of the patient's initial methanol level and her weight, we estimated that 6 hours of hemodialysis would be sufficient to clear methanol and its toxic metabolites. Because methanol levels can take hours to obtain, we used surrogate markers of methanol to approximate when it had been fully cleared from the patient's circulation. We stopped hemodialysis once the blood pH and blood bicarbonate level had normalized and once the osmolar gap fell below 10. When the serial methanol levels eventually became available, they confirmed a rapid decline, from 190 mg per deciliter to below the limit of detection within approximately 5 hours after initiation of hemodialysis.

The source of the methanol in this case was never definitively established. The patient consistently reported no ingestion of any specific substance and expressed that she did not have concern about any risk of harm from others. The psychiatric hold, which had been in place since her presentation given the inability to rule out intentional ingestion, was lifted on hospital day 3, and the patient pursued a self-directed discharge shortly thereafter.

The estimated methanol concentration is **78 mmol/L** or **249.6 mg/dL** in this patient.

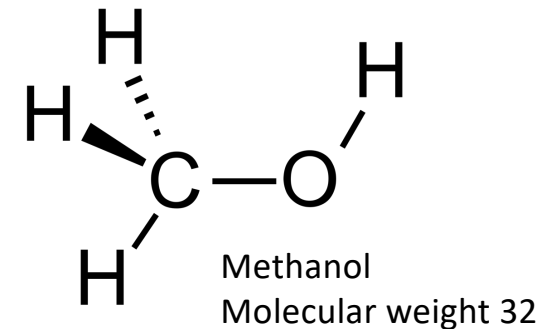
1. Calculate the osmolal gap

The osmolal gap represents the difference between the measured serum osmolality and the calculated baseline serum osmolality. To determine the change caused by the unmeasured solute (methanol), subtract the initial osmolality from the elevated osmolality:

2. Convert to millimoles per liter

Because methanol is a small, uncharged molecule that does not dissociate in solution, each millimole of methanol per liter of water contributes approximately 1 mOsm/kg to the serum osmolality. Therefore, the osmolal gap translates directly to the molar concentration of the substance:

Methanol Concentration = 78×3.2 or 249.6 mg/dL



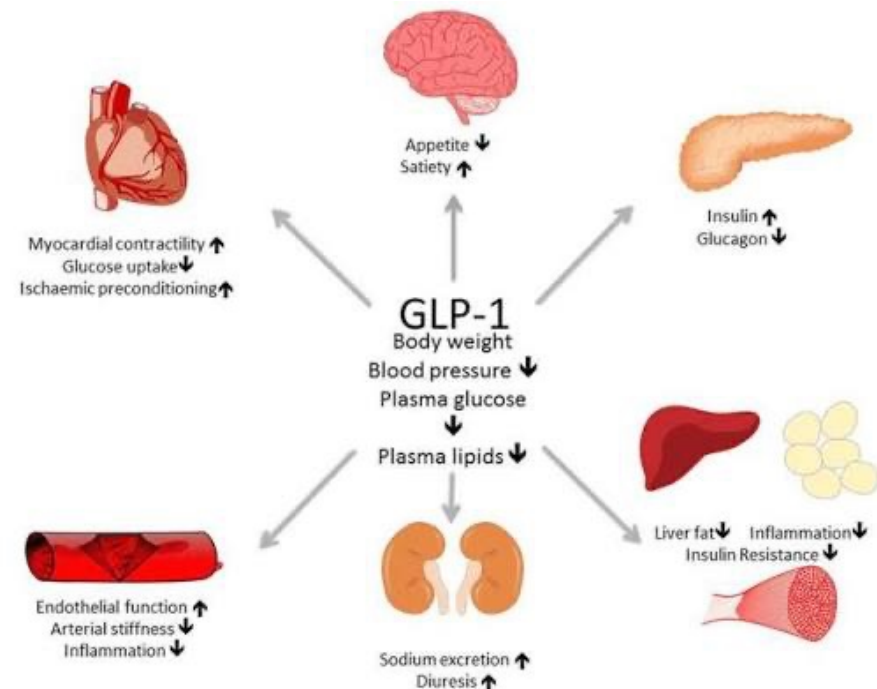
Häufige Methanol-Quellen

- **Gepanschter oder schwarz gebrannter Alkohol:** Illegale Spirituosen oder fehlerhafter Selbstgebrannter, bei dem der Vorlauf nicht richtig abgetrennt wurde.
- **KFZ- und Haushaltsprodukte:** Frostschutzmittel für Scheibenwaschanlagen, Spiritus-Ersatz oder Spezialreiniger.
- **Hobby und Handwerk:** Brennstoffe für Modellmotoren (Modellbau) oder technischer Alkohol aus dem Labor- und Industriebereich.

GLP-1 steht für *Glucagon-like Peptide-1* und ist ein natürliches Darmhormon, das nach dem Essen freigesetzt wird. Es regt die Insulinausschüttung an, hemmt den Gegenspieler Glukagon, verlangsamt die Magenentleerung und sorgt im Gehirn für ein frühes Sättigungsgefühl. Künstliche Nachbauten (GLP-1-Rezeptoragonisten) werden als Medikamente eingesetzt.

Was GLP-1 bewirkt

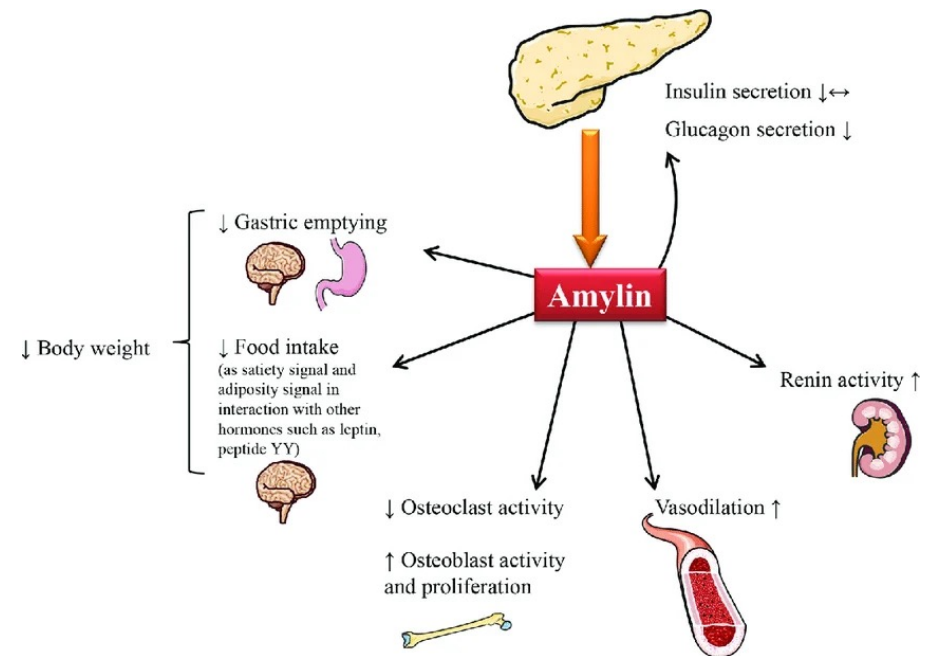
- **Blutzuckersenkung:** Hilft bei Typ-2-Diabetes, da es die Insulinproduktion anregt.
- **Gewichtsverlust:** Dämpft den Hunger und führt zu einer starken Sättigung.
- **Verzögerte Verdauung:** Lässt den Magen den Nahrungsbrei langsamer abtransportieren.



Amylin (auch Insel-Amyloid-Polypeptid oder IAPP) ist ein Peptidhormon, das von den Beta-Zellen der Bauchspeicheldrüse gemeinsam mit Insulin nach der Nahrungsaufnahme ausgeschüttet wird. Es reguliert den Blutzucker, indem es die Glukosefreisetzung hemmt, und dämpft den Appetit durch ein verstärktes Sättigungsgefühl sowie eine verlangsamte Magenentleerung.

Biologische Funktion

- **Blutzuckerkontrolle:** Unterdrückt die Ausschüttung von Glukagon und verhindert so zu hohe Blutzuckerspitzen nach dem Essen.
- **Sättigungsgefühl:** Signalisiert dem Gehirn (im Bereich des Hypothalamus und Hirnstamms), dass der Magen voll ist, und verlangsamt die Magenpassage der Nahrung.
- **Gemeinsame Ausschüttung:** Wird im gesunden Körper im konstanten Verhältnis zu Insulin freigesetzt (allerdings in deutlich geringerer Menge)



Weder GLP-1 noch Amylin ist pauschal „wichtiger“, da beide Hormone im menschlichen Stoffwechsel unterschiedliche, aber sich ergänzende Aufgaben erfüllen. **GLP-1 (Glucagon-like Peptide-1)** ist primär der Leitspieler für die Blutzuckerregulation und Insulinausschüttung, während **Amylin** gemeinsam mit Insulin den Blutzucker nach Mahlzeiten dämpft und das Sättigungsgefühl verstärkt.

Efficacy and safety of once-daily oral zenagamtide, a novel unimolecular GLP-1 and amylin receptor agonist, in adults with type 2 diabetes: a multicentre, randomised, parallel, double-blind, placebo-controlled, dose-finding, phase 2 trial

Summary

Background Zenagamtide (formerly amycletin) is a unimolecular peptide agonist of GLP-1, amylin, and calcitonin receptors. We aimed to investigate the dose–response relationship with respect to the efficacy and safety of once-daily oral zenagamtide compared with placebo in adults with type 2 diabetes.

Methods This 36-week, randomised, parallel, double-blind, placebo-controlled, dose-finding, phase 2 trial was conducted at 83 hospital and clinic sites across 11 countries. The trial consisted of a 3-week screening period, a 36-week intervention period, and a 4-week follow-up period. Adults (aged 18–75 years) with type 2 diabetes (glycated haemoglobin [HbA_{1c}] 7·0–10·0% [53–86 mmol/mol]), treated with stable doses of metformin with or without a SGLT2 inhibitor, and with a BMI of 23·0 to <50·0 kg/m² were randomly assigned (5:1) to oral zenagamtide or placebo using a randomisation and trial supplies management system, then further randomly assigned (1:1:1) to one of three dose groups (6, 25, or 50 mg). Participants assigned to placebo were similarly assigned to matched placebo regimens corresponding to each dosing schedule. Randomisation was stratified by HbA_{1c} (<8·5% or ≥8·5%) at screening and country of residence (Japan or other countries). The starting dose of oral zenagamtide was 1·5 mg, with dose escalations every 4 weeks until the maintenance dose was reached (6, 25, or 50 mg). Participants and staff were masked within each dose level to placebo or zenagamtide. The primary outcome was change in HbA_{1c} from baseline to week 36. The primary outcome was assessed in all randomly assigned participants using the efficacy estimand based on on-treatment data without rescue medication. Safety outcomes were assessed in all randomly assigned participants exposed to treatment. This trial is registered with ClinicalTrials.gov, NCT06542874, and is completed.

Findings Between Aug 7 and Dec 27, 2024, 186 (20%) of 915 screened participants were randomly assigned to oral zenagamtide (54 participants to 6 mg, 51 participants to 25 mg, and 51 participants to 50 mg) or placebo (30 participants) and were included in the full analysis set. At week 36, from baseline (mean range 7·9–8·1%), estimated mean change in HbA_{1c} was –0·9% with zenagamtide 6 mg (estimated treatment difference [ETD] *vs* placebo –0·5% [95% CI –1·04 to –0·04]; *p*=0·033), –1·3% with zenagamtide 25 mg (–0·99% [–1·49 to –0·49]; *p*=0·0001), and –1·4% with zenagamtide 50 mg (–1·09% [–1·59 to –0·59]; *p*<0·0001). The most common adverse events were gastrointestinal, occurring in 14 (26%) of 54 participants in the zenagamtide 6 mg group, 21 (41%) of 51 participants in the zenagamtide 25 mg group, 24 (47%) of 51 participants in the zenagamtide 50 mg group, and seven (23%) of 30 participants in the placebo group. Serious adverse events were reported in seven (4%) of 186 participants receiving zenagamtide: two in the 6 mg group, two in the 25 mg group, and three in 50 mg group. No serious adverse events were reported in the placebo group. No deaths occurred during the trial.

Interpretation In people with type 2 diabetes, once-daily oral zenagamtide showed clinically meaningful and significant improvements in HbA_{1c} from baseline to week 36 compared with placebo at all three dose levels (6, 25, and 50 mg). The safety and tolerability of oral zenagamtide was consistent with other GLP-1 and amylin receptor agonists.

Funding Novo Nordisk.

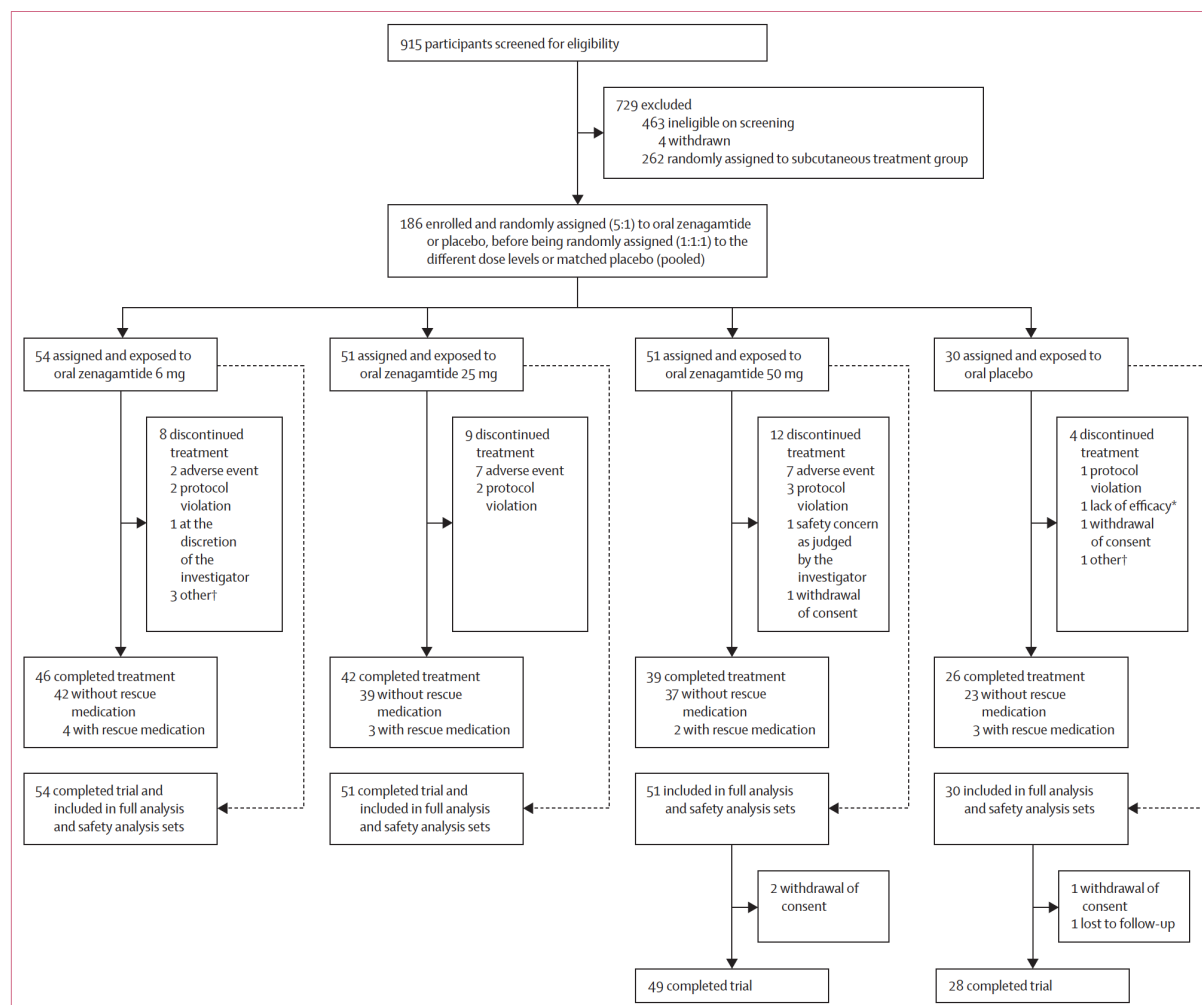


Figure 1: Trial profile

Details of screening failures are reported in the appendix (p 8). Treatment completers were defined as participants who completed treatment with the trial product according to the end-of-investigational medicinal product treatment form. *Lack of efficacy was an option that the investigator could choose in the electronic case report form; no additional details available. †As reported by the investigator, other reasons for discontinuation included missed doses as per protocol (one participant receiving 6 mg), participant's last dose was taken >9 days ago (one participant receiving 6 mg), participant decided to discontinue treatment following adverse events (one participant receiving 6 mg), and personal reasons (one participant receiving placebo).

	Zenagamtide 6 mg (n=54)	Zenagamtide 25 mg (n=51)	Zenagamtide 50 mg (n=51)	Pooled placebo (n=30)
Sex				
Male	33 (61%)	27 (53%)	32 (63%)	21 (70%)
Female	21 (39%)	24 (47%)	19 (37%)	9 (30%)
Age, years	54.9 (9.8)	58.0 (8.6)	54.4 (9.7)	55.1 (10.8)
HbA _{1c} , %	8.1 (0.9)	8.0 (0.9)	7.9 (0.7)	8.0 (0.8)
HbA _{1c} , mmol/mol	65.1 (9.5)	64.1 (9.6)	62.6 (8.0)	64.3 (8.3)
HbA _{1c} strata				
<8.5%	36 (67%)	36 (71%)	40 (78%)	22 (73%)
≥8.5%	18 (33%)	15 (29%)	11 (22%)	8 (27%)
FPG, mmol/L	9.5 (3.7)	8.8 (2.2)	8.9 (2.5)	8.7 (2.4)
FPG, mg/dL	171.2 (66.0)	157.9 (39.2)	160.7 (44.2)	156.1 (42.9)
Diabetes duration, years	7 (6)	7 (4)	8 (7)	10 (7)
Bodyweight, kg	100.7 (21.7)	99.5 (23.1)	104.1 (21.6)	99.7 (18.4)
BMI, kg/m ²	34.6 (6.1)	35.0 (6.5)	35.0 (6.4)	34.5 (6.1)
Waist circumference, cm	113.8 (16.1)	111.0 (15.6)	114.7 (14.9)	112.9 (13.4)
Systolic blood pressure, mm Hg	131.6 (13.0)	132.6 (14.2)	129.7 (12.2)	128.5 (11.2)
Diastolic blood pressure, mm Hg	81.4 (9.6)	81.3 (7.9)	80.5 (8.5)	79.7 (8.1)
eGFR, * mL/min per 1.73 m ²	97 (20)	97 (16)	98 (17)	101 (18)
SGLT2 inhibitor use at randomisation	16 (30%)	23 (45%)	21 (41%)	9 (30%)
Race				
White	42 (78%)	44 (86%)	42 (82%)	24 (80%)
Asian	10 (19%)	7 (14%)	8 (16%)	5 (17%)
Black or African American	1 (2%)	0	1 (2%)	1 (3%)
Native Hawaiian or other Pacific Islander	1 (2%)	0	0	0

Data are n (%) or mean (SD). The full analysis set included all randomly assigned participants. CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration. eGFR=estimated glomerular filtration rate. FPG=fasting plasma glucose. *eGFR calculated using the CKD-EPI (Creatinine-Cystatin C) equation (2021).⁷³

Table 1: Participant demographics and baseline characteristics (full analysis set)

	Zenagamtide 6 mg (n=54)	Zenagamtide 25 mg (n=51)	Zenagamtide 50 mg (n=51)	Pooled placebo (n=30)
HbA _{1c} , %				
Baseline	8.1 (0.9)	8.0 (0.9)	7.9 (0.7)	8.0 (0.8)
Change from baseline at week 36	-0.9	-1.3	-1.4	-0.4
ETD vs placebo (95% CI); p value	-0.54 (-1.04 to -0.04); 0.033	-0.99 (-1.49 to -0.49); 0.0001	-1.09 (-1.59 to -0.59); <0.0001	..
TIR 3.9-10.0 mmol/L (70-180 mg/dL), %				
Baseline	50.6 (31.2)	56.4 (28.3)	55.2 (28.1)	55.6 (22.5)
Change from baseline at week 20	22.8	28.0	32.9	1.5
ETD vs placebo (95% CI); p value	21.2 (10.22 to 32.25); 0.0002	26.5 (15.62 to 37.37); <0.0001	31.4 (20.62 to 42.13); <0.0001	..
Change from baseline at week 36	16.7	22.2	28.2	3.8
ETD vs placebo (95% CI); p value	12.9 (-3.61 to 29.39); 0.12	18.4 (2.68 to 34.12); 0.022	24.3 (8.70 to 39.94); 0.0026	..
FPG, mmol/L				
Baseline	9.5 (3.7)	8.8 (2.2)	8.9 (2.5)	8.7 (2.4)
Change from baseline at week 36	-1.3	-2.1	-2.3	-0.4
ETD vs placebo (95% CI); p value	-0.87 (-1.97 to 0.23); 0.12	-1.66 (-2.71 to -0.60); 0.0023	-1.93 (-2.99 to -0.87); 0.0005	..
FPG, mg/dL				
Baseline	171.2 (66.0)	157.9 (39.2)	160.7 (44.2)	156.1 (42.9)
Change from baseline at week 36	-23.3	-37.4	-42.3	-7.5
ETD vs placebo (95% CI); p value	-15.76 (-35.59 to 4.07); 0.12	-29.88 (-48.90 to -10.85); 0.0023	-34.77 (-53.94 to -15.60); 0.0005	..
Bodyweight change, %				
Baseline, kg	100.7 (21.7)	99.5 (23.1)	104.1 (21.6)	99.7 (18.4)
Change from baseline at week 36	-5.0	-10.3	-9.0	-3.0
ETD vs placebo (95% CI); p value	-1.91 (-5.01 to 1.20); 0.23	-7.29 (-10.44 to -4.15); <0.0001	-5.92 (-9.08 to -2.77); 0.0003	..
Bodyweight, kg				
Baseline	100.7 (21.7)	99.5 (23.1)	104.1 (21.6)	99.7 (18.4)
Change from baseline at week 36	-5.1	-10.1	-8.8	-3.3
ETD vs placebo (95% CI); p value	-1.77 (-4.88 to 1.33); 0.26	-6.82 (-9.97 to -3.66); <0.0001	-5.45 (-8.63 to -2.28); 0.0009	..
BMI, kg/m ²				
Baseline	34.6 (6.1)	35.0 (6.5)	35.0 (6.4)	34.5 (6.1)
Change from baseline at week 36	-1.8	-3.6	-3.0	-1.2
ETD vs placebo (95% CI); p value	-0.6 (-1.72 to 0.45); 0.25	-2.4 (-3.51 to -1.30); <0.0001	-1.8 (-2.95 to -0.73); 0.0013	..
Waist circumference, cm				
Baseline	113.8 (16.1)	111.0 (15.6)	114.7 (14.9)	112.9 (13.4)
Change from baseline at week 36	-3.5	-7.6	-5.9	-3.7
ETD vs placebo (95% CI); p value	0.25 (-3.00 to 3.51); 0.88	-3.84 (-7.22 to -0.46); 0.026	-2.18 (-5.47 to 1.11); 0.19	..
hsCRP, mg/L				
Baseline	5.1 (5.6)	7.1 (19.4)	5.4 (5.4)	4.4 (4.9)
Ratio to baseline at week 36	0.8	0.4	0.7	0.8
ETR vs placebo (95% CI); p value	1.00 (0.58 to 1.71); 0.99	0.55 (0.32 to 0.93); 0.027	0.85 (0.49 to 1.48); 0.57	..
HDL cholesterol, mmol/L				
Baseline	1.2 (0.2)	1.2 (0.2)	1.2 (0.3)	1.2 (0.3)
Ratio to baseline at week 36	1.0	1.1	1.0	1.1
ETR vs placebo (95% CI); p value	0.99 (0.91 to 1.07); 0.75	1.05 (0.97 to 1.14); 0.27	0.98 (0.91 to 1.06); 0.64	..

(Table 2 continues on next page)

	Zenagamtide 6 mg (n=54)	Zenagamtide 25 mg (n=51)	Zenagamtide 50 mg (n=51)	Pooled placebo (n=30)
HbA_{1c}, %				
Baseline	8.1 (0.9)	8.0 (0.9)	7.9 (0.7)	8.0 (0.8)
Change from baseline at week 36	−0.9	−1.3	−1.4	−0.4
ETD vs placebo (95% CI); p value	−0.54 (−1.04 to −0.04); 0.033	−0.99 (−1.49 to −0.49); 0.0001	−1.09 (−1.59 to −0.59); <0.0001	..
TIR 3.9–10.0 mmol/L (7.0–18.0 mg/dL), %				
Baseline	50.6 (31.2)	56.4 (28.3)	55.2 (28.1)	55.6 (22.5)
Change from baseline at week 20	22.8	28.0	32.9	1.5
ETD vs placebo (95% CI); p value	21.2 (10.22 to 32.25); 0.0002	26.5 (15.62 to 37.37); <0.0001	31.4 (20.62 to 42.13); <0.0001	..
Change from baseline at week 36	16.7	22.2	28.2	3.8
ETD vs placebo (95% CI); p value	12.9 (−3.61 to 29.39); 0.12	18.4 (2.68 to 34.12); 0.022	24.3 (8.70 to 39.94); 0.0026	..
FPG, mmol/L				
Baseline	9.5 (3.7)	8.8 (2.2)	8.9 (2.5)	8.7 (2.4)
Change from baseline at week 36	−1.3	−2.1	−2.3	−0.4
ETD vs placebo (95% CI); p value	−0.87 (−1.97 to 0.23); 0.12	−1.66 (−2.71 to −0.60); 0.0023	−1.93 (−2.99 to −0.87); 0.0005	..
FPG, mg/dL				
Baseline	171.2 (66.0)	157.9 (39.2)	160.7 (44.2)	156.1 (42.9)
Change from baseline at week 36	−23.3	−37.4	−42.3	−7.5
ETD vs placebo (95% CI); p value	−15.76 (−35.59 to 4.07); 0.12	−29.88 (−48.90 to −10.85); 0.0023	−34.77 (−53.94 to −15.60); 0.0005	..
Bodyweight change, %				
Baseline, kg	100.7 (21.7)	99.5 (23.1)	104.1 (21.6)	99.7 (18.4)
Change from baseline at week 36	−5.0	−10.3	−9.0	−3.0
ETD vs placebo (95% CI); p value	−1.91 (−5.01 to 1.20); 0.23	−7.29 (−10.44 to −4.15); <0.0001	−5.92 (−9.08 to −2.77); 0.0003	..
Bodyweight, kg				
Baseline	100.7 (21.7)	99.5 (23.1)	104.1 (21.6)	99.7 (18.4)
Change from baseline at week 36	−5.1	−10.1	−8.8	−3.3
ETD vs placebo (95% CI); p value	−1.77 (−4.88 to 1.33); 0.26	−6.82 (−9.97 to −3.66); <0.0001	−5.45 (−8.63 to −2.28); 0.0009	..
BMI, kg/m²				
Baseline	34.6 (6.1)	35.0 (6.5)	35.0 (6.4)	34.5 (6.1)
Change from baseline at week 36	−1.8	−3.6	−3.0	−1.2
ETD vs placebo (95% CI); p value	−0.6 (−1.72 to 0.45); 0.25	−2.4 (−3.51 to −1.30); <0.0001	−1.8 (−2.95 to −0.73); 0.0013	..
Waist circumference, cm				
Baseline	113.8 (16.1)	111.0 (15.6)	114.7 (14.9)	112.9 (13.4)
Change from baseline at week 36	−3.5	−7.6	−5.9	−3.7
ETD vs placebo (95% CI); p value	0.25 (−3.00 to 3.51); 0.88	−3.84 (−7.22 to −0.46); 0.026	−2.18 (−5.47 to 1.11); 0.19	..
hsCRP, mg/L				
Baseline	5.1 (5.6)	7.1 (19.4)	5.4 (5.4)	4.4 (4.9)
Ratio to baseline at week 36	0.8	0.4	0.7	0.8
ETR vs placebo (95% CI); p value	1.00 (0.58 to 1.71); 0.99	0.55 (0.32 to 0.93); 0.027	0.85 (0.49 to 1.48); 0.57	..
HDL cholesterol, mmol/L				
Baseline	1.2 (0.2)	1.2 (0.2)	1.2 (0.3)	1.2 (0.3)
Ratio to baseline at week 36	1.0	1.1	1.0	1.1
ETR vs placebo (95% CI); p value	0.99 (0.91 to 1.07); 0.75	1.05 (0.97 to 1.14); 0.27	0.98 (0.91 to 1.06); 0.64	..

Table 2 continues on next page

	Zenagamtide 6 mg (n=54)	Zenagamtide 25 mg (n=51)	Zenagamtide 50 mg (n=51)	Pooled placebo (n=30)
(Continued from previous page)				
LDL cholesterol, mmol/L				
Baseline	2.6 (1.1)	2.3 (1.0)	2.6 (1.0)	2.9 (0.9)
Ratio to baseline at week 36	0.9	1.0	0.9	0.9
ETR vs placebo (95% CI); p value	0.99 (0.83 to 1.18); 0.87	1.09 (0.92 to 1.30); 0.33	1.02 (0.86 to 1.22); 0.83	..
Total cholesterol, mmol/L				
Baseline	4.7 (1.2)	4.3 (1.1)	4.7 (1.1)	5.0 (1.2)
Ratio to baseline at week 36	0.9	1.0	0.9	0.9
ETR vs placebo (95% CI); p value	0.97 (0.88 to 1.07); 0.58	1.03 (0.93 to 1.14); 0.55	0.98 (0.89 to 1.08); 0.70	..
Triglycerides, mmol/L				
Baseline	2.4 (1.5)	1.7 (0.7)	1.9 (0.8)	2.0 (1.1)
Ratio to baseline at week 36	0.9	0.8	0.9	1.0
ETR vs placebo (95% CI); p value	0.87 (0.70 to 1.08); 0.21	0.80 (0.65 to 1.00); 0.048	0.87 (0.70 to 1.09); 0.23	..
SBP, mm Hg				
Baseline	131.6 (13.1)	132.6 (14.2)	129.7 (12.2)	128.5 (11.2)
Change from baseline at week 36	−4.0	−8.5	−10.7	−3.1
ETD vs placebo (95% CI); p value	−0.92 (−8.01 to 6.17); 0.80	−5.42 (−12.80 to 1.96); 0.15	−7.56 (−14.69 to −0.43); 0.038	..
24 h SBP, mm Hg				
Baseline	126.8 (11.9)	132.4 (17.2)	128.2 (12.4)	127.0 (10.8)
Change from baseline at week 36	−2.8	−3.7	−7.0	−2.7
ETD vs placebo (95% CI); p value	−0.10 (−6.04 to 5.83); 0.97	−0.97 (−7.35 to 5.40); 0.76	−4.27 (−11.01 to 2.46); 0.21	..
eGFR, * mL/min per 1.73 m²				
Baseline	97 (20)	97 (16)	98 (17)	101 (18)
Change from baseline at week 36	2	4	5	0
ETD vs placebo (95% CI); p value	1.95 (−2.30 to 6.20); 0.37	3.90 (−0.53 to 8.32); 0.084	4.97 (0.66 to 9.28); 0.024	..
UACR, mg/g				
Baseline†	28.3 (199.8)	29.4 (148.1)	20.4 (126.8)	16.2 (140.6)
Ratio to baseline at week 36	0.7	0.7	0.6	0.7
ETR vs placebo (95% CI); p value	0.99 (0.52 to 1.88); 0.97	1.09 (0.56 to 2.10); 0.80	0.91 (0.45 to 1.86); 0.80	..
The full analysis set included all randomly assigned participants. Data at baseline are observed values and are shown as mean (SD), unless otherwise stated. All other data are estimated values based on the efficacy estimand, incorporating the full analysis set and the on-treatment without rescue medication datapoint set. CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration. eGFR=estimated glomerular filtration rate. ETD=estimated treatment difference. ETR=estimated treatment ratio. FPG=fasting plasma glucose. hsCRP=high-sensitivity C-reactive protein. SBP=systolic blood pressure. TIR=time in range. UACR=urinary albumin-to-creatinine ratio. *eGFR calculated using the CKD-EPI (Creatinine-Cystatin C) equation (2021). ²³ †Geometric mean (coefficient of variation).				

Table 2: Summary of key outcomes (full analysis set)

All improve,
green
moves up

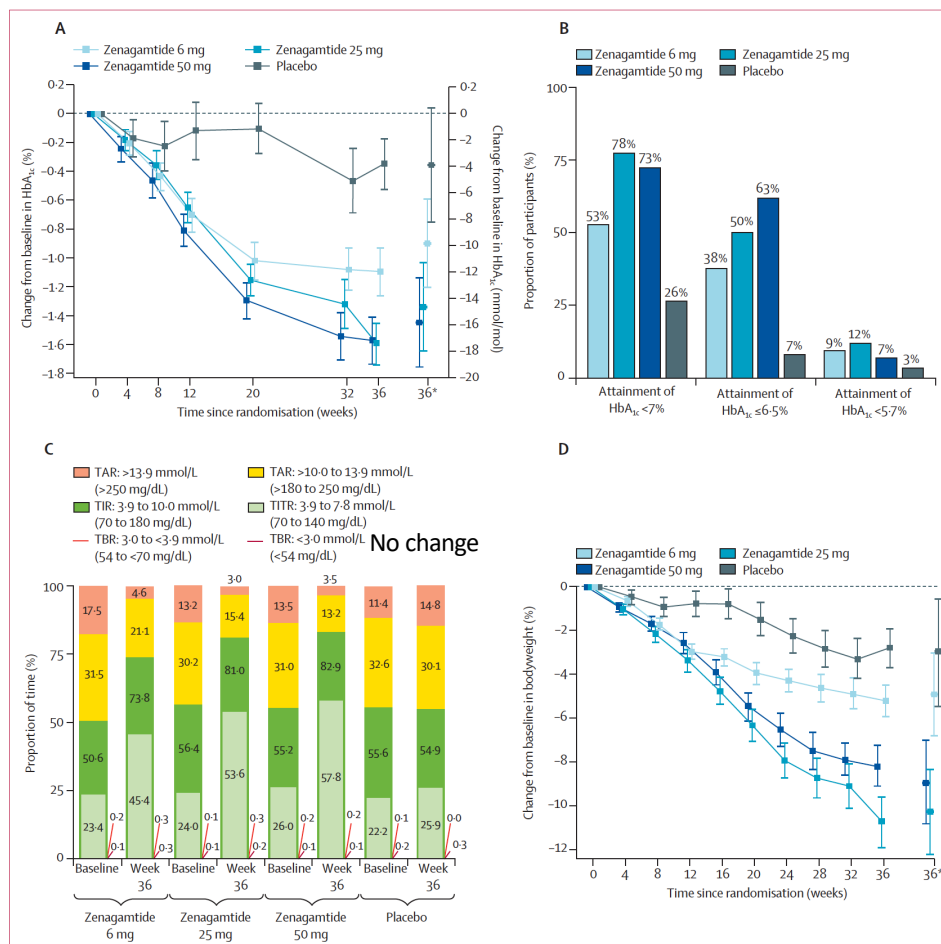


Figure 2: Key efficacy outcomes

Data from the on-treatment without rescue medication observation period. (A) Mean change in HbA_{1c} from baseline to week 36. Error bars show standard error of the mean. Estimated values from the primary analysis. (B) Proportion of participants who attained HbA_{1c} targets at week 36. Each binary responder outcome was analysed using a logistic regression model with the outcome as the dependent variable, with randomly assigned treatment and strata as fixed-effect factors, and with baseline of the underlying parameter as a fixed-effect covariate. Missing data were imputed using multiple imputation. (C) CGM metrics at baseline and week 36. Outcomes assessed as observed means. CGM assessments are averages calculated over a 10-day period. Time spent is defined as the proportion of time spent in a given range. (D) Mean change in bodyweight from baseline to week 36. Error bars show standard error of the mean. Estimated values from the primary analysis. CGM=continuous glucose monitoring. TAR=time above range. TBR=time below range. TIR=time in range. TITR=time in tight range. *Data shown at week 36 are the estimated mean values and the corresponding standard error from statistical analysis.

	Zenagamtide 6 mg (n=54)	Zenagamtide 25 mg (n=51)	Zenagamtide 50 mg (n=51)	Pooled placebo (n=30)
Adverse events				
Total adverse events	36 (67%)	39 (77%)	36 (71%)	20 (67%)
Serious adverse events	2 (4%)	2 (4%)	3 (6%)	0
Severe adverse events	1 (2%)	1 (2%)	3 (6%)	0
Moderate adverse events	10 (19%)	15 (29%)	19 (37%)	4 (13%)
Mild adverse events	33 (61%)	36 (71%)	29 (57%)	18 (60%)
Adverse events probably related to trial product	9 (17%)	16 (31%)	17 (33%)	6 (20%)
Adverse events possibly related to trial product	14 (26%)	16 (31%)	13 (26%)	2 (7%)
Outcome: not recovered*	10 (19%)	17 (33%)	12 (24%)	7 (23%)
Outcome: fatal	0	0	0	0
Action taken: trial treatment discontinued	2 (4%)	7 (14%)	7 (14%)	0
Adverse events reported by ≥5% of participants†				
Nausea	6 (11%)	17 (33%)	18 (35%)	1 (3%)
Vomiting	4 (7%)	5 (10%)	8 (16%)	0
Diarrhoea	4 (7%)	4 (8%)	3 (6%)	2 (7%)
Constipation	4 (7%)	3 (6%)	2 (4%)	1 (3%)
Gastro-oesophageal reflux disease	2 (4%)	5 (10%)	2 (4%)	1 (3%)
Dyspepsia	2 (4%)	3 (6%)	0	0
Eructation	1 (2%)	3 (6%)	0	0
Frequent bowel movements	0	0	0	2 (7%)
Nasopharyngitis	5 (9%)	6 (12%)	4 (8%)	1 (3%)
Influenza	5 (9%)	0	1 (2%)	0
CRP increased	3 (6%)	0	2 (4%)	1 (3%)
Headache	1 (2%)	0	1 (2%)	2 (7%)
Decreased appetite	1 (2%)	6 (12%)	4 (8%)	0
Dyslipidaemia	1 (2%)	0	0	2 (7%)
Fatigue	3 (6%)	1 (2%)	4 (8%)	1 (3%)
Asthenia	1 (2%)	2 (4%)	3 (6%)	0
Back pain	0	3 (6%)	1 (2%)	1 (3%)
Hypotension	0	0	0	2 (7%)
Adverse events of special interest‡				
Gastrointestinal§	14 (26%)	21 (41%)	24 (47%)	7 (23%)
Cardiovascular disorders	2 (4%)	4 (8%)	4 (8%)	3 (10%)
Allergic reactions§	3 (6%)	0	0	2 (7%)
Neoplasms	1 (2%)	2 (4%)	4 (8%)	0
Drug-related hepatic disorders§	0	2 (4%)	3 (6%)	..
Retinal disorders	2 (4%)	4 (8%)	2 (4%)	1 (3%)
Rare events	0	0	2 (4%)	..
Dysaesthesia§	0	0	1 (2%)	0
Malignant tumours§	0	1 (2%)	0	0
Medication errors, abuse, and misuse§	1 (2%)	1 (2%)	0	1 (3%)
Pancreatitis§	1 (2%)	0	0	0
Acute gallstone diseases§	0	0	0	0
Hypoglycaemia§¶	0	0	0	0

Data are the number of participants with an event (%). The safety analysis set included all randomly assigned participants. CRP=C-reactive protein. MedDRA=Medical Dictionary for Regulatory Activities. *Not recovered by the data cutoff date of Nov 3, 2025. †In any treatment group. ‡Evaluated using prespecified standardised MedDRA search queries or customised clusters of MedDRA preferred terms. §On-treatment adverse events (ie, those occurring from the first dose until 29 days after the last dose or last study site contact). ¶Severe hypoglycaemia (level 3).

Table 3: Adverse events from baseline to week 40 (safety analysis set)

Research in context

Evidence before this study

GLP-1 and amylin receptor agonists have complementary mechanisms of action for providing glycaemic control, weight management, and improvements in cardiometabolic parameters. Combination therapy with GLP-1 and amylin receptor agonists could therefore provide greater glycaemic control and weight loss than the individual components alone in individuals with overweight or obesity, with or without type 2 diabetes. Literature searches were conducted using PubMed for studies in any language published between Feb 12, 2016, and Feb 13, 2026, using search terms including “glucagon-like peptide AND amylin AND type 2 diabetes” and “glucagon-like peptide-1 AND amylin AND obesity”. Relevant publications identified included phase 3 clinical trials for the GLP-1 analogue, semaglutide, the amylin analogue, cagrilintide, and a cagrilintide and semaglutide combination therapy, CagriSema. The REDEFINE 2 trial of once-weekly subcutaneous cagrilintide and semaglutide combination therapy (cagrilintide 2.4 mg and semaglutide 2.4 mg) in individuals with overweight or obesity and type 2 diabetes resulted in superior reductions in bodyweight compared with placebo. The combination therapy also provided clinically relevant improvements in glycaemic parameters, including glycated haemoglobin (HbA_{1c}) and continuous glucose monitoring metrics, and improved cardiovascular risk markers.

Zenagamtide (formerly known as amycratin), a unimolecular peptide agonist of GLP-1, amylin, and calcitonin receptors, has been investigated as both subcutaneous and oral formulations in individuals with overweight or obesity without type 2 diabetes. In both the phase 1b/2a trial of the subcutaneous formulation and the phase 1 trial of the oral formulation, zenagamtide resulted in significantly greater weight loss than placebo. The oral formulation of zenagamtide also resulted in greater reductions in HbA_{1c} than placebo. These trials supported further investigation of both the subcutaneous and oral

formulations of zenagamtide in a dose-finding phase 2 trial in individuals with type 2 diabetes.

Added value of this study

To our knowledge, this was the first dose-finding trial to investigate the efficacy and safety of once-daily oral zenagamtide (6, 25, and 50 mg) compared with placebo in adults with type 2 diabetes. All doses of zenagamtide showed clinically meaningful and significantly greater reductions in HbA_{1c}, supported by improvements in time in range (TIR; 3.9–10.0 mmol/L [70–180 mg/dL]) from baseline to week 36. There was an estimated mean change from baseline in HbA_{1c} of up to –1.4% with zenagamtide 50 mg at week 36. The observed mean percentage of TIR at week 36 ranged from 73.8% to 82.9% (equivalent to approximately 17 h 43 min to 20 h per day) for the zenagamtide doses. Significantly greater percentage changes in bodyweight were also observed with zenagamtide 25 mg and 50 mg, with no signs of plateauing. The largest estimated percentage change in bodyweight with zenagamtide from baseline to week 36 was –10.3% for the 25 mg dose. Zenagamtide had a safety and tolerability profile consistent with GLP-1 and amylin receptor agonists and the previous trial with oral zenagamtide. The most common adverse events were gastrointestinal and were mild to moderate in severity.

Implications of all the available evidence

The results from this trial provide evidence of the therapeutic potential of the unimolecular agonist, zenagamtide, and support further investigation of once-daily oral zenagamtide in phase 3 trials. Given that people have individual preferences on the mode of delivery of medications (oral vs subcutaneous), the continued development of the oral formulation of zenagamtide could help to support individual choice, potentially increasing treatment acceptance and adherence while improving glycaemic control, facilitating attainment of weight loss goals, and improving other cardiometabolic parameters.

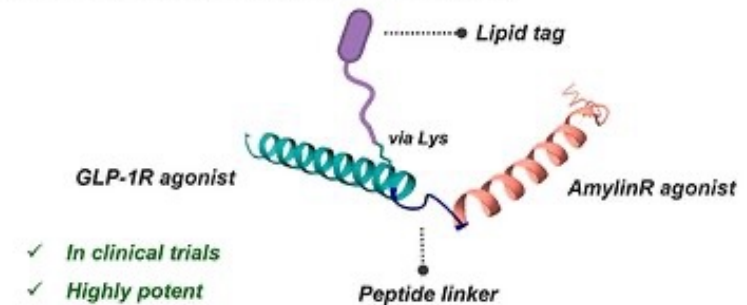
Drug did
pretty
well.

Zenagamtide (zuvor bekannt unter dem Entwicklungsnamen **Amycretin**) ist ein neuartiger, noch in der Entwicklung befindlicher Wirkstoff zur Behandlung von **Typ-2-Diabetes** und **Adipositas** (starkem Übergewicht). Er wird vom dänischen Pharmaunternehmen **Novo Nordisk** entwickelt. Das Medikament kombiniert zwei verschiedene Wirkmechanismen in einem einzigen Molekül und gilt in der Forschung als potenzieller Nachfolger von bekannten Präparaten wie Wegovy oder Ozempic.

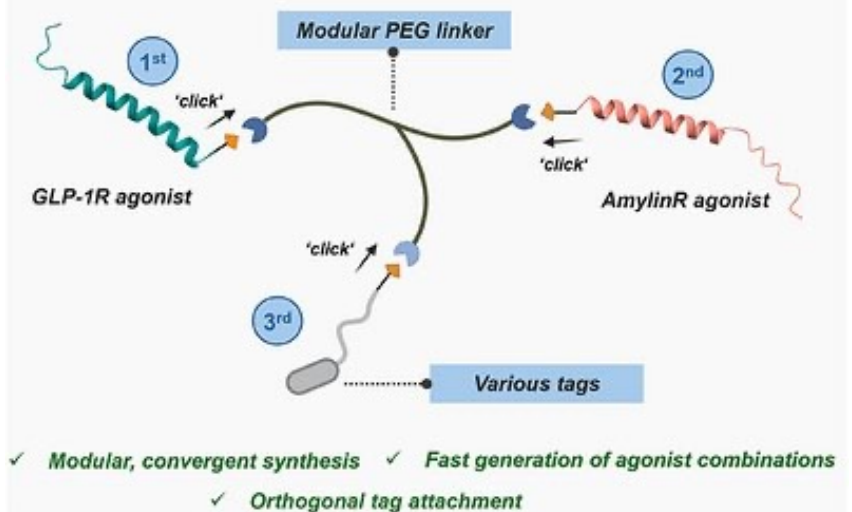
Im Gegensatz zu reinen GLP-1-Präparaten greift Zenagamtide an zwei hormonellen Signalwegen gleichzeitig an:

- **GLP-1-Rezeptor-Agonist:** Reduziert den Blutzucker und verzögert die Magenentleerung, um das Sättigungsgefühl zu verlängern.
- **Amylin-Rezeptor-Agonist:** Amylin ist ein Hormon, das den Appetit im Gehirn reguliert und das Sättigungsgefühl nach dem Essen maßgeblich steuert.

A. Previous work: Zenagamtide (Amycretin)



B. This work: Modular Platform for Multi-agonist Assembly



Efficacy and safety of once-weekly subcutaneous zenagamtide, a novel unimolecular GLP-1 and amylin receptor agonist, in type 2 diabetes: a multicentre, randomised, parallel, double-blind, placebo-controlled, dose-finding, phase 2 trial

Summary

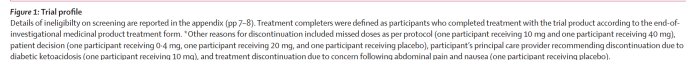
Background Zenagamtide (formerly amycletin) is a unimolecular agonist of GLP-1, amylin, and calcitonin receptors. We aimed to investigate the dose–response relationship with respect to the efficacy and safety of once-weekly subcutaneous zenagamtide compared with placebo in adults with type 2 diabetes.

Methods This 36-week, randomised, parallel, double-blind, placebo-controlled, dose-finding, phase 2 trial was conducted at 83 hospital and clinic sites across 11 countries. The trial consisted of a 3-week screening period, a 36-week intervention period, and a 4-week follow-up period. Adults (aged 18–75 years) with type 2 diabetes (glycated haemoglobin [HbA_{1c}] 7·0–10·0% [53–86 mmol/mol]), treated with stable doses of metformin with or without a SGLT2 inhibitor, and with a BMI of 23·0 to <50·0 kg/m² were randomly assigned (6:1) to once-weekly subcutaneous zenagamtide or placebo using a randomisation and trial supplies management system, before being further randomly assigned to one of six dose groups (1:1:1:1:1:1; 0·4, 1·5, 5, 10, 20, or 40 mg). Participants assigned to placebo were similarly allocated to matched placebo regimens corresponding to each dosing schedule. Randomisation was stratified by HbA_{1c} (<8·5% or ≥8·5%) at screening and country of residence (Japan or other countries). The starting dose of subcutaneous zenagamtide was 0·2 mg, with dose escalations every 4 weeks until the maintenance dose was reached (0·4–40 mg). Participants and staff were masked within each dose level to placebo or zenagamtide. The primary outcome was change in HbA_{1c} from baseline to week 36. The primary outcome was assessed in all randomly assigned participants using the efficacy estimand based on on-treatment data without rescue medication. Safety outcomes were assessed in all randomly assigned participants exposed to treatment. The trial is registered with ClinicalTrials.gov, NCT06542874, and is completed.

Findings Between Aug 7 and Dec 27, 2024, 262 (29%) of 915 screened individuals were randomly assigned to subcutaneous zenagamtide (n=225) or placebo (n=37). Participants were further randomly assigned (1:1:1:1:1:1) to one of six doses (38 participants to 0.4 mg, 36 participants to 1.5 mg, 37 participants to 5 mg, 38 participants to 10 mg, 38 participants to 20 mg, and 38 participants to 40 mg) or placebo (37 participants). 261 participants were exposed to treatment. At week 36, estimated change in HbA_{1c} (mean across all groups at baseline 7.8% [SD 0.8]) ranged from -0.9% with zenagamtide 0.4 mg (estimated treatment difference *vs* placebo: -0.77% [95% CI -1.26 to -0.28]; p=0.0021) to -1.7% with zenagamtide 40 mg (-1.56% [-2.05 to -1.07]; p<0.0001). Most adverse events were gastrointestinal and mild to moderate in severity. 21 (8%) of 261 participants reported serious adverse events (four with zenagamtide 0.4 mg, three with 1.5 mg, two with 5 mg, five with 10 mg, three with 20 mg, one with 40 mg, and three with placebo). No deaths occurred.

Interpretation In people with type 2 diabetes, once-weekly subcutaneous zenagamtide 0.4–40 mg demonstrated clinically meaningful and significant improvements in change in HbA_{1c} from baseline to week 36 compared with placebo, with a safety and tolerability profile consistent with that of other GLP-1-based and amylin-based therapies.

Funding Novo Nordisk.



Data are n (%) or mean (SD). The full analysis set included all randomly assigned participants. CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration. eGFR=estimated glomerular filtration rate. FPG=fasting plasma glucose. *eGFR calculated using the CKD-EPI (Creatinine-Cystatin C) equation (2021).²⁵ †Self-reported by participants.

Table 1: Participant demographics and baseline characteristics (full analysis set)

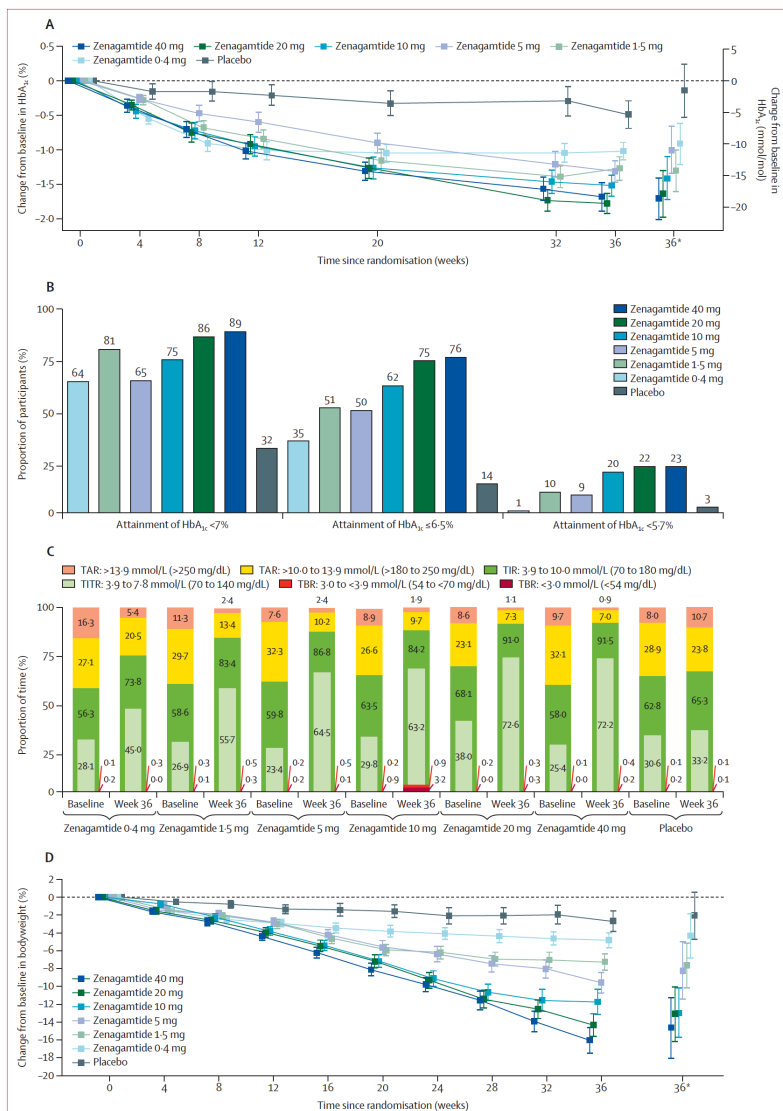


Figure 2: Key efficacy outcomes

(A) Mean change in HbA_{1c} from baseline to week 36. Error bars show SE of the mean. Estimated values based on the efficacy estimand, incorporating the full analysis set (all randomly assigned participants) and the on-treatment without rescue medication datapoint set.

(B) Proportion of participant attaining HbA_{1c} targets at week 36. Each binary responder outcome was analysed using a logistic regression model with the outcome as the dependent variable and with randomly assigned treatment and strata as fixed-effect factors and baseline of the underlying parameter as a fixed-effect covariate. Missing data were imputed using multiple imputation.

(C) CGM metrics at baseline and week 36. Outcomes assessed as observed means. CGM assessments are averages calculated over a 10-day period. Time spent is defined as the proportion of time spent in a given range.

(D) Mean change in bodyweight from baseline to week 36. Error bars show SE of the mean. Estimated values based on the efficacy estimand, incorporating the full analysis set (all randomly assigned participants) and the on-treatment without rescue medication datapoint set. Missing data were imputed using multiple imputation; data from the on-treatment without rescue medication observation period.

CGM=continuous glucose monitoring; TAR=time above range; TBR=time below range; TIR=time in range; TIR-tin in tight range. *Data shown week 36 are the estimated mean values and the corresponding SE from statistical analysis.

	Zenagamtide 0.4 mg (n=38)	Zenagamtide 1.5 mg (n=36)	Zenagamtide 5 mg (n=37)	Zenagamtide 10 mg (n=38)	Zenagamtide 20 mg (n=38)	Zenagamtide 40 mg (n=38)	Pooled placebo (n=37)
HbA_{1c} %							
Baseline	8.0 (0.8)	7.7 (0.9)	7.8 (0.7)	7.9 (0.8)	7.7 (0.6)	7.8 (0.8)	8.0 (0.7)
Change from baseline at week 36	-0.9	-1.3	-1.0	-1.4	-1.6	-1.7	-0.1
ETD vs placebo (95% CI); p value	-0.77 (-1.26 to -0.28); 0.0021	-1.17 (-1.66 to -0.67); <0.0001	-0.86 (-1.38 to -0.34); 0.0013	-1.27 (-1.77 to -0.77); <0.0001	-1.49 (-2.00 to -0.98); <0.0001	-1.56 (-2.05 to -1.07); <0.0001	..
TIR 3.9-10.0 mmol/L (70-180 mg/dL), %							
Baseline	56.3 (33.3)	58.6 (26.1)	59.8 (20.9)	63.5 (22.9)	68.1 (25.3)	58.0 (24.6)	62.8 (26.5)
Change from baseline at week 20	20.8	25.9	27.8	26.9	20.9	29.9	9.8
ETD vs placebo (95% CI); p value	11.02 (1.93 to 20.10); 0.018	16.09 (6.61 to 25.57); 0.0010	18.05 (9.03 to 27.07); 0.0001	17.15 (7.99 to 26.30); 0.0003	11.09 (1.23 to 20.95); 0.028	20.10 (10.97 to 29.24); <0.0001	..
Change from baseline at week 36	13.9	23.7	24.8	23.7	24.0	30.4	-0.4
ETD vs placebo (95% CI); p value	14.37 (-0.08 to 28.83); 0.051	24.11 (9.62 to 38.60); 0.0013	25.25 (10.59 to 39.90); 0.0009	24.15 (9.18 to 39.11); 0.0019	24.41 (9.65 to 39.18); 0.0014	30.85 (16.74 to 44.95); <0.0001	..
FPG, mmol/L							
Baseline	8.6 (2.2)	8.6 (2.3)	9.1 (1.8)	8.3 (1.8)	8.2 (1.9)	8.9 (2.5)	8.9 (2.2)
Change from baseline at week 36	-1.3	-2.2	-2.1	-2.3	-2.4	-2.8	0.3
ETD vs placebo (95% CI); p value	-1.68 (-2.95 to -0.42); 0.0094	-2.54 (-3.81 to -1.26); 0.0001	-2.41 (-3.90 to -0.91); 0.0020	-2.63 (-3.93 to -1.33); 0.0001	-2.73 (-4.02 to -1.44); p<0.0001	-3.11 (-4.39 to -1.82); p<0.0001	..
FPG, mg/dL							
Baseline	155.1 (39.5)	154.8 (41.7)	164.1 (31.7)	149.2 (33.2)	148.3 (33.8)	160.6 (44.2)	159.4 (39.6)
Change from baseline at week 36	-24.1	-39.5	-37.1	-41.1	-43.0	-49.8	6.2
ETD vs placebo (95% CI); p value	-30.34 (-53.09 to -7.59); 0.0094	-45.72 (-68.71 to -22.73); 0.0001	-43.37 (-70.35 to -16.39); 0.0020	-47.37 (-70.86 to -23.88); 0.0001	-49.24 (-72.51 to -25.97); <0.0001	-55.98 (-79.17 to -32.79); <0.0001	..
Bodyweight change, %							
Baseline, kg	102.4 (25.2)	99.9 (20.2)	98.9 (20.1)	95.8 (21.0)	98.4 (21.0)	99.5 (25.2)	99.8 (22.8)
Change from baseline at week 36	-4.3	-7.6	-8.2	-12.9	-13.1	-14.6	-2.1
ETD vs placebo (95% CI); p value	-2.25 (-5.83 to 1.34); 0.22	-5.52 (-9.15 to -1.90); 0.0030	-6.09 (-10.20 to -1.99); 0.0039	-10.82 (-14.61 to -7.03); <0.0001	-11.04 (-15.04 to -7.03); <0.0001	-12.50 (-16.79 to -8.21); <0.0001	..
Bodyweight, kg							
Baseline	102.4 (25.2)	99.9 (20.2)	98.9 (20.1)	95.8 (21.0)	98.4 (21.0)	99.5 (25.2)	99.8 (22.8)
Change from baseline at week 36	-4.0	-7.5	-8.4	-12.1	-12.3	-14.9	-1.8
ETD vs placebo (95% CI); p value	-2.23 (-5.68 to 1.22); 0.20	-5.72 (-9.22 to -2.23); 0.0014	-6.63 (-10.43 to -2.84); 0.0007	-10.30 (-13.90 to -6.71); <0.0001	-10.51 (-14.40 to -6.63); <0.0001	-13.11 (-17.14 to -9.08); <0.0001	..
BMI, kg/m²							
Baseline	35.3 (6.6)	34.8 (6.7)	33.7 (6.2)	32.9 (6.4)	32.6 (5.4)	32.9 (6.1)	33.9 (5.9)
Change from baseline at week 36	-1.4	-2.6	-2.9	-4.2	-4.2	-5.0	-0.6
ETD vs placebo (95% CI); p value	-0.74 (-1.92 to 0.44); 0.22	-1.96 (-3.15 to -0.76); 0.0015	-2.25 (-3.54 to -0.95); 0.0008	-3.57 (-4.80 to -2.33); <0.0001	-3.60 (-4.95 to -2.26); <0.0001	-4.33 (-5.70 to -2.96); <0.0001	..
Waist circumference, cm							
Baseline	115.7 (16.9)	114.6 (15.3)	112.7 (12.5)	108.3 (14.4)	108.5 (12.7)	112.2 (15.1)	122.2 (13.3)
Change from baseline at week 36	-3.2	-6.5	-6.5	-9.9	-11.5	-11.7	-0.9
ETD vs placebo (95% CI); p value	-2.28 (-5.62 to 1.06); 0.18	-5.60 (-8.96 to -2.23); 0.0012	-5.61 (-9.22 to -2.00); 0.0025	-8.98 (-12.50 to -5.46); <0.0001	-10.58 (-14.36 to -6.81); <0.0001	-10.76 (-15.96 to -5.56); <0.0001	..

(Table 2 continues on next page)

	Zenagamtide 0.4 mg (n=38)	Zenagamtide 1.5 mg (n=36)	Zenagamtide 5 mg (n=37)	Zenagamtide 10 mg (n=38)	Zenagamtide 20 mg (n=38)	Zenagamtide 40 mg (n=38)	Pooled placebo (n=37)
HbA_{1c} %							
Baseline	8.0 (0.8)	7.7 (0.9)	7.8 (0.7)	7.9 (0.8)	7.7 (0.6)	7.8 (0.8)	8.0 (0.7)
Change from baseline at week 36	-0.9	-1.3	-1.0	-1.4	-1.6	-1.7	-0.1
ETD vs placebo (95% CI); p value	-0.77 (-1.26 to -0.28); 0.0021	-1.17 (-1.66 to -0.67); <0.0001	-0.86 (-1.38 to -0.34); 0.0013	-1.27 (-1.77 to -0.77); <0.0001	-1.49 (-2.00 to -0.98); <0.0001	-1.56 (-2.05 to -1.07); <0.0001	..
TIR 3.9-10.0 mmol/L (7.0-18.0 mg/dL), %							
Baseline	56.3 (33.3)	58.6 (26.1)	59.8 (20.9)	63.5 (22.9)	68.1 (25.3)	58.0 (24.6)	62.8 (26.5)
Change from baseline at week 20	20.8	25.9	27.8	26.9	20.9	29.9	9.8
ETD vs placebo (95% CI); p value	11.02 (1.93 to 20.10); 0.018	16.09 (6.61 to 25.57); 0.0010	18.05 (9.03 to 27.07); 0.0001	17.15 (7.99 to 26.30); 0.0003	11.09 (1.23 to 20.95); 0.028	20.10 (10.97 to 29.24); <0.0001	..
Change from baseline at week 36	13.9	23.7	24.8	23.7	24.0	30.4	-0.4
ETD vs placebo (95% CI); p value	14.37 (-0.08 to 28.83); 0.051	24.11 (9.62 to 38.60); 0.0013	25.25 (10.59 to 39.90); 0.0009	24.15 (9.18 to 39.11); 0.0019	24.41 (9.65 to 39.18); 0.0014	30.85 (16.74 to 44.95); <0.0001	..
FPG, mmol/L							
Baseline	8.6 (2.2)	8.6 (2.3)	9.1 (1.8)	8.3 (1.8)	8.2 (1.9)	8.9 (2.5)	8.9 (2.2)
Change from baseline at week 36	-1.3	-2.2	-2.1	-2.3	-2.4	-2.8	0.3
ETD vs placebo (95% CI); p value	-1.68 (-2.95 to -0.42); 0.0094	-2.54 (-3.81 to -1.26); 0.0001	-2.1 (-3.90 to -0.91); 0.0020	-2.63 (-3.93 to -1.33); 0.0001	-2.73 (-4.02 to -1.44) p<0.0001	-3.11 (-4.42 to -1.82) p<0.0001	..
FPG, mg/dL							
Baseline	155.1 (39.5)	154.8 (41.7)	164.1 (31.7)	149.2 (33.2)	148.3 (33.8)	160.6 (44.2)	159.4 (39.6)
Change from baseline at week 36	-24.1	-39.5	-37.1	-41.1	-43.0	-49.8	6.2
ETD vs placebo (95% CI); p value	-30.34 (-53.09 to -7.59); 0.0094	-45.72 (-68.71 to -22.73); 0.0001	-43.37 (-70.35 to -16.39); 0.0020	-47.37 (-70.86 to -23.88); 0.0001	-49.24 (-72.51 to -25.97); <0.0001	-55.98 (-79.17 to -32.79); <0.0001	..
Bodyweight change, %							
Baseline, kg	102.4 (25.2)	99.9 (20.2)	98.9 (20.1)	95.8 (21.0)	98.4 (21.0)	99.5 (25.2)	99.8 (22.8)
Change from baseline at week 36	-4.3	-7.6	-8.2	-12.9	-13.1	-14.6	-2.1
ETD vs placebo (95% CI); p value	-2.25 (-5.83 to 1.34); 0.22	-5.52 (-9.15 to -1.90); 0.0030	-6.09 (-10.20 to -1.99); 0.0039	-10.82 (-14.61 to -7.03); <0.0001	-11.04 (-15.04 to -7.03); <0.0001	-12.50 (-16.79 to -8.21); <0.0001	..
Bodyweight, kg							
Baseline	102.4 (25.2)	99.9 (20.2)	98.9 (20.1)	95.8 (21.0)	98.4 (21.0)	99.5 (25.2)	99.8 (22.8)
Change from baseline at week 36	-4.0	-7.5	-8.4	-12.1	-12.3	-14.9	-1.8
ETD vs placebo (95% CI); p value	-2.23 (-5.68 to 1.22); 0.20	-5.72 (-9.22 to -2.23); 0.0014	-6.63 (-10.43 to -2.84); 0.0007	-10.30 (-13.90 to -6.71); <0.0001	-10.51 (-14.40 to -6.63); <0.0001	-13.11 (-17.14 to -9.08); <0.0001	..
BMI, kg/m²							
Baseline	35.3 (6.6)	34.8 (6.7)	33.7 (6.2)	32.9 (6.4)	32.6 (5.4)	32.9 (6.1)	33.9 (5.9)
Change from baseline at week 36	-1.4	-2.6	-2.9	-4.2	-4.2	-5.0	-0.6
ETD vs placebo (95% CI); p value	-0.74 (-1.92 to 0.44); 0.22	-1.96 (-3.15 to -0.76); 0.0015	-2.25 (-3.54 to -0.95); 0.0008	-3.57 (-4.80 to -2.33); <0.0001	-3.60 (-4.95 to -2.26); <0.0001	-4.33 (-5.70 to -2.96); <0.0001	..
Waist circumference, cm							
Baseline	115.7 (16.9)	114.6 (15.3)	112.7 (12.5)	108.3 (14.4)	108.5 (12.7)	112.2 (15.1)	122.2 (13.3)
Change from baseline at week 36	-3.2	-6.5	-6.5	-9.9	-11.5	-7.42	-0.9
ETD vs placebo (95% CI); p value	-2.28 (-5.62 to 1.06); 0.18	-5.60 (-8.96 to -2.23); 0.0012	-5.61 (-9.22 to -2.00); 0.0025	-8.98 (-12.50 to -5.46); <0.0001	-10.58 (-15.96 to -5.56); <0.0001	-10.76 (-15.96 to -5.56); <0.0001	..

(Table 2 continues on next page)

	Zenagamtide 0.4 mg (n=38)	Zenagamtide 1.5 mg (n=36)	Zenagamtide 5 mg (n=37)	Zenagamtide 10 mg (n=38)	Zenagamtide 20 mg (n=38)	Zenagamtide 40 mg (n=38)	Pooled placebo (n=37)
(Continued from previous page)							
hsCRP, mg/L							
Baseline	4.7 (5.2)	4.0 (4.4)	6.0 (10.5)	3.8 (4.9)	3.2 (3.6)	4.2 (4.1)	3.5 (4.2)
Ratio to baseline at week 36	0.8	0.7	0.6	0.5	0.6	0.3	1.2
ETD vs placebo (95% CI); p value	0.71 (0.27 to 1.87); 0.48	0.60 (0.23 to 1.59); 0.30	0.52 (0.19 to 1.38); 0.19	0.41 (0.15 to 1.10); 0.077	0.54 (0.17 to 1.69); 0.29	0.26 (0.09 to 0.76); 0.015	..
HDL cholesterol, mmol/L							
Baseline	1.1 (0.3)	1.2 (0.3)	1.1 (0.2)	1.1 (0.3)	1.2 (0.3)	1.1 (0.3)	1.1 (0.2)
Ratio to baseline at week 36	1.1	1.0	1.1	1.0	1.1	1.1	1.0
ETD vs placebo (95% CI)	1.06 (0.97 to 1.14); 0.19	1.04 (0.96 to 1.13); 0.33	1.07 (0.99 to 1.17); 0.099	1.05 (0.97 to 1.15); 0.23	1.09 (1.00 to 1.19); 0.047	1.14 (1.04 to 1.24); 0.0044	..
LDL cholesterol, mmol/L							
Baseline	2.7 (0.8)	2.7 (0.9)	2.6 (0.9)	2.3 (0.9)	2.5 (1.0)	2.5 (0.9)	2.5 (0.8)
Ratio to baseline at week 36	0.9	0.9	0.7	0.8	0.8	0.8	0.8
ETD vs placebo (95% CI); p value	1.15 (0.94 to 1.40); 0.17	1.19 (0.97 to 1.45); 0.090	0.95 (0.76 to 1.18); 0.62	1.05 (0.85 to 1.32); 0.64	1.07 (0.87 to 1.33); 0.52	1.02 (0.82 to 1.26); 0.86	..
Total cholesterol, mmol/L							
Baseline	4.7 (0.9)	4.8 (1.1)	4.6 (1.0)	4.3 (1.0)	4.5 (1.2)	4.4 (1.0)	4.5 (0.9)
Ratio to baseline at week 36	0.9	0.9	0.9	0.9	0.9	0.8	1.0
ETD vs placebo (95% CI); p value	0.98 (0.86 to 1.12); 0.75	0.97 (0.85 to 1.11); 0.66	0.91 (0.79 to 1.04); 0.17	0.91 (0.78 to 1.05); 0.18	0.88 (0.77 to 1.02); 0.085	0.88 (0.76 to 1.01); 0.074	..
Triglycerides, mmol/L							
Baseline	2.0 (1.0)	2.0 (1.0)	2.0 (0.9)	2.0 (1.1)	2.0 (1.2)	2.0 (0.9)	2.0 (0.9)
Ratio to baseline at week 36	0.9	0.8	0.8	0.7	0.6	0.6	1.1
ETD vs placebo (95% CI); p value	0.80 (0.60 to 1.06); 0.12	0.75 (0.56 to 1.00); 0.048	0.76 (0.57 to 1.03); 0.076	0.63 (0.47 to 0.84); 0.0022	0.57 (0.43 to 0.76); 0.0002	0.52 (0.38 to 0.71); <0.0001	..
SBP, mm Hg							
Baseline	131.1 (14.7)	133.6 (13.6)	133.2 (13.9)	129.4 (13.8)	129.2 (12.7)	130.4 (13.8)	129.9 (13.8)
Change from baseline at week 36	-5.8	-3.4	-7.7	-9.4	-7.2	-10.6	-3.5
ETD vs placebo (95% CI); p value	-2.28 (-11.10 to 6.53); 0.61	0.09 (-8.82 to 9.00); 0.98	-4.17 (-13.68 to 5.34); 0.39	-5.87 (-14.97 to 3.24); 0.21	-3.70 (-14.27 to 6.87); 0.49	-7.13 (-19.24 to 4.98); 0.25	..
24 h SBP, mm Hg							
Baseline	130.2 (16.7)	129.2 (9.5)	131.7 (11.1)	126.1 (10.0)	128.9 (15.5)	129.4 (13.4)	127.4 (11.4)
Change from baseline at week 36	-3.9	-4.0	-6.6	-6.7	-10.1	-9.9	-0.9
ETD vs placebo (95% CI); p value	-3.05 (-9.73 to 3.64); 0.37	-3.12 (-9.61 to 3.37); 0.34	-5.76 (-12.55 to 1.03); 0.096	-5.85 (-13.76 to 2.06); 0.15	-9.20 (-16.44 to -1.96); 0.013	-9.06 (-2.97 to 16.40); 0.0050	..
eGFR, * mL/min per 1.73 m²							
Baseline	88 (20)	88 (19)	92 (16)	90 (19)	88 (19)	84 (22)	87 (21)
Change from baseline at week 36	3	1	6	11	8	8	-2
ETD vs placebo (95% CI); p value	4.25 (-1.85 to 10.35); 0.17	2.84 (-3.30 to 8.99); 0.36	7.42 (0.71 to 14.13); 0.031	12.59 (6.27 to 18.92); 0.0001	9.55 (2.64 to 16.46); 0.0072	9.69 (2.97 to 16.40); 0.0050	..

(Table 2 continues on next page)

	Zenagamtide 0.4 mg (n=38)	Zenagamtide 1.5 mg (n=36)	Zenagamtide 5 mg (n=37)	Zenagamtide 10 mg (n=38)	Zenagamtide 20 mg (n=38)	Zenagamtide 40 mg (n=38)	Pooled placebo (n=37)
(Continued from previous page)							
UACR, mg/g							
Baseline†	19.7 (107.9)	25.7 (226.8)	19.7 (98.4)	16.3 (119.9)	20.9 (113.8)	15.8 (126.2)	28.0 (163.4)
Ratio to baseline at week 36	0.6	0.8	0.6	0.8	0.5	0.7	1.2
ETR vs placebo (95% CI); p value	0.51 (0.26 to 1.00); 0.051	0.62 (0.31 to 1.24); 0.18	0.44 (0.21 to 0.92); 0.029	0.68 (0.32 to 1.46); 0.32	0.39 (0.19 to 0.80); 0.012	0.58 (0.27 to 1.25); 0.16	..
The full analysis set included all randomly assigned participants. Data at baseline are observed values and are shown as mean (SD), unless otherwise stated. All other data are estimated values based on the efficacy estimand, incorporating the full analysis set and the on-treatment without rescue medication datapoint set. CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration. eGFR=estimated glomerular filtration rate. ETD=estimated treatment difference. ETR=estimated treatment ratio. FPG=fasting plasma glucose. hsCRP=high-sensitivity C-reactive protein. SBP=systolic blood pressure. TIR=time in range. UACR=urinary albumin-to-creatinine ratio. *eGFR calculated using the CKD-EPI (Creatinine-Cystatin C) equation (2021).²⁸ †Geometric mean (coefficient of variation).							
Table 2: Summary of key outcomes (full analysis set)							

Implications of all the available evidence

The results from this phase 2 trial provide evidence of the therapeutic potential of the novel unimolecular agonist zenagamtide and support further investigation of once-weekly subcutaneous zenagamtide in phase 3 clinical trials in individuals with type 2 diabetes.

Drug did pretty well.

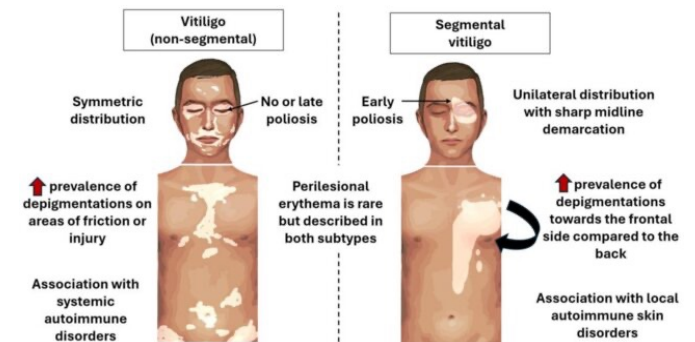
	Zenagamtide 0·4 mg (n=38)	Zenagamtide 1·5 mg (n=36)	Zenagamtide 5 mg (n=37)	Zenagamtide 10 mg (n=38)	Zenagamtide 20 mg (n=38)	Zenagamtide 40 mg (n=38)	Pooled placebo (n=36)
Adverse events							
Total adverse events	26 (68%)	24 (67%)	27 (73%)	26 (68%)	34 (90%)	34 (90%)	21 (58%)
Serious adverse events	4 (11%)	3 (8%)	2 (5%)	5 (13%)	3 (8%)	1 (3%)	3 (8%)
Severe adverse events	2 (5%)	2 (6%)	0	5 (13%)	3 (8%)	4 (11%)	0
Moderate adverse events	7 (18%)	11 (31%)	14 (38%)	14 (37%)	18 (47%)	22 (58%)	8 (22%)
Mild adverse events	21 (55%)	18 (50%)	23 (62%)	23 (61%)	31 (82%)	30 (79%)	19 (53%)
Adverse events probably related to trial product	9 (24%)	4 (11%)	12 (32%)	16 (42%)	23 (61%)	27 (71%)	7 (19%)
Adverse events possibly related to trial product	4 (11%)	12 (33%)	13 (35%)	14 (37%)	15 (40%)	14 (37%)	5 (14%)
Outcome: not recovered*	9 (24%)	5 (14%)	9 (24%)	6 (16%)	10 (26%)	12 (32%)	8 (22%)
Outcome: fatal	0	0	0	0	0	0	0
Action taken: trial treatment discontinued	3 (8%)	1 (3%)	6 (16%)	8 (21%)	13 (34%)	13 (34%)	2 (6%)
Adverse events reported by ≥5% of participants†							
Nausea	4 (11%)	6 (17%)	14 (38%)	10 (26%)	19 (50%)	14 (37%)	5 (14%)
Vomiting	1 (3%)	1 (3%)	6 (16%)	4 (11%)	9 (24%)	11 (29%)	2 (6%)
Diarrhoea	2 (5%)	2 (6%)	4 (11%)	4 (11%)	6 (16%)	14 (37%)	2 (6%)
Constipation	2 (5%)	1 (3%)	2 (5%)	2 (5%)	3 (8%)	4 (11%)	1 (3%)
Dyspepsia	0	1 (3%)	2 (5%)	2 (5%)	3 (8%)	3 (8%)	0
Abdominal discomfort	0	1 (3%)	1 (3%)	3 (8%)	2 (5%)	3 (8%)	0
Nasopharyngitis	0	1 (3%)	2 (5%)	1 (3%)	6 (16%)	7 (18%)	3 (8%)
Influenza	1 (3%)	1 (3%)	1 (3%)	2 (5%)	0	2 (5%)	2 (6%)
Lipase increased	2 (5%)	2 (6%)	5 (14%)	0	3 (8%)	3 (8%)	0
Headache	0	1 (3%)	2 (5%)	1 (3%)	3 (8%)	0	0
Decreased appetite	0	0	2 (5%)	3 (8%)	1 (3%)	6 (16%)	0
Adverse events of special interest‡							
Gastrointestinal adverse events§	9 (24%)	11 (31%)	21 (57%)	18 (47%)	24 (63%)	28 (74%)	9 (25%)
Dysaesthesia§	0	0	0	3 (8%)	2 (5%)	8 (21%)	0
Cardiovascular disorders	5 (13%)	4 (11%)	1 (3%)	2 (5%)	6 (16%)	3 (8%)	3 (8%)
Drug-related hepatic disorders§	1 (3%)	4 (11%)	1 (3%)	0	1 (3%)	2 (5%)	1 (3%)
Hypoglycaemia¶	0	0	0	0	1 (3%)	0	0
Allergic reactions§	0	0	1 (3%)	2 (5%)	2 (5%)	0	1 (3%)
Medication errors, abuse, and misuse§	2 (5%)	1 (3%)	1 (3%)	2 (5%)	4 (11%)	2 (5%)	2 (6%)
Pancreatitis§	0	0	0	0	0	0	0
Neoplasms	1 (3%)	3 (8%)	1 (3%)	0	0	2 (5%)	1 (3%)
Malignant tumours§	1 (3%)	0	0	0	0	0	0
Retinal disorders	3 (8%)	1 (3%)	2 (5%)	3 (8%)	3 (8%)	0	1 (3%)
Acute gallstone disease§	0	1 (3%)	1 (3%)	0	0	0	1 (3%)

Data are the number of participants with an event (%). The safety analysis set included all randomly assigned participants. MedDRA=Medical Dictionary for Regulatory Activities. *Not recovered by the data cutoff date of Nov 3, 2025. †In any treatment group. ‡Evaluated using prespecified standardised MedDRA search queries or customised clusters of MedDRA preferred terms. §Values are for adverse events of special interest that occurred during study treatment; all other values are for the trial period (treatment period plus follow-up period). ¶Severe hypoglycaemia (level 3).

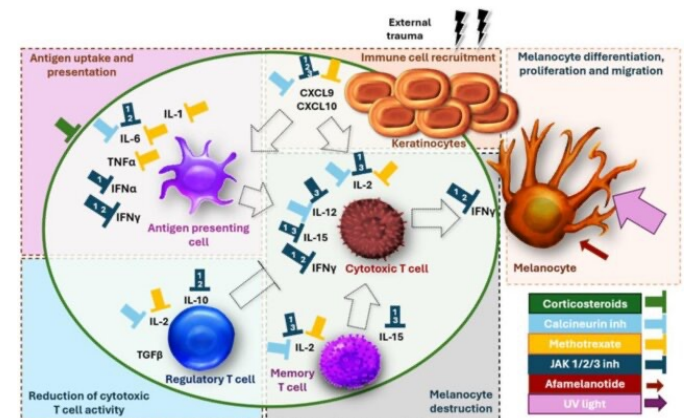
Table 3: Participants with adverse events from baseline to week 40 (safety analysis set)

Die **nicht-segmentale Vitiligo (NSV)** – auch bekannt als generalisierte Vitiligo – ist eine **chronische Autoimmunerkrankung der Haut**, die durch den **Verlust von funktionellen Pigmentzellen (Melanozyten)** zu charakteristischen weißen Flecken führt. Sie ist mit rund **90 % aller Fälle** die mit Abstand häufigste Form der Weißfleckenkrankheit. Im Gegensatz zur selteneren segmentalen Form verläuft die nicht-segmentale Vitiligo typischerweise **symmetrisch und betrifft beide Körperhälften parallel**. Die Erkrankung verläuft oft unvorhersehbar in Schüben und kann sich im Laufe des Lebens schrittweise ausweiten.

- **Symmetrische Verteilung:** Die pigmentfreien Flecken treten meist spiegelbildlich auf beiden Seiten des Körpers auf. Typische Areale sind Handrücken, Arme, Knie, Ellenbogen sowie die Hautbereiche um Körperöffnungen wie Augen und Mund.
- **Autoimmune Ursache:** Das körpereigene Immunsystem greift fälschlicherweise die Melanozyten an und zerstört sie. Betroffene haben ein erhöhtes Risiko für andere Autoimmunerkrankungen, insbesondere Schilddrüsenstörungen wie Hashimoto-Thyreoiditis oder Morbus Basedow.
- **Unvorhersehbarer Verlauf:** Die Flecken können über Jahre stabil bleiben oder sich plötzlich in Schüben vergrößern.
- **Psychosoziale Belastung:** Da die Erkrankung oft an gut sichtbaren Stellen auftritt, führt sie bei vielen Betroffenen zu einer spürbaren psychischen Belastung, Schamgefühlen oder sozialem Rückzug.



Segmental vitiligo is widely thought to involve **neuronal mechanisms**, though modern research views it as part of a broader combined process rather than a purely neurological event.

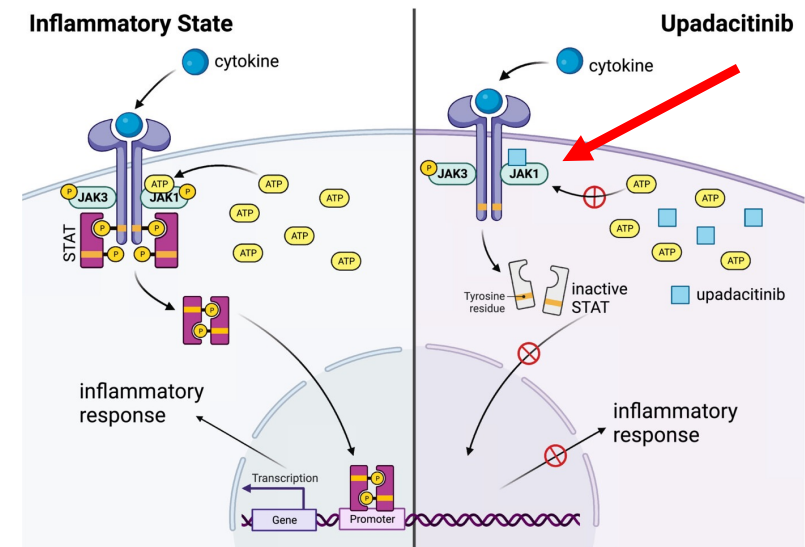


Upadacitinib (bekannt unter dem Markennamen **Rinvoq**) ist ein verschreibungspflichtiger **Januskinase-(JAK)-Inhibitor**, der gezielt das Enzym JAK1 hemmt. Es wird als Tablette eingenommen, um überschießende Entzündungsreaktionen des Immunsystems bei chronischen Autoimmunerkrankungen zu dämpfen.

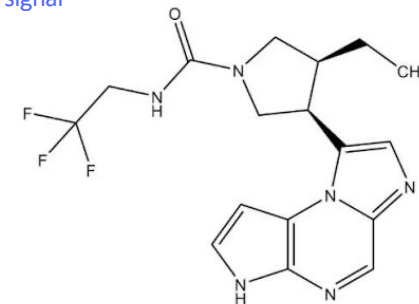
Anwendungsgebiete

Upadacitinib ist in Europa unter anderem zugelassen für die Behandlung von:

- **Rheumatoider Arthritis (RA)** und Psoriasis-Arthritis
- **Morbus Bechterew** (ankylosierender Spondylitis)
- **Atopischer Dermatitis** (Neurodermitis) ab 12 Jahren
- **Colitis ulcerosa** und **Morbus Crohn** (chronisch-entzündliche Darmerkrankungen)
- **Alopecia areata** (kreisrunder Haarausfall) und **Vitiligo** (Weißfleckenkrankheit)



Janus kinases (JAKs) are non-covalently attached to the intracellular, membrane-proximal regions of transmembrane cytokine receptors (such as Type I and Type II cytokine receptors). When a cytokine binds to its receptor, it brings the attached JAKs close together so they can activate each other and trigger the cell signal



Efficacy and safety of upadacitinib in adults and adolescents for treatment of non-segmental vitiligo (Viti-Up): results of two phase 3 randomised controlled studies

Summary

Background Non-segmental vitiligo is an autoimmune inflammatory disease characterised by loss of melanocytes leading to skin depigmentation. No systemic therapies have been approved, and additional therapeutic options are needed. Here, we report the efficacy and safety of upadacitinib, a selective once-daily Janus kinase inhibitor, in adults and adolescents with non-segmental vitiligo.

Methods Viti-Up includes two phase 3, global, multicentre, randomised, double-blind, placebo-controlled studies conducted at 138 institutions in 18 countries in Asia, Europe, North America, and South America. Eligible patients were adults and adolescents aged 12 years or older with non-segmental vitiligo involving the face and body with a Facial Vitiligo Scoring Index (F-VASI) of 0·5 or greater and Total Vitiligo Area Scoring Index (T-VASI) of 5 to less than 50. Patients were randomly assigned (2:1) to receive either upadacitinib 15 mg or placebo orally once daily. The coprimary efficacy endpoints for both studies were T-VASI 50 ($\geq 50\%$ reduction in T-VASI score from baseline) at week 48 and F-VASI 75 ($\geq 75\%$ reduction in F-VASI score from baseline) at week 48 (ie, clinically meaningful repigmentation). Efficacy endpoints were analysed in the intention-to-treat population; safety endpoints were assessed in all randomly assigned patients who received at least one dose of study drug during the 48-week double-blind period. Viti-Up is registered on ClinicalTrials.gov, NCT06118411, and is ongoing.

Findings Between Dec 19, 2023, and Oct 14, 2024, 750 individuals were assessed for eligibility. 308 individuals in Viti-Up-1 (206 assigned to upadacitinib and 102 assigned to placebo; 156 [51%] female and 152 [49%] male) and 306 in Viti-Up-2 (205 assigned to upadacitinib and 101 assigned to placebo; 151 [49%] female and 155 [51%] male) were randomly assigned. At week 48, a greater proportion receiving upadacitinib versus placebo reached the coprimary endpoints of T-VASI 50 (Viti-Up-1: upadacitinib 40 [19%] participants vs placebo six [6%]; Viti-Up-2: upadacitinib 44 [21%] vs placebo six [6%]; $p < 0\cdot001$) and F-VASI 75 (Viti-Up-1: upadacitinib 52 [25%] vs placebo six [6%]; Viti-Up-2: upadacitinib 48 [23%] vs placebo seven [7%]; $p < 0\cdot001$). There were no reports of adjudicated major adverse cardiovascular events, adjudicated venous thromboembolic events, adjudicated gastrointestinal perforations, active tuberculosis, lymphoma, non-melanoma skin cancer, or opportunistic infections other than herpes zoster in either study. Safety data were consistent with the overall upadacitinib safety profile.

Interpretation Upadacitinib 15 mg daily provides clinically meaningful repigmentation of both the face and total body for adults and adolescents with non-segmental vitiligo, with no new safety signals identified.

Funding AbbVie.

Conventional treatment for non-segmental vitiligo has historically relied on topical therapies, including corticosteroids and calcineurin inhibitors, as well as phototherapy.^{10,11} The recent approval of ruxolitinib, a topical Janus kinase (JAK) 1 and 2 inhibitor, represents a substantial advancement, because this is the only approved pharmacological treatment for vitiligo.¹² It can be used alone or in combination with phototherapy, but its use is restricted to a maximum of 10% of the body surface area.^{13,14} Although systemic therapies such as oral corticosteroids or conventional non-corticosteroid immunosuppressants are sometimes used off-label for actively progressing or extensive vitiligo in clinical practice, no systemic therapy is currently approved for vitiligo. As a result, a considerable unmet therapeutic need remains, requiring the development and approval of effective systemic therapy options.

Janus kinases are involved in the pathogenesis of many immune-mediated inflammatory diseases, including vitiligo.² Inhibition of the JAK-STAT pathway holds promise for the treatment of vitiligo by disrupting autoimmune-induced melanocyte loss.² Upadacitinib (brand name Rinvoq; AbbVie, North Chicago, IL, USA) is an oral, once-daily, reversible JAK inhibitor with greater inhibitory potency for JAK1 than JAK2, JAK3, or tyrosine kinase 2, which has been approved for the treatment of several immune-mediated inflammatory diseases, including atopic dermatitis.^{15,16} In a phase 2 clinical trial, upadacitinib treatment led to substantial repigmentation of facial and total body lesions in patients with non-segmental vitiligo.¹⁷ Here, we report the primary results up to week 48 from two phase 3 randomised clinical trials (Viti-Up-1 and Viti-Up-2) assessing the efficacy and safety of upadacitinib monotherapy for the treatment of non-segmental vitiligo in adults and adolescents.

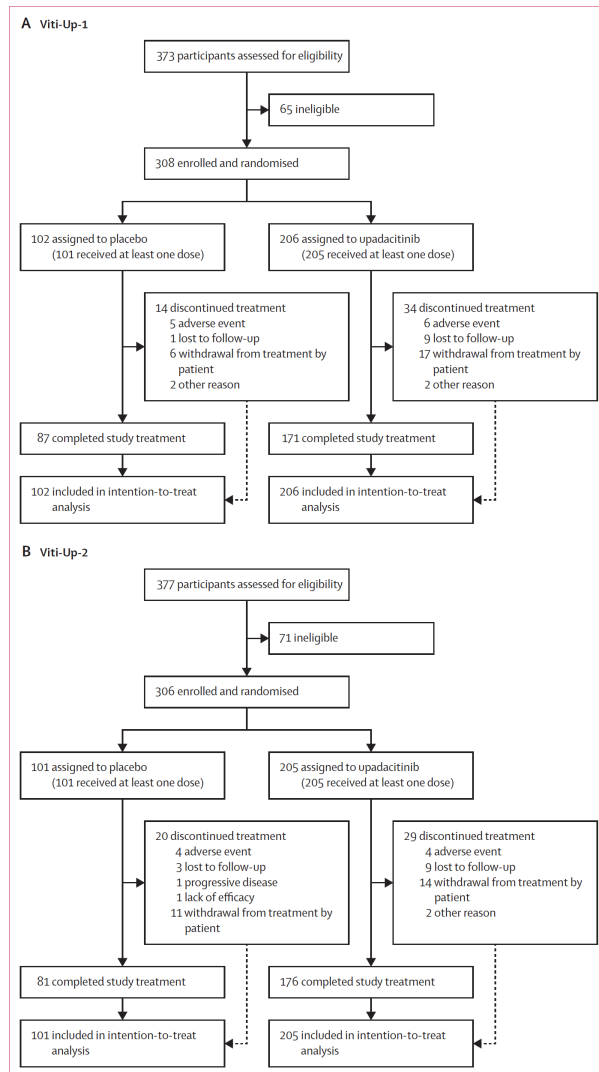


Figure 1: Trial profiles
Flow of participants in Viti-Up-1 (A) and Viti-Up-2 (B). In Viti-Up-1, one patient in each group chose not to receive a dose after randomisation.

	Viti-Up-1			Viti-Up-2		
	Placebo group (N=102)	Upadacitinib group (N=206)	Total (N=308)	Placebo group (N=101)	Upadacitinib group (N=205)	Total (N=306)
Sex						
Female	48 (47%)	108 (52%)	156 (51%)	44 (44%)	107 (52%)	151 (49%)
Male	54 (53%)	98 (48%)	152 (49%)	57 (56%)	98 (48%)	155 (51%)
Age, years	43.6 (14.7)	44.9 (15.4)	44.5 (15.1)	45.6 (15.7)	44.1 (15.3)	44.6 (15.4)
Race or ethnicity*						
Asian	23 (23%)	41 (20%)	64 (21%)	10 (10%)	23 (11%)	33 (11%)
Black	2 (2%)	9 (4%)	11 (4%)	6 (6%)	6 (3%)	12 (4%)
Hispanic or Latino	21 (21%)	60 (29%)	81 (26%)	33 (33%)	67 (33%)	100 (33%)
White	74 (73%)	152 (74%)	226 (73%)	85 (84%)	170 (85%)†	255 (84%)†
Adolescent (≥12 to <18 years)	8 (8%)	15 (7%)	23 (7%)	8 (8%)	22 (11%)	30 (10%)
BMI, kg/m²	26.0 (4.3)	26.3 (5.7)	26.2 (5.3)	26.8 (5.2)	25.9 (5.1)	26.2 (5.1)
Active vitiligo	63 (62%)	141 (68%)	204 (66%)	59 (58%)	119 (58%)	178 (58%)
T-VASI >10	73 (72%)	149 (72%)	222 (72%)	68 (67%)	141 (69%)	209 (68%)
F-VASI	1.1 (0.7)	1.0 (0.6)	1.1 (0.6)	1.0 (0.6)	1.1 (0.7)	1.1 (0.6)
T-VASI	20.7 (12.9)	18.7 (11.7)	19.4 (12.1)	17.6 (11.6)	16.5 (10.1)	16.8 (10.6)
Fitzpatrick skin type						
Type ≤II	17 (17%)	42 (20%)	59 (19%)	38 (38%)	80 (39%)	118 (39%)
Type >III	38 (37%)	85 (41%)	123 (40%)	20 (20%)	53 (26%)	73 (24%)
Type I	1 (1%)	4 (2%)	5 (2%)	5 (5%)	8 (4%)	13 (4%)
Type II	16 (16%)	38 (18%)	54 (18%)	33 (33%)	72 (35%)	105 (34%)
Type III	47 (46%)	79 (38%)	126 (41%)	43 (43%)	72 (35%)	115 (38%)
Type IV	31 (30%)	64 (31%)	95 (31%)	15 (15%)	41 (20%)	56 (18%)
Type V	6 (6%)	15 (7%)	21 (7%)	5 (5%)	10 (5%)	15 (5%)
Type VI	1 (1%)	6 (3%)	7 (2%)	0	2 (1%)	2 (1%)
Previous topical therapy for vitiligo‡	54 (53%)	117 (57%)	171 (56%)	64 (63%)	118 (58%)	182 (59%)
Previous phototherapy for vitiligo§	35 (34%)	67 (33%)	102 (33%)	32 (32%)	67 (33%)	99 (32%)
Vitiligo disease diagnosis duration, years	16.7 (14.4)	16.7 (14.8)	16.7 (14.6)	15.6 (12.0)	15.7 (12.6)	15.7 (12.4)
VitiQoL total score	33.3 (24.2)	36.2 (26.3)	35.3 (25.6)	34.4 (24.7)	38.1 (24.7)	36.9 (24.7)

Data are n (%) or mean (SD). F-VASI=Facial Vitiligo Area Scoring Index. T-VASI=Total Vitiligo Area Scoring Index. VitiQoL=Vitiligo-Specific Quality-of-Life Instrument.
 *Participants could choose multiple options. †Four participants did not report race or ethnicity in the upadacitinib group; percentages have been calculated from available data. ‡Includes topical corticosteroids and topical calcineurin inhibitors. §Previous phototherapy includes phototherapy, photochemotherapy, and laser (phototherapy equivalent).

Table 1: Demographics and baseline characteristics

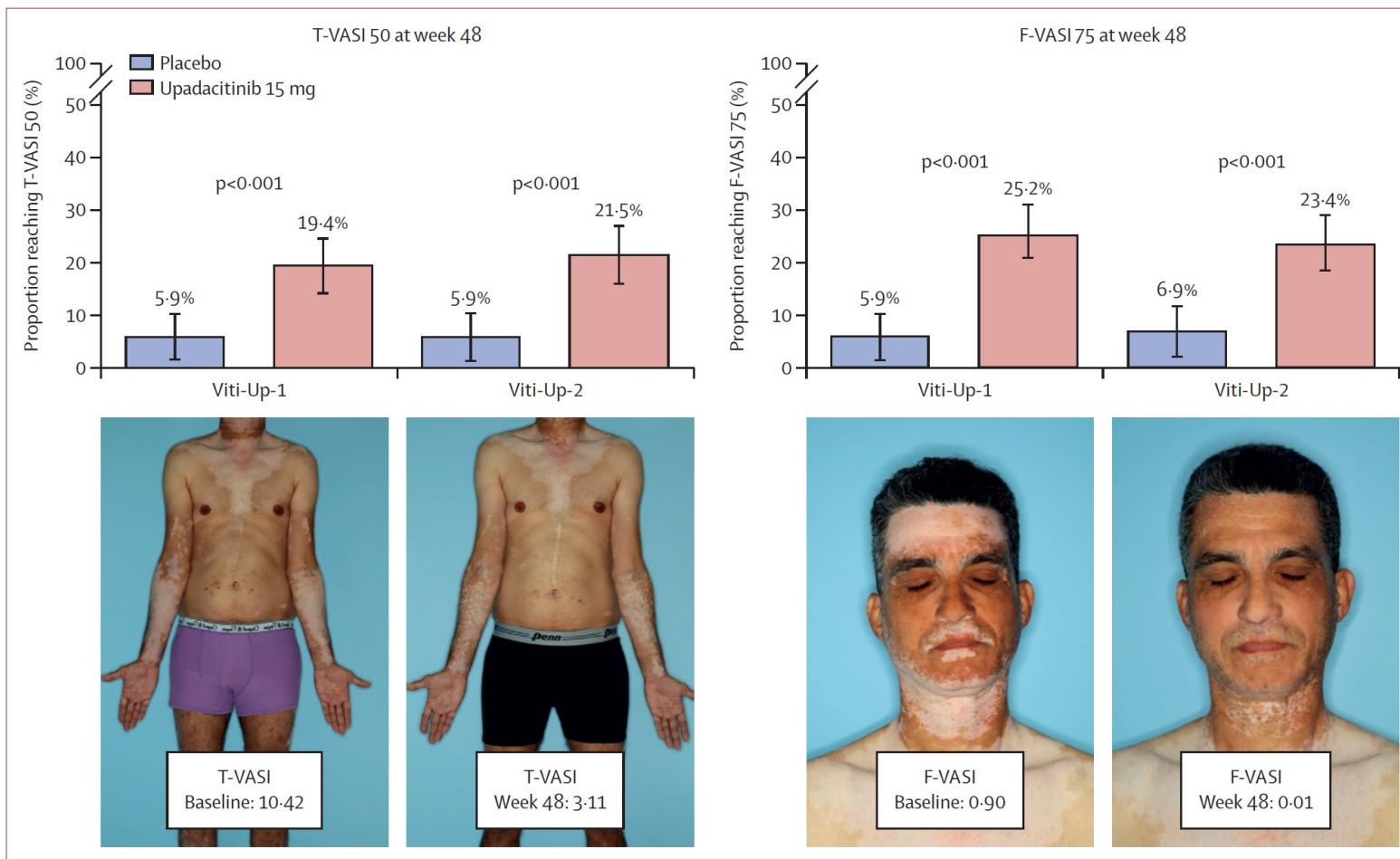


Figure 2: Proportions of patients who reached coprimary endpoints at week 48 and representative clinical images

Non-responder imputation while incorporating multiple imputation was the primary approach to handle missing data; however, as no missing data were observed that could be reasonably assumed to be missing at random, non-responder imputation was used instead. Patients were considered non-responders at visits affected by intercurrent events. F-VASI=Facial Vitiligo Area Scoring Index. T-VASI=Total Vitiligo Area Scoring Index.

	Viti-Up-1				Viti-Up-2			
	Placebo group (N=102)	Upadacitinib group (N=206)	Adjusted difference vs placebo (95% CI)	p value	Placebo group (N=101)	Upadacitinib group (N=205)	Adjusted difference vs placebo (95% CI)	p value
Coprimary endpoints								
T-VASI 50 (≥50% reduction from baseline) at week 48	6 (6%)	40 (19%)	13.1 (6.3 to 19.8)	<0.001	6 (6%)	44 (21%)	14.7 (7.5 to 21.9)	<0.001
F-VASI 75 (≥75% reduction from baseline) at week 48	6 (6%)	52 (25%)	18.7 (11.5 to 25.9)	<0.001	7 (7%)	48 (23%)	16.9 (9.2 to 24.5)	<0.001
Secondary endpoints								
F-VASI 50 at week 48	13 (13%)	99 (48%)	33.8 (24.8 to 42.9)	<0.001	13 (13%)	89 (43%)	30.1 (20.8 to 39.4)	<0.001
F-VASI 75 at week 24	2 (2%)	31 (15%)	13.1 (7.7 to 18.5)	<0.001	1 (1%)	23 (11%)	10.6 (5.8 to 15.5)	<0.001
F-VASI 90 at week 48	2 (2%)	32 (16%)	13.0 (7.8 to 18.3)	<0.001	3 (3%)	25 (12%)	9.4 (3.7 to 15.1)	0.001
Percentage change from baseline in F-VASI at week 24, LSM (SE)	-13% (5)	-42% (4)	-29% (-38 to -21)	<0.001	-2% (4)	-28% (3)	-26% (-34 to -18)	<0.001
Percentage change from baseline in T-VASI at week 48, LSM (SE)	-9% (5)	-29% (4)	-19% (-28 to -11)	<0.001	-13% (4)	-33% (3)	-20% (-29 to -12)	<0.001
T-VASI 75 at week 48	3 (3%)	10 (5%)	1.7 (-2.2 to 5.5)	0.40	2 (2%)	10 (5%)	2.2 (-1.6 to 6.0)	0.255
No increase from baseline in T-VASI at both week 8 and week 12 among participants with actively progressing vitiligo at baseline								
N	63	141	..	..	59	119	..	..
n (%)	38 (60%)	107 (76%)	15.8 (2.0 to 29.7)	0.025	36 (61%)	90 (76%)	14.9 (0.5 to 29.2)	0.042
PhGIC-V of “Much better (1)” at week 48	6 (6%)	41 (20%)	12.8 (6.2 to 19.4)	<0.001	1 (1%)	34 (17%)	15.4 (10.2 to 20.6)	<0.001
PaGIC-V of “Much better (1)” at week 48	4 (4%)	32 (16%)	11.2 (5.1 to 17.3)	<0.001	1 (1%)	37 (18%)	16.9 (11.3 to 22.5)	<0.001
VNS score of “A lot less noticeable (4)” or “No longer noticeable (5)” at week 48	2 (2%)	26 (13%)	10.5 (5.3 to 15.8)	<0.001	1 (1%)	30 (15%)	13.9 (8.7 to 19.1)	<0.001

Data are n (%) unless otherwise indicated. T-VASI=Total Vitiligo Area Scoring Index. F-VASI=Facial Vitiligo Area Scoring Index. LSM=least squares mean. PhGIC-V=Physician's Global Impression of Change—Vitiligo. PaGIC-V=Patient's Global Impression of Change—Vitiligo. VNS=Vitiligo Noticeability Scale. 95% CIs for adjusted differences and p values were calculated according to the Cochran–Mantel–Haenszel test adjusted for strata and based on a non-responder imputation approach for binary endpoints, and an ANCOVA model based on a return-to-baseline multiple imputation approach for continuous endpoints.

Table 2: Coprimary and secondary endpoints

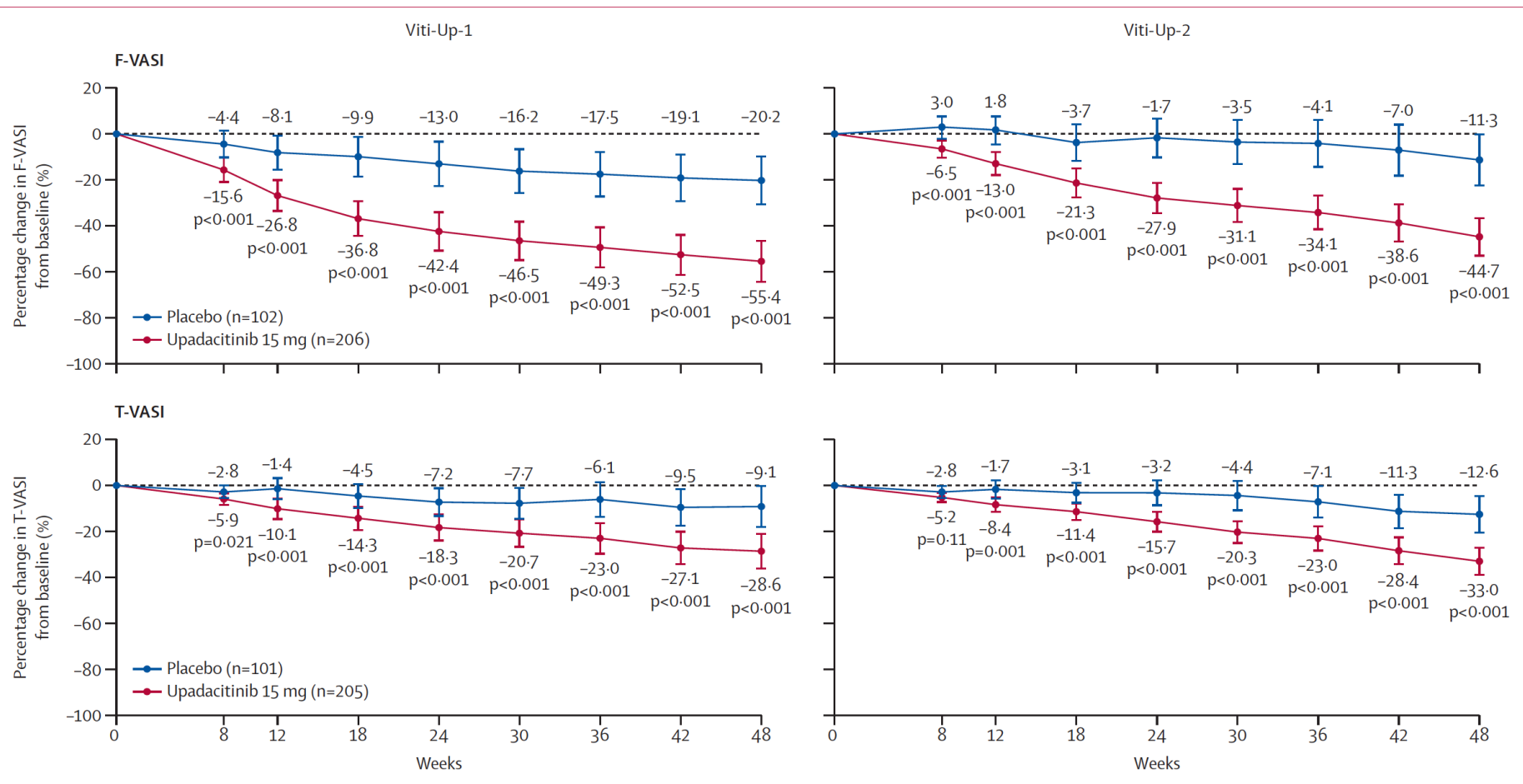


Figure 3: Change from baseline in F-VASI and T-VASI across 48 weeks

Multiple imputation was the primary approach for handling missing values, with the exception of missing data after discontinuation of study treatment due to lack of efficacy, which were handled by return-to-baseline. F-VASI=Facial Vitiligo Area Scoring Index. T-VASI=Total Vitiligo Area Scoring Index.

	Viti-Up-1		Viti-Up-2	
	Placebo group (N=101)	Upadacitinib group (N=205)	Placebo group (N=101)	Upadacitinib group (N=205)
Any TEAE	61 (60%)	166 (81%)	63 (62%)	143 (70%)
Any TEAE related to study drug according to investigator	28 (28%)	100 (49%)	22 (22%)	60 (29%)
Any severe TEAE	6 (6%)	14 (7%)	3 (3%)	12 (6%)
Any serious TEAE	4 (4%)	8 (4%)	1 (1%)	4 (2%)
Any TEAE leading to discontinuation of study drug	5 (5%)	6 (3%)	4 (4%)	4 (2%)
Any TEAE leading to death	0	0	1 (1%)*	0
TEAEs of special interest				
Serious infections	0	3 (1%)	0	0
Herpes zoster	0	4 (2%)	1 (1%)	3 (1%)
Malignancy (all types)	1 (1%)	1 (<1%)	1 (1%)	0
Non-melanoma skin cancer	0	0	0	0
Malignancies excluding non-melanoma skin cancer	1 (1%)	1 (<1%)†	1 (1%)	0
Lymphoma	0	0	0	0
Hepatic disorders	4 (4%)	8 (4%)	2 (2%)	3 (1%)
Anaemia	0	3 (1%)	1 (1%)	2 (1%)
Neutropenia	3 (3%)	8 (4%)	1 (1%)	5 (2%)
Lymphopenia	1 (1%)	1 (<1%)	1 (1%)	4 (2%)
Bone fractures	1 (1%)	5 (2%)	0	3 (1%)
Retinal detachment	0	0	0	0
Serious hypersensitivity reactions	0	0	0	0
Adjudicated major adverse cardiovascular events	0	0	0	0
Adjudicated venous thromboembolic events	0	0	0	0
Opportunistic infections	0	0	0	0
Active tuberculosis	0	0	0	0
Adjudicated gastrointestinal perforations	0	0	0	0
Renal dysfunction	0	0	0	0
Most frequently reported TEAEs (≥5% of patients in any treatment group)				
Upper respiratory tract infection	8 (8%)	29 (14%)	11 (11%)	20 (10%)
Acne	5 (5%)	23 (11%)	3 (3%)	24 (12%)
Nasopharyngitis	8 (8%)	21 (10%)	14 (14%)	36 (18%)
Headache	5 (5%)	18 (9%)	5 (5%)	17 (8%)

Data are n (%). Adjudicated refers to review by an independent panel of medical experts. Events were categorised as serious if they could result in death, hospitalisation or prolongation of hospitalisation, congenital anomaly, persistent or significant disability or incapacity, were life-threatening, or could require medical or surgical intervention to prevent a serious outcome. Events were rated for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. TEAE=treatment-emergent adverse event. * Cause of death was drowning. †Genital neoplasm, malignant, in 69-year-old female participant 46 days after start of upadacitinib.

Table 3: Treatment-emergent adverse events across 48 weeks

Added value of this study

To the best of our knowledge, Viti-Up-1 and Viti-Up-2 are the first phase 3 clinical trials to report the efficacy and safety of a systemic once-daily oral selective JAK1 inhibitor (upadacitinib) for the treatment of non-segmental vitiligo. The coprimary efficacy endpoints of T-VASI 50 (≥50% reduction in T-VASI score from baseline) and F-VASI 75 (≥75% reduction in F-VASI score from baseline) at 48 weeks of treatment were met in two phase 3 clinical trials. No new safety signals beyond the known profile of upadacitinib were reported.

Implications of all the available evidence

Results of the current study demonstrate that upadacitinib is a safe, effective treatment for adults and adolescents with non-segmental vitiligo.

Pretty convincing

Retroperitoneal fibrosis

Retroperitoneal fibrosis is a rare immune-mediated disease characterised by a periaortoiliac fibro-inflammatory tissue that often encases neighbouring structures (eg, ureters). Idiopathic retroperitoneal fibrosis can be isolated or part of IgG4-related disease, whereas secondary forms recognise different aetiologies, such as histiocytosis, malignancies, and infections. Idiopathic retroperitoneal fibrosis has a multifactorial origin, with genetic, environmental, and lifestyle factors being main contributors. The immunopathogenesis of the disease involves B-lymphocyte and T-lymphocyte crosstalk, macrophage and fibrocyte chemotaxis, and recruitment of eosinophils and mast cells. Idiopathic retroperitoneal fibrosis can cause severe complications, such as acute or chronic kidney injury, caval occlusion, and deep vein thrombosis. Although interventional or surgical procedures can be necessary to manage these complications, medical therapy remains the cornerstone of treatment. Glucocorticoids are effective, and B-cell-targeting therapies are increasingly used. However, relapses are frequent after treatment discontinuation. In this Seminar, we provide a contemporary overview of retroperitoneal fibrosis focusing on pathophysiology, differential diagnosis, and management.

IgG4 plays a role but does not seem to be the driver

Anti B-cell therapies

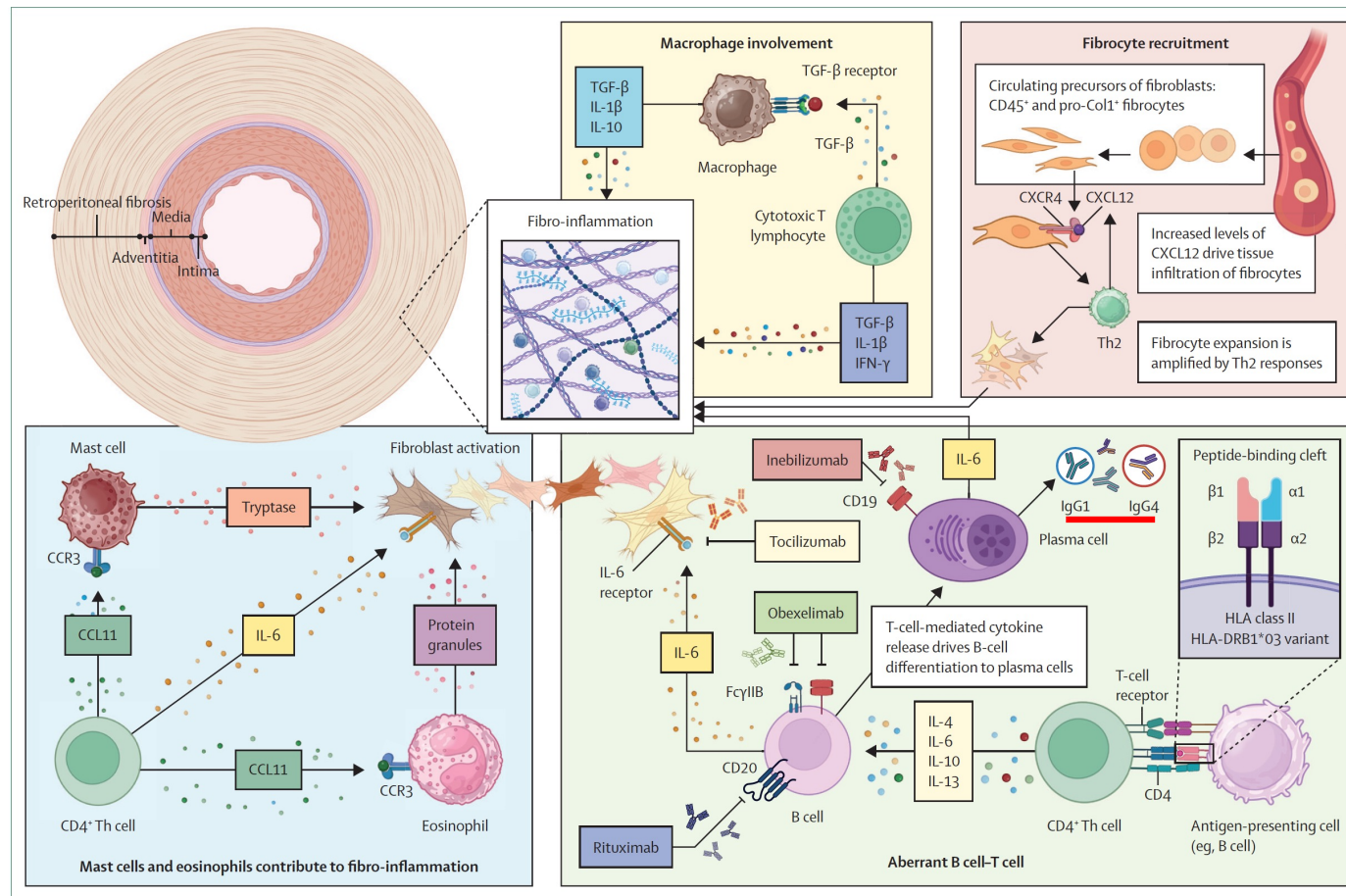


Figure 2: Immunopathogenesis of idiopathic retroperitoneal fibrosis

The main immunopathogenic mechanisms of idiopathic retroperitoneal fibrosis are summarised in the text (see Pathophysiology section). The figure illustrates key mechanisms, such as: (1) B-cell-T-cell interactions, which lead to T-cell activation and Th2 polarisation, B-cell activation, expansion, and differentiation into plasma cells, which produce immunoglobulins with a putative role in idiopathic retroperitoneal fibrosis pathogenesis (eg, IgG1 and IgG4); (2) recruitment from the circulation into tissue of fibrocytes, precursors of fibroblasts; (3) involvement of macrophages, which can be activated directly by cytotoxic T lymphocytes; and (4) recruitment into tissue of eosinophils and mast cells via the CCR3-CCL11 axis. Most of these mechanisms culminate into an enhanced fibro-inflammatory process, which eventually gives rise to the periaortic tissue that characterises idiopathic retroperitoneal fibrosis. The figure also depicts the molecular targets of biologic therapies currently used for idiopathic retroperitoneal fibrosis, as CD20 (target of rituximab), the IL-6 receptor (tocilizumab), CD19 (inebilizumab), and CD19-FcγRIIB (obexelimab). CCL11=C-C motif chemokine ligand 11. CCR3=C-C chemokine receptor type 3. CXCR4=C-X-C motif chemokine receptor 4. CXCL12=CXC receptor 12. FcγRIIB=Fcγ receptor IIB. Th2=type 2 helper T cell.

	Rochester, USA ³⁶ (n=185)	Baltimore, USA ¹⁰ (n=48)	Dordrecht, Netherlands ⁸ (n=53)	Shanghai, China ³⁸ (n=83)	Florence, Italy (n=343)
Demographics					
Male sex	61%	54%	77%	78%	69%
Mean age at diagnosis (years)	58	54	64	61 (median)	57
Clinical manifestations					
Constitutional or systemic manifestations*	27%	60%	92%	NA	55%
Pain (lower back, flank, abdomen)	78%	94%	92%	NA	89%
Testicular manifestations†	13%	27%	46%	NA	27%
Constipation	12%	NA	30%	45%‡	23%
Lower limb oedema	13%	23%	8%	NA	11%
Lower limb claudication	2%	NA	11%	1%	4%
Kidney involvement					
Hydronephrosis	57%	67%	55%	63%	75%
Unilateral	44%	31%	73%	NA	45%
Bilateral	56%	69%	27%	NA	55%
Renal atrophy at diagnosis	8%	NA	21%	NA	7%
Median (IQR) serum creatinine (mg/dL)	1.3 (1.1-2.1)	NA	1.4 (1.1-1.9)	NA	1.4 (0.9-3.7)
Median (IQR) eGFR (mL/min/1.73 m ²)	NA	NA	NA	NA	57 (16-90)
Impaired renal function at diagnosis§	42%	NA	66%	37%	51%
Other laboratory tests					
Elevated erythrocyte sedimentation rate	53%	NA	74%	77%	81%
Elevated C-reactive protein	47%	NA	62%	85%	79%
Mean haemoglobin (g/dL)	12.6	11.6	12.4	NA	12.3
Elevated serum IgG4	NA	NA	NA	52%	21%
The series included in this table were selected based on their sample size and the accuracy of data reporting. Data were collected retrospectively in the series from Rochester, whereas in the series from Baltimore, Shanghai, and Florence, they were collected prospectively. eGFR=estimated glomerular filtration rate, calculated using CKD-EPI 2021, Chronic Kidney Disease Epidemiology 2021 equation. NA=not available. *Constitutional or systemic manifestations include fatigue, anorexia, weight loss, and low-grade fever. †For testicular manifestations, the percentage was calculated for male patients only. ‡In this series, the percentage refers to digestive tract-related symptoms. §Impaired renal function indicates a serum creatinine level greater than 1.2 mg/dL.					
Table 1: Clinical characteristics of idiopathic retroperitoneal fibrosis across different series					

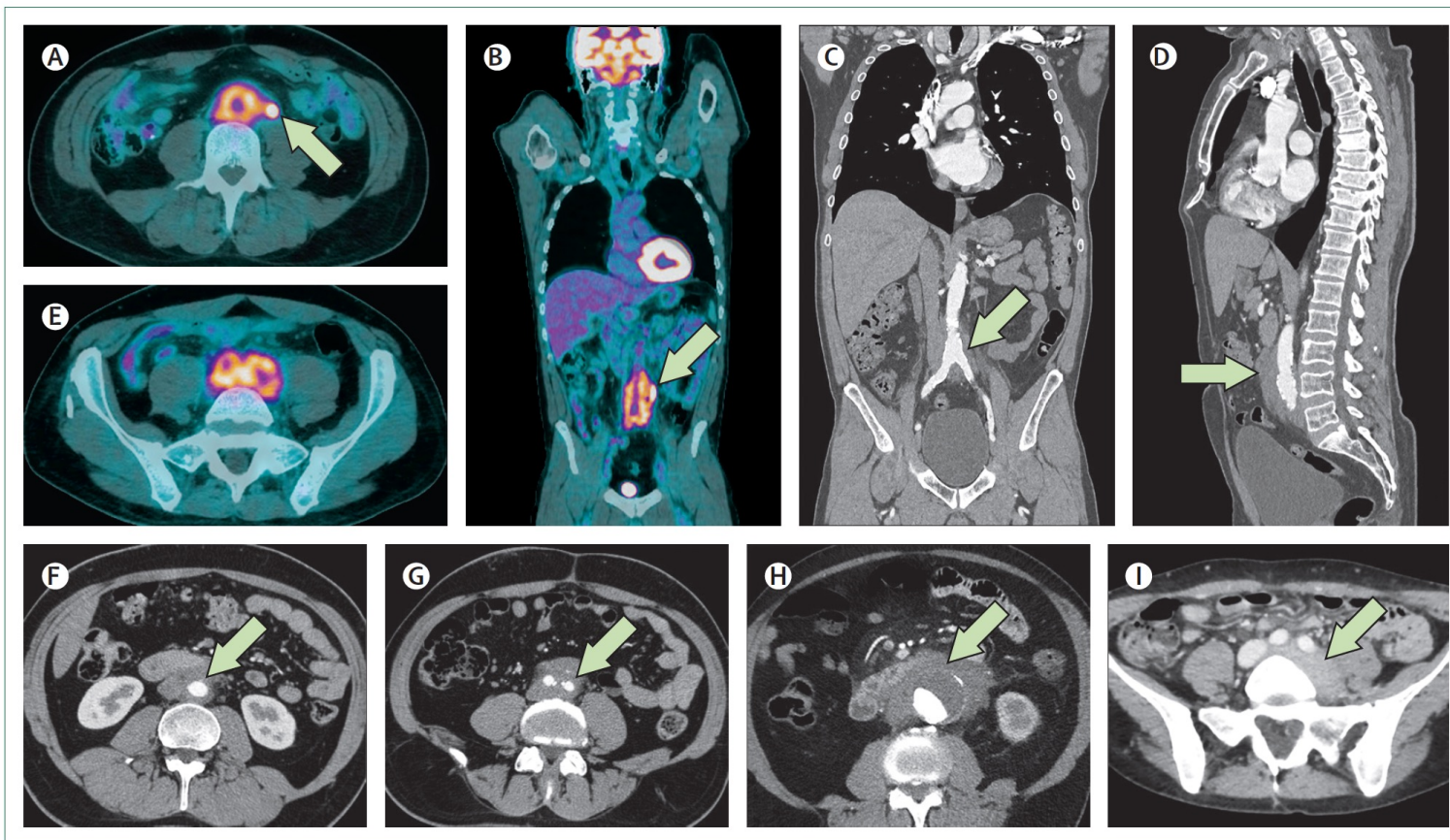


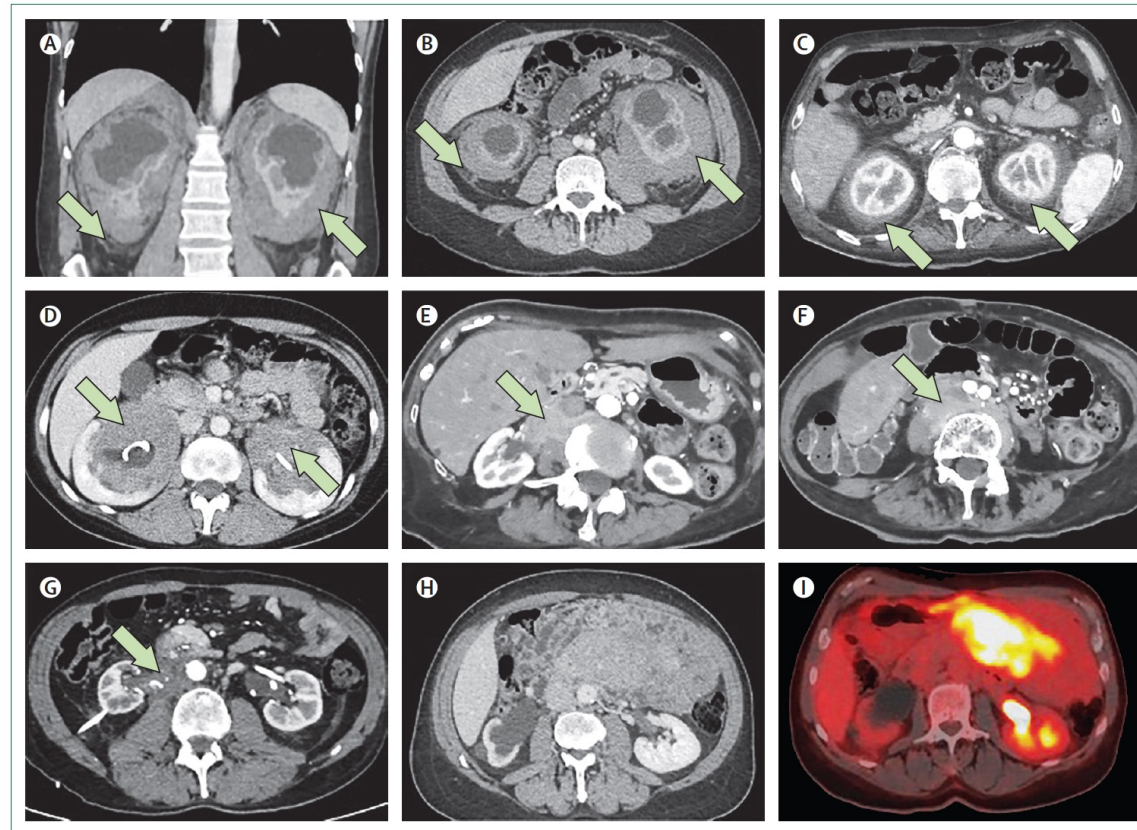
Figure 3: Imaging of idiopathic retroperitoneal fibrosis

[¹⁸F]-fluorodeoxyglucose-PET scans in a patient with idiopathic retroperitoneal fibrosis showing a hypermetabolic tissue surrounding the lower abdominal aorta (A: axial view and C: coronal view) and the common iliac arteries (B: axial view); the left ureter is also encased (A, C, and arrows). (D, E) CT scans in a patient with idiopathic retroperitoneal fibrosis showing the typical periaorto-iliac tissue (arrows; D: coronal view and E: sagittal view). (F, G) Contrast-enhanced CT scans of the abdomen in a patient with idiopathic retroperitoneal fibrosis showing the periaortic (F: arrow) and peri-iliac (G: arrow) tissue. (H) Contrast-enhanced CT scan of the abdomen in a patient with perianeurysmal retroperitoneal fibrosis showing a soft-tissue mass (arrow) surrounding an aneurysmal aorta; the aortic lumen is partly occupied by a large thrombus. (I) Contrast-enhanced CT scan of the abdomen in a patient with retroiliac, paravertebral idiopathic retroperitoneal fibrosis (arrow; atypical localisation).

Pattern of retroperitoneal infiltration		Systemic features	Laboratory findings
Idiopathic retroperitoneal fibrosis			
Non-IgG4-related disease related	Typical: retroperitoneal infiltration around the antero-lateral abdominal aorta (below the origin of the renal arteries), common iliac arteries, and inferior vena cava; possible involvement of the upper or lower mesenteric arteries; encasement of the distal ureter. Atypical (ie, requires biopsy): isolated periureteral; pelvic, pre-sacral; perirenal space and renal vascular peduncle	Constitutional symptoms moderately common. Not uncommon the involvement of local and distant lymph nodes, thoracic aorta, mediastinum, thyroid (autoimmune thyroiditis)	ESR and CRP usually high at disease onset. High IgG4 serum levels in ~30% of patients
Retroperitoneal fibrosis in the context of IgG4-related disease	Usually indistinguishable from IgG4-related retroperitoneal fibrosis. Retroperitoneal infiltration around the abdominal aorta, common iliac arteries, and inferior vena cava; encasement of the distal ureters; perirenal infiltration	Lacrimal or salivary gland involvement; pancreaticobiliary involvement; lymphadenopathy; orbital infiltration; other large vessels	Increased serum IgG4 levels; polyclonal hypergammaglobulinaemia; often low serum C3 and C4 levels
Secondary retroperitoneal fibrosis: histiocytosis			
Erdheim-Chester disease	Circumferential sheathing of the abdominal aorta (less frequently of its major branches); bilateral perinephric infiltration with encasement of the proximal ureter and the vascular peduncle	Bilateral sclerosis of the long bones; pleural or pericardial thickening with effusion and myocardial infiltration; cerebellar and brainstem lesions; interstitial lung involvement; xanthelasma-like lesions; exophthalmos	Elevated CRP; BRAF, MAP2K1, or RAS mutations on the pathologic tissue.
Rosai-Dorfman-Destombes disease	Unilateral (more rarely bilateral) pararenal bulky masses often involving the medial portions of the kidneys and the proximal ureters	Bilateral, massive cervical lymphadenopathy; skin lesions; CNS masses; sinusitis; bone lesions	Autoimmune tests reflecting underlying autoimmune conditions
Secondary retroperitoneal fibrosis: malignancies			
Lymphoma	Large retroperitoneal masses or confluent lymphadenopathy that infiltrate adjacent structures (eg, bone and muscle)	Constitutional symptoms; lymphadenopathy; hepatosplenomegaly; mediastinal mass; bone marrow infiltration	Complete blood count abnormalities; elevated lactate dehydrogenase and uric acid; elevated CRP or ESR
Liposarcoma	Lobulated mass with fatty appearance; rare periaortiliac localisation	Uncommon	Non-specific
Metastasis	Inhomogeneous lesions infiltrating different structures; rare periaortiliac localisation	Primary cancer lesions	Depending on primary cancer and localisation
Secondary retroperitoneal fibrosis: iatrogenic			
Drugs*	Might be similar to idiopathic retroperitoneal fibrosis localisation	Non-specific	Elevated CRP or ESR
Radiotherapy	Generally localised in the irradiated areas, often encasing the ureters	Uncommon	Non-specific
Post-surgery	Generally localised in the areas of previous major surgery, often encasing the ureters	Uncommon	Non-specific
Secondary retroperitoneal fibrosis: infections			
Tuberculosis	Fibrotic tissue encasing the ureters, the aorta, or other retroperitoneal structures, resulting from retroperitoneal lymphadenitis, genitourinary infection, or Pott's disease	Constitutional symptoms	Elevated CRP or ESR; positive tuberculin skin test or interferon-γ release assay
Actinomycosis	Dense fibrosis and abscesses due to direct extension from pelvic or bowel disease	Constitutional symptoms; other disease localisations (CNS, cervical, thoracic)	Elevated CRP or ESR
Histoplasmosis	Fibrosis around the abdominal aorta and its branches	Chronic or disseminated infection (immunodepression)	Elevated CRP or ESR
Secondary retroperitoneal fibrosis: others			
Amyloidosis	Unifocal amyloid deposition involving the ureter with linear calcification of the renal pelvis and ureters	Constitutional symptoms; restrictive cardiomyopathy; proteinuria and kidney failure; peripheral or autonomic neuropathy; macroglossia; malabsorption; periorbital purpura; arthropathy. Systemic features might be absent in case of localised amyloidosis	Monoclonal hypergammaglobulinaemia; anaemia; elevated ESR; proteinuria and kidney function abnormalities; elevated alkaline phosphatase levels
Large-vessel vasculitis	Extremely rare retroperitoneal fibrosis in giant cell arteritis; abdominal aorta thickening more often in Takayasu arteritis	Constitutional symptoms. Giant cell arteritis: headache; jaw claudication; visual symptoms; polymyalgia rheumatica; aortic aneurysms or dissections. Takayasu arteritis: vascular claudication; renovascular hypertension; cerebrovascular ischaemia; aortic aneurysms or dissection	Elevated CRP or ESR; anaemia; thrombocytosis
Trauma	Non-specific	Non-specific	Non-specific
CRP=C-reactive protein. ESR=erythrocyte sedimentation rate. *Methysergide, pergolide, bromocriptine, ergotamine, methyl dopa, hydralazine, analgesics, beta blockers, immune checkpoint inhibitors, and anti-TNF.			
Table 2: Idiopathic and secondary forms of retroperitoneal fibrosis: main radiological, clinical, and laboratory elements			

EC disease

Die **Rosai-Dorfman-Erkrankung** (auch bekannt als Sinushistiozytose mit massiver Lymphadenopathie oder RDD) ist eine **sehr seltene, gutartige Erkrankung des Immunsystems**, die zu den sogenannten [Histiozytosen](#) zählt.



Hairy kidney
with EC
disease

B-cell
lymphomas

Figure 4: Imaging of secondary forms of retroperitoneal fibrosis

(A, B) Contrast-enhanced CT scans in a patient with Erdheim-Chester disease and retroperitoneal involvement. The scans show a thick retroperitoneal, perirenal tissue (arrows, coronal view in A and axial view in B), which causes pelvic or ureteral obstruction (not visible) and marked calycoectasia. (C) Contrast-enhanced CT scan (axial view) in a patient with Erdheim-Chester disease and retroperitoneal, perirenal involvement shows the typical hairy kidney appearance (arrows). (D) Contrast-enhanced CT scan (axial view) in a patient with Rosai-Dorfman-Destombes disease shows infiltration of the medial perirenal retroperitoneal space (arrows); the disease causes ureteral obstruction requiring ureteral stent placements (the stents are visible in the pelvis of both kidneys). (E, F) Contrast-enhanced CT scans (axial view) in a patient with retroperitoneal follicular B-cell lymphoma shows a large, inhomogeneous bulky mass occupying the retroperitoneal space between the inferior vena cava and the right kidney (E: arrows) and between the iliac vessels and the right psoas muscle (F: arrows). (G) Contrast-enhanced CT scan (axial view) in a patient with poorly differentiated urothelial carcinoma occupying the retroperitoneal space between the aorta, the inferior vena cava, and the right kidney; this ill-defined mass (arrow) causes ureteral obstruction and the patient bears a right-sided nephrostomy tube. (H, I) Contrast-enhanced CT scan (H: axial view) and [^{18}F]-fluorodeoxyglucose (I: axial view) scans in a patient with a large abdominal B-cell lymphoma also occupying the retroperitoneum; the mass is bulky, ill defined, and inhomogeneous.

Panel 1: Imaging findings prompting diagnostic biopsy in patients with suspected retroperitoneal fibrosis

- Extension from above the origin of the renal arteries to below the bifurcation of the common iliac arteries
- Isolated pelvic, periureteral, perirenal, or peribladder localisation
- Bulky, non-homogeneous mass
- Confluent lymphadenopathy
- Bone or muscle infiltration
- Retroaortic localisation and anterior aortic displacement
- Ureteral displacement (laterally)
- Typical Erdheim–Chester disease retroperitoneal pattern (ie, hairy kidney)

IgG4

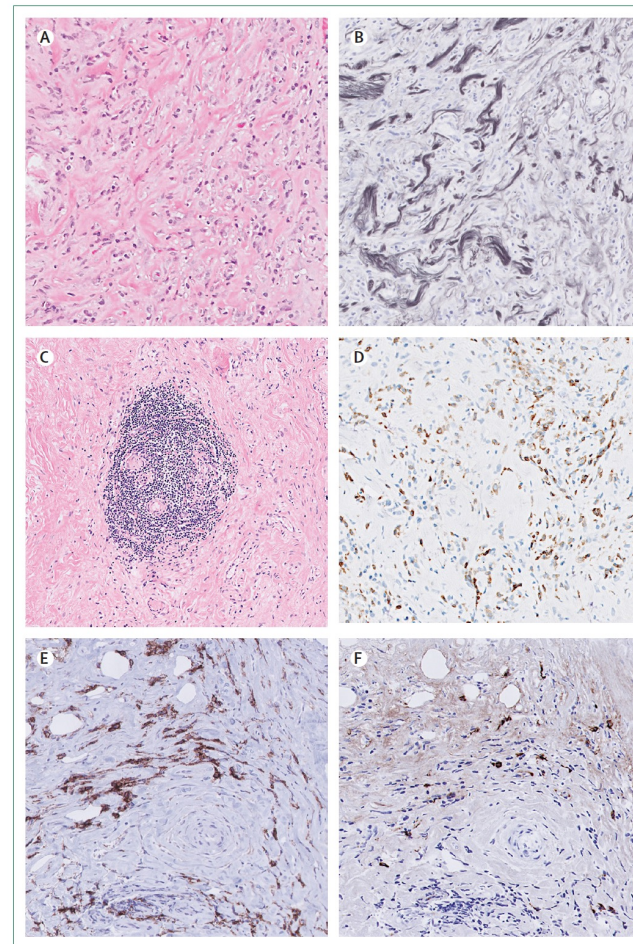


Figure 5: Histopathology of idiopathic retroperitoneal fibrosis

The hallmark of idiopathic retroperitoneal fibrosis is fibrosis with variable amounts of inflammatory cells. Biopsies should be carefully investigated to have no signs of differential diagnoses: the inflammatory infiltrate should be a non-specific lymphocytic infiltrate interspersed with macrophages and with immunohistochemical staining ruling out lymphoma and other causes of retroperitoneal fibrosis. Haematoxylin and eosin staining (A) shows moderately dense infiltrate against a background of fibrosis, the pattern of which is revealed by a (B) silver staining. (C) The inflammatory infiltrate mostly consists of CD3-positive T cells. (D) Lymphofollicular infiltrates can be present. There can be areas with plasma cells (CD138 staining in E) but in idiopathic retroperitoneal fibrosis, only few of those are positive for IgG4 (E: consecutive slides of E). All magnifications at 200× except for D (100×).

Panel 2: Questions, controversies, and uncertainties around retroperitoneal fibrosis

When should retroperitoneal fibrosis be labelled as IgG4-related disease?

In retroperitoneal fibrosis, serum IgG4 levels are often normal and, when available, histology frequently fails to meet the quantitative IgG4⁺-to-IgG⁺ plasma cell thresholds proposed for IgG4-related disease. Many patients lie along a continuum that ranges from isolated retroperitoneal fibrosis to multisystemic IgG4-related disease with retroperitoneal involvement, challenging the concept of distinct entities. Strict categorical boundaries can be more semantic than biological and risk to fragment what could represent a single immunopathological spectrum. Clinically, distinguishing non-IgG4-related from IgG4-related retroperitoneal fibrosis, provided that these forms are not secondary to specific aetiologies, has limited therapeutic relevance, as both respond similarly to glucocorticoids and B-cell-targeted therapies. Rigid adherence to classification criteria for IgG4-related disease can lead to the exclusion of IgG4-negative cases from clinical trials of emerging therapies for IgG4-related disease, thereby hindering therapeutic innovation for the broader fibro-inflammatory spectrum. Whether the IgG4 response identifies a distinct pathogenic pathway or merely reflects a disease stage remains uncertain. A pragmatic, inclusive view recognising retroperitoneal fibrosis as part of an overlapping spectrum of fibro-inflammatory disorders might be more appropriate than a dichotomous framework.

Can imaging alone establish the diagnosis?

Radiological findings often provide a compelling picture of peri-aortoiliac tissue; however, they cannot reliably exclude

malignancy, histiocytosis, or infections.

[¹⁸F]-fluorodeoxyglucose-PET helps assess metabolic activity and can detect extra-retroperitoneal involvement but lacks specificity and validated thresholds for diagnosis. Moreover, the breadth of ancillary workup, such as whole-body imaging or targeted laboratory tests to exclude alternative diagnoses, remains debated. Consequently, the decision to perform a biopsy varies widely: many centres reserve biopsy to retroperitoneal fibrosis with atypical locations or when clinical or imaging features raise the suspicion of malignancy, whereas others rely on imaging and follow-up alone, with a potential risk of misclassification. Defining when imaging findings are sufficiently characteristic to safely avoid biopsy remains a key unresolved issue.

Are there patient subsets who particularly benefit from targeted biologic therapy?

Glucocorticoids remain the standard first-line treatment for retroperitoneal fibrosis, providing rapid improvement, but carrying substantial toxicity and frequent relapse after withdrawal. B-cell-depleting therapy with rituximab and other agents and, more recently inebilizumab, have emerged as an effective alternative. Clinicians should aim at individualising induction strategies according to disease severity, comorbidities, and risk of long-term glucocorticoid toxicity, but validated criteria for such stratification are lacking. Beyond B-cell depletion, targeted approaches, such as IL-6 receptor blockade have shown promising results. Identifying molecular or clinical predictors that guide early biologic use and define optimal targeted therapies represents an important frontier in retroperitoneal fibrosis.

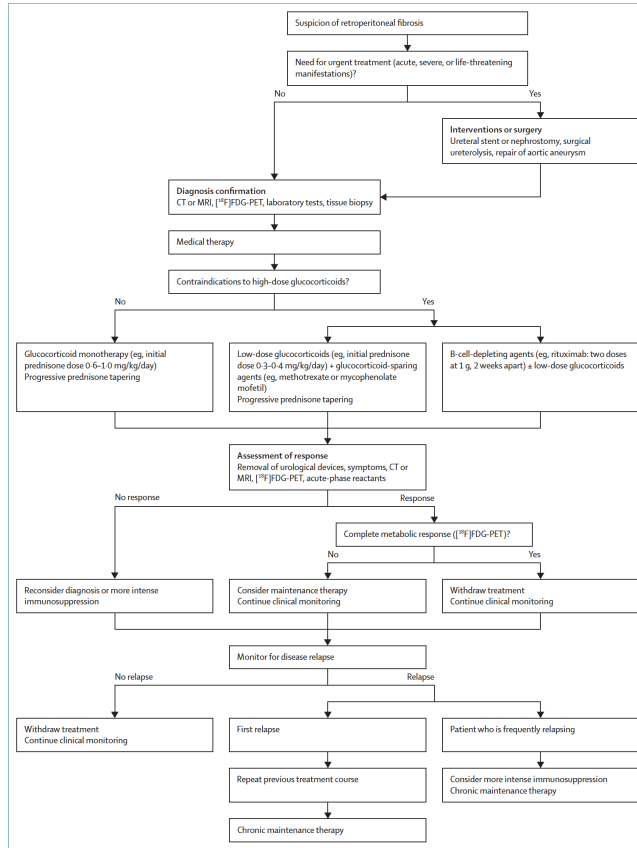


Figure 6: Treatment algorithm for idiopathic retroperitoneal fibrosis
The figure illustrates the main diagnostic and therapeutic steps for patients with a suspicion of retroperitoneal fibrosis. FDG=[¹⁸F]-fluorodeoxyglucose.

Panel 3: Outstanding research questions

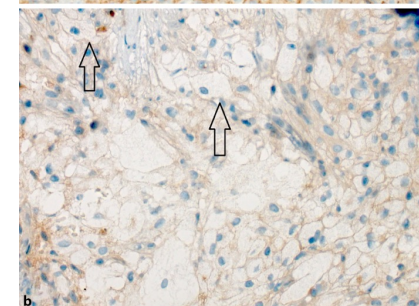
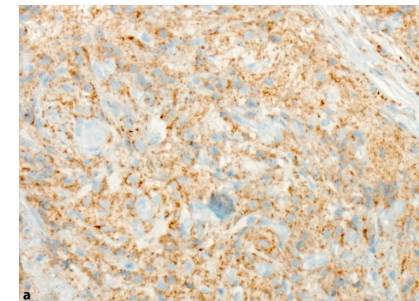
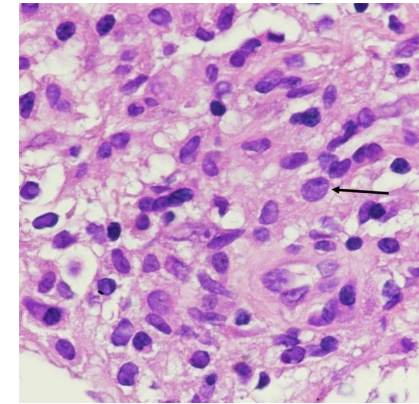
- Disease biomarkers: is there a non-invasive, reliable, and reproducible biomarker of disease activity or relapse? Can some of the proposed candidates (eg, soluble IL-2 receptor, IL-6, and CCL18) be validated for clinical use in standardised monitoring protocols?
- PET-guided management: what standardised uptake value or visual thresholds and timepoints best stratify relapse risk and guide treatment management? Does PET negativity justify treatment withdrawal?
- Maintenance therapy: how long should treatment be continued and which patients truly need maintenance therapy? Considering B-cell-depleting agents, what are the optimal dose and time intervals for maintenance?
- Ureteral obstruction relief: does early ureterolysis improve long-term renal outcomes? Which patients would benefit most?
- Renal outcomes: which factors drive progression to chronic kidney disease despite clinical and radiological remission?

Conclusion

Retroperitoneal fibrosis encompasses fibro-inflammatory lesions that can be idiopathic or secondary to specific aetiologies. The idiopathic form can also be a manifestation of IgG4-related disease. Controversies still exist about the nosology of retroperitoneal fibrosis and the most appropriate diagnostic and therapeutic approach (panel 2), although remarkable progress was made in the past decades in understanding the pathophysiology of the disease and in developing novel therapeutic approaches. Deep knowledge of the differential diagnoses is also essential for retroperitoneal fibrosis management. There are many issues to address in the future, including the need for disease-specific biomarkers, the identification of reliable predictors of response and outcome, and the definition of cost-effective long-term maintenance treatments (panel 3).

Die **Erdheim-Chester-Erkrankung (ECD)** ist eine extrem seltene, bösartige Multisystemerkrankung aus der Gruppe der **Histiozytosen**, die heute als eine **Form von Blutkrebs (myeloische Neoplasie)** eingestuft wird. Bei dieser Erkrankung vermehren sich bestimmte weiße Blutkörperchen (**Histiozyten/Makrophagen**) unkontrolliert und infiltrieren verschiedene Organe und Gewebe. Dies führt zu chronischen Entzündungen, Gewebeverdickungen und fortschreitenden Vernarbungen (**Fibrose**).

- **Skelettsystem (ca. 95 %):** Typisch sind symmetrische Knochenverdichtungen (Osteosklerose) in den langen Röhrenknochen der Beine, die chronische Knochenschmerzen verursachen.
- **Nieren:** Die Infiltration des Gewebes um die Nieren führt im CT-Scan zum charakteristischen Bild einer sogenannten „haarigen Niere“ (*hairy kidney*).
- **Herz-Kreislauf-System:** Häufig zeigt sich eine Ummantelung der Hauptschlagader („beschichtete Aorta“). Zudem können tumorartige Gewebe im rechten Vorhof entstehen.
- **Zentralnervensystem (ZNS):** Ein Befall des Gehirns kann Gleichgewichtsstörungen, Kopfschmerzen, kognitive Einschränkungen oder Krampfanfälle auslösen.



CD68+
BRAF v600e Mutation

Massive bilateral perirenal infiltration in Erdheim-Chester disease

Case presentation

A 63-year-old man with a reported history of sarcoidosis, without histological confirmation, was referred for evaluation of persistent fever of unknown origin. Laboratory investigations showed microcytic anaemia (haemoglobin 9.1 g/dL, mean corpuscular volume 70 fL), elevated C-reactive protein (173 mg/L), hypergamma-globulinaemia (23% of total gamma globulins), and a trace monoclonal IgG λ component. Kidney function was normal (serum creatinine 0.7 mg/dL, estimated glomerular filtration rate 97 mL/min per 1.73 m²). Abdominal CT revealed bulky bilateral perirenal soft-tissue masses, each measuring over 20 cm in maximal diameter, causing circumferential encasement of the kidneys without parenchymal invasion. No clinically significant lymphadenopathy was detected.

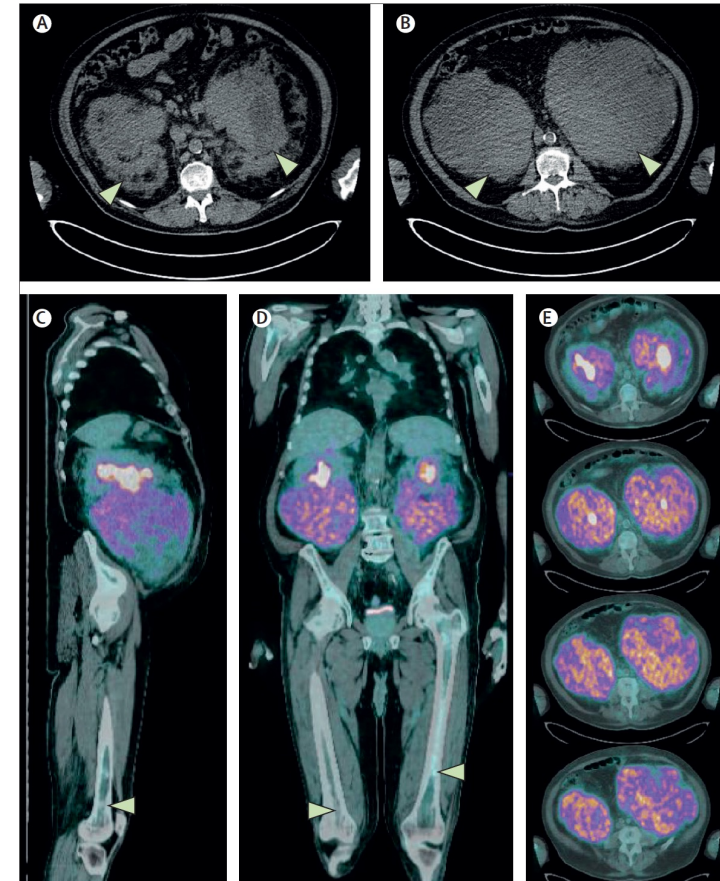


Figure: Bilateral perirenal infiltration and skeletal involvement on CT and PET-CT
(A, B) CT scans showing bulky bilateral perirenal masses (arrows). (C, D) ¹⁸F-fluorodeoxyglucose PET-CT images (sagittal and coronal views) showing intense ¹⁸F-fluorodeoxyglucose uptake in both perirenal regions, together with symmetrical metabolic activity in the long bones, particularly the femurs (arrows). (E) Sequential axial PET images showing the marked hypermetabolic activity of the bilateral perirenal masses (maximal standardised uptake value 8.4 on the left side).

Given the suspicion of a retroperitoneal inflammatory or infiltrative disorder, whole-body (vertex to toes) [^{18}F] fluorodeoxyglucose PET–CT was performed and revealed intense uptake in both perirenal regions, together with symmetrical metabolic activity in the long bones (figure). At this stage, the differential diagnosis included retroperitoneal fibrosis, either idiopathic or IgG4-related, Erdheim-Chester disease (ECD), or malignancies. The combination of massive bilateral perirenal encasement and symmetrical long-bone involvement favoured a histiocytic disorder over other conditions. A perirenal tissue biopsy revealed infiltration by foamy histiocytes that were CD68-positive and CD1a-negative, consistent with the diagnosis of ECD. Molecular analysis revealed the presence of the $\text{BRAF}^{\text{V600E}}$ mutation, and the patient was started on targeted therapy with the $\text{BRAF}^{\text{V600E}}$ inhibitor vemurafenib, receiving 480 mg orally twice a day.

CD68 ist ein Eiweiß (Protein), das vor allem auf der Oberfläche von Makrophagen (Fresszellen des Immunsystems) sitzt. In der Medizin und Pathologie wird es als wichtiger Labor-Marker genutzt, um diese Immunzellen in Gewebeproben sichtbar zu machen. Ein Nachweis von CD68 in einer Biopsie zeigt an, dass das Immunsystem aktiv ist, oft als Zeichen für eine Entzündung oder eine andere Gewebeveränderung.

Discussion

ECD is a rare histiocytosis, often characterised by multisystem involvement. Retroperitoneal infiltration is frequent and commonly leads to ureteral obstruction and hydronephrosis.¹ On imaging, ECD can mimic other retroperitoneal disorders, including IgG4-related or idiopathic retroperitoneal fibrosis, lymphoma, and metastatic disease.² A key radiological distinction between ECD and retroperitoneal fibrosis lies in the topography of ureteral involvement. Retroperitoneal fibrosis typically affects the distal third of the ureters, often leading to medial deviation and obstruction, whereas ECD typically involves the renal pelvis and proximal ureters as part of a circumferential perirenal infiltration.

Die **BRAF-V600E-Mutation** ist eine Genveränderung, bei der im BRAF-Gen an Position 600 die Aminosäure Valin durch Glutaminsäure ersetzt wird. Dies führt zu einer ständigen Aktivierung des MAPK/ERK-Signalwegs, was unkontrolliertes Zellwachstum antreibt und bei verschiedenen Krebsarten wie dem malignen Melanom, Darmkrebs und Schilddrüsenkrebs vorkommt.



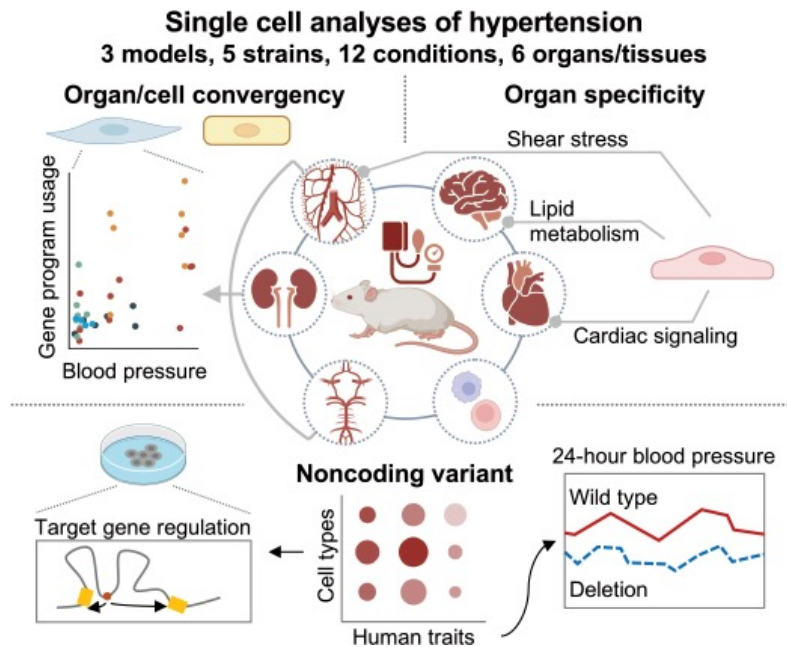
A cross-organ single-cell analysis of hypertension

INTRODUCTION: Hypertension is a leading global cause of disease burden and mortality, affecting around 33% of adults worldwide and contributing substantially to health care costs through complications such as heart disease, stroke, and kidney failure. Most patients with hypertension cannot be cured, and millions remain hypertensive despite multidrug treatments. The molecular understanding of hypertension and its associated end-organ damage lags behind that for other major diseases, limiting the development of more targeted therapeutic strategies.



RESULTS: We developed an integrated single-cell atlas of hypertension and hypertensive end-organ damage across three widely used animal models representing major and complementary pathophysiological mechanisms of the disease: angiotensin II-treated mice (neurohormonal), Dahl salt-sensitive rats (salt-sensitive hypertension), and spontaneous hypertensive rats (genetic, age-associated hypertension). We analyzed six organs and tissues, including the hypothalamus, kidney, third-order mesenteric artery, cardiac left ventricle, middle cerebral artery, and peripheral blood mononuclear cells. Our atlas includes single-nucleus RNA sequencing (snRNA-seq), single-cell RNA sequencing (scRNA-seq), and snMultiome-seq [snRNA-seq + single-nucleus assay for transposase-accessible chromatin sequencing (snATAC-seq)] in select samples to capture a rich landscape of transcriptional and epigenetic changes during the progression of hypertension.

Analysis of this dataset revealed both consistent transcriptional changes across models and organs and model- and tissue-specific adaptations and maladaptations. We identified a conserved vascular smooth muscle cell gene expression program, the activity of which was associated with blood pressure; a group of cross-segment renal tubular gene programs associated with renal injury and blood pressure; tissue-specialized endothelial adaptations involving lipid handling, shear stress, and cardioprotective signaling; and coordinated changes across cell types in select organs including the hypothalamus. Integration with human genomic data, including GWAS findings across nine traits including blood pressure and related end-organ damage, revealed model-specific and shared cell type-trait links, with results suggesting that different models captured complementary aspects of the hypertension-related human genetic architecture. We prioritized a noncoding variant ([rs28451064](#)) and used genome editing to demonstrate its in vivo effect on blood pressure and allele-specific regulation of local genes, including *SLC5A3* and *RCAN1*, possibly through epigenetic mechanisms including long-range chromatin interaction.



Summary of the multiorgan single-cell analyses of hypertension across animal models. The study identified shared and organ-specialized cellular responses associated with blood pressure and related tissue injury and integrated these findings with human genetic variation and noncoding regulatory mechanisms.

CONCLUSION: Our study provides a cross-organ, multimodel cell and molecular resource for hypertension research. Through integrated analysis combining this resource with other data types and targeted experiments, we have identified shared and model-and tissue-specific changes potentially underlying the development and consequences of hypertension and uncovered gene-regulatory mechanisms in hypertension.

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The genetic variant [rs28451064](#) is located on [chromosome 21](#). Located near or regulating local genes such as [MRPS6](#), [KCNE2](#), [SLC5A3](#), and [AP000318.2](#).

Die **UK Biobank** ist die weltweit umfassendste biomedizinische Datenbank und eine der wichtigsten globalen Forschungsressourcen für die moderne Medizin. Seit dem Start im Jahr 2006 erfasst das Langzeitprojekt tiefgreifende biologische, medizinische und lebensstilbezogene Daten von **über 500.000 freiwilligen Teilnehmern** aus ganz Großbritannien. Das Ziel ist es, die Entstehung schwerer Krankheiten besser zu verstehen und die Gesundheitsversorgung zu transformieren.

Was macht die UK Biobank so einzigartig?

- **Umfang der Daten:** Für die **rund 500.000 Probanden** (im Alter von anfangs 40 bis 69 Jahren) liegen genomische Sequenzierungen, Blut-, Urin- und Speichelproben vor.
- **Multidimensionale Erfassung:** Die Datenbank verknüpft genetische Profile mit elektronischen Krankenakten, detaillierten Lebensstil-Fragebögen, **Fitness-Tracking-Daten** und MRT-Scans von Organen wie Herz und Gehirn.
- **Langzeitbeobachtung:** Da die Probanden über Jahrzehnte hinweg begleitet werden, lässt sich präzise nachvollziehen, welche genetischen Merkmale oder Lebensgewohnheiten zur Entstehung von Krankheiten wie Krebs, Demenz oder Herzerkrankungen führen.



3 minutes of this activity may cut the risk of 13 cancers, study finds

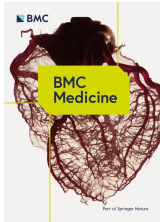


To reduce your risks for at least 13 types of cancer, jog up and down the nearest steps for three minutes or stand up from your desk or couch for 30.

Either strategy might help drop your risks of certain cancers by as much as 7 percent, according to a new study of how the ways we move — and don't move — during the day affect our chances of malignancies.

The study, published in July in BMC Medicine, is one of the first to examine in detail how replacing sitting time with almost any kind of activity alters cancer risk.

Relying on extensive activity data from nearly 60,000 men and women, it used statistical models to determine which movements, from standing to strolling to rushing around the block, seem most strongly associated with fewer cancer cases, including breast, colorectal and lung cancers.



Device-measured movement behaviours and cancer incidence in a population sample of UK adults: Dual 24-hour analyses of postural and intensity compositions

Abstract

Background

Insufficient physical activity (PA) and excessive sedentary behaviour is associated with several cancers. Personalised approaches to increasing healthy movement behaviours over unhealthy behaviours may be more effective than a one-size-fits-all approach. Exploring both postures, and intensities across the 24-hour day may reveal actionable behavioural alternatives from current guidance.

Methods

Using a novel dual-compositional approach, we assessed how differences in participant's composition of 24-hour daily movement (postures and intensities) and sleep are differentially associated with PA-related cancer incidence (a composite of 13 sites linked with physical inactivity). This prospective analysis involved adults drawn from the UK Biobank accelerometry subsample each followed-up by health linkage. Participant's daily movement was classified into two 24-hour compositions. Composition 1 (posture-focused): sleep duration, sedentary behaviour (SB), standing, moving at any intensity. Composition 2 (intensity-focused): sleep duration, sedentary time (ST), light PA (LPA), moderate PA (MPA), and vigorous PA (VPA). Secondary analysis combined VPA and MPA as moderate-to-vigorous PA (MVPA). PA-related cancer diagnoses were captured from health registry data for up to 9.5 years (y). Cox-proportional hazards models were adjusted for age, sex, education, smoking, alcohol, diet, parental cancer history, cardiovascular disease and medication use.

Results

Analyses included 59,218 (55% female) participants (mean [SD] age: 61.7 [7.8]y), with a median follow-up of 8.0y [IQR: 7.4–8.5y; 464,640 person years] with 2,385 (4%) incident cancer events. Among the average, active participant, greater moving in place of other behaviours was associated with lower cancer risk, e.g. theoretically replacing 15 min of sleep or SB with 15 min of moving was associated with hazard ratios (HR) of 0.98 (95% Confidence Interval (95%CI): 0.97–0.99) and 0.98 (95%CI: 0.97–0.99), respectively. Similar risk reduction was observed with 30 min additional standing in place of sleep or SB. Regarding intensity, greater MVPA, in place of any behaviour proved most robustly associated with lower risk, although notably, the VPA component within MVPA proved the critical intensity.

Conclusions

Beyond MVPA, moving at any intensity, in place of other postures, was associated with reduced risk of cancer. However, greater standing may also provide a plausible behavioural adjunct or alternative, warranting further investigation.

(Fairly trivial, but a nice thought nonetheless)